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Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

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Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Disease Control and Prevention (CDC) requested and provided funding for this report.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the Evidence-based Practice Center (EPC) consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, the Evidence-based Practice Center (EPC) sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

Structured Abstract

Objective. To estimate the overall balance of harms and benefits from the potential use of oral contraceptives (OCs) for the primary prevention of ovarian cancer

Data sources. We searched PubMed®, Embase®, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov for English-language studies published from January 1990 to June 2012 that evaluated the potential benefits (reduction in ovarian, colorectal, and endometrial cancers) and harms (increase in breast and cervical cancer, and vascular complications) of OC use.

Review methods. Two investigators screened each abstract and full-text article for inclusion; the investigators abstracted data, and they performed quality ratings, applicability ratings, and evidence grading. Random-effects models were used to compute summary estimates of effects. A simulation model was used to estimate the effects of OC use on the overall balance of benefits and harms.

Results. We reviewed 55 studies relevant to ovarian cancer outcomes, 66 relevant to other cancers, and 50 relevant to vascular events. Ovarian cancer incidence was significantly reduced in OC users (OR [odds ratio], 0.73; 95% CI [confidence interval], 0.66 to 0.81), with greater reductions seen with longer duration of use. Breast cancer incidence was slightly but significantly increased in OC users (OR, 1.08; 95% CI, 1.00 to 1.17), with a significant reduction in risk as time since last use increased. The risk of cervical cancer was significantly increased in women with persistent human papillomavirus infection who used OCs, but heterogeneity prevented a formal meta-analysis. Incidences of both colorectal cancer (OR, 0.86; 95% CI, 0.79 to 0.95) and endometrial cancer (OR, 0.57; 95% CI, 0.43 to 0.76) were significantly reduced by OC use. The risk of vascular events was increased in current OC users compared with nonusers, although the increase in myocardial infarction was not statistically significant. The overall strength of evidence for ovarian cancer prevention was moderate to low, primarily because of the lack of randomized trials and inconsistent reporting of important characteristics of use, such as duration. The simulation model predicted that the combined increase in risk of breast and cervical cancers and vascular events was likely to be equivalent to or greater than the decreased risk in ovarian cancer, although the harm/benefit ratio was much more favorable when protection against endometrial and colorectal cancers was added, resulting in net gains in life expectancy of approximately 1 month.

Conclusions. There is insufficient evidence to recommend for or against the use of OCs solely for the primary prevention of ovarian cancer. Although the net effects of the current patterns of OC use likely result in increased life expectancy when other noncontraceptive benefits are included, the harm/benefit ratio for ovarian cancer prevention alone is uncertain, particularly when the potential quality-of-life impact of breast cancer and vascular events are considered.

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Executive Summary

Background

Ovarian cancer is the eighth most common cancer in women and is the fifth leading cause of cancer death, with an age-adjusted rate of 8.2 deaths per 100,000 women.[1] Given current age-specific incidence and demographic projections, the number of cases of ovarian cancer will almost double over the next 35 years as women born between 1946 and 1964 (the "baby boom" generation) reach the age of highest incidence (60 years and older).[2]

While advances in surgery, chemotherapy, and radiation therapy over the past 20 years have led to improved outcomes, overall 5-year survival is only 42 percent for ovarian cancer compared with 88 percent for breast cancer and 63 percent for colorectal cancer. The high mortality rate in women with ovarian cancer is largely attributed to the later stage at presentation compared with other common cancers. This has led to intense research efforts to identify effective screening strategies for ovarian cancer, but results have been disappointing, particularly with regard to decreases in mortality.

The lack of a detectible preinvasive lesion, as well as the lack of physical barriers to metastasis because of the ovary's location in the abdominal cavity, raise the possibility that effective screening strategies may not be possible outside of high-risk populations because the time from initial cancer development to metastasis may be too short to allow for feasible screening intervals. This possibility has been supported by mathematical modeling studies. The required high frequency of screening, combined with the relatively low incidence of ovarian cancer, would lead to high numbers of false positive results, even with a highly specific test. Given this, one reasonable alternative approach to reducing morbidity and mortality from ovarian cancer would be to identify effective primary prevention strategies.

Surgical prophylaxis through removal of the tubes and ovaries (bilateral salpingo-oophorectomy) has been used in women who are at a high risk of developing ovarian cancer due to the presence of a BRCA1 or BRCA2 mutation, and there are ongoing trials of its effectiveness compared with intense screening. However, given the morbidity associated with surgery, and the potential effects of early menopause, this is not considered a reasonable option for the general population. Similarly, although observational studies suggest that both hysterectomy with ovarian preservation and tubal sterilization reduce the risk of ovarian cancer, this potential benefit is not typically part of the decisionmaking process that leads a patient to undergo one of the procedures.

There is consistent evidence from a variety of sources that oral contraceptive (OC) use reduces ovarian cancer risk. This evidence includes declining age-specific ovarian cancer incidence and mortality in cohorts of women who had access to OCs throughout their reproductive life, and there are several biologically plausible mechanisms for a protective effect.

The potential benefit of using OCs solely to reduce the risk of ovarian cancer must be weighed with knowledge of other potential noncontraceptive health benefits of OCs and potential harms. No comparative effectiveness analyses have been conducted to inform decisions about the use of OCs as a primary preventive strategy for ovarian cancer. Also, because the majority of evidence on noncontraceptive benefits and harms of OC use is derived from observational studies (case control and cohort), careful consideration must be given to the potential biases inherent in those study designs when developing a research agenda and clinical recommendations, as evidenced by the experience with hormone replacement therapy for prevention of cardiovascular morbidity and mortality. The combination of systematic review and

decision-analytic modeling presented in this report allows us to estimate the tradeoff between the harms and benefits of OC use for the overall population and for individual women , accounting for the potential influence of other factors, such as timing of OC use or presence of risk factors such as family history.

Scope and Key Questions

This evidence report was funded by the Centers for Disease Control and Prevention (CDC) in conjunction with the Agency for Healthcare Research and Quality (AHRQ), and was designed to evaluate the benefits and harms of the use of oral contraceptives as a primary preventive measure against ovarian cancer. We focused on synthesizing the available evidence for the effectiveness of this strategy in a general population and in groups at elevated risk. We also evaluated benefits and harms of OC use that are not related to the development of ovarian cancer. Finally, we designed a comparative effectiveness model to inform the questions generated by this review.

The scope of the review specifically excluded the unquestioned effectiveness of OCs in preventing unintended pregnancies; the potential effectiveness of OCs as primary or adjunctive treatments for conditions such as menstrual disorders (e.g., dysmenorrhea or menorrhagia), endometriosis, or premenstrual dysphoric disorder; and the potential role of OCs in preventing the onset of these conditions.

Key Questions

With input from AHRQ, the CDC, and a Technical Expert Panel of external stakeholders, we defined Key Questions using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The Key Questions (KQs) considered in this systematic review are:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only OCs for reducing the risk of ovarian cancer?

KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure A shows the analytic framework for this systematic review.

Figure A. Analytic framework for systematic review
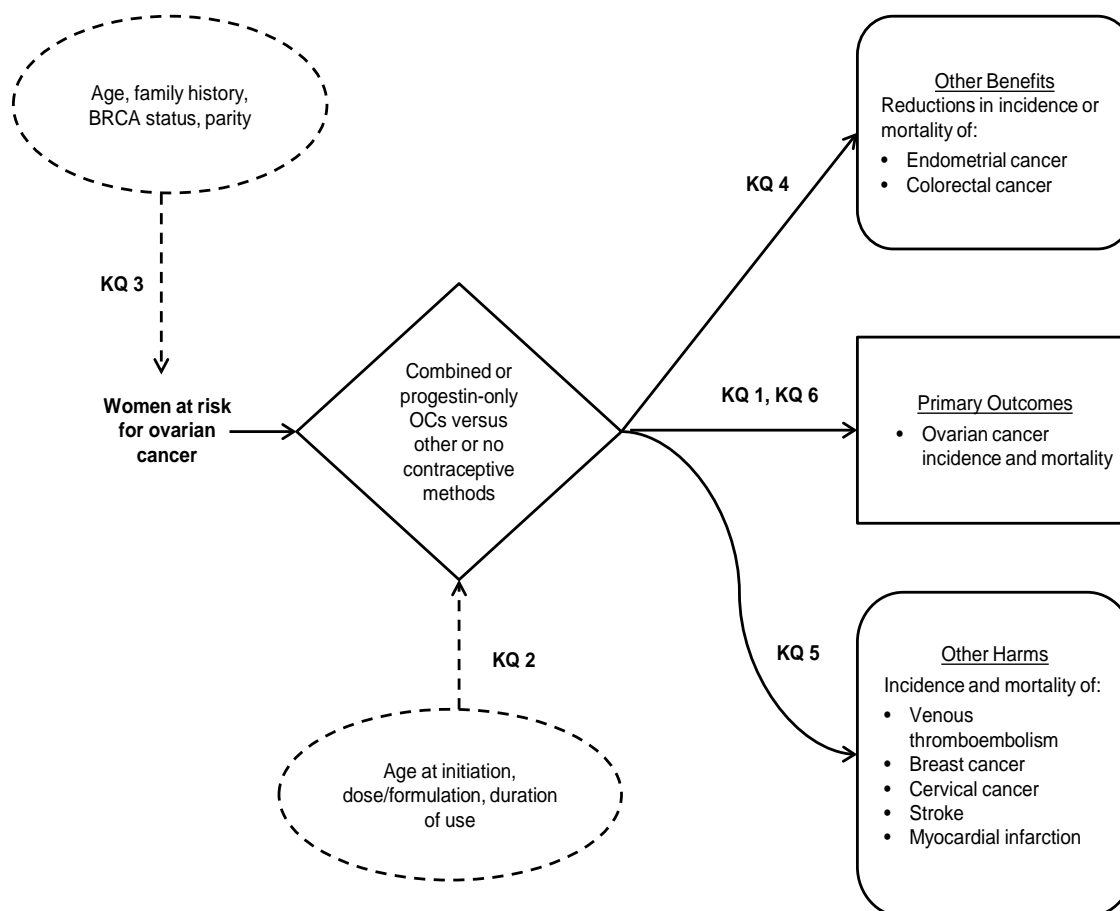
BRCA = breast cancer genetic mutation; KQ = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

Organization of Report and Executive Summary

This report departs from the standard AHRQ evidence-report organization. The evidence is instead presented in four topic-focused sections. Three of the sections address the relationship between OC use and specific groups of benefits and/or harms: ovarian cancer (KQ 1, KQ 2, and KQ 3); breast, cervical, colorectal, and endometrial cancers (KQ 4 and KQ 5); and venous thromboembolism, stroke, and myocardial infarction (KQ 5). Within each section, the benefits and/or harms of OC use are considered for both the general population and specific populations of women for whom the risk levels of ovarian cancer are elevated. Each section also assesses

potential modifying factors such as dose, formulation, and duration of OC use, and considers specific evidence gaps and needs for future research regarding the association between OC use and the specific outcomes (KQ 7). The final section of the report uses a decision analytic framework to explore the overall benefits and harms from all outcomes considered in the report for both the general population and specific populations (KQ 6), as well as identifies additional evidence gaps and needs for future research related to the potential overall benefits and harms of OCs for the prevention of ovarian cancer (KQ 7). For the purposes of this Executive Summary, we present the results organized by Key Question.

Methods

The methods for this evidence report follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews," hereafter referred to as "Methods Guide" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm).[3]

Literature Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant literature published from January 1990 to June 2012, using the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. We restricted the search to articles published subsequent to January 1990 to increase the likelihood that the types of OCs used by the women in the studies we retrieved were similar to those currently available, maximizing the generalizability and clinical relevance of the results. We also searched the ClinicalTrials.gov registry to identify additional relevant articles from completed studies.

We supplemented the electronic searches with a manual search of citations from a set of key review articles. The reference lists from these articles were hand-searched and cross-referenced against our library of database search results. Additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). We did not systematically search gray literature databases beyond ClinicalTrials.gov, since the high volume of literature identified through our searches of peer-reviewed articles made it unlikely that further searching of gray literature would substantially increase the chances of identifying relevant data that would meet inclusion criteria. We invited drug manufacturers to submit additional information through a scientific information packets request, which was sent by AHRQ on our behalf. Submissions received through this mechanism were reviewed, and relevant citations were screened against the review inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

Table A presents the inclusion/exclusion criteria for this systematic review.

Table A. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Population	• All KQs:
	  o Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a]
	  o Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy
	• KQs 3 and 6:
	  o Women with a family history of ovarian or premenopausal breast cancer, suggesting increased risk according to current recommendations
	  o Women with a known BRCA1/BRCA2 mutation
		Nonhuman studies

Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Studies that do not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use (Not required for studies reporting ovarian cancer outcomes or conducted in a population taking OCs for primary prevention of ovarian cancer)
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Studies that do not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) Studies comparing OC formulations (without including a non-OC control) are acceptable for studies reporting venous thromboembolism, stroke, or MI outcomes

Outcomes	Study reports quantitative association between exposure to OCs and one of the outcomes listed below:
	• KQs 1, 2, 3, 6:
	  o Diagnosis of ovarian cancer, ovarian cancer mortality
	  o Adverse effects (see KQ 5)
	• KQ 4:
	  o Diagnosis of endometrial cancer, endometrial cancer mortality, diagnosis of colorectal cancer, colorectal cancer mortality
	  o Adverse effects (see KQ 5)
	• KQ 5:
	  o Diagnosis of breast cancer, cervical cancer, venous thromboembolic event, stroke, or myocardial infarction; disease-specific mortality associated with these outcomes
	• KQ 7: Not applicable
		Study only reports outcomes related to assisted reproductive technologies or abortion

Table A. Summary of inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor) • Exploratory study with inadequate sample size

Publications	• English-language only
	• Peer-reviewed articles
	• Outcome reporting falls within the following publication ranges:
	  o Study reports an ovarian cancer outcome of interest and was published on or after Jan. 1,1990[d]
	  o Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after Jan. 1, 2000[e]
	  o Study reports a venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after Jan. 1, 1995[f]
		Non-English articles[g]

BRCA = breast cancer (genetic mutation); KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be for contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction, while those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies less than 100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary, ovarian cancer, outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses, allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).

[f]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[g]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies), and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Study Selection

Using the inclusion and exclusion criteria described in Table A, two investigators independently reviewed the titles and abstracts of articles retrieved through the search strategies for potential relevance to the KQs. Articles included by either reviewer were promoted to full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reconciled the difference through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners, Manotick, ON, Canada).

Data Extraction

The investigative team created forms for abstracting the data elements for the KQs, which were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors for accuracy. A pair of researchers with complementary clinical and methodological expertise was assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third researcher's opinion if consensus could not be reached by the first two researchers.

To aid in both reproducibility and standardization of data collection, guidance documents were drafted and given to the researchers as reference material. The forms for the researchers, created via the DistillerSR data synthesis software, contained further data abstraction instructions. We designed the data abstraction forms to collect information required to conduct the review, which included the following: data needed to evaluate the specified eligibility criteria for inclusion; demographic and other relevant patient characteristics (e.g., family history of ovarian cancer); details of the interventions and comparators (e.g., OC dose, formulation, patterns of use); outcome measures and adjustment factors applied in study analyses; and data needed to assess quality and applicability.

Risk-of-Bias Assessment of Individual Studies

The included studies were assessed using the approach described in AHRQ's "Methods Guide."[3] To assess quality, we used the approach to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from core elements described in the "Methods Guide." Criteria of interest for all studies included similarity of groups at baseline, the extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. No randomized controlled trials were identified for inclusion in this review; thus, criteria specific to randomized studies (e.g., methods of randomization and allocation concealment) were not considered.

Additional elements considered for observational studies included methods for selection of participants and management of selection bias, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding. To indicate the summary judgment of the quality for the individual studies, we used the summary ratings of good, fair, and poor. For each study, one investigator assigned a summary-quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. In some cases, data from a study composed of more than one article could not be combined into one abstraction. In those instances, the quality ratings for individual abstractions within a study grouping could vary based on the specific component articles' quality of reporting, the evaluated outcomes, and the statistical and analytical methods used.

Data Synthesis

After data extraction, we determined the feasibility of completing a quantitative synthesis by assessing the volume of relevant literature, the conceptual homogeneity of studies, and the completeness of results reporting. Outcomes assessed by meta-analysis, if feasible, included disease-specific incidence, disease-specific mortality, and disease-specific survival. Our general approach for each outcome was to analyze, if possible, the following associations: (1) temporal relationships (current vs. noncurrent OC use, ever vs. never OC use, and duration of current OC use), (2) OC formulation (estrogen dose [high vs. low], progestin generation [first, second, third, and fourth generations]), and (3) special populations (such as women with known family history or genetic predisposition).

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% confidence intervals [CIs]) using a random-effects model. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (i.e., case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2.0.[4]

Results were discussed qualitatively when study numbers were insufficient for meta-analysis (less than three), when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that was not likely to be representative of the general population of women aged 15 to 44.

We included data from pooled analysis articles in our meta-analysis if (1) none of the individual studies included in the pooled analysis had already been included for meta-analysis, (2) at least half the studies in the pooled analysis were published on or after the date threshold applied for the outcome under consideration in the analysis, and (3) data in the pooled analysis were presented such that inclusion in the current meta-analysis was feasible.

For the outcomes of cumulative lifetime incidence and mortality, life expectancy, numbers needed to harm and prevent, and harm-to-benefit ratios, we constructed a semi-Markov state-transition model of a cohort of women aged 10 to 100, using TreeAge Pro 2012 (TreeAge Software, Inc., Williamstown, MA). Relative risk estimates were derived from the meta-analyses and other age-specific and race-specific probabilities that were obtained from the literature or publicly-available data sources. The model was run as a microsimulation, which allowed for conditioning of probabilities based on past history. Depending on the analysis, each model run included 5,000 to 1,000,000 simulated individuals; estimates of the outcomes of interest were based on the mean value of each model run (or, in some cases, the weighted average of multiple model runs).

Estimates were derived for both the overall population, given current OC use patterns (i.e., the cumulative effect of current patterns of age of starting OCs, as well as duration of use, on the outcomes of interest [based on the risk estimates] compared with a scenario where OCs had no effect on risk), as well as on an individual level (the cumulative effect of OC use in all users, based on current patterns of use, vs. nonusers). The impact of varying age of starting OC use and duration of use was assessed in a separate analysis.

Finally, we assessed the impact of uncertainty in the estimates of OC effects by using a method analogous to cost-effectiveness analysis. Instead of estimating a cost-effectiveness ratio, we estimated harm-to-benefit ratios, where total harms were considered "costs," and total benefits "effectiveness." We assessed the impact of uncertainty in the effects of OC use on both harms and benefits (based on the confidence intervals of the relative risk estimate) and on

whether OC use would be recommended based on different "willingness-to-pay" thresholds according to the harm-to-benefit ratio.

Strength of the Body of Evidence

The strength of evidence for each Key Question and outcome was assessed using the approach described in the "Methods Guide."[3,5] The evidence was evaluated using the four required domains of (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that diminished an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" for strength of evidence was assigned by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make (for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit a conclusion to be drawn). In these situations, a grade of "insufficient" was assigned.

Applicability

To assess applicability, we used the PICOTS format to identify specific issues that could limit the applicability of individual studies or a body of evidence, as recommended in the "Methods Guide."[3,6] We used data abstracted on the populations studied, the interventions and comparators, the outcomes measured, study settings, and timing of assessments to identify specific issues that could limit the applicability of individual studies or a body of evidence.

Specific factors affecting applicability included (but were not limited to):
(1) population, including indication for use (we anticipated that most of the literature would be based on women using OCs for contraception, not for primary prevention of ovarian cancer), and the distribution of risk factors, such as genetic predisposition, age, reproductive history, and smoking, that might affect the relative likelihood of different harms and benefits; (2) intervention and comparator, particularly the OC formulation since the lag time between exposure and onset of cancer means that the OCs used by women in observational studies may differ from currently available OCs; and (3) outcomes, since data on all relevant outcomes, particularly cancers, may not be available for newer OCs.

We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use, and clinical relevance and timing of the outcome measures.

Results

The main results of the review are presented in this Executive Summary organized by KQ; more detailed descriptions are provided in the full report.

Literature Search Results

Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 7,196 citations, 767 of which were duplicates. Manual searching and contacts with drug manufacturers via the scientific information packet requests identified 47 additional citations, for a total of 6,476. No additional relevant citations beyond those already identified were found

during a search of relevant studies listed on ClinicalTrials.gov. After applying inclusion and exclusion criteria at the title-and-abstract level, 1,919 full-text articles were retrieved and screened. Of those, 1,671 were excluded at the full-text screening stage, leaving 248 articles (representing 157 unique studies) for data abstraction. As indicated in Figure 8 in the full report, several articles and studies were relevant to more than one outcome of interest—55 relevant to ovarian cancer outcomes (KQ 1, KQ 2, KQ 3), 66 to other cancers of interest (KQ 4, KQ 5), and 50 to vascular events (KQ 5).

Key Question 1. Effectiveness of OC Use for Reducing Incidence of Ovarian Cancer

Table B shows the strength of evidence for the effect of OC use on ovarian cancer. We identified 55 studies that evaluated the association between OC use and the incidence of ovarian cancer. Of these, 39 were case-control studies, 10 were cohort studies, and 6 were pooled analyses. None of the pooled analyses met criteria for inclusion in the meta-analyses examining OC use and ovarian cancer incidence. (Criteria for inclusion of studies in the meta-analyses, and reasons for excluding any studies that were not incorporated, are described in the full report.) Ever use of OCs was consistently associated with a decreased risk of developing invasive ovarian cancer (odds ratio [OR], 0.73; 95% CI, 0.66 to 0.81). Ever use of OCs was significantly associated with a decreased risk of dying from invasive ovarian cancer in two large cohort studies, although formal meta-analysis was not performed. Although results were consistent, direct, and precise for ever use versus never use and for duration of use, strength of evidence was moderate because of the persistent risk of bias due to the observational nature of the studies.

Table B. Strength of evidence domains for the effect of OC use on ovarian cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population						
Ever vs. never use	24 (657,055 women and 3,981,072 person-years)	Medium	Consistent	Direct	Precise	**Moderate** 0.73 (0.66 to 0.81)
Duration of use	15 (547,363 women and 3,493,072 person-years)	Medium	Consistent	Direct	Precise	**Moderate** 1–12 mo: 0.91 (0.78 to 1.07) 13–60 mo: 0.77 (0.66 to 0.89) 61–120 mo: 0.65 (0.55 to 0.77) >120 mo: 0.43 (0.37 to 0.51)
Age at first use	6 (111,817 women)	High	Consistent	Direct	Imprecise	**Low** <20 yr: 0.63 (0.45 to 0.89) 20–24 yr: 0.71 (0.51 to 0.99) 25–30 yr: 0.67 (0.46 to 0.99) > 30 yr: 0.89 (0.60 to 1.32)

Table B. Strength of evidence domains for the effect of OC use on ovarian cancer (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population (continued)						
Time since last use	8 (210,069 women and 1,083,000 person-years)	High	Inconsistent	Direct	Imprecise	**Low** 0–10 yr: 0.41 (0.34 to 0.50) 10–20 yr: 0.65 (0.56 to 0.74) 20–30 yr: 0.92 (0.76 to 1.12) >30 yr: 0.79 (0.58 to 1.12)
High-dose vs. low-dose estrogen	6 (9,007 women)	High	Consistent	Indirect	Imprecise	**Low** 1.25 (0.95 to 1.64)
High-dose vs. low-dose progestin	4 (7,528 women)	High	Inconsistent	Indirect	Imprecise	**Low** 0.86 (0.60 to 1.21)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	3 (6,855 women)	Medium	Consistent	Direct	Precise	**Moderate** 0.58 (0.46 to 0.73)
Incidence in BRCA1-Positive Women						
Ever vs. never use	4 (5,519 women)	Medium	Consistent	Direct	Precise	**Moderate** 0.55 (0.47 to 0.66)
Incidence in BRCA2-Positive Women						
Ever vs. never use	3 (1,592 women)	Medium	Inconsistent	Direct	Imprecise	**Low** 0.65 (0.34 to 1.24)
Incidence in Women With Family History						
Ever vs. never use	3 (9,193 women)	High	Inconsistent	Direct	Imprecise	**Low** Decreased incidence
Incidence in Gravid/Parous and NulligravidNulliparous Women						
Ever vs. never use	2 (4,732 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient**
Mortality From Ovarian Cancer						
Ever vs. never use	2 (46,112 women and 602,700 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** Decreased cause-specific mortality
Survival Among Women With Ovarian Cancer						
Ever vs. never use	1 (676 women)	High	NA	Direct	Imprecise	**Insufficient** (not performed)[a]

BRCA = breast cancer genetic mutation; CI = confidence interval; mo = month/months; NA = not applicable; SOE = strength of evidence; yr = year/years

[a]The available data were not sufficient to perform a meta-analysis; refer to full report for details.

Key Question 2. Effect of Specifics of OC Use on Ovarian Cancer Incidence

Longer duration of OC use is significantly associated with greater reductions in ovarian cancer incidence (Table B). This conclusion is based on a meta-analysis of 15 studies. Of these,

10 were case-control studies representing 6,901 cases and 15,999 controls, and 5 were cohort studies representing 524,463 participants in 3 of the studies and 3,493,072 person-years in the other two studies. Seven studies were rated good quality, seven fair quality, and one poor quality. We excluded study datasets that reported fewer than three duration categories; reported odds ratios only for specific subpopulations of women; lacked a "never use" reference group; reported duration data from the same trial as another included study; or reported duration odds ratios for only the year of OC use.

Earlier age at first OC use was associated with a nonsignificant trend toward a greater reduction in ovarian cancer incidence, but most studies did not adjust for potential confounding due to duration of use. This conclusion is based on a meta-analysis of six studies. Of these, 5 were case-control studies representing 3,552 cases and 4,713 controls, and 1 was a cohort study representing 103,552 participants. Four studies were rated good quality and two were rated fair quality. We excluded studies that reported on fewer than three age categories and studies that provided odds ratios for subpopulations only.

Time since last use was significantly associated with ovarian cancer incidence, based on a meta-analysis of eight studies. Of these, 5 were case-control studies representing 3,606 cases and 7,759 controls, and 3 were cohort studies representing 198,704 participants and 1,083,000 person years. Four studies were rated good quality and four were rated fair quality. We excluded studies that used fewer than three comparisons and studies that presented categories that were not amenable to a combined analysis. There was substantial heterogeneity among studies.

Separate meta-analyses of 6 studies of estrogen formulation (all case-control studies representing 2,607 cases and 6,400 controls, with 5 studies rated good quality and 1 rated fair quality, and with 1 exclusion because of insufficient dose information) and 4 studies of progestin formulation (all case-control studies, representing 2,049 cases and 5,479 controls, and all of good quality, with 3 exclusions because of incompatible progestin-dosing categorization) did not show any significant effect of steroid potency on the association between OC use and ovarian cancer; risk reductions were similar for high potency estrogen, low potency estrogen, high potency progestin, and low potency progestin.

Key Question 3. Relative Risk of Ovarian Cancer in OC Users in Subpopulations

Separate meta-analyses were performed for the following (Table B):
- BRCA1 and BRCA2 carriers (4 studies [1 good quality and 1 fair quality]: 3 were case-control studies with 1,096 cases and 2,878 controls, and 1 was a cohort study with 3,181 participants)
- Women of different gravidity and parity (2 case-control studies [both good quality] with 1,595 cases and 3,137 controls; 1 study was excluded because of data included in another paper)

Both analyses showed similar reductions in ovarian cancer risk with OC use independent of BRCA carrier status or gravidity/parity. Three case-control studies, one of good quality and two of fair quality, were identified that examined the effect of family history on the association between OC use and ovarian cancer. These studies were too heterogeneous in their description of subgroups for meaningful meta-analysis but, qualitatively, all showed similar reduction in ovarian cancer risk with OC use.

Key Question 4. Other Benefits of OC Use

Colorectal Cancer

Table C shows the strength of evidence for the effect of OC use on colorectal cancer. A pooled meta-analysis of 11 studies (3 case-control, 1 pooled analysis, and 7 cohort, of which 4 were good quality, 6 fair, and 1 poor) showed a significant reduction in the risk of colorectal cancer among ever users compared with never users (OR, 0.86; 95% CI, 0.79 to 0.95). There was no significant effect of duration of use. The two large United Kingdom (U.K.) cohort studies had conflicting results for colorectal cancer mortality in women with a history of OC use. As with ovarian cancer, the overall strength of evidence is reduced because of the risk of bias in observational studies.

Table C. Strength of evidence domains for the effect of OC use on colorectal cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Colorectal Cancer in Overall Population						
Ever vs. never use	11 (503,816 women across 8 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 0.86 (0.79 to 0.95)
Duration of use	10 (167,555 women across 7 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	**Low** No increase in protective effect with prolonged use
Mortality From Colorectal Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in a second study)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** Mixed results for risk of death with ever use, and no trend toward increased protective effect with longer duration of use

CI = confidence interval; SOE = strength of evidence

Endometrial Cancer

Table D shows the strength of evidence for the effect of OC use on endometrial cancer. Seven studies (three case-control studies and four cohort studies: four good quality, two fair quality, and one poor quality) met inclusion/exclusion criteria for a meta-analysis of the association between OC use and endometrial cancer incidence; two studies were excluded for not reporting point estimates for ever versus never use. OC use significantly reduced the incidence of endometrial cancer (OR, 0.57; 95% CI, 0.43 to 0.76).

In a separate meta-analysis including eight studies (three case-control studies and five cohort studies: five good quality, two fair quality, and one poor quality), there was a significant trend toward a greater reduction in risk with increased duration of use. Two large U.K. cohort studies

showed a significant reduction in endometrial cancer mortality in women with a history of OC use. As with ovarian cancer, the overall strength of evidence is reduced because of the risk of bias in the observational studies.

Table D. Strength of evidence domains for the effect of OC use on endometrial cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Endometrial Cancer in Overall Population						
Ever vs. never use	7 (308,198 women across 4 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 0.57 (0.43 to 0.76)
Duration of use	8 (352,915 women across 5 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	**Low** <60 months:0.78 (0.54 to 1.15) >60 months: 0.44 (0.29 to 0.65)
Mortality						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Precise	**Moderate** Overall protective effect for ever use, which is greater for longer durations of use

CI = confidence interval; SOE = strength of evidence

Key Question 5. Harms of OC Use

Breast Cancer

Table E shows the strength of evidence for the effect of OC use on breast cancer. Ever use of OCs is associated with a small but significant increase in breast cancer risk, based on a combined meta-analysis of 15 case-control studies (9 good quality, 5 fair quality, and 1 poor quality) and 8 cohort studies (3 good quality, 4 fair, and 1 poor), with an odds ratio of 1.08 (95% CI, 1.00 to 1.17). Despite the increased incidence, there was no evidence of increased mortality from breast cancer (OR, 0.94; 95% CI, 0.87 to 1.02). We did not identify a relationship between duration of use and breast cancer risk, but risk significantly decreased with time since last use. The magnitude of the association between OC use and breast cancer was similar in BRCA1 and BRCA2 carriers, although confidence intervals included 1. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table E. Strength of evidence domains for the effect of OC use on breast cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Breast Cancer in Overall Population						
Ever vs. never use	23 (356,023 women across 20 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 1.08 (1.00 to 1.17)
Duration of use	14 (291,407 women across 12 studies and 2,898,072 person-years across 2 studies)	Medium	Inconsistent	Direct	Imprecise	**Low** No increase in risk for longer durations of use
Time since last use	11 (200,258 women)	High	Inconsistent	Direct	Imprecise	**Low** Reduced risk over time since last use 0–5 yr: 1.21 (1.04 to 1.41) 5–10 yr: 1.17 (0.98 to 1.38) 10–20 yr: 1.13 (0.97 to 1.31) >20 yr: 1.02 (0.88 to 1.18)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	5 (4,555 women across 4 studies and 65,180 person-years in 1 study)	Medium	Inconsistent	Direct	Imprecise	**Low** Trend toward slight increase in risk 1.21 (0.93 to 1.58)
Incidence in Women With Family History						
Ever vs. never use	3 (9,280 women)	High	Inconsistent	Direct	Imprecise	**Insufficient** Not performed
Incidence in Young Women						
Ever vs. never use	3 (5,716 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** Not performed
Mortality From Breast Cancer						
Ever vs. never use	3 (54,606 women across 2 studies and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Imprecise	**Low** No significant increase in risk 0.94 (0.87 to 1.02)
Survival After Diagnosis of Breast Cancer						
Ever vs. never use	3 (9,606 women)	Medium	Consistent	Direct	Imprecise	**Low** No significant increase in risk

BRCA = breast cancer genetic mutation; CI = confidence interval; SOE = strength of evidence; yr = year/years

Cervical Cancer

Table F shows the strength of evidence for the effect of OC use on cervical cancer. One fair-quality pooled analysis of eight separate case-control studies and two, poor quality, individual

case-control studies showed significant associations between OC use and an increased risk of invasive cervical cancer among women who were positive for human papillomavirus (HPV); risk was significantly associated with duration of use. Differences between studies precluded meta-analysis.

Because persistent HPV infection is a cause of cervical cancer, and because OC users may have other factors that put them at a higher risk of acquiring HPV, restricting analysis of the association between OCs and cervical cancer to HPV-positive women may be most informative. However, as a complement, we also performed a meta-analysis of nine studies that found a nonsignificant increase in cervical cancer risk among ever users (OR, 1.21; 95% CI, 0.91 to 1.61). Six studies (five case-control studies and one cohort study: three good quality and three fair quality) showed a nonsignificant increase in cervical cancer incidence with increasing duration of use (OR, 1.47; 95% CI, 0.91 to 2.38 for more than 60 months compared with never users).

Two large, fair-quality cohort studies conducted in the U.K. found an increased risk of cervical cancer mortality among OC users, with a trend toward increased mortality with a longer duration of use. The overall strength of evidence for the cervical cancer outcomes is reduced because of the risk of bias in observational studies.

Table F. Strength of evidence domains for the effect of OC use on cervical cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Cervical Cancer in HPV-Positive Population						
Ever vs. never use	3 (2,592 women)	High	Inconsistent	Direct	Imprecise	**Insufficient** Unable to draw summary conclusion
Mortality from Cervical Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	High	Consistent	Direct	Imprecise	**Low** Increased risk with ever use and longer duration of use

CI = confidence interval; HPV = human papillomavirus; SOE = strength of evidence

Venous Thromboembolism

Table G shows the strength of evidence for the effect of OC use on venous thromboembolic events. Based on a meta-analysis of 14 studies (6 good quality, 6 fair quality, 2 poor quality), current users of OCs have a three-fold increased risk of venous thromboembolism (OR, 2.97; 95% CI, 2.46 to 3.59). This elevated risk appears to be associated only with current use; we were unable to perform a meta-analysis because of the high degree of heterogeneity between studies. There was some evidence that risk of thromboembolism decreased with an increased duration of use, but there were not enough studies for a meta-analysis.

Although most studies included pulmonary embolism as one of several potential venous thromboembolic events, several studies that examined pulmonary embolism alone also found consistent increases in risk; however, the risk was somewhat smaller than for combined thromboembolism.

Results of a meta-analysis of three studies yielded inconclusive evidence regarding risk of venous thromboembolism (VTE) by estrogen dose. Another meta-analysis of six studies suggested a not statistically significant trend toward increased risk of VTE associated with third- and fourth-generation progestins. Results of a qualitative analysis of additional studies that directly compared progestin generations suggested that the risk of VTE is highest for third-generation progestins compared with levonorgestrel, a second-generation progestin. Although there were too few studies of progestin-only pills to perform meta-analysis, the studies that were identified showed no increase in risk in users of progestin-only pills compared with nonusers. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table G. Strength of evidence domains for the effect of OC use on venous thromboembolism

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of All VTE and Mixed DVT/PE						
Current vs. noncurrent use/never	14 (15,466 women plus 9,906,890 person-years)	Medium	Consistent	Direct	Precise	**High** 2.97 (2.46 to 3.59)
Incidence of PE Only						
Current vs. noncurrent use/never	3 (863 women plus 2,124,474 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk appears similar to that of VTE
Incidence of all VTE And Mixed DVT/PE						
Duration of use	5 (6,955 women plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk may be present during first year of use
Estrogen	3 (6,102 women plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**High** Low dose: 3.39 (2.32 to 4.96) High dose: 3.06 (1.32 to 7.10)
Progestin	6 (16,048 women)	Medium	Consistent	Direct	Precise	**High** First generation: 4.06 (2.66 to 6.19) Second generation: 3.28 (2.49 to 4.31) Third generation: 4.06 (3.09 to 5.32) Fourth generation: 5.36 (2.78 to 10.32)
Mortality From VTE						
Current vs. noncurrent use/never	0	NA	NA	NA	NA	**Insufficient** NA

CI = confidence interval; DVT = deep venous thrombosis; NA = not available; PE = pulmonary embolism; SOE = strength of evidence; VTE = venous thromboembolism

Stroke

Table H shows the strength of evidence for the effect of OC use on stroke. In a meta-analysis of nine studies of ischemic or undifferentiated stroke, current OC users had a significant increase in risk compared with nonusers (OR, 2.15; 95% CI, 1.49 to 3.11). Results were similar when restricted to five case-control studies and two cohort studies of ischemic stroke (OR, 1.90; CI, 1.24 to 2.91), but not for four case-control studies of hemorrhagic stroke (OR, 1.03; CI, 0.71 to 1.49).

Past use or duration of use did not appear to be related to stroke risk, although we were unable to perform a meta-analysis. We were able to perform a meta-analysis of three case-control studies of estrogen level, which found a significant increase in risk with increased estrogen dose (although stroke risk with low-dose formulations was still significantly elevated compared with nonusers).

Evidence from three cohort studies did not show a significant increase in stroke-related mortality. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table H. Strength of evidence domains for the effect of OC use on stroke

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ischemic/Undifferentiated Stroke						
Current vs. noncurrent use/never	9 (54,767 women plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 2.15 (1.49 to 3.11)
Duration	4 (51,038 women plus 310,626 person-years)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR (Insufficient evidence to support quantitative synthesis of findings)
Estrogen	3 (9,977 women)	Medium	Consistent	Direct	Precise	**High** Low dose: 1.73 (1.29 to 2.32) High dose: 4.10 (1.91 to 8.80)
Progestin	3 (6,994 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** NR (heterogeneity in evidence about specific progestin generation)
Incidence of Ischemic Stroke						
Current vs. noncurrent use/never	7 (49,803 women plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 1.90 (1.24 to 2.91)

Table H. Strength of evidence domains for the effect of OC use on stroke (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Hemorrhagic Stroke						
Current vs. noncurrent use/never	4 (48,382 women)	Medium	Inconsistent	Direct	Imprecise	**Low** No difference, 1.03 (0.71 to 1.49)
Mortality From Stroke						
Current vs. noncurrent use/never	3 (46,112 women plus 3,091,673 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** 0.80 (0.59 to 1.08)

CI = confidence interval; NR = not reported; SOE = strength of evidence

Myocardial Infarction

Table I shows the strength of evidence for the effect of OC use on myocardial infarction (MI). A meta-analysis of eight studies (five case-control, two cohort, and one pooled case-control) found a nonsignificant increase in risk of MI among current users (OR, 1.34; 95% CI, 0.87 to 2.08). There were too few studies to perform a meta-analysis of duration of use or of estrogen dose. Risks were significantly higher with first-generation progestins compared with second- and third-generation formulations. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table I. Strength of evidence domains for the effect of OC use on myocardial infarction

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Myocardial Infarction						
Current vs. noncurrent use/never	8 (24,901 women plus 310,626 person-years)	Medium	Inconsistent	Direct	Imprecise	**Low** 1.34 (0.87 to 2.08)
Estrogen	2 (15,903 women)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR
Progestin	5 (8,875 women)	Medium	Consistent	Direct	Precise	**High** First generation: 3.37 (2.04 to 5.54) Second generation: 1.79 (1.16 to 2.75) Third generation: 1.34 (0.91 to 1.98)

Table I. Strength of evidence domains for the effect of OC use on myocardial infarction (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Mortality From Myocardial Infarction						
Current vs. noncurrent use/never	3 (46,112 women plus 3,091,673 person-years)	Medium	Inconsistent	Direct	Imprecise	**Low** 0.85 (0.67 to 1.07)

CI = confidence interval; NR = not reported; SOE = strength of evidence

Key Question 6. Decision Analysis: Benefits and Harms of OC Use and Ovarian Cancer Risk

Using the point estimates from the ORs derived by the meta-analyses for each outcome (including those for MI and cervical cancer, which were not statistically significant), we estimated differences in age-specific incidence of cancers in OC ever users compared with never users (Figure B), and vascular events in current OC users versus noncurrent users (Figure C). Note that estimates are not adjusted for competing risks, such as hysterectomy or other-cause mortality, or for time-dependent factors, such as duration of use or time since last use.

Figure B. Increase or decrease in age-specific incidence of cancers in ever OC users versus never users

Estimated Difference in Age-Specific Incidence in Ever Users of OCs compared to Never Users
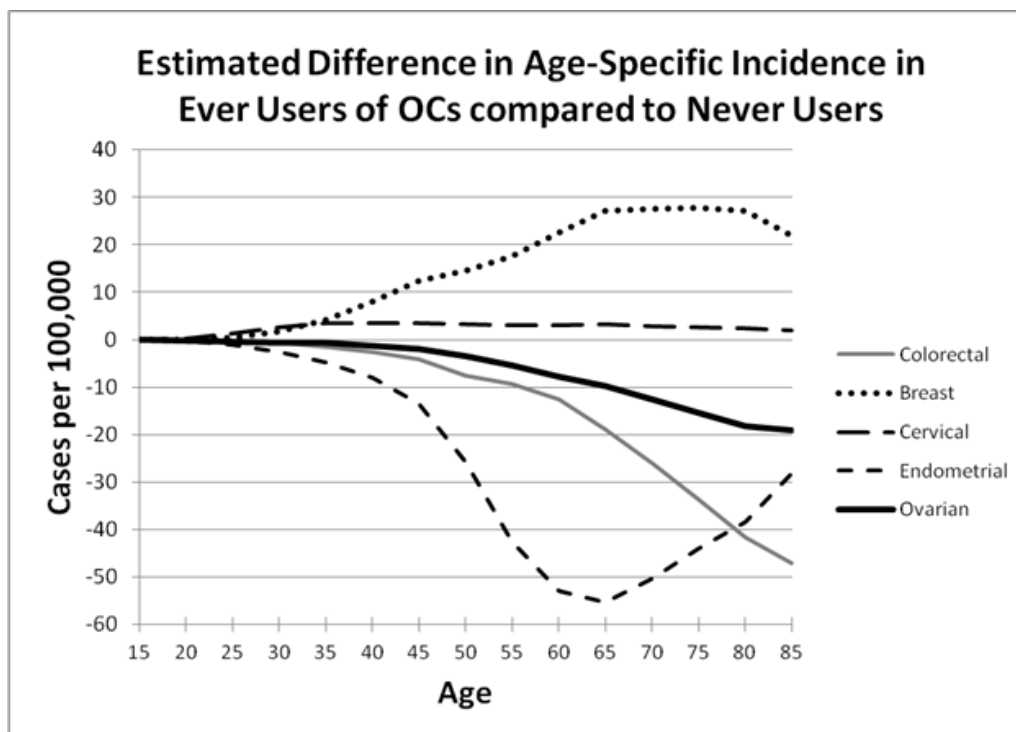
Figure C. Increase in age-specific incidence of vascular events in current OC users versus noncurrent users

Estimated Increase in Age-Specific Incidence among Current OC users
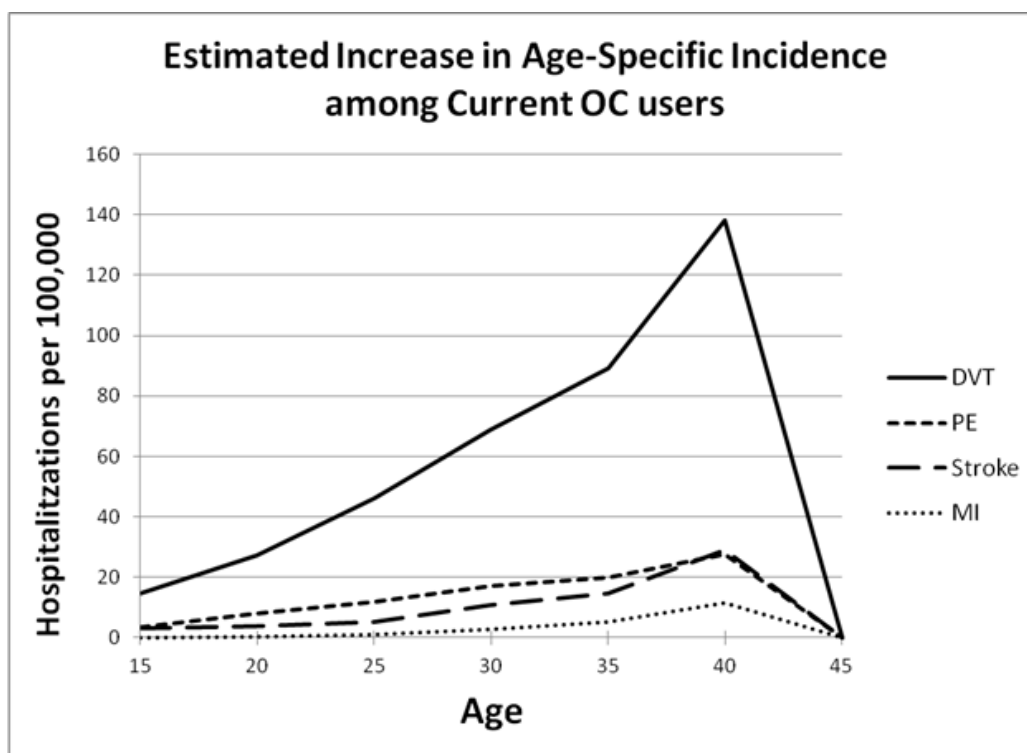
DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism

We also developed a computer simulation model that integrated the findings of the meta-analyses with available data on population patterns of OC use, along with incidence and mortality data for cancers and vascular events, to estimate overall life expectancy and lifetime incidence and mortality for the general population given current patterns of OC use. We used two main types of comparisons. First, we performed a "counterfactual analysis," based on current population use, to estimate the population difference in outcomes if OCs were not associated with any of the harms or benefits considered in the review. The second analysis was a direct comparison to estimate the difference in outcomes between the average population of women who never used OCs and those who did.

At the population level, the model predicted decreases in incidence and mortality from ovarian, colorectal, and endometrial cancers, and increases in breast cancer incidence and mortality. Vascular events were increased in incidence. Mortality was increased to a lesser degree than incidence. For stroke, projected mortality incidence was decreased, likely due to a younger age distribution in OC users and subsequent higher post-event survival.

Using a model based on ever versus never use of OCs, mean life expectancy increased by approximately 1 month in users, a gain similar to that seen with other cancer prevention strategies in average-risk populations. An alternate version of the model that incorporated the effects of duration of OC use on ovarian cancer risk (increased duration associated with decreased risk), and time since last use on breast cancer risk (longer time associated with decreased risk) resulted in an estimated mean life expectancy gains of 2 months among users. When restricted to BRCA1 or BRCA2 carriers, the model predicted gains in women who used

OCs of almost 10 months in BRCA1 carriers (because of the much higher ovarian cancer risk) and 1 month in BRCA2 carriers.

For the second analysis (estimating the difference in outcomes between users and nonusers), the qualitative effects of OC use were similar to the population level analysis, but the magnitude was larger—estimated life expectancy gains of 10 months in the general population, 5 months in BRCA2 carriers, and over a year in BRCA1 carriers, for users compared with never users. Cause-specific mortality for some harms (particularly stroke) was reduced in OC users in this version of the model, which may be due to relatively small numbers of simulated subjects, the effect of different competing risks within the model structure, and/or the shift in age distribution.

Systematically varying age at first OC use and duration of use suggested that the harm-to-benefit ratio and life expectancy were optimized by 5 years' duration of use across all ages, with a relatively high harm-to-benefit ratio and decreased life expectancy with 10 years' duration of use for all but those who start OCs prior to age 20. Larger numbers of simulations are required to generate stable numbers given the low probability of many of these events, particularly in young women.

Using a net-benefits approach, we assessed the impact of different "willingness-to-pay" thresholds in terms of harms incurred versus benefits gained for both incidence and mortality, along with the relative contribution of specific clinical harms and benefits. The increase in breast cancer incidence was the greatest contributor to uncertainty regarding harms. For incident harms and benefits, the likelihood that benefits outweighed harms was less than 40 percent when only prevention of incident ovarian cancer was considered. Results were more favorable for mortality prevention, emphasizing the need for methods to incorporate quality of life, as well as mortality, into these analyses.

Key Question 7. Research Gaps

There were consistent evidence gaps across all of the literature we reviewed, and the modeling results suggested a few areas that should be prioritized. The greatest limitation to the existing literature is the potential for unmeasured confounding, which biases the estimates of the effects of OC use on these outcomes. Unfortunately, the size and duration of a randomized trial to definitively address the potential role of OCs as primary prevention for ovarian cancer would be unprecedented. Further work—using quantitative methods to estimate the potential benefit of primary prevention strategies for ovarian cancer, incorporating OCs—is needed to help clarify whether investing in such a large trial is worthwhile. There are few available data on patient preferences relevant to the use of OCs as primary prevention. Better data on the relative quality-of-life effects of regular OC use, and the outcomes we reviewed here, would allow for better assessment of the overall tradeoffs between harms and benefits at both the individual and population level.

There was inconsistent reporting of how variables, such as time since last use, duration of use, or OC formulation, were categorized. This was a major barrier to evidence synthesis, particularly since the model results showed that differences in assumptions about how these factors affect the association between OC use and outcomes can alter the overall balance of harms and benefits. Efforts to standardize reporting across studies should be strongly encouraged; study designs and analytic plans should be optimized to address these factors. Alternatively, pooled analyses of individual data collected across multiple studies offers an opportunity to address some of these shortcomings of reporting, but this approach is still

dependent on consistency in how data is collected. Given the feasibility issues of a randomized trial, this may be one of the only ways to better address confounding.

The overall impact on net harms and benefits of progestin-only pills, particularly for vascular events, is potentially better than for combination pills. Although this suggests progestin-only pills might be particularly well suited for primary prevention, there are fewer data available on cancer outcomes.

The effects of OC use on colorectal and breast cancer incidence were a major contributor to the overall balance of harms and benefits, and efforts to resolve remaining uncertainties regarding these two cancers should be prioritized.

Discussion

Key Findings and Strength of Evidence

The direction and size of the effect of OC use on the individual outcomes we assessed was consistent with previous systematic reviews. Previous modeling studies have suggested no net effect of OC use on life expectancy, while we estimated a gain of approximately 1 month. This difference likely reflects differences in the literature reviewed based on inclusion/exclusion criteria and the availability of more recent data, the inclusion of additional outcomes (particularly colorectal cancer), and the use of a stochastic microsimulation model to generate lifetime estimates in the face of competing risks.

The overall strength of evidence was moderate to low. There was general consistency across studies in both the direction and magnitude of the effect of OCs on disease incidence, but all of the empiric evidence was derived from observational studies, raising the possibility of unmeasured confounding. The results of the decision model do not contribute to the strength of evidence.

The noncontraceptive harms (increased risk of breast and cervical cancer and vascular events) and benefits (decreased risk of ovarian, colorectal, and endometrial cancers) associated with OC use can affect both quality of life and mortality. Based on the available evidence, the current patterns of combination OC use in the general population, likely result in a net increase in life expectancy of at least 1 to 2 months, which is comparable to many other preventive interventions. This is in addition to the beneficial effects of prevention of unwanted pregnancy. The likelihood that OC use decreases life expectancy is low, but there is insufficient evidence to estimate the overall effects on quality of life. It is important to note that there is substantially more evidence on the effects of OCs on the incidence of relevant outcomes than there is on mortality related to those outcomes, and estimates of their effect on mortality derived from a model are even more uncertain than estimates for incident events.

These results may be reassuring to women considering OCs for contraception and to women who are prescribed OCs for treatment of other conditions. There is substantial remaining uncertainty about the joint effects of age at first OC use and duration of use on optimizing the net noncontraceptive benefits of OCs. There is insufficient evidence to recommend OCs solely for the prevention of ovarian cancer for women who would not be considering OC use for another indication. For these women, the available evidence suggests that the increase in risk of developing breast cancer or having a vascular event is likely to be approximately the same as, or slightly greater than, the decrease in risk of developing ovarian cancer. Because deaths from those harms, even in the aggregate, are lower than for ovarian cancer, there may be benefits in terms of mortality. However, the quality-of-life impact of those harms, particularly stroke and

MI, may be substantial. The benefit-to-harm ratio for both incident benefits and harms, and mortality from those outcomes, from using OCs as a primary preventive agent is substantially improved when potential reductions in colorectal and endometrial cancers are included.

Applicability

Applicability of the evidence to current U.S. practice is limited by several factors. Most importantly, the long duration between exposure to OCs and development of cancers means that the available evidence is based on a different distribution of OC formulations than are currently on the market. This long lag time may also contribute to unmeasured cohort effects in factors such as smoking, parity, or hysterectomy rates, which alter the risk of the outcomes we considered in both OC users and nonusers.

Many of the largest and most complete studies were performed outside of the United States. Differences in formulations, in prevalence of genetic and acquired factors affecting outcome risk, and in health-system characteristics, such as population coverage for cancer screening, may affect study results.

Finally, OCs have been available only since the 1960s, meaning that birth cohorts of women with a high prevalence of OC use are only now entering the age of peak incidence for many cancers. Predictions of the long-term effects of OC use are necessarily based on population-based, age-specific incidence and mortality data. Because these data are cross-sectional, estimates for older women reflect cohorts that were relatively unexposed to OCs. If OC use does significantly affect the incidence of certain cancers, then predictions of the long-term impact of prescribing OCs today will be in error.

Conclusions

The available evidence suggests that incident harms associated with OC use are likely to exceed prevented cases of ovarian cancer. The overall net effect of current patterns of OC use on deaths from noncontraceptive outcomes is positive, with reductions in mortality from ovarian, colorectal, and endometrial cancers exceeding increased deaths from breast cancer and vascular events. There is uncertainty about the magnitude of this effect, but the probability of a negative impact on life expectancy is small and may be reassuring to women considering OCs as a contraceptive method. There is insufficient evidence to recommend for or against the use of OCs solely for the primary prevention of ovarian cancer.

Abbreviations

AHRQ   Agency for Healthcare Research and Quality
BRCA   breast cancer genetic mutation
CDC   Centers for Disease Control and Prevention
CI   confidence interval
HPV   human papilloma virus
KQ   Key Question
MI   myocardial infarction
OC   oral contraceptive
OR   odds ratio
PICOTS   population, interventions, comparators, outcomes, timing, settings
VTE   venous thromboembolism

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Section 1. Introduction and Methods

This evidence report was funded by the Centers for Disease Control and Prevention (CDC) in conjunction with the Agency for Healthcare Research and Quality (AHRQ) and was designed to evaluate the benefits and harms of the use of oral contraceptives as a primary preventive measure against ovarian cancer.

Background

Ovarian Cancer Incidence and Mortality

Although ovarian cancer is only the eighth most common cancer in women (annual age-adjusted incidence 12.3 per 100,000), it is the fifth leading cause of women's cancer deaths (8.2 per 100,000).[1] Given current age-specific incidence data and U.S. Census demographic projections, the estimated annual number of new ovarian cancer cases will almost double (to 40,000) over the next 35 years as women born between 1946 and 1964 (the "baby boom" generation) reach the ages of highest risk (Figure 1).[2]

Figure 1. Projected ovarian cancer incidence and mortality for 2010 to 2050
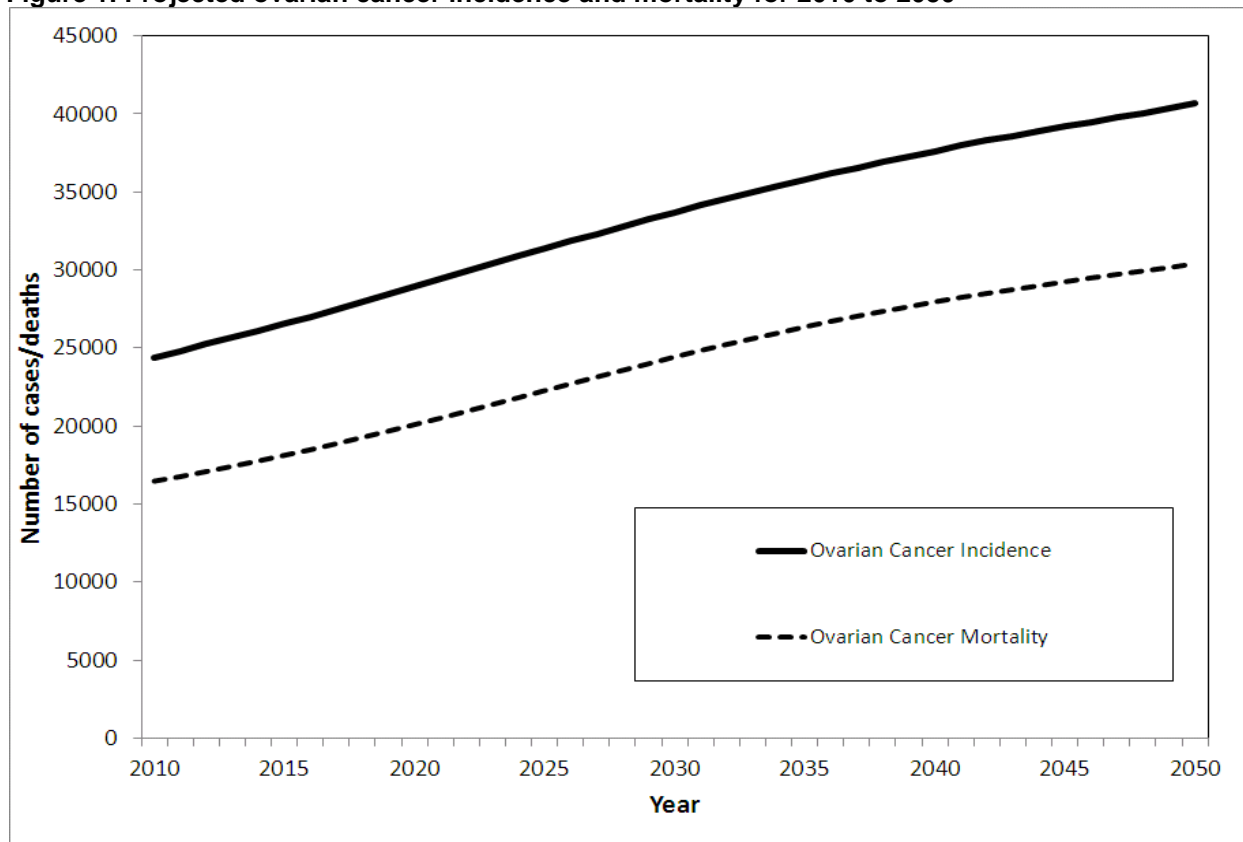
Trends

Age-Specific Incidence and Mortality

Age-specific ovarian cancer incidence and mortality follow a similar pattern that is consistent with the high case-to-fatality ratio of ovarian cancer (Figure 2).

Figure 2. Age-specific incidence and mortality for ovarian cancer[a]

[a]Surveillance, Epidemiology, and End Results (SEER), 2000–2008.

After a slight decline from 1975 through 1985, age-adjusted ovarian cancer mortality was mostly stable until 2002, when mortality had dropped by an annual rate of 1.7 percent (Figure 3). At the same time, age-adjusted incidence was also declining.[3] There are three potential explanations for this decreased mortality: improved survival after diagnosis because of improved treatments, improved survival through effective screening, or decreased incidence. Some of this decrease in mortality may be attributed to the cumulative effects of recent advancements in the treatment of ovarian cancer, which include recognition of the importance of aggressive primary cytoreductive surgery, introduction of platinum- and taxane-based chemotherapy, and introduction of the intraperitoneal route of chemotherapy administration.

Figure 3. Age-adjusted ovarian cancer incidence and mortality rates
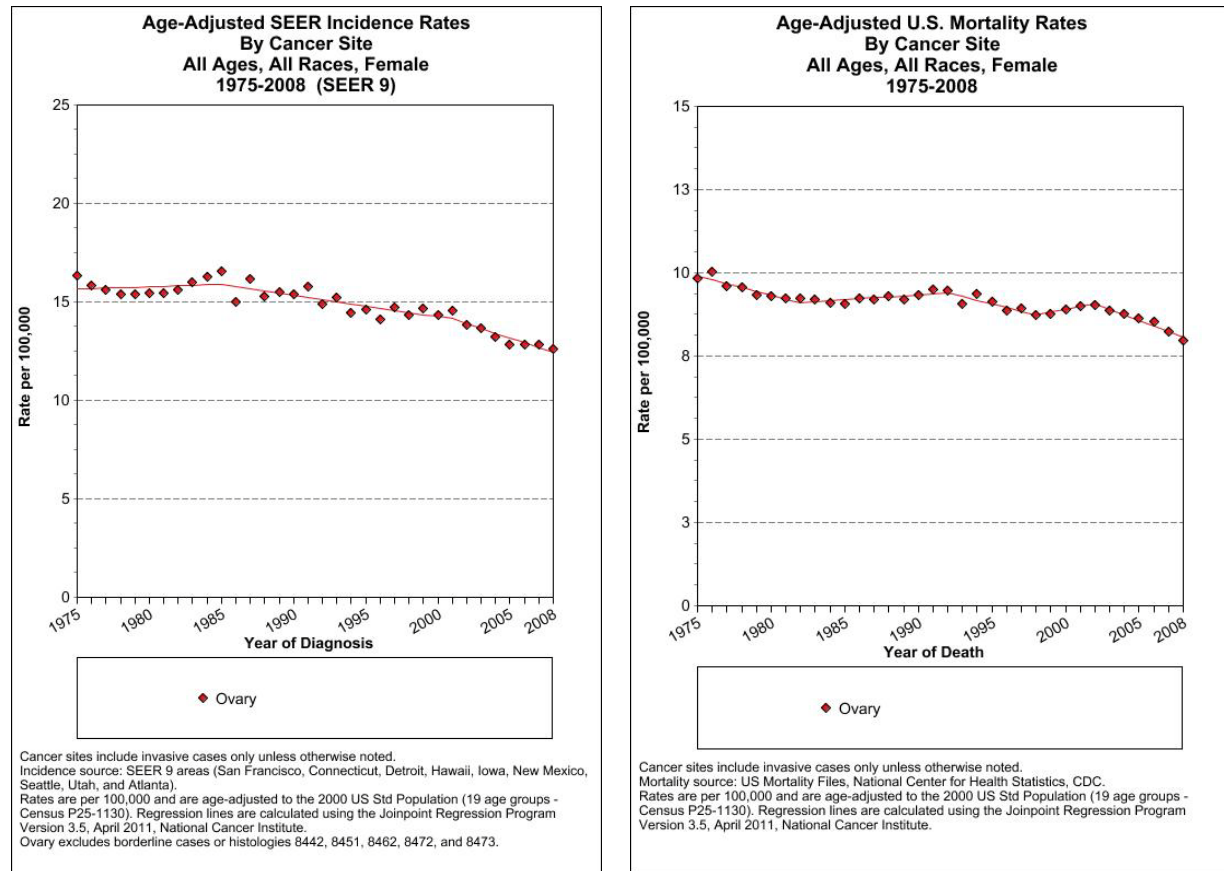
Lack of Effectiveness of Screening

Despite the advances in primary treatment, the mortality rate for ovarian cancer remains the highest among the gynecologic malignancies. Because ovarian cancer typically presents at a much later stage (with concomitant higher mortality) than other common cancers,[1] there has been intense interest in developing effective screening strategies.

Unfortunately, these efforts have had disappointing results to date, especially in the ability of screening to result in reduced mortality.[4-10] Several factors limit the success of screening for ovarian cancer. First, the cause and pathogenesis of the disease remain unknown. While certain histologic subtypes have been associated with precursor lesions, there is still no preinvasive "Stage 0" lesion that is universal, definitive, and detectible. Second, there is no physical barrier to impede rapid spread of malignant cells from the surface of the ovary (FIGO Stage I) (or, as a growing body of evidence suggests, from the epithelium of the fallopian tube) to the upper abdomen (FIGO Stage III).[11] The possibility of rapid spread from the ovary means that many of the cancers identified at Stage I may represent a subgroup of less aggressive tumors rather than a necessary first step in the development of all tumors. Recent pathogenetic studies support the heterogeneity of ovarian cancer, with some subtypes acting as more indolent lesions that are more likely to be detected in an early stage and to be more curable.[12] If this is the case, screening, which is more likely to identify slower growing tumors, may have only a limited impact on overall ovarian cancer mortality.[13] Recently, the Prostate, Lung, Colorectal, and

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Ovarian Phase III ovarian cancer screening trial reported no clinical benefit—and noted possible harm due to false-positive results—when postmenopausal women were screened annually for up to 6 years with CA-125 and pelvic ultrasound.[10]

A second large Phase III trial, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS),[7] randomized women to usual care, ultrasound-based screening, or a multimodality screening algorithm consisting of a CA-125 followed by ultrasound for those with abnormal or rising CA-125 results. The UKCTOCS trial has released the results of prevalence screening, with an encouraging shift toward detection at earlier disease stages noted. However, the mortality outcomes of this trial are not yet known and, as such, the benefit of screening for ovarian cancer remains unproven.

Primary Prevention

Given that the potential effectiveness of screening to reduce morbidity and mortality from ovarian cancer appears to be limited by the underlying biology of the disease, alternative strategies—including the use of more efficacious and less toxic therapies after diagnosis as well as primary prevention—need to be considered and evaluated.

Surgery

Surgical prophylaxis, in the form of bilateral salpingo-oophorectomy (BSO), is a primary preventive approach to ovarian cancer that has been widely used only for women at high genetic risk. In a BRCA1/2 mutation–carrying population, BSO has been demonstrated to reduce the risk of ovarian, tubal, or peritoneal cancers by 80 percent and the risk of breast cancers by 50 percent.[14] The Gynecologic Oncology Group is currently completing a nonrandomized prospective trial comparing risk-reducing salpingo-oophorectomy to longitudinal screening with CA-125 and ultrasound. Several groups have performed health-economic models suggesting that prophylactic surgery is both effective and cost-effective in the BRCA carrier population.[15,16] Given the potential harms of prophylactic surgery and premature loss of ovarian function, surgical prophylaxis in the absence of other indications for pelvic surgery has not been recommended in the general premenopausal population. There is also evidence from observational studies that two gynecological surgical procedures performed for other indications, tubal sterilization and hysterectomy,[17-19] also reduce ovarian cancer risk, even without removal of the ovaries. In light of accumulating evidence that many, if not most, ovarian cancers originate in the fallopian tube, some groups, notably the British Columbia Cancer Association, are advocating removal of the tubes at the time of surgical sterilization or hysterectomy for other indications, but there is no evidence on potential effectiveness.[20]

Oral Contraceptives

Oral contraceptives (OCs) represent a potentially promising primary prevention strategy for ovarian cancer. Several studies suggest a protective effect of OCs on ovarian cancer risk, with a reduction in risk of up to 50 percent with long-term use.[21,22]

Age-Period Cohort

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry suggest a reduction in both age-specific incidence and mortality in cohorts born in 1940 or later (i.e., those who had access to OCs during their entire reproductive life span). Figure 4 shows age-specific incidence, and Figure 5 shows age-specific mortality by age-period

cohort, derived from SEER age-specific incidence and mortality data from 1974 to 2008. Lines refer to women born in the indicated year.

Figure 4. Age-specific incidence by age-period cohort
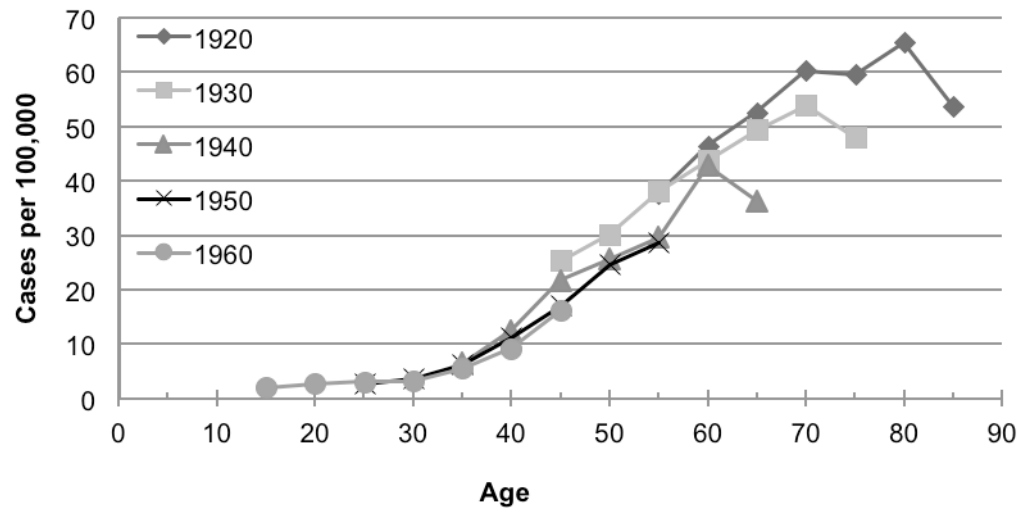
Figure 5. Age-specific mortality by age-period cohort
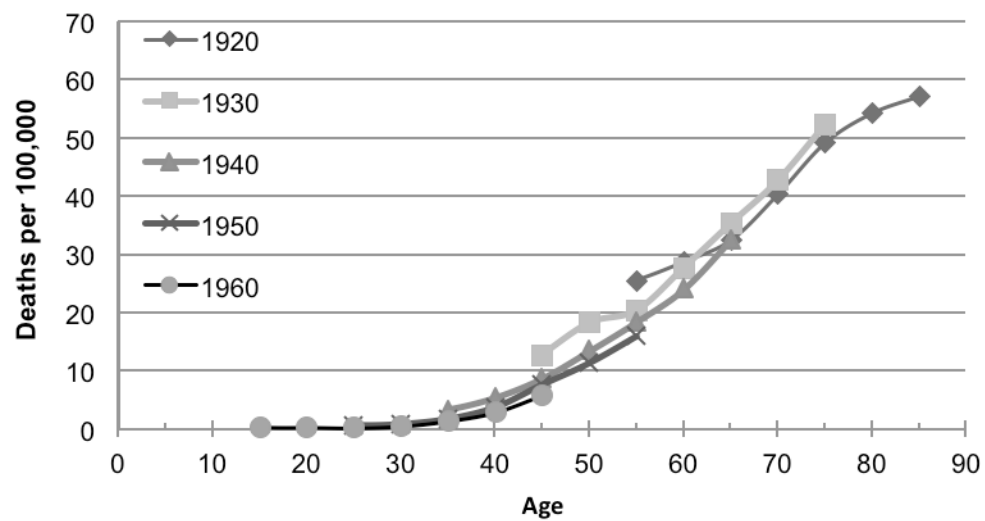
Clinical Data

A large number of observational studies provide evidence that OC use has a protective effect on ovarian cancer incidence and mortality. The largest pooled analysis combined data from 45 epidemiological studies in 21 countries representing 23,257 women with ovarian cancer and 87,303 controls. This analysis described an odds ratio for ever OC use of 0.73 (95% CI, 0.70 to 0.76). There was a strong relationship between degree of risk and duration of OC use, with the overall risk decreased by 20 percent (95% CI, 18% to 23%) for every 5 years of OC use. Based on these findings the authors estimated that use of OCs has already prevented 200,000 ovarian cancers and 100,000 deaths from ovarian cancer.[21] Two other pooled analyses of epithelial ovarian cancer had consistent findings, with odds ratios for ever OC use of 0.66 (95% CI, 0.56 to 0.79) and 0.6 (95% CI, 0.4 to 0.8).[23,24]

Modeling Results

There have been no prior modeling studies to inform the possible preventive effects of OCs on ovarian cancer incidence and mortality.

Biological Plausibility

The mechanisms underlying a potential protective effect of OCs on ovarian cancer risk are not entirely clear. One longstanding hypothesis ("the incessant ovulation theory") is that repetitive ovulations throughout reproductive life result in epithelial damage and repair cycles that subsequently increase the risk of developing ovarian cancer. Factors that decrease the number of ovulations such as pregnancies, breastfeeding, and use of OCs, therefore, are expected to reduce ovarian cancer risk.[25]

A protective effect of OCs may also be due to direct effects of the hormones on the ovarian epithelium, a theory that is supported by some biological evidence. First, the incidence of ovarian cancer is significantly elevated in poultry hens, which ovulate daily.[26] Second, in a 3-year study, macaque monkeys treated either with combination OCs or their individual estrogen or progestin components or with controls, a significant increase in apoptosis of the ovarian epithelium was demonstrated in the groups receiving progestins.[27] The apoptosis pathway preferentially eliminates cells that have sustained genetic damage.[28] The finding that progestins activate this critical pathway in the ovarian epithelium raises the possibility that progestin-mediated apoptotic effects, and not solely inhibition of ovulation, may be responsible for the reduction in ovarian cancer risk that is associated with OC use.[29] Finally, Schildkraudt et al. reported an increase in the protective effect of OCs when a high potency progestin was used.[29]

Although there are some biologically plausible mechanisms for a protective effect of OCs on ovarian cancer risk, recent pathogenetic data now suggest that many high-grade serous epithelial ovarian cancers arise not from the ovarian epithelium but from the distal fallopian tube.[30] Consistent with the epidemiologic data regarding OC use, prior work suggests that the fallopian tube epithelium is influenced by ovulatory cycles, with ovulation exerting an inhibitory effect.[31]

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Rationale for Review

Although the evidence suggests that most women can take OCs safely,[32] the potential benefit of using OCs to reduce the risk of ovarian cancer must be weighed with knowledge of both the potential noncontraceptive health benefits of OCs[33,34] and their potential harms.[35-38] No comparative effectiveness analyses have been conducted to inform decisions about the use of OCs as a primary preventive strategy for ovarian cancer. Also, because the majority of evidence on noncontraceptive benefits and harms of OC use is derived from observational studies, careful consideration must be given to the potential biases inherent in those study designs when developing a research agenda and clinical recommendations. The combination of systematic review and decision-analytic modeling presented in this report allows us to estimate the tradeoffs between the harms and benefits of OC use for the overall population and for individual women, accounting for the potential influence of other factors.

Scope and Key Questions

Scope of Review

To evaluate the benefits and harms of the use of OCs as a primary preventive measure against ovarian cancer, we focused on synthesizing the available evidence for the effectiveness of this strategy in a general population and in groups at elevated risk. We also evaluated benefits and harms of OC use that are not related to the development of ovarian cancer. Finally, we designed a comparative effectiveness model to inform the questions generated by this review.

The scope of the review specifically excluded the unquestioned effectiveness of OCs in preventing unintended pregnancies; the potential effectiveness of OCs as primary or adjunctive treatments for conditions such as menstrual disorders (e.g., dysmenorrhea or menorrhagia), endometriosis, or premenstrual dysphoric disorder; and the potential role of OCs in preventing the onset of these conditions. For women considering the use of OCs for contraception or as treatment for symptomatic conditions, these effects are clearly the most important consideration. However, our overall focus was on the potential role of OCs as primary prevention for ovarian cancer. The overall clinical question we addressed was not, "What are the overall benefits and harms of OCs as a method of contraception or as treatment for certain conditions?"—a question that would require explicit comparisons of different contraceptive methods on all the relevant outcomes. Rather, the implicit question was, "Do the benefits and harms of OCs potentially justify their use *solely* as a primary preventive intervention (analogous to aspirin for the prevention of myocardial infarction) even in women who do not need contraception?"

Key Questions

With input from AHRQ, the CDC, and a Technical Expert Panel (TEP) of external stakeholders, we defined Key Questions using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods section for details). The Key Questions (KQs) considered in this systematic review were:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only oral contraceptives (OCs) for reducing the risk of ovarian cancer?

KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure 6 shows the analytic framework for this systematic review.

Figure 6. Analytic framework for systematic review
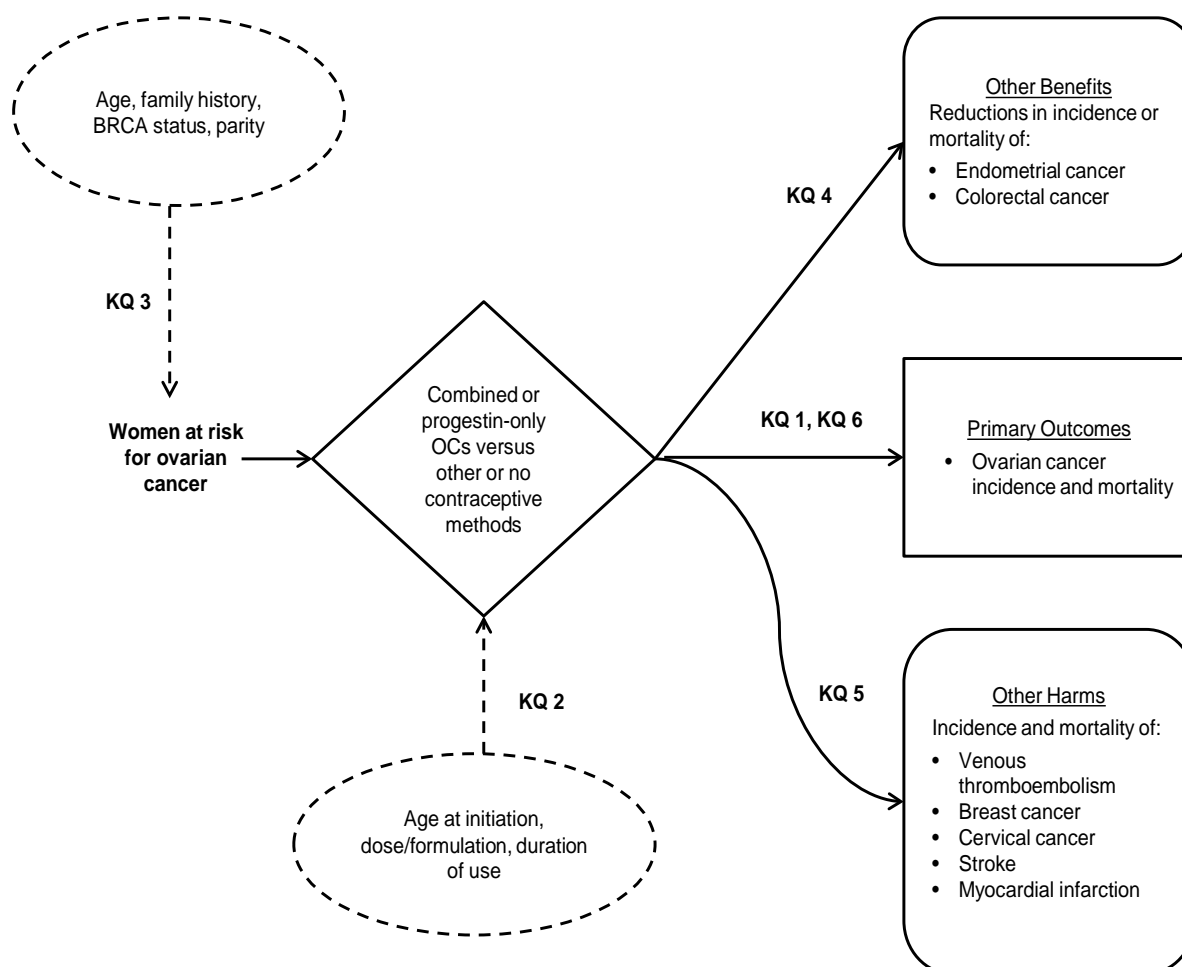
BRCA = breast cancer (genetic mutation); K = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

Organization of Report

This report departs from the standard AHRQ evidence report organization. The evidence is instead presented in four topic-focused sections. Figure 7 shows the relationship between the Key Questions and the report sections. Three of these sections address the relationship between OC use and specific groups of benefits and/or harms. The first such section, "Oral Contraceptives and Ovarian Cancer," focuses on ovarian cancer outcomes (KQ 1, KQ 2, and KQ 3); the second section, "Oral Contraceptives and Other Cancers," on breast, cervical, colorectal, and endometrial cancers (KQ 4 and KQ 5); and the third, "Oral Contraceptives and Vascular Events," on venous thromboembolism, stroke, and myocardial infarction (KQ 5). Within each section, the benefits and/or harms of OC use are considered for both the general population and specific populations of women for whom the risk levels of ovarian cancer are elevated. Where possible, our analyses also consider potential modifying factors such as dose, formulation, and

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duration of OC use. Each section also considers specific evidence gaps and needs for future research regarding the association between OC use and the specific outcomes (KQ 7).

The final section of the report, "Overall Benefits and Harms of Oral Contraceptives for Prevention of Ovarian Cancer," uses a decision analytic framework to explore the overall benefits and harms of all outcomes considered in the report. In this section, we present the results of our comparative effectiveness decision model, considering the overall effect of OC use on benefits and harms for both the general population and specific populations of women at varying levels of risk (KQ 6). In this final section, we also use the modeling framework to identify additional evidence gaps and needs for future research related to the potential overall benefits and harms of OCs for prevention of ovarian cancer (KQ 7).

Figure 7. Report roadmap

Key Questions   **Report Structure**

KQ 1: Effectiveness of OC Use for Reducing Incidence of Ovarian Cancer

KQ 2: Effect of Specifics of OC Use on Ovarian Cancer Incidence

KQ 3. Relative Risk of Ovarian Cancer With OC Use in Subpopulations

KQ 4: Other Benefits of OC Use

KQ 5: Harms of OC Use

KQ 6: Decision Analysis: Benefits and Harms of OC Use and Ovarian Cancer Risk

KQ 7: Research Gaps

Section 1: Introduction and Methods
  Background for report
  General methods for review and model

Section 2: OCs and Ovarian Cancer
  Brief specific background
  Brief specific methods
  Results
  Discussion of specific results
  Specific future research needs

Section 3: OCs and Other Cancers
  Breast, cervical, colorectal, and endometrial
  Brief specific background
  Brief specific methods
  Results
  Discussion of specific results
  Specific future research needs

Section 4: OCs and Vascular Events
  Venous thromboembolism, stroke, and myocardial infarction
  Brief specific background
  Brief specific methods
  Results
  Discussion of specific results
  Specific future research needs

Section 5*: Overall Benefits and Harms of OCs for Prevention of Ovarian Cancer
  Brief specific methods
  Results
  Discussion of model results
  Discussion of overall results
  Discussion of overall evidence gaps/research needs
  Public health implications

KQ = Key Question; OC = oral contraceptive
*Note that Section 5 also summarizes the Key Questions.

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Methods

The methods for this evidence report follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the "Methods Guide").[39] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[40] All methods and analyses were guided by a review protocol, which was developed as described below.

Review Protocol

At the outset of this review, the Key Questions were defined collaboratively with input from AHRQ, the CDC, and the TEP. The TEP comprised individuals representing medical professional societies/clinicians in the areas of obstetrics, gynecology, reproductive health, and gynecologic oncology; Federal health agencies with an interest in cancer care/prevention, oral contraceptive benefits/harms, and women's health research; scientific and methodological experts; a nonprofit cancer advocacy organization; and representatives of ovarian cancer patient and women's reproductive health groups. The TEP was convened to provide input in defining populations, interventions, comparisons, and outcomes; considering potential analysis and modeling approaches; and aiding in identifying particular studies or databases to search. Members of the TEP were required to disclose any relevant business or professional conflicts of interest and any financial conflicts of interest greater than $10,000. Potential conflicts of interest were balanced or mitigated. Members of the TEP did not perform analyses of any kind and did not contribute to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ and the CDC, and posted for public access at the AHRQ Effective Health Care Web site.[41]

Literature Search Strategy

Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant literature published from January 1990 to June 2012. Our search strategies used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. We date-limited our searches to articles published since January 1990 because, given the lag time between OC exposure and subsequent ovarian cancer development, much of the older literature concerning OC use and ovarian cancer is based on OC formulations that are no longer on the market. In addition, many of the other benefits and harms of OC use are observed within several years of initial use. Restricting the search to 1990 forward increases the likelihood that the types of OCs used by the women in the studies we retrieved were similar to those currently available, and thus aids in maximizing the generalizability and clinical relevance of the results. In addition to the databases listed above, we also searched ClinicalTrials.gov to identify additional relevant articles from completed studies. Search dates and exact search strings for all searches are provided in Appendix A. All searches were designed and conducted in collaboration with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key review articles.[42-67] The reference lists from these articles were hand-searched and cross-referenced against our library of database search results. Additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). We did not systematically search gray literature databases beyond our review of potentially relevant studies listed in ClinicalTrials.gov—the high volume of literature identified through our searches of peer-reviewed articles made it unlikely that further searching of gray literature would substantially increase the chances of identifying relevant data that would meet inclusion criteria. However, we did invite additional information through a request for scientific information packets that was submitted to drug manufacturers on our behalf by AHRQ. Submissions received through this mechanism were reviewed and relevant citations screened against the review inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

The PICOTS-based criteria developed to screen articles for inclusion/exclusion at the title/abstract and full-text levels are detailed in Table 1.

Table 1. Summary of inclusion and exclusion criteria for the systematic review

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• All KQs: o Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a] o Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy • KQs 3 and 6: o Women with a family history of ovarian or premenopausal breast cancer suggesting increased risk based on current recommendations o Women with a known BRCA1/BRCA2 mutation	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use (Not required for studies reporting ovarian cancer outcomes or conducted in a population taking OCs for primary prevention of ovarian cancer)
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) Studies comparing OC formulations (without including a non-OC control) are acceptable for studies reporting venous thromboembolism, stroke, or MI outcomes

Table 1. Summary of inclusion and exclusion criteria for the systematic review (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Outcomes	Study reports quantitative association between exposure to OCs and one of the outcomes listed below:
	• KQs 1, 2, 3, 6:
	   ○ Diagnosis of ovarian cancer, ovarian cancer mortality
	   ○ Adverse effects (see KQ 5)
	• KQ 4:
	   ○ Diagnosis of endometrial cancer, endometrial cancer mortality, diagnosis of colorectal cancer, colorectal cancer mortality
	   ○ Adverse effects (see KQ 5)
	• KQ 5:
	   ○ Diagnosis of breast cancer, cervical cancer, venous thromboembolic event, stroke, or myocardial infarction; disease-specific mortality associated with these outcomes
	• KQ 7: Not applicable
		Study only reports outcomes related to assisted reproductive technologies or abortion

Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, non–systematic review, or letter to the editor) • Exploratory study with inadequate sample size

Publications	• English-language only
	• Peer-reviewed articles
	• Outcome reporting falls within the following publication ranges:
	   ○ Study reports an ovarian cancer outcome of interest and was published on or after 01-Jan-1990[d]
	   ○ Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after 01-Jan-2000[e]
	   ○ Study reports a venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after 01-Jan-1995[f]
		Non-English articles[g]

KQ=Key Question; MI = myocardial infarction; OC=oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary ovarian cancer outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).

[f]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[g]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Study Selection

Using the inclusion and exclusion criteria described in Table 1, two investigators independently reviewed the titles and abstracts of articles retrieved through the search strategies for potential relevance to the KQs. Articles included by either reviewer were promoted to full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reconciled the difference through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created forms for abstracting the data elements for the KQs. The abstraction forms were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors for accuracy. Based on clinical and methodological expertise, pairs of researchers were assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first two researchers.

To aid in both reproducibility and standardization of data collection, guidance documents were drafted and given to the researchers as reference material, and researchers received further data abstraction instructions directly on each form created specifically for this project within the DistillerSR data synthesis software. We designed the data abstraction forms for this project to collect information required to conduct the review, including data needed to evaluate the specified eligibility criteria for inclusion; demographic and other patient characteristics of relevance (e.g., family history of ovarian cancer); details of the interventions and comparators (e.g., OC dose, formulation, patterns of use); outcome measures and adjustment factors applied in study analyses; and data needed to assess quality and applicability. Appendix B provides a detailed listing of the data elements abstracted.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in AHRQ's "Methods Guide."[39] To assess quality, we used the approach to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from core elements described in the "Methods Guide." Criteria of interest for all studies included similarity of groups at baseline, the extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. No randomized controlled trials were identified for inclusion in this review, thus criteria specific to randomized studies (e.g., methods of randomization and allocation concealment) were not considered.

Additional elements considered for observational studies included methods for selection of participants and management of selection bias, measurement of interventions/exposures,

addressing any design-specific issues, and controlling confounding. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, and poor (Table 2). For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. Several studies are represented by more than one article. In some of those cases, the study data could not be combined into one abstraction. In those instances, the quality ratings for individual abstractions within a study grouping could vary based on the specific component articles' quality of reporting, the evaluated outcomes, and the statistical and analytical methods used.

Table 2. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. In addition, specific to cohort and case-control studies, inclusion/exclusion criteria were applied consistently to all comparison groups; cases and controls were selected appropriately; strategies for recruiting patients were consistent across study groups; and confounding variables were assessed using valid and reliable measures and implemented consistently across all study participants.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Data Synthesis

We used two complementary approaches to data synthesis. First, we summarized the primary literature by abstracting relevant continuous (e.g., age and categorical data (e.g., BRCA1/2 mutation status). We then determined the feasibility of completing a quantitative synthesis. Feasibility generally depended on the volume of relevant literature, the conceptual homogeneity of the studies, and the completeness of the reporting of results. For this topic, meta-analysis was particularly challenging, because (1) all of the literature was observational, increasing the methodological complexity of the meta-analysis, and (2) there was substantial heterogeneity in the types of exposures (e.g., OC formulation), timing of exposures (e.g., intermittent use of OCs over the course of a reproductive lifetime) and how exposures were measured and reported (ever users versus never users or current versus noncurrent users, duration of use as a continuous or categorical variable). Despite the challenges, we determined that meta-analysis was indicated for a number of the outcomes of interest considered in this review; other outcomes for which meta-analysis was not feasible are summarized using descriptive statistics.

Even when meta-analysis was feasible, at best the results provide evidence for whether there is an association between OC use and a specific outcome, the direction of that association (toward harm or benefit), and the magnitude and precision of that association, which allows estimation of the probability of developing that outcome in OC users *relative* to nonusers.

Estimating the impact of the association on the *absolute* probability of developing that outcome, for either an individual or a population, requires additional methods. First, in order to estimate the absolute increase or decrease in risk based on the results of the meta-analysis, we used the results of the meta-analyses, together with data on the overall incidence of the outcome and the prevalence of OC use, to estimate age-specific incidence in ever versus never users (for cancer outcomes) and current versus noncurrent users (for acute vascular events). Although these results are useful for estimating the risk of individual outcomes, they do not account for the interaction of multiple competing risks, including both the outcomes of interest and other events, such as death from other causes or surgical removal of the ovaries for benign conditions, that affect the overall impact of OC use at the individual and population level. In order to estimate these joint effects, we developed a comparative effectiveness decision model that allowed us to simulate the joint effects of OC use on cancer and vascular events on the overall balance of benefits and harms. The model also allows exploration of the effects of variation in different aspects of OC use (such as age at first use, duration of use, or individual risk of various outcomes) on the overall impact of OC use. Finally, the model allows estimation of uncertainty in the individual estimates of OC effects on overall uncertainty about the balance of benefits and harms, which in turn may help prioritize future research needs.

Outcome Measures

For each disease/condition of interest, we estimated the effect of OC use on a number of outcomes. Outcome measures considered for the meta-analyses were:

- Disease-specific incidence (i.e., were OC users more or less likely to develop the disease/condition?)
- Disease-specific mortality (i.e., were OC users more or less likely to die from a given cause than nonusers?)
- Disease-specific survival (i.e., among women who developed the outcome, were OC users more or less likely to die than nonusers?)

The following outcome measures were considered for modeling:

- Age-specific incidence
- Cumulative lifetime incidence
- Cumulative lifetime mortality from outcomes
- Life expectancy
- Quality-adjusted life expectancy
- Number needed to harm and number needed to prevent (derived from absolute differences in lifetime incidence and mortality)
- Harm/benefit ratio for disease incidence (defined as the sum of excess cases of breast cancer, cervical cancer, myocardial infarction, deep venous thrombosis, pulmonary embolism, and stroke in OC users, divided by the sum of prevented cases of ovarian, colorectal, and endometrial cancers); each cancer also was considered individually
- Harm/benefit ratio for disease mortality (defined as the sum of excess deaths from breast cancer, cervical cancer, myocardial infarction, deep venous thrombosis, pulmonary embolism, and stroke in OC users, divided by the sum of prevented deaths from ovarian, colorectal, and endometrial cancers); each cancer also was considered individually

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Meta-Analytic Methods

Details of the specific approaches to the meta-analysis of the effects of OC use on ovarian cancer, other cancers, and acute vascular events are provided in the relevant sections. Our general approach for each outcome was to analyze, if possible, the following associations:

- Temporal relationships:
  - Ever versus never OC use
  - Current versus noncurrent OC use
  - Duration of current OC use
  - Age at first OC use
  - Time since last OC use
- OC formulation:
  - Estrogen dose (high versus low)
  - Progestin generation (first, second, third, and fourth generations)
- Special populations (such as women with known family history or genetic predisposition)

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not Factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68]

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Results were discussed qualitatively when study numbers were insufficient for meta-analysis (less than three), when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that is not likely to be representative of the general population of reproductive age women.

We included data from pooled analysis articles in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after the date threshold applied for the outcome under consideration in the analysis (January 1, 2000, for ovarian cancer outcomes; January 1, 2000, for other included cancer outcomes; and January 1, 1995, for acute vascular events)
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Estimation of Absolute Risks

We estimated the impact of OC use on age-specific absolute risk from population-based estimates of age-specific incidence, age-specific exposure estimates for OCs, and the derived odds ratios from the meta-analyses. For any outcome,

Overall Incidence = (Incidence in OC users) * (Prevalence OC use) + (Incidence in nonusers) * (Prevalence nonuse).

since

Incidence in OC users = (Incidence in nonusers) * (Relative risk in OC users),

and

Prevalence nonuse = 1 – (Prevalence OC use),

separate estimates for age-specific incidence in users and nonusers can be derived from the overall incidence, the prevalence of OC use, and the relative risks (estimated here from the odds ratios from the respective meta-analyses).

Simulation Model

We constructed a semi-Markov state-transition model that modeled a cohort of women aged 10 to 100, using TreeAge Pro 2012 (Williamstown, MA: TreeAge, Inc.). Age-specific and race-specific probabilities of OC use and important competing risks or effect modifiers, such as all-cause mortality, tubal ligation, hysterectomy, and oophorectomy, were obtained from the literature or publicly available data sources. Estimates for the effect of OC use on cancers and vascular events were based on the results of the meta-analysis, based on either ever or current use of OCs. Other factors, such as duration of use, were included if they were statistically significant in the meta-analysis.

The model was run as a microsimulation, which allowed conditioning of probabilities on past history. Depending on the analysis, each model run included 5,000 to 1,000,000 simulated individuals, with estimates of the outcomes of interest based on the mean value of each model run (or, in some cases, the weighted average of multiple model runs).

Estimates were derived for both the overall population given current OC use patterns (i.e., the cumulative effect of current patterns of age of starting OCs and duration of use on the outcomes of interest based on the risk estimates compared with a scenario where OCs had no effect on risk), as well as at the individual level (the cumulative effect of OC use in all users, based on current patterns of use, vs. nonusers).

The impact of varying age of starting and duration of use was assessed in a separate analysis.

Finally, we assessed the impact of uncertainty in the estimates of OC effects by using a method analogous to cost-effectiveness analysis, where total harms were considered as "costs" and assessing the effect of uncertainty in the effects (based on the confidence intervals of the relative risk estimate) on whether OC use would be recommended based on different "willingness-to-pay" thresholds for harm/benefit ratio.

Strength of Evidence

The strength of evidence for each Key Question and outcome was assessed using the approach described in the "Methods Guide."[39,69] The evidence was evaluated using the four required domains (Table 3).

Table 3. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT vs. observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons (e.g., direct comparison of stroke risk in women using OCs compared with women using IUDs) or indirect comparisons through use of surrogate outcomes (e.g., measurement of blood-clotting factors in women using OCs vs. IUDs) or use of separate bodies of evidence (risk of stroke in OC users vs. placebo, and risk of stroke in IUD users vs. placebo)
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates

IUD = intrauterine device; OC = oral contraceptive; RCT = randomized controlled trial

Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that diminished an observed effect, strength of association (magnitude of effect), and publication bias. The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to the following four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Applicability

To assess applicability, we used the PICOTS format to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the "Methods Guide."[39,70] We used data abstracted on the population studied, the intervention and comparator, the outcomes measured, study settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the "Methods Guide."

Specific factors affecting applicability included (but were not limited to):

- Population: We anticipated that most of the literature was based on women using OCs for contraception, not as prevention for ovarian cancer. Factors such as parity and BRCA status, which affect underlying ovarian cancer risk, may differ (or not be reported) compared with current relevant groups. The balance of other benefits and harms (particularly cardiovascular and thrombotic risks) may differ based on age of use, which would be relevant in some subpopulations (e.g., women over 35 who have not previously used OCs).
- Intervention and comparator: The formulation of OCs used in the literature may not reflect currently available OCs, and the duration and pattern of use may not reflect potential duration and pattern in the setting of primary ovarian cancer prevention. Currently available alternatives to OCs may not have been included in "nonuser" groups in the literature.
- Outcomes: Data on all the relevant outcomes is unlikely to be available for all potentially applicable comparators, particularly newer contraceptive methods.

We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively throughout the sections of the report.

Peer Review and Public Commentary
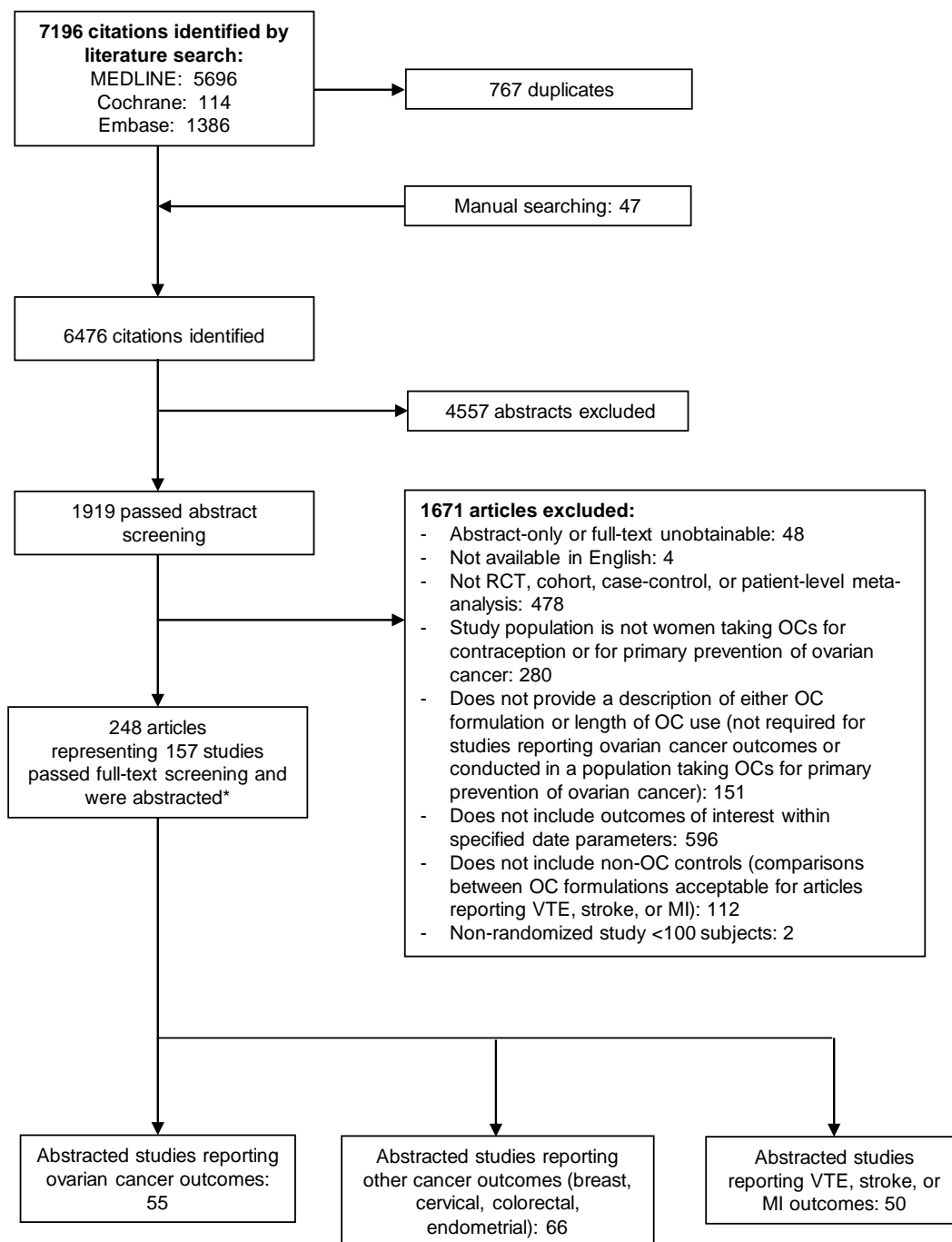
The peer review process is our principal external quality-monitoring device. Experts in key clinical and research areas (obstetrics/gynecology; gynecologic oncology; prevention, screening, treatment, and management of gynecologic cancers; chemoprevention of cancer; women's health), methodological areas (cancer epidemiology, decision modeling, systematic review), along with individuals representing ovarian cancer patient interest communities and women's reproductive health stakeholders were invited to provide external peer review of this draft report. AHRQ, CDC representatives, and an associate editor provided comments, as did members of the Technical Expert Panel. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site.

Literature Search Results

In Figure 8, we depict the flow of articles through the literature search and screening process for the review as a whole. Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 7,196 citations, 767 of which were duplicates. Manual searching and contacts to drug manufacturers identified 47 additional citations, for a total of 6476. No additional relevant citations beyond those already identified were found from a search for relevant studies listed on ClinicalTrials.gov. After applying inclusion/exclusion criteria at the title-and-abstract level, 1919 full-text articles were retrieved and screened. Of these, 1671 were excluded at the full-text screening stage, leaving 248 articles (representing 157 unique studies) for data abstraction. As indicated in Figure 8, several articles/studies were relevant to more than one outcome of interest (55 relevant to ovarian cancer outcomes (KQ 1, KQ 2, KQ 3), 66 to other cancers of interest (KQ 4, KQ 5), and 50 to vascular events (KQ 5).

Subsequent sections of this report describe the key points of the findings, summaries of the included studies relevant to each section, and a detailed synthesis of the evidence. Appendix C provides full citations of included articles as well as the relationship between related articles for the same study/patient population. Note that in the descriptive portions of the text, related data from articles considered to be part of one study grouping may be represented in both the case-control and cohort categories (if both designs are applicable) due to a relationship between the represented patient populations. Similarly, related data from articles considered to be part of one study grouping may be represented in more than one quality category (see the Methods section for a full description of quality assessment). Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 8. Literature flow diagram

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┌─────────────────────────┐
│ 7196 citations identified│          ┌──────────────────────┐
│ by literature search:   │─────────▶│ 767 duplicates        │
│  MEDLINE:  5696         │          └──────────────────────┘
│  Cochrane:  114         │
│  Embase:   1386         │
└─────────────────────────┘
            │                          ┌──────────────────────┐
            │◀─────────────────────────│ Manual searching: 47 │
            │                          └──────────────────────┘
            ▼
┌─────────────────────────┐
│ 6476 citations identified│
└─────────────────────────┘
            │                          ┌──────────────────────┐
            │─────────────────────────▶│ 4557 abstracts excluded│
            ▼                          └──────────────────────┘
┌─────────────────────────┐
│ 1919 passed abstract    │
│ screening               │
└─────────────────────────┘
```

1671 articles excluded:
- Abstract-only or full-text unobtainable: 48
- Not available in English: 4
- Not RCT, cohort, case-control, or patient-level meta-analysis: 478
- Study population is not women taking OCs for contraception or for primary prevention of ovarian cancer: 280
- Does not provide a description of either OC formulation or length of OC use (not required for studies reporting ovarian cancer outcomes or conducted in a population taking OCs for primary prevention of ovarian cancer): 151
- Does not include outcomes of interest within specified date parameters: 596
- Does not include non-OC controls (comparisons between OC formulations acceptable for articles reporting VTE, stroke, or MI): 112
- Non-randomized study <100 subjects: 2

248 articles representing 157 studies passed full-text screening and were abstracted*

Abstracted studies reporting ovarian cancer outcomes: 55

Abstracted studies reporting other cancer outcomes (breast, cervical, colorectal, endometrial): 66

Abstracted studies reporting VTE, stroke, or MI outcomes: 50

MI = myocardial infarction; OC = oral contraceptive; RCT = randomized controlled trial; VTE = venous thromboembolism
*Note that a given study may address more than one outcome group.

Section 2. Oral Contraceptives and Ovarian Cancer

Background

Ovarian cancer has a lifetime incidence of about 1.4 percent and kills over 15,000 women in the United States annually.[1] While the concept of an early detection strategy is attractive for this disease, no screening strategy has yet been proven effective.[10] The stage distribution is weighted heavily toward Stage III and IV disease, suggesting that most ovarian cancers progress rapidly; indeed, a growing body of evidence suggests that many epithelial ovarian cancers initially arise in the epithelium of the fallopian tube. Based on this and pathogenetic evidence, the underlying biology of the disease may limit the potential effectiveness of screening to reduce morbidity and mortality from ovarian cancer.[12,71] Alternative strategies, including the use of novel therapies and primary prevention, need to be considered and evaluated.

Primary Prevention Strategies

Prevention strategies, including surgical prophylaxis and chemoprevention, may be of particular interest to women who are at an elevated risk of ovarian cancer due to a strong family history or a known inherited genetic mutation. Women who are carriers of genetic mutations in BRCA1 or BRCA2 are at markedly increased risk for ovarian cancer. A pooled analysis of 22 studies estimated the average risk of developing ovarian cancer by age 70 is 39 percent (95% confidence interval [CI], 18% to 54%) for BRCA1 mutation carriers and 11 percent (CI, 2.4% to 19%) for BRCA2 mutation carriers.[72] Likewise, women with Lynch syndrome–associated MLH1 and MSH2 mutations have 20 percent (CI, 1% to 65%) and 24 percent (CI, 3% to 52%) risk, respectively, of developing ovarian cancer by the same age.[73] Although the prevalence of genetic mutations predisposing women to ovarian cancer in the general population is low (approximately 0.12% for BRCA1 and 0.2% for BRCA2),[74] the high risk of cancer among women who are mutation carriers underscores the importance of understanding factors that may modify their likelihood of developing cancer.

Oral contraceptives (OCs) represent a potentially promising primary prevention strategy for ovarian cancer. Several large pooled analyses suggest that OCs confer a protective effect on ovarian cancer risk, with a reduction in risk of up to 50 percent with long-term use of OCs.[21-24] The largest pooled analysis to date estimates that OC use has already prevented 200,000 cases of ovarian cancer and 100,000 deaths from this disease worldwide.[21]

In women at high risk of developing ovarian cancer due to family history or a known genetic mutation, the effect of OC use on ovarian cancer risk is relevant for multiple reasons. First, the incomplete penetrance of hereditary cancer genes suggests that there are other factors—either environmental or genetic—that affect whether or not women who are mutation carriers develop ovarian cancer. Thus, from an etiologic standpoint, it is important to understand whether a common environmental exposure such as OCs influences the risk of developing ovarian cancer among mutation carriers. Second, women who are at high genetic risk have a need to understand the options available for reducing morbidity and mortality from ovarian cancer.

The choice of a risk-reduction strategy for women at elevated risk is an individual choice and commonly includes screening strategies and prophylactic surgery. Unfortunately, screening high-risk women with available modalities has not yet proven successful.[75-77] In a BRCA1/2 mutation–carrying population, bilateral salpingo-oophorectomy (BSO) has been demonstrated to reduce the risk of ovarian, tubal, or peritoneal cancers by 80 percent and the risk of breast cancer

by 50 percent.[14] In addition, several groups have used health-economic decision models to suggest that prophylactic surgery is both effective and cost-effective in the BRCA carrier population.[15,16] However, surgical prophylaxis is accompanied both by potential harms and the certain premature loss of ovarian function. Despite the effectiveness of prophylactic BSO, some women at high risk prefer alternatives that are less invasive, do not result in early menopause, and preserve fertility. The Gynecologic Oncology Group is currently completing a nonrandomized prospective trial comparing longitudinal screening with CA-125 and ultrasound to risk-reducing BSO in a high genetic risk population.[78] This trial includes both subsequent cancer diagnoses and quality-of-life assessments and may be informative from a comparative effectiveness standpoint.

Chemoprevention may be a viable option for ovarian cancer risk reduction, and particularly among women at high genetic risk. If OCs confer a comparable reduction in ovarian cancer risk in genetic mutation carriers as that observed in the general population, they could be a reasonable chemoprevention strategy for those who have not completed childbearing or who wish to avoid surgery.

In Section 2 of our systematic review and meta-analysis, we quantify the potential benefits of OC use in reducing the incidence of ovarian cancer. We address the effect of OCs on ovarian cancer risk, both in the general population and in specific populations of interest, as well as examining relationships between specific characteristics of OC use and ovarian cancer incidence and mortality.

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 2, we performed a systematic review and meta-analysis of three of the seven KQs that address the effectiveness of OCs in reducing the risk of developing ovarian cancer:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only OCs for reducing the risk of ovarian cancer?

KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

Analytic Framework

Figure 9 shows the analytic framework that guided this section of the review.

Figure 9. Analytic framework for OCs and ovarian cancer
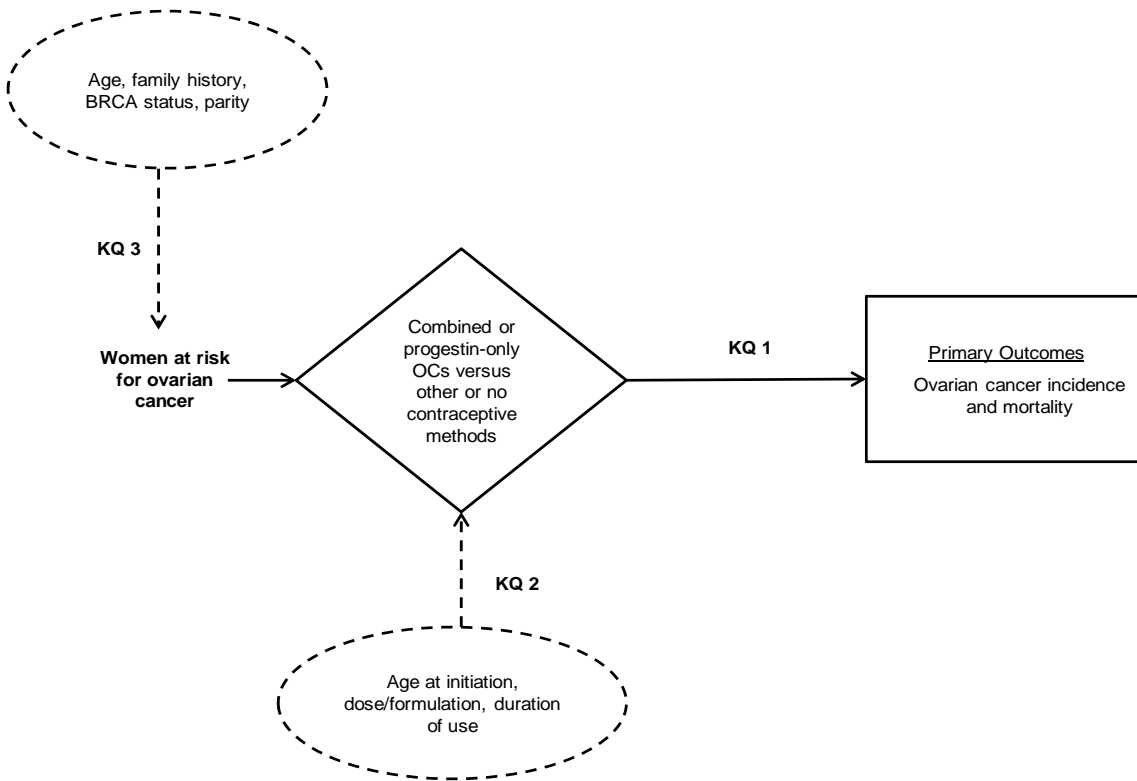
BRCA = breast cancer genetic mutation; KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 4 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 4. Summary of inclusion and exclusion criteria for OCs and ovarian cancer

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	- All KQs - Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a] - Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy - KQ 3: - Women with a strong family history of ovarian or premenopausal breast cancer - Women with a known BRCA1/BRCA2 mutation	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	None
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable)
Outcomes	Study reports quantitative association between exposure to OCs and either ovarian cancer incidence or ovarian cancer mortality	Study only reports outcomes related to assisted reproductive technologies or abortion
Timing	Studies of any duration	None
Setting	All settings	None
Study design	- Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] - Study sample size ≥ 100 subjects for nonrandomized studies[c]	- Not a clinical study (e.g., editorial, non–systematic review, letter to the editor) - Exploratory study with inadequate sample size
Publications	- English-language only - Peer-reviewed articles - Study reports an ovarian cancer outcome of interest and was published on or after 01-Jan-1990[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded as confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary ovarian cancer outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine quantitatively the effect of OCs on the risk of ovarian cancer, we performed meta-analyses on the following relationships:

- Ever OC use
- Temporal relationships:
    - Duration of OC use
    - Age at first OC use
    - Time since last OC use
- OC formulation:
    - Estrogen
    - Progestin
- Special populations:
    - BRCA1 and BRCA2 genetic mutation carriers
    - Family history
    - Parity/gravidity

To perform a meta-analysis, we required that at least three individual studies address the relationship in question. Each included study must also report odds ratios and either report 95 percent confidence intervals (95% CIs) or provide sufficient data to allow us to calculate the 95% CI describing the relationship. We performed meta-analyses using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68] All analyses were done using a random-effects model.

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

1. None of the individual studies included in the pooled analysis had already been included for meta-analysis.
2. At least half of the studies in the pooled analysis were published on or after January 1, 2000.
3. Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Ever OC Use

For the primary ever OC use meta-analysis, we excluded studies that reported effects for only a particular subpopulation (e.g., studies reporting odds ratios only for women with a BRCA mutation) but not the effects for the general population. (Separate analyses were performed for the subpopulations of BRCA mutation carriers and are described below.) Studies that reported ever OC use odds ratios for two or more mutually exclusive subpopulations (e.g., mucinous and

nonmucinous tumors) were included in the meta-analysis, and results for the subpopulations were combined.

Temporal Relationships

Evaluation of clinical relationships for which multiple temporal stratifications were possible—such as duration of OC use, age at first OC use, and time since last OC use (recency)—required creation of several additional simplifying assumptions:

- To facilitate identification of any existing dose-response or duration-response effects, we included only studies that reported odds ratios for at least three different time intervals. Studies that had a median split often had that split in the first interval. Thus, the rate for the upper half would be used to help estimate the rate for all three intervals. It seemed as if this would dilute any dose-response relationship.
- We required that the odds ratios were reported relative to no OC use.

Duration of OC Use

The challenge of performing a meta-analysis on duration of OC use is that individual studies reported the odds ratios for different duration intervals. Simplifying assumptions for this analysis are listed above. We assumed that each odds ratio, OR_{ij}, could be described by the following model:

$$Ln\left[OR_{ij}\right] = \alpha_i + \sum_{j=1}^{k} x_{ij}\,\beta_j,$$

where i denotes the study, j denotes the specific time interval, and k is the number of time intervals used in the model. The α_i are assumed to be random and normal with mean 0 and variance $(SE_{ij}^2 + \sigma^2)$. SE_{ij} is the standard error of the j^{th} odds ratio from the i^{th} study. σ^2 is the extra variation from the random effects model. The x_{ij} are the fixed terms that describe the time period covered by that particular odds ratio. The β_j ($j=1, \ldots, k$) are the odds ratios to be estimated for each duration interval.

We originally assumed that there was a term for each year (up to 10) and a final term for greater than 10 years. However, the large number of terms resulted in very unstable estimates. For that reason, we broke the time points into 4 intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 36 months, then the vector of x_{ij} would be (1/3, 2/3, 0, 0, 0). This would reflect that one-third of the patients in the interval were in the 1 to 12 month interval and two-thirds of the patients were in the 13 to 60 month interval. Using this methodology, any interval could be described.

The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, i.

Age at First OC Use

Using the equation above, we assumed that there were only four different intervals for age at first use: (1) under 20 years of age, (2) 20 to 24 years of age, (3) 25 to 30 years of age, and (4) over 30 years of age. We then used the x_{ij} to create the time period desired. For example, if the second interval from a particular study were from 20 to 28 years of age, then the vector of x_{ij} would be (0, 1/2, 1/2, 0, 0). This would reflect that half the patients in the interval were in the 20

to 24 year interval and half the patients were in the 25 to 30 year interval. Using this methodology, any interval could be described.

Time Since Last OC Use

Using the equation above, we broke time since last OC use into 4 intervals: (1) 0 to 10 years, (2) 10 to 20 years, (3) 20 to 30 years, and (4) more than 30 years. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 15 years, then the vector of x_{ij} would be (2/3, 1/3, 0, 0, 0). This would reflect that two-thirds of the patients in the interval were in the 0 to 10 year interval and one-third of the patients were in the 10 to 20 year interval. Using this methodology, any interval could be described.

OC Formulation

Estrogen

Studies were included in the meta-analysis if they reported the effect of low-dose and/or high-dose estrogen-containing OCs on ovarian cancer incidence and included methodology regarding the definition of low- and high-dose estrogen.[79,80] For studies that presented estrogen dose results stratified by low or high progestin dose, odds ratios for groups with identical estrogen doses were combined across progestin arms using an inverse weighted meta-analysis. In order to compare high- to low-dose estrogen, we included those studies that had odds ratios for each with "never use" as a reference category and divided the high-dose odds ratio by the low-dose odds ratio. This has the effect of canceling out the never-use category. All analyses were made using a random-effects model.

Progestin

Studies were included in the meta-analysis if they reported the effect of low- and/or high-dose progestin on ovarian cancer incidence and presented an established reference for determination of progestin potency. For studies that stratified these results based on low or high estrogen dose, odds ratios for identical progestin dose groups were combined across estrogen arms using an inverse weighted meta-analysis. In order to compare high- to low-dose progestin, we included those studies that had odds ratios for each with "never use" as a reference category and divided the high-dose odds ratio by the low-dose odds ratio. This has the effect of canceling out the never-use category. All analyses were made using a random-effects model.

Special Populations

BRCA Mutation Carriers

Studies were included in the meta-analyses of BRCA mutation carriers if they reported the effect of OCs on ovarian cancer risk comparing mutation carriers with ovarian cancer to unaffected mutation carriers. The analyses were restricted to these study populations because they address the most relevant clinical question: If a woman tests positive for mutations in BRCA1 or BRCA2, can she reduce her risk for ovarian cancer by taking OCs? Studies that compare cases who are mutation carriers with controls who are not mutation carriers do not provide a direct answer to the clinical question because the comparison involves both a genetic factor (BRCA1 or BRCA2 mutation) and an environmental factor (OC use)—this study design does not allow us to sort out the relative contributions of these factors to ovarian cancer risk.

Separate meta-analyses were performed for studies reporting results for BRCA1 mutation carriers, BRCA2 mutation carriers, and BRCA1 and BRCA2 mutation carriers combined.

Family History of Ovarian Cancer

Studies were considered eligible for inclusion if they reported the effect of OCs on ovarian cancer risk stratified by family history.

Parity/Gravidity

Studies were included in the meta-analysis if they reported the effect of OCs on ovarian cancer risk stratified by parity or gravidity. We did not distinguish between parity and gravidity in our analyses. For studies that split parity into multiple categories (i.e., 0, 1, 2, 3+), the results were combined across parity categories using an inverse weighted meta-analysis, and these were labeled parity 1+. To compare parity 0 to parity 1+, we computed the ratio of the parity 0 odds ratio and the parity 1 odds ratio for each study. This has the effect of canceling out the never-use category, which is the reference. All analyses were performed using a random-effects model.

Results

This section presents results of our detailed analysis of the relationship between OCs and ovarian cancer incidence and ovarian cancer mortality.

OC Use and Ovarian Cancer Incidence

We identified 55 studies that evaluated the association between OC use and the incidence of ovarian cancer.[21,23,24,29,37,81-162] In Table 5, we list the studies that reported odds ratios for ever versus never OC use. Of these studies, 28 were case-control studies, 10 were cohort studies, and the remaining 4 were pooled analyses. Of the case-control and cohort studies, 17 studies were rated good quality, 20 fair quality, and 5 poor quality. (As described in the Methods, studies represented by multiple articles and abstracted into more than one dataset may be counted in more than one quality category. Quality ratings specific to each of these datasets are provided in Table 5). Note that none of the pooled analyses met criteria for inclusion in the meta-analyses examining OC use and ovarian cancer incidence.

Table 5. Study characteristics and association between OC use and ovarian cancer incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Case-Control						
Gwinn, 1990[96]	**Women <55 yr enrolled in the Cancer and Steroid Hormone Study** Cases: 436 epithelial ovarian cancers including borderline tumors Controls: 3833 population-based controls	0.566	0.48 to 0.69	Age, parity, breastfeeding	U.S.	Good	8
Parazzini, 1991[128]	**Italian women <60 yr** Cases: 505 epithelial ovarian cancers Controls: 1375 hospital-based controls	0.7	0.5 to 1.0	Age, parity, menopausal status, age at menarche, education, marital status, lifelong menstrual pattern, age at menopause	Europe	Good	3[127]
	Parity 0 Cases: 137 epithelial ovarian cancers Controls: 273 hospital-based controls	0.6	0.3 to 1.3				
	Parity 1-2 Cases: 266 epithelial ovarian cancers Controls: 795 hospital-based controls	0.5	0.3 to 0.9				
	Parity 3+ Cases: 102 epithelial ovarian cancers Controls: 307 hospital-based controls	0.8	0.3 to 1.7				
Parazzini, 1991[129]	**Italian women <65 yr with borderline tumors** Cases: 91 borderline ovarian tumors Controls: 273 hospital-based controls	0.3	0.2 to 0.6	Age, parity, education, age at menopause	Europe	Good	8

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Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Case-Control (continued)						
Thomas, 1991[150]	**WHO Collaborative Study of Neoplasia and Steroid Contraceptives** Cases: 368 epithelial ovarian cancers Controls: 2397 hospital-based controls	0.75	0.56 to 1.01	Age, parity, hospital, year of interview	Europe, Asia, Africa, Australia/ NZ, Israel, Mexico	Fair	8
	Borderline tumors Cases and controls: NR	0.81	0.45 to 1.47				
	Invasive ovarian cancer Cases and controls: NR	0.72	0.51 to 1.02				
	Nulliparous women Cases and controls: NR	0.16	0.05 to 0.54				
	Parous women Cases and controls: NR	0.85	0.63 to 1.16				
Badawy, 1992[82]	**Saudi Arabian women** Cases: 52 ovarian cancer cases Controls: 52 population-based controls	0.4	0.2 to 0.8	None	Saudi Arabia	Poor	8
Poly-chronopoulou, 1993[131]	**Greek women age <75 yr** Cases: 189 malignant epithelial ovarian tumors Controls: 200 population-based controls	0.8	0.17 to 3.67	Age, parity, menopausal status, age at menarche, smoking, education, weight, age at menopause, coffee, alcohol, age at first birth	Europe	Poor	8
Rosenberg, 1994[137]	**Women age <65 yr** Cases: 441 invasive ovarian cancer cases Controls: 2065 hospital-based controls	0.8	0.6 to 1.0	Age, race, parity, family history, hysterectomy, tubal ligation, removal of one ovary, geographic area, interview year	U.S.	Fair	8

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Narod, 1998[122]	**International consortium of women with BRCA1/2 mutations** Cases: 207 invasive epithelial ovarian cancer Controls: 161 sisters of women with mutations and ovarian cancers Cases: 207 invasive epithelial ovarian cancer Controls: 53 sisters of women with mutations and ovarian cancers who are also known mutation carriers without a personal history of ovarian cancer	0.5 0.4	0.3 to 0.8 0.2 to 0.7	Age, parity, age at first birth, geographic area of residence	U.S., Canada, UK, Europe	Fair	2
Wittenberg, 1999[161]	*Mucinous ovarian cancers* Cases: 43 mucinous epithelial ovarian cancers Controls: 426 population-based controls *Nonmucinous ovarian cancers* Cases: 279 nonmucinous epithelial ovarian cancers Controls: 426 population-based controls	0.9 0.8	0.4 to 2.1 0.6 to 1.3	Age, parity, duration of OC use	U.S.	Fair	8
Beard, 2000[83]	**Olmstead County women** Cases: 103 women with invasive epithelial ovarian cancers Controls: 103 population-based controls	1.1	0.6 to 2.3	No adjustment, but matched by age	U.S.	Fair	1
Greggi, 2000[93]	**Italian women** Cases: 440 epithelial ovarian cancer Controls: 868 hospital-based controls	0.4	0.3 to 0.6	Age, parity, family history, breastfeeding , education, OC use, age at first birth, breast feeding, duration of use	Europe	Good	1
Ness, 2000[125]	**SHARE Study participants age <70 yr** Cases: 767 Controls: 1367	0.6	0.5 to 0.8	Age, race, family history, number of pregnancies	U.S.	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Parazzini, 2000[127]	**Italian women** Cases: 971 epithelial ovarian cancer cases Controls: 2758 hospital-based controls	1.2	1.0 to 1.7	Age, parity, calendar year of interview, age at menopause, family history of breast or ovarian cancer, green vegetable consumption, fat-intake score	Europe	Good	1
Sanderson, 2000[143]	**White women age <70 yr** Cases: 276 epithelial ovarian cancer cases Controls: 388 population-based controls	0.8	0.5 to 1.1	Age, parity	U.S.	Good	1
Siskind, 2000[145]	**Australian women** *Nonmucinous ovarian cancers* Cases: 677 Controls: 853 *Mucinous ovarian cancers* Cases: 114 Controls: 853	0.64 0.61	0.48 to 0.85 0.36 to 1.04	Age, parity, BMI, family history, breastfeeding , age squared, alcohol, hysterectomy, tubal, infertility, number of lifetime ovulation	Australia/ NZ	Good	1[144]
Chiaffarino, 2001[87]	**Italian women** Cases: 1031 ovarian cancer cases Controls: 2411 hospital-based controls	0.9	0.7 to 1.2	Age, parity, family history, center, education	Europe	Fair	1
Riman, 2001[133]	**Swedish women with borderline ovarian tumors** Cases: 193 borderline cases Controls: 3899 population-based controls	1.23	0.86 to 1.76	Age, parity, BMI, age menopause, HRT	Europe	Fair	1
Royar, 2001[141]	**German women** Cases: 282 invasive ovarian cancer cases Controls: 533 population-based controls	0.48	0.33 to 0.68	Parity, Family History, Breastfeeding , tubal ligation, hysterectomy	Europe	Fair	1
Riman, 2002[134]	**Swedish women with epithelial ovarian cancer** Cases: 655 ovarian cancer cases Controls: 3899 population-based controls	0.73	0.59 to 0.90	Age, parity, BMI, age at menopause, HRT	Europe	Fair	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Tung, 2003[152]	**Residents of Hawaii or Los Angeles County** Cases: 603 ovarian cancer cases Controls: 607 population-based controls	0.6	0.4 to 0.8	Age, race, parity, study site, education, tubal ligation	U.S.	Good	3[114]
McGuire, 2004[115]	**Women in Northern California** *Women with BRCA1 mutations* Cases: 36 epithelial ovarian cancer cases Controls: 568 population-based controls *Women without BRCA1 mutations* Cases: 381 epithelial ovarian cancer cases Controls: 568 population-based controls	0.54 0.55	0.26 to 1.13 0.41 to 0.73	Age, race, parity	U.S.	Good	1
Whittemore, 2004[159]	**International database of BRCA1/2 carriers** Cases: 147 BRCA carriers with epithelial ovarian cancer Controls: 304 BRCA carriers without epithelial ovarian cancer	0.85	0.53 to 1.4	Age, parity, center	U.S., Canada, UK, Australia/ NZ	Fair	2
Quirk, 2004[132]	**Women from Roswell Park Cancer Institute, New York** Cases: 418 invasive ovarian cancer cases Controls: 836 hospital-based controls	1.22	0.88 to 1.68	Age, parity, family history, history of tubal ligation, noncontraceptive estrogen use	U.S.	Poor	1
Greer, 2005[91]	**Women from the Study of Health and Reproduction (SHARE)** Cases: 405 Controls: 592 *Compared never users with nonandrogenic OC users* Cases: 381 Controls: 761 *Compared never users with both androgenic and nonandrogenic OC users* Cases: 364 Controls: 529	0.52 0.59 0.29	0.35 to 0.76 0.45 to 0.78 0.17 to 0.48	Age, parity, family history, BTL	U.S.	Fair	3[125]
Gronwald, 2006[94]	**Polish BRCA1 carriers** Cases: 150 ovarian cancer cases Controls: 150 population-based controls	0.4	0.2 to 1.0	None	Europe	Fair	2

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Huusom, 2006[107]	**Women participating in the MALOVA study** <u>Cases:</u> 202 ovarian borderline cases <u>Controls:</u> 1564 population-based controls	0.81	0.56 to 1.16	Age, parity, smoking, breastfeeding , age at first birth, duration of contraception use, intake of milk	Denmark	Fair	1
Lurie, 2007[113]	**Residents of Hawaii or Los Angeles County** <u>Cases:</u> 745 epithelial ovarian cancer cases <u>Controls:</u> 943 population-based controls	0.51	0.26 to 0.98	Unclear	U.S.	Good	3[114]
McLaughlin, 2007[116]	**International consortium of women with BRCA1** and/or BRCA2 mutations <u>Cases:</u> 799 mutation carriers with ovarian cancer <u>Controls:</u> 2424 mutation carriers without ovarian cancer *BRCA1 carriers only* <u>Cases:</u> 670 mutation carriers with ovarian cancer <u>Controls:</u> 2043 mutation carriers without ovarian cancer *BRCA2 carriers only* <u>Cases:</u> 128 mutation carriers with ovarian cancer <u>Controls:</u> 380 mutation carriers without ovarian cancer	0.53 0.56 0.39	0.43 to 0.66 0.45 to 0.71 0.23 to 0.66	Parity, breastfeeding , tubal ligation, ethnicity	U.S., Canada, UK, Europe, Asia	Good	2

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Soegaard, 2007[146]	**Women participating in the MALOVA study** Cases: 554 ovarian cancer cases Controls: 1564 population-based controls *Mucinous ovarian cancers* Cases: 50 ovarian cancer cases Controls: 1564 population-based controls *Serous ovarian cancers* Cases: 343 ovarian cancer cases Controls: 1564 population-based controls *Endometrioid ovarian cancers* Cases: 75 ovarian cancer cases Controls: 1564 population-based controls *"Other" histologic types of ovarian cancer* Cases: 86 ovarian cancer cases Controls: 1564 population-based controls	0.67 0.49 0.7 0.76 0.62	0.53 to 0.85 0.25 to 0.97 0.52 to 0.94 0.42 to 1.35 0.36 to 1.06	Age, parity	Denmark	Good	1
Lurie, 2008[114]	**Residents of Hawaii or Los Angeles County** Cases: 813 epithelial ovarian cancer cases Controls: 993 population-based controls	0.59	0.42 to 0.84	Age, race, menopausal status, family history, education, gravidity, age at last pregnancy, tubal ligation, OC potency, hysterectomy, age at menopause, use of menopausal hormones	U.S.	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Moorman, 2008[121]	**Women in the North Carolina Ovarian Cancer Study** *Premenopausal* Cases: 314 epithelial ovarian cancer cases Controls: 360 population-based controls *Postmenopausal* Cases: 582 epithelial ovarian cancer cases Controls: 607 population-based controls	0.5 0.8	0.3 to 0.8 0.6 to 1.1	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	U.S.	Good	1
Boyce, 2009[84]	*Granulosa cell tumors* Cases: 72 GCT cases Controls: 1578 population-based controls *Granulosa cell tumors vs. epithelial ovarian cancer* Cases: 72 GCT cases Controls: 1511 epithelial ovarian cancer cases	0.32 0.6	0.17 to 0.63 0.32 to 1.14	Age, race	U.S.	Fair	4
Ness, 2011[123]	**HOPE study participants** Cases: 869 women with invasive and borderline ovarian cancer Controls: 1779 population-based controls	0.67	0.55 to 0.81	Age, race, family history, gravidity, infertility, ever use of IUDs or barrier contraceptives, tubal ligation, and vasectomy	U.S.	Good	1
Urban, 2012[155]	**Black South African women aged 18–79 yr** Cases: 182 ovarian cancer cases Controls: 1492 women with cancers with no known relationship to oral or injectable contraception Recruitment period: 1995–2006	0.88	0.52 to 1.50	Age, parity, smoking, year of diagnosis, education, alcohol consumption, number of sexual partners, urban/rural residence, province of birth	South Africa	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Wilailak, 2012[160]	**Thai women** Cases: 330 epithelial ovarian cancer cases Controls: 982 hospital-based controls	0.71	0.51 to 0.98	Parity, family history, breastfeeding, depot medroxy-progesterone acetate use	Thailand	Fair	1
Cohort							
Hankinson, 1995[98]	**Nurses' Health Study** Exposed: 592,056 person-years OC exposed Unexposed: 599,301 person-years OC unexposed	1.08	0.83 to 1.43	Age, parity, menopausal status, age at menarche, smoking, BTL, Quetelet's Index	U.S.	Fair	8
Vessey, 1995[157]	**Oxford Family Planning Association Contraceptive Study** Exposed: 3520 women >8 years OC exposed Unexposed: 5881 women OC unexposed	0.4	0.2 to 0.8	Age, parity	UK	Poor	3[156]
Kumle, 2004[110]	**Norwegian-Swedish Women's Lifestyle and Health cohort** Exposed: 75,533 women OC exposed Unexposed: 28,019 women OC unexposed *Invasive ovarian cancers* *Borderline ovarian tumors*	0.6 0.6 0.7	0.5 to 0.8 0.4 to 0.8 0.5 to 1.2	Age, parity, menopausal status, HRT, country	Europe	Fair	1
Vessey, 2006[156]	**Oxford Family Planning Association Contraceptive Study** Exposed: 301,000 person-years OC exposed Unexposed: 187,000 person-years OC unexposed	0.5	0.3 to 0.7	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Hannaford, 2007[37]	**Royal College of General Practitioners Oral Contraception Study** *Main dataset* Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation *General practitioner dataset* Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation	0.54 0.51	0.40 to 1.71 0.33 to 0.78	Age, parity, smoking, social status	UK	Fair	1
Antoniou, 2009[81]	**International BRCA1/2 Carrier Cohort Study** *BRCA1/2 mutation carriers* Exposed: 2415 women OC exposed Unexposed: 766 women OC unexposed *BRCA1 mutation carriers* Exposed: 1655 women OC exposed Unexposed: 512 women OC unexposed *BRCA2 mutation carriers* Exposed: 760 women OC exposed Unexposed: 245 women OC unexposed	0.55 0.52 1.04	0.40 to 0.76 0.37 to 0.73 0.42 to 2.54	Parity	Canada, UK, Europe	Fair	2
Dorjgochoo, 2009[88]	**Shanghai Women's Health Study** Exposed: 12,957 women OC exposed Unexposed:15,557 women OC unexposed	1.19	0.66 to 1.84	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	Asia	Fair	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Rosenblatt, 2009[138]	**Cohort of female textile workers in Shanghai** Exposed: 352,695 person-years OC exposed Unexposed: 2,057,377 person-years OC unexposed	1.17	0.86 to 1.60	Age, parity, injectable contraceptive use	Asia	Poor	1
Braem, 2010[85]	**Netherlands Cohort Study on Diet and Cancer** Exposed: 8668 person-years OC exposed Unexposed: 25,916 person-years OC unexposed	0.71	0.52 to 0.97	Age, parity	UK, not multi-center	Fair	5
Tsilidis, 2011[151]	**EPIC Cohort** Exposed: 192,836 women OC exposed Unexposed: 132,923 women OC unexposed	0.86	0.73 to 1.00	Age, parity, menopausal status, BMI, smoking, center, unilateral oophorectomy, hysterectomy, menopausal hormones, age at menarche	Europe	Good	1
Yang, 2012[162]	**NIH-AARP Diet and Health Study** Exposed: 67,870 women OC exposed Unexposed: 100,304 women OC unexposed	0.74	0.63 to 0.87	Age, parity, menopausal hormone therapy	U.S.	Good	1
Pooled							
Franceschi, 1991[24]	Cases: 971 women with epithelial ovarian cancer Controls: 2258 hospital controls	0.6	0.4 to 0.8	Study, age, marital status, socioeconomic status, parity, menopause, contraceptive habits	Europe	Fair	7
Harris, 1992[101]	**Collaborative Ovarian Cancer Group** Cases: 327 white women with ovarian borderline tumors Controls: 4144 white controls	0.80	0.59 to 1.1	Study, age, parity	U.S.	Good	7

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Pooled (continued)							
Horn-Ross, 1992[106]	**Collaborative Ovarian Cancer Group** *Germ cell tumors* Cases: 38 Controls: 1142 general population controls	2.0	0.77 to 5.1	Study, age, year of birth	U.S.	Fair	4, 7
	Sex cord-stromal tumors Cases: 45 Controls: 2617 general population controls	0.37	0.16 to 0.83				
Bosetti, 2002[23]	Cases: 2,768 women with epithelial ovarian cancer Controls: 6,274 hospital controls	0.66	0.56 to 0.79	Study, age, year, socioeconomic status, parity, menopause, age at menopause	Europe	Fair	6
Beral, 2008[21]	Cases: 23,257 women with malignant ovarian tumors Controls: 87,303 women without malignant ovarian tumors	0.73	0.70 to 0.76	Study, age, parity, hysterectomy	21 countries	Good	6

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = Intrauterine device; OC = oral contraceptive; OR = odds ratio; NR = not reported; NZ = New Zealand; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to odds ratios reported for BRCA mutation carriers only; 3 = Excluded due to odds ratios for this population reported by another included article (primary abstraction ID given); 4 = Excluded due to epithelial ovarian cancers not included; 5 = Excluded due to case-cohort study reported hazard ratio only; 6 = Excluded pooled study due to inclusion of component studies; 7 = Excluded pooled study due to >50% of component studies published prior to 1990; 8 = Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

Ever Versus Never OC Use

Seventeen case-control studies representing 10,031 cases and 21,025 controls[83,87,93,107,114,115,121,123,125,127,132-134,141,143-146,155,160] and including two instances of paired articles from the same studies with distinct cases[107,133,134,146] were included in this meta-analysis examining the effect of ever versus never OC use on ovarian cancer incidence. Of these studies, 11 were rated good quality, 6 fair quality, and 1 poor quality. Note that the articles from the MALOVA study are represented in two different quality categories based on varying characteristics of the two publications. Abstracted data not included in this analysis are specified (with rationale) in Table 5. Reasons for exclusion from the analysis included reporting ever versus never data from the same study as another article already included in the analysis; reporting only on BRCA mutation carriers; and including only women with nonepithelial ovarian cancers. Figure 10 shows that the odds ratio for the meta-analysis of ever versus never use of OCs was 0.72 (95% CI, 0.64 to 0.81), which demonstrates an almost 28-percent reduction in ovarian cancer risk in women who have ever used OCs.
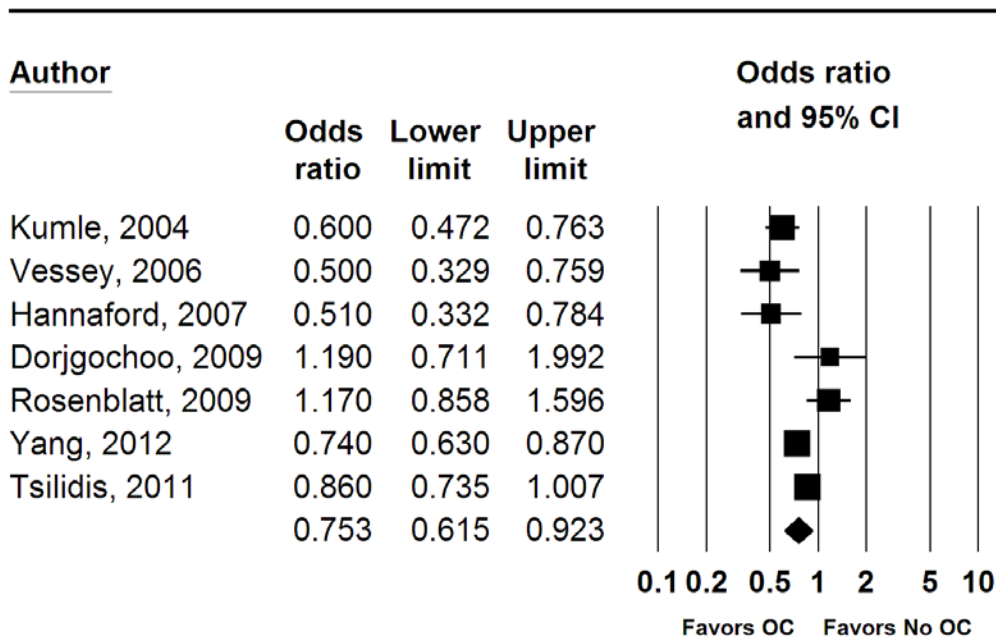
Figure 10. Forest plot for ever versus never OC use (case-control studies, ovarian cancer incidence)

Author	Odds ratio	Lower limit	Upper limit
Ness, 2000	0.600	0.472	0.763
Parazzini, 2000	0.830	0.636	1.083
Sanderson, 2000	0.800	0.621	1.031
Beard, 2000	1.100	0.561	2.155
Greggi, 2000	0.400	0.280	0.571
Purdie, 2001	0.630	0.490	0.810
Chiaffarino, 2001	0.900	0.688	1.177
Riman, 2001	1.230	0.860	1.760
Royar, 2001	0.480	0.334	0.689
Riman, 2002	0.730	0.591	0.902
McGuire, 2004	0.550	0.420	0.720
Quirk, 2004	1.220	0.883	1.686
Huusom, 2006	0.810	0.563	1.166
Lurie, 2008	0.590	0.417	0.834
Soegaard, 2007	0.700	0.521	0.941
Moorman, 2008	0.703	0.543	0.910
Ness, 2011	0.670	0.552	0.813
Wilailak, 2012	0.710	0.512	0.984
Urban, 2012	0.880	0.518	1.495
	0.721	0.643	0.808

Odds ratio and 95% CI

Favors OC — Favors No OC

CI = confidence interval; OC = oral contraceptive

Seven cohort studies[37,88,110,138,151,156,162] were included in this meta-analysis. There was a total of 625,999 participants in four of these studies[88,110,151,162] and a total of 3,981,072 person-years of followup in the other three.[37,138,156] Of these studies, three were rated good quality, three fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 5. Reasons for exclusion from this analysis included reporting only on BRCA mutation carriers; reporting ever versus never data from the same study as another article already included in the analysis; and for one case-cohort study, reporting hazard ratios rather than odds ratios. Figure 11 shows that the odds ratio for the meta-analysis of ever versus never use of OCs was 0.75 (95% CI, 0.62 to 0.92).

Figure 11. Forest plot for ever versus never OC use (cohort studies, ovarian cancer incidence)

Author	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Kumle, 2004	0.600	0.472	0.763	
Vessey, 2006	0.500	0.329	0.759	
Hannaford, 2007	0.510	0.332	0.784	
Dorjgochoo, 2009	1.190	0.711	1.992	
Rosenblatt, 2009	1.170	0.858	1.596	
Yang, 2012	0.740	0.630	0.870	
Tsilidis, 2011	0.860	0.735	1.007	
	0.753	0.615	0.923	

0.1 0.2 0.5 1 2 5 10
Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

A combined meta-analysis of all 24 case-control and cohort studies resulted in an odds ratio for ever versus never use of 0.73 (95% CI, 0.66 to 0.81). Both groups of studies showed heterogeneity due to heterogeneous populations and varying durations of followup.

Sensitivity Analyses

Analyses were repeated excluding the studies rated as poor quality (1 case-control and 1 cohort). These exclusions had a minor effect on the odds ratio estimates. Estimates were 0.70 (95% CI, 0.63 to 0.78) for the case-control studies; 0.70 (CI, 0.58 to 0.85) for the cohort studies; and 0.70 (CI, 0.64 to 0.77) for all studies combined. We also repeated our analyses of the case-control studies excluding those without patients from the United States (9 studies). The meta-analysis of the remaining eight case-control studies revealed an odds ratio for ever OC use of 0.72 (CI, 0.61 to 0.85). A similar analysis was not performed for the cohort studies because only one of the seven studies was conducted in the United States.

Additional analyses were done including studies published from 1990 forward. Estimates were 0.70 (CI, 0.63 to 0.77) for the 26 case-control studies, 0.79 (CI, 0.65 to 0.96) for the 8 cohort studies and 0.72 (CI, 0.66 to 0.79) for a combined analysis of the case-control and cohort studies.

Pooled Analyses

Two pooled analyses that reported on ever versus never OC use but did not meet inclusion criteria for the meta-analysis are of particular note. One of these[23] included only epithelial ovarian cancers as cases and reported odds ratios for ever versus never use of 0.66 (95% CI, 0.56 to 0.79). The other[21] reported the largest pooled analysis of 45 studies (47 referenced publications) with 23,257 cases of epithelial or nonepithelial ovarian cancer and 87,303 controls—with a combined odds ratio of 0.73 (CI, 0.70 to 0.76). Our systematic review included 13 of the 47 studies referenced by Beral et al.[21] Of the remaining 34 studies, 16 were not included due to publication prior to 2000; 16 were not identified by our literature search, and manual review of these confirmed that they were not relevant to our question of interest; and 2 were identified by the literature search but excluded at the abstract screening stage.

Temporal Relationships

Duration of OC Use

Fifteen studies[37,87,109,110,114,117,118,125,133,134,138,141,145,152,154,160,162] were included in this meta-analysis examining the effect of duration of OC use on ovarian cancer incidence. Of these, 10 were case-control studies representing 6901 cases and 15,999 controls. Five were cohort studies, with 524,463 participants in 3 of the studies and 3,493,072 person-years in the other 2 studies. Seven studies were rated good quality, 7 fair quality, and 1 poor quality. Reasons for exclusion from this meta-analysis included reporting fewer than 3 duration categories; reporting odds ratios only for specific subpopulations of women; lacking a "never use" reference group; reporting duration data from the same study as another article already included in the analysis; and reporting duration odds ratios for only the year of OC use (Table 6).

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control					
Harlow, 1991[100]	Cases: 194 Controls: 193	Used OC for <3 mo or never (reference) 3 to 12 mo 13 to 48 mo >48 mo	1.0 1.5 0.7 0.5	NA (reference) 0.8 to 3.1 0.3 to 1.4 0.2 to 0.9	Age, parity, religion		3
Parazzini, 1991[128]	Cases: 505 Controls: 1375	<2 yr ≥2 yr	0.9 0.5	0.5 to .5 0.3 to 0.9	Age, parity, menopausal status, age at menarche, education, marital status, lifelong menstrual pattern, age at menopause		2
Parazzini, 1991[129]	Cases: 91 Controls: 273	<24 mo ≥24 mo	0.3 0.2	0.1 to 0.4 0.1 to 0.6	Age, parity, education, age at menopause		2
Thomas, 1991[150]	Cases: 368 Controls: 2397	1 to 11 mo 12 to 59 mo 60+ mo	0.86 0.69 0.50	0.58 to 1.28 0.45 to 1.10 0.26 to 0.98	Age, menopausal status, hospital, year of interview		2
Badawy, 1992[82]	Cases: 52 Controls: 52	<5 yr 5+ yr	0.9 0.2	0.3 to 2.5 0.1 to 0.5	Crude		2
Chen, 1992[86]	Cases: 112 Controls: 224	<12 mo 12 to 35 mo 36+ mo	0.7 1.4 1.1	Reference 0.3 to 1.8 0.5 to 3.4 0.4 to 2.9	Parity, education		7
Gross, 1992[95]	Cases: 225 Controls: 2252	3 to 11 mo 12 to 24 mo 25 to 36 37 to 60 ≥61	0.6 0.6 0.7 0.7 0.3		Age, parity	Cases and controls with no family history of ovarian cancer	4
	Cases: 31 Controls: 99	3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	3.1 1.7 1.5 1.1 0.3		Age, parity	Women with a family history of ovarian cancer	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	High dose 1 to 6 mo High dose 7 to 18 mo High dose 19 to 60 mo High dose 61+ mo Low dose 1 to 6 mo Low dose 7 to 18 mo Low dose 19 to 60 mo Low dose 61+ mo	0.60 1.07 0.48 0.49 0.45 1.36 1.47 0.75	0.28 to 1.28 0.50 to 2.29 0.20 to 1.18 0.17 to 1.43 0.18 to 1.10 0.59 to 3.10 0.68 to 3.18 0.26 to 2.19	Age, parity, center, year of diagnosis		4
Tavani, 1993[148]	Cases: 194 Controls: 710	2 yr or less 2 to <5 yr 5+ yr	0.9 1.1 0.3	0.5 to 1.4 0.5 to 2.4 0.1 to 0.7	Age, parity, family history, education, abortions, OC use	Only women <45 yr	7
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	1 to 5 mo 6 to 11 mo 1 yr 2 yr 3 to 4 yr 5 to 9 yr ≥10 yr	1.1 0.9 1.3 1.2 0.5 0.7 0.5	0.7 to 1.7 0.5 to 1.7 0.8 to 2.0 0.7 to 2.0 0.3 to 1.1 0.4 to 1.1 0.2 to 0.9	Age, race, parity, family history, hysterectomy, removal of one ovary, geographic area, interview year	Formulation data refers only to use >3 yr	7
Risch, 1996[136]	Cases: 367 Controls: 564	OR per yr OC use	0.89	0.84 to 0.94	Age, parity, family history, breastfeeding, duration of OC use, BTL, HRT, hysterectomy	Invasive serous ovarian cancers	5
	Cases: 83 Controls: 564	OR per yr OC use	0.95	0.9 to 1.01	Age, parity, family history, breastfeeding, duration of OC use, BTL, HRT, hysterectomy	Borderline tumors	5
	Cases: 40 Controls: 564	OR per yr OC use	0.97	0.89 to 1.05	Age, parity, family history, breastfeeding, duration of OC use, tubal ligation, HRT, hysterectomy	Mucinous invasive cancers	5

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Risch, 1996[136] (continued)	Cases: 42 Controls: 564	OR per yr OC use	0.86	0.77 to 0.96	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	Borderline serous tumors	5
	Cases: 40 Controls: 564	OR per yr OC use	1.00	0.93 to 1.07	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	Borderline mucinous tumors	5
	Cases: 254 Controls: 564	OR per yr OC use	0.88	0.84 to 0.93	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	All serous tumors both borderline and invasive	5
	Cases: 367 Controls: 564	OR per yr of OC use	0.9	0.86 to 0.94	Age, parity, family history, breastfeeding, BTL, HRT, hysterectomy, duration of OC use	Invasive ovarian cancers	5
Godard, 1998[89]	Cases: 153 Controls: 152	0 to 1 yr 1 to 5 yr 6 to 10 yr 11 to 25 yr Per yr of use	1.0 0.77 0.49 0.33 0.89	Reference 0.44 to 1.36 0.27 to 0.91 0.13 to 0.82	Crude		3

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Narod, 1998[122]	Cases: 207 Controls: 53	<3 yr 3 to <6 yr ≥6 yr	0.4 0.4 0.3	0.3 to 0.9 0.1 to 1.0 0.1 to 0.7	Age, parity, age at first birth, geographic area of residence	Ovarian cancer cases with BRCA1 or BRCA2 mutations, controls are sisters of cases (53 of 161 controls had BRCA1 or BRCA2 mutations).Cases compared with controls with BRCA1/2 mutations	4
	Cases: 207 Controls: 161	<3 yr 3 to <6 yr ≥6 yr	0.8 0.4 0.4	0.4 to 1.4 0.2 to 0.9 0.2 to 0.7	Age, parity, age at first birth, geographic area of residence	Cases with BRCA1 or BRCA2 mutations, controls are sisters of cases (53 of 161 had BRCA1 or BRCA2 mutations)	4
Salazar-Martinez, 1999[142]	Cases: 84 Controls: 668	1 to 12 mo 13+ mo	0.56 0.36	0.22 to 1.3 0.15 to 0.83	Age, parity, BMI, smoking, breastfeeding , diabetes, hypertension, physical activity, menopausal status		2

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control (continued)					
Wittenberg, 1999[161]	Cases: 322 Controls: 426	<5 yr 5+ yr	1.0 0.6	0.7 to 1.6 0.4 to 1.0	Age, parity	Nonmucinous cases	2
	Cases: 322 Controls: 426	<5 yr 5+ yr	1.2 0.4	0.5 to 3.0 0.1 to 1.4	Age, parity	Mucinous ovarian cases	2
Greggi, 2000[93]	Cases: 440 Controls: 868	< 24 mo ≥24 mo	0.5 0.3	0.3 to 0.9 0.2 to 0.5	Age, parity, family history, breastfeeding, education, OC use, age at first birth, breast feeding, OC use		2
Ness, 2000[125]	Cases: 616 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	0.7 0.7 0.7 0.4	0.5 to 1.0 0.5 to 0.9 0.5 to 0.9 0.2 to 0.6	Age, race, family history, number of pregnancies	Invasive ovarian cancer (N=616)	1
	Cases: 767 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	0.7 0.7 0.6 0.3	0.6 to 1.0 0.5 to 0.9 0.5 to 0.9 0.2 to 0.5	Age, race, family history, number of pregnancies	All cases combined	1
	Cases: 151 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	1.0 0.8 0.7 0.3	0.6 to 1.7 0.5 to 1.3 0.4 to 1.2 0.1 to 0.7	Age, race, family history, number of pregnancies	Borderline ovarian cancer (N=151)	1
Sanderson, 2000[143]	Cases: 276 Controls: 388	<5 yr >5 yr	1.0 0.6	0.6 to 1.5 0.3 to 0.9	Age, parity		2

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Siskind, 2000[145]	Cases: 794 Controls: 853	1 to 12 mo 13 to 60 mo 61 to 120 mo 120 to 180 mo >180 mo 1 to 12 mo prior to first pregnancy 13 to 36 mo prior to first pregnancy 36 to 60 mo prior to first pregnancy >60 mo prior to first pregnancy	0.57 0.73 0.50 0.35 0.25 1.01 0.97 0.89 0.54	0.40 to 0.82 0.52 to 1.03 0.34 to 0.73 0.21 to 0.56 0.13 to 0.49 0.57 to 1.80 0.58 to 1.63 0.47 to 1.68 0.26 to 1.11	Parity, smoking, ovulatory life, tubal ligation, and hysterectomy		1
	Cases: 114 Controls: 853	OR per year of OC use	0.92	0.88 to 0.97	Age, parity, BMI, family history, smoking, breastfeeding , alcohol, BTL, hysterectomy, infertility, number of lifetime ovulations	Mucinous ovarian cancers	1
	Cases: 677 Controls: 853	OR per year of OC use	0.93	0.90 to 0.96	Age, parity, BMI, smoking, age squared, alcohol, hysterectomy, tubal, infertility, number of lifetime ovulation	Nonmucinous ovarian cancer	1
Chiaffarino, 2001[87]	Cases: 1031 Controls: 2411	<25 mo 25 to 59 mo ≥60 mo	1.0 1.3 0.5	0.7 to 1.4 0.7 to 2.2 0.3 to 0.9	Age, parity, family history, center, education		1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Modan, 2001[118]	Cases: 240 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.14 0.77 1.07	0.67 to 1.94 0.41 to 1.44 0.63 to 1.83	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; cases with BRCA1 or 2 mutations (N=240)	1
	Cases: 832 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.15 0.77 0.69	0.84 to 1.57 0.53 to 1.12 0.48 to 0.98	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; high prevalence of BRCA mutation carriers	1
	Cases: 592 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.13 0.74 0.53	0.79 to 1.62 0.48 to 1.16 0.34 to 0.84	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; cases without BRCA mutations (N=592)	1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Modugno, 2001[119]	Cases: 616 Controls: 1367	Per one year of use	0.94	0.92 to 0.97	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen use, tubal ligation, hysterectomy, family history of breast cancer	Invasive ovarian cancer (N=616)	5
	Cases: 151 Controls: 1367	Per one year of use	0.92	0.85 to 0.98	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen use, tubal ligation, hysterectomy, family history of breast cancer	Borderline ovarian cancer (N=151)	5
	Cases: 767 Controls: 1367	Per year of use	0.94	0.91 to 0.96	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen, tubal ligation, hysterectomy, family history of breast cancer		5

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control (continued)					
Ness, 2001[126]	Cases: 727 Controls: 1359	OCs for contraception ≤4 yr OCs for contraception 5 to 9 yr OCs for contraception ≥10 yr OCs for noncontraception ≤4 yr OCs for noncontraception 5 to 9 yr OCs for noncontraception ≥10 yr OCs for both ≤4 yr OCs for both 5 to 9 yr OCs for both ≥10 yr	0.6 0.5 0.3 0.7 NR NR 0.7 0.8 0.2	0.5 to 0.8 0.4 to 0.8 0.2 to 0.6 0.4 to 1.0 0.5 to 1.1 0.5 to 1.4 0.5 to 1.4 (Not plausible for reported OR)	Age, race, family history, pregnancies		4
Riman, 2001[133]	Cases: 193 Controls: 3899	<2 y 2 to 4 y 5 to 9 y ≥10 y	0.96 1.34 1.29 1.16	0.55 to 1.66 0.73 to 2.43 0.68 to 2.43 0.61 to 2.18	Age, parity, BMI, age menopause, HRT	Borderline ovarian tumors versus disease free controls	1
Royar, 2001[141]	Cases: 282 Controls: 533	1 to 2 yr 3 to 5 yr 6 to 10 yr 11 to 15 yr 16 to 20 yr 21+ yr	0.89 0.45 0.37 0.42 0.32 0.12	0.47 to 1.67 0.22 to 0.92 0.22 to 0.79 0.22 to 0.79 0.14 to 0.73 0.03 to 0.53	Parity, family history, breastfeeding , tubal ligation, hysterectomy		1
Riman, 2002[134]	Cases: 655 Controls: 3899	<2y 2 to 4 y 5 to 9 y ≥10 y	0.95 0.88 0.5 0.36	0.71 to 1.26 0.61 to 1.25 0.32 to 0.80 0.22 to 0.59	Age, parity, BMI, age menopause, HRT		1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control (continued)					
Schildkraut, 2002[29]	Cases: 22 Controls: 351	3 to 18 mo 19 to 59 mo >60 mo	0.4 0.3 0.2	0.2 to 0.8 0.2 to 0.7 0.1 to 0.5	Age	High progestin	4
	Cases: 71 Controls: 831	3 to 18 mo 19 to 59 mo >60 mo	0.6 0.5 0.4	0.4 to 0.9 0.3 to 0.7 0.2 to 0.6	Age	High potency estrogen	4
	Cases: 82 Controls: 803	3 to 18 mo 19 to 59 mo >60 mo	0.7 0.7 0.4	0.4 to 1.0 0.4 to 1.0 0.2 to 0.6	Age	Low potency progestins	4
	Cases: 33 Controls: 323	3 to 18 mo 19 to 59 mo >60 mo	0.5 0.8 0.3	0.3 to 1.0 0.5 to 1.5 0.1 to 0.6	Age	Low potency estrogen	4
Walker, 2002[158]	Cases: 692 Controls: 1279	≤48 mo 49+ mo Never OC use	0.72 0.51 1	0.59 to 0.88 0.40 to 0.65	Age, race, parity, BTL	No family history of ovarian cancer	2
	Cases: 33 Controls: 24	≤48 mo use 49+ mo use Never use	0.34 0.07 1	0.08 to 1.55 0.01 to 0.44	Age, race, parity, BTL	Positive family history of ovarian cancer	2
Tung, 2003[152]	Cases: 603 Controls: 607	<1.5 yr 1.6 to 5 yr >5 yr	0.8 0.6 0.4	0.5 to 1.1 0.4 to 0.8 0.3 to 0.6	Age, race, parity, study site, education, tubal ligation		1
McGuire, 2004[115]	Cases: 36 Controls: 568	<1 year 1 to 2 yr 3 to 6 yr ≥ yr	1.00 1.18 0.46 0.22	Reference 0.50 to 2.75 0.16 to 1.28 0.07 to 0.71	Age, race, parity	Cases with BRCA1 mutations (N=36)	4
	Cases: 381 Controls: 568	<1 year 1 to 2 yr 3 to 6 yr ≥7 yr	1.00 0.81 0.48 0.43	Reference 0.55 to 1.19 0.32 to 0.72 0.30 to 0.63	Age, race, parity	Cases without BRCA1 mutations (N=381)	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Mills, 2004[117]	Cases: 256 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.89 0.82 0.62 0.37	0.59 to 1.36 0.55 to 1.21 0.38 to 1.00 0.20 to 0.68	Age, race, breastfeeding		1
	Cases: 182 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.90 0.74 0.67 0.26	0.56 to 1.46 0.46 to 1.18 0.39 to 1.15 0.12 to 0.60	Age, race, breastfeeding	Invasive ovarian cancer (N=182)	1
	Cases: 74 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.93 1.00 0.57 0.67	0.45 to 1.93 0.57 to 2.07 0.23 to 1.42 0.27 to 1.68	Age, race, breastfeeding	Borderline ovarian cancer (N=74)	1
Pike, 2004[130]	Cases: 477 Controls: 660	<5 yr 5 to 9 yr 10+ yr	1.0 0.72 0.48	0.72 to 1.39 0.46 to 1.13 0.29 to 0.78	Age, race, parity, menopausal status, BMI, family history, SES, education, age at last birth, gravidity, OC use		2
Quirk, 2004[132]	Cases: 418 Controls: 836	≤5 yr >5 yr	1.22 1.18	0.84 to 1.79 0.78 to 1.79	Age, parity, family history, history of tubal ligation, noncontraceptive estrogen use		2
Tavani, 2004[147]	Cases: 1031 Controls: 2411	60+ mo <60 mo or never	1 2.01	Reference 1.11 to 3.66	Age, center, year at interview, education		2
Whittemore, 2004[159]	Cases: 147 Controls: 304	<1 year 1 to 2 yr 3 to 5 yr 6+ yr	1.0 1.5 0.69 0.62	Reference 0.82 to 2.9 0.33 to 1.4 0.35 to 1.1	Age, parity, study center	BRCA1 and BRCA2 carriers	4

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control (continued)					
Greer, 2005[91]	Cases: 364 Controls: 529	< 5 yr 5+ yr	0.39 0.22	0.18 to 0.85 0.12 to 0.43	Age, parity, family history, tubal ligation	Compared never users to both androgenic and nonandrogenic OC users	2
	Cases: 405 Controls: 592	< 5 yr 5+ yr	0.58 0.35	0.37 to 0.93 0.2 to 0.61	Age, parity, family history, tubal ligation	Compared never users to androgenic only OC users	2
	Cases: 381 Controls: 761	< 5 yr 5+ yr	0.56 0.73	0.41 to 0.76 0.5 to 1.07	Age, parity, family history, BTL	Compared never users to nonandrogenic only OC users	2
Greer, 2005[92]	Cases: 715 Controls: 1631	Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	0.71 1.04 0.66 0.71 0.97 0.62	0.50 to 0.99 0.66 to 1.63 0.48 to 0.90 0.51 to 0.99 0.64 to 1.47 0.48 to 0.81	Age	Parous women	4
	Cases: 608 Controls: 926	Single episode use: 1 to 6 mo Single episode use: 7 to 12 mo Single episode use: ≥13 mo >1 episode of use: 1 to 6 mo >1 episode of use: 7 to 12 mo >1 episode of use: ≥13 mo	.73 1.0 .63 .75 .96 .56	.54 to .99 .67 to 1.50 .48 to 82 .56 to 1.0 .66 to 1.38 .45 to .71	Age, parity		4
	Cases: 216 Controls: 168	Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.04 1.08 0.84 1.05 1.08 0.68	0.52 to 2.08 0.42 to 2.78 0.46 to 1.56 0.55 to 2.01 0.49 to 2.34 0.42 to 1.11	Age	Nulliparous women	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Tung, 2005[153]	Cases: 558 Controls: 607	0.1 to 1.8 yr (all women) 1.9 to 5.3 yr (all women) 5.4+ yr (all women) 0.1 to 1.8 yr (premenopausal women) 1.9 to 5.3 yr (premenopausal women) 5.4+ yr (premenopausal women) 0.1 to 1.8 yr (postmenopausal women) 1.9 to 5.3 yr (postmenopausal women) 1.9 to 5.3 yr (postmenopausal women)	0.74 0.60 0.45 0.52 0.34 0.28 0.75 0.86 0.58	0.50 to 1.07 0.41 to 0.88 0.30 to 0.69 0.30 to 0.90 0.19 to 0.61 0.15 to 0.52 0.43 to 1.29 0.51 to 1.45 0.31 to 1.08	Age, race, parity, study center, education, BTL, HRT, ovulation variables	Data presented as whole sample and subgrouped by menopausal status (pre/post)	6[152]
Gronwald, 2006[94]	Cases: 150 Controls: 150	≤2 yr >2 yr	0.8 0.2	0.2 to 2.5 0.1 to 0.7	NR	BRCA1 carriers	2
Huusom, 2006[107]	Cases: 202 Controls: 1564	<1 year 1 to 4 yr 5 to 9 yr 10+ yr	1.39 1.00 1.23 0.77	0.77 to 2.54 Reference 0.70 to 2.16 0.45 to 1.34	Age, parity, smoking, breastfeeding , age at first birth, duration of contraception use, intake of milk		2
McLaughlin, 2007[116]	Cases: 128 Controls: 380	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.56 0.42 0.14 0.37	0.28 to 1.10 0.20 to 0.88 0.05 to 0.46 0.19 to 0.72	Parity, breastfeeding , tubal ligation, ethnicity	BRCA2 carriers only	4
	Cases: 799 Controls: 2424	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.67 0.63 0.36 0.47	0.50 to 0.89 0.46 to 0.86 0.25 to 0.53 0.35 to 0.62	Parity, breastfeeding , tubal ligation, ethnicity	All cases and controls have BRCA1 and/or BRCA2 mutations	4
	Cases: 670 Controls: 2043	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.69 0.67 0.41 0.48	0.50 to 0.95 0.47 to 0.96 0.27 to 0.63 0.35 to 0.66	Parity, breastfeeding , tubal ligation, ethnicity	BRCA1 carriers only	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Soegaard, 2007[146]	Cases: 50 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 1.60 0.95 1.32	Reference 0.45 to 5.65 0.20 to 4.49 0.38 to 4.64	Age, parity	Mucinous tumors	3
	Cases: 86 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.88 0.36 0.37	Reference 0.38 to 2.03 0.10 to 1.29 0.14 to 0.99	Age, parity	"Other" tumors	3
	Cases: 554 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.90 0.40 0.40	Reference 0.63 to 1.30 0.24 to 0.66 0.26 to 0.60	Age, parity		3
	Cases: 343 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.80 0.42 0.31	Reference 0.52 to 1.23 0.23 to 0.74 0.18 to 0.51	Age, parity	Serous tumors	3
	Cases: 75 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 1.27 0.15 0.62	Reference 0.53 to 3.05 0.02 to 1.18 0.24 to 1.62	Age, parity	Endometrioid tumors	3
Jordan, 2008[109]	Cases: 627 Controls: 1508	1 to 12 mo 13 to 60 mo 61 to 120 mo 212 to 180 mo 181 to 240 mo >240 mo per year	1.02 0.71 0.52 0.51 0.36 0.22 0.95	0.72 to 1.44 0.53 to 0.95 0.38 to 0.70 0.36 to 0.73 0.23 to 0.58 0.12 to 0.42	Parity, family history, BTL, OC use, hysterectomy, education		1
Lurie, 2008[114]	Cases: 813 Controls: 993	<1 year 1 to 2 yr 3 to 6 yr 7 to 9 yr ≥10 yr	0.74 0.47 0.59 0.49 0.30	0.53 to 1.01 0.33 to 0.67 0.42 to 0.81 0.31 to 0.78 0.19 to 0.47	Age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Moorman, 2008[121]	Cases: 314 Controls: 360	<1 year 1 to <5 yr 5 to 10 yr >10 yr	0.8 0.6 0.5 0.3	0.4 to 1.7 0.4 to 1.0 0.3 to 0.9 0.2 to 0.6	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women	4
	Cases: 582 Controls: 607	<1 year 1 to <5 yr 5 to 10 yr >10 yr	1.1 0.7 0.8 0.9	0.7 to 1.6 0.5 to 1.0 0.6 to 1.2 0.6 to 1.5	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Postmenopausal women	4
Grant, 2010[90]	Cases: 62 Controls: 1086	0 to <1 yr 1 to <5 yr 5+ yr	0.63 0.80 1.13	0.24 to 1.71 0.38 to 1.70 0.56 to 2.26	Age	Serous primary peritoneal cancer	4
	Cases: 495 Controls: 1086	0 to <1 yr 1 to <5 yr 5+ yr	1.14 0.82 0.74	0.79 to 1.65 0.61 to 1.11 0.55 to 1.00	Age	Serous ovarian cancer	4
Ness, 2011[123]	Cases: 869 Controls: 1779	OCs for contraception ≤4 yr OCs for contraception 5 to 9 yr OCs for contraception ≥10 yr OCs for noncontraception ≤4 yr OCs for noncontraception 5 to 9 yr OCs for noncontraception ≥10 yr OCs for both ≤4 yr OCs for both 5 to 9 yr OCs for both ≥10 yr	0.91 0.78 0.52 0.93 1.60 0.53 1.22 0.72 0.40	0.75 to 1.10 0.59 to 1.05 0.35 to 0.76 0.64 to 1.36 0.58 to 4.47 0.11 to 2.62 0.87 to 1.73 0.46 to 1.12 0.25 to 0.67	Age, race, family history, number of pregnancies, infertility		4
Wilailak, 2012[160]	Cases: 330 Controls: 982	1 to 12 months 13 to 24 months 25 to 26 months >36 months	0.86 0.84 0.56 0.43	0.61 to 1.20 0.47 to 1.51 0.28 to 1.14 0.29 to 0.64			1
Cohort							
Hankinson, 1995[98]	Exposed: 592,056 person-yr Unexposed: 599,301 person-yr	Past <1 yr Past 1 to <3 yr Past 3 to <5 yr Past ≥5 yr Current	1.21 1.09 0.8 0.65 1.92	0.8 to 1.86 0.69 to 1.71 0.42 to 1.52 0.4 to 1.05 0.69 to 5.33	Age, parity, smoking, BTL, age at menopause, Quetelet's Index		7
Vessey, 1995[157]	Exposed: 3520 Unexposed: 5881	Up to 48 total mo of use 49 to 96 total mo of use 97+ mo of use	1.0 0.3 0.3	0.4 to 2.5 0.0 to 1.1 0.1 to 0.7	Age, parity		7

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
*Cohort (continued)*						
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	<1 yr 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr Current Former	0.9 0.5 0.6 0.5 0.1 0.5 0.6	0.5 to 1.4 0.4 to 0.8 0.4 to 0.9 0.3 to 1.0 0.01 to 0.6 0.2 to 0.9 0.5 to 0.8	Age, parity, menopausal status, HRT, country		1
		Current Former <1 year 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr per year	0.5 0.7 0.2 0.6 0.7 0.9 NR 0.96	0.2 to 1.6 0.5 to 1.2 0.1 to 1.0 0.3 to 1.2 0.4 to 1.4 0.4 to 2.0 NR 0.91 to 1.0	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer only	1
		<1 yr 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr Current Former	1.2 0.5 0.6 0.3 0.1 0.4 0.6	0.7 to 2.0 0.3 to 0.8 0.3 to 0.9 0.1 to 0.8 0.02 to 0.8 0.2 to 1.0 0.4 to 0.8	Age, parity, menopausal status, HRT, country	Invasive ovarian cancer only	1
Vessey, 2006[156]	Exposed: 301,000 person-years Unexposed: 187,000 person-years	up to 48 mo 48 to 96 mo 97+ mo	1.0 0.3 0.3	0.6 to 1.7 0.1 to 0.6 0.1 to 0.5	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	Ovarian cancer	2
Hannaford, 2007[37]	Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation	<48 mo 49 to 96 mo >96 mo	0.58 0.57 0.38	0.33 to 1.04 0.30 to 1.07 0.16 to 0.88	Age, parity, smoking, social status, ever use of HRT	General practitioner dataset	1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tworoger, 2007[154]	Exposed: 41,125 Unexposed: 54,027	≤3 yr >3 to 5 yr >5 to 10 yr >10 yr	1.12 0.97 0.75 0.62	0.90 to 1.38 0.66 to 1.41 0.54 to 1.05 0.37 to 1.04	Age, parity, menopausal status, BMI, age at menarche, smoking, BTL and HRT use		1
Antoniou, 2009[81]	Exposed: 2415 Unexposed: 766	>0 to 1 yr >1 to 3 yr >3 to 5 yr >5 yr	1.04 0.60 0.41 0.35	0.66 to 1.62 0.35 to 1.03 0.19 to 0.87 0.22 to 0.55	Parity	BRCA1 and BRCA2 mutation carriers	4
	Exposed: 1655 Unexposed: 512	>0 to 1 year >1 to 3 yr >3 to 5 yr >5 yr	1.03 0.51 0.40 0.34	0.64 to 1.65 0.28 to 0.93 0.17 to 0.91 0.21 to 0.54	Parity	BRCA1 mutation carriers	4
	Exposed: 760 Unexposed: 245	>0 to 5 yr >5 yr	1.33 0.59	0.52 to 3.39 0.16 to 2.24	Parity	BRCA2 mutation carriers	4
Dorjgochoo, 2009[88]	Exposed: 12,957 Unexposed: 15,557	<2 yr ≥2 yr	1.58 0.65	0.89 to 2.83 0.29 to 1.44	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	Only reporting for women using OC as others in the cohort used other forms of contraception.	2
Rosenblatt, 2009[138]	Exposed: 352,695 person-years Unexposed: 2,057,377 person-years	1 to 11 mo 12 to 59 mo 60+ mo	1.36 0.82 1.44	0.87 to 2.13 0.47 to 1.41 0.87 to 2.39	Age, parity, use of injectable contraceptives		1
Braem, 2010[85]	Exposed: 8,668 person-years Unexposed: 25,916 person-years	≤5 yr >5 yr per year	0.92 0.47 0.95	0.61 to 1.38 0.30 to 0.76 0.91 to 0.99	Age, parity		2

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tsilidis, 2011[151]	Exposed: 67,870 women OC exposed Unexposed: 100,304 women OC unexposed	≤1 yr 2 to 4 yr 5 to 9 yr ≥10 yr	1.00 1.05 0.80 0.55	Reference 0.79 to 1.38 0.59 to 108 0.41 to 0.75	Age, parity, menopausal status, BMI, smoking, center, unilateral oophorectomy, hysterectomy, menopausal hormones, age at menarche		3
Yang, 2012[162]	Exposed: 192,836 women OC exposed Unexposed: 132,923 women OC unexposed	1 to 4 yr 5 to 9 yr ≥10 yr	0.82 0.78 0.56	0.67 to 1.00 0.62 to 0.98 0.42 to 0.75	Age, parity, menopausal hormone therapy		1

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; OC = oral contraceptive; OR = odds ratio; NR = not reported; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code:1=Included in this meta-analysis; 2=Excluded due to less than three duration categories; 3=Excluded due to never use is not the reference group; 4=Excluded due to odds ratios only provided for subpopulations; 5=Excluded due to odds ratios only provided per year of OC use; 6=Excluded due to study is grouped with another included article also reporting duration data; 7=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

Table 7 and Figure 12 show the odds ratios for the meta-analysis of duration of OC use. These findings indicate a significant duration-response relationship between OC use and ovarian cancer incidence, with higher levels of protection afforded to women who use OCs for longer duration. Women using oral contraceptives for 10 or more years show a reduction in ovarian cancer incidence of more than 50 percent. There is no evidence of heterogeneity. The estimated value of σ is 0.15.

Table 7. Estimated odds ratios by duration of OC use (ovarian cancer incidence)

Duration Interval	Odds Ratio (95% Confidence Interval)	P-Value
1–12 months	0.91 (0.78 to 1.07)	0.2504
13–60 months	0.77 (0.66 to 0.89)	0.0014
61–120 months	0.65 (0.55 to 0.77)	<0.0001
>120 months	0.43 (0.37 to 0.51)	<0.0001

Figure 12. Impact of duration of OC use on ovarian cancer incidence
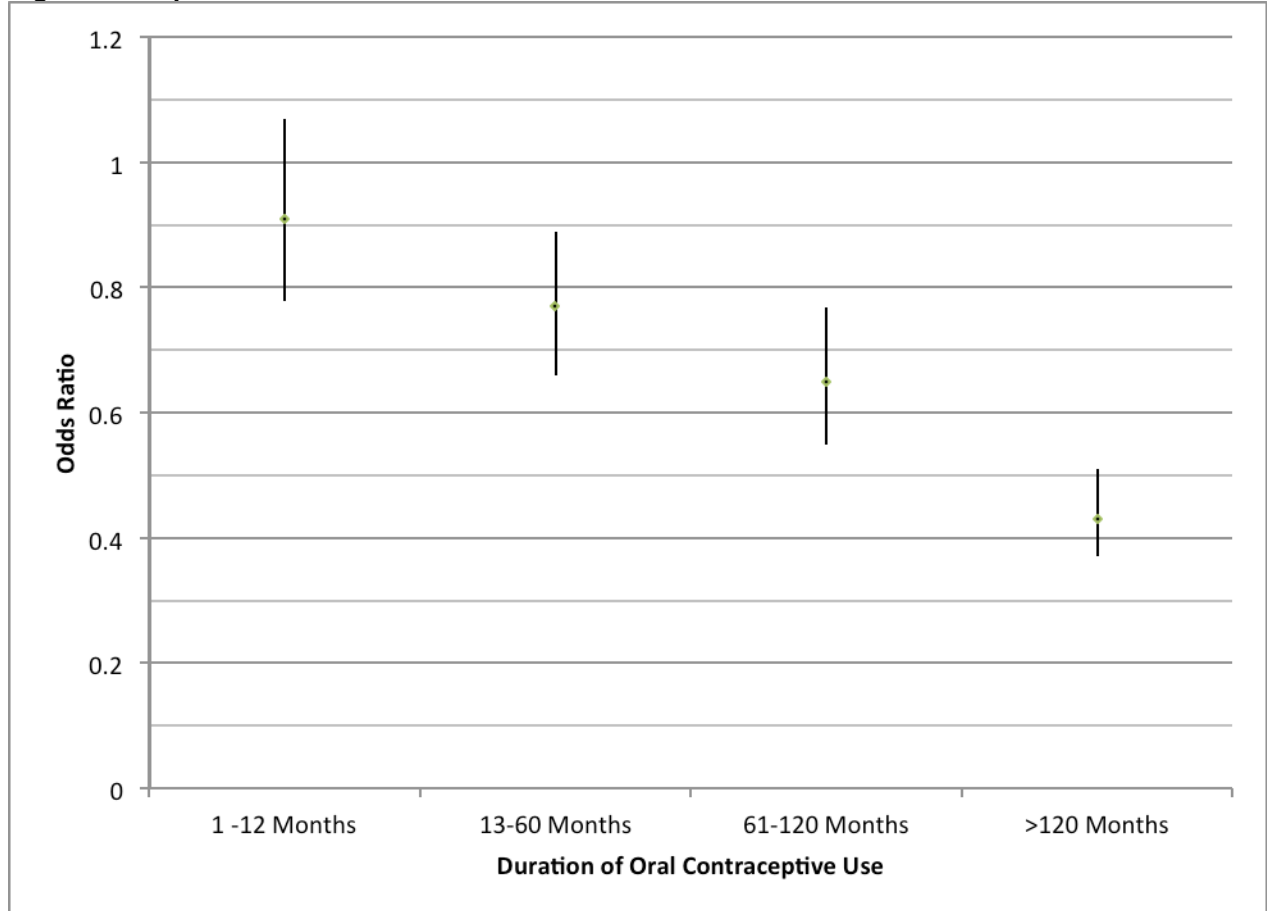
Pooled Analyses

Four pooled analyses[21,23,105,120] reported on duration of OC use but did not meet criteria for inclusion in the meta-analysis. The three largest of these studies reported a significantly lower incidence of ovarian cancer following longer duration of OC use.[21,23,120] The one remaining study[105] examined only OC use of less than or greater than 1 year and did not identify a clear trend.

Sensitivity Analyses

We repeated our analyses excluding the 10 studies not conducted within the United States. The estimates for the remaining 5 studies (3 case-control and 2 cohort) were 0.84 (95% CI, 0.67 to 1.05) for <1 year duration, 0.72 (CI, 0.59 to 0.89) for 1 to 5 years' duration, 0.64 (CI, 0.51 to 0.81) for >5 to 10 years' duration, and 0.42 (CI, 0.32 to 0.56) for >10 years' duration.

We also performed analyses for studies published from 1990 forward (18 studies, 13 case-control and 5 cohort). The estimates were 0.93 (95% CI, 0.81 to 1.06) for <1 year duration, 0.81 (CI, 0.72 to 0.91) for 1 to 5 years' duration, 0.65 (CI, 0.56 to 0.75) for >5 to 10 years' duration, and 0.44 (CI, 0.39 to 0.51) for >10 years' duration.

We also conducted a sensitivity analysis in which we included the large pooled analysis by Beral et al.[21] but excluded the individual studies from our meta-analysis that had been included in their pooled analysis.[87,110,118,125,133,141] The estimates were 0.91 (95% CI, 0.75 to 1.09) for <1 year duration, 0.75 (CI, 0.63 to 0.91) for 1 to 5 years' duration, 0.57 (CI, 0.47 to 0.69) for >5 to 10 years' duration, and 0.43 (CI, 0.35 to 0.51) for >10 years' duration, similar to the estimates from the main meta-analysis.

Age at First OC Use

Six studies[110,114,121,125,141,144,145] were included in the primary meta-analysis examining the effect of age at first OC use on ovarian cancer incidence. Of these, 5 were case-control studies representing 3,552 cases and 4,713 controls, and 1 was a cohort study representing 103,552 participants. Four studies were rated good quality and 2 fair quality. Abstracted data not included in this analysis are specified (with rationale) in Table 8. Reasons for exclusion from this analysis included the following: reporting data for fewer than three age categories; providing odds ratios for subpopulations only; or in one instance,[100] not meeting publication date criteria to include in the primary meta-analysis.

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Harlow, 1991[100]	Cases: 194 Controls: 193	<21 22 to 26 >26	0.8 0.7 0.8	0.4 to 1.8 0.3 to 1.4 0.4 to 1.4	Age, parity, religion		4
Ness, 2000[125]	Cases: 767 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	0.6 0.6 0.5 0.8 0.8	0.4 to 0.8 0.5 to 0.8 0.4 to 0.8 0.5 to 1.2 0.4 to 1.3	Age, race, family history, number of pregnancies		1
	Cases: 616 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	1.0 1.0 0.8 0.9 0.8	Reference 0.7 to 1.4 0.5 to 1.2 0.5 to 1.7 0.4 to 1.7	Age, race, family history, number of pregnancies	Invasive ovarian cancer (N=616)	1
	Cases: 151 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	1.0 1.0 0.5 0.8 0.7	Reference 0.6 to 1.6 0.2 to 1.2 0.3 to 2.5 0.2 to 2.7	Age, race, family history, number of pregnancies	Borderline ovarian cancer (N=151)	1
Siskind, 2000[145]	Cases: 794 Controls: 853	<20 20 to 24 25 to 29 30 to 34 >35	1.0 1.34 1.82 2.1 1.66	Reference 0.82 to 2.2 0.96 to 3.4 0.98 to 4.6 0.68 to 4.0	Duration of use, overall and before 1st pregnancy, age at first use, time since last use		1
Royar, 2001[141]	Cases: 282 Controls: 533	14 to 16 17 to 19 20 to 24 25 to 29 30+	0.31 0.18 0.20 0.40 0.69	0.12 to 0.80 0.08 to 0.40 0.10 to 0.45 0.21 to 0.76 0.42 to 1.11	Parity, family history, breastfeeding, tubal ligation, hysterectomy		1

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
			*Case-Control (continued)*				
Greer, 2005[91]	Cases: 405 Controls: 592	<20 >20	0.42 0.51	0.23 to 0.75 0.32 to 0.79	age, parity, family history, tubal ligation	Compared never users to androgenic only OC users	2, 3
	Cases: 381 Controls: 761	<20 ≥20	0.54 0.63	0.34 to 0.85 0.47 to 0.85	Age, parity, family history, BTL	Compared never users to nonandrogenic only OC users	2, 3
	Cases: 364 Controls: 529	<20 20+	0.26 0.28	0.13 to 0.52 0.13 to 0.58	Age, parity, family history, tubal ligation	Compared never users to both androgenic and nonandrogenic OC users	2, 3
Lurie, 2008[114]	Cases: 813 Controls: 993	<20 20 to 24 25 to 29 ≥30	0.39 0.59 0.54 0.58	0.27 to 0.56 0.44 to 0.79 0.37 to 0.79 0.39 to 0.86	Age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1
Moorman, 2008[121]	Cases: 314 Controls: 360	<20 20 to 24 25 to 29 >29	0.5 0.5 0.4 1.2	0.3 to 0.8 0.3 to 0.9 0.2 to 1.0 0.3 to 4.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women	1
	Cases: 582 Controls: 607	<20 20 to 24 25 to 29 >29	0.9 0.8 0.8 0.9	0.5 to 1.3 0.6 to 1.1 0.5 to 1.2 0.6 to 1.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Postmenopausal women	1

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort							
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	<20 20 to 24 25+	0.5 0.4 0.7	0.3 to 1.0 0.3 to 0.7 0.5 to 1.1	Age, parity, menopausal status, HRT, country	Invasive ovarian Cancer only	1
	Exposed: 75,533 Unexposed: 28,019	<20 20 to 24 25+	0.4 0.8 0.8	0.2 to 0.9 0.5 to 1.4 0.4 to 1.4	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer only	1
	Exposed: 75,533 women exposed Unexposed: 28,019 women unexposed	<20 yr 20 to 24 25+	0.6 0.7 1.0	0.3 to 1.0 0.5 to 1.1 0.6 to 1.5	Age, parity, menopausal status, HRT, country, duration of use		1
Antoniou, 2009[81]	Exposed: 2415 Unexposed: 766	Never <20 20 to 24 ≥25	1.72 1.00 0.88 0.96	1.05 to 2.82 Reference 0.51 to 1.50 0.53 to 1.73	Parity	BRCA1 and BRCA2 mutation carriers	2
	Exposed: 1655 Unexposed: 512	Never <20 20 to 24 ≥25	1.75 1.00 0.86 0.87	1.05 to 2.90 Reference 0.49 to 1.50 0.46 to 1.65	Parity	BRCA1 mutation carriers	2
	Exposed: 760 Unexposed: 245	Never <20 >20	1.25 1.00 1.46	0.31 to 5.08 Reference 0.35 to 6.01	Parity	BRCA2 mutation carriers	2

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Dorjgochoo, 2009[88]	Exposed: 12,957 Unexposed: 15,557	<29 ≥29	1.26 0.99	0.64 to 2.46 0.51 to 1.92	Parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods		3
Braem, 2010[85]	Exposed: 8,668 person-years Unexposed: 25,916 person-years	≤40 >40	1.0 1.28	Reference 0.68 to 2.43	Age, parity, duration of OC use		3

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = intrauterine device; NR=not reported; OC = oral contraceptive; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1=Included in this meta-analysis; 2=Excluded due to odds ratios provided for subpopulations only; 3=Excluded due to less than three age-at-first-use categories provided; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

Table 9 lists the odds ratios for the meta-analysis of age at first OC use. The results show a relatively strong relationship between age at first use and ovarian cancer incidence, although confidence intervals overlap. If there is an effect of earlier age, it is unclear whether the relation is linear or whether there is a threshold effect (i.e., less protection in women who start OCs after age 30). Unfortunately, most studies did not control for duration of use. This potential confounder lessens the strength of this finding.

Table 9. Estimated odds ratios by age at first OC use (ovarian cancer incidence)

Age Interval	Odds Ratio (95% Confidence Interval)	P-Value
< 20 years	0.63 (0.45 to 0.89)	0.018
20–24 years	0.71 (0.51 to 0.99)	0.044
25–30 years	0.67 (0.46 to 0.99)	0.045
> 30 years	0.89 (0.60 to 1.32)	0.489

Pooled Analyses

Two pooled analyses[21,23] reported on age at first use, with none reporting significant trends. One study[21] reported that there was no heterogeneity in the decline in relative risk of ovarian cancer with increasing duration of use across women who started OCs at different ages.

Sensitivity Analyses

We repeated our analyses excluding the three studies not conducted within the United States. The estimates for the remaining three studies, all case-control, were 0.70 (95% CI, 0.27 to 1.75) for age <20 years, 0.86 (CI, 0.34 to 2.20) for age 20 to <24 years, 0.83 (CI, 0.30 to 2.27) for age 24 to <30 years, and 0.93 (CI, 0.33 to 1.67) for age ≥30 years.

We also performed analyses for studies published from 1990 forward (7 studies, 6 case-control and 1 cohort). The estimates were 0.64 (95% CI, 0.47 to 0.87) for age <20 years, 0.71 (CI, 0.53 to 0.96) for age 20 to <24 years, 0.67 (CI, 0.48 to 0.95) for age 24 to <30 years, and 0.89 (CI, 0.63 to 1.28) for age ≥30 years.

Time Since Last OC Use

Eight studies[37,110,114,121,125,133,134,141,154] were included in this meta-analysis examining the effect of time since last OC use on ovarian cancer incidence. Of these, 5 were case-control studies representing 3606 cases and 7759 controls, and 3 were cohort studies representing 198,704 participants and 1,083,000 person years. Four studies were rated good quality and 4 fair quality. Abstracted data not included in this analysis are specified (with rationale) in Table 10. Reasons for exclusion from this analysis included the following: using fewer than three comparisons; presenting categories that were not amenable to a combined analysis; and reporting time since last use data from the same study as another article already included in the analysis (Table 10). None of the three pooled analyses reporting on time since last use met inclusion criteria for meta-analysis.

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	1 to 24 mo 25 to 84 mo 85 to 132 mo 133+ mo	0.69 0.76 0.88 0.44	0.26 to 1.82 0.35 to 1.68 0.38 to 2.05 0.22 to 0.99	Age, center, years of disease, live births	High dose	4
		1 to 24 mo 25 to 84 mo 85 to 132 mo 133+ mo	1.45 0.70 0.77 0.48	0.74 to 2.85 0.28 to 1.75 0.27 to 2.21 0.16 to 1.39	Age, center, years of disease, live births	Low dose	4
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	<15 yr 15 to 19 yr 20+	0.4 0.5 0.8	0.2 to 0.8 0.3 to 1.0 0.4 to 1.5	Parity, hysterectomy, BTL, removal of one ovary, race, family history, age, geographic area		4
Wittenberg, 1999[161]	Cases: 322 Controls: 426	≤5 yr 6 to 15 yr 15+ yr	0.6 0.6 1.2	0.2 to 2.2 0.2 to 1.7 0.5 to 2.9	Age, parity, duration of use	Mucinous ovarian cases	4
	Cases: 322 Controls: 426	≤5 yr 6 to 15 yr 15+ yr	0.6 0.6 1.1	0.3 to 1.3 0.3 to 1.0 0.7 to 1.7	Age, parity, duration of use	Nonmucinous cases	4
Huusom, 2000[107]	Cases: 202 Controls: 1564	0 to 10 yr 11 to 20 yr 21+ yr	1 1.59 1.63	Reference 0.80 to 3.16 0.72 to 3.70	Age, childbirth, additional births, first birth, breastfeeding, duration of use, smoking, intake of milk	Borderline ovarian cancer	2
Ness, 2000[125]	Cases: 767 Controls: 1367	<10 yr 10 to 19 yr 20 to 29 yr ≥30 yr	0.4 0.6 0.6 1.0	0.3 to 0.6 0.4 to 0.8 0.5 to 0.8 0.6 to 1.4	Age, number of pregnancies, family history of ovarian cancer, race		1
Sanderson, 2000[143]	Cases: 276 Controls: 388	Never or < 3 mo <10 yr 10+ yr	1 0.7 0.8	Reference 0.4 to 1.3 0.5 to 1.2	Age, parity		2
Siskind, 2000[145]	Cases: 794 Controls: 853	<1 yr 1 to <5 yr 5 to <10 yr 10 to <20 yr 20+ yr	0.78 1.46 1.02 1.4 1	0.30 to 2.0 0.58 to 3.6 0.48 to 2.2 0.91 to 2.1 Reference			3

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Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Chiaffarino, 2001[87]	Cases: 1031 Controls: 2411	<10 yr ≥10 yr	0.5 0.5	0.2 to 1.1 0.2 to 1.2	Age, parity, family history, center, education		2
Royar, 2001[141]	Cases: 282 Controls: 533	0 yr 1 to 5 yr 6 to 10 yr 11 to 20 yr 21+ yr	0.17 0.34 0.49 0.45 0.52	0.07 to 0.43 0.16 to 0.73 0.23 to 1.03 0.28 to 0.73 0.28 to 0.96	Parity, breastfeeding, family history, BTL, hysterectomy		1
Riman, 2002[134]	Cases: 655 Controls: 3899	<15 yr 15 to 19 yr 20 to 24 yr 25+ yr	0.45 0.66 0.71 0.9	0.27 to 0.73 0.43 to 0.99 0.51 to 0.99 0.27 to 1.22	Age, parity, BMI, age of menopause		1
Riman, 2001[133]	Cases: 193 Controls: 3899	<15 yr 15 to 19 yr 20 to 24 yr 25+ yr	1.16 1.67 0.92 1.14	0.45 to 3.02 0.74 to 3.80 0.43 to 1.94 0.62 to 2.10	Age, parity, BMI, age of menopause, ever use of unopposed estrogen, estrogens with cyclic progestins, estrogens with continuous progestins	Borderline ovarian cancer	1
Lurie, 2008[114]	Cases: 813 Controls: 993	≤5 yr 6 to 9 yr 10 to 19 yr 20 to 29 yr 30+yr	0.19 0.33 0.47 0.64 0.72	0.12 to 0.30 0.16 to 0.67 0.33 to 0.68 0.48 to 0.86 0.49 to 1.06	Formulation potency and duration of use, age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1
Moorman, 2008[121]	Cases: 314 Controls: 360	<5 yr 5+ to <10 yr 10 to 20 yr >20 yr	0.3 0.4 0.6 0.8	0.2 to 0.6 0.2 to 0.9 0.3 to 1.0 0.5 to 1.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women only	1

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort							
Hankinson, 1995[98]	Exposed: 592,056 person-years <u>Unexposed</u>: 599,301 person-years	Current <5 yr 5 to <10 yr 10 to <15 yr 15+ yr	1.86 0.86 0.77 1.01 1.11	0.67 to 5.19 0.48 to 1.56 0.48 to 1.26 0.66 to 1.54 0.68 to 1.81	Age, parity, BTL, age at menarche, age at menopause, smoking, Quetelet's index		5
Vessey, 1995[157]	Exposed: 3520 <u>Unexposed</u>: 5881	≤48 mo 49 to 96 mo 97+ mo	0.1 0.3 0.8	0 to 0.5 0 to 1.1 0.4 to 1.7	Age, parity		4
Kumle, 2004[110]	Exposed: 75,533 <u>Unexposed</u>: 28,019	0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.5 0.5 0.6 0.6	0.3 to .08 0.2 to 0.9 0.3 to 1.0 0.3 to 1.0	Age, parity, use of HRT, menopause, country	Invasive ovarian cancer	1
		0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.5 0.7 0.6 0.5	0.3 to 0.7 0.4 to 1.1 0.45 to 0.9 0.3 to 0.9		All ovarian cancers	1
		0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.4 1.1 0.6 0.4	0.2 to 0.9 0.6 to 2.1 0.3 to 1.3 0.2 to 1.0		Borderline ovarian cancer	1
Hannaford, 2007[37]	Exposed: 744,000 person-years <u>Unexposed</u>: 339,000 person-years	Current and <60 mo 61 to 120 mo 121 to 180 mo 181 to 240 mo 241+ mo	0.5 0.42 0.28 0.79 0.61	0.24 to 1.01 0.18 to 0.97 0.11 to 0.71 0.38 to 1.67 0.24 to 1.52	Age, parity, smoking, social class, HRT use	Main dataset	1

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tworoger, 2007[154]	Exposed: 41,125 women years Unexposed: 54,027 women years	Current to <5 yr >5 yr to 10 yr >10 to 15 yr >15 to 20 yr >20 to 25 yr >25 to 30 yr >30 yr	1.05 0.53 0.9 0.88 1.15 1.24 1.13	0.60 to 1.83 0.30 to 0.94 0.61 to 1.33 0.61 to 1.27 0.81 to 1.63 0.86 to 1.80 0.71 to 1.80	Age, BMI, parity, BTL, smoking, age at menarche, age at menopause, duration of HRT use		1
Dorjgochoo 2009[88]	Exposed: 12,957 Unexposed: 15,557	Last used <19 yr ago Last used 19+ yr ago	0.99 1.21	0.48 to 2.01 0.64 to 2.29	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods		2

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval;
HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; NR=not reported; OC = oral contraceptive; OR = odds ratio; yr=year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Unless otherwise presented, never use is the reference category with an OR=1.0.
[c]Meta-analysis code: 1=Included in this meta-analysis; 2=Excluded due to study used fewer than three comparisons; 3=Excluded due to categories presented are not amenable to combined analysis; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward; 5=Excluded due to grouping with another included article from the same study also reporting duration data.

Table 11 lists the odds ratios for the meta-analysis of time since last OC use. The individual odds ratios show no evidence of a relationship as a function of time since last use. However, a test for differences between the four odds ratios gives a chi-square of 14.0 for 3 degrees of freedom, p=0.002.

Table 11. Estimated odds ratios by time since last OC use (ovarian cancer incidence)

Time Interval	Odds Ratio (95% Confidence Interval)	P-value
0–10 years	0.41 (0.34 to 0.50)	<0.0001
10–20 years	0.65 (0.56 to 0.74)	<0.0001
20–30 years	0.92 (0.76 to 1.12)	0.3692
>30 years	0.79 (0.58 to 1.12)	0.1036

We then ran an analysis using the midpoint of each interval as the estimate of the time for each subgroup. This resulted in the following model:

OR = Exp(-8729 + 0.0217 * years)

The slope was highly significant (p=0.0013). There is significant heterogeneity. The estimated value of σ is 0.25. The t-value is 4.81 for 8 degrees of freedom, p<0.0013. The value of σ is larger than many of the standard errors for the observed odds ratios.

Pooled Analyses

Among the three pooled analyses that reported time since last OC use, one study[21] reported that the relative risk of developing ovarian cancer was lower with more recent OC use. Women who had used OCs less than 10 years previously had a 29-percent decline in the risk of ovarian cancer for every 5 years of OC use, while those who last used OCs 20 to 29 years previously had a 15-percent reduction in risk. A second study[23] reported on the time since last OC use but found no clear trend in ovarian cancer risk, while a third study[24] found that risk reduction associated with OC use persisted regardless of the time elapsed since last use.

Sensitivity Analyses

We repeated our analyses excluding the five studies without patients from the United States. The estimates for the remaining four studies, three case-control and one cohort, were 0.40 (95% CI, 0.26 to 0.62 for use within the last 10 years, 0.66 (CI, 0.45 to 0.98) for use 10 to 20 years ago, 0.95 (CI, 0.58 to 1.56) for use 20 to 30 years ago, and 0.83 (CI, 0.46 to 1.50) for use >30 years ago.

We also performed analyses for studies published from 1990 forward (12 studies, 8 case-control and 4 cohort). The estimates were 0.45 (95% CI, 0.37 to 0.56 for use within the last 10 years, 0.70 (CI, 0.57 to 0.86) for use 10 to 20 years ago, 0.85 (CI, 0.63 to 1.14) for use 20 to 30 years ago and 0.88 (CI, 0.61 to 1.27) for use >30 years ago.

OC Formulations

Estrogen

Six studies[29,113,125,130,141,143] were included in this meta-analysis examining the effect of estrogen formulation on ovarian cancer incidence. All were case-control studies, and represented 2607 cases and 6400 controls. Five studies were rated good quality and one fair quality. We excluded one cohort study from the analysis[110] that did not contain dose information (Table 12).

The definition of a low-estrogen OC formulation varied among the six studies included in the meta-analysis, with three studies using a cutoff of 35 mcg estradiol,[29,113,130] two studies using a cutoff of 50 mcg estradiol,[125,143] and one study[141] reporting results for three separate doses of estradiol (20–34 mcg, 35–44 mcg, and ≥45 mcg).

Five studies[113,125,130,141,143] calculated odds ratios separately for high-dose or low-dose estrogen-containing OCs compared with never use. Of these, two studies[125,130] presented estrogen dose results stratified by low or high progestin dose.

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	High dose Low dose	0.68 0.81	0.44 to 1.05 0.051 to 1.29	Age, parity, center, year of diagnosis		4
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	Norethindrone Norethindrone acetate Norethynodrel Ethynodiol diacetate Norgestrel Any mestranol >50mcg mestranol 50mcg mestranol Any ethinyl estradiol ≥50mcg ethinyl estradiol	0.5 0.7 0.9 1.3 0.2 0.6 0.9 0.7 0.5 0.4	0.3 to 0.9 0.2 to 3.2 0.2 to 3.2 0.5 to 3.1 0.1 to 0.7 0.4 to 1.0 0.5 to 1.8 0.2 to 2.0 0.2 to 1.0 0.1 to 1.0	Age, race, parity, family history, hysterectomy, removal of one ovary, geographic area, interview year	Formulation data refer only to use for >3 yr	4
Beard, 2000[83]	Cases: 103 Controls: 103	Any oral OC (as reported above) Substantial OC Any steroidal estrogen Substantial steroidal estrogen Any nonsteroidal estrogen Any progesterone Substantial progesterone	1.1 0.8 0.9 1.0 0.5 1.2 4.0	0.6 to 2.3 0.4 to 1.7 0.5 to 1.7 0.4 to 2.3 0.2 to 0.9 0.5 to 2.8 0.4 to 36	Crude		3
Ness, 2000[125]	Cases: 767 Controls: 1367	High estrogen/high progestin High estrogen/low progestin Low estrogen/high progestin Low estrogen/low progestin	0.5 0.7 0.6 0.5	0.3 to 0.7 0.3 to 1.8 0.3 to 1.3 0.3 to 0.6	Age, race, family history, number of pregnancies		1, 2
	Cases: 616 Controls: 1367	High estrogen/high progestin Low estrogen/low progestin	1.0 1.2	Reference 0.8 to 1.9	Age, race, family history, number of pregnancies	Invasive ovarian cancer N=616	1, 2
	Cases: 151 Controls: 1367	High estrogen/high progestin Low estrogen/low progestin	1.0 0.7	Reference 0.3 to 1.3	Age, race, family history, number of pregnancies	Borderline ovarian cancer N=151	1, 2
Sanderson, 2000[143]	Cases: 276 Controls: 388	Low dose estrogen Low and high dose estrogen High dose estrogen Unknown	0.6 0.6 0.8 0.9	0.3 to 1.1 0.3 to 1.3 0.5 to 1.2 0.6 to 1.5	Age, parity		1

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control (continued)					
Royar, 2001[141]	Cases: 282 Controls: 533	Low dose ≤35mcg ethinyl estradiol High dose >35mcg ethinyl estradiol	0.20 0.65	0.08 to 0.47 0.40 to 1.05	Parity, family history, breastfeeding, tubal ligation, hysterectomy		1
		Different formulations Avg daily ethinyl estradiol 20 to 34mcg Avg daily ethinyl estradiol 35 to 44 mcg Avg daily ethinyl estradiol 45 mcg or more No ethinyl estradiol or unknown ethinyl estradiol	0.46 0.14 0.33 0.57 0.55	0.30 to 0.71 0.06 to 0.36 0.15 to 0.72 0.36 to 0.90 0.34 to 0.89			
Schildkraut, 2002[29]	Cases: 390 Controls: 2865	High estrogen Low estrogen Nonuser	1.0 .07 2.0	Reference 0.4 to 1.2 1.5 to 2.7			1, 2
	Cases: 390 Controls: 2865	High progesterone Low progesterone Nonuser	1.0 2.2 3.0	Reference 1.3 to 3.9 1.9 to 4.7	Age, parity, duration in months of use, latency, estrogen level		1, 2
	Cases: 390 Controls: 2865	High/high High/low Low/high Low/low Nonusers	1.0 0.0 2.1 1.6 2.9	Reference 0.0 to not estimable 1.2 to 3.7 0.9 to 3.0 1.8 to 4.5	Age, parity, latency, duration of use in months		1, 2
Pike, 2004[130]	Cases: 147 Controls: 304	High estrogen + high progestin High estrogen + low progestin Low estrogen + high progestin Low estrogen + low progestin Unknown	0.88 0.94 0.66 0.95 0.96	0.81 to 0.97 0.88 to 1.0 0.36 to 1.21 0.92 to 0.99 0.90 to 1.02	Age, race, parity, menopausal status, BMI, family history, SES, education, age at last birth, gravidity, OC use		1, 2

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
*Case-Control (continued)*
Lurie, 2007[113]	Cases: 745 Controls: 943	Any estrogen and high progestin Any estrogen and low progestin Various potency Never use High estrogen and any progestin Low estrogen and any progestin Various potency	0.54 0.41 0.22 1.00 0.61 0.33 0.45	0.38 to 0.75 0.18 to 0.94 0.12 to 0.41 Reference 0.42 to 0.89 0.21 to 0.52 0.24 to 0.85	Age, race, menopausal status, family history, center, education, gravidity, age at last pregnancy, tubal ligation, type of menopause, age at menopause, use of menopausal hormones, duration of OC use, time since first OC use		1, 2
	Cases: 745 Controls: 943	High estrogen and high progestin High estrogen and low progestin Low estrogen and high progestin Low estrogen and low progestin Various potencies	0.62 0.55 0.45 0.19 0.26	0.43 to 0.92 0.19 to 1.59 0.28 to 0.72 0.05 to 0.75 0.15 to 0.44	Age, race, menopausal status, center, education, gravidity, age at last pregnancy, tubal ligation, type of menopause, use of menopausal hormones, duration of OC use, time since first OC use		1, 2
*Cohort*
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	Progestin only Combination OCs Progestin only and combination OCs	0.3 0.5 0.7	0.1 to 1.1 0.3 to 0.8 0.4 to 1.0	Age, parity, menopausal status, HRT, country	Invasive ovarian cancer	3
		Progestin only Combination OCs Progestin only and combination OCs	0.5 0.5 0.7	0.2 to 1.2 0.4 to 0.7 0.5 to 1.0	Age, parity, menopausal status, HRT, country	All	3
		Progestin only Combination OCs Progestin only and combination OCs	1.0 0.6 0.9	0.4 to 2.9 0.3 to 1.0 0.5 to 1.5	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer	3

Avg = average; BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; EE = ethinyl estradiol; HRT = hormone replacement therapy; IUD = intrauterine device; NR=not reported; OC = oral contraceptive; OR = odds ratio; yr=year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Unless otherwise presented, never use is the reference category with an OR=1.0.
[c]Meta-analysis code: 1=Included in estrogen formulation meta-analysis; 2=Included in progestin formulation meta-analysis; 3=Excluded due to study contained no dose information; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

Figures 13 to 15 show the odds ratios for the meta-analyses on estrogen formulation. Compared with never use, the odds ratio for high-dose estrogen-containing OCs was 0.69 (95% CI, 0.53 to 0.91) (Figure 13). There was significant heterogeneity, with a Q-value of 16.44 for 4 degrees of freedom, p=0.002. Compared with never use, the odds ratio for low-dose estrogen-containing OCs was 0.50 (CI, 0.30 to 0.85) (Figure 14). There was significant heterogeneity, with a Q-value of 51.243 for 3 degrees of freedom, p≤0.001. One additional study calculated a direct odds ratio comparing high-dose to low-dose estrogen OC use.[29] When this was combined with the other five included studies, the odds ratio was 1.25 (CI, 0.95 to 1.64) (Figure 15). These results do not suggest a relationship between estrogen dose and ovarian cancer incidence. There was some evidence of heterogeneity, with a Q-value of 10.611 for 5 degrees of freedom, p=0.06.

Figure 13. Forest plot for high-dose estrogen (ovarian cancer incidence)
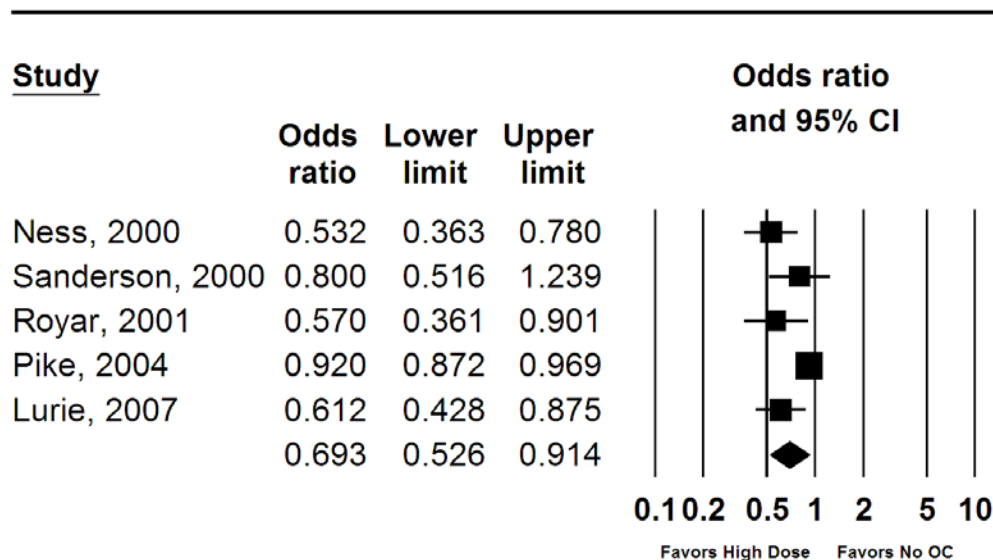
CI = confidence interval; OC = oral contraceptive

Figure 14. Forest plot for low-dose estrogen (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Ness, 2000	0.517	0.378	0.707	
Sanderson, 2000	0.600	0.313	1.149	
Royar, 2001	0.228	0.126	0.410	
Pike, 2004	0.949	0.915	0.984	
Lurie, 2007	0.410	0.262	0.640	
	0.503	0.298	0.850	

0.1 0.2 0.5 1 2 5 10

Favors Low Dose   Favors No OC
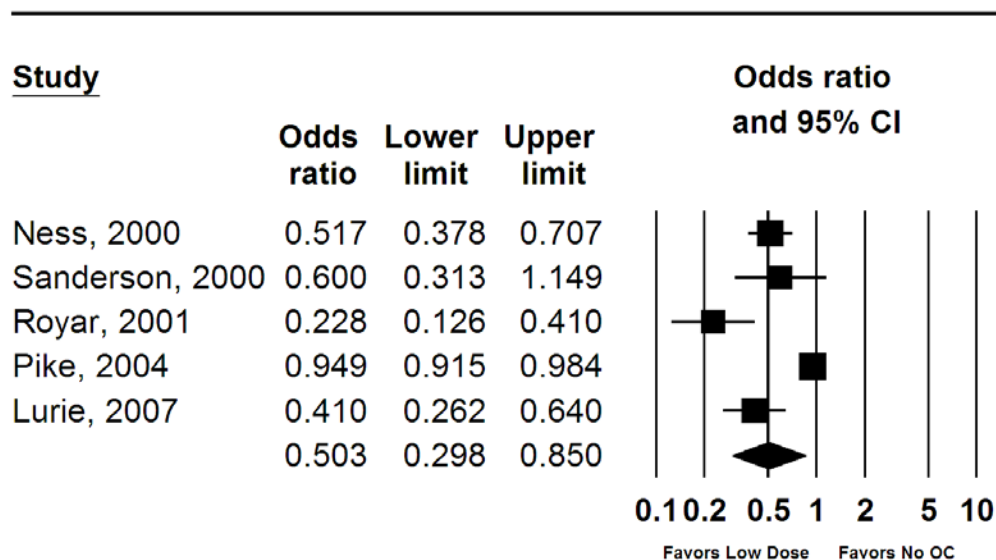
CI = confidence interval; OC = oral contraceptive

Figure 15. Forest plot for high-dose versus low-dose estrogen (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Ness, 2000	1.029	0.627	1.688	
Sanderson, 2000	1.333	0.603	2.949	
Royar, 2001	2.505	1.187	5.287	
Schildkraut, 2002	1.429	0.825	2.475	
Pike, 2004	0.969	0.909	1.033	
Lurie, 2007	1.492	0.842	2.643	
	1.246	0.946	1.640	

0.1 0.2 0.5 1 2 5 10

Favors High Dose Favors Low Dose
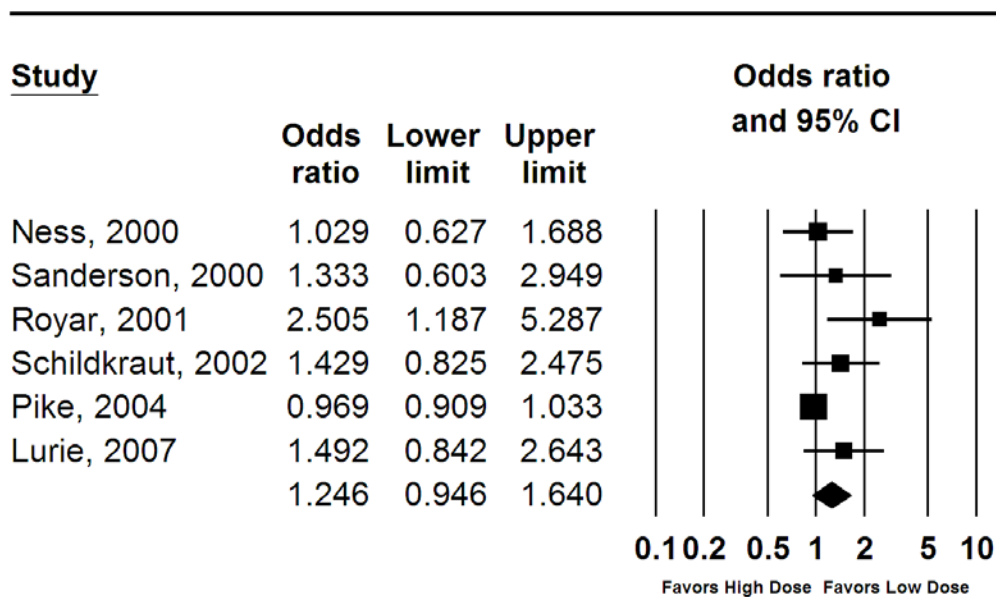
CI = confidence interval

Sensitivity Analyses

Analyses were repeated excluding one case-control study that was not performed within the United States. After this exclusion, a meta-analysis of the remaining five case-control studies revealed an odds ratio for high-dose estrogen-containing OC use of 0.69 (95% CI, 0.53 to 0.91), and for low-dose estrogen-containing OC use, an odds ratio of 0.60 (CI, 0.37 to 0.98). The odds ratio comparing high-dose with low-dose estrogen-containing OCs was 1.04 (CI, 0.90 to 1.21).

We also conducted analyses of studies published from 1990 forward (eight case-control studies). The odds ratio for high-dose estrogen-containing OC use was 0.68 (95% CI, 0.53 to 0.87), and for low-dose estrogen-containing OC use, an odds ratio of 0.55 (CI, 0.37 to 0.83). The odds ratio comparing high-dose to low-dose estrogen-containing OCs was 1.19 (CI, 0.93 to 1.51).

Progestin

Four studies[29,113,125,130] were included in this meta-analysis examining the effect of progestin formulation on ovarian cancer incidence (Table 12). Of these, all four were case-control studies representing 2049 cases and 5479 controls. All four studies were rated good quality. We excluded data from this analysis from reports that did not use progesterone-dosing terminology that facilitated a combined analysis.

The four included studies classified progesterone potency based on a subnuclear vacuolation assay and a delay of menses test. These methods have previously been described by Dickey and Stone,[163] who classified low-dose progestin OCs as those containing a relative potency cutoff of 0.2 mg norgestrel or less. Three studies stratified progestin results based on low or high estrogen dose.[113,125,130]

Figures 16 to18 show the odds ratios for the meta-analyses on progestin formulation. The odds ratio was 0.65 (95% CI, 0.44 to 0.95) for the three case-control studies of ovarian cancer incidence as a function of high-dose progestin (Figure 16). There was significant heterogeneity, with a Q-value of 14.97 for 2 degrees of freedom, p=0.001. The odds ratio was 0.62 (CI, 0.36 to 1.08) for the case-control studies of ovarian cancer incidence as a function of low-dose progestin (Figure 17). There was significant heterogeneity, with a Q-value of 17.80 for 2 degrees of freedom, p<0.001. One additional study calculated a direct odds ratio comparing high-dose with low-dose progestin OC use[29] (Figure 18). The random-effects meta-analysis of all four case-control studies reveals an odds ratio of 0.86 (CI, 0.60 to 1.21) for ovarian cancer incidence as a function of the ratio of high-dose progestin to low-dose. These results do not support a relationship between OC progestin dose and ovarian cancer incidence. There was some evidence of heterogeneity, with a Q-value of 7.52 for 3 degrees of freedom, p=0.057.

Figure 16. Forest plot for high-dose progestin (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Ness, 2000	0.523	0.363	0.755	
Pike, 2004	0.875	0.800	0.956	
Lurie, 2007	0.547	0.407	0.735	
	0.647	0.439	0.954	

0.1 0.2 0.5 1 2 5 10

Favors High Dose   Favors No OC
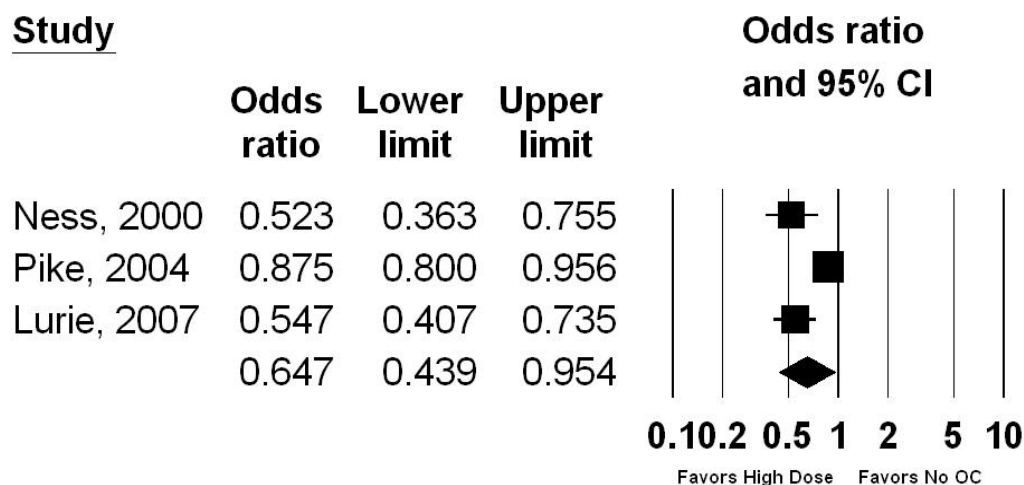
CI = confidence interval; OC = oral contraceptive

Figure 17. Forest plot for low-dose progestin (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Ness, 2000	0.522	0.378	0.722	
Pike, 2004	0.948	0.918	0.978	
Lurie, 2007	0.367	0.159	0.846	
	0.622	0.358	1.079	

0.1 0.2 0.5 1 2 5 10

Favors Low Dose   Favors No OC
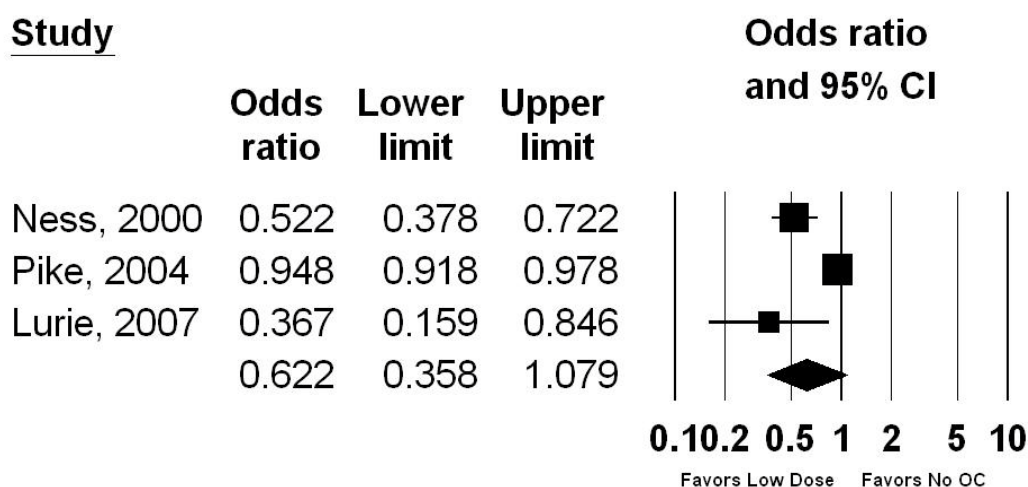
CI = confidence interval; OC = oral contraceptive

Figure 18. Forest plot for high- versus low-dose progestin (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Ness, 2000	1.002	0.615	1.633	
Pike, 2004	0.923	0.839	1.015	
Lurie, 2007	1.490	0.614	3.616	
Schildkraut, 2002	0.455	0.263	0.789	
	0.856	0.604	1.214	

0.1 0.2 0.5 1 2 5 10

Favors High Dose   Favors Low Dose
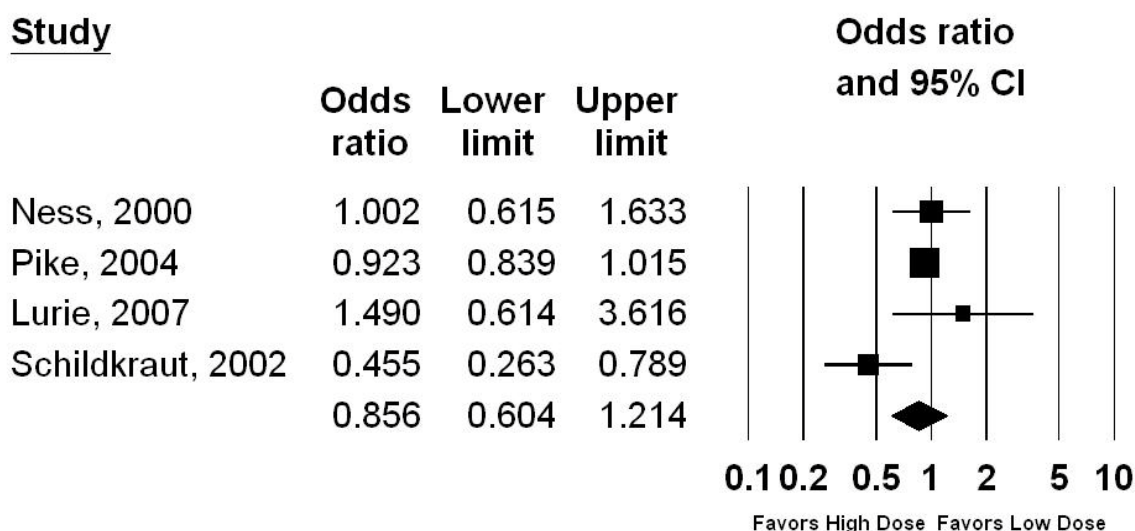
CI = confidence interval

Sensitivity Analyses

There were no poor-quality studies performed outside of the United States or studies published before 2000 addressing progestin dose. Therefore, sensitivity analyses were not performed.

Special Populations

BRCA Mutation Carriers

Four studies[81,94,116,159] were included in the meta-analyses examining the relationship between carriers of BRCA1 and BRCA2 genetic mutations and ovarian cancer incidence. Of these, three were case-control studies representing 1096 cases and 2878 controls and 1 cohort study representing 3181 participants. One study was rated good quality and three fair quality (Table 5).

Data were available to compare affected and unaffected BRCA1 mutation carriers; affected and unaffected BRCA2 mutation carriers; and a combined group of affected and unaffected BRCA1 or BRCA2 carriers. We excluded studies[115,118] from the analyses that compared mutation carriers with ovarian cancer to control groups who were predominantly noncarriers or who were not tested for BRCA1 or BRCA2.

Figures 19 to 21 show the odds ratios for the meta-analyses on BRCA1 mutation carriers. The odds ratio was 0.55 (95% CI, 0.47 to 0.66) for the four studies of ovarian cancer incidence in patients with the BRCA1 gene as a function of OC use (Figure 19). There was no significant heterogeneity, with a Q-value of 1.24 for 3 degrees of freedom, p=0.743. The odds ratio was 0.65 (CI, 0.34 to 1.24) for the three studies of ovarian cancer incidence in patients with the BRCA2 gene as a function of OC use (Figure 20). There was no significant heterogeneity, with a Q-value of 4.68 for 2 degrees of freedom, p=0.096. The odds ratio was 0.58 (CI, 0.46 to 0.73) for the three studies of ovarian cancer incidence that combined women with either the BRCA1 gene or BRCA2 gene (Figure 21). There was no significant heterogeneity, with a Q-value of 3.12 for 2

degrees of freedom, p=0.210. These analyses suggest that OCs reduce ovarian cancer incidence in all three gene categories. The odds ratios for the three groups were quite similar, and a test for a difference results in a p-value of 0.975.

Figure 19. Forest plot for BRCA1 carriers (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Whittemore I, 2004	0.650	0.410	1.030	
Gronwald, 2006	0.400	0.180	0.889	
McLaughlin, 2007	0.560	0.446	0.703	
Antoniou, 2009	0.520	0.370	0.730	
	0.552	0.466	0.655	

0.1 0.2 0.5 1 2 5 10
Favors OC   Favors No OC
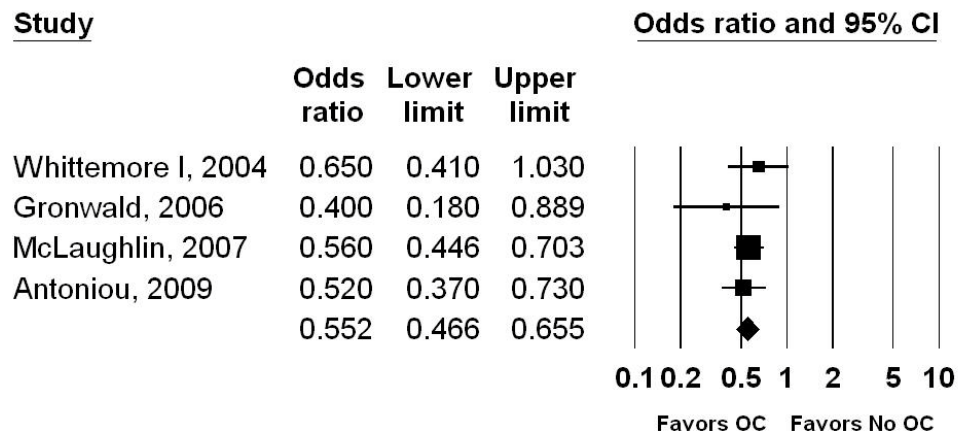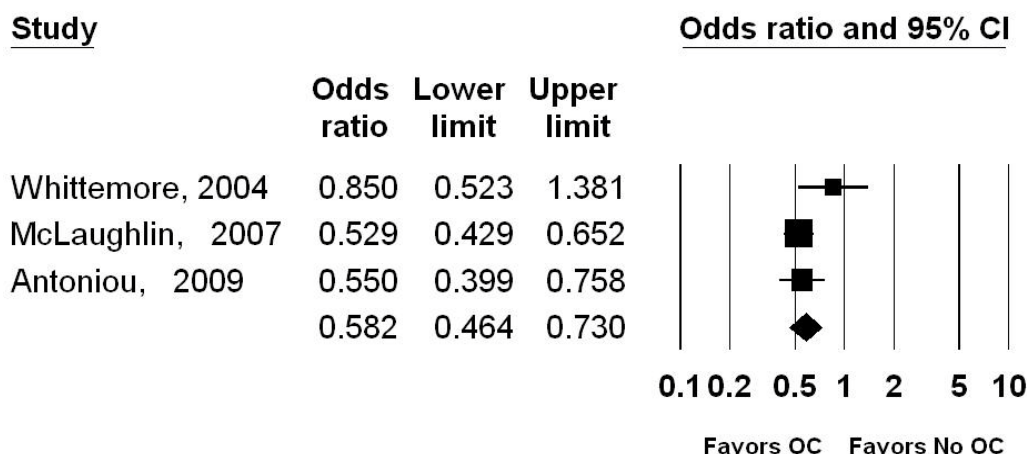
CI = confidence interval; OC = oral contraceptive

Figure 20. Forest plot for BRCA2 carriers (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Whittemore II, 2004	0.860	0.380	1.948	
McLaughlin, 2007	0.390	0.230	0.661	
Antoniou, 2009	1.040	0.423	2.558	
	0.649	0.339	1.244	

0.1 0.2 0.5 1 2 5 10
Favors OC   Favors No OC
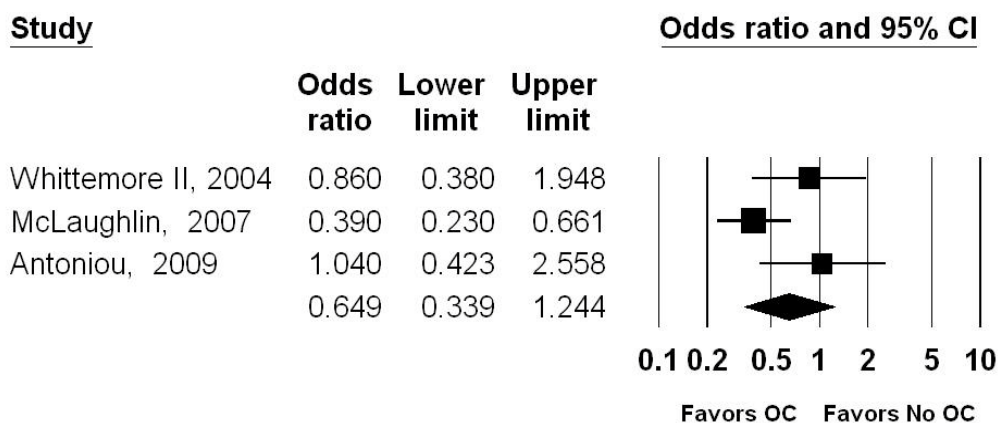
CI = confidence interval; OC = oral contraceptive

Figure 21. Forest plot for BRCA1 or BRCA2 carriers (ovarian cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Whittemore, 2004	0.850	0.523	1.381	
McLaughlin, 2007	0.529	0.429	0.652	
Antoniou, 2009	0.550	0.399	0.758	
	0.582	0.464	0.730	

0.1 0.2 0.5 1 2 5 10

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

Analyses were repeated for the combined group of BRCA1 or BRCA2 mutation carriers including one additional study published in 1998. The odds ratio was 0.56 (CI, 0.45 to 0.69).

Sensitivity analyses were not done for study quality because no studies were rated as poor quality, and none were done comparing U.S. with non-U.S. studies because excluding non-U.S. studies left only two studies.

Family History of Ovarian Cancer

Three studies[87,149,158] were identified that examined the effect of family history on ovarian cancer incidence. All three were case-control studies: one was rated good quality and two fair quality. We excluded one pooled analysis[23] because it included some of the individual studies that were identified (Table 13).

Among these studies, two different definitions of a positive family history were used: (1) breast or ovarian cancer in a first-degree relative,[87,149] and (2) history of ovarian cancer in a sister or mother.[158] The studies also used two different categorizations of the referent group for OC use: (1) no OC use[149,158] or (2) use for less than 60 months.[87] The lack of consistency across studies precluded performing a meaningful meta-analysis by family history subgroups.

Table 13. Data for outcomes on family history (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Case-Control					
Gross, 1992[95]	With family history Cases: 31 Controls: 99	Never use 3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	1.0 3.1 1.7 1.5 1.1 0.3		Age, parity	Family history of ovarian cancer in mother, grandmother, sister, daughter or aunt	2
	No family history Cases: 225 Controls: 2351	Never use 3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	1.0 0.6 0.6 0.7 0.7 0.3		Age, parity	No family history	2
Godard, 1998[89]	Familial Cases Cases: 51 Controls: 152	Age at last OC use Never use 17 to 25 yr 25 to 35 yr 35 to 43 yr	1.0 0.99 0.26 0.17	Reference 0.28 to 3.51 0.08 to 0.79 0.036 to 0.83	Age at menarche, age at diagnosis, age at last childbirth, tubal ligation or hysterectomy, talc use, alcohol use	Family history of ≥1 person with breast cancer diagnosed <55 years or ovarian cancer	2
	Sporadic Cases Cases: 101 Controls: 152	Age at last OC use Never use 17 to 25 yr 25 to 35 yr 35 to 43 yr	1.0 0.84 0.25 0.25	Reference 0.28 to 2.55 0.10 to 0.62 0.10 to 0.64	Age at menarche, age at diagnosis, age at last childbirth, tubal ligation or hysterectomy, talc use, alcohol use	No family history	2
Tavani, 2000[149]	With family history Cases: 93 Controls: 139	Ever use Never use	1 1.4	Reference 0.4 to 4.4	Age, area of residence	Family history of breast and/or ovarian cancer in first-degree relatives	2
	No family history Cases: 878 Controls: 2619	Ever use Never use	1 1.2	Reference 0.9 to 1.7	Age, area of residence	No family history	2

Table 13. Data for outcomes on family history (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Chiaffarino, 2001[87]	With family history <u>Cases:</u> 129 <u>Controls:</u> 120	Never used or <60 mo ≥60 mo	1 1.0	Reference 0.2 to 4.2	Age, parity, family history, center, education	Family history of breast and/or ovarian cancer in first degree relatives	2
	No family history <u>Cases:</u> 901 <u>Controls:</u> 2286	Never used or <60 mo ≥60 mo	1 0.5	Reference 0.2 to 0.9	Age, parity, family history, center, education	No family history	2
Walker, 2002[158]	With family history <u>Cases:</u> 33 <u>Controls:</u> 24	≤48 mo use 49+ mo use Never use	0.34 0.07 1	0.08 to 1.55 0.01 to 0.44 Reference	Age, race, parity, tubal ligation	Family history of ovarian cancer in first-degree relative	2
	No family history <u>Cases:</u> 692 <u>Controls:</u> 1279	≤48 mo 49+ mo Never OC use	0.72 0.51 1	0.59 to 0.88 0.40 to 0.65 Reference	Age, race, parity, tubal ligation	No family history	2

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; NR = not reported; OC = oral contraceptive; OR = odds ratio; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR = 1.0.

[c]Meta-analysis code: 2 = Meta-analysis was not performed due to differences in definitions of positive family history and nonusers of OCs.

Parity and Gravidity

Two studies[123,126] were identified that examined the effect of gravidity on ovarian cancer incidence (Table 14). Both were case-control studies; in total they represented 1595 cases and 3137 controls. Both studies were rated good quality. When determining possible meta-analysis, we excluded one set of data from consideration[92] due to representation of that data in another included report and therefore did not have sufficient studies to warrant a formal meta-analysis.

Among nulliparous women, one study reported a significantly reduced risk of ovarian cancer among OC users (OR 0.43; 95% CI, 0.28 to 0.66),[123] and the other found no difference (OR 0.98; CI, 0.65 to 1.49).[126] Both studies reported a significantly reduced risk of ovarian cancer among parous women who were OC users (OR 0.72; CI, 0.61 to 0.85[123] and OR 0.68; CI, 0.56 to 0.83).[126] The odds ratios comparing gravidity 0 to gravidity 1+ were 0.60 (CI, 0.38 to 0.94)[123] and 1.44 (CI, 0.91 to 2.27).[126]

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Parazzini, 1991[128]	Parity=0 <u>Cases:</u> 137 <u>Controls:</u> 273	Never Ever	1.0 0.6	Reference 0.3 to 1.3	Age	Nulliparous women	4
	Parity=1-2 <u>Cases:</u> 266 <u>Controls:</u> 795	Never Ever	1.0 0.5	Reference 0.3 to 0.9	Age	Women with parity 1-2	4
	Parity≥3 <u>Cases:</u> 102 <u>Controls:</u> 307	Never Ever	1.0 0.8	Reference 0.3 to 1.7	Age	Women with parity ≥3	4
Thomas, 1991[150]	Parity=0 Not reported	Never Ever	1.0 0.16	Reference 0.05 to 0.54		Nulliparous women	4
	Parity ≥1 Not reported	Never Ever	1.0 0.85	Reference 0.63 to 1.16		Women with parity ≥1	4
Ness, 2001[126]	Gravidity=0 <u>Cases:</u> 137 <u>Controls:</u> 119	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.9 1.3 0.9	Reference 0.5 to 1.7 0.6 to 3.2 0.4 to 1.8	Age, race, family history		1
	Gravidity=1 <u>Cases:</u> 107 <u>Controls:</u> 140	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.6 0.5 0.9	Reference 0.3 to 1.1 0.2 to 1.7 0.4 to 2.1	Age, race, family history		1
	Gravidity=2 <u>Cases:</u> 177 <u>Controls:</u> 346	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.6 0.7 1.0	Reference 0.4 to 1.0 0.3 to 1.6 0.5 to 2.0	Age, race, family history		1
	Gravidity≥3 <u>Cases:</u> 306 <u>Controls:</u> 754	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.7 0.9 0.5	Reference 0.5 to 1.0 0.5 to 1.6 0.3 to 0.9	Age, race, family history		1

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Greer, 2005[92]	Parous women Cases: 715 Controls: 1631	Never Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.00 0.71 1.04 0.66 0.71 0.97 0.62	Reference 0.50 to 0.99 0.66 to 1.63 0.48 to 0.90 0.51 to 0.99 0.64 to 1.47 0.48 to 0.81	Age		2
	Nulliparous women Cases: 216 Controls: 168	Never user Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.00 1.04 1.08 0.84 1.05 1.08 0.68	Reference 0.52 to 2.08 0.42 to 2.78 0.46 to 1.56 0.55 to 2.01 0.49 to 2.34 0.42 to 1.11	Age		2
Ness, 2011[123]	Gravidity=0 Cases: 134 Controls: 143	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.46 0.61 0.31	Reference 0.25 to 0.86 0.25 to 1.52 0.15 to 0.67	Age, race, family history, infertility		1
	Gravidity=1 Cases: 114 Controls: 188	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.99 0.60 0.99	Reference 0.58 to 2.02 0.44 to 2.23 0.22 to 1.69	Age, race, family history, infertility		1
	Gravidity=2 Cases: 216 Controls: 458	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.51 0.89 0.50	Reference 0.34 to 0.77 0.40 to 1.99 0.28 to 0.88	Age, race, family history, infertility		1
	Gravidity≥3 Cases: 404 Controls: 989	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.85 0.77 0.70	Reference 0.64 to 1.14 0.45 to 1.32 0.45 to 1.09	Age, race, family history, infertility		1

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
		Pooled					
Hartge, 1994[104]	Parity>=3 <u>Cases</u>: 333 <u>Controls</u>: 2466	No OC OCs for 1-3 yr OCs for ≥4 yr	1.0 1.8 2.2	Reference 1.2 to 2.7 1.6 to 3.2	Tubal ligation, hysterectomy		3
	Parity=1-2 <u>Cases</u>: 448 <u>Controls</u>:2029	No OC OCs for 1-3 yr OCs for ≥4 yr	1.5 2.6 3.7	0.95 to 2.3 1.7 to 3.9 2.6 to 5.4			3
	Parity=0 <u>Cases</u>:295 <u>Control</u>: 816	No OC OCs for 1-3 yr OCs for ≥4 yr	2.2 5.8 5.5	1.3 to 3.9 3.6 to 9.3 3.7 to 8.0			3

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; mo = month/months; OC = oral contraceptive; OR = odds ratio; NR = not reported; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1 = Study meets inclusion criteria for meta-analysis; 2 = Excluded from possible meta-analysis due to grouping with another included article also reporting results by gravidity; 3 = Excluded pooled analysis due to no other studies to combine it with; 4 = Excluded from possible meta-analysis in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

Sensitivity Analyses

No sensitivity analyses were performed because there were too few studies.

OC Use and Ovarian Cancer Mortality

Three studies[33,164-167] were identified that examined the effect of OC use on ovarian cancer mortality. All three were cohort studies and were rated fair quality. Two of the included studies[33,165] were large, population-based cohort studies representing 46,112 subjects and 602,700 reported person-years and assessed death from ovarian cancer as a primary outcome among ever versus never OC users. Both of these studies reported a significant reduction in ovarian cancer mortality among OC users that was similar in magnitude and direction as the reduction in incidence discussed above. The third study[167] identified a cohort of women with ovarian cancer and subsequently compared survival outcomes between OC users (n=310) and nonusers (n=366), with nonsignificant findings (Table 15).

Table 15. Data for ovarian cancer mortality

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort							
Survival After Diagnosis of Ovarian Cancer							
Nagle, 2008[167]	Cohort of women with ovarian cancer in three Australian states Exposed: 310 women Unexposed: 366 women	0.88	0.70 to 1.11	Stage, age group, histologic grade, residual disease, smoking	Australia/NZ	Fair	2
Population-Level Mortality							
Hannaford, 2010[33]	Royal College General Practitioners Oral Contraceptive Study Exposed: 28,806 women Unexposed: 17,306 women	0.53	0.38 to 0.72	Age, parity, smoking and social class	UK	Fair	2
Vessey, 2010[165]	Oxford Family Planning Association contraception study 602,700 person-years of observation for unexposed and exposed	0.87	0.79 to 0.96	Age, parity, social class, smoking, BMI	UK	Fair	2

CI = confidence interval; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Meta-analysis code: 2 = Excluded from the meta-analysis due to differences in study populations.

Strength of Evidence for OC Use and Risk of Ovarian Cancer

The strength of evidence for each outcome is described in Table 16 using the four domains listed as guidance. Because no randomized controlled trials were included in our analysis, the risk of bias was categorized as medium at best and high if other possible sources of bias were identified. With regard to directness of evidence, relationships between high and low steroid hormone doses and ovarian cancer incidence were considered to be indirect based on the use of "never OC use" as the reference category in those studies.

We graded as moderate the strength of evidence for relationships between ever OC use and ovarian cancer incidence and mortality in the general population and between ever OC use and ovarian cancer incidence in the BRCA mutation-carrying population. The relationship between duration of OC use and ovarian cancer incidence was also graded as moderate. The strength of evidence for the remaining relationships was graded as low.

Table 16. Strength of evidence domains for the effect of OC use on ovarian cancer

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population						
Ever vs. never use	24 (657,055 and 3,981,072 person-years)	Medium	Consistent	Direct	Precise	Moderate 0.73 (0.66 to 0.81)
Duration of use	15 (574,363 and 3,493,072 person-years)	Medium	Consistent	Direct	Precise	Moderate 1–12 mo: 0.91 (0.78 to 1.07) 13–60 mo: 0.77 (0.66 to 0.89) 61–120 mo: 0.65 (0.55 to 0.77) >120 mo: 0.43 (0.37 to 0.51)
Age at first use	6 (111,817)	High	Consistent	Direct	Imprecise	Low <20 yr: 0.63 (0.45 to 0.89) 20–24 yr: 0.71 (0.51 to 0.99) 25–30 yr: 0.67 (0.46 to 0.99) > 30 yr: 0.89 (0.60 to 1.32)
Time since last use	8 (210,069 and 1,083,000 person-years)	High	Inconsistent	Direct	Imprecise	Low 0–10 yr: 0.41 (0.34 to 0.50) 10–20 yr: 0.65 (0.56 to 0.74) 20–30 yr: 0.92 (0.76 to 1.12) >30 yr: 0.79 (0.58 to 1.12)

Table 16. Strength of evidence domains for the effect of OC use on ovarian cancer (continued)

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population (continued)						
High-dose vs. low-dose estrogen	6 (9007)	High	Consistent	Indirect	Imprecise	Low 1.25 (0.95 to 1.64)
High-dose vs. low-dose progestin	4 (7528)	High	Inconsistent	Indirect	Imprecise	Low 0.86 (0.60 to 1.21)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	3 (6855)	Medium	Consistent	Direct	Precise	Moderate 0.58 (0.46 to 0.73)
Incidence in BRCA1-Positive Women						
Ever vs. never use	4 (5519)	Medium	Consistent	Direct	Precise	Moderate 0.55 (0.47 to 0.66)
Incidence in BRCA2-Positive Women						
Ever vs. never use	3 (1592)	Medium	Inconsistent	Direct	Imprecise	Low 0.65 (0.34 to 1.24)
Incidence in Women With Family History						
Ever vs. never use	3 (9193)	High	Inconsistent	Direct	Imprecise	Low Decreased incidence
Incidence in Gravid/Parous and Nulligravid/Nulliparous Women						
Ever vs. never use	2 (4732)	Medium	Inconsistent	Direct	Imprecise	Insufficient
Mortality From Ovarian Cancer						
Ever vs. never use	2 (46,112 and 602,700 person-years)	Medium	Consistent	Direct	Imprecise	Moderate Decreased cause-specific mortality
Survival Among Women With Ovarian Cancer						
Ever vs. never use	1 (676)	High	NA	Direct	Imprecise	Insufficient (not performed)

CI = confidence interval; mo = month/months; NA = not applicable; SOE = strength of evidence; yr = year/years

Discussion

In the systematic review and meta-analysis for Section 2, OC use was associated with a decreased incidence of ovarian cancer (OR 0.73, 95% CI, 0.66-0.81), with results from two large cohort studies showing a concomitant decrease in mortality. There is a positive relationship between the duration of OC use and the degree of the protective effect. These findings are consistent with prior pooled analyses,[21,23,24] which reported odds ratios for ever versus never OC use of between 0.60 and 0.73 and similarly identified a relationship between longer duration of OC use and lower incidence of ovarian cancer. We did not identify a significant relationship between time since last OC use and degree of protection—although such a relationship has been identified in the largest prior pooled analysis.[21] Note that we found no evidence for publication bias in any of the meta-analyses (Appendix E).

Temporal Relationships in OC Use

The results of our meta-analysis show a strong relationship between duration of OC use and the incidence of ovarian cancer (Figure 12). Women who use OCs for 10 or more years show a reduction in ovarian cancer incidence of more than 50 percent. Prior pooled analyses are consistent with these findings.[21,23,24] While our reported odds ratio comparing OC use for less than 12 months with never use does not meet criteria for statistical significance, our duration analysis suggests that there is no time threshold for OC effectiveness, and the duration-response relationship likely starts as soon as a woman commences OC use.

Regarding age at first OC use, the odds ratios also appear to show a clearly positive relationship. This suggests that the earlier a woman begins using OCs, the greater the reduction in ovarian cancer incidence. However, it is not possible to differentiate the effects of age at first use from the effects of duration of use. Our findings are consistent with the largest pooled analysis,[21] and are not unexpected, since the earlier a woman starts using OCs, the longer the potential duration of use. The number of studies (6) in our primary analysis of age at first OC use was much lower than the number of studies (15) in the analysis of duration, and so it is not possible to determine which factor is more predictive. The protective effect of OCs appears to attenuate with increasing time since last use, again consistent with the findings of the Collaborative Group,[21] although it remains significantly reduced even up to 30 years after stopping. Although the data available at the study level preclude estimation of the joint effect of duration and time since last use, stratified analysis of the pooled individual data by the Collaborative Group suggest that the magnitude of protection with increased duration is greater than the attenuation with time since last use.

Women at Elevated Genetic Risk for Ovarian Cancer

The results of our meta-analysis suggest that ever use of OCs reduces the risk of ovarian cancer in BRCA1 or BRCA2 mutation carriers similar to what has been observed consistently in the general population. The odds ratio for ever use of OCs (OR 0.58; 95% CI, 0.46 to 0.73) for BRCA1 or BRCA2 mutation carriers was lower than the odds ratio calculated from the overall meta-analysis (OR 0.73, 95% CI, 0.66 to 0.81).

Although the breast cancer literature clearly demonstrates that clinical and pathologic characteristics of BRCA1-associated cancers differ from BRCA2-associated cancers and sporadic cancers, the same does not appear to be true for ovarian cancer.[168] Our analyses of the effects of OCs in BRCA1 and BRCA2 mutation carriers found similar odds ratios for ovarian cancer in each group, and a test for differences between groups was not statistically significant (p=0.916). Although the analyses did not suggest there were statistically significant differences between BRCA1 and BRCA2 mutation carriers, these results should be interpreted cautiously because of the small number of studies and the relatively small sample sizes for BRCA2 mutation carriers.

For women that do not have a known BRCA1 or BRCA2 mutation but are at increased risk for ovarian cancer due to a family history of breast or ovarian cancer, the data were inadequate to perform a meta-analysis because of differences between studies in their definitions of family history and the reference group to which OC users were compared. Within individual studies, particularly those focusing specifically on a family history of ovarian cancer, the relatively small numbers within the strata defined by a positive family history led to unstable estimates. The possible use of OCs as an ovarian cancer prevention strategy is clearly of interest to women with

a family history of ovarian or breast cancer; however, the published data do not provide consistent evidence to support a recommendation for use.

Limitations

In an effort to enhance the applicability of these findings to contemporary OC formulations and dosages, we included only studies published on or after January 1, 2000, for the primary analysis and 1990 for the sensitivity analysis. However, our meta-analysis produced a very similar odds ratio comparing ever use with never use (0.73) to odds ratios reported in the sensitivity analysis (0.72) and a pooled analyses that included older studies. This suggests that current OC formulations may have a similar effectiveness to older formulations in reducing the incidence of ovarian cancer. This is supported by our finding that the relative estrogen and progestin doses in OCs do not appear to have an impact on ovarian cancer incidence. However, given that the age of peak incidence of ovarian cancer is in a woman's early 60s, even more recent publications do not capture the potential long-term effect of formulations introduced in the past 20 years.

Another limitation of the current analysis is the degree of generalizability of the included studies to clinical decisionmaking. The included studies almost never specifically reported the reasons for OC use. It is likely that most women who have taken OCs have done so for contraception or to control symptoms related to menses. Therefore, the use of OCs specifically to prevent ovarian cancer has not been addressed in reported studies, and use of the currently available data to guide a risk/benefit discussion regarding chemoprophylaxis is premature.

The main limitation of our analysis is the lack of any randomized, prospective trials examining the preventive effect of OCs on ovarian cancer, raising the potential for bias. The most common study design within our primary ever/never incidence analyses was case-control (71%), with a minority being cohort studies (29%); given that ovarian cancer is relatively uncommon, this is not unexpected. The point estimate for case-control studies (0.72) was lower than for cohort studies (0.75), suggesting that there may be some residual confounding in the case-control studies. Likewise, although the vast majority of studies were rated as good or fair quality (92%), there was marked inconsistency across studies, particularly in the methods for adjustment of confounding. Individual odds ratios or relative risks were always adjusted for potential confounders, but both the choice of covariates and the way the covariates were modeled in the reported results were not consistent among studies (Tables 5, 6, 8, 10, 12–15). For example, relevant ages and durations of exposure were described using a variety of categories with widely varying definitions.

The observed association between OC use and reduced ovarian cancer risk (and for many of the other associations discussed in Sections 3 and 4) fulfills many of the classic criteria for causal inference in epidemiology,[169] including strength of association, consistency across studies, temporality, a biological gradient, biological plausibility, and coherence. However, the potential for the limitations discussed above to lead to biased estimates of the effects of OC require considerable caution when using the results for clinical decisionmaking. Although the literature synthesis for each outcome and the model (described in Section 5) represent our best efforts at integrating the available data quantitatively, the inherent limitations of observational studies mean that we cannot rule out the possibility that some or all of the observed associations between OC use and both harmful and beneficial outcomes are the result of unmeasured confounding.

Future Research

The current literature consistently shows a statistically significant reduction in ovarian cancer risk among women with a history of OC uses, with greater reductions in risk with longer duration of use. Results were similar across different subgroups with varying degrees of risk, such as nulliparous women and BRCA1 and BRCA2 mutation carriers. While the overall body of evidence is supportive of the beneficial effects of OCs on ovarian cancer, the potential for unmeasured bias is substantial. Even if the magnitude of the observed protective association is accurate, our analysis demonstrates that there is insufficient evidence to guide more specific recommendations regarding the preferred OC formulation and dose, the optimal time period of use for ovarian cancer prevention, and the benefits in certain high-risk women. Ideally, many of these issues would be resolved by a randomized trial, but, as discussed in Section 5, the challenges to conducting such a trial may be insurmountable.

While the current analysis did not identify a relationship between estrogen or progestin formulation and incidence of ovarian cancer, there were a limited number of studies meeting criteria for these meta-analyses. In particular, the progestin component of the OC formulation appears to have an effect on the ovarian epithelium in animal studies.[170] Given that only four studies defined progestin dose uniformly and were included in the meta-analysis, further investigation into the relationship between progestin dose/formulation and ovarian cancer incidence is warranted. This is particularly important given that both the estrogen and progestin components are likely related to the risk of some of the adverse outcomes associated with OC use—especially acute vascular events (see Section 4).

Our analyses were based on more recently published data than previous pooled analyses were, yet we arrived at a similar estimate of the odds ratio associated with ever OC use. This suggests that lower dose OCs—which are more commonly evaluated in recent studies—are potentially as effective as higher dose OCs in reducing ovarian cancer risk. Continued evaluation of effects by dose of OCs is warranted, especially since some of the older women included in studies published since 1990 would have taken OCs when higher doses were more commonly prescribed.

Further research is needed to sort out the relative importance of the duration and timing of use of OCs. Greater reductions in risk were observed for women who were younger at first use of OCs; however, data were not available to determine whether this was due to longer duration of use among women who initiated OC use at younger ages. Analogously, although ovarian cancer risk was lower among more recent OC users compared with those with a longer time since last use, these analyses did not account for duration of use. Understanding the combined effects of timing and duration is particularly important for making recommendations to women of mid-to-late reproductive age who are considering OC use for ovarian cancer prevention but not necessarily for contraception. To facilitate future systematic reviews, one step would be to standardize the categories and descriptive statistics for reporting results. Although particular categorization choices may be best suited for analyzing individual studies on the basis of study design and characteristics of a given population, reporting of standardized results—perhaps as an appendix to the main analysis—would greatly improve the ability to combine published results in meta-analysis.

Additional research is also needed to learn whether women at high risk for ovarian cancer due to their family history show a similar benefit with OC use as women from the general population. The proportion of women with a reported family history of ovarian cancer is quite small in most studies; however, this group may be keenly interested in chemoprevention given

the high mortality of ovarian cancer. It would be highly desirable for pooled analyses to include a sufficient number of women with a positive family history to provide stable risk estimates.

Section 3. Oral Contraceptives and Other Cancers

Background

Nearly half (49%) of all pregnancies in the United States are unintended, with 19 percent considered unwanted pregnancies.[171] Oral contraceptives (OCs) are the most common form of effective and reversible contraception in the United States.[172] Use of OCs significantly decreases personal and societal burdens associated with unintended or unwanted pregnancy.[173,174] Additionally, OCs have significant noncontraceptive health benefits, such as improving acne or regulating dysmenorrhoea.[175-178] Using OCs, however, is not without risks. Numerous studies demonstrate serious complications associated with OC use including venous thromboembolic disease, myocardial infarction, and stroke.[179-181]

Use of OCs also may influence the risk of certain cancers.[56] OC use may promote or initiate tumors of the breast or cervix.[50,67,182] For breast cancer, these risks may be even greater for populations at elevated risk due to family history of cancer or genetic mutation carrier status (e.g., BRCA1/2); however, results from studies are inconclusive.[51,183] Moreover, the use of OCs has also been associated with a greater risk of certain clinically challenging types of breast tumors.[184] Conversely, OC use is associated with significant reductions in colorectal and endometrial cancers.[54,56] Our systematic review and meta-analyses support a significant risk reduction for ovarian cancer incidence and mortality associated with OC use (Section 2). However, assessment of the risk of cancer associated with OC use is fraught with difficulties. For example, cancer is a disease with a long latency period, and the time between exposure to OCs and diagnosis of cancer may span decades. Also, temporal variations in the OC formulations available on the market and used over a woman's lifetime may influence associations between cancer risk and OC use. Further, patterns of OC use over a lifetime may be influenced by factors that also affect cancer risks (e.g., gravidity, parity, breastfeeding). Last, duration of OC use or length of time since ceasing use (i.e., recency) may moderate the risk of cancers associated with OCs.[50,121]

In this section of our systematic review, we summarize the current data on associations between OC use and four common cancers among women—breast, cervical, colorectal, and endometrial. When possible, we conducted meta-analyses of the literature assessing the risk of cancer incidence and mortality associated with the use of OCs. We date-limited our search to studies published after 1999 to minimize the influence of OC formulations that are no longer available on the U.S. market and to increase generalizability to current clinical practice. When possible, we also examined associations by duration of OC use and time since last OC use on incidence of these cancers.

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 3, we performed a systematic review and meta-analysis for the cancer outcomes described in two of the seven KQs that address the potential effect of OCs on the risk of developing other cancers (breast, cervical, colorectal, and endometrial):

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

Analytic Framework

Figure 22 shows the analytic framework that guided this section of the review.

Figure 22. Analytic framework for OCs and other cancers
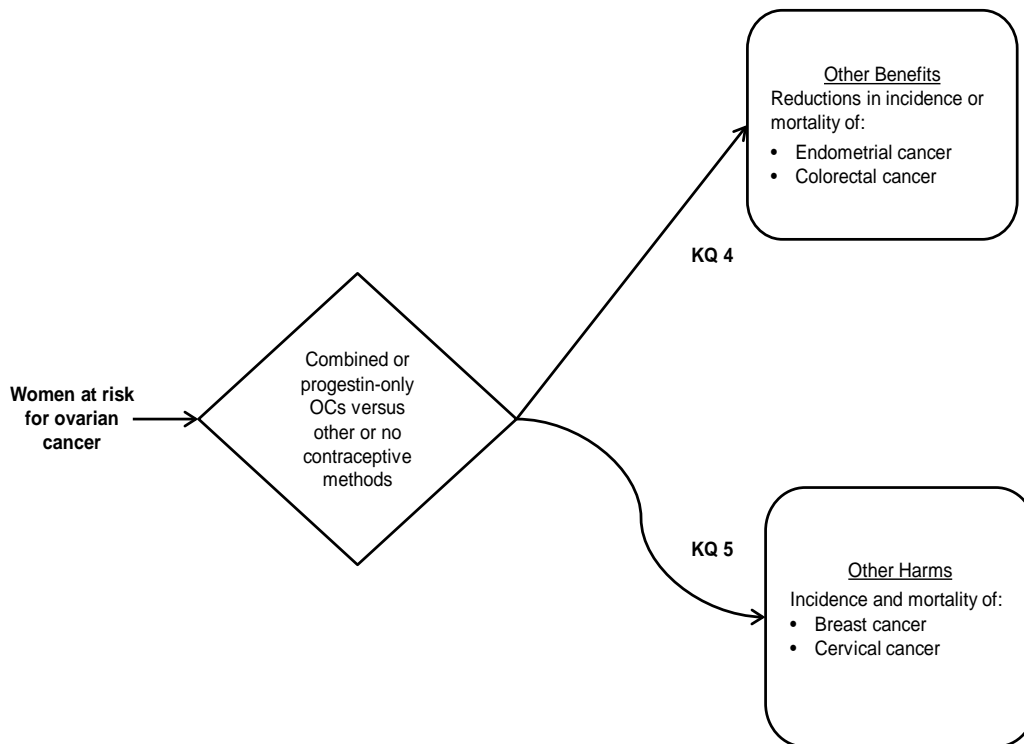
KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 17 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 17. Summary of inclusion and exclusion criteria for OCs and other cancers

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Population	• All KQs:
	  o Women taking oral contraceptives (OCs) for contraception or women taking OCs for primary prevention of ovarian cancer[a]
	  o Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy
		Nonhuman studies

Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable)

Outcomes	Study reports quantitative association between exposure to OCs and either incidence or disease-specific mortality for any of the following:
	• KQ 4:
	  o Endometrial cancer
	  o Colorectal cancer
	• KQ 5:
	  o Breast cancer
	  o Cervical cancer
		Study only reports outcomes related to assisted reproductive technologies or abortion

Timing	Studies of any duration	None
Setting	All settings	None

Table 17. Summary of inclusion and exclusion criteria for OCs and other cancers (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, non–systematic review, or letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after 01-Jan-2000[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).

[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine quantitatively the effect of OCs on the risk of breast, cervical, colorectal, or endometrial cancer, we performed meta-analyses on the following relationships when we had sufficient studies:

- Ever versus never OC use:
  - Ever versus never OC use among BRCA1 and BRCA2 genetic mutation carriers (breast cancer only)
- Temporal relationships:
  - Duration of OC use
  - Time since last OC use (breast cancer only)

We performed the meta-analyses using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68] Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

We excluded studies that were conducted in special populations, such as BRCA mutation carriers, women with family histories of cancer, or specific cancer subtypes. When studies only gave results by subgroup (premenopausal, postmenopausal), we combined subgroups only when the combined group represented the total study population. We estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model when study designs and

outcomes reported were similar. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10 to define significant heterogeneity. We stratified analyses by study type (case-control, cohort).

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after January 1, 2000.
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Ever Versus Never OC Use

For the ever versus never OC use meta-analysis, we excluded studies that reported effects for only a particular subpopulation (e.g., studies reporting odds ratios only for women with a BRCA mutation) but that did not report the effects for the general population. Studies that reported ever OC use odds ratios for two or more mutually exclusive subpopulations were included in the meta-analysis and results for the subpopulations were combined.

Temporal Relationships

Duration of OC Use

We used a random-effects model to compute odds ratios after determination that sufficient studies met criteria to perform a meta-analysis on the effect of duration of OC use. We required that the odds ratios were given relative to no OC use and that the population studied was not restricted to a particular special population. We assumed that each odds ratio, OR_{ij}, could be described by the following model:

$$Ln\left[OR_{ij}\right] = \alpha_i + \sum_{j=1}^{k} x_{ij}\,\beta_j,$$

where i denotes the study, j denotes the specific time interval, and k is the number of time intervals used in the model. The α_i are assumed to be random and normal with mean 0 and variance $(SE_{ij}^2 + \sigma^2)$. SE_{ij} is the standard error of the j^{th} odds ratio from the i^{th} study. σ^2 is the extra variation from the random effects model. The x_{ij} are the fixed terms that describe the time period covered by that particular odds ratio. The β_j ($j=1, ..., k$) are the odds ratios to be estimated for each duration interval.

We originally assumed that there was a term for each year (up to 10) and a final term for greater than 10 years. However, the large number of terms resulted in very unstable estimates. For that reason, we broke the time points into 4 intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 36 months, then the vector of x_{ij} would be (1/3, 2/3, 0, 0, 0). This would reflect that one-third of the patients in the interval were in the 1 to 12 month interval and two-thirds of the patients were in the 13 to 60 month interval. Using this methodology, any interval could be described. The model was fitted using

SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, i.

Time Since Last OC Use

Using the equation above, we grouped time since last OC use into 4 intervals: (1) 0 to 5 years, (2) 5 to 10 years, (3) 10 to 20 years (4) more than 20 years. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 15 years, then the vector of x_{ij} would be (2/3, 1/3, 0, 0, 0). This would reflect that two-thirds of the patients in the interval were in the 0 to 10 year interval and one-third of the patients were in the 10 to 20 year interval. Using this methodology, any interval could be described. The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, i.

Results

This section presents results of our detailed analysis of the relationship between OCs and the following outcomes:

- Breast cancer incidence and mortality
- Cervical cancer incidence and mortality
- Colorectal cancer incidence and mortality
- Endometrial cancer incidence and mortality

OC Use and Breast Cancer Incidence

We identified 44 studies that evaluated the association between OC use and the incidence of breast cancer.[37,88,94,99,138,139,155,156,183-228] Of these, 29 were case-control studies, 14 cohort studies, and 1 pooled analysis; 19 studies were rated good quality, 25 fair quality, and 3 poor quality. Roughly half of the studies (21) assembled cohorts fully or partially based in the United States (Table 18).

Table 18. Study characteristics and association between OC use and breast cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Shapiro, 2000[185]	Black or Colored women aged 20–54 yr in Cape Town Cases: 484 invasive breast cancer, hospital Controls: 1625, hospital Recruitment period: 1994–1997	1.2	1.0 to 1.5	Age, sex, injectable progesterone use, ethnicity	South Africa	Fair	1
Van Hoften, 2000[186]	Women aged 41–52 yr in Doorlopend Onderzoek Morbiditeit/Mortaliteit Cohort Study Cases: 309 incident breast cancer, breast cancer screening program Controls: 610 cohort members Recruitment period: 1982–1984	1.24	0.96 to 1.78	Age, parity, menopausal status, age at menarche, smoking, marital status, education, age at first delivery, maternal history of breast cancer	Netherlands	Good	1
Gomes, 2001[187]	Hospital patients in Belo Horizonte (age NR) Cases: 280 breast cancer, hospital Controls: 569 outpatients or gynecology inpatients Recruitment period: 1978–1987	1.93	1.19 to 3.11	Parity, menopausal status, family history, occupation (housewife, housekeeper, other) irregular menstrual cycles, and possibly other (hard to tell)	Brazil	Poor	1

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
	Case-Control (continued)						
Moorman, 2001[188]	Women aged 20–74 yr in Carolina Breast Cancer Study *White <50 yr* Cases: 328 invasive breast cancer, registry Controls: 236, DMV or Medicare lists	1.27	0.76 to 2.21	Age, family history, age at menarche, breastfeeding , age at first pregnancy, age at menopause	U.S.	Fair	1
	African American <50 yr Cases: 175 invasive breast cancer, registry Controls: 171, DMV or Medicare lists	1.41	0.82 to 2.41				
	White ≥50 yr Cases: 195 invasive breast cancer, registry Controls: 221, DMV or Medicare lists	0.95	0.59 to 1.53				
	African American ≥50 yr Cases: 160 invasive breast cancer, registry Controls: 161, DMV or Medicare lists Recruitment period: 1993–1996	0.90	0.51 to 1.57				
Heimdal, 2002[189]	Women aged 40–60 yr from breast cancer families in a cancer family clinic Cases: 380 breast cancer Controls: 1043 Recruitment period: 1999	0.90	0.68 to 1.19	Parity, age at menarche, BRCA1 mutation status	Norway	Fair	2
Marchbanks, 2002[183]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 4575 breast cancer, SEER registries Controls: 4682, community Recruitment period: 1994–1998	0.9	0.80 to 1.01	Age, race, parity, menopausal status, BMI, family history, age at menarche, study site, age at menopause, age at first term pregnancy, hormone replacement therapy	U.S.	Good	1

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Narod, 2002[190]	Known carriers of BRCA1 or BRCA2 mutations *BRCA1 carriers* Cases: 981 breast cancer, research studies Controls: 981, research studies *BRCA2 carriers* Cases: 330 breast cancer, research studies Controls: 330, research studies Mean age of cases at diagnosis: 39.1 yr (SD 8.1) Recruitment period: 1977–2001	1.20 0.94	1.02 to 1.40 0.72 to 1.24	Race, parity	52 centers in 11 countries	Fair	3
Tryggvadottir, 2002[227]	All Icelandic women diagnosed with first invasive breast cancer from 1979–1995 Cases: 1120, registry Controls: 10,537, registry Recruitment period: 1979–1995	NR	NR	NA	Iceland	Good	5
Althuis, 2003[191]	Premenopausal women aged 20–54 yr Cases: 265 breast cancer, <35 yr Controls: 280 community controls, <35 yr Cases: 1214 breast cancer, 35–44 yr Controls: 1033 community controls, 35–44 yr Cases: 271 breast cancer, 45–54 yr Controls: 244 community controls, 45–54 yr Recruitment period: 1990–1992	0.73 1.13 2.03	0.5 to 1.1 0.9 to 1.4 1.3 to 3.1	Age, race, BMI, age at menarche, study site, number of mammograms within 5 yr prior to diagnosis, recent oral contraceptive use, a combination variable for age at birth and number of full-term births, family history of breast cancer, alcohol consumption	U.S.	Good	1
Althuis, 2003[192]	Women aged 20–54 yr in 5 metropolitan areas Cases: 1640 invasive or *in situ* breast cancer, registries Controls: 1492 no breast cancer, community Recruitment period: 1990–1992	NR	NR	NA	U.S.	Fair	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Newcomer, 2003[193]	Women <75 yr in Collaborative Breast Cancer Study Cases: 5510 breast cancer, registries Controls: 9311, community Note: ductal cancer only (lobular cancer cases excluded) Recruitment period: NR	1.00	0.90 to 1.11	Age, race, BMI, family history, type of and age at menopause, state, education, alcohol	U.S.	Fair	10
Norman, 2003[194]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 1847 breast cancer, SEER registries Controls: 1932, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Fair	5
Suter, 2003[195]	Women <45 yr in Western Washington Cases: 524 breast cancer, SEER registry Controls: 461, community Recruitment period: 1990–1992	1.3	0.9 to 1.8	Age	U.S.	Fair	1
Wrensch, 2003[228]	Residents of Marin County, California *All subjects* Cases: 285, registry Controls: 286, community *Age <50* Cases: 201, registry Controls: 201, community *Age >50* Cases: 84, registry Controls: 85, community Recruitment period: 1997–1999	0.43 0.41 0.15	0.26 to 0.72 0.22 to 0.75 0.03 to 0.65	Age, residence at birth	U.S.	Good	1

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
		Case-Control (continued)					
Fowke, 2004[196]	Women aged 25–70 yr in Shanghai Breast Cancer Study *Premenopausal* Cases: 103 breast cancer, hospitals and registry Controls:103, resident registry *Postmenopausal* Cases: 110 breast cancer, hospitals and registry Controls: 127, resident registry Recruitment period: 1996–1998	0.92 0.96	0.67 to 1.26 0.70 to 1.32	Age, parity, BMI, age at menarche, education, fibroadenoma history, leisure time activity, age at first live birth	China	Fair	9
Jernstrom, 2005[197]	Women <40 yr in South Swedish Health Care Region Cases: 245 breast cancer, registry Controls: 735, community Recruitment period: 1990–1995	1.65	0.95 to 2.87	Parity, family history, age at menarche, smoking	Sweden	Fair	4
Milne, 2005[198]	Women <40 yr in San Francisco, Ontario, Melbourne, and Sydney *Cases with BRCA1 mutation* Cases: 47 breast cancer, registries Controls: 815, community *Cases with BRCA2 mutation* Cases: 36 breast cancer, regional registries Controls: 815, community *Cases with neither BRCA1 or 2 mutations* Cases: 1073 breast cancer, registries Controls: 815, community Recruitment period: 1995–1998	0.22 1.02 0.93	0.10 to 0.49 0.34 to 3.09 0.69 to 1.24	Age, parity, family history, age at menarche, study location/period, education, marital status, country of birth	U.S., Canada, Australia	Good	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Gronwald, 2006[94]	BRCA1 carriers, Hereditary Cancer Center (age NR) Cases: 348 breast cancer, cancer center Controls: 348, cancer center Recruitment period: NR	0.80	0.50 to 1.20	NR	Poland	Fair	3
Haile, 2006[199]	White women <40 yr BRCA1 or BRCA2 carriers *BRCA1 carriers (cases and controls)* Cases: 111 breast cancer, registries Controls: 185, registries *BRCA2 carriers (cases and controls)* Cases: 71 breast cancer, registries Controls, 94, registries Recruitment period: NR	0.64 1.29	0.35 to 1.16 0.61 to 2.76	Age, parity, family history, study site	U.S., Canada, Australia	Good	3
Ma, 2006[201]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 1725 breast cancer, SEER registries Controls: 440, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Good	5
Rosenberg, 2006[200]	Extension of a case-control study among Swedish residents aged 50–74 yr Cases: 2289 ductal, lobular, or tubular cancer, registries Controls: 3065, population registry Recruitment period: 1993–1995	NR	NR	NA	Sweden	Fair	5
Faheem, 2007[202]	Hospital patients in Islamabad Cases: 150,breast cancer, hospital Controls: 159, community Mean age of cases: 42 yr (SD 12) Recruitment period: 2005	NR	NR	NA	Pakistan	Poor	5

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Folger, 2007[203]	Women aged 35–64 yr with history of short-term OC use, Women's CARE study *Premenopausal* <u>Cases</u>: 497 breast cancer, SEER registries <u>Controls</u>: 456, community *Postmenopausal* <u>Cases</u>: 729 breast cancer, SEER registries <u>Controls</u>: 707, community Recruitment period: 1994–1998	NR	NR	NR	U.S.	Fair	5
Nichols, 2007[204]	Women aged 20–74 yr in Collaborative Breast Cancer Study <u>Cases</u>: 1878 breast cancer *in situ,* registry <u>Controls</u>: 8041*,* community Recruitment period: 1997–2001	1.10	0.99 to 1.25	Age, parity, menopausal status, family history, age at menarche, smoking, state, age at first birth, age at menopause, HRT, weight at age 18, height, weight gain since age 18, education, mammography screening, history of benign breast disease	U.S.	Good	6

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Shantakumar, 2007[205]	Long Island Breast Cancer Study Project (age NR) *Premenopausal women* <u>Cases</u>: 468 *in situ* or invasive breast cancer, rapid case ascertainment <u>Controls</u>: 500, community	0.82	0.57 to 1.19	Age	U.S.	Good	1
	Postmenopausal <65 years old <u>Cases</u>: 491 *in situ* or invasive breast cancer, registry, rapid case ascertainment <u>Controls</u>: 554, community	0.95	0.74 to 1.22				
	Postmenopausal >65 years old <u>Cases</u>: 519 *in situ* or invasive breast cancer, registry <u>Controls</u>: 439, community Recruitment period: 1996–1997	1.37	1.04 to 1.81				
Sweeney, 2007[206]	Hispanic and non-Hispanic white women ≤64 yr *All subjects* <u>Cases</u>: 2303 breast cancer, registries <u>Controls</u>: 2513, community	1.08	0.94 to 1.24	Age, parity, menopausal status, family history, study center, education, alcohol, language acculturation, years since last birth, use of contraception injections and HRT	U.S.	Good	1
	Hispanics only <u>Cases</u>: 796 breast cancer, registries <u>Controls</u>: 919, community	1.08	0.90 to 1.29				
	Non-Hispanic Whites <u>Cases</u>: 1522 breast cancer, registries <u>Controls</u>: 1586, community Recruitment period: 1999–2004	1.10	0.88 to 1.37				

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Figueiredo, 2008[207]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study *Women with history of unilateral breast cancer* Cases: 708 asynchronous bilateral breast cancer, registry Controls: 1399 unilateral breast cancer only, registry Recruitment period: 1985–2000	0.88	0.67 to 1.16	Parity, menopausal status, family history, age at menarche, counter-matching sampling, age at diagnosis of first breast cancer, family history of breast cancer in a first degree relative, histology, stage, chemotherapy, hormonal therapy, radiation therapy	U.S.	Fair	7
Lee, 2008[208]	Women aged 20–49 yr in Women's Learning the Influence of Family and Environment Study Cases: 94, breast cancer and BRCA1/2 carrier, registry Controls: 444 BRCA1/2 unknown, community Cases: 1375 breast cancer, not BRCA1/2 carrier, registry Controls: 444 BRCA1/2 unknown, community Recruitment period: 1998–2003	0.68 0.81	0.33 to 1.38 0.57 to 1.14	Age, race, parity, family history, education, Ashkenazi Jewish	U.S.	Good	3 1
Nyante, 2008[209]	Women aged 20–44 yr in Women's Interview Study of Health *Ductal cancer* Cases: 1164 invasive or *in situ* cancer, rapid reporting system Controls: 1501, community *Lobular cancer* Cases: 100, invasive or *in situ* cancer, rapid reporting system Controls: 1501, community Recruitment period: 1990–1992	1.21 1.10	1.01 to 1.45 0.68 to 1.78	Age, site, frequency of pap smears	U.S.	Fair	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
	Case-Control (continued)						
Phillips, 2009[211]	Women aged 20–74 yr in Carolina Breast Cancer Study Cases: 1808 invasive breast cancer, registry Controls: 1564, community Cases: 446 *in situ* cancer, registry Controls: 458, community Recruitment period: 1993–2001	1.11 1.11	0.94 to 1.32 0.80 to 1.53	Age, race	U.S.	Fair	1
Rosenberg, 2009[210]	Women aged 25–69 yr in Case-Control Surveillance Study *Cases: all invasive cancers* Cases: 907 breast cancer, hospital Controls: 1711, hospital *Age <50* Cases: 431 breast cancer, hospital Controls: 939, hospital *Age ≥50* Cases: 476 breast cancer, hospital Controls: 772, no breast cancer, hospital *Black women* Cases: 176 breast cancer, hospital Controls: 559, hospital *White women* Cases: 731 breast cancer, hospital Controls: 1152, hospital Recruitment period: 1976–1996	NR	NR	NA	U.S.	Fair	5

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
			Case-Control (continued)				
Figueiredo, 2010[212]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study *BRCA1 carriers (cases and controls)* <u>Cases:</u> 67 contralateral breast cancer, registry <u>Controls:</u> 42 unilateral breast cancer, registry *BRCA2 carriers (cases and controls)* <u>Cases:</u> 41 contralateral breast cancer, registry <u>Controls:</u> 31 contralateral breast cancer, registry Recruitment period: 1985–2000	0.82 2.38	0.21 to 3.13 0.72 to 7.83	Age	U.S.	Fair	7
Lumachi, 2010[213]	Women who underwent curative surgery for breast cancer *Postmenopausal women* <u>Cases:</u> 238 breast cancer, surgically treated <u>Controls:</u> 255, mammography screening Mean age of cases at diagnosis: 62 yr (SD 10) Recruitment period: NR	2.06	1.14 to 3.70	Unadjusted	Italy	Fair	1

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
	Case-Control (continued)						
Ma, 2010[214]	White or African-American women aged 35–64 yr Cases: 335 triple-negative breast cancer, registries Controls: 2015, community	0.93	0.74 to 1.17	Age, race, parity, menopausal status, BMI, family history, age at menarche, study site, education	U.S.	Good	8
	Cases: 97 ER-/PR/HER2+ breast cancer, registries Controls: 2015, community	1.00	0.72 to 1.39				
	Cases: 645 luminal A breast cancer, registries Controls: 2015, community	1.21	0.69 to 2.11				
	Cases: 120 luminal B breast cancer, registries Controls: 2015, community Recruitment period: 2000–2003	1.23	0.73 to 2.10				
Xu, 2011[224]	Women aged 25–65 yr in Shanghai Breast Cancer Study Cases: 2073 breast cancer, hospitals and registry Controls: 2084, resident registry Recruitment periods: 1996–1998; 2002–2005	0.98	0.83 to 1.15	Age, parity, menopausal status, BMI, family history, age at menarche, education	China	Good	1
Marchbanks, 2012[226]	White or black women aged 35–64 yr Cases: 2282, registries Controls: 2424, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Good	5

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Urban, 2012[155]	Black South African women aged 18–79 yr <u>Cases</u>: 256, hospital <u>Controls</u>: 156, hospital Recruitment period: 1995–2006	1.28	1.0 to 1.64	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Grabrick, 2000[215]	Family members of women aged 21–88 yr diagnosed with breast cancer between 1944 and 1952 <u>Exposed</u>: 3156 <u>Unexposed</u>: 2994 Recruitment period: 1991–1996	1.4	1.0 to 2.0	Age, birth cohort, class effect of family	U.S.	Good	2
Kumle, 2002[216]	Women aged 30–49 yr in prospective cohort study <u>Exposed</u>: 74,856 <u>Unexposed</u>: 28,171 Recruitment period: 1991–1992	1.3	1.1 to 1.5	Age, parity, menopausal status, BMI, family history, age at menarche, breastfeeding , age at first birth, HRT use, region, BMI times menopausal status	Norway, Sweden	Good	1
Dumeaux, 2003[217]	Women aged 30–70 yr in Norwegian Women and Cancer Study <u>Exposed</u>: 49,322 <u>Unexposed</u>: 37,690 Recruitment period: 1991–1997	1.25	1.07 to1.46	Age, parity, menopausal status, BMI, family history, age at menarche, geographic area, invitation of breast cancer screening, age at first birth, HRT use, alcohol consumption	Norway	Fair	1

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
	Cohort (continued)						
Dumeaux, 2005[218]	E3N-EPIC Cohort women aged 40–60 yr Exposed: 28,251 Unexposed: 40,419 Recruitment period: 1990	0.91	0.81 to 1.03	Parity, BMI, family history, age at menarche, frequency of pap smears, history of benign breast disease, alcohol consumption, time since menopause	France	Fair	1
Silvera, 2005[219]	Women aged 40–59 yr in Canadian National Breast Screening Study *Women with first- or second-degree relatives with breast cancer* Exposed: 962 Unexposed: 745 *Women with first-degree relatives with breast cancer* Exposed: 433 Unexposed: 362 *Women with second-degree relatives with breast cancer* Exposed: 414 Unexposed: 284 Recruitment period: 1980–1985	0.88 1.03 0.74	0.73 to 1.07 0.78 to 1.38 0.54 to 1.00	Age, parity, menopausal status, BMI, age at menarche, alcohol, history of breast disease, age at first birth, HRT use, study center, randomization group	Canada	Good	2
Vessey, 2006[156]	Women aged 25–39 yr at study entry in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	1.0	0.8 to 1.1	Age, parity, BMI, breastfeeding, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1
Brohet, 2007[220]	Women aged 19–74 yr in International BRCA1/2 Carrier Cohort Study Exposed: 21,569 person-years Unexposed: 43,611 person-years Recruitment period: NR	1.47	1.16 to 1.87	Age, parity, family clustering, history of oophorectomy before right censoring	UK, France, Netherlands	Fair	3

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.98	0.87 to 1.10	Age, parity, smoking, social status; ever use HRT	UK	Fair	1
Lund, 2007[221]	Women aged 34–70 yr in Norwegian Women and Cancer Study Exposed: 11,371 Unexposed: 18,747 Recruitment period: 1991–1997	1.33	1.11 to 1.59	Parity, BMI, family history, age at menarche, mammography, age at first delivery	Norway	Good	1
Dorjgochoo, 2009[88]	Women aged 40–70 yr in Shanghai Women's Health Study Exposed: 12,957 Unexposed: 15,557 Recruitment period: 1997–2000	1.05	0.84 to 1.31	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	China	Fair	1
Rosenblatt, 2009[138]	Textile Workers aged 30–64 yr in Shanghai Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.9	0.78 to 1.03	Age, parity	China	Poor	1
Hunter, 2010[222]	Nurses' Health Study II of women aged 24–43 yr at study entry Exposed: 1,070,386 person-years Unexposed: 176,581 person-years Recruitment period: 1989–2001	NR	NR	NA	U.S.	Good	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Rosenberg, 2010[223]	Women aged 21–69 yr in Black Women's Health Study Exposed: 445,824 person-years Unexposed: 128,768 person-years *ER+/PR+ receptor status* Cases: 284 *ER+/PR- receptor status* Cases: 80 *ER-/PR- receptor status* Cases: 46 Recruitment period: 1995	IRR=1.11 IRR=0.97 IRR=1.65	0.86 to 1.42 0.61 to1.54 1.19 to 2.30	Age, parity, BMI, family history, age at menarche, education, age at first birth, age at menopause, HRT, exercise, alcohol, questionnaire cycle	U.S.	Fair	8
Bernholtz, 2011[225]	Jewish women at high risk of developing breast or ovarian cancer *BRCA1 or BRCA2 carriers* Exposed: 403 Unexposed: 373 *BRCA1 carriers* Exposed: 309 Unexposed: 182 *BRCA2 carriers* Exposed: 136 Unexposed: 72 Recruitment period: 1996–2010	1.84 1.72 2.07	1.47 to 2.31 1.31 to 2.25 1.34 to 3.20	Age at menarche, breastfeeding, year of birth	Israel	Fair	3

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
		Pooled					
Dolle, 2009[184]	Women aged 21–45 yr in Seattle-Puget Sound Cases: 897 with invasive cancer; 187 with triple negative cancer; registries Controls: 1569, not reported Recruitment periods: 1983–1990; 1990–1992	1.3 (all subjects) 2.5 (triple-negative subjects)	1.0 to 1.7 1.4 to 4.3	Age, family history, breastfeeding history, oral contraceptive duration	U.S.	Fair	8

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; IRR = incidence rate ratio; NR = not reported; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; SEER = Surveillance, Epidemiology, and End Results registry; UK = United Kingdom; U.S. = United States; yr = year/years
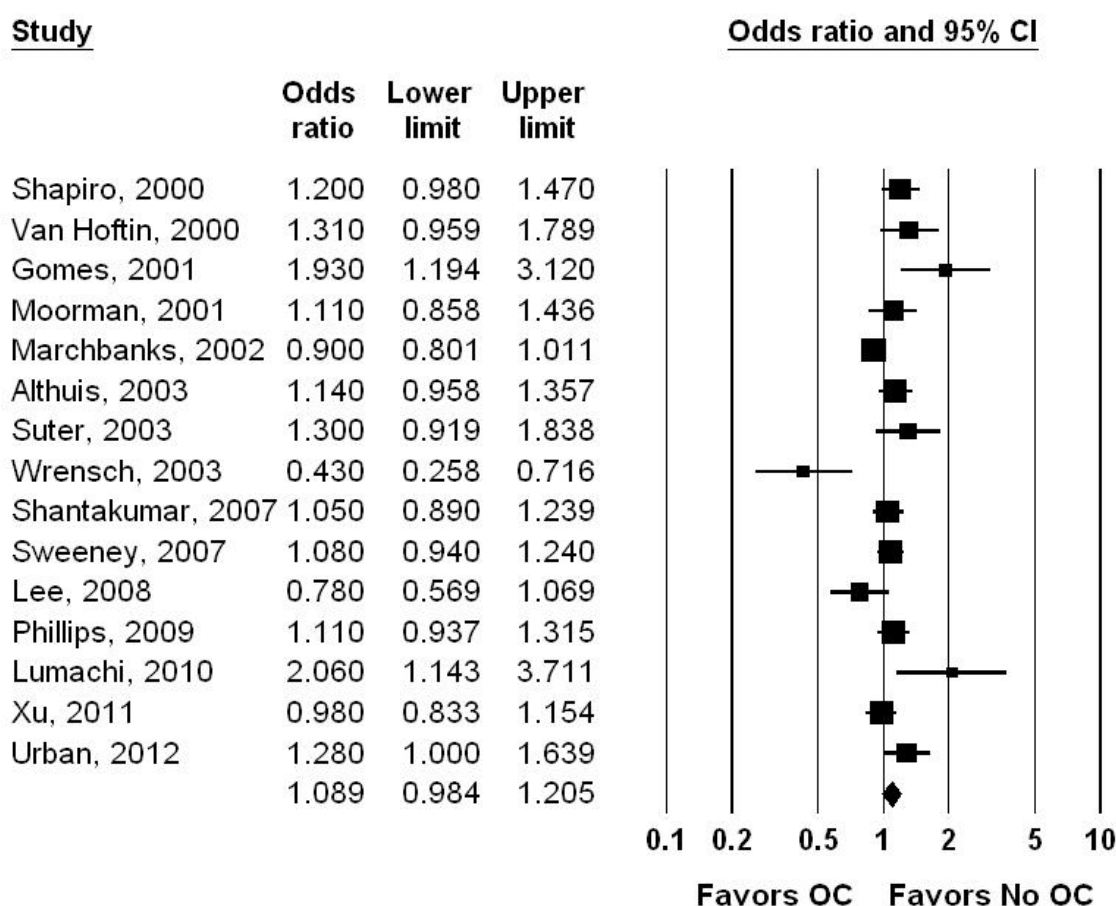
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Odds ratios for meta-analysis of ever versus never OC use.
[c]Meta-analysis code: 1= Included in meta-analysis; 2 = Excluded due to family history of breast cancer; 3 = Excluded due to BRCA mutation carriers; 4 = Excluded due to age at diagnosis ≤45 yr; 5 = Excluded due to overall ever versus never OR not reported or not calculable; 6 = Excluded due to cancer in situ only; 7 = Excluded due to all cases and controls having breast cancer; 8 = Excluded due to ER/PR/HER2 subtypes; 9 = Excluded due to data are subset of Shanghai Breast Cancer Study[224]; 10 = Excluded due to targeting certain subtypes of cancer only.

Ever Versus Never OC Use

Fifteen case-control studies representing 38,682 women[155,183,185-188,191,195,205,206,208,211,213,224,228] were included in this meta-analysis examining the effect of ever versus never OC use on the incidence of breast cancer (Table 18). Of these studies, nine were rated good quality, five fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 18. Reasons for exclusion from this analysis included the following: study populations representing specialized subgroups (e.g., BRCA mutation populations, family history, cancer subtype); reporting a subset of results from the same study as another article already included in the analysis; and not reporting an odds ratio for ever versus never OC use. Some studies gave results only by subgroup; however, in some instances we were able to combine the subgroups to calculate the odds ratio for the entire study population. Figure 23 shows the results; ever use of OCs increased the risk of breast cancer compared with never use, but the confidence interval included 1 (OR 1.09; 95% CI, 0.98 to 1.21).
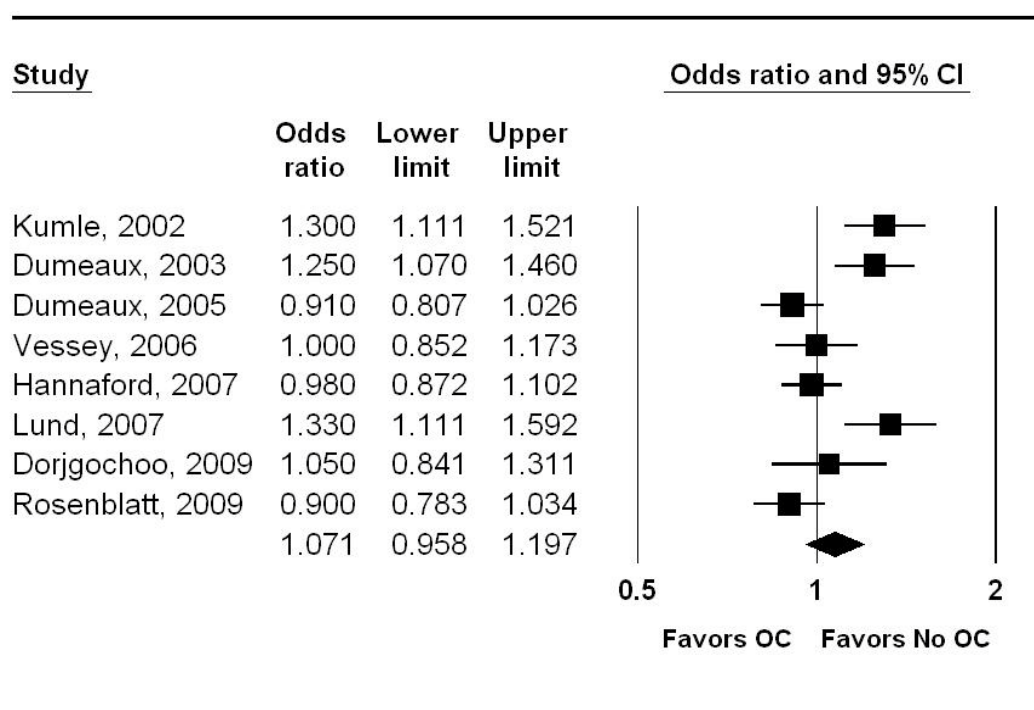
Figure 23. Forest plot for ever versus never OC use (case-control studies, breast cancer incidence)

Study	Odds ratio	Lower limit	Upper limit
Shapiro, 2000	1.200	0.980	1.470
Van Hoftin, 2000	1.310	0.959	1.789
Gomes, 2001	1.930	1.194	3.120
Moorman, 2001	1.110	0.858	1.436
Marchbanks, 2002	0.900	0.801	1.011
Althuis, 2003	1.140	0.958	1.357
Suter, 2003	1.300	0.919	1.838
Wrensch, 2003	0.430	0.258	0.716
Shantakumar, 2007	1.050	0.890	1.239
Sweeney, 2007	1.080	0.940	1.240
Lee, 2008	0.780	0.569	1.069
Phillips, 2009	1.110	0.937	1.315
Lumachi, 2010	2.060	1.143	3.711
Xu, 2011	0.980	0.833	1.154
Urban, 2012	1.280	1.000	1.639
	1.089	0.984	1.205

CI = confidence interval; OC = oral contraceptive

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Eight cohort studies representing 317,341 women across five studies and 3,981,072 person-years across three studies[37,88,138,156,216-218,221] met inclusion criteria for this meta-analysis (Table 18). Of these studies, three were rated good quality, four fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 18. Reasons for exclusion from this analysis included the following: study populations representing specialized subgroups; and not computing an effect size for ever use versus never OC use. As shown in Figure 24, the odds ratio for ever versus never use of OCs was similar to that for the case-control studies (OR 1.07; 95% CI, 0.96 to 1.20).

Figure 24. Forest plot for ever versus never OC use (cohort studies, breast cancer incidence)

CI = confidence interval; OC = oral contraceptive

The pooled effect sizes for the two groups were similar, with a test for a difference resulting in a p-value of 0.81. Therefore, we combined case-control studies and cohort studies. Across all included studies, results suggest that a history of OC use slightly but significantly increases the incidence of breast cancer compared with women who never used OCs. The odds ratio was 1.08 (95% CI, 1.00 to 1.17), with a Q-value of 73.35 for 21 degrees of freedom, p<0.001.

Sensitivity Analyses

Analyses were repeated excluding the one cohort study rated poor quality. This exclusion had a minor effect on the odds ratio estimates for all studies combined (OR 1.08; 95% CI, 1.00 to 1.16). We also conducted sensitivity analyses among U.S.-based studies only; effect sizes were smaller and no longer statistically significant (OR 1.03; CI, 0.93 to 1.14).

Duration of OC Use

Fourteen studies[138,156,183,185,188,194,195,201,205,206,211,216-218,228] were included in this meta-analysis examining the effect of duration of OC use on breast cancer incidence (Table 19). Of these, 9 were case-control studies. Six studies were rated good quality, eight fair quality, and one poor quality. We did not include data in the meta-analysis for studies that were conducted in a special population, did not have at least 3 categories for duration of use, or used a referent category other than never users.

Table 19. Data for outcomes on duration of use (breast cancer incidence)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control				
Shapiro, 2000[185]		< 1 yr 1–4 yr 5–9 yr > 10 yr	1.3 1.3 1.4 1.2	0.8 to 1.4 1.0 to 1.8 0.9 to 2.1 0.7 to 2.3
Van Hoften, 2000[186]	Total sample	1–10 yr > 10 yr	1.27 1.43	0.92 to 1.77 0.92 to 2.22
	Women ≤55 yr	1–10 yr > 10 yr	1.25 1.22	0.85 to 1.82 0.72 to 2.07
	Women ≥56 yr	1–10 yr > 10 yr	1.26 2.05	0.74 to 2.14 1.07 to 3.95
Moorman, 2001[188]	White women <50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	1.29 1.49 0.94 1.41	0.68 to 2.47 0.85 to 2.64 0.52 to 1.70 0.74 to 2.70
	African-American women <50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	1.29 1.23 1.64 1.61	0.61 to 2.72 0.66 to 2.32 0.82 to 3.28 0.77 to 3.35
	White women ≥50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	0.92 0.90 0.80 1.34	0.49 to 1.73 0.43 to 1.89 0.38 to 1.67 0.59 to 3.07
	African-American women ≥50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	0.90 0.39 2.06 1.37	0.40 to 2.01 0.16 to 0.99 0.77 to 5.53 0.27 to 6.90
Marchbanks, 2002[183]		< 1 yr 1 to < 5 yr 5 to < 10 yr 10 to < 15 yr	0.9 0.9 0.9 0.8	0.8 to 1.1 0.8 to 1.0 0.8 to 1.0 0.7 to 1.0
Narod, 2002[190]	BRCA1 carriers	0–4 yr 5–9 yr 10–14 yr 15–30 yr	1.10 1.36 1.27 1.30	0.92 to 1.31 1.11 to 1.67 0.99 to 1.64 0.91 to 1.87
	BRCA2 carriers	0–4 yr 5–9 yr 10–14 yr 15–30 yr	0.90 0.82 1.16 1.35	0.67 to 1.20 0.56 to 1.91 0.75 to 1.78 0.71 to 2.56

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Newcomer, 2003[193]	Ductal carcinoma vs. controls	< 1 yr	1.1	1.0 to 1.3
		1–4 yr	1.0	0.9 to 1.1
		5–9 yr	1.0	0.9 to 1.2
		10–14 yr	1.0	0.9 to 1.3
		> 15 yr	1.0	0.7 to 1.3
	Lobular carcinoma vs. controls	< 1 yr	1.4	1.0 to 2.0
		1–4 yr	1.1	0.8 to 1.6
		5–9 yr	1.1	0.7 to 1.7
		10–14 yr	1.1	0.7 to 1.9
		> 15 yr	1.7	0.9 to 3.5
Norman, 2003[194]		< 0.5 yr	0.73	0.5 to 1.05
		0.5 to < 2 yr	0.91	0.63 to 1.31
		2 to < 5 yr	0.83	0.56 to 1.22
		5 to < 10 yr	0.81	0.55 to 1.19
		> 10 yr	0.62	0.41 to 0.95
Suter, 2003[195]		< 1 yr	1.3	0.9 to 1.8
		5 to <10 yr	1.4	0.9 to 2.1
		> 10 yr	1.2	0.7 to 1.8
Wrensch, 2003[228]		< 2 yr	0.55	0,33 to 0.93
		2-6 yr	0.52	0.30 to 0.89
		6-10 yr	0.57	0.32 to 1.00
		>10 yr	0.47	0.27 to 0.82
Dumeaux, 2005[218]		< 5 yr	0.94	0.81 to 1.09
		5–9 yr	0.91	0.75 to 1.11
		> 10 yr	0.87	0.72 to 1.06
Milne, 2005[198]	BRCA1 carriers	1–4 yr	0.25	0.09 to 0.70
		5–9 yr	0.22	0.09 to 0.58
		> 10 yr	0.20	0.08 to 0.54
	BRCA2 carriers	1–4 yr	0.97	0.26 to 3.56
		5–9 yr	1.34	0.41 to 4.45
		> 10 yr	0.73	0.20 to 2.65
	Noncarriers	1–4 yr	0.76	0.54 to 1.07
		5–9 yr	0.97	0.70 to 1.34
		> 10 yr	1.02	0.74 to 1.41
Gronwald, 2006[94]		< 2 yr	0.9	0.5 to 1.2
		≥ 2 yr	0.8	0.5 to 1.4
Haile, 2006[199]	BRCA1 carriers	1–4 yr	0.61	0.31 to 1.17
		≥ 5	0.61	0.32 to 1.16
	BRCA2 carriers	1–4 yr	0.79	0.26 to 2.37
		≥ 5 yr	1.45	0.64 to 3.27
Ma, 2006[201]		< 1 yr	0.78	0.51 to 1.18
		1–4 yr	0.80	0.54 to 1.19
		5–9 yr	0.62	0.42 to 0.93
		> 10 yr	0.84	0.56 to 1.26

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Rosenberg, 2006[200]	Ductal breast cancer	< 5 yr > 5 yr	0.9 0.9	0.7 to 1.0 0.7 to 1.1
	Lobular cancer	< 5 yr > 5 yr	0.6 0.9	0.4 to 0.9 0.6 to 1.4
	Tubular cancer	< 5 yr > 5 yr	1.3 1.0	0.7 to 2.2 0.5 to 1.9
Folger, 2007[203]	Premenopausal	< 6 mo	1.3	0.60 to 1.0
	Postmenopausal	< 6 mo	0.8	0.60 to 1.28
Nichols, 2007[204]		1–1.9 yr 2–2.4 yr 4.5–8.9 yr > 9 yr	1.13 1.22 1.04 1.06	0.96 to 1.33 1.04 to 1.44 0.86 to 1.25 0.88 to 1.27
Shantakumar, 2007[205]	Premenopausal women	< 6 mo 6–12 mo 13–60 mo > 60 mo	1.31 1.38 1.27 1.54	0.68 to 2.55 0.93 to 2.03 0.90 to 1.79 1.06 to 2.24
	Postmenopausal <65 yr	< 6 mo 6–12 mo 13–60 mo > 60 mo	1.52 0.78 0.88 1.01	0.77 to 3.03 0.53 to 1.16 0.60 to 1.28 0.69 to 1.48
	Postmenopausal >65 yr	< 6 mo 6–12 mo 13–60 mo > 60 mo	0.93 0.51 1.15 0.86	0.23 to 3.77 0.27 to 0.95 0.58 to 2.31 0.44 to 1.66
Sweeney, 2007[206]	Hispanics only	< 5 yr 5–9 yr 10–19 yr > 20 yr	1.14 1.06 1.03 1.43	0.87 to 1.49 0.77 to 1.46 0.74 to 1.43 0.69 to 2.95
	Non-Hispanic whites	< 5 yr 5–9 yr 10–19 yr > 20 yr	1.14 0.99 0.96 1.49	0.93 to 1.40 0.78 to 1.25 0.75 to 1.23 0.96 to 2.30
Figueiredo, 2008[207]		< 5 yr ≥ 5 yr	0.88 0.82	0.65 to 1.20 0.61 to 1.10
Lee, 2008[208]	BRCA1/2 carriers	< 4 yr 5–9 yr ≥ 10 yr	0.65 0.78 0.63	0.30 to 1.42 0.34 to 1.77 0.26 to 1.51
	Noncarriers	≤ 4 yr 5–9 yr ≥ 10 yr	0.80 0.66 0.95	0.55 to 1.16 0.45 to 0.98 0.64 to 1.42
Nyante, 2008[209]	Ductal carcinoma	< 1 yr 1–3 yr > 4 yr	1.13 1.11 1.30	0.80 to 1.61 0.89 to 1.38 1.06 to 1.59
	Lobular breast carcinoma	< 1 yr 1–3 yr > 4 yr	1.63 1.23 0.92	0.72 to 3.65 0.70 to 2.14 0.53 to 1.59

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Phillips, 2009[211]	Invasive breast carcinoma	< 5 yr 5–10 yr > 10 yr	1.06 1.15 1.21	0.88 to 1.28 0.93 to 1.42 0.94 to 1.56
	DCIS	< 5 yr 5–10 yr > 10 yr	0.75 1.27 0.94	0.49 to 1.15 0.79 to 2.04 0.59 to 1.49
Rosenberg, 2009[210]	All invasive breast cancers	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.6 1.9 1.7	1.0 to 1.6 1.2 to 2.1 1.4 to 2.7 1.0 to 2.9
	Women <50 yr	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.9 1.8 1.3	1.0 to 1.8 1.3 to 2.7 1.1 to 2.8 0.6 to 2.7
	Women >50 yr	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.3 2.0 2.4	0.9 to 1.8 0.8 to 2.0 1.2 to 3.5 1.0 to 5.5
	Black women	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 2.3 2.5 NR	0.8 to 2.1 1.3 to 3.9 1.3 to 4.7 NR
	White women	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.4 1.8 1.4	1.0 to 1.7 1.0 to 1.9 1.2 to 2.5 0.8 to 2.6
Figueiredo, 2010[212]	BRCA1 carriers	< 5 yr ≥ 5 yr	2.91 2.07	0.75 to 11.30 0.60 to 7.11
	BRCA2 carriers	< 5 yr ≥ 5 yr	0.86 2.02	0.21 to 3.57 0.52 to 7.81
Ma, 2010[214]	Triple-negative breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	0.94 0.93 1.12 1.06	0.63 to 1.42 0.63 to 1.36 0.75 to 1.66 0.70 to 1.61
	ER-/PR-/HER2+ breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	1.22 1.15 0.86 1.59	0.61 to 2.43 0.59 to 2.23 0.40 to 1.85 0.81 to 3.10
	Luminal A breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	0.98 1.04 0.78 0.87	0.73 to 1.32 0.79 to 1.37 0.57 to 1.06 0.63 to 1.19
	Luminal B breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	1.17 1.12 1.50 1.20	0.62 to 2.24 0.60 to 2.07 1.80 to 2.78 0.62 to 2.32

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Xu, 2011[224]		< 18 months ≥ 18 months	0.96 1.11	0.78 to 1.18 0.89 to 1.37
Marchbanks, 2012[226]	100 mcg mestranol/ 1.0 mg ethynodiol diacetate	< 2 yr ≥ 2 yr	0.8 0.8	0.4 to 1.5 0.5 to 1.1
	35 mcg ethinyl estradiol/0.5 mg norethindrone	< 2 yr ≥ 2 yr	1.2 1.2	0.7 to 2.0 0.6 to 1.4
	35 mcg ethinyl estradiol/1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.9 1.0	0.6 to 1.4 0.8 to 1.4
	50 mcg mestranol/ 1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.8 0.8	0.5 to 1.2 0.6 to 1.1
	80 mcg mestranol/ 1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.6 0.8	0.4 to 0.99 0.6 to 1.0
	100 mcg mestranol/ 2.0 mg norethindrone	< 2 yr ≥ 2 yr	1.1 0.7	0.7 to 1.6 0.5 to 0.9
	100 mcg mestranol/ 2.5 mg norethindrone	< 2 yr ≥ 2 yr	0.8 1.0	0.4 to 1.4 0.6 to 1.7
	30 mcg ethinyl estradiol/0.3 mg norgestrel	< 2 yr ≥ 2 yr	1.5 0.8	0.9 to 2.6 0.5 to 1.1
	50 mcg ethinyl estradiol/0.5 mg norgestrel	< 2 yr ≥ 2 yr	1.1 0.6	0.6 to 2.0 0.4 to 0.98
	35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone	< 2 yr ≥ 2 yr	0.5 0.4	0.2 to 1.4 0.2 to 0.8

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Cohort				
Grabrick, 2000[215]		1–4 yr	1.5	1.0 to 2.3
		> 4 yr	1.3	0.9 to 1.9
Kumle, 2002[216]		< 5 yr	1.2	1.0 to 1.5
		5–9 yr	1.2	1.0 to 1.5
		10–14 yr	1.4	1.1 to 1.8
		> 15 yr	1.3	1.0 to 1.8
Dumeaux, 2003[217]		0–4 yr	0.94	0.81 to 1.09
		5–9 yr	0.91	0.75 to 1.11
		> 10 yr	0.87	0.72 to 1.06
Silvera, 2005[219]	Women with any family history of breast cancer	1–12 mo	1.05	0.79 to 1.42
		12–36 mo	0.94	0.70 to 1.26
		36–84 mo	0.85	0.64 to 1.12
		> 84 mo	0.74	0.55 to 0.99
	Women with first-degree relatives of breast cancer	1–12 mo	1.18	0.75 to 1.38
		12–36 mo	1.24	0.82 to 1.88
		36–84 mo	1.07	0.72 to 1.59
		> 84 mo	0.75	0.47 to 1.19
	Women with second-degree relatives with breast cancer	1–12 mo	0.92	0.58 to 1.44
		12–36 mo	0.72	0.45 to 1.17
		36–84 mo	0.52	0.32 to 0.84
		> 84 mo	0.84	0.55 to 1.27
Vessey, 2006[156]		< 48 mo	0.9	0.8 to 1.1
		49–96 mo	0.9	0.8 to 1.1
		> 97 mo	1.0	0.8 to 1.1
Brohet, 2007[220]		1–3 yr	1.34	1.00 to 2.78
		4–8 yr	1.59	1.19 to 2.13
		> 9 yr	1.61	1.18 to 2.20
Hannaford, 2007[37]		< 48 mo	1.00	0.81 to 1.23
		49–96 mo	0.95	0.75 to 1.21
		> 96 mo	1.22	0.97 to 1.52
Dorjgochoo, 2009[88]		< 2 yr	1.18	0.89 to 1.56
		> 2 yr	0.93	0.68 to 1.25
Rosenblatt, 2009[138]		1–11 mo	0.71	0.56 to 0.90
		12–59 mo	1.04	0.86 to 1.27
		60–119 mo	0.97	0.69 to 1.36
		> 120 mo	0.94	0.66 to 1.32
Hannaford, 2010[33]		< 4 yr	0.92	0.64 to 1.34
		4–8 yr	0.87	0.58 to 1.31
		> 8 yr	1.13	0.75 to 1.70
Hunter, 2010[222]		0–8 yr	1.16	0.80 to 1.69
		> 8 yr	1.42	1.05 to 1.94

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Cohort (continued)				
Rosenberg, 2010[223]	ER+/PR+ breast cancers	< 5 yr 5–9 yr 10–14 yr > 15 yr	1.03 1.09 1.45 1.24	0.79 to 1.35 0.78 to 1.52 1.02 to 2.07 0.74 to 2.09
	ER-/PR- breast cancers	< 5 yr 5–9 yr 10–14 yr > 15 yr	1.67 1.37 1.83 2.25	1.18 to 2.36 0.89 to 2.11 1.11 to 2.90 1.23 to 4.11
	ER+/PR- breast cancer	< 5 yr 5–9 yr 10–14 yr > 15 yr	0.91 1.31 0.82 0.75	0.55 to 1.49 0.74 to 2.33 0.37 to 1.78 0.22 to 2.54
Pooled				
Dolle, 2009[184]	All subjects	1–2 yr 3–5 yr > 6 yr	1.3 1.4 1.3	0.9 to1.7 1.0 to 2.0 1.0 to1.8
	Women with triple-negative breast cancer	1–2 yr 3–5 yr > 6 yr	1.6 2.8 2.9	0.9 to 3.3 1.5 to 5.3 1.6 to 5.3

BRCA = breast cancer genetic mutation; CI = confidence interval; ER = estrogen receptor; mo = month/months; NR = not reported; OR = odds ratio; PR = progesterone receptor; yr = year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

As described in the Methods section, we categorized duration of OC use in the included studies into four intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. These results, summarized in Table 20, show no time-dependent relationship as a function of duration of use. There was significant heterogeneity, with a t-value of 5.84 for 19 degrees of freedom, $p < 0.0001$. However, the test was underpowered; there would have to be a 40-percent difference in risk of breast cancer by time period in order to detect significant differences.

Table 20. Estimated odds ratios by duration of OC use (breast cancer incidence)

Duration Interval	Odds Ratio (95% Confidence Interval)	P-Value
0–12 months	0.95 (0.83 to 1.09)	0.465
13–60 months	1.03 (0.92 to 1.15)	0.644
61–120 months	1.01 (0.90 to 1.13)	0.895
>120 months	1.04 (0.93 to 1.17)	0.457

Time Since Last OC Use

Eleven studies[183,185,188,191,195,196,203,206,208,210,216,218] were included in this meta-analysis examining the effect of time since last OC use on breast cancer incidence. Of these, 9 were case-control studies and 2 cohort studies. Five studies were rated good quality and seven fair quality. We did not include data in the meta-analysis for studies that only reported time since last use

data for a special population, did not have at least three categories for duration of use, or used a referent category other than never users.

As described in the Methods, we categorized time since last OC use into four intervals: (1) 0 to 5 years, (2) 5 to 10 years (3) 10 to 20 years, (4) more than 20 years. These results, summarized in Table 21, show a time-dependent relationship as a function of time since last OC use, with higher risk associated with more recent use of OCs and the odds ratio approaching 1 (no effect) by 20+ years of use. There was significant heterogeneity. The estimated value of σ is 0.12. The t-value is 4.95 for 11 degrees of freedom, p=0.0004.

Table 21. Estimated odds ratios by time since last OC use (breast cancer incidence)

Time Interval	Odds Ratio (95% Confidence Interval)	P-Value
0–5 years	1.21 (1.04 to 1.41)	0.0178
5–10 years	1.17 (0.98 to 1.38)	0.0776
10–20 years	1.13 (0.97 to 1.31)	0.1705
>20 years	1.02 (0.88 to 1.18)	0.7686

We also fitted a model to the individual reported odds ratios. The time (in years) was assumed to be the middle of the interval reported. The fitted model was odds ratio equals (1 + 0.2711 * EXP(-0.06551 * years) (Figure 25). The slope was significant, with a chi-square of 4.8 for 1 degree of freedom, p=0.0285. The model produced a slightly better fit than did the individual odds ratios in Table 21 and show a time-dependent relationship.

Figure 25. Estimated and model-fitted odds ratios for time since last OC use (breast cancer incidence)
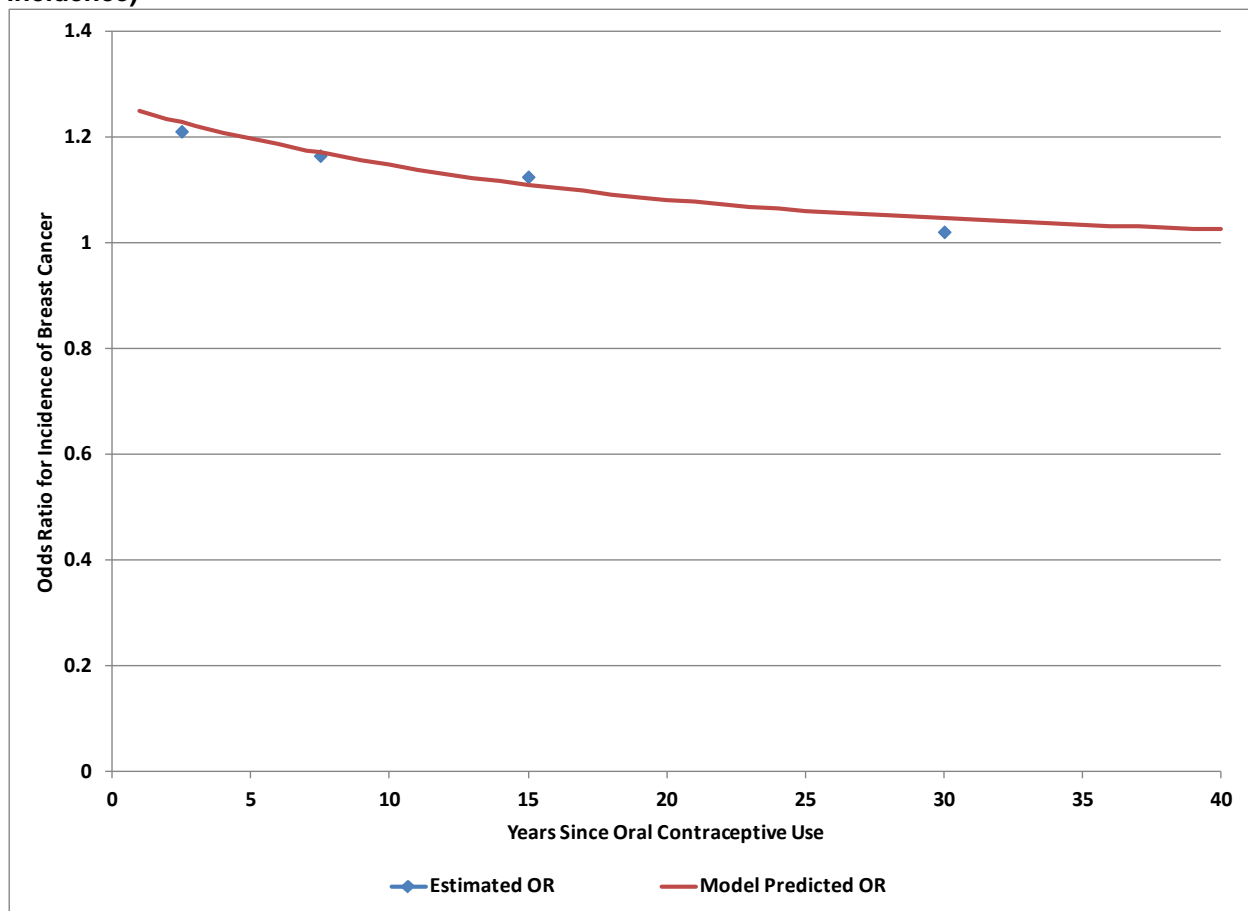
OR = odds ratio
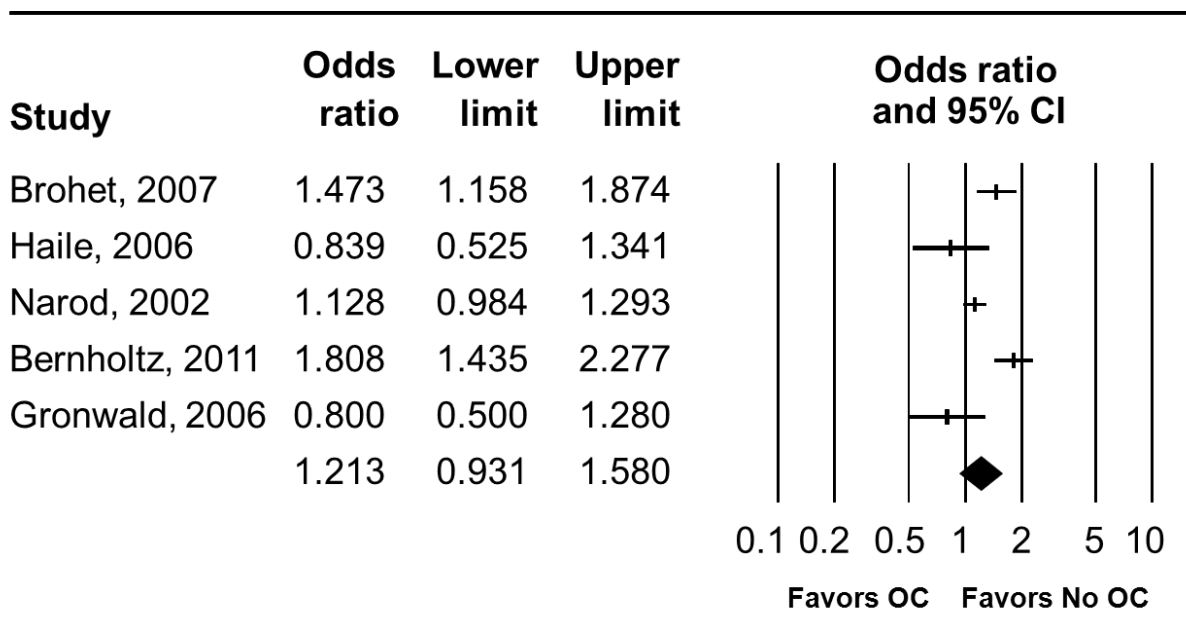
Special Populations

BRCA Mutation Carriers

We identified eight studies that were conducted with women who were BRCA1 or BRCA2 carriers.[94,190,198,199,208,212,220,225] Five BRCA1/2 carrier studies representing 4555 women across 4 studies and 65,180 person-years in 1 study assessed the risk of breast cancer as a function of OC use comparing BRCA carriers with each other and were included in a meta-analysis.[94,190,199,220,225] Three were case-control studies and two cohort studies; one was rated good quality and four fair quality. Two additional studies[198,208] examined the risk of breast cancer incidence in OC users among carriers of the BRCA mutation compared with control groups who were noncarriers, and one report[212] was conducted with BRCA carriers with either bilateral (cases) or unilateral (controls) cancers. Data from these three articles were not included in this meta-analysis.

Figure 26 shows pooled results indicating a slight, but not significant, increase in the risk of breast cancer among BRCA carriers who have ever used OCs, with an odds ratio of 1.21 (95% CI, 0.93 to 1.58). There was evidence of heterogeneity, with a Q-value of 20.005 for 4 degrees of freedom, p<0.001.

Figure 26. Forest plot for BRCA carriers compared with each other (breast cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Brohet, 2007	1.473	1.158	1.874	
Haile, 2006	0.839	0.525	1.341	
Narod, 2002	1.128	0.984	1.293	
Bernholtz, 2011	1.808	1.435	2.277	
Gronwald, 2006	0.800	0.500	1.280	
	1.213	0.931	1.580	

0.1 0.2 0.5 1 2 5 10

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Family History of Breast Cancer

We identified one case-control study[189] and two cohort studies[215,219] that assessed the risk of breast cancer among OC users with family histories of breast cancer, but these studies could not be pooled due to differences in study design and comparisons (Table 22). Of these studies, two were rated good quality and one fair quality. Overall, study results were mixed, possibly due to variation in how family history was defined across studies. One study[215] recruited first-degree, second-degree, and marry-in relatives of patients with breast cancer. Overall, this study found a significant increase in breast cancer for ever use (risk ratio [RR] 1.4; 95% CI, 1.0 to 2.0). This effect was greater among sisters and daughters (RR 3.3; CI, 1.6 to 6.7) but not among granddaughters and nieces of the affected family member (RR 1.2; CI, 0.8 to 2.0).

Another study[189] identified breast cancer families. A breast cancer family was defined as four cases of breast cancer (at any age), two breast cancer cases younger than 55 years of age, one case younger than 50 years, or a combination of breast cancer younger than 60 years of age and ovarian cancer (at any age) in a family. First-degree family members of affected women 40 to 60 years of age made up the pool of subjects for cases and controls. OC use was not associated with an increase in breast cancer (RR 0.90; 95% CI, 0.68 to 1.18). However, among BRCA1 mutation carriers, risk of breast cancer was associated with OC use, but the test was not significant (RR 2.00; CI, 0.36 to 10.9).

Another study[219] recruited women with either a first-degree or second-degree family member with breast cancer. OC use was associated with a reduction in risk of breast cancer among all women with breast cancer (hazard ratio [HR], 0.88; 95% CI, 0.73 to 1.07). However, among first-degree relatives, OC use did not reduce the risk of breast cancer (HR, 1.03; CI, 0.78 to 1.38). Among second-degree relatives, a protective effect for OC use was observed, but the comparison was not significant (HR, 0.74; CI, 0.54 to 1.00). This study highlights the heterogeneity of effects associated with multiple definitions of family history of breast cancer.

Table 22. Family history and association between OC use and breast cancer incidence

Study[a]	Study Details	Definition of Family History	OR	95% CI	Region	Study Quality
Case-Control						
Heimdal, 2002[189]	Women aged 40–60 yr Cases: 380 Controls: 1043	First-degree family member	0.90	0.68 to 1.19	Norway	Fair
Cohort						
Grabrick, 2000[215]	Family members of women aged 21–88 yr Exposed: 3156 Unexposed: 2994	First-degree, second-degree, or marry-in family member	1.4	1.0 to 2.0	U.S.	Good
Silvera, 2005[219]	Women aged 40–59 yr Exposed: 962 Unexposed: 745	First-degree or second-degree family member	0.88	0.73 to 1.07	Canada	Good
	Women with first-degree relatives Exposed: 433 Unexposed: 362		1.03	0.78 to 1.38		
	Women with second-degree relatives Exposed: 414 Unexposed: 284		0.74	0.54 to 1.00		

CI = confidence interval; OC = oral contraceptive; OR = odds ratio; U.S. = United States; yr = year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

Breast Cancer in Younger Women

Three case-control studies[197,198,209] assessed the risk of breast cancer among younger women, defined as under 45 years of age at time of diagnosis (Table 18). Of these studies, one was good quality and two fair quality; all were conducted in Western countries. We were not able to quantitatively synthesize studies because one study was conducted in a special population[209] leaving only two studies. No clear pattern emerged from these studies. One study conducted among women with either ductal or lobular carcinomas[209] reported a significant increase in the odds of breast cancer among younger women who had ever used OCs (OR 1.21; 95% CI, 1.01 to 1.45). Two studies not conduced among special populations[197,198] did not find significant effects for ever use of OCs on risk of breast cancer (OR 1.65; 95% CI, 0.95 to 1.45[197] and OR 0.93; 95% CI, 0.69 to 1.24[198]).

Specific Types of Breast Cancers

Three case-control studies,[204,207,214], one cohort study,[223] and one pooled analysis[184] reported on associations between OCs and specific subtypes of breast cancer. Study characteristic and results of ever versus never use are presented in Table 23.

Three studies[184,214,223] assessed the risk of breast cancer subtypes defined by tumor hormone receptor protein expression status; i.e., estrogen receptor (ER), progesterone receptor, (PR) and human epidermal growth factor (HER2) protein expression or gene amplification. Differences in populations and methods precluded pooling studies. Overall, the two case-control studied did not demonstrate a statistically significant increase in the risk of these cancers associated with OC use. However, pooled analyses reported a significantly higher odds of triple-negative breast

cancer associated with OC use. Doole also reported that fewer years since last use and longer use of OCs significantly increased the risk of triple-negative breast cancers.

Two other studies[204,207] assessed the association of OC use and breast cancer subtypes not categorized by ER, PR, or HER2 status. One study[207] compared women in the United States with asynchronous bilateral breast cancer (cases) to women with unilateral breast cancer (controls) and found no significant association. One study[204] compared healthy community-based controls to women with cancer in situ 20 to 74 years of age. Similar to population studies of invasive breast cancer, this study found a small and significant increase in breast cancer in situ.

Table 23. Breast cancer subtype and association between OC use and breast cancer incidence

Study[a]	Study Details	Subtype of Breast Cancer	OR	95% CI	Region	Study Quality
Case-Control						
Nichols, 2007[204]	Women aged 20–74 yr in Collaborative Breast Cancer Study Cases: 1878 Controls: 8041 Recruitment period: 1997–2001	Breast cancer *in situ*	1.10	0.99 to 1.25	U.S.	Good
Figueiredo, 2008[207]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study Cases: 708 asynchronous bilateral breast cancer Controls: 1399 unilateral breast cancer only Recruitment period: 1985–2000	Unilateral or bilateral breast cancer	0.88	0.67 to 1.16	U.S.	Fair
Ma, 2010[214]	White or African-American women aged 35–64 yr Cases: 335 triple-negative breast cancer, registries Controls: 2015, community Cases: 97 ER-/PR/HER2+ breast cancer, registries Controls: 2015, community Cases: 645 luminal A breast cancer, registries Controls: 2015, community Cases: 120 luminal B breast cancer, registries Controls: 2015, community Recruitment period: 2000–2003	Triple-negative, luminal A, luminal B, or ER-/PR-/HER2+ breast cancers	0.93 1.00 1.21 1.23	0.74 to 1.17 0.72 to 1.39 0.69 to 2.11 0.73 to 2.10	U.S.	Good

Table 23. Breast cancer subtype and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	Subtype of Breast Cancer	OR	95% CI	Region	Study Quality
Cohort						
Rosenberg, 2010[223]	Women aged 21–69 yr in Black Women's Health Study Exposed: 445,824 person-years Unexposed: 128,768 person-years *ER+/PR+ receptor status* Cases: 284 *ER+/PR- receptor status* Cases: 80 *ER-/PR- receptor status* Cases: 46 Recruitment period: 1995	ER/PR receptor status breast cancers	IRR=1.11 IRR=0.97 IRR=1.65	0.86 to 1.42 0.61 to 1.54 1.19 to 2.30	U.S.	Fair
Pooled						
Dolle, 2009[184]	Women aged 21–45 yr in Seattle-Puget Sound Cases: 187 Controls: 1569 Recruitment periods: 1983–1990; 1990–1992	Triple-negative breast cancers	2.5	1.4 to 4.3	U.S.	Fair

CI = confidence interval; ER = estrogen receptor; HER = human epidermal growth factor receptor; IRR = incidence rate ratio; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; U.S. = United States; yr=year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

OC Use and Breast Cancer Mortality

We identified six studies;[33,164-166,229-232] all six were cohort studies, and of these, three were rated good quality and three fair quality (Table 24). Three studies were based in the United States,[229,231,232] and the remaining studies were conducted in the United Kingdom.[33,165,230]

As with ovarian cancer mortality, the studies evaluated two different populations and questions. Three studies[33,165,232] evaluated population-level, cause-specific mortality from breast cancer (as well as other cancers, including ovarian cancer). The general question addressed was, "Are women who used OCs more likely to die from breast cancer than women who did not use OCs?" These studies did not find that OC use significantly increased risk.

Three other cohort studies[229-231] addressed the question, "Among women who develop breast cancer, are women who used OCs more or less likely to die from breast cancer within a certain time period than those who did not use OCs?" Again, no studies detected significant differences. Because studies did not report comparable statistics (e.g., hazard ratios, odds ratios), we did not perform meta-analyses.

Table 24. Study characteristics and association between OC use and breast cancer mortality

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality
Cohort						
Postdiagnosis Survival						
Trivers, 2007[231]	Women aged 20–54 yr with invasive breast cancer Exposed: 897 Unexposed: 367 Recruitment period: 1990–1992	1.00	0.77 to 1.29	Age, income	U.S.	Good
Wingo, 2007[229]	Women aged 20–54 yr in Cancer and Steroid Hormone Study Exposed: 2237 Unexposed: 1679 Recruitment period: 1980–1982	0.94	0.83 to 1.06	Age, race, menopausal status, BMI, education, income, time since last birth, use of HRT, radiation therapy	U.S.	Good
Barnett, 2008[230]	Women <55 yr in Studies of Epidemiology and Risk Factors in Cancer Heredity Exposed: 3069 Unexposed: 1357 Recruitment period: 1991–1996	0.93	0.78 to 1.1	Crude	UK	Fair
Population-Level Mortality						
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	0.9	0.74 to 1.08	Age, parity, smoking, social class, HRT	UK	Fair
Vessey, 2010[165]	Oxford Family Planning Association Contraceptive Study (age NR) 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	1	0.8 to 1.2	Age, parity, BMI, smoking, social class	UK	Fair

Table 24. Study characteristics and association between OC use and breast cancer mortality (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality
	Cohort (continued)					
	Population-Level Mortality (continued)					
Lu, 2011[232]	Women in the Women's Contraceptive and Reproductive Study (CARE) and the California Teachers Study (CTS) *CARE* <u>Exposed</u>: 3524 <u>Unexposed</u>: 1041	1.03	0.85 to 1.25	Age, race, BMI, age at menarche, smoking, study site, ER status, tumor stage, education, alcohol consumption, number of comorbidities, number of mammograms	U.S.	Good
	CTS <u>Exposed</u>: 2439 <u>Unexposed</u>: 1490	0.89	0.64 to 1.23	Age, race, BMI, age at menarche, smoking, CARE breast cancer cases		

BMI = body mass index; CI = confidence interval; HRT = hormone replacement therapy; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratios for meta-analysis of ever versus never OC use.

Strength of Evidence for OC Use and Risk of Breast Cancer

As described in the Methods section, strength of evidence (SOE) assessments are based on consideration of four domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as SOE and can be insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both quantity and quality, and whether the entire body of current research provides a consistent and precise estimate of effect. Interventions that have shown significant benefit in a small number of studies or have not yet been replicated using rigorous study designs will have insufficient or low strength of evidence, despite potentially offering clinically important benefits. Future research may find that the intervention is either effective or ineffective.

We rated the strength of evidence for the effect of ever use of OC on breast cancer incidence as moderate (Table 25). Future studies are not likely to impact the direction but may influence the magnitude of the effect toward a small but significant increase in the risk of breast cancer associated with having ever used OCs. Most studies were of good or fair quality and exhibited consistent findings. The overall confidence interval for the summary estimate demonstrates a high level of precision. However, all included studies were observational thus; some risk of bias due to limitations of the study designs may exist. The SOE for the duration of use on risk of breast cancer incidence is low; future studies may impact strength and direction of estimates. Results were inconsistent with high level of heterogeneity across studies. Furthermore, the quantitative synthesis of these studies was underpowered resulting in low precision and confidence in point estimates. As with the overall effect of OCs, there may be some risk of bias due to limitations of the observational study designs. The SOE for time since last use on the risk of breast cancer incidence was graded as low. It is likely that future studies may impact strength of estimates. There was significant heterogeneity of effects. Moreover, we were not able to assess the interaction of time since last use with other important time-dependent factors that could impact the overall estimate of effect (e.g., times since last use by age at first use).

The SOE for the association of OC use on breast cancers among women with a family history of breast cancer and in younger women at time of diagnosis was graded as insufficient. Differences in studies designs, such as how family history was defined, precluded quantitative synthesis. Moreover, there were only a handful of studies in each of these special populations and results were heterogeneous and exhibited inconsistent and imprecise findings. We graded the evidence as low among BRCA1/2 carriers. We were able to conduct a meta-analysis, but with only three studies; thus, precision and consistence were not optimal.

We graded the SOE for the risk of breast cancer mortality as moderate. The summary estimate included six large cohort studies that contributed a high level of precision. Results were consistent across studies. It is unlikely that future studies will influence the direction of this effect.

Table 25. Strength of evidence domains for the effect of OC use on breast cancer

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Breast Cancer in Overall Population						
Ever vs. never use	23 (356,023 across 20 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 1.08 (1.00 to 1.17)
Duration of use	14 (291,407 across 12 studies and 2,898,072 person-years across 2 studies)	Medium	Inconsistent	Direct	Imprecise	Low No increase in risk for longer durations of use
Time since last use	11 (200,258)	High	Inconsistent	Direct	Imprecise	Low Reduced risk over time since last use 0–5 yr: 1.21 (1.04 to 1.41) 5–10 yr: 1.17 (0.98 to 1.38) 10–20 yr: 1.13 (0.97 to 1.31) >20 yr: 1.02 (0.88 to 1.18)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	5 (4555 across 4 studies, and 65,180 person-years in 1 study)	Medium	Inconsistent	Direct	Imprecise	Low Trend toward slight increase in risk 1.21 (0.93 to 1.58)
Incidence in Women With Family History						
Ever vs. never use	3 (9280)	High	Inconsistent	Direct	Imprecise	Insufficient Not performed
Incidence in Young Women						
Ever vs. never use	3 (5716)	Medium	Inconsistent	Direct	Imprecise	Insufficient Not performed
Mortality From Breast Cancer						
Ever vs. never use	3 (54,606 across 2 studies and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Imprecise	Low No significant increase in risk 0.94 (0.87 to 1.02)
Survival After Diagnosis of Breast Cancer						
Ever vs. never use	3 (9606)	Medium	Consistent	Direct	Imprecise	Low No significant increase in risk

BRCA = breast cancer genetic mutation; CI = confidence interval; SOE = strength of evidence; yr = year/years

OC Use and Cervical Cancer Incidence

We identified 12 studies that evaluated the association between OC use and the incidence of cervical cancer.[37,138,155,156,233-241] including two articles from an International Agency for Research on Cancer (IARC) study representing distinct populations.[240,241] Of these, nine were case-control studies, three cohort studies, and one pooled analysis; five studies were rated good quality, four fair quality, and four poor quality. Of the two articles from the IARC study, one was a pooled analysis and one a case-control design. Only two studies were conducted with U.S.-based populations and three were conducted among women selected for HPV+ infection status (Table 26).

Table 26. Study characteristics and association between OC use and cervical cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
		Case-Control					
Madeleine, 2001[233]	Women aged 18–70 yr in U.S. Surveillance, Epidemiology, and End Results (SEER) Cases: 150 cervical cancer, SEER registry Controls: 651, population Recruitment period: 1990–1996	2.7	1.2 to 5.8	Age, lifetime number of sex partners, interval since last screening pap smea	U.S.	Good	1
Santos, 2001[234]	Women recruited from hospitals in Lima (age NR) Cases: 186 invasive cervical cancer, hospitals Controls: 31, hospitals Recruitment period: 1996–1997	2.7	0.9 to 8.4	Age, screening history, age at first intercourse, ever pregnancy	Peru	Poor	2
Green, 2003[235]	White women aged 20–44 yr selected from 5 UK cancer registries Cases: 391 squamous cancer, registries Controls: 923, outpatients Cases: 180 adenocarcinoma, registries Controls: 923, outpatients Recruitment period: 1987–1989	1.37 1.56	0.97 to 1.94 1.01 to 2.42	Age, smoking, region, total number of sexual partners, age at first intercourse, duration of oral contraceptive use, number of negative screening results and education	UK	Good	1
Shapiro, 2003[236]	Women <60 yr at gynecological oncology clinics at tertiary care hospitals in Cape Town Cases: 524, invasive cervical cancer, hospitals Controls: 1541, hospitals Recruitment period: 1998–2001	0.8	0.7 to 1.1	Age, race, smoking, age at first sexual intercourse, lifetime sexual partners, number of pap smears, education, rural vs. urban	South Africa	Fair	1
Shields, 2004[237]	Patients aged 20–74 yr from hospitals in 5 U.S. cities Cases: 235 squamous cervical cancer, hospitals Controls: 209, community Recruitment period: 1982–1984	NR	NR	NA	U.S.	Poor	2

Table 26. Study characteristics and association between OC use and cervical cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Hammouda, 2005[241]	Women in Algeria Cases: 190, hospital Controls: 197, hospital Recruitment period: 1997–1999	NR	NR	NA	Algeria	Good	2
Nojomi, 2008[238]	Patients >30 yr from 1 of 7 general hospitals in Tehran Cases: 300, invasive cervical cancer, hospitals Controls: 319, hospitals Recruitment period: 2005–2006	0.9	0.6 to 1.2	NA (unadjusted)	Iran	Poor	1
Vanakankovit, 2008[239]	Patients aged 30–70 yr at a hospital in Bangkok Cases: 60 invasive cervical CA, hospital Controls: 180, hospital Recruitment period: 2006–2007	1.45	0.79 to 2.64	NA (unadjusted)	Thailand	Fair	1
Urban, 2012[155]	Black South African women aged 18–79 yr Cases: 241, hospital Controls: 156, hospital Recruitment period: 1995–2006	0.97	0.76 to 1.24	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	4.2	1.8 to 12.0	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

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Table 26. Study characteristics and association between OC use and cervical cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
*Cohort (continued)*						
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at study entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	1.33	0.92 to 1.94	Age, parity, smoking, social status	UK	Fair	1
Rosenblatt, 2009[138]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.13	0.02 to 0.96	Age, parity	China	Poor	1
*Pooled*						
Moreno, 2002[240]	HPV-positive women in Europe, South America, and Asia Total sample Cases: 1,676 Controls: 255 Cases: 1,465 invasive cervical cancer Controls: 227 Cases: 211 cervical cancer *in situ* Controls: 28 Mean age of cases: 49 yr Recruitment period: NR	1.42 1.29 2.54	0.99 to2.04 0.88 to1.91 0.95 to6.78	Age, parity, study site, education, screening history, age at first intercourse, number of partners	Europe, South America, Asia	Fair	2

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; NA = not applicable; NR = not reported; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; UK = United Kingdom; U.S. = United States; yr = year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Odds ratios for meta-analysis of ever versus never OC use.
[c]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to HPV-positive population

Ever Versus Never OC Use

HPV-Positive Populations

Persistent infection with one or more oncogenic HPV types is required for cervical carcinogenesis; thus, women with HPV represent the most relevant population to assess the risks associated of cervical cancer associated with OC use. Only three studies[234,237,240] assessed the association between OC use and cervical cancers among women positive for HPV (HPV+). Limited studies across comparisons precluded quantitative synthesis. We summarize each study below.

One fair-quality study[240] pooled data from eight case-control studies of HPV+ patients with cervical cancer. Ever use of OCs was associated with a statistically nonsignificant increase in the odds of invasive cervical cancer (OR 1.29; 95% CI, 0.88 to 1.91) and cervical cancer in situ (OR 2.54; CI, 0.95 to 6.78). However, duration of use was significantly associated with cancer incidence such that HPV+ women who used OCs for 5 to 9 years (OR 2.82; CI, 1.46 to 5.42) and 10 or more years (OR 4.03; CI, 2.09 to 8.02) experienced a significant increase in the risk of cervical cancers compared with never users. This estimate did not vary by time since first or last use. However, this trend was not observed for women who used OCs for less than 5 years.

Two case-control studies,[234,237] both rated poor quality, also assessed the risk of cervical cancer associated with OC use among HPV+ women. One study[234] recruited hospital based HPV+ cases and controls in Lima, Peru. Results of this study were included in the pooled analysis above, and thus, could not be combined again. Compared with HPV+ controls, HPV+ women who had ever used OCs were at elevated risk of cervical cancer compared with women who had never used OCs (OR 2.7; 95% CI, 0.90 to 8.4), but the contrast was not significant. This study did not compute any analysis by duration of use.

The other case-control study[237] assessed the association between OC use and cervical cancer among hospital-based HPV+ cases and HPV+ community controls in the United States. This study assessed the effect of duration of use on cervical cancer; the effect of ever use compared with never use was not calculated. Increasing the duration of OC use—categorized as less than 5 years, 5 to 10 years, and greater than 10 years—was associated with a decrease in cervical cancers. This trend was significant only in women with less than 5 years of use compared with never users (OR 0.6; 95% CI, 0.4 to 0.9).
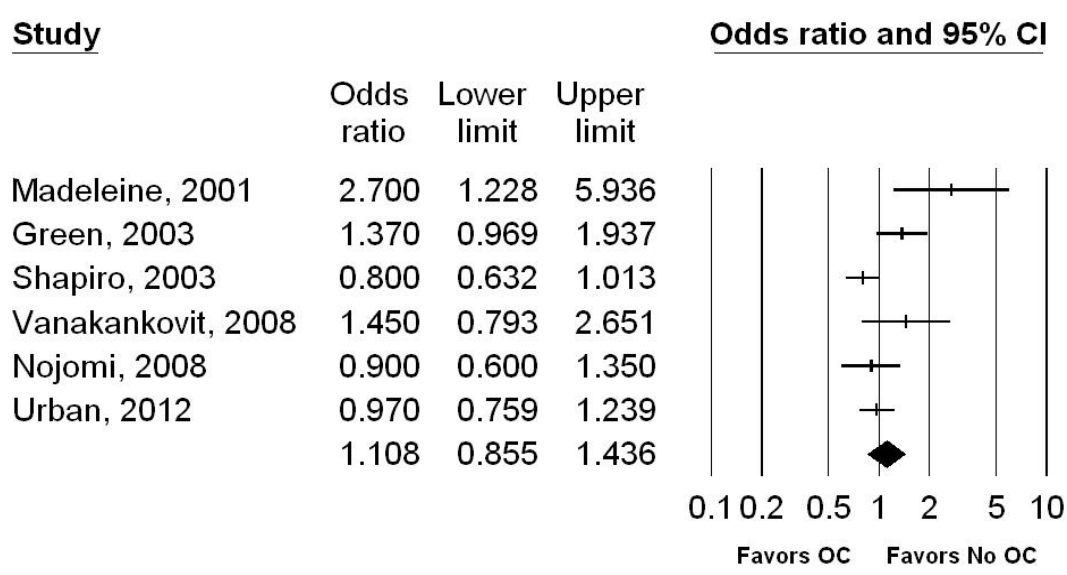
Populations Not Selected for HPV-Positive Status

Six case-control studies representing 5436 women[155,233,235,236,238,239] and three cohort studies[37,138,156] representing 3,981,072 person-years were included in this meta-analysis examining the effect of ever versus never OC use on cervical cancer incidence (Table 26). Of these studies, four were rated good quality, three fair quality, and two poor quality. We excluded datasets from this analysis for studies that were conducted among women who were HPV-positive or did not provide an estimate for ever versus never OC use.

Stratified by study type, pooled case-control studies (OR 1.11, 95% CI, 0.86 to 1.44) (Figure 27) and cohort studies (OR 1.20; CI, 0.33 to 4.34) (Figure 28) suggest an increased risk of cervical cancer among women who ever used OCs although these increases were not statistically significant. A meta-analysis of all nine included studies showed an increase in the odds of cervical cancer for women who had ever used OCs compared with women who never used OCs (OR 1.21; CI, 0.91 to 1.61), but the comparison again was not significant. There was a large
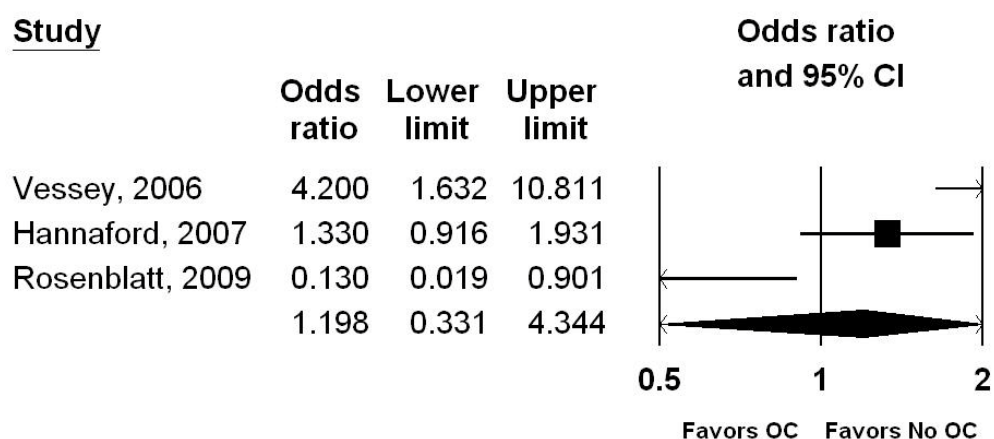
amount of heterogeneity, with a Q-value of 25.52 for 7 degrees of freedom, p<0.001, possibly due to HPV status differences among case-control studies, making the estimates unstable.

Figure 27. Forest plot for ever versus never OC use (case-control studies, cervical cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Madeleine, 2001	2.700	1.228	5.936	
Green, 2003	1.370	0.969	1.937	
Shapiro, 2003	0.800	0.632	1.013	
Vanakankovit, 2008	1.450	0.793	2.651	
Nojomi, 2008	0.900	0.600	1.350	
Urban, 2012	0.970	0.759	1.239	
	1.108	0.855	1.436	

0.1 0.2 0.5 1 2 5 10

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Figure 28. Forest plot for ever versus never OC use (cohort studies, cervical cancer incidence)

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Vessey, 2006	4.200	1.632	10.811	
Hannaford, 2007	1.330	0.916	1.931	
Rosenblatt, 2009	0.130	0.019	0.901	
	1.198	0.331	4.344	

0.5   1   2

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

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Sensitivity Analyses

We conducted additional analyses with only studies of good or fair quality. The magnitude of the effect was larger, but confidence intervals still included 1.0 (OR 2.17; 95% CI, 0.71 to 6.61). Only one study was conducted within the United States; results from this case-control study[233] show a similar quantitative increase in risk with ever use of OCs that was statistically significant (OR 2.7; CI, 1.2 to 5.8).

Duration of OC Use

Six studies[156,233,235,236,239,241] were included in this meta-analysis examining the effect of duration of OC use on cervical cancer incidence (Table 27). Of these, five were case-control studies and one was a cohort study; three were rated good quality and three fair quality. We excluded three studies from the meta-analysis[234,237,240] that presented duration data for a unique population (HPV+ women only).

Table 27. Data for outcomes on duration of OC use (cervical cancer incidence)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control				
Madeleine, 2001[233]		1–71 mo	2.1	1.0 to 4.8
		72–143 mo	3.4	1.5 to 8.0
		≥144 mo	5.5	2.1 to 14.6
Santos, 2001[234]		≤ 3 yr	1.0	0.3 to 2.9
		≥ 4 yr	1.9	NR
Green, 2003[235]	Adenocarcinoma	1–5 yr	1.06	0.63 to 1.78
		5–10 yr	1.90	1.16 to 3.11
		≥ 10 yr	2.06	1.19 to 3.57
	Squamous cell cancer	1–5 yr	1.01	0.67 to 1.50
		5–10 yr	1.55	1.05 to 2.29
		≥ 10 yr	1.89	1.22 to 2.93
Shapiro, 2003[236]		≤ 1 yr	0.8	0.6 to 1.1
		1–4 yr	0.8	0.6 to 1.2
		5–9 yr	0.5	0.3 to 1.0
		≥ 10 yr	1.7	0.9 to 3.1
Shields, 2004[237]		≤ 5 yr	0.6	0.4 to 0.9
		5–10 yr	0.7	0.4 to 1.3
		≥ 10 yr	0.5	0.3 to 1.0
Hammouda, 2005[241]		< 5 yr	0.6	0.3 to 1.2
		5-9 yr	0.5	0.3 to 1.1
		≥ 10 yr	0.8	0.4 to 1.6
Vanakankovit, 2008[239]		≤ 3 yr	0.78	0.33 to 1.77
		≥ 3 yr	2.57	1.22 to 5.49
Cohort				
Vessey, 2006[156]		≤ 48 mo	2.9	0.9 to 9.9
		49–96 mo	3.3	1.2 to 10.4
		≥ 97 mo	6.1	2.5 to 17.0
Pooled				
Moreno, 2002[240]		≤ 1 yr	0.67	0.41 to1.08
		2–4 yr	0.80	0.51 to1.24
		5–9 yr	2.82	1.46 to5.42
		> 10 yr	4.03	2.09 to7.79

CI = confidence interval; mo = month/months; NR = not reported; OR = odds ratio; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

For the included studies we categorized duration of OC use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 28, show no time-dependent relationship as a function of duration. There was significant heterogeneity, with a t-value of 4.72 for 5 degrees of freedom, p=0.0033. The test was underpowered; there would have to be a 50-percent difference in risk of cervical cancer by time period in order to detect significant differences.

Table 28. Estimated odds ratios by duration of OC use (cervical cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.99 (0.58 to 1.70)	0.975
> 60 months	1.47 (0.91 to 2.38)	0.097

OC Use and Cervical Cancer Mortality

We identified two studies that evaluated the association between OC use and cervical cancer mortality (Table 29).[33,164-166] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Vessey et al.[165] found an increased risk of cervical cancer mortality associated with OC use, with a very wide confidence interval, with a risk ratio of 7.3 (95% CI, 1.2 to 305). Hannaford et al.[33] found an increased risk of mortality among those exposed to OCs; however, these effects were not statistically significant, with a risk ratio of 1.52 (CI, 0.67 to 3.48). Both studies also assessed mortality as a function of duration of OC use; results showed a trend of increased risk of death with longer duration of use with a statistically significant increased risk of death for 8 or more years of use compared with never users.

Table 29. Study characteristics and association between OC use and cervical cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	1.34 (0.74 to 2.44)	< 4 yr 4–8 yr ≥ 8+ yr	1.08 (0.35 to 3.31) 1.60 (0.56 to 4.62) 2.97 (1.12 to 7.92)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	7.3 (1.2 to 305.0)	< 48 mo 49–96 mo ≥ 97 mo	3.8 (0.30 to 1.98) 7.7 (0.9 to 3.56) 10.2 (1.40, to 4.47)	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; IRR = incidence rate ratio; mo = month; NR = not reported; OC = oral contraceptive; SD = standard deviation; UK = United Kingdom; yr = year/years
[a]Point estimate for meta-analysis of ever versus never OC use.
[b]Point estimate for meta-analysis of duration of OC use.
[c]Meta-analysis code: 1 = Met inclusion criteria for possible meta-analysis.

Strength of Evidence for OC Use and Risk of Cervical Cancer

We graded the SOE for the association of ever use of OC on the risk of cervical cancer among HPV+ women as insufficient (Table 30). We identified only three studies and most were of poor quality. Studies did not control for factors that may influence risk such as age at first use by duration or age at sexual debut, which is likely highly correlated with age at first use. Moreover, results were inconsistent; sensitivity analysis yielded qualitatively different estimates of effects; and confidence intervals were wide. Future studies will likely influence magnitude and, possibly, direction of effect.

The SOE for the risk of cervical cancer mortality associated with the use of OCs was graded as low. Though results were consistent and suggest increased risk of death associated with prolonged use, we identified only two studies. Results lacked precision; studies reported very wide confidence intervals. Risk of bias was graded as high; studies did not account for HPV status and both were rated only fair quality. Future research will likely moderate the magnitude and direction of effects.

Table 30. Strength of evidence domains for the effect of OC use on cervical cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Cervical Cancer in HPV-Positive Population						
Ever vs. never use	3 (2592)	High	Inconsistent	Direct	Imprecise	Insufficient Unable to draw summary conclusion
Mortality From Cervical Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	High	Consistent	Direct	Imprecise	Low Increased risk with ever use and longer duration of use

CI = confidence interval; HPV = human papillomaviruses; SOE = strength of evidence

OC Use and Colorectal Cancer Incidence

We identified 11 studies that evaluated the association between OC use and the incidence of colorectal cancer.[37,88,99,156,242-249] Of these, 3 were case-control studies, 7 cohort studies, and 1 pooled analysis; 4 studies were rated good quality, 6 fair quality and 1 poor quality (Table 31). Nine studies were conducted in Western countries and two in China.

Table 31. Study characteristics and association between OC use and colorectal cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control							
Levi, 2003[242]	Women aged 28–74 yr in Canton of Vaud Cases: 131 colorectal cancer, hospital Controls: 373, hospital Recruitment period: 1992–2001	0.83	0.4 to 1.7	Age, parity, family history, fiber intake, physical activity	Switzerland	Poor	1
Campbell, 2007[243]	Women aged 20–74 yr in Ontario, Newfoundland, Labrador Cases: 1404 colorectal cancer, registry Controls: 1203, property records Recruitment period: 2003–2006	0.77	0.65 to 0.91	Age, province of residence, education, ever use postmenopausal hormones, colorectal cancer screening endoscopy, physical activity, BMI, menopausal status	Canada	Fair	1
Long, 2010[244]	Women aged 40–80 yr in North Carolina Colon Cancer Study-II Cases: 443 distal large bowel cancer, registry Controls: 405, community Recruitment period: 2001–2006	0.95	0.67 to 1.34	Age, race, BMI, family history, smoking, family history of colorectal cancer, education, HRT use, physical activity	U.S.	Good	1
Cohort							
Rosenblatt, 2004[249]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,851 person-years Unexposed: 1,045,388 person-years Recruitment period: 1989–1991	1.09	0.86 to 1.37	Age, parity	China	Fair	1
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	0.8	0.6 to 1.2	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

Table 31. Study characteristics and association between OC use and colorectal cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at entry: 29 (SD6.6) Recruitment period: 1968–NR	0.72	0.58 to 0.90	Age, parity, smoking, social status	UK	Fair	1
Lin, 2007[246]	Women ≥45 yr in Women's Health Study Exposed: 27,440 Unexposed: 12,060 Recruitment period: 1992–NR	0.67	0.50 to 0.89	Age, BMI, family history, smoking, randomized treatment assignment, family history of colorectal cancer, previous history of benign colorectal polyps, physical activity, red meat intake, alcohol consumption, baseline aspirin use, multivitamin use, baseline postmenopausal hormone use	U.S.	Good	1
Kabat, 2008[245]	Women aged 40–59 yr in Canadian National Breast Screening Study Exposed: 1142 Unexposed: 88,655 Recruitment period: 1980–1985	0.83	0.73 to 0.94	Age, parity, smoking, social status, ever use of HRT	Canada	Fair	1
Dorjgochoo, 2009[88]	Women aged 40–70 yr in Shanghai Women's Health Study Exposed: 12,957 Unexposed: 15,557 Recruitment period: 1997–2000	1.24	0.87 to 1.78	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	China	Fair	1

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Table 31. Study characteristics and association between OC use and colorectal cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Tsilidis, 2010[247]	Women aged 35–70 yr in European Prospective Investigation into Cancer and Nutrition Exposed: 196,862 Unexposed: 139,399 Recruitment period: 1990s	0.92	0.83 to 1.02	Age, BMI, smoking, diabetes mellitus, physical activity, alcohol use	10 European countries	Good	1
Pooled							
Nichols, 2005[248]	Women in Wisconsin aged 20–74 yr Cases: 1488 colorectal cancer, registry Controls: 4297, community Recruitment periods: 1988–1991; 1997–2001	0.89	0.75 to 1.06	BMI, family history, smoking, conditional on age and study of enrollment; adjusted for family history of colorectal cancer, education, screening, hormone replacement therapy, age at first birth	U.S.	Fair	1

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratio for meta-analysis of ever versus never OC use.

[c]Meta-analysis code: 1 = included in this meta-analysis.

Ever Versus Never OC Use

Three case-control studies,[242-244] one pooled analysis,[248] and seven cohort studies[37,88,156,245-247,249] representing 503,816 women across 8 studies and 2,969,189 person-years across 3 studies were included in this meta-analysis examining the effect of ever versus never OC use on colorectal cancer incidence (Table 31). Of these studies, four were rated good quality, six fair quality and one poor quality.

Stratified by study type, both case-control studies (OR 0.84; 95% CI, 0.75 to 0.94) (Figure 29) and cohort studies (OR 0.87; CI, 0.77 to 0.98) (Figure 30) demonstrated a decrease in the risk of colorectal cancers among women who ever used OCs. The odds ratios for the two types of studies were similar; a test of differences was not significant (p=0.791). In a meta-analysis including the 11 studies of all designs, the odds of colorectal cancer were significantly decreased for women who had ever used OCs compared with women who never used OCs (OR 0.86; CI, 0.79 to 0.95; Q value of 17.17, p<0.046).

Figure 29. Forest plot for ever versus never OC use (case-control and pooled studies, colorectal cancer incidence)
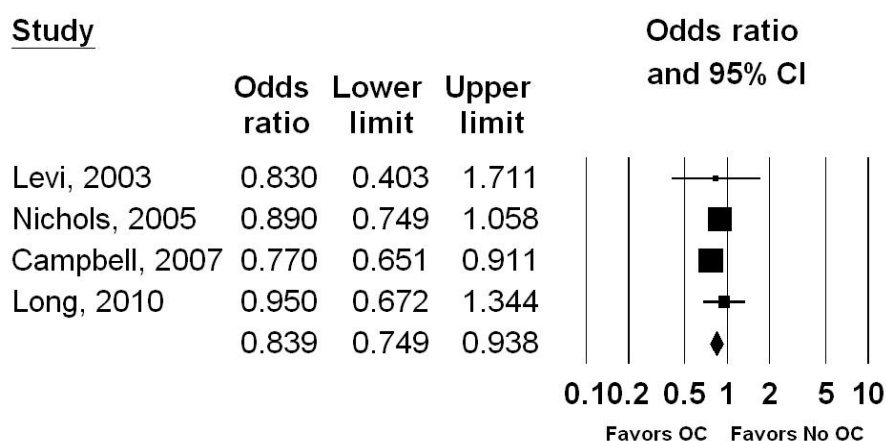
CI = confidence interval; OC = oral contraceptive

Figure 30. Forest plot for ever versus never OC use (cohort studies, colorectal cancer incidence)
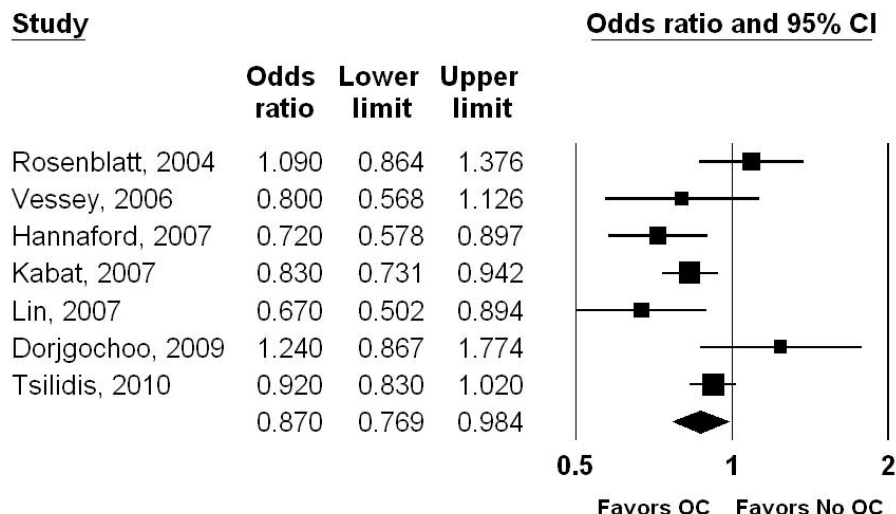
Study	Odds ratio	Lower limit	Upper limit
Rosenblatt, 2004	1.090	0.864	1.376
Vessey, 2006	0.800	0.568	1.126
Hannaford, 2007	0.720	0.578	0.897
Kabat, 2007	0.830	0.731	0.942
Lin, 2007	0.670	0.502	0.894
Dorjgochoo, 2009	1.240	0.867	1.774
Tsilidis, 2010	0.920	0.830	1.020
	0.870	0.769	0.984

Odds ratio and 95% CI

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

We conducted additional analyses including only studies of good or fair quality. Results were similar to those including all studies (OR 0.86; 95% CI, 0.79 to 0.94). We also conducted sensitivity analyses of studies that only included patients from the United States; results were similar to those containing all studies but the confidence interval eclipsed 1 (OR 0.83; CI, 0.69 to 1.01).

Duration of OC Use

Ten studies[37,88,156,242-246,248,249] were included in this meta-analysis examining the effect of duration of OC use on colorectal cancer incidence (Table 32). Of these, 3 were case-control studies, 6 cohort studies, and 1 pooled analysis; three were rated good quality, six fair quality and one poor quality. We excluded one study from the meta-analysis[247] that used less than 1 year of use as the reference group.

Table 32. Data for outcomes on duration of OC use (colorectal cancer incidence)

Study[a]	Duration	OR	95% CI
Case-Control			
Levi, 2003[242]	< 5 yr	0.74	0.2 to 2.4
	> 5 yr	0.87	0.4 to 2.0
Campbell, 2007[243]	1–4 yr	0.77	0.62 to 0.97
	≥ 5 yr	0.77	0.62 to 0.95
Long, 2010[244]	0–2 yr	0.63	0.38 to 1.03
	>2 to < 5 yr	1.11	0.61 to 2.00
	5 to < 10 yr	1.18	0.70 to 2.00
	> 10 yr	1.32	0.79 to 2.21
Cohort			
Rosenblatt, 2004[249]	< 6 mo	0.97	0.64 to 1.47
	7–24 mo	0.96	0.67 to 1.38
	25–36 mo	1.13	0.65 to 1.97
	≥ 37 mo	1.56	1.01 to 2.40
Vessey, 2006[156]	< 48 mo	1.1	0.6 to 1.7
	49–96 mo	0.8	0.4 to 1.2
	≥ 97 mo	0.8	0.5 to 1.2
Hannaford, 2007[37]	<48 mo	0.82	0.51 to 1.31
	49–96 mo	0.72	0.43 to 1.21
	≥ 96 mo	0.95	0.59 to 1.54
Lin, 2007[246]	< 6 mo	0.65	0.39 to 1.08
	6–35 mo	0.61	0.40 to 0.94
	36–59 mo	0.79	0.51 to 1.23
	≥ 60 mo	0.68	0.47 to 0.99
Kabat, 2008[245]	1–11 mo	0.86	0.70 to 1.06
	12–25 mo	0.89	0.73 to 1.09
	26–71 mo	0.75	0.63 to 0.90
	≥ 72 mo	0.84	0.69 to 1.03
Dorjgochoo, 2009[88]	< 2 yr	1.39	0.86 to 2.23
	≥ 2 yr	1.14	0.73 to 1.78
Tsilidis, 2010[247]	2–4 yr	0.99	0.80 to1.23
	5–9 yr	0.93	0.74 to 1.17
	≥ 10 yr	1.09	0.89 to 1.35
Pooled			
Nichols, 2005[248]	1–23 mo	0.88	0.67 to 1.15
	24–53 mo	0.96	0.74 to 1.25
	54–107 mo	0.90	0.69 to 1.17
	≥ 108 mo	0.84	0.64 to 1.09

CI = confidence interval; mo = month/months; OR = odds ratio; yr = year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

For the included studies, we categorized duration of use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 33, show no time-dependent relationship as a function of duration. There was no significant heterogeneity, with a t-value of 1.52 for 9 degrees of freedom, p=0.164. As with most of the other analyses of duration of exposure, the test was underpowered; there would have to be a 20-percent difference in risk of colorectal cancer by time period in order to detect significant differences.

Table 33. Estimated odds ratios by duration of OC use (colorectal cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.88 (0.77 to 1.01)	0.063
> 60 months	0.88 (0.76 to 1.01)	0.061

OC Use and Colorectal Cancer Mortality

We identified two studies that evaluated the association between OC use and colorectal cancer mortality (Table 34).[33,164-166] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Results were mixed. One study[33] found a decrease in the risk of mortality among those exposed to OCs; however, these effects were not statistically significant. The other study[165] showed an increase in colorectal cancer mortality associated with having ever used OCs. Both studies also assessed mortality as a function of duration of OC use; results showed no clear trend of a greater protective effect associated with longer duration of use.

Table 34. Study characteristics and association between OC use and colorectal cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.62 (0.46 to 0.83)	< 4 yr 4–8 yr ≥ 8+ yr	1.02 (0.52 to 2.0) 0.65 (0.30 to 1.43) 0.45 (0.16, 1.28)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	1.2 (0.8 to 2.0)	< 48 mo 49–96 mo ≥ 97 mo	1.2 (0.6 to 2.4) 1.4 (0.7 to 2.5) 1.1 (0.6 to 2.0	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; mo = month/months; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; yr = year/years
[a]Point estimate for meta-analysis of ever versus never OC use.
[b]Point estimate for meta-analysis of duration of OC use.
[c]Meta-analysis code: 1=Met inclusion criteria for possible meta-analysis

Strength of Evidence for OC Use and Risk of Colorectal Cancer

We graded the SOE for the association of OC use and incidence of colorectal cancer as moderate (Table 35). We were able to include all 11 studies in meta-analysis, results were consistent across studies and sensitivity analyses, and summary estimate demonstrated high precision with at tight confidence interval. Future studies will likely not impact direction of effect but may slightly influence magnitude of the effect. The SOE for duration was graded as insufficient. The test was underpowered and we found significant heterogeneity. Future studies will likely influence magnitude of effect across duration categories.

We also graded the SOE at insufficient for the risk of death associated with ever use of OCs. We identified only two fair-quality studies with inconsistent effects for ever use and duration of use. It is likely that future studies will impact direction and magnitude of effects.

Table 35. Strength of evidence domains for the effect of OC use on colorectal cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Colorectal Cancer in Overall Population						
Ever vs. never use	11 (503,816 across 8 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 0.86 (0.79 to 0.95)
Duration of use	10 (167,555 across 7 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	Low No increase in protective effect with prolonged use
Mortality From Colorectal Cancer						
Ever vs. never use	2 (46,112 in 1 study and 602,700 person-years in a second study)	Medium	Inconsistent	Direct	Imprecise	Insufficient Mixed results for risk of death with ever use and no trend toward increased protective effect with longer duration of use

CI = confidence interval; SOE = strength of evidence

OC Use and Endometrial Cancer Incidence

We identified nine studies that evaluated the association between OC use and the incidence of endometrial cancer.[37,138,155,156,250-254] Of these, four were case-control studies and five cohort studies; six were rated good quality, two fair quality, and one poor quality. Only two studies were conducted in the United States (Table 36).

Table 36. Study characteristics and association between OC use and endometrial cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control							
Parslov, 2000[250]	Danish women aged 25–49 yr Cases: 237 endometrial cancer, hospital Controls: 538, Central Person Register Recruitment period: 1987–1994	NR	NR	NA	Denmark	Good	2
Maxwell, 2006[251]	Women aged 20–54 yr in Cancer and Steroid Hormone Study Cases: 434 endometrial cancer, SEER registry Controls: 2557, population *High progestin/high estrogen* *High progestin/low estrogen* *Low progestin/high estrogen* *Low progestin/Low estrogen* Recruitment period: 1980–1982	0.21 0.00 0.39 0.40	0.10 to 0.43 0.00 to 5.59 0.25 to 0.60 0.21 to 0.76	NA	U.S.	Good	1
Tao, 2006[254]	Women aged 30–69 yr in Shanghai Endometrial Cancer Study Cases: 1204 endometrial cancer, registry Controls: 1212 no history of hysterectomy, resident registry Recruitment period: 1997–2003	0.75	0.60 to 0.93	Age, parity, menopausal status, BMI, family history, age at menarche, education, yr of menstruation, family history of breast, endometrial, and colon cancers, age at last live birth, physical activity, exogenous hormone use	China	Good	1

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Table 36. Study characteristics and association between OC use and endometrial cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Urban, 2012[155]	Black South African women aged 18–79 yr Cases: 17, hospital Controls: 156, hospital Recruitment period: 1995–2006	1.01	0.55 to 1.85	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	0.3	0.2 to 0.6	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	0.58	0.42 to 0.79	Age, parity, smoking, social status	UK	Fair	1
Setiawan, 2007[253]	Women aged 45–75 yr in Multiethnic Cohort Study Hawaii and Los Angeles 46,933 (total population of exposed and unexposed, postmenopausal women) Recruitment period: 1993–1996	NR	NR	NA	U.S.	Good	2
Rosenblatt, 2009[138]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.68	0.45 to 1.04	Age, parity, tubal ligation	China	Poor	1

Table 36. Study characteristics and association between OC use and endometrial cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Dossus, 2010[252]	European Prospective Investigation into Cancer and Nutrition Exposed: 1017 Unexposed: 301,601 1017 Cases, 301601 Cases Mean age of cases at entry: 56.2 Recruitment period: 1992–NR	0.65	0.56 to 0.75	BMI, smoking, physical activity, alcohol, diabetes, education	10 European countries	Fair	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]Odds ratio for meta-analysis of ever versus never OC use.
[c]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to ever versus never OR not reported.

Ever Versus Never OC Use

Three case-control[155,251,254] and 4 cohort studies[37,138,156,252] representing 308,198 women (within 4 studies) and an additional 3,981,072 person-years (within the other 3 studies) were included in this meta-analysis examining the effect of ever versus never OC use on endometrial cancer incidence (Table 36). Of these studies, four were rated good quality, two fair quality, and 1 poor quality. We excluded two studies from the meta-analysis that did not report point estimates for ever versus never OC use.

Figure 31 indicates a protective effect for endometrial cancer associated with having ever used OCs (OR 0.57; 95% CI, 0.43 to 0.76). The test of heterogeneity was significant, with a Q-value of 26.11 for 6 degrees of freedom, p<0.001. However, test for a difference between the cohort and case-control studies was not significant, with a Q-value of 0.113 for 1 degree of freedom, p=0.736.

Figure 31. Forest plot for ever versus never OC use (case-control and cohort studies, endometrial cancer incidence)

Group by Study Design	Author	Odds ratio	Lower limit	Upper limit
Case-control	Tao, 2006	0.750	0.602	0.934
Case-control	Maxwell, 2006	0.343	0.250	0.470
Case-control	Urban, 2012	1.010	0.551	1.852
Case-control		0.608	0.391	0.946
Cohort	Vessey, 2006	0.300	0.172	0.525
Cohort	Hannaford, 2007	0.580	0.423	0.795
Cohort	Rosenblatt, 2009	0.680	0.447	1.034
Cohort	Dossus, 2010	0.650	0.562	0.752
Cohort		0.550	0.376	0.804
Overall		0.574	0.430	0.765
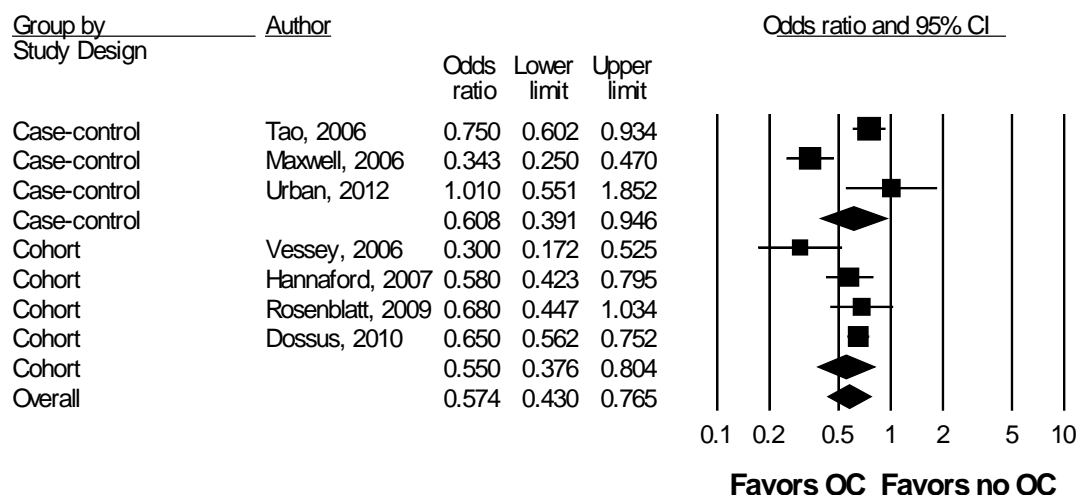
CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

We conducted an additional analysis to assess the impact of study quality; results were similar when including only the four good- and two fair-quality studies (OR 0.56; 95% CI, 0.43 to 0.74). We also explored how our findings changed when including only U.S.-based studies in our quantitative synthesis. Only one study was conducted with patients from the United States; the results of this study reported a somewhat greater protective effect than summary estimates for all studies (OR 0.34; CI, 0.25 to 0.47).

Duration of OC Use

Eight studies[37,138,155,156,250,252-254] were included in this meta-analysis examining the effect of duration of use on endometrial cancer incidence (Table 37). Of these, three were case-control studies and five cohort studies; five were rated good quality, two fair quality, and one poor quality. We excluded one study that did not report duration of use estimates.

Table 37. Data for outcomes on duration of OC use (endometrial cancer incidence)

Study	Duration	OR	95% CI
Case-Control			
Parslov, 2000[250]	< 1 yr 1–5 yr > 5 yr	0.4 0.2 0.2	0.3 to 0.7 0.1 to 0.3 0.1 to 0.4
Tao, 2006[254]	< 6 mo 6–23 mo 24–72 mo > 72 mo	0.94 0.74 0.75 0.50	0.64 to 1.38 0.50 to 1.09 0.52 to 1.07 0.30 to 0.85
Urban, 2012[155]	< 5 yr ≥ 5 yr	1.57 0.64	0.72 to 3.41 0.27 to 1.51
Cohort			
Vessey, 2006[156]	≤ 48 mo 49–96 mo ≥ 97 mo	0.6 0.4 0.1	0.3 to 1.1 0.2 to 0.8 0 to 0.4
Hannaford, 2007[37]	< 48 mo 49–96 mo > 97 mo	0.60 0.14 0.57	0.30 to 1.21 0.03 to 0.58 0.27 to 1.19
Setiawan, 2007[253]	< 5 yr ≥ 5 yr	0.96 0.60	0.71 to 1.30 0.39 to 0.91
Rosenblatt, 2009[138]	1–11 mo ≥ 12 mo	1.15 0.48	0.65 to 2.01 0.27 to 0.85
Dossus, 2010[252]	2–4 yr 5–9 yr ≥ 10 yr	1.06 0.66 0.58	0.79 to 1.41 0.47 to 0.91 0.42 to 0.79

CI = confidence interval; mo = month/months; OR = odds ratio; yr = year/years

For the included studies, we categorized duration of use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 38, show a time-dependent relationship as a function of duration. The duration trend was strong, and the two odds ratios were significantly different (p=0.007). There was significant heterogeneity, with a t-value of 4.39 for 7 degrees of freedom, p=0.003.

Table 38. Estimated odds ratios by duration of OC use (endometrial cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.78 (0.54 to 1.15)	0.162
> 60 months	0.44 (0.29 to 0.65)	0.002

OC Use and Endometrial Cancer Mortality

We identified two studies that evaluated the association between OC use and endometrial cancer mortality (Table 39).[33,165] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Both studies demonstrated a strong, significant protective effect for endometrial cancer mortality associated with having ever used OCs. Results also showed a trend

of a greater protective effect associated with longer duration of use; however, the number of subjects within each category was small and point estimates for some duration categories were not calculable.

Table 39. Study characteristics and association between OC use and endometrial cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.43 (0.21 to 0.88)	< 4 yr 4–8 yr ≥ 8+ yr	0.9 (0.3 to 2.5) Not calculable 0.2 (0.0 to 1.0)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	0.3 (0.1 to 0.8)	< 48 mo 49–96 mo ≥ 97 mo	0.42 (0.05 to 3.45) Not calculable Not calculable	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Point estimate for meta-analysis of ever versus never OC use.

[b]Point estimate for meta-analysis of duration of OC use.

[c]Meta-analysis code: 1 = Met inclusion criteria for possible meta-analysis.

Strength of Evidence for OC Use and Risk of Endometrial Cancer

We graded the SOE for the association of ever use of OCs and risk of endometrial cancer as moderate (Table 40). We were able to quantitatively synthesize results across six studies. Results consistently showed a protective effect for ever use of OCs and the majority of studies were of good or fair quality. Confidence intervals displayed a satisfactory level of precision. Future studies may further improve precision but the overall magnitude of effect is unlikely to shift significantly.

We graded the SOE as low for the association between duration of OC us and endometrial cancer incidence. We found significant heterogeneity and confidence intervals were wide, decreasing precision. Future studies will likely impact the magnitude of effect but not the direction.

The SOE for endometrial cancer mortality and OC use was graded as moderate. We identified two large cohort studies that reported consistent results. Future studies may improve estimates of the magnitude of the effect but not the direction of effect.

Table 40. Strength of evidence domains for the effect of OC use on endometrial cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Endometrial Cancer in Overall Population						
Ever vs. never use	7 (308,198 across 4 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 0.57 (0.43 to 0.76)
Duration of use	8 (352,915 across 5 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	Low <60 months:0.78 (0.54 to 1.15) >60 months: 0.44 (0.29 to 0.65)
Mortality						
Ever vs. never use	2 (46,112 in 1 study and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Precise	Moderate Overall protective effect for ever use which is greater for longer durations of use

CI = confidence interval; SOE = strength of evidence

Discussion

Our study complements the prior literature by limiting the scope to studies conducted after 1999 in order to minimize the influence of older OC formulations that are no longer available on the U.S. market—thus potentially increasing generalizability for current clinical practice. In this systematic review and meta-analysis, we found that OC use is associated, to a varying degree, with breast, cervical, colorectal, and endometrial cancers. Below, we synthesize the main results for each cancer and compare to other contemporary reviews. We then highlight limitations of this review and areas for future research. Note that we found no evidence for publication bias in any of the meta-analyses (Appendix E).

Breast Cancer

The role of reproductive factors on the risk of developing breast cancer has been a topic of much study and debate. Thus, we sought to synthesize the evidence on the role of OCs on breast cancer incidence and mortality. We were able to pool results from 23 studies involving 356,023 women across 20 studies and 3,981,072 person-years across 3 studies that examined the effect of ever versus never OC use on the incidence of breast cancer. We found that the risk of breast cancer was slightly—but significantly—elevated for women who ever used OCs compared with women who never used OCs (OR 1.08; 95% CI, 1.00 to 1.17). A similar effect was seen among BRCA mutation carriers, although the results were not statistically significant (OR 1.21; CI, 0.93 to 1.58). (Although the inclusion of 1.0 in the 95% CI is considered nonsignificant using traditional rules of statistical inference, it is worth noting that the likelihood of the risk truly being increased when the lower bound is 1.0 is approximately 97.5%, and at a lower bound of 0.99, it is above 95%). Thus, as with ovarian cancer, the qualitative effect of OC use on breast cancer risk appears similar whether or not a BRCA gene mutation is present.

We found no time-dependent relationship as a function of duration of OC use across 14 pooled studies. Our duration of use results should be interpreted with caution; there was significant heterogeneity and the test was underpowered—which is not surprising, given that breast cancer is relatively uncommon during the ages when women are most likely to be using OCs. We did find a significant relationship with time since last OC use: women with more recent use had an elevated risk of breast cancers, with decreasing risk over time, so that by 10 years since last use, the risk among users was equivalent to never users. We did not identify sufficient studies meeting our inclusion criteria to calculate risk by age at first use. One collaborative reanalysis demonstrated an elevated risk of breast cancer for women who initiated use before age 20, an effect that diminished over time since last use.[182] We also found no evidence of increased breast cancer mortality associated with having used OCs compared with never use across four pooled studies.

Our results are consistent with the results of other meta-analyses and pooled analyses that identified a small increase in the relative risk of breast cancers associated with having ever used OCs, a risk that diminishes over time since last use.[182,255] The Collaborative Group on Hormonal Factors in Breast Cancer, a collaborative reanalysis of individual data in 153,536 women, found a small significant increase in the relative risk of breast cancers (OR 1.07 ± 0.02).[182] Similar to our results, the Collaborative Group did not identify an increase in risk with increasing duration of use or after discontinuation of use for 10 or more years. Another more recent meta-analysis of premenopausal breast cancers across 37 studies found a somewhat larger increase in the risk of breast cancer with the use of OCs (OR 1.19; CI, 1.09 to 1.29) with the greatest risk associated

with use of OCs prior to first full-term pregnancy (OR 1.44; CI, 1.28 to 1.62).[52] These results provide support for our finding that recent use (within 5 or fewer years) is associated with an increased risk of breast cancers. Women who delay first full-term pregnancies may also be more likely to be recent users of OCs relative to a breast cancer diagnosis. However, these results cannot be directly compared with ours, as this meta-analysis was restricted to premenopausal women or women younger than age 50 who may be at elevated risk due to other factors (e.g., genetic mutations) or represent cancer subtypes that differentially affect younger women. No pooled analyses or meta-analyses have assessed the excess risk of breast cancer mortality associated with OC use. However, our findings of an increased incidence, but no significant change in overall mortality, suggest that some of the increase in breast cancer incidence may be due to increased surveillance in women who use OCs. Women who use OCs must come in contact with the health care system on a regular basis, thus increasing their chances of receiving referrals for preventive screenings such as mammography. Another potential explanation would be an OC-induced change in the natural history of breast cancer or an increase in ER-positive breast cancers, which have higher survival, resulting in improved survival. Although the relative increase in breast cancer risk is small, the relative frequency of breast cancer diagnosis means that OC use may contribute to a substantial number of cases, an issue that is explored further in Section 5.

Cervical Cancer

While persistent infection with oncogenic HPV types has been identified as the necessary cause for the overwhelming majority of cancers of the cervix, it is not sufficient; OC use may represent an important cofactor. We identified 12 studies that assessed the risk of cervical cancer associated with OC use. Pooled results across 9 studies (representing 5,436 women across 6 studies and 3,981,072 person-years across 3 studies) found no significant increase in the risk of cervical cancer among ever users of OCs compared with never users. We also did not find a time-dependent relationship as a function of duration of OC use on cervical cancer. It is important to note that this contrast was underpowered with only five included studies. However, women who had long-term use of OCs (5 or more years) were at an elevated risk of cervical cancer compared with never users. Three studies (with 2592 subjects) assessed OC use and cervical cancer incidence among HPV-positive women. Results were similar to those of women not selected for HPV status. We only identified two studies that assessed the risk of cervical cancer mortality; results were mixed. Many studies did not control for factors that may influence risk, such as age at first OC use by duration or age at sexual debut, which is likely highly correlated with age at first use. Future research is needed to assess the additional cervical cancer risk associated with OC use among HPV-positive women. However, both studies reported statistically significant increased risk of death with 8 or more years of OC use compared with never use.

Results of this review differ in some ways from other evidence syntheses published over the last 10 years. Smith et al.[50] pooled study-level data across 28 studies and found an overall significant increase in the risk of cervical cancer when comparing ever versus never users of hormonal contraceptives (RR 1.2; 95% CI,1.1 to 1.3). We found a similar increase in the risk of cervical cancers, but our summary estimate was not significant. Both our review and the Smith et al. study found the risk of cervical cancer increased with prolonged exposure. This effect weakened but remained significant when stratifying duration by time since use. For our review, this effect was only significant for women who used OCs for 5 or more years compared with

never users; we did not have sufficient studies to stratify by time since last use. The International Collaborative of Epidemiological Studies of Cervical Cancer undertook a collaborative patient-level reanalysis of 24 observational studies.[49] Results expand the duration by recency effect. The collaborative analysis found that excess risk of cervical cancers increase with duration of use, but this effect declined after discontinuing OCs and was equivalent to the risk of nonusers after 10 years of nonuse.

There are key methodological differences between our study and the two recent syntheses that preclude drawing exact comparisons. First, we only included studies of invasive cervical cancers; the other studies also included carcinoma in situ and cervical intraepithelial neoplasia grade 3 (CIN 3). It is likely that effects differ between invasive cancers and cancer-precursor lesions. In fact, a case-case comparison in the collaborative reanalysis demonstrated significant differences in the risks for in situ and invasive cervical cancers for nearly every category of time since last use by duration of use.

Second, we only included studies assessing the effects of *oral* contraceptives or presented those data separately; the two other recent syntheses included all forms of hormonal contraceptive. It is also possible that formulation differences contribute to some of the differences we found between our results and their findings. However, the collaborative reanalysis reported separate findings for progestogen-only injectable contraceptives and found a similar pattern to those reported for OCs.

Third, we did not include the three identified studies conducted with women selected for HPV infection status. The effects of this decision appear to be negligible; both prior reviews noted similar patterns of findings when controlling for HPV status as a covariate[50] compared with HPV uncontrolled studies or among the subset of women with a confirmed HPV infection compared with populations not selected for HPV status.[49]

Fourth, we data-limited our search from 2000 forward in order to minimize the effect of older formulations that are no longer on the market; the other studies had no such date restrictions. Despite these differences, we found similar patterns of increased risk by duration of use. There is no direct evidence to suggest that cervical cancer screening recommendations should be different based on duration of OC use.

Colorectal Cancer

Many studies have suggested a protective effect of reproductive factors such as OCs on colorectal cancer risk. We identified 11 studies involving 503,816 women across 8 studies and 2,969,189 person-years across 3 studies that assessed the risk of colorectal cancers associated with the use of OCs. We found that the risk of colorectal cancer was significantly decreased for women who had ever used OCs compared with women who never used OCs (OR 0.86; CI, 0.79 to 0.95). However, we found no evidence of a time-dependent relationship as a function of duration. We found no significant heterogeneity. Duration results should be interpreted with caution; the test was underpowered. We had insufficient studies to assess a trend based on time since last use. We also identified two population cohort studies that assessed burden of colorectal cancer mortality associated with OC use. Results were mixed and neither study achieved statistically significant findings. The other study showed an increase in colorectal cancer mortality associated with having ever used OCs. Both studies also assessed mortality as a function of duration of OC use; results showed no clear trend of a greater protective effect associated with longer duration of use.

Our results are similar to two other evidence syntheses that also assessed the risk of colorectal cancers associated with OC use.[55,56] These meta-analyses both found a pooled relative risk of approximately 0.82, which is comparable to our pooled findings. These reviews also found no increase in the protective effect by duration of use. The similarity between our finding and those of the other two reviews is noteworthy. We limited our studies from January 2000 forward so that we had a greater probability of capturing a set of studies with newer OC formulations that may confer differential effects. Thus, we shared no studies in common with the Fernandez et al. study,[55] excluded 12 older or non-English studies, and included five newer studies[88,156,244,247,249] compared with the systematic review by Bosetti et al.[56] Similarity in our findings with these earlier evidence syntheses suggest that newer formulations of OCs still confer a significant protective effect for colorectal cancer and future research may be conducted to investigate its potential as a beneficial therapy for chemoprevention.

Endometrial Cancer

Estrogen and progestin both influence cell proliferation of endometrial tissue. Thus, we summarized the evidence on the use of OCs and risk of endometrial cancer incidence and mortality. We identified nine studies that evaluated the association between OC use and the incidence of endometrial cancers; seven studies were included in our meta-analysis to assess the effects of ever versus never use of OCs and represented 308,198 women across 4 studies and 3,981,072 person-years across 3 studies We found a significant protective effect associated with having ever used OCs (OR 0.57, 95% CI, 0.43-0.76). We also found a time-dependent relationship as a function of duration categorized as less than 60 months and 60 months or greater of total use. The duration trend was strong; however, the comparison of the two odds ratios was not significant, and heterogeneity limits conclusion about this analysis.

Our study is one of the few systematic reviews and meta-analyses to summarize the evidence on the effects of OCs on endometrial cancers. Grimes et al.[256] conducted a systematic review and qualitative synthesis of studies up to 1993. They identified 13 case-control studies with protective odds ratios ranging from 0.1 to 0.6, with most effects clustering around 0.5 (CI not reported). Two of the three cohort studies identified also found protective effects of OC use on endometrial cancer incidence. Schlesselman et al.[257] conducted a meta-analysis of 11 case-control studies. A significant duration trend was reported such that longer durations of use conferred greater protection against endometrial cancers (RR 0.44 for 4 years of use; RR 0.33 for 8 years of use; RR 0.28 for 12 years of use; p<0.0001). We found a similar trend but used a different analytic approach; direct comparisons are difficult to draw. This meta-analysis also reported on time since last use and found that the protective effect of OCs is diminished after they are discontinued but still persists even 20 years after cessation of use. We did not have sufficient studies to assess the effect of time since last use. Protective effect of OCs may vary with formulation. However, our results are similar to other studies conducted in the 1990s that may have included different formulations based on market availability. Our results—in combination with other evidence reviews—confirm that OCs confer a significant and lasting protective effect on the risk of endometrial cancers.

Issues Related to Cancer Screening

Of the five cancers considered in this report, effective screening is available for three: breast, cervical, and colorectal cancers. Differential screening behaviors among OC users and nonusers may affect both incidence and mortality, depending on the cancer targeted by screening.

As previously discussed, there are no effective screening tests for ovarian cancer, and although screening is possible for endometrial cancer, screening is not recommended outside of certain high-risk groups. Thus, the observed decrease in incidence and mortality for both cancers cannot be related to screening. However, as shown in Table 41, there is potential for confounding by variations in screening behaviors for the other cancers. This may be particularly important in U.S.-based studies, where there is much greater variation in access to screening, and where reproductive health services, including contraceptive services, have traditionally been closely linked with preventive care. Breast cancer screening primarily detects early malignancies, rather than preinvasive disease. Screened women will have a higher incidence (particularly at younger ages), but lower mortality, since effective treatment is available for many of these early malignancies. This is similar to the pattern observed in OC users, suggesting that some of the effects may be related to differential screening.

Conversely, cervical and colorectal cancer screenings detect both premalignant lesions and early cancers, leading to both decreased incidence and mortality. The observed protective association between OC use and colorectal cancer is consistent with this effect. However, the increased incidence associated with cervical cancer is in the opposite direction from any potential screening bias.

Table 41. Variation in screening behaviors by cancer type and potential confounding on incidence and mortality estimates

Cancer Type	Screening Detects		Predicted Effect if OC Users More Likely To Be Screened		Observed Effect in OC Users	
	Preinvasive Disease	Early Invasive Disease	Incidence	Mortality	Incidence	Mortality
Breast	No	Yes	Increased	Decreased	Increased	Uncertain
Cervical	Yes	Yes	Decreased	Decreased	Increased	Increased
Colorectal	Yes	Yes	Decreased	Decreased	Decreased	Uncertain
Endometrial	No screening	No screening	None	None	Decreased	Decreased
Ovarian	No screening	No screening	None	None	Decreased	Decreased

OC = oral contraceptive

Limitations

While we performed a comprehensive systematic review and evidence synthesis of the current research on OCs and breast, cervical, colorectal, and endometrial cancer, there are limitations to our approach and findings. First, as expected, we identified no randomized trials. Such studies are likely not feasible. Thus, we only included case-control, cohort, and pooled observational studies in our meta-analyses. Even the highest quality observational studies are susceptible to multiple forms of bias. The majority of studies in this review were rated good quality or fair quality as observational studies. Sensitivity analyses restricted to only good and fair studies found similar patterns of results.

Second, confounding is also another major limitation of observational studies. Again, most included studies adjusted for multiple likely sources of cofounding. When possible, we used the most adjusted point estimates in our meta-analyses. However, these covariates were not consistent between studies. Recall bias is also a common source of diminished quality in observational studies. Our findings were remarkably similar across case-control studies and cohort studies, which suggests a lack of evidence for recall bias of OC use across study types.

Third, we found significant heterogeneity across many of our comparisons. There are multiple potential sources of this heterogeneity. We included a diverse group of studies conducted across the world; differences in study populations and geographic variability in other

risk factors not routinely assessed (e.g., access to health care) likely contributed to this heterogeneity. This may be particularly true for cancers such as breast, cervical, and colorectal where screening can affect both incidence and mortality, and where there may be associations between OC use and screening behaviors. Sensitivity analyses with only U.S.-based studies (or with patients from the United States) showed similar patterns to unrestricted analyses. Other potential sources of heterogeneity include change in patterns of OC use associated with delayed parity over the last 30 year, variable date of diagnosis, and change in OC formulations available on the market. While date limiting our review from 2000 forward likely diminished some of these sources of heterogeneity, this approach may not be adequate to control for these effects. Also, studies varied considerably in the type and specification of covariates across studies, which may be a likely source of heterogeneity.

Fourth, we found limited data on special populations. For breast cancer, we identified only three studies on the effect of OCs on women with family histories, only seven studies with BRCA1/2 carriers, and five studies related to subtypes of cancers. Studies with special populations for cervical, colorectal, and endometrial cancers were even more limited. Underlying risk factors related to family history or genetic mutation carrier status, tumor type, or health behaviors (e.g., smoking, obesity) may interact with OC use to attenuate or enhance effects. Thus, we are not able to make specific recommendations for specific populations.

Last, we date-limited our search to studies after 1999 in order to minimize the influence of older OC formulations that are no longer available on the U.S. market and increase generalizability for current clinical practice. However, study publication date is a gross estimate of OC formulation exposure since observational studies published after 1999 may still represent cohorts exposed to earlier formulations of OCs. It may have been preferable to limit studies on the basis of year of diagnosis than date of publication. However, many of our findings are consistent with other meta-analyses without date restrictions. This suggests that current OC formulations may have similar carcinogenic or protective effects compared with older formulations. However, given the long latent period between exposure and tumor development, recent publications may not fully assess the effect of formulations introduced in the past 20 years.

Future Research

This comprehensive review of the literature on the risk of breast, cervical, colorectal, and endometrial cancers associated with OC use identified several gaps in the current state of the evidence that warrant future investigation. We detail these gaps below.

Special Populations

Several subgroups deserve further attention. There are limited data on the effects of OCs on cancer risk in women at elevated risk due to behavioral risk factors such as smoking, heavy alcohol consumption, obesity, or physical inactivity. These factors are known to be associated with cancer development; therefore, behavioral risk factors may modify the association between OCs and cancers. Moreover, we found limited studies with women of known genetic predisposition. Either known gene mutations that predispose to cancer or a strong family history can increase women's chance of breast, endometrial and colon cancers. These subgroups deserve further study as to whether they have the same or different benefit from OC use. Also, cancer is not a homogeneous disease; thus, certain types of tumors may differently be affected by OC use. Futures studies should assess the effectiveness of OCs among cancer subtypes. While it is

unlikely and unfeasible that large randomized trials on the effect of OC use will be conducted, long-term prospective studies of adequate size could be beneficial in disentangling the effects of OC and cancer among special populations.

Interactions by Patterns of Use

Our findings demonstrate a statistically significant increase in breast cancer and a statistically significant decrease in colorectal and endometrial cancers for ever OC use versus never OC use. We found that duration of use conferred a different pattern of risks; however, we found limited support of a time-dependent relationship. These analyses were underpowered; we found significant heterogeneity. We also found limited data to assess a trend in time since last use, age at first use or age at last use. As the benefits and risks associated with OC use differ by pattern of use, more research is needed on the interaction of different patterns of use (e.g., duration by time since last use, age at initiation by duration) on the risk of breast, cervical, colorectal, and endometrial cancers in order to optimize the risks and benefits of OC use.

Newer OC Formulations

Our analyses were based on more recently published data than previous evidence syntheses; however, we found similar estimates associated with ever use. This suggests that the lower dose OCs that would have been used more commonly by those women included in more recently published studies confer similar effects than higher dose OCs on the risk of breast, cervical, endometrial, and colorectal cancers. However, continued investigation is needed. The long lag time for cancer development, and the potential for significant discrepancy between dates in which cohorts were assembled relative to publication dates, make it difficult to assess if we were successful in limiting this review to more modern formulations of OCs than prior evidence synthesizes. Thus, prospective studies with continued evaluation of effects by dose of OCs are warranted.

Population-based Mortality Studies

We found relatively few population-based studies that assessed the risk of breast, cervical, colorectal, and endometrial cancer mortality associated with OC use. Future research should continue to assess this relationship. Findings from both incidence and mortality studies are needed to assess if associations are related to enhanced or obstructed cell proliferation or screening uptake and adherence among OC users.

Patient-level Meta-analyses

Given the high levels of heterogeneity across comparisons, variability in measurement related to patterns of use, and limited data on special populations who may be differentially affected by the use of OCs, we acknowledge that a study-level meta-analysis may be inadequate to answer important questions in this area. Thus, patient-level meta-analysis may provide critical information to assess gaps related to interactions between patterns of use, effects by subpopulations, and specific estrogen and progestin formulations.

Study Design and Reporting

One step that would facilitate future systematic reviews would be standardization of categories and descriptive statistics for reporting results. While categorization choices will vary

for individual studies, reporting of standardized results, perhaps as an appendix to the main analysis, would greatly improve the ability to combine published results in meta-analysis.

Section 4. Oral Contraceptives and Vascular Events

Background

Oral contraceptives (OCs) are the most common form of birth control in the United States.[172] Over 10 million women aged 15 to 44 (17%) are current users of OCs, and 45 million women have used OCs at some time in their life ("ever users").

Since the 1960s, several life-threatening vascular events have been reported to be associated with OC use.[258] These include venous thromboembolic (VTE) disease (encompassing deep venous thrombosis [DVT] and pulmonary embolism [PE]), stroke, and myocardial infarction [MI]). Ischemic heart disease and stroke are the leading cause of death in the United States and worldwide, accounting for greater than 30 percent of all deaths.[259] Given the large number of women currently using OCs, an increased risk of such vascular events associated with OC use is an important public health issue.

Over the last several decades, formulations of OCs have drastically changed. Many formulations that were used by participants in earlier studies are no longer available. Most contemporary OCs contain lower doses of estrogen and new generations of progestins. Progestin-only OCs are also commonly prescribed. Women using progestin-only OCs, lower dose estrogen OCs, or OCs with newer progestins may experience modified risks of VTE, stroke, and MI compared with users of older OCs.[260,261] There are few studies focusing on the acute vascular risks associated with contemporary OC use. In addition, more information is needed to understand whether particular groups of women may be at heightened risk of VTE, stroke, or MI due to use of specific OC formulations or presence of thromboembolic risk factors.

In Section 4 of our systematic review and meta-analysis, we evaluate the association between contemporary OC use and the risks of developing VTE, stroke, or MI. We also investigate whether the risk of these acute vascular complications varies according to estrogen dose, progestin generation, or duration of OC use or among populations of women with elevated risk for thromboembolic events.

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 4, we performed a systematic review and meta-analysis on the part of KQ 5 that addresses the acute vascular events associated with OC use; namely, VTE, stroke, and MI.

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

Analytic Framework

Figure 32 shows the analytic framework that guided this section of the review.

Figure 32. Analytic framework for OCs and vascular events
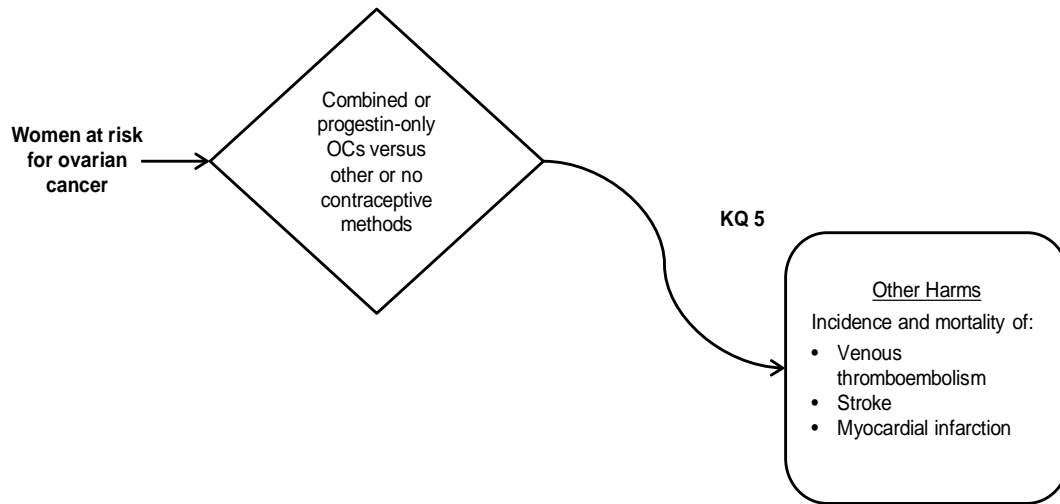
KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 42 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 42. Summary of inclusion and exclusion criteria for OCs and vascular events

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Population	• All KQs
	   o Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a]
	   o Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy
		Nonhuman studies

Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) length of OC use

Table 42. Summary of inclusion and exclusion criteria for OCs and vascular events (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include non-OC controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) or a comparison between OC formulations
Outcomes	Study reports quantitative association between exposure to OCs and either incidence or disease-specific mortality for any of the following: • Venous thromboembolic disease (including deep vein thrombosis or pulmonary embolus) • Stroke • Myocardial infarction	Study only reports outcomes related to assisted reproductive technologies or abortion
Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Study reports venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after 01-Jan-1995[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded as confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine the effect of OCs on the risk of developing acute vascular complications, we analyzed the following relationships:

- Temporal relationships:
  - Current versus noncurrent OC use
  - Ever versus never OC use
  - Duration of current OC use
- OC formulation:
  - Estrogen dose (high versus low)

- o Progestin generation (first, second, third, and fourth generations)
- Special populations:
  - o Blood-clotting disorders
  - o Cardiovascular risk factors
  - o Migraines

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not Factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68]

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Results were discussed qualitatively when study numbers were insufficient for meta-analysis, when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that is not likely to be representative of the general population of reproductive age women.

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after January 1, 1995.
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Temporal Relationships

Current OC Use

For prior sections of this report, the primary exposure to OCs was defined as ever use compared with never use of OCs. While the exact mechanisms responsible for the increased risk of VTE, stroke, or MI among OC users are unknown, there is evidence that the risk is increased in *current users* of OCs, with past users demonstrating either no risk or lower risk than current users of OCs.[262-265] Indeed, the majority of studies identified for these outcomes defined the primary exposure as current versus noncurrent OC use. Therefore, for Section 4, we defined the primary exposure as current use of OCs. Current use is defined as use within the year preceding the diagnosis of each outcome. The referent category was noncurrent use of OCs, which can consist of never users, former users, or both.

Ever OC Use

As noted above, our primary exposure was defined as current use (use within 1 year preceding diagnosis) rather than ever use as defined in the other sections.

Duration of OC Use

We were unable to perform meta-analyses for any of the outcomes of interest in relation to duration of OC use because there were too few studies to power the analysis. In order to have adequate power in the analysis, 20 or more studies would be needed for a particular outcome. The results of our included studies are therefore discussed qualitatively.

OC Formulation

All current OC formulations contain ethinyl estradiol, but the dose of this estrogen varies and may modify the risk of vascular events. We divided OC formulations by high-dose estrogen (assumed to be ≥50 mcg ethinyl estradiol) and low-dose estrogen (assumed to be <50mcg ethinyl estradiol). For estrogen dose formulation analyses, we included studies that compared the risks of developing VTE, stroke, or MI among current OC users by low versus high estrogen dose.

OC formulations were also categorized according to generation of progestin. Originally, progestins used in OCs were developed for their antigonadotropin effects leading to contraception. The resulting progestins also had effects on other steroid receptors including estrogen receptors, androgen receptors, glucocorticoid receptors, and mineralocorticoid receptors. Each progestin may increase or decrease the activity of these receptors, leading to various symptom profiles (acne, water retention, etc.). Newer progestins have been developed with a goal of not only preventing conception but also offering the best side effect profile: lighter bleeding, less acne, no bloating. Progestins have been classified in generations according to their appearance in the market and not on their chemical structure or interactions.[266] For the purpose of our analyses, first-generation progestins include norethindrone and ethynodiol diacetate; second-generation include levonorgestrel and norgestrel; third-generation include gestodene, desogestrel, and norgestimate; and fourth-generation include drospirenone, dienogest, and cytoproterone acetate. When an odds ratio was presented for a specific OC formulation, we included that odds ratio categorized by the generation of the progestin used.

Results

This section presents results of our detailed analysis of the relationship between OCs and acute vascular events, which include VTE (DVT and PE), stroke, and MI. Of note, no randomized controlled studies were identified for any of the outcomes of interest; therefore, the analyses are based on observational studies.

OC Use and Venous Thromboembolism Incidence

We identified 33 studies that evaluated the association between OC use and the incidence of VTE.[181,260-264,267-313] Of these studies, 20 were case-control studies and 14 were cohort studies; 10 studies were rated good quality, 21 fair quality, and 3 poor quality. Twenty-five studies assembled patient groups that were fully or partially based in Europe or the UK; only 7 included patients from the United States (Table 43).

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control							
Anonymous, 1995[181] Anonymous, 1995[268] Anonymous, 1998[267]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception** Cases: 372 VTE, hospital Controls: 460 no VTE, hospital Recruitment period: 1990–1994	4.1	3.2 to 5.2	BMI, smoking, alcohol consumption, varicose veins, hypertension in pregnancy	Africa, Asia, Europe, Latin America	Good	1
Bloemenkamp, 1995[260] Bloemenkamp 2000[302]	**Consecutive women aged 15–49 yr with a first episode of proven DVT** Cases: 126 DVT, anticoagulation clinics Controls: 159 no DVT, source NR Recruitment period: 1988--1992	NR	NR	NA	Netherlands	Fair	2
Andersen, 1998[269]	**Women aged 18–49 yr in regional discharge summaries from 10 hospitals** *First- and second-generation users* Cases: 24 VTE (including PE), hospital Controls: 134 no VTE, blood donors *Third-generation users* Cases: 16 VTE (including PE), hospital Controls: 134 no VTE, blood donors Recruitment period: 1997–NR	5.2 48.6	1.6 to 16.4 5.6 to 423.0	Parity, BMI, Smoking	Denmark	Fair	1
Lidegaard, 1998[270]	**Women aged 15–44 yr in all hospitals in Denmark** Cases: 375 VTE, hospital registry Controls: 1041 no VTE, source NR Recruitment period: 1980–1993	NR	NR	NA	Denmark	Fair	2
Bloemenkamp, 1999[271]	**Women aged 15–49 yr in medical centers in Amsterdam** Cases: 185 VTE, hospital Controls: 591 no VTE, hospital Recruitment period: 1982–1995	3.9	2.6 to 5.7	Age, family history, center, calendar time	Netherlands	Good	1

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
*Case-Control (continued)*							
Lewis, 1999[261] Heinemann, 1999[272] Suissa, 1997[273] Suissa, 2000[274]	**Women aged 16–44 yr in Transnational Study on Oral Contraceptives and the Health of Young Women** <u>Cases</u>: 505 VTE, hospital <u>Controls</u>: 2270 no MI, thromboembolic CVA, or VTE, hospital and community Recruitment period: 1993–1996	2.90	2.06 to 4.09	Age, BMI, smoking, alcohol use, duration of use by generation, duration of previous use by generation, switching by generation	Austria, France, Germany, Switzerland, UK	Fair	1
Todd, 1999[299]	**Women aged 15–49 in the UK MediPlus database** <u>Cases</u>: 106, idiopathic VTE, registry <u>Controls</u>: 569, no VTE, registry Recruitment period: 1992–1997	NR	NR	NA	UK	Fair	2
Jick, 2000[296]	**Women aged 15–39 yr taking third-generation OCs or OCs with levonorgestrel** <u>Cases</u>: 99, VTE, registry <u>Controls</u>: 366, no VTE, registry Recruitment period: 1993–1999	NR	NR	NA	UK	Good	2
Spannagl, 2000[275]	**Women aged 15–49 yr in population-based cohort study** <u>Cases</u>: 80 VTE including PE, from cohort study <u>Controls</u>: 406 no VTE or PE, from cohort study Recruitment period: 1995–1997	3.0	1.8 to 5.0	BMI, varicose veins, family history of VTE	Germany	Poor	1
Lidegaard, 2002[276]	**Women aged 15–44 in national patient registry** <u>Cases</u>: 987 VTE including PE, registry <u>Controls</u>: 4054 Recruitment period: 1994–1998	NR	NR	NA	Denmark	Good	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Case-Control (continued)						
Legnani, 2002[277]	**Women aged 15–68 with specific genetic mutations** Cases: 301 VTE including PE, hospital Controls: 650, population Recruitment period: 1994--2000	NR	NR	NA	Italy	Fair	2
Legnani, 2004[278]	**Women aged 15–68 yr with specific genetic mutations** Cases: 195 VTE including PE, hospital Controls: 488, population Recruitment period: 1994–2000	NR	NR	NA	Italy	Fair	2
Sidney, 2004[262]	**Members of California Kaiser Permanente Medical Care Program aged 18–44 yr** Cases: 196 VTE hospital and administrative records Controls: 746, hospital and administrative records Recruitment period: 1998–2000	2.99	1.86 to 4.81	Age	U.S.	Good	1
Jick, 2006[298]	**Women aged 15–39 yr in the PharMetrics database who were prescribed OCs containing norgestimate, desogestrel, or levonorgestrel** Cases: 281 VTE including PE, registry Controls: 1055, registry Recruitment period: 2000–2005	NR	NR	NA	U.S.	Fair	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Case-Control (continued)						
Huerta, 2007[264] Farmer, 2000[279]	**Women aged 20–79 yr in UK General Practice Research Database** *VTE* Cases: 197 VTE, registry Controls: 788, no VTE, registry *DVT* Cases: 122 DVT, registry Controls: 788, no DVT, registry *PE* Cases: 75 PE, registry Controls: 788 no PE, registry Recruitment period: 1994–NR	1.85 2.05[c] 1.56[c]	1.38 to 2.48 1.46 to 2.89 1.04 to 2.35	Age, BMI, smoking, calendar year, cancer, fractures in last month, surgery in last 6 mo, use of warfarin sodium, visits to family physician in last yr	UK	Good	1
Austin, 2009[280]	**African-American women aged 18–49 yr** Cases: 60 DVT or PE, hospital Controls: 196 no DVT or PE, outpatients Recruitment period: NR	2.8	1.4 to 5.7	Age	U.S.	Fair	1
Van Hylckama Vlieg, 2009[281]	**Women <50 yr in anticoagulation clinics MEGA study** Cases: 1524 DVT or PE, anticoagulation clinic Controls: 1760 no DVT or PE, partners of cases Recruitment period: 1999–2004	4.39[d]	3.87 to 5.09	Age, period of inclusion	Netherlands	Good	1
Barsoum, 2010[282]	**Rochester Epidemiology Project, age NR** Cases: 726 VTE, registry Controls: 830 no VTE, registry Recruitment period: 1988–2000	4.03	1.83 to 8.89	BMI, "previously identified risk factors"	U.S.	Good	1

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Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Dinger, 2010[283]	**Women aged 15–49 in survey of primary care and specialty physicians** Cases: 680 DVT or PE, outpatients Controls: 2720 no DVT or PE, outpatients Recruitment period: 2002–2008	2.4	1.8 to 3.2	Parity, BMI, family history, smoking, personal history of VTE, duration of OC use, education, chronic disease, concomitant medication	Germany	Fair	1
Heinemann, 2010[284]	**Women aged 15–49 yr in survey of physicians, and registry** Cases: 434 DVT or PE, outpatients and registry Controls: 1920 no DVT or PE, community Recruitment period: 2002–2006	NR	NR	NA	Austria	Good	2
Jick, 2011[312]	**Women aged 15–44 yr in the PharMetrics database in the U.S.** Cases: 186 OC users with VTE, registry Controls: 681 OC users and no VTE, registry Recruitment period: After 2001	NR	NR	NA	U.S.	Fair	2
Parkin, 2011[300]	**Women aged 15-44 yr in UK General Practice Research Database** Cases: 61 VTE, registry Controls: 215 no VTE, registry Recruitment period: 2002–2009	NR	NR	NA	UK	Fair	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Cohort						
Farmer, 1995[285]	**Women aged 14–45 registered with participating general practices in the UK** Exposed: 111,449 person-years Unexposed: 542,906 person-years Recruitment period: 1990–1991	NR	NR	NA	UK	Fair	2
Grodstein, 1996[286]	**Women ≥30 yr in Nurses' Health Study** Exposed: 731,326 person-years Unexposed: 829,240 person-years Recruitment period: 1976–1992	2.2	0.8 to 5.9	Age, parity, BMI, smoking, postmenopausal hormone use, diabetes, high blood pressure, high cholesterol, time period	U.S.	Fair	1
Farmer, 1997[287]	**Women aged 15–49 in General Practice Research Database** Exposed: 234,899 Unexposed: NR (database includes ~1.1 million women) Recruitment period: 1992–1997	NR	NR	NA	UK	Fair	2
Hannaford, 1998[288]	**Royal College of General Practitioners' (RCGP) Oral Contraception Study** *DVT* Exposed: 335,181 person-years Unexposed: 228,727 person-years *PE* Exposed: 335,181 person-years Unexposed: 228,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	1.6 1.56	1.25 to 2.04 1.14 to 2.14	Age, parity, smoking, social class	UK	Poor	1

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Herings, 1999[301]	**Women aged 15-49 yr in eight Dutch cities** Exposed to 3rd generation progestins: 29,986 person-years Exposed to 2nd generation progestins: 24,953 person-years Recruitment period: 1986–1995	NR	NR	NA	Denmark	Fair	2
Conard, 2004[289]	**Women aged 15–50 yr in Hemostasis and Thrombosis Unit** Exposed: 102 Unexposed: 102 Recruitment period:1992–1997	0.8	0.2 to 3.9	Age, BMI, thrombophilia	France	Fair	4
Samuelsson, 2004[290]	**Women aged 15–44 yr in hospital in Jamtland** Exposed: 43 Unexposed: 32 Recruitment period: 1991–2000	NR	NR	NA	Sweden	Fair	2
Dinger, 2007[297]	**Women in the EURAS study** Exposed: 16,534 prescribed DRSP-containing OCs Unexposed: 26,341 prescribed other OCs Recruitment period: 2000–2004	NR	NR	NA	Austria, Belgium, Denmark, France, Germany, Netherlands, UK	Good	3
Seeger, 2007[291]	**Women aged 10–59 yr in health insurance database** Exposed: 22,429 Unexposed: 4858 Recruitment period: 2001–2004	NR	NR	NA	U.S.	Fair	2
van Vlijmen, 2007[292]	**Women aged 15–50 yr in specialty clinic** Exposed: 135 Unexposed: 87 Recruitment period: NR	9.7	3.0 to 42.4	Clustering of women within families	Netherlands	Fair	4

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Gronich, 2011[311]	**Women aged 12–50 yr in a health care plan in Israel** Exposed: 431,223 use episodes. Total of 819,749 woman-years of followup Recruitment period: 2002–2008	NR	NR	NA	Israel	Fair	2
Lidegaard, 2011[293]	**Women aged 15–49 yr in national registries** Exposed: 2,821,686 person-years Unexposed: 4,960,730 person-years Recruitment period: 1995–2005	2.83	2.65 to 3.01	NA Age, calendar year, education level	Denmark	Fair	1, 2
Le Gal, 2010[294]	**Women >18 yr in 12 thrombosis clinics** Exposed: 49 Unexposed: 247 Recruitment period: 2001–2006	0.6	0.1 to 2.8	Age	U.S., Canada, France, Switzerland	Fair	4
van Vlijmen, 2011[295]	**Female relatives from 4 family cohorts (first-degree relatives of consecutive patients with VTE or premature atherosclerosis)** Exposed: 571 Unexposed: 227 Recruitment period: 1995–2004	2.1	1.1 to 4.1	Pregnancy and clotting defects	Netherlands	Fair	4

BMI = body mass index; CI = confidence interval; DRSP = drospirenone; DVT = deep venous thrombosis; mo = month/months; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; PE = pulmonary embolism; UK = United Kingdom; U.S. = United States; VTE = venous thromboembolism; WHO = World Health Organization; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis of current versus noncurrent OC use; 2 = Excluded due to current versus noncurrent OR not reported or not calculable; 3 = Excluded due to progesterone-only OC use; 4 = Excluded due to family history of VTE or thrombophilia.

[c]This odds ratio is not included in the meta-analysis because it represents a subset of the total VTE population (OR=1.85).

[d]Calculated by pooling the ORs of individual subgroups.

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Current Versus Noncurrent OC Use

Fourteen studies[261-264,268,269,271,275,280-283,286,288] were included in this meta-analysis examining the effect of current versus noncurrent OC use on VTE incidence. Of these, 11 were case-control studies representing a combined 4565 cases and 10,901 controls; and 3 were cohort studies representing 3,888,193 exposed person-years and 6,018,697 unexposed person-years. Six studies were rated good quality, 6 fair quality, and two poor quality (Table 43). Only four studies in this meta-analysis included patients from the United States.[262,280,282,286]

In addition to the 14 studies included in the meta-analysis, a recently published, good-quality study[293] reported relative risks of VTE associated with several different progestin formulations compared with no OC use. The data from this important study were not included in the meta-analysis so as not to inappropriately pool odds ratios with adjusted relative risks, with the latter calculated based on person-years of exposure. This study also included patients from an earlier publication by Lidegaard et al.[263] Data from the earlier study are included in the meta-analysis. The study by Andersen et al.[269] contributed two ratio measures because the risk was only reported separately by progestin generation. The VTE outcome included PE and DVT in the majority of studies. One study[286] included only PE cases. The comparison groups for noncurrent OC users was (1) never users in six studies, (2) former and never users in seven studies, and (3) unspecified in one study.

Abstracted data not included in this meta-analysis are specified (with rationale) in Table 43. Reasons for exclusion from this analysis included the following: no reporting of odds ratios for current versus noncurrent OC users;[260,277,278,284,285,287,290,291,296,298-301,311,312] family history of VTE or thrombophilia in control group and cases;[289,292,294,295] and only including progesterone only OCs.[297]

Figure 33 shows the random-effects meta-analysis of the 14 studies. The result is an estimated odds ratio of 2.97 (95% CI, 2.46 to 3.59), demonstrating a significant increase in VTE risk with current OC use. There was significant heterogeneity, with a Q-value of 82.207 for 14 degrees of freedom, $p < 0.001$.

Figure 33. Forest plot for current versus noncurrent OC use and the risk of VTE

Study	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
WHO Collab., 1995	4.100	3.216	5.226	
Grodstein, 1996	2.200	0.810	5.975	
Andersen, 1998	5.200	1.624	16.648	
Andersen 2, 1998	48.600	5.592	422.389	
Hannaford, 1998	1.600	1.252	2.044	
Bloemenkamp, 1999	3.900	2.634	5.775	
Lewis, 1999	2.900	2.058	4.086	
Spannagl, 2000	3.000	1.800	5.000	
Sidney, 2004	2.990	1.859	4.808	
Huerta, 2007	1.850	1.380	2.480	
Austin, 2009	2.800	1.388	5.650	
van Hylckama, 2009	4.388	3.784	5.089	
Lidegaard, 2009	2.830	2.655	3.016	
Barsoum, 2010	4.030	1.828	8.882	
Dinger, 2010	2.400	1.800	3.200	
	2.970	2.456	3.591	

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Note: the study by Andersen (1998) contributed two ratio estimates because the risk was reported separately by progestin generation.

Sensitivity Analyses

We performed sensitivity analyses by excluding studies that did not include patients from the United States. The odds ratio for the remaining four studies was essentially unchanged from the larger analysis (OR, 3.00; 95% CI, 2.15 to 4.19). A second sensitivity analysis excluded the two poor-quality studies and resulted in a similar OR of 3.17 (95% CI, 2.62 to 3.83).

Ever Versus Never OC Use

One cohort study[288] examined the effect of ever versus never OC use on the risk of VTE. The risks of DVT and PE were significantly increased in ever versus never users with a risk ratio of 1.56 (95% CI, 1.14 to 2.14) for PE and 1.66 (95% CI, 1.25 to 2.04) for PE. However, these "ever users" included current and past users.

Three studies represented in the current versus noncurrent meta-analysis[262-264] stratified ever users by current and former users to examine whether current versus ever use conferred different risk for VTE. In all three studies, the odds of developing VTE were significantly increased among current users. However, one case-control study[262] found no difference in the odds of VTE

for ever versus never users (OR, 1.25; 95% CI, 0.78 to 2.01) and no difference in the odds of VTE for former versus never users (OR, 0.73; 95% CI, 0.44 to 1.21). A second case-control study[264] found only slightly increased odds of PE for former versus never users (OR 1.27; 95% CI, 1.08 to 1.49) but no difference in the odds of DVT (OR 1.14; 95% CI, 0.98 to 1.34). The cohort study[263] found no increased odds of VTE among former versus never users (OR 1.08; 95% CI, 0.98 to 1.18). We did not conduct a meta-analysis of ever versus never OC use because of the high heterogeneity of the studies and the low clinical relevance of the question.

PE Incidence Among OC Users

Most studies included PE in the definition of VTE. Three studies, however, examined the relationship between OC use and the incidence of PE separately from DVT. Two studies looked at the risk among current users. The third looked at the risk among ever versus never users. There were not enough data for a meta-analysis. One good-quality case-control study[264] evaluated the odds of developing PE, DVT, or both PE and DVT among current versus noncurrent OC users. The adjusted odds ratios were similar for all comparisons. For DVT, the odds ratio was 2.05 (95% CI, 1.46 to 2.89); for PE, odds ratio was 1.56 (95% CI, 1.04 to 2.35); and for both DVT and PE, 1.85 (95% CI, 1.38 to 2.48). A fair-quality cohort study[286] that evaluated the risk of PE for current or former OC users demonstrated a trend toward increased risk among current users, but the confidence intervals were not significant, with a risk ratio of 2.2 (95% CI, 0.8 to 5.9). For former OC users, the odds ratio was 0.8 (95% CI, 0.5 to 1.2). A poor-quality cohort study[288] evaluated the risk of PE among ever versus never users and found a risk ratio of 1.56 (95% CI, 1.14 to 2.14) and a similar risk ratio of 1.60 for DVT alone (95% CI, 1.25 to 2.04). Ever users included current and former users of OCs.

Duration of OC Use

Two fair-quality cohort studies[263,292] and four case-control studies (3 good quality and 1 fair)[262,276,296,302] evaluated the relationship between duration of OC use and risk of VTE. Related data from articles considered part of one study grouping[263,276] are represented in both the case-control and cohort categories due to a relationship between the represented patient populations. There were not enough data for a meta-analysis of the risk of VTE among current OC users by duration of use because of the varying time periods of duration of OC use reported in these 5 studies.

In a European case-control study,[302] women using OCs for 6 months or less had an increased odds of VTE compared with longer users (OR, 3.0; 95% CI, 0.6 to 14.8); however, the vast majority of VTEs (97 of 109) occurred in women using OCs for more than a year. In a second European case-control study,[276] current OC users of more than 1 year had 0.5 times the odds of developing VTE compared with users of less than 1 year. In a good-quality case-control study from the United States,[262] the odds of VTE among current versus noncurrent users was 5.43 (95% CI, 2.12 to 13.94) for use less than 1 year. For women using OCs for 1 to 5 years, the odds were similar at 5.73 (95% CI, 2.98 to 10.99) and were lower for those using OCs for greater than 5 years at 3.12 (95% CI, 1.99 to 4.88). In a European cohort study,[263] the rate ratio (RR) of VTE for current users was higher among women who had used for less than 1 year (RR, 4.17; 95% CI, 3.73 to 4.66) than for those who used OCs 1 to 4 years (RR, 2.98; 95% CI, 2.73 to 3.26) or greater than 4 years (RR, 2.76; 95% CI, 2.53 to 3.02). In a fair-quality case-control study from Europe,[296] the odds of VTE was higher among users of all types of OCs during the first 6 months versus 7 months or more of use (OR, 3.8; 95% CI, 1.8 to 9.0).

OC Formulation

Estrogen Dose

Three studies[260,271,276,293] evaluated the relationship between high estrogen (≥50 mcg) and low estrogen (<50 mcg) OCs on the risk of VTE (Table 44). Of these, two were case-control studies representing 1298 cases and 4804 controls and one cohort study representing 7,782,416 person-years. One study was rated good quality and two fair quality.

Table 44. Data for risk of VTE on low-dose versus high-dose estrogen

Study[a]	Formulation	OR or RR	95% CI	Notes
Low-Dose EE vs. Noncurrent Use				
Bloemenkamp, 1995[260]	EE 30 mcg and desogestrel EE 30 mcg and levonorgestrel EE 35 mcg and noresthisterone or lynestrenol	8.7 3.8 3.8	3.9 to 19.3 1.7 to 8.4 1.2 to 12.5	Premenopausal women
Bloemenkamp, 1999[271]	EE 30 mcg and levonorgestrel EE 30 mcg and desogestrel EE 30 mcg and gestodene EE 20 mcg and desogestrel	3.7 4.9 5.2 24.7	1.9 to 7.2 2.5 to 9.4 1.3 to 20.6 2.8 to 213.5	
Lidegaard, 2002[276]	30-40 EE 20 EE	3.4 4.3	2.4 to 7.1 2.8 to 4.2	<1 year vs nonuse (never + former)
Lidegaard, 2011[293]	EE 30-40 mcg and norethisterone EE 30-40 mcg and phasic levonorgestrel EE 30-40 mcg and levonorgestrel EE 30-40 mcg and norgestimate EE 30-40 mcg and desogestrel EE 30-40 mcg and gestodene EE 30-40 mcg and drospirenone EE 30-40 mcg and cyproterone EE 20 mcg and desogestrel EE 20 mcg and gestodene EE 20 mcg and drospirenone	1.57 2.28 2.19 2.56 4.21 4.23 4.47 4.10 3.26 3.50 4.84	0.84 to 2.92 1.85 to 2.83 1.74 to 2.75 2.18 to 3.01 3.63 to 4.87 3.87 to 4.63 3.91 to 5.11 3.37 to 4.99 2.88 to 3.69 3.09 to 3.97 3.19 to 7.33	Adjusted relative risk
High-dose EE vs. Noncurrent Use				
Bloemenkamp, 1995[260]	EE 50 mcg and levonorgestrel or lynestrenol	3.4	1.1 to 10.7	Premenopausal women
Bloemenkamp, 1999[271]	EE 50 mcg and lynestrenol or levonorgestrel or noresthisterone	8.7	2.9 to 25.8	
Lidegaard, 2002[276]	50 EE	4.2	2.4 to 7.1	<1 year vs nonuse (never + former)
Lidegaard, 2011[293]	EE 50 mcg and norethisterone EE 50 mcg and levonorgestrel	5.66 3.54	3.12 to 10.3 2.48 to 5.05	Adjusted relative risk

CI = confidence interval; EE = ethinyl estradiol; OR = odds ratio; RR = relative risk
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

Table 45 lists the odds ratios for the meta-analysis of estrogen dose level. The cohort study[293] was not included in the meta-analysis due to the inability to calculate an odds ratio for the data. The results show no differences in the incidence of VTE by estrogen dose level. A formal test for difference gives a p-value of 0.7974. There was no significant heterogeneity. The estimated value of σ is 0.0.

Table 45. Estimated odds ratio by estrogen-dose level (VTE incidence)

Estrogen Dose	Odds Ratio (95% Confidence Interval)
Low	3.39 (2.32 to 4.96)
High	3.06 (1.32 to 7.10)

However, in the study by Lidegaard et al.,[293] which was not included in this meta-analysis, the first-generation progestin norethisterone in combination with 50 mcg of ethinyl estradiol was associated with a higher risk (RR 5.66; 95% CI, 3.12 to 10.3) than all of the other formulations studied, including norethisterone in combination with 30 to 40 mcg of ethinyl estradiol (RR 1.57; CI, 0.84 to 2.92) and norethisterone without estrogen (RR 0.56; CI, 0.29 to 1.07). These findings suggest that an increase in the ethinyl estradiol dose in combination with norethisterone from 30–40 mcg to 50 mcg may be associated with a more than doubling of risk of VTE. Notably, there was not as large an increase in VTE risk associated with high-dose versus low-dose estrogen in combination with levonorgestrel (RR 3.54 with high-dose and RR 2.19 with low-dose, overlapping confidence intervals).

We were unable to conduct a meta-analysis for the odds of VTE among progestin-only OC users (i.e., pills containing no estrogen); however, several studies addressed this question. A European case-control study[276] found a nonsignificant increase in the odds of VTE (OR 2.0; 95% CI, 0.8 to 5.1) for progestin-only OC users compared with nonusers. This same group of investigators[293] subsequently reported data from a large cohort of women in Denmark that demonstrated a nonsignificant decrease in the relative risk of VTE for progestin-only OC users compared with nonusers (RR for norethisterone 0.56; CI, 0.29 to 1.07 and RR for desogestrel 0.64; CI, 0.29 to 1.42). A multinational case-control study[272] also found no difference in the odds of VTE (OR 0.68; CI, 0.28 to 1.66) among current users of progestin-only OCs versus nonusers.

Progestin Generation

As discussed previously, for the purpose of our analyses, first-generation progestins include norethindrone and ethynodiol diacetate; second-generation include levonorgestrel and norgestrel; third-generation include gestodene, desogestrel, and norgestimate; and fourth-generation include drospirenone, dienogest, and cytoproterone acetate. Six case-control studies representing 4257 cases and 11,791 controls[181,261,270,273,276,280,281,284] were included in this meta-analysis examining the effect on VTE incidence of varying progestin generations in current users of combination OCs.

Four studies were rated good quality and three fair quality. Only one study[280] included patients from the United States. Table 46 lists the included studies, generation of progesterone studied, and odds ratios. An additional large cohort study representing 8,010,290 person-years[293] reported relative risks of VTE associated with several different progestin generations. The findings from this study are summarized in Table 46 but could not be included in the meta-analysis because odds ratios were not reported.

Table 46. Data for outcomes on progestin generation (VTE incidence)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
First Generation				
Anonymous, 1995[181]	First generation/ EE < 50 mcg First generation/EE ≥ 50 mcg	3.37 4.05	1.44 to 7.93 1.92 to 8.54	Europe only (developing countries excluded)
Lidegaard, 1998[270]	First generation	1.8	0.9 to 3.6	VTE (PE + DVT)
Lewis, 1999[261]	First generation	8.48	3.03 to 23.86	
Lidegaard, 2002[276]	<1 year of use first generation	4.1	2.4 to 7.1	
Austin, 2009[280]	First generation	4.1	1.1 to 14.9	African-American women
Van Hylckama Vlieg, 2009[281]	Lynestrenol Noresthisterone	5.6 3.9	3.0 to 10.2 1.4 to 10.6	
Lidegaard, 2011[293]	Norethisterone/EE 50 mcg Norethisterone/EE 30-40 mcg Norethisterone (no estrogen)	5.66 1.57 0.56	3.12 to 10.3 0.84 to 2.92 0.29 to 1.07	Adjusted relative risk (not included in meta-analysis of odds ratios)
Second Generation				
Anonymous, 1995[181]	Second generation/EE ≥ 50 mcg Second generation/EE < 50 mcg	3.83 3.61	2.44 to 6.02 2.53 to 5.13	Europe only (developing countries excluded)
Suissa, 1997[273]	Second generation	6.6	2.5 to 17.8	<1 year of use
Lidegaard, 1998[270]	Second generation	1.6	1.0 to 2.5	
Lewis, 1999[261]	Second generation Other second generation Levonorgestrel	2.85 3.25 2.63	1.92 to 4.22 1.89 to 5.58 1.75 to 3.95	
Lidegaard, 2002[276]	Second generation Levonorgestrel	2.9 3.6	2.2 to 3.8 2.6 to 4.9	
Austin, 2009[280]	Second generation	2.9	0.9 to 9.3	African-American women
Van Hylckama Vlieg, 2009[281]	Second generation (levonorgestrel) vs. none	3.6	2.9, 4.6	
Heinemann, 2010[284]	Second generation	3.14	2.21 to 4.47	
Lidegaard, 2011[293]	Levonorgestrel/EE 50 mcg Levonorgestrel/EE 30-40 mcg Phasic levonorgestrel/EE 30-40 mcg	3.54 2.19 2.28	2.48 to 5.05 1.74 to 2.75 1.85 to 2.83	Adjusted relative risk (not included in meta-analysis of odds ratios)
Third Generation				
Anonymous, 1995[181]	Third generation/EE < 50 mcg	7.36	4.20 to 12.90	Europe only (developing countries excluded)
Lewis, 1999[261]	Third generation Norgestimate Desogestrel 30 mcg Gestodene Desogestrel 20 mcg	2.26 3.65 2.52 2.25 1.56	1.46 to 3.50 2.17 to 6.12 1.56 to 4.09 1.40 to 3.60 0.85 to 2.86	
Austin, 2009[280]	Third generation	3.4	0.48 to 20.3	African-American women
Lidegaard, 2011[293]	Norgestimate/EE 30-40 mcg Desogestrel/EE 30-40 mcg Gestodene/EE 30-40 mcg	2.56 4.21 4.23	2.18 to 3.01 3.63 to 4.87 3.87 to 4.63	Adjusted relative risk (not included in meta-analysis of odds ratios)

Table 46. Data for outcomes on progestin generation (VTE incidence) (continued)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
Fourth Generation				
Van Hylckama Vlieg, 2009[281]	Drospirenone Cyproterone acetate	6.3 6.8	2.9 to 13.7 4.7 to 10.0	
Lidegaard, 2011[293]	Drospirenone/EE 30-40 mcg Cyproterone/EE 30-40 mcg Drospirenone/EE 20 mcg	4.47 4.10 4.84	3.91 to 5.11 3.37 to 4.99 3.19 to 7.33	Adjusted relative risk (not included in meta-analysis of odds ratios)

CI = confidence interval; EE = ethinyl estradiol; OC = oral contraceptive; OR = odds ratio
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]First-generation progestins = norethindrone and ethynodiol diacetate; second-generation = levonorgestrel and norgestrel; third-generation = gestodene, desogestrel, and norgestimate; fourth-generation = drospirenone, dienogest, and cytoproterone acetate.

Table 47 lists the results of the meta-analysis. We found no difference in the odds of VTE by progestin generation. An overall test for differences gives a chi-square value of 8.1 for 3 degrees of freedom, p=0.044. There was significant heterogeneity. The estimated value of σ is 0.24. The t-value is 4.89 for 11 degrees of freedom, p=0.0005. The value of σ is larger than many of the standard errors for the observed odds ratios.

Table 47. Estimated odds ratio by progestin generation of combined OCs relative to noncurrent use (VTE incidence)

Generation	Odds Ratio (95% Confidence Interval)
First	4.06 (2.66 to 6.19)
Second	3.28 (2,49 to 4.31)
Third	4.06 (3.09 to 5.32)
Fourth	5.36 (2.78 to 10.32)

Additional reports[260,268,271,279,283,287,291,296,297,299-301,311,312] giving information about the risk of VTE associated with different generations of progestin use are provided in Table 48. These data were not in a format that was useful for meta-analysis because the comparisons were between users of various types of OCs, and the studies did not report odds of VTE between current and noncurrent users. There were also many overlapping patients between these studies and between some of these studies and those included in the meta-analysis reported above. One fair-quality cohort study,[287] one good-quality case-control study,[279] and one fair-quality case-control study,[299] all conducted in the United Kingdom, found no difference in the odds or risk of VTE among users of OCs containing progestins of different generations but similar ethinyl estradiol doses. A good quality large European cohort study[297] found no difference in VTE odds among current users of dienogest- or drospirenone-containing OCs and those using other OCs containing similar estrogen dose. Another fair quality case control study[283] had similar findings. Another fair-quality European case-control study[260] found a significant increase in odds of VTE among current users of desogestrel, a third-generation OC, compared with first- and second-generation OCs (OR, 2.5; 95% CI, 1.2 to 5.2). A separate, good-quality case-control study[271] found no difference in VTE risk between OC users of third-generation progestins versus those using second-generation progestins. A large, fair-quality cohort study[291] reported VTE incidence among initiators of OCs containing drospirenone (a fourth-generation OC) versus initiators of

other OCs followed on average for 7.6 months. They found no significant difference in risk (RR, 0.9; 95% CI, 0.5 to 1.6).

On the other hand, a good-quality analysis of the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Conception[268] reported statistically significant increases in the odds of VTE associated with third-generation progestins desogestrel (OR, 2.4; 95% CI, 1.3 to 4.6) and gestodene (OR, 3.1; 95% CI, 1.6 to 5.9) compared with the second-generation progestin levonorgestrel. Jick et al.[296] also reported higher odds of VTE associated with third-generation OCs compared with the second-generation progestin levonorgestrel (OR, 2.3; 95% CI, 1.3 to 3.9) in a good-quality case-control study using the U.K. General Practice Research Database. Herings et al.[301] reported similar findings among a population of Dutch women; in a fair-quality cohort study, they reported a risk ratio of 4.2 (95% CI, 1.7 to 10.2) for VTE among new users of third-generation progestins compared with new users of levonorgestrel. Another fair-quality case-control study conducted in the United States[312] demonstrated an increased odds ratio of VTE associated with the fourth-generation progestin drospirenone compared with levonorgestrel (OR, 2.4; 95% CI, 1.7 to 3.4). Similarly, Parkin et al.[300] reported an increased risk of nonfatal VTE associated with the fourth-generation progestin drospirenone compared with levonorgestrel (OR, 3.3; 95% CI, 1.4 to 7.6) in a fair-quality case-control study that used the U.K. General Practice Research Database. Finally, a fair-quality cohort study conducted in Israel[311] reported an elevated risk ratio for VTE of 1.43 (95% CI, 1.15 to 1.78) associated with OCs that contained drospirenone, relative to OCs that contained a third-generation progestin.

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Anonymous, 1995[268]	Desogestrel Gestodene Desogestrel or gestodene	Levonorgestrel Levonorgestrel Levonorgestrel	2.4 3.1 2.7	1.3 to 4.6 1.6 to 5.9 1.6 to 4.6	OR adjusted for BMI, alcohol consumption, Oxford region varicose veins, HTN in pregnancy, smoking
Bloemenkamp, 1995[260]	Desogestrel Desogestrel with 30 mcg EE	Levonorgestrel All other OCs	2.2 2.5	0.9 to 5.4 1.2 to 5.2	RR adjusted for age
Farmer, 1997[287]	All second generation Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Monophasic levonorgestrel Monophasic levonorgestrel	All third generation Other second generation Desogestrel/EE 30 mcg Desogestrel/EE 20 mcg All desogestrel Gestodene Sequential levonorgestrel All third generation	1.68 0.51 1.17 2.51 1.76 1.32 2.09 1.97	1.04 to 2.75 0.19 to 1.33 0.60 to 2.26 1.09 to 5.44 0.91 to 3.48 0.70 to 2.49 0.93 to 4.70 1.00 to 3.87	RR adjusted for 5-year bands
Bloemenkamp, 1999[271]	Monophasic third generation	Levonorgestrel	1.9	0.8 to 4.5	OR adjusted for age, family history, center, calendar time
Herings, 1999[301]	Third-generation OC	Second-generation OC	4.2	1.7 to 10.2	RR adjusted for year and age
Todd, 1999[299]	Desogestrel Gestodene Norethisterone Norgestimate Cyproterone acetate	Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel	1.4 1.3 0.5 0.7 0.8	0.7 to 2.8 0.7 to 2.7 0.2 to 1.6 0.2 to 2.4 0.2 to 3.3	OR adjusted for BMI, smoking, diastolic blood pressure, non-OC prescriptions

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence) (continued)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Farmer, 2000[279c]	Desogestrel/EE 30 mcg Gestodene/EE 30 mcg Desogestrel/EE 20 mcg Triphasic levonorgestrel/EE Norgestimate/EE 35 mcg Norethisterone/EE 35 mcg Cyproterone/EE 35 mcg Drospirenone Gestodene Norgestimate	Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel Levonorgestrel Levonorgestrel	1.0 0.8 1.3 1.4 0.9 3.3 0.7 0.9 0.7 0.7	0.6 to 1.6 0.5 to 1.3 0.6 to 2.5 0.6 to 0.8 1.6 to 0.4 1.0 to 10 0.3 to 1.4 0.6 to 1.4 0.4 to 1.1 0.3 to 1.4	OR adjusted for BMI, smoking status, diastolic BP, asthma, duration of OC exposure, and non-OC/nonasthma prescriptions OR adjusted by year of birth
Jick, 2000[296]	Third-generation OCs	Levonorgestrel	2.3	1.3 to 3.9	OR adjusted for BMI, smoking, duration of OC use, OC switching. Controls matched by year of birth, index date, general practice
Dinger, 2007[297c]	Desogestrel Desogestrel Desogestrel	Levonorgestrel and other OCs Levonorgestrel Other OCs	1.1 1.0 1.3	0.7 to 1.7 0.6 to 1.7 0.8 to 2.0	HR adjusted for age, BMI, duration of OC use, VTE history
Seeger, 2007[291]	Drospirenone/EE	Other OCs	1.0	0.5 to 1.9	RR Current OC use
Dinger, 2010[283]	Dienogest/EE Dienogest/EE Desogestrel/EE	Other low-dose OC Low-dose levonorgestrel/EE Low-dose levonorgestrel/EE	0.9 1.0 1.0	0.6 to 1.4 0.6 to 1.8 0.5 to 1.8	OR adjusted for history of VTE, BMI, duration of OC use, parity, education, chronic disease, medications, smoking
Gronich, 2011[311]	Drospirenone	Third-generation OC	1.43	1.15 to 1.78	Rate ratio adjusted for age, diabetes, hyperlipidemia, hypertension, cancer, smoking, obesity, duration of use

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence) (continued)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Jick, 2011[312]	Drospirenone	Levonorgestrel	2.4	1.7 to 3.4	OR adjusted for age, index year, and duration of OC use
Parkin, 2011[300]	Drospirenone	Levonorgestrel	3.3	1.4 to 7.6	OR adjusted for BMI, using multiple imputation analysis

BMI = body mass index; CI = confidence interval; EE = ethinyl estradiol; HR = hazard ratio; OC = oral contraceptive; OR = odds ratio; RR = risk ratio; VTE = venous thromboembolism

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins=norethindrone and ethynodiol diacetate; second-generation=levonorgestrel and norgestrel; third-generation=gestodene, desogestrel, and norgestimate; fourth-generation=drospirenone, dienogest, and cytoproterone acetate.

[c]Published study reported odds ratios and 95% CIs with levonorgestrel as the index value. For consistency in this table, we reversed the direction of this comparison and converted the odds ratios and 95% CIs to reflect the relative odds of VTE with use of levonorgestrel as the reference group.

Special Populations and Risk of VTE with OC use

Blood-Clotting Disorders

Several studies evaluated the risk of VTE among special populations, including women with known predispositions to blood clotting. We were not able to perform a meta-analysis on this relationship because of a small number of studies that differed from each other in several important ways, including patient population and selections of controls.

One fair-quality case-control study[269] found an interaction between the use of OCs and the presence of inherited thrombophilia—protein C, protein S, antithrombin deficiencies, or Factor V Leiden mutation—such that OC users with inherited thrombophilia had a higher risk of VTE than is explained by the presence of either risk factor (i.e., a "multiplicative" effect). The odds ratio for inherited thrombophilia was 2.6 (95% CI, 0.7 to 9.3), and the odds ratio for inherited thrombophilia plus OC use was 63 (CI, 6.2 to 65). A second, poor-quality case-control study[275] found that Factor V Leiden carriers compared with noncarriers had an odds ratio of 1.7 (CI, 0.6 to 4.8), while carriers plus OC users had an odds ratio of 6.4 (CI, 2.8 to 14.3). Another fair-quality case-control study[280] showed a similar finding for a population of OC users with and without sickle cell trait. Compared with a reference group of nonusers without sickle cell trait, OC users without sickle cell trait had an odds ratio for VTE of 2.6 (CI, 1.1 to 6.2) and nonusers with sickle cell trait had an odds ratio of 1.8 (CI, 0.51 to 6.3). However, sickle cell trait patients who also used OCs had an odds ratio of 12.1 (CI, 2.8 to 52) for VTE. The sample size was too small to allow correction for potential confounding variables. Two cohorts of women whose family members had been diagnosed with VTE[292,295] had a two-fold increased risk of VTE during current OC use and risk regardless of presence of known thrombophilias.

OC Use and Venous Thromboembolism Mortality

No studies evaluated the association between OC use and mortality from VTE events.

Strength of Evidence for OC Use and Risk of Venous Thromboembolism

We found strong evidence that current OC use conferred a three-fold increased risk of VTE and PE when compared with the risk among noncurrent users (Table 49). The risk of VTE did not change among users of pills containing varying estrogen doses or progestin generations.

Table 49. Strength of evidence domains for the effect of OC use on venous thromboembolic events

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of All VTE and Mixed DVT/PE						
Current vs. noncurrent use/never	14 (15,466 plus 9,906,890 person-years)	Medium	Consistent	Direct	Precise	**High** 2.97 (2.46 to 3.59)
Incidence of PE Only						
Current vs. noncurrent use/never	3 (863 plus 2,124,474 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk appears similar to that of VTE
Incidence of All VTE and Mixed DVT/PE						
Duration of use	5 (6955 plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk may be present during first year of use
Estrogen	3 (6102 plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**High** Low dose: 3.39 (2.32 to 4.96) High dose: 3.06 (1.32 to 7.10)
Progestin	6 (16,048)	Medium	Consistent	Direct	Precise	**High** First generation: 4.06 (2.66 to 6.19) Second generation: 3.28 (2.49 to 4.31) Third generation: 4.06 (3.09 to 5.32) Fourth generation: 5.36 (2.78 to 10.32)
Mortality From VTE						
Current vs. noncurrent use/never	0	NA	NA	NA	NA	**Insufficient** NA

CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; SOE = strength of evidence; VTE = venous thromboembolism

OC Use and Stroke Incidence

We identified 15 studies that evaluated the association between OC use and the incidence of stroke, including ischemic, hemorrhagic, and undifferentiated stroke.[261,265,267,272,288,304-307,314-333] Of these, 10 were case-control studies, 4 were cohort studies, and 1 was a pooled analysis; 5 studies were rated good quality, 9 fair quality, and 3 poor quality (Table 50). The pooled analysis[332] includes data from the individual studies by Petitti et al.[315] and Schwartz et al.[333] Nine

studies assembled cohorts that were either fully or partially based in Europe or the United Kingdom; three studies occurred in the United States. All 10 case-control studies recruited or identified patients from hospitals or hospital databases.

Table 50. Study characteristics and association between OC use and stroke incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Case-Control				
Tzourio,1995[314]	**Patients <45 yr in 5 hospitals in Paris** Cases: 72 ischemic stroke, hospital Controls: 173 no stroke, hospital Recruitment period: 1990–1993 Type of stroke: Ischemic	NA	NA	NA	France	Fair	3
Petitti,1996[315]	**Members of California Kaiser Permanente Medical Care Program aged 15–44 yr** *Ischemic stroke* Cases: 144 ischemic stroke, hospital and administrative records Controls: 744, hospital and administrative records *Hemorrhagic stroke* Cases: 151 hemorrhagic stroke, hospital and administrative records Controls: 744 hospital and administrative records Recruitment period: 1991–1994	1.18 1.14	0.54 to 2.59 0.60 to 1.16	Race, BMI, smoking, treated diabetes and hypertension	U.S.	Fair	1 2
Anonymous, 1996[317] Anonymous, 1996[318] Anonymous, 1998[267] Chang, 1999[316]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone** Contraception Cases: Hospital* Controls: No stroke, hospital* *Different sample size across articles Recruitment period: 1990–1994	4.20[316] (ischemic stroke) 1.10[316] (hemor-rhagic stroke)	1.74 to 10.12 0.63 to 1.93	Smoking, history of hypertension	UK, Germany, Hungary, Yugoslavia, Slovenia	Good	1 2

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Heinemann, 1997[326] Heinemann, 1999[272] Lewis, 1999[261]	**Women aged 16–44 yr in Transnational Study on Oral Contraceptives and the Health of Young Women** Cases: Undifferentiated stroke, hospital* Controls: No MI, thromboembolic CVA, or VTE, hospital and community* *Different sample size across articles Recruitment period: 1993–1996	2.86[261]	2.02 to 4.04	Hypertension, occupation, education level, hyperlipidemia, genetic polymorphisms of ACE gene	Austria, France, Germany, Switzerland, UK	Fair	1
Schwartz, 1997[333]	**Members of California Kaiser Permanente Medical Care Program aged 15–44 yr** *Ischemic stroke* Cases: 60 ischemic stroke, hospital and administrative records Controls: 485, community *Hemorrhagic stroke* Cases: 102 hemorrhagic stroke, hospital and administrative records Controls: 485 community Recruitment period: 1991–1994	0.90 0.93	0.27 to 2.94 0.37 to 2.31	Age, treated hypertension, smoking, race, alcohol use	U.S.	Good	1 2
Barinagarrementeria, 1998[327]	**Women aged 11–44 yr in stroke clinic and neurology department of a hospital in Mexico City** Cases: 130 undifferentiated stroke, hospital Controls: 122 no stroke, hospital Recruitment period: "Last 11 years"	2.5	0.8 to 8.1	Unadjusted	Mexico	Poor	1
Kemmeren, 2002[320]	**Women aged 19–49 yr in Risk of Arterial Thrombosis in Relation to Oral Contraceptives Study** Cases: 203 ischemic stroke, hospital Controls: 925, community Recruitment period: 1990–1995	2.1	1.5 to 3.1	Age, area of residence, calendar yr	Netherlands	Good	3

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued) (continued)							
Siritho, 2003[322]	**Patients aged 15–55 yr in 4 city hospitals in Melbourne** Cases: 234 ischemic stroke, hospital discharge records Controls: 234, community Recruitment period: 1984–1996	1.62	0.69 to 3.83	Smoking, alcohol, exercise, cholesterol, MI, hypertension, TIA, diabetes	Australia	Fair	1
Martinelli, 2006[323]	**Woman <45 yr referred to a thrombosis center** Cases: 105, ischemic stroke, hospital Controls: 293, healthy, partner or friend of cases	NA	NA	NA	Italy	Poor	4
Wang, 2012[325] Li, 2010[324]	**25 towns in Jiangsu Province** *Either ischemic or hemorrhagic stroke* Cases: 449 either ischemic or hemorrhagic stroke, hospital Controls: 830 no stroke, hospital	4.05	2.19 to 7.47	Parity, BMI, smoking, hypertension, hyperlipidemia, alcohol use, diabetes, family history of stroke, duration of current OC use	China	Fair	1
Cohort							
Hannaford, 1998[288]	**Royal College of General Practitioner's Oral Contraception study** Exposed: 335,181 person-years Unexposed: 28,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	NA	NA	NA	UK	Poor	3
Mant, 1998[265]	**Women aged 25–39 yr in Oxford Family Planning Association Study** Exposed: 186,848 person-years Unexposed: 123,716 person-years Note: After age 45, only women who had never used OCs or those who had used it for ≥8 yr were followed until 1994. Recruitment period: 1968–1974	2.9	1.3 to 6.7	Age, parity, BMI, smoking, social class	UK	Fair	1

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Cohort (continued)						
Yang, 2009[319]	**Women aged 30–49 yr in Women's Lifestyle and Health Cohort Study** Exposed: 38,258 Unexposed: 7471 Recruitment period: 1991–1992	1.1 0.4	0.6 to 2.0 0.1 to 2.1	Age, BMI, smoking, education, physical activity, alcohol use, high blood pressure, diabetes	Sweden	Fair	1 2
Lidegaard, 2012[329]	**Women aged 15–49 yr in Denmark** *Either ischemic or undifferentiated stroke* Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years *Ischemic stroke* Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years Recruitment period: 1995–2009	NR	NR NR	Age, education, year, risk factors	Denmark	Fair	5

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Pooled						
Schwartz, 1998[332]	**Members of California Kaiser Permanente Medical Care Program and Washington State aged 18–44 yr** *Ischemic stroke* <u>Cases</u>: 175 ischemic stroke, hospital and administrative records <u>Controls</u>: 485, hospital and administrative records and community *Hemorrhagic stroke* <u>Cases</u>: 198 hemorrhagic stroke, hospital and administrative records <u>Controls</u>: 485 hospital and administrative records and community Recruitment period: 1991–1994	NR	NR	NA	U.S.	Good	6

BMI = body mass index; CI = confidence interval; mo = month/months; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; VTE = venous thromboembolism; WHO = World Health Organization; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1=Included in ischemic stroke meta-analysis; 2=Included in hemorrhagic stroke meta-analysis; 3=Excluded due to current versus noncurrent OC use odds ratio not reported; 4=Excluded due to population of high-risk patients recruited from a thrombosis center; 5=Excluded due to adjusted relative risks as calculated from person-years of exposure cannot be converted to odds ratios; 6=Excluded this pooled study due to having duplicate patients reported in single studies above.

Current Versus Noncurrent OC Use

Of the 15 studies that evaluated the association between OC use and the incidence of stroke, nine[261,265,315,316,319,322,325,327,333] were included in a meta-analysis examining the effect of current versus noncurrent OC use on ischemic or undifferentiated stroke incidence. Of these, 7 were case-control studies representing 1490 cases and 3786 controls, and 2 were cohort studies representing 45,729 participants and 310,564 person-years. Two studies were rated good quality, six studies were rated fair quality, and one poor quality (Table 50). One study[327] did not specify whether the patients included in the analysis had ischemic or hemorrhagic stroke; we assumed that the majority of strokes were ischemic, and therefore we included this study in the meta-analysis. Abstracted data not included in this meta-analysis is specified (with rationale) in Table 50. Reasons for exclusion from this analysis included the following: no reporting of an odds ratio for current versus noncurrent use of OCs; representing a special, high-risk population; and reporting results not as odds ratios, but as relative risks calculated from person-years of exposure.

We also conducted separate meta-analyses of the seven studies of known ischemic stroke[261,265,315,316,319,322,333] representing 911 cases, 2834 controls, 38,258 exposed people, 7471 unexposed people, 186,848 person-years of exposure, and 123,716 unexposed person-years. We conducted a separate meta-analysis of the four studies that reported data separately for known hemorrhagic stroke representing 688 cases, 1965 controls, 38,258 exposed people, and 7471 unexposed people.[315,316,319,333]

Ischemic/Undifferentiated Stroke

We included all ischemic study results and also included any study of undifferentiated stroke if the ischemic stroke results were not available. Figure 34 shows that the random effects estimated odds ratio is 2.15 (95% CI, 1.49 to 3.11), demonstrating a significant increase in stroke risk for current OC use. There was significant heterogeneity, with a Q-value of 818.47 for 8 degrees of freedom, p=0.018.

Figure 34. Forest plot for ischemic/undifferentiated stroke

Author	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Petitti, 1996	1.180	0.539	2.584	
Chang, 1999	4.200	1.743	10.119	
Yang, 2009	1.100	0.602	2.008	
Siritho, 2003	1.620	0.688	3.817	
Lewis, 1999	2.860	2.022	4.045	
Barinagarrementeria, 1998	2.500	0.771	8.108	
Mant, 1998	2.900	1.277	6.584	
Wang, 2012	4.050	2.193	7.480	
Schwartz, 1997	0.900	0.273	2.969	
	2.150	1.485	3.114	
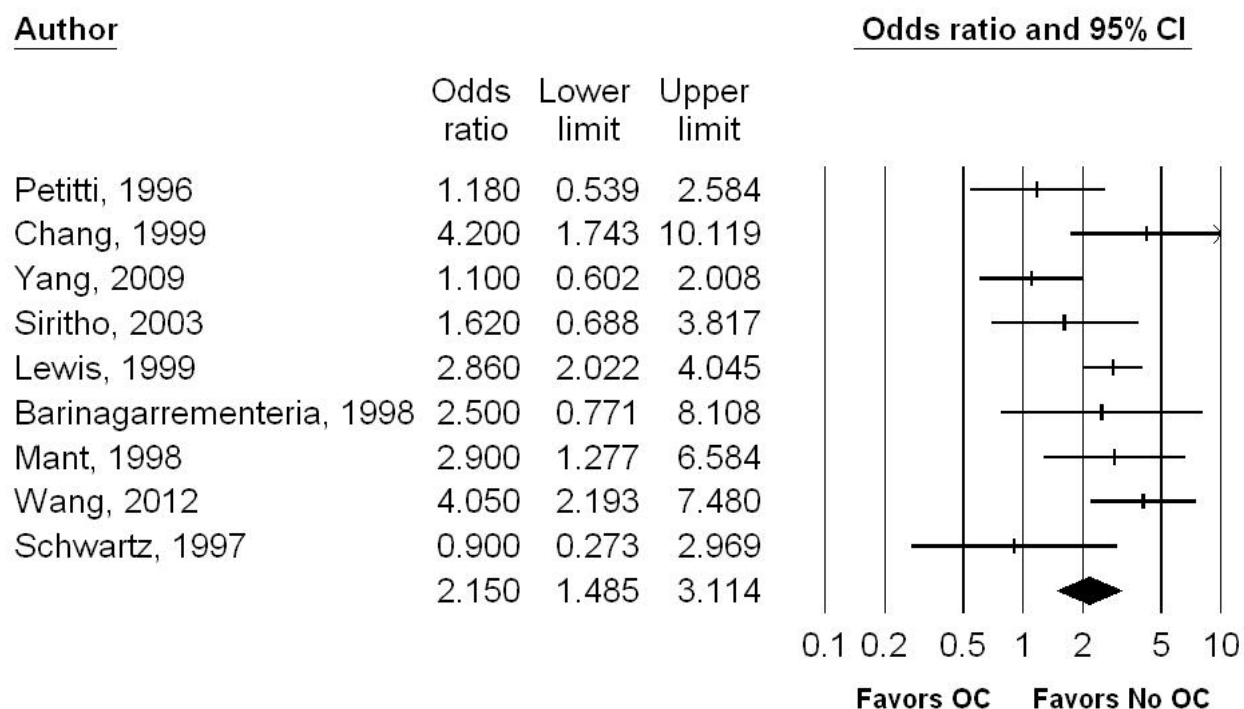
CI = confidence interval; OC = oral contraceptive
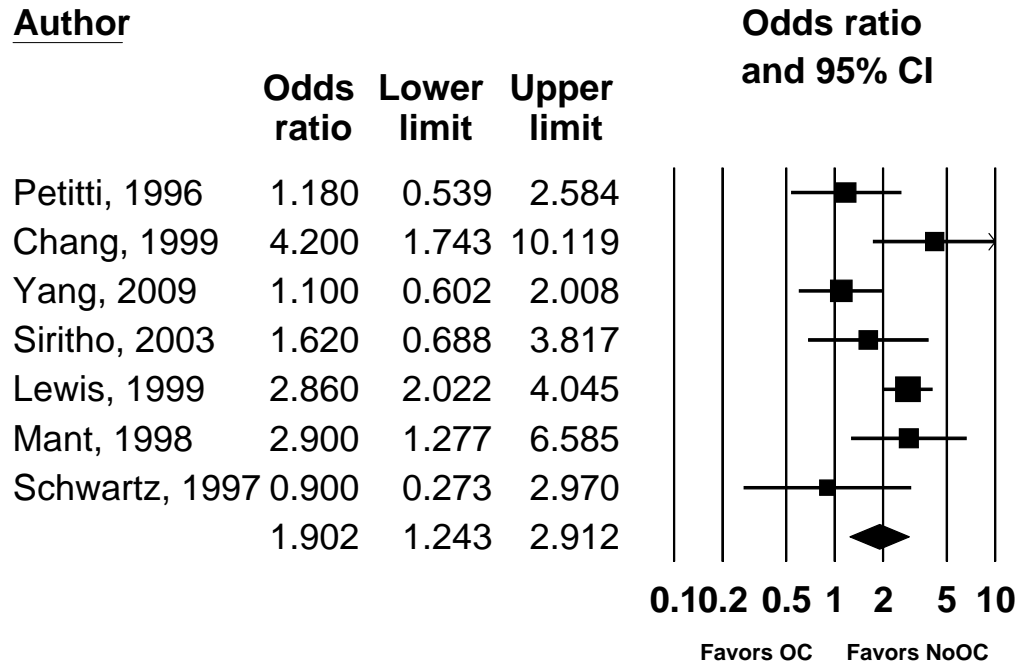
Sensitivity Analyses

We performed a sensitivity analysis by dropping the single poor-quality study.[327] The results were essentially unchanged with an odds ratio of 2.12 (95% CI, 1.42 to 3.16). Only two of the studies in this meta-analysis[315,333] were conducted in the United States; we did not, therefore, conduct a sensitivity analysis by excluding studies that did not include patients in the United States.

Ischemic Stroke

Figure 35 shows the odds ratios for the five case-control and two cohort studies of ischemic stroke incidence as a function of OC use. These studies represent a total of 1,100 cases, 2,975 controls, 38,258 exposed people, 7471 unexposed people, 186,848 person-years of exposure, and 123,716 unexposed person-years. The random-effects estimated odds ratio is 1.90 (95% CI, 1.24 to 2.91). There was significant heterogeneity, with a Q-value of 5.76 for 6 degrees of freedom, p=0.036.

Figure 35. Forest plot for ischemic stroke

Author	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Petitti, 1996	1.180	0.539	2.584	
Chang, 1999	4.200	1.743	10.119	
Yang, 2009	1.100	0.602	2.008	
Siritho, 2003	1.620	0.688	3.817	
Lewis, 1999	2.860	2.022	4.045	
Mant, 1998	2.900	1.277	6.585	
Schwartz, 1997	0.900	0.273	2.970	
	1.902	1.243	2.912	

0.1 0.2 0.5 1 2 5 10

Favors OC   Favors NoOC

CI = confidence interval; OC = oral contraceptive

Hemorrhagic Stroke

Figure 36 shows the odds ratios for the three case-control studies and one cohort study of hemorrhagic stroke incidence as a function of OC use. The random-effects estimated odds ratio is 1.03 (95% CI, 0.71 to 1.49), showing no evidence of increased hemorrhagic stroke risk among current OC users. There was no significant heterogeneity, with a Q-value of 1.48 for 3 degrees of freedom, p=0.489. Although current OC use is associated with a doubling of risk for ischemic/undifferentiated stroke, current OC use does not appear to be associated with an increased risk of hemorrhagic stroke.

Figure 36. Forest plot for hemorrhagic stroke

Author	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI
Petitti, 1996	1.140	0.601	2.163	
Chang, 1999	1.100	0.627	1.930	
Yang, 2009	0.400	0.078	2.049	
Schwartz, 1997	0.930	0.372	2.324	
	1.027	0.707	1.492	

0.1 0.2 0.5 1 2 5 10

Favors OC   Favors NoOC
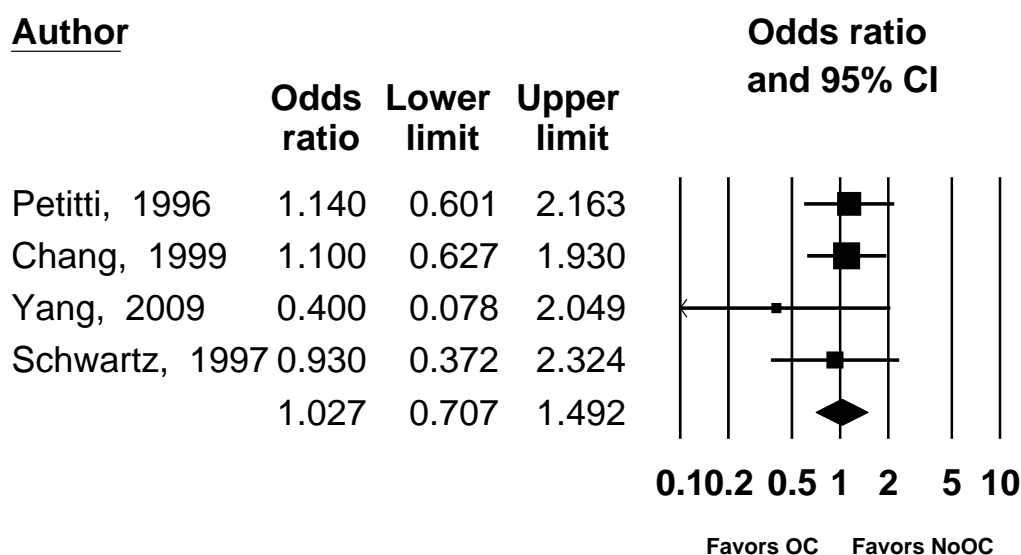
CI = confidence interval; OC = oral contraceptive

Past OC Use and Stroke Incidence

The majority of studies evaluated the risk of stroke among current users compared with noncurrent users; however, three studies evaluated whether there was any risk associated with ever versus never use of OCs. One poor-quality cohort study[288] found an elevated risk for cerebrovascular disease associated with ever OC use compared with never use (RR 1.37; 95% CI, 1.12 to 1.67). OC users in this study included current users. One Australian case-control study[322] found a trend toward increased odds of ischemic stroke among current OC users but no evidence of increased odds among past users. A case-control study from China[324,325] found a mildly increased risk of stroke among past users (OR 1.36; CI,1.04 to 1.77) but a much greater increased risk of stroke among current users (OR 4.05; CI,2.19 to 7.47). A fair-quality cohort study[319] found no elevated risk of stroke among current OC users (RR 1.1; CI, 0.6 to 2.0) or past users (RR 0.9; CI, 0.6 to 1.4). In a second fair-quality cohort study,[265] the significant increased risk of ischemic stroke among current users of OCs disappeared among past users (RR 0.7; CI, 0.2 to 2.2).

Duration of OC Use

There was an insufficient number of studies to conduct a meta-analysis examining the effect of duration of OC use on risk of stroke. A fair-quality European cohort study[319] demonstrated no increased risk of stroke with ever OC use; this did not change when stratified by duration of use by less than 5 years, 5 to 10 years, or more than 10 years. A fair-quality U.K. cohort study[265] found no significant difference in stroke risk for ever users who used OCs less than 5 years, 5 to 10 years, 10 to 15 years, 15 to 20 years, or greater than 20 years. A fair-quality Australian case-control study[322] similarly found no significant increased stroke risk by duration of use (up to 8 years or more than 8 years). In a European case-control study,[321] there were similar odds of cerebral thrombosis of any type among current users compared with never users when stratified by duration of use (<1 year, 1–5 years, and >5 years). In a fair-quality nested case-control study from China,[325] ever users of OCs for 15 years or more had increased odds of hemorrhagic stroke

(OR 3.7; CI, 1.9 to 7.3) but not ischemic stroke (OR 1.3; CI, 0.8 to 2.2) when compared with never users.

OC Formulation

Estrogen Dose

Two good-quality and one fair-quality case-control studies[317,320,321] representing 1897 cases and 8080 controls were included in a meta-analysis to evaluate the relationship between high-dose and low-dose estrogen on the risk of ischemic or undifferentiated stroke. Additional data abstracted from a cohort study[329] representing 13,988,428 person-years, and a case-control study involving women without migraines are summarized in Tzourio et al.[314] (Table 51) were not included in the meta-analysis because the former reported relative risks that could not be readily converted to odds ratios, and the latter did not provide confidence intervals. None of these studies included women from the United States.

Table 51. Stroke incidence odds by estrogen dose compared with nonuse of OCs

Study[a]	Comparison[b]	OR	95% CI	Comparison[b]	OR	95% CI	Notes
	Low-Dose vs. Nonuse			**High-Dose vs. Nonuse**			
Tzourio, 1995[314]	Low (20) Low (30-40)	1.7 2.7	NA NA	High (50)	4.8	NA	Women without migraines; undifferentiated stroke
Anonymous, 1996[317]	Low (<50)	1.27	0.70 to 2.32	High (≥50)	1.42	0.67 to 2.97	Undifferentiated stroke
Kemmeren, 2002[320]	Low (<50)	2.3	1.5 to 3.4	High (50)	3.1	1.2 to 7.9	Undifferentiated stroke
Lidegaard, 2002[321]	Low (20) Low (30-40)	1.7 1.6	1.0 to 3.1 1.3 to 2.0	High (50)	4.5	2.6 to 7.7	Current vs. never use; undifferentiated stroke
Lidegaard, 2012[329]	Norethindrone/ EE 30-40	2.17	1.49 to 3.15				
	Levonorgestrel/ EE 30-40	1.65	1.39 to 1.95				
	Norgestimate/ EE 30-40	1.52	1.21 to 1.91				
	Desogestrel/EE 30-40	2.20	1.79 to 2.69				
	Gestodene/EE 30-40	1.80	1.58 to 2.04	Norethindrone/ EE 50	1.27	0.66 to 2.45	Adjusted relative risk, based on person-years of exposure
	Drospirenone/ EE 30-40	1.64	1.24 to 2.18	Levonorgestrel/ EE 50	2.26	1.59 to 3.20	
	Cyproterone/EE 30-40	1.40	0.97 to 2.03				
	Desogestrel/EE 20	1.53	1.26 to 1.87				
	Gestodene/EE 20	1.70	1.37 to 2.12				
	Drospirenone/ EE 20	0.88	0.22 to 3.53				

CI = confidence interval; EE = ethinyl estradiol; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins=norethindrone and ethynodiol diacetate; second-generation=levonorgestrel and norgestrel; third-generation=gestodene, desogestrel, and norgestimate; fourth-generation=drospirenone, dienogest, and cyptoterone acetate.

Table 52 lists the odds ratios for the meta-analysis of the risk of ischemic/undifferentiated stroke by estrogen dose level. The results show a significant difference by dose. The estimated odds ratio comparing high dose with low dose is 2.37 (95% CI, 1.05 to 5.38, p-value for no difference=0.0437). There was no significant heterogeneity. The estimated value of σ is 0.0.

Table 52. Estimated odds ratios by estrogen dose compared with nonuse of OCs (stroke incidence)

Estrogen Dose	Odds Ratio (95% Confidence Interval)
Low	1.73 (1.29 to 2.32)
High	4.10 (1.91 to 8.80)

The findings from the large cohort study by Lidegaard, et al. provide additional evidence that estrogen dose may affect risk of stroke associated with OC use. This may be modified by the type of progestin the estrogen is combined with. Compared with nonusers of OCs, users of high-dose estrogen with norethindrone had a relative risk for stroke of 1.27 (95% CI, 0.66 to 2.45) compared with a relative risk of 2.17 (95% CI, 1.49 to 3.15) for low-dose estrogen and norethindrone. Interestingly, high-dose estrogen in combination with levonorgestrel was associated with a relative risk for stroke of 2.26 (95% CI, 1.59 to 3.20) compared with a relative risk of 1.65 (95% CI, 1.39 to 1.95) when low-dose estrogen was combined with levonorgestrel.

Two studies investigated the use of progestin-only OCs. A fair-quality U.K. case-control study[272] found no significant increased risk of stroke among current OC users versus nonusers; however, the confidence intervals were very wide (RR, 1.60; 95% CI, 0.24 to 10.72). A good-quality, multinational case-control study[267] found no increased risk of stroke among current versus noncurrent progestin-only OC users (OR, 1.07; 95% CI, 0.62 to 1.86).

Progestin Generation

There was an insufficient number of studies to do a meta-analysis regarding the risk of stroke according to OC use of varying progestin generation. In a fair-quality European case-control study,[321] there was a significantly increased risk for cerebral thrombus among current users of first-generation progestins (OR, 1.8; 95% CI, 1.0 to 3.3) compared with the reference group of second-generation OC users. There was also a slightly decreased risk for third-generation progestin users (OR, 0.6; 95% CI, 0.4 to 0.9) compared with second-generation users. In another good-quality European case-control study,[320] the increased odds of ischemic stroke among current users of contraceptives remained similar when stratified by first-, second- or third-generation OC users. A fair-quality U.K. case-control study[326] also found no significant difference in stroke risk between first-, second-, and third-generation OC users. In a recently published, fair-quality cohort study in which 1,626,158 women contributed 14,251,063 person-years of observation, Lidegaard et al.[329] reported relative risks of thrombotic stroke associated with several different OC formulations compared with nonusers. Relative risks were reported for OCs representing all four progestin generations. No clear pattern emerged regarding potentially different risks of stroke by progestin generation.

Special Populations

Several populations of women are known to be at increased risk for stroke, including women with migraines, thrombophilias, cardiovascular risk factors, and women of older age. We did not identify enough studies to conduct meta-analyses to determine if these risk factors modified the

risk of stroke in OC users. Several studies, however, did provide preliminary information about stroke risk in these populations.

Migraines

Two studies evaluated the risk of stroke among women with migraines who also used OCs. A fair-quality European case-control study[314] found the odds of stroke for OC users with migraines to be 13.9 times that of nonusers without migraines. However, this odds ratio statistically was not significantly different from the four-fold increase in odds reported for both women with migraines only and women who used OCs only. A fair-quality European case-control study[316] found the use of OCs had greater than multiplicative effects on the odds ratios for ischemic stroke among users with migraines (17-fold odds compared with 3-fold for OC users without migraine and 2-fold for women not using OCs who had migraines). This difference was not statistically significant.

Blood-Clotting Disorders

One poor-quality European case-control study[323] found a two-fold increase in odds of stroke in women with a Factor V Leiden mutation; this risk was significantly increased to 13-fold among current OC users with Factor V Leiden. A similar finding was obtained for women with hyperhomocysteinemia (two-fold odds increased to six-fold odds). It is unclear whether these differences were statistically significant. There was no increased risk among women with prothrombin gene mutation whether or not they were users of OCs. One study[324,325] found that women with specific genetic polymorphisms such as ACE I/D, rs10958409GA/AA and rs1333040CT/TT had a greater than multiplicative odds of stroke.

Age

One good-quality European case-control study[320] found the risk of first ischemic stroke among OC users that increased by age. The odds of stroke was 1.3 (95% CI, 0.5 to 3.3) for women 18 to 29 years of age; 2.3 (CI, 1.2 to 4.3) for women 30 to 39 years; and 2.6 (CI, 1.6 to 4.2) for women 40 to 49 years. There was no statistical test of the difference reported.

OC Use and Stroke Mortality

We identified two fair-quality studies and one poor-quality study that evaluated the association between ever versus never OC use and stroke mortality[33,164-166,334] (Table 53).

Table 53. Study characteristics and association between OC use and stroke mortality

Study	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[a]
Case-Control							
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	NR	NR	NA	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	NR	NR	NA	UK	Fair	1
Gallagher, 2011[334]	Female workers in 526 textile factories in Shanghai Exposed: 366,890 person-years Unexposed: 2,122,083 person-years Recruitment period: 1989–2000	0.65	0.46 to 0.91	Age	China	Poor	1

CI = confidence interval; NA = not applicable; NR = not reported; OR = odds ratio; SD = standard deviation; UK = United Kingdom; yr = year/years
[a]Meta-analysis code: 1 = Included in meta-analysis.

The results of a meta-analysis of these three studies of stroke mortality as a function of OC use are shown in Figure 37. The random-effects estimated odds ratio is 0.80 (95% CI, 0.59 to 1.08). There was no evidence of heterogeneity, with a Q-value of 2.91 for 2 degrees of freedom, p=0.234.

Figure 37. Effect of OC use on stroke mortality

Study name	Rate ratio	Lower limit	Upper limit	Rate ratio and 95% CI
Hannaford, 2010	1.010	0.694	1.469	
Vessey, 2010	0.800	0.400	1.600	
Gallagher, 2011	0.650	0.462	0.914	
	0.800	0.593	1.080	
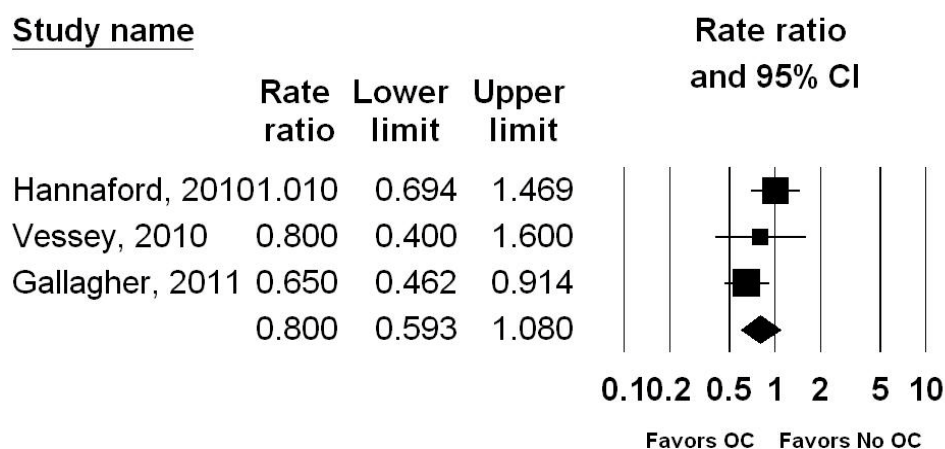
CI = confidence interval; OC = oral contraceptive

Vessey et al.[165] reported the risk of ischemic stroke mortality in ever users by duration of OC use and by time since last use. The risk ratios of mortality from hemorrhagic stroke compared with never OC use were 0.7 (95% CI, 0.4 to 1.3) for less than 4 years of total use; 1.4 (CI, 0.6 to 3.1) for 4 to 8 years of use; and 0.5 (CI, 0.2 to 1.2) for more than 8 years of use. In a second cohort study, calculating the risk of stroke mortality for ever users of OCs, the risk ratio was 1.1 (CI, 0.0 to 6.6) for those who had used within the last 4 years or at the time of death; 0.6 (CI, 0.0 to 3.6) for those who last used between 4 to 12 years prior to death; 0.7 (CI, 0.1 to 2.2) for those who last used 12 to 20 years prior to death; and 0.9 (CI, 0.4 to 1.8) for those who last used more than 20 years prior to death. Similar findings were noted for hemorrhagic stroke.[334]

Strength of Evidence for OC Use and Risk of Stroke

Table 54 shows the strength of evidence for the effects of OC use on the risk of stroke.

Table 54. Strength of evidence domains for the effect of OC use on stroke

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ischemic/Undifferentiated Stroke						
Current vs. noncurrent use/never	9 (54,767 plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 2.15 (1.49 to 3.11)
Duration	4 (51,038 plus 310,626 person-years)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR (Insufficient evidence to support quantitative synthesis of findings)
Estrogen	3 (9977)	Medium	Consistent	Direct	Precise	**High** Low dose: 1.73 (1.29 to 2.32) High dose: 4.10 (1.91 to 8.80)
Progestin	3 (6994)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** NR (heterogeneity in evidence about specific progestin generation)
Incidence of Ischemic Stroke						
Current vs. noncurrent use/never	7 (49,803 plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 1.90 (1.24 to 2.91)
Incidence of Hemorrhagic Stroke						
Current vs. noncurrent use/never	4 (48,382)	Medium	Inconsistent	Direct	Imprecise	**Low** No difference, 1.03 (0.71 to 1.49)
Mortality From Stroke						
Current vs. noncurrent use/never	3 (46,112 plus 3,091,673 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** 0.80 (0.59 to 1.08)

CI = confidence interval; SOE = strength of evidence

OC Use and Myocardial Infarction Incidence

We identified 11 studies that evaluated the association between OC use and the incidence of myocardial infarction.[261,265,267,270,272,288,304-307,309,313,321,329,331,335-342] Of these, 7 were case-control studies, 4 cohort studies, and 1 pooled analysis of two case-control studies that include data presented in one of the individually included case-control reports. Note that evidence from Lidegaard et al. was abstracted from several publications and included both case-control[270] and cohort[329] study designs. Six studies were rated good quality, 4 fair quality, and 1 poor quality (Table 55). Eight studies (73%) were conducted either fully or partially in Europe or the United Kingdom. Three studies (27%) were conducted in the United States. In the seven case-control

studies, cases were recruited from hospitals or identified by hospital databases. Of these, two studies recruited controls from hospitals, two studies from either hospitals or other settings, and two studies from outpatient-only or community settings. The recruitment source for controls was not clearly indicated in one study.

Table 55. Study characteristics and association between OC use and myocardial infarction incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control							
Anonymous, 1997[337] Anonymous, 1998[267]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception** <u>Cases</u>: 267 acute MI, hospital <u>Controls</u>: 822 patients hospitalized for reasons other than MI Recruitment period: 1989–1995	5.64	2.49 to 12.80	History of hypertension, diabetes, BMI, abnormal blood lipids, smoking status	Africa, Asia, Europe, Latin America	Good	1
Lidegaard, 1998[270]	**Patients aged 15–44 yr from all Danish hospitals** <u>Cases</u>: 94 acute MI, hospital <u>Controls</u>: 1041, source NR Recruitment period: 1994–1995	NR	NR	NA	Denmark	Fair	2
Dunn, 1999[339] Dunn, 1999[338]	**Women aged 16–44 yr in MICA study** <u>Cases</u>: 448 incident MI, hospital <u>Controls</u>: 1728 no MI, outpatient Recruitment period:1993–1995	0.79	0.54 to 1.16	Crude	Denmark	Good	1
Lewis, 1999[261] Heinemann, 1999[272]	**Transnational Study on Oral Contraceptives and the Health of Young Women aged 16–44 yr** <u>Cases</u>: 182 MI, hospital <u>Controls</u>: 635 no MI or thromboembolic CVA, hospital and community Recruitment period: 1993–1996	0.94	0.31 to 2.91	Smoking, hypertension, diabetes, education	Austria, France, Germany, Switzerland, UK	Fair	1

Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Rosenberg, 2001[340]	**Hospitalized patients <45 yr** Cases: 627 MI, hospital Controls: 2947 no MI, hospital Recruitment period: 1985–1999	1.3	0.8 to 2.2	Age, menopausal status, family history, smoking, region, interview yr, type of interview, hypertension, diabetes mellitus, history of elevated serum cholesterol	U.S.	Good	1
Tanis, 2001[341]	**Women aged 18–49 in Risk of Arterial Thrombosis in Relation to Oral Contraception study** Cases: 248 MI, hospital databases Controls: 925 no history of coronary, cerebral, or peripheral artery disease, community Recruitment period: 1990–1995	2.0	1.5 to 2.8	Age, area of residence and calendar yr	Netherlands	Good	1

Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
	Cohort						
Hannaford, 1998[288]	**Royal College of General Practitioner's Oral Contraception study** <u>Exposed</u>: 335,181 person-years <u>Unexposed</u>: 228,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	NR	NR	NA	UK	Poor	2
Mant, 1998[265]	**Women aged 25–39 in Oxford Family Planning Association Study** <u>Exposed</u>: 186,910 person-years <u>Unexposed</u>: 123,716 person-years Recruitment period: 1968–1974	1.5	0.6 to 3.2	Age, parity, BMI, smoking, social class	UK	Fair	1
Margolis, 2007[342]	**Women aged 30–49 yr in Women's Lifestyle and Health Study** <u>Exposed</u>: 6801 <u>Unexposed</u>: 8013 Recruitment period: 1990–1991	0.7	0.4 to 1.4	Age, BMI, smoking, education, alcohol intake, physical activity, history of hypertension, history of diabetes, menopausal status	Norway, Sweden	Fair	1
Lidegaard, 2012[329]	**Women aged 15–49 yr in Denmark** Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years Recruitment period: 1995–2009	NR	NR	Age, education, year, risk factors	Denmark	Fair	3

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Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Pooled							
Sidney, 1998[336] Sidney, 1996[335]	**Women aged 15–44 yr in pooled data from Kaiser Permanente Medical Care Program and University of Washington** Cases: 166 MI, Kaiser Permanente members and 101 MI, University of Washington patients Controls: 479 no MI, Kaiser Permanente members and 512 no MI, community Recruitment period: 1991–1995	0.94	0.40 to 2.20	Age, race, BMI, smoking, education, menopause, whether treated for hypertension or diabetes	U.S.	Good	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis of current versus noncurrent OC use; 2 = Excluded due to current versus noncurrent OR not reported; 3 = Adjusted relative risks as calculated from person-years of exposure cannot be converted to odds ratios.
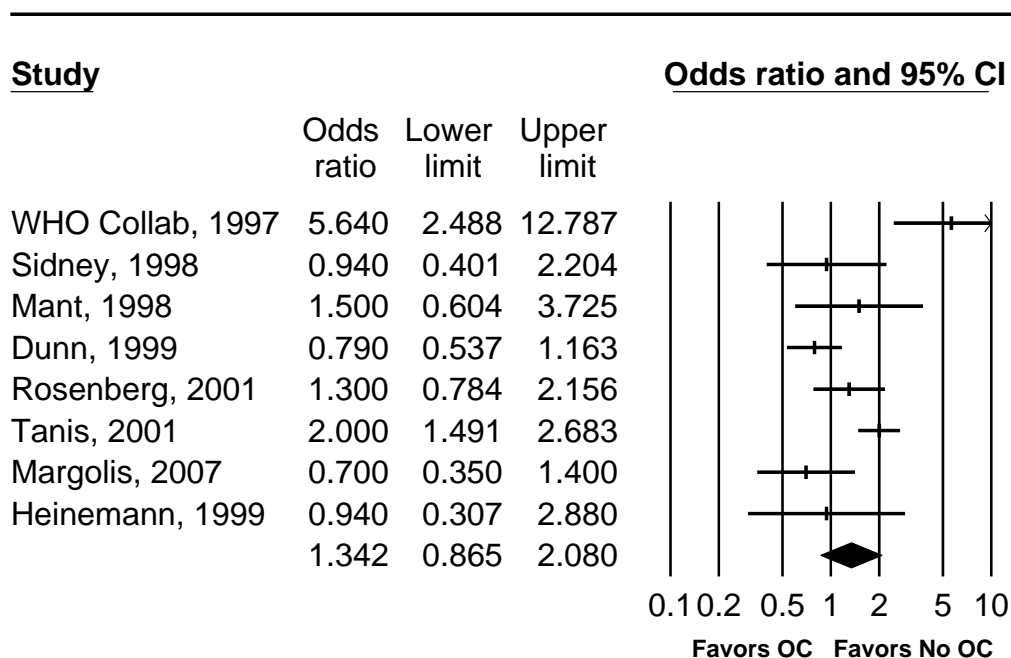
Current Versus Noncurrent OC Use

Eight studies[265,272,336,337,339-342] were included in this meta-analysis examining the effect of current versus noncurrent OC use on MI incidence. Of these, five were case-control studies representing 1772 cases and 7057 controls, two were cohort studies representing 310,626 person-years and 14,814 people, and one was a pooled analysis representing 267 cases and 991 controls.

The pooled analysis[336] was included in the meta-analysis rather than its individual case-control report.[335] The pooled analysis included previously unpublished data on 104 additional patients from a second site using identical methods and analysis as the case-control report, and therefore the pooled patient-level analysis provided the greatest evidence concerning current versus noncurrent OC use and myocardial infarction.

Five studies were rated good quality and three fair quality. Two studies[336,340] included patients from the United States; the remaining studies were either fully or partially based in Europe or the United Kingdom. Abstracted data not included in this meta-analysis are specified (with rationale) in Table 55. Reasons include not reporting a current versus noncurrent odds ratio and not providing data in a format that can be converted to an odds ratio.

Figure 38 shows the results of the meta-analysis. The odds ratio of MI among current versus noncurrent OC users was 1.34 (95% CI, 0.87 to 2.08) demonstrating a small increase in MI incidence among current OC users that did not reach statistical significance. There was significant heterogeneity, with a Q-value of 34.47 for 7 degrees of freedom, $p < 0.001$. Most of the heterogeneity was from the WHO Collaborative study.[267,337] This study was unique in that it included participants from Africa, Asia, and Latin American in addition to Europe and the United Kingdom. No sensitivity analyses were performed because all included studies were fair or good quality, and only two studies[336,340] included participants from the United States.

Figure 38. Forest plot for current versus noncurrent OC use (myocardial infarction incidence)

Study	Odds ratio	Lower limit	Upper limit
WHO Collab, 1997	5.640	2.488	12.787
Sidney, 1998	0.940	0.401	2.204
Mant, 1998	1.500	0.604	3.725
Dunn, 1999	0.790	0.537	1.163
Rosenberg, 2001	1.300	0.784	2.156
Tanis, 2001	2.000	1.491	2.683
Margolis, 2007	0.700	0.350	1.400
Heinemann, 1999	0.940	0.307	2.880
	1.342	0.865	2.080

Odds ratio and 95% CI

Favors OC   Favors No OC

CI = confidence interval; OC = oral contraceptive

Duration of OC Use

There were too few studies to perform a meta-analysis of the risk of MI by duration of current OC use. A large, fair-quality European cohort study[342] found no change in the relative risk of MI according to increasing duration of OC use for less than 5 years, 5 to 9 years, 10 to 14 years, or 15 years or more. In fair-quality cohort study from the United Kingdom,[265] ever users of OCs for up to 8 years had 1.9 times the risk of MI (95% CI, 1.0 to 3.5) compared with never users, while ever users for more than 8 years had no change in risk compared with never users (RR 1.0; CI, 0.6 to 1.8). However, in a later analysis of the same cohort,[165] there was no difference in ischemic heart disease mortality by the duration of ever use of OCs. This study is discussed in more detail in the section on OC use and MI mortality.

OC Formulation

Estrogen Dose

We investigated whether the dose of estrogen in OCs is related to risk of MI (high dose was ≥50 mcg of ethinyl estradiol and low dose was <50 mcg of ethinyl estradiol). One fair-quality cohort study[342] evaluated the risk of MI associated with low-dose versus high-dose estrogen and reported no difference in risk between these two groups (relative risks were not reported). A good-quality case-control study[267,337] evaluated the risk of MI associated with high-dose estrogen use in several European countries. They found a risk ratio of 7.69 (95% CI, 3.29 to 18.0) among users of high-dose estrogen OCs compared with nonusers and a risk ratio of 2.93 (CI, 1.23 to 6.97) for users of low-dose estrogen OCs. This study was unique in that it included populations from Africa, Asia, and Latin America.

Users of OCs containing no estrogen (i.e., progestin-only OCs) were found to have an odds ratio of 0.94 (95% CI, 0.31 to 2.91) for MI in one multinational case-control study.[272] In a second multinational case-control study,[267] progestin-only OC users were found to have an odds ratio of 0.98 (CI, 0.16 to 5.97).

Progestin Generation

Five case-control studies[261,270,338,340,341] were included in a meta-analysis examining the effect of current versus noncurrent OC use on MI incidence by progestin generation (Table 56). Three were rated good quality and two fair quality. Only one study[340] included patients from the United States. These five studies represented 1599 cases and 7276 controls. A good-quality, large cohort trial[329] reported adjusted relative risks of MI associated with progestin formulations across all four generations, but this study was not included in the meta-analysis because the relative risks could not be converted to odds ratios.

Table 56. Data for outcomes on progestin generation (myocardial infarction incidence)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
First Generation				
Lidegaard, 1998[270]	First generation	4.8	2.1 to 11	
Dunn, 1999[338]	Noresthisterone	1.83	0.15 to 22.7	
Lewis, 1999[261]	First generation	4.66	1.52 to 14.33	
Tanis, 2001[341]	First generation	2.7	1.0 to 7.3	
Rosenberg, 2001[340]	Progestogen containing <50 mcg of norethindrone	2.5	1.1 to 5.5	Current vs. never use
Lidegaard, 2012[329]	Norethindrone/EE 50 mcg Norethindrone/EE 30-40 mcg Norethindrone (no estrogen)	2.74 2.28 0.81	1.51 to 4.97 1.34 to 3.87 0.42 to 1.56	Adjusted relative risk, based on person-years of exposure
Second Generation				
Lidegaard, 1998[270]	Second generation	1.8	0.8 to 4.3	
Dunn, 1999[338]	Levonorgestrel	0.93	0.45 to 1.95	
Lewis, 1999[261]	Second generation	2.99	1.51 to 5.91	
Tanis, 2001[341]	Second generation	2.5	1.5 to 4.1	
Rosenberg, 2001[340]	Progestogen containing <50 mcg levonorgestrel	1.6	0.5 to 5.2	Current vs. never use
Lidegaard, 2012[329]	Levonorgestrel/EE 50 mcg Levonorgestrel/EE 30-40 mcg Levonorgestrel (no estrogen)	4.31 2.02 0	3.09 to 6.00 1.63 to 2.50 0.00 to 35.01	Adjusted relative risk, based on person-years of exposure
Third Generation				
Lidegaard, 1998[270]	Third generation	1.1	0.5 to 2.5	
Dunn, 1999[338]	Third generation Desogestrel Gestodene	1.66 1.20 2.41	0.75 to 3.67 0.40 to 3.57 0.80 to 7.30	
Lewis, 1999[261]	Third generation	0.85	0.30 to 2.39	
Tanis, 2001[341]	Third generation	1.3	0.7 to 2.5	
Lidegaard, 2012[329]	Norgestimate/EE 30-40 mcg Desogestrel/EE 30-40 mcg Gestodene/EE 30-40 mcg Desogestrel/EE 20 mcg Gestodene/EE 20 mcg Desogestrel (no estrogen)	1.33 2.09 1.94 1.55 1.20 1.46	0.91 to 1.94 1.54 to 2.84 1.62 to 2.33 1.13 to 2.13 0.77 to 1.85 0.55 to 3.90	Adjusted relative risk, based on person-years of exposure
Fourth Generation				
Lidegaard, 2012[329]	Drospirenone/EE 30-40 mcg Cyproterone/EE 30-40 mcg Drospirenone/EE 20 mcg	1.65 1.47 0	1.03 to 2.63 0.83 to 2.61 0.00 to 12.99	Adjusted relative risk, based on person-years of exposure

CI = confidence interval; EE = ethinyl estradiol; OC = oral contraceptive; OR = odds ratio
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.
[b]First-generation progestins = norethindrone and ethynodiol diacetate; second-generation = levonorgestrel and norgestrel; third-generation = gestodene, desogestrel, and norgestimate; fourth-generation = drospirenone, dienogest, and cytoproterone acetate.

Table 57 lists the results for the meta-analysis of MI odds by progestin generation. MI risk appears to be highest among first generation progestin users. The formal test for difference gives a chi-square value of 8.78 for 2 degrees of freedom, p=0.0125. There is no significant heterogeneity. The estimated value of σ is 0.0.

Table 57. OC progestin generation and myocardial infarction risk in current OC users compared with nonusers

Generation	Odds Ratio (95% Confidence Interval)
First	3.37 (2.04 to 5.54)
Second	1.79 (1.16 to 2.75)
Third	1.34 (0.91 to 1.98)

Most of the risk ratios reported by Lidegaard et al.[329] across all four generations of progestins seemed to show no increased risk of MI by progestin generation, pointing instead to a possible increased risk of MI with increasing estrogen dose.

Special Populations

Cardiovascular Risk Factors

Age, Diabetes, Hypertension, Dyslipidemia

There was insufficient information to perform a meta-analysis evaluating the risk of MI among users of OCs with cardiovascular risk factors, but several studies did provide information regarding this question. In a large, fair-quality European cohort study,[342] the risk ratio of MI was not elevated among former or current users of OCs, and there was no effect modification by age, hypertension, or diabetes status. The only group with a significant elevated risk of MI were women who had ever been advised by a physician to stop OCs (RR, 1.4; 95% CI, 1.0 to 2.1). A good-quality European case-control study[341] found an elevated risk of MI among ever users of OCs in all age categories. There was no reported statistical difference according to age. The risks of MI were highest among OC users who were smokers or who had hypertension, hypercholesterolemia, diabetes, or obesity. In some cases, the risks appeared to be multiplicative.

Smoking

In a fair-quality U.K. cohort,[265] the risk of MI was not elevated in OC users who were nonsmokers, OC nonusers who were smokers, or OC users who smoked less than 15 cigarettes per day. However, compared with never users, the risk of MI increased four-fold among smokers of 15 or more cigarettes per day whether they were former users (RR, 4.0; 95% CI, 1.3 to 16.2) or current users (RR, 4.9; CI, 1.2 to 23.6). A good-quality U.S. case-control study[340] had similar findings; the odds of MI associated with current OC use were not elevated in those who smoked 1 to 25 cigarettes a day. However, the odds were elevated for nonusers who smoked more than 25 cigarettes a day (OR 12; CI, 9 to 16) and significantly more elevated for current users of OCs who smoked more than 25 cigarettes a day (OR 32; CI, 12 to 81; p=0.05). A third fair-quality U.K. case-control study[339] found no interaction between smoking and use of OCs on the risk of MI; in this study, the definition of "nonusers" is not clear.

Blood-clotting Disorders

A good-quality European case-control study[341] evaluated the relationship between inherited clotting disorders and the risk of MI. With a reference group of nonusers with no Factor V Leiden or prothrombin G201210A mutation, the estimated odds ratios were 1.4 (95% CI, 0.7 to 2.7) for nonusers with a mutation; 2.1 (CI, 1.5 to 3.0) for OC users without a mutation; and 1.9 (CI, 0.6 to 5.5) for OC users with a mutation. These findings suggest that there is no interaction between Factor V Leiden or prothrombin G20210A carrier status and OC use upon the odds of MI.

OC Use and Myocardial Infarction Mortality

We identified three cohort studies[33,164-166,334] evaluating the risk of MI mortality in OC ever users versus never users that could be combined into a meta-analysis (Table 58). These studies represent 46,112 participants in one study and 3,091,673 person-years in the other two. Two of the studies were based in the United Kingdom and one in China. The U.K. studies recruited women in the 1960s and 1970s[33,165] and were fair quality. The study in China was poor quality.

A fourth study[343] reported on the relationship between OC use and MI mortality. We did not include this secondary analysis of a case-control study[338] conducted in the United Kingdom in the meta-analysis because the reference group and the definition of OC use differed from the other three studies. This poor-quality study compared 148 women who died within 28 days of an MI to 24 women who died more than 28 days after an MI plus 413 MI survivors. The authors reported adjusted ORs of 0.83 (95% CI, 0.25 to 2.81), 2.88 (CI, 1.22 to 6.77), and 0.89 (CI, 0.27 to 2.92) for third-generation OC use, second-generation OC use, and other OC use, respectively, compared with no OC use, with OC use in all cases being defined as OC use the 3 months prior to the MI.

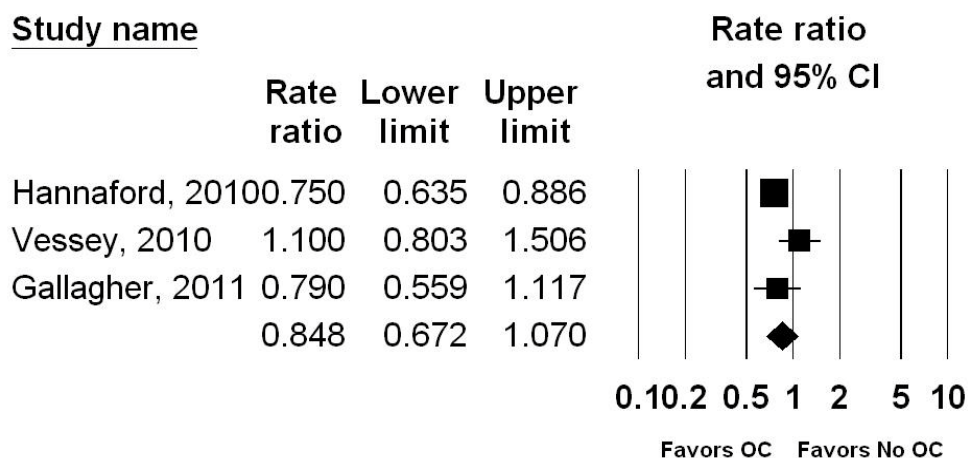**Table 58. Study characteristics and association between OC use and myocardial infarction mortality**

Study	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[a]
Case-control (continued)							
Dunn, 2001 #1726[343]	**Women aged 16-44 from the Myocardial Infarction Causality study** <u>Cases:</u> 148 who died within 28 days of an MI <u>Controls:</u> 24 who died more than 28 days after an MI and 413 MI survivors Recruitment period: 1993—1995	NR	NR	NA	UK	Poor	2
Cohort							
Hannaford, 2010[33]	**Royal College of General Practitioner's Oral Contraception study** <u>Exposed:</u> 28,806 <u>Unexposed:</u> 17,306 Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	NR	NR	NA	UK	Fair	1
Vessey, 2010[165]	**Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study** 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	NR	NR	NA	UK	Fair	1
Gallagher, 2011[334]	**Female workers in 526 textile factories in Shanghai** <u>Exposed:</u> 366,890 person-years <u>Unexposed:</u> 2,122,083 person-years Recruitment period: 1989–1991	0.79	0.56 to 1.12	Age	China	Poor	1

CI = confidence interval; NA = not applicable; NR = not reported; OR = odds ratio; SD = standard deviation; UK = United Kingdom; yr = year/years
[a]Meta-analysis code: 1 = Included in meta-analysis; 2 = Excluded due to difference in reference group and definition of OC use.

The results of a meta-analysis of these three studies of MI mortality as a function of oral contraceptive use are shown in Figure 39 The random-effects estimated odds ratio is 0.85 (95% CI, 0.67 to 1.07). There was some evidence of heterogeneity, with a Q-value of 4.48 for 2 degrees of freedom, p=0.107. Of note, the risk of MI mortality trended higher among current users (as opposed to ever users) in the Chinese cohort (OR 2.38), but the finding was not statistically significant (CI, 0.58 to 9.76).

Figure 39. Effect of OC use on myocardial infarction mortality

Study name	Rate ratio	Lower limit	Upper limit	Rate ratio and 95% CI
Hannaford, 2010	0.750	0.635	0.886	
Vessey, 2010	1.100	0.803	1.506	
Gallagher, 2011	0.790	0.559	1.117	
	0.848	0.672	1.070	

CI = confidence interval; OC = oral contraceptive

Strength of Evidence for OC Use and Risk of Myocardial Infarction

Table 59 shows the strength of evidence for the effect of OC use on the risk of myocardial infarction.

Table 59. Strength of evidence domains for the effect of OC use on myocardial infarction

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Myocardial Infarction						
Current vs. noncurrent use/never	8 (24,901 plus 310,626 person-years)	Medium	Inconsistent	Direct	Imprecise	Low 1.34 (0.87 to 2.08)
Estrogen	2 (15,903)	Medium	Consistent	Direct	Imprecise	Insufficient NR
Progestin	5 (8875)	Medium	Consistent	Direct	Precise	High First generation: 3.37 (2.04 to 5.54) Second generation: 1.79 (1.16 to 2.75) Third generation: 1.34 (0.91 to 1.98)
Mortality From Myocardial Infarction						
Current vs. noncurrent use/never	3 (46,112 plus 3,091,673 person-years)	Medium	Inconsistent	Direct	Imprecise	Low 0.85 (0.67 to 1.07)

CI = confidence interval; SOE = strength of evidence

Discussion

We found strong evidence of a three-fold increased risk of VTE among current users of OCs and a two-fold increased risk of ischemic and undifferentiated stroke among current users of OCs. We found no conclusive evidence of an increased risk of MI or hemorrhagic stroke. The implications of OC use for each of these outcomes are discussed in detail below.

OC Use and Venous Thromboembolism

We found a three-fold increase in the odds of VTE diagnosis among current users of OCs (95% CI, 2.46 to 3.59). There was significant heterogeneity among the study characteristics and among the risk estimates noted by the Q scores. However, the finding was robust in our sensitivity analysis and was almost identical to the findings in a recent meta-analysis.[43] The odds ratio for VTE among current versus noncurrent OC users in that analysis was 3.41 (95% CI, 2.98 to 3.92). They analyzed 55 manuscripts, of which 32 were included in their meta-analysis of current versus noncurrent OC use and VTE risk. These manuscripts overlapped with 9 studies in our meta-analysis of 14 studies. The authors included all studies indexed in MEDLINE, Embase, and HealthSTAR regardless of date of publication. The odds of developing PE specifically appeared to be similar to that of developing VTE. The increased risk of DVT associated with OC use appears to be due to current use and not ever use. The only study to report a significantly increased risk among ever users also included current users in that group. The three studies that

separately analyzed former and current use of OCs found increased odds of VTE for current users but not for former users.

Duration and Formulation

There was some evidence that the risk of VTE among current users was higher in the first few years of use. Manzoli et al.[43] found a pooled odds ratio of 5.28 (95% CI, 4.27 to 6.55) for those who had used OCs for less than 1 year, and a pooled odds ratio of 3.52 (CI, 2.83 to 4.37) for those who had used OCs for more than 1 year. One potential explanation for this finding is that some women who develop VTE while on OCs may have an undiscovered predisposition to blood clots. Therefore, they develop VTE quickly after initiation of OC use, while women who are on OCs for years without forming a VTE presumably are less likely to have a predisposition to blood clotting. On the other hand, many factors that predispose women to blood clots will vary over time (e.g., trauma, sedentary lifestyle, and antiphosopholipid antibodies) and these risk factors have not been studied in a longitudinal fashion.

We found inconclusive evidence that estrogen dose or progestin generation was associated with VTE risk among current users of OCs. However, Manzoli et al.[43] found a mildly increased risk of VTE among current users of high-dose versus low-dose estrogen (OR 1.42; 95% CI, 1.15 to 1.76). They also found an increased risk for third-generation versus second-generation progestin users (OR 1.57; CI, 1.24 to 1.98). However, as was similar with our findings, they did not find an increased risk of VTE among drospirenone users compared with other OC users. This question has generated recent media attention since several studies indicated an increased risk of DVT among users of OCs containing fourth-generation progesterones.

Special Populations

There may be a multiplicative relationship in the risk of VTE among users of OCs who had concomitant Factor V Leiden, sickle cell trait, or elevated homocysteine levels; however ,these findings would need to be confirmed in additional studies.

Clinical Application

The three-fold increased odds of VTE among current users of OCs is important given the life-threatening nature of VTE. The mortality rate of DVT in the general population is 5 percent within the first month after diagnosis; for PE, it is 12 percent within the first month after diagnosis.[344] However, these estimates come from cohorts that include males, older individuals, and patients with cancers or heart disease. Young, healthy women who take OCs likely have lower mortality rates, but there is a paucity of data addressing this question. In one cohort of patients from the United States with DVT or PE, the univariate hazard ratio of death within the first week after VTE diagnosis among OC users was 0.08 (95% CI, 0.03 to 0.26) compared with other patients with VTE.[345] The clinical significance of the increased incidence of VTE among OC users must also be understood in the context of the low prevalence of VTE in this population. The annual incidence of VTE among childbearing-age women is 2 to 3 per 10,000 people.[346] Therefore, a three-fold increased risk translates to a still low absolute risk of fewer than 10 per 10,000 people per year. Perhaps most importantly, the incidence of VTE is four times higher among pregnant or postpartum women than among nonpregnant women. Therefore, the VTE risks associated with using OCs to prevent pregnancy are thought to be outweighed by the benefits of preventing pregnancy. Our findings will be used in a Markov model that estimates the overall risks and benefits of OC use for the prevention of ovarian cancer.

OC Use and Stroke

We found a two-fold risk of both undifferentiated and ischemic stroke among current OC users, but no increased risk of hemorrhagic stroke. As with VTE, this risk seemed to be due to current and not ever use. Many of the studies that evaluated the relationship between OC use and stroke did not differentiate between hemorrhagic and ischemic stroke. Since most cerebral vascular accidents have an ischemic etiology, we combined studies of patients with known ischemic stroke and studies of undifferentiated stroke. To the extent that studies of undifferentiated stroke included hemorrhagic patients, this approach would be expected to underestimate the true association between OC use and ischemic stroke.

Duration and Formulation

We found inconclusive evidence that the risk of stroke changed with duration of OC use or progestin generation. There was, however, evidence that the risk of stroke increased with increasing estrogen dose (from 1.7 to 4.1). This evidence was confirmed by trials of progestin-only OCs that showed no elevated ischemic stroke risk.

Special Populations

Women with migraines, Factor V Leiden, and elevated homocysteine levels who use OCs may have a multiplicative increase in the risk of stroke. However, these findings need to be confirmed in larger studies. Increasing age of OC users may be associated with increasing risk of ischemic stroke. However, these data also need to be confirmed in larger studies.

Clinical Implications

As with VTE, the two-fold risk of ischemic stroke is important because stroke is both life-threatening and morbid.[347] Between 8 to 12 percent of ischemic stroke victims die within one month of the diagnosis—and the vast majority have major neurologic deficits. Stroke is the leading cause of long-term disability in the United States. However, ischemic stroke incidence among women aged 15 to 44 is only 10.7 per 100,000 women-years[348] and, similarly to VTE, pregnant and postpartum women have a three- to eight-fold increased risk of ischemic stroke.[347] Therefore, the stroke risks associated with OC use are likely balanced by the benefits of preventing pregnancy. This may not be the case for women who are using OCs for ovarian cancer prevention and are not planning pregnancy.

OC Use and Myocardial Infarction

We found a small increased risk of MI among current OC users (1.2), but the confidence intervals were not significant. There was also inconclusive evidence that duration of OC use or estrogen dose increased the risk. However, we did note a significant increased risk for first-generation progesterone users compared with second-and third-generation users. There may be a small increased risk of MI among current OC users that our meta-analysis is underpowered to find. This risk may be greater among specific groups, such as users of first-generation progestins, heavy smokers (15 cigarettes or more daily), or women with cardiovascular disease risk factors.

Notably, one study found a decreased mortality from MI among ever users of OCs. Reasons for this could be decreases in competing risks associated with pregnancy, bias of ascertainment in women who were known OC users, or decreased prescribing of OCs to women with

cardiovascular disease risk factors. These issues may not have been fully adjusted for in the analysis.

Clinical Implications

For now, there is inconclusive evidence about increased MI risk associated with current OC use. Like VTE, MI is rare in women of reproductive age. In the United States, the annual incidence of MI is 0.3 to 0.7 percent among women; however, it is the sixth leading cause of death. Additional evidence is needed to effectively counsel patients about the risk of MI associated with OC use.

Limitations

The major limitation to our findings is the lack of randomized trials available to determine if OCs cause increased risk of VTE, stroke, or MI. Of the studies included, the majority were case-control studies, likely due to the relative rarity of the outcomes in young women. Observational data are limited by unmeasurable confounding and inability to establish causation.

A second limitation of these data is the high degree of heterogeneity among the studies. There were many differences across studies in the covariates used in the analyses to adjust for potential confounding. For example, few studies of stroke incidence adequately controlled for well-established stroke risk factors such as hypertension, diabetes, and hyperlipidemia. The outcome definitions were also heterogeneous between studies. In the case of VTE, several studies included central venous thrombosis and superficial venous thromboembolism despite the fact that VTE is traditionally defined as DVT and/or PE. Further, some investigators excluded "nonidiopathic" or unexplained DVT from the analysis, but the majority did not. In the case of stroke, some investigators included central venous thrombosis, and transient ischemic attacks in the definition of stroke. Others did not differentiate between ischemic and hemorrhagic stroke.

Finally, the definition of the exposure varied by studies. A minority of studies compared ever OC users with never users. The majority of studies used current OC use as the exposure; however, many different definitions of current use existed (e.g., recently filled prescriptions, reported use in the last 3 months, or reported use in the last month). We included all studies that defined current use as sometime within the year prior to outcome assessment. The referent group also varied. In some cases, this was never users and in others this was noncurrent users, which included past and never users.

A limitation for all our formulation analyses is the large number of OC formulations that have been available during the course of these studies. Not only is it difficult to correctly identify a formulation used, but it is also impossible to know if that formulation was the one most proximal to an outcome of interest. Women taking OCs frequently change formulations due to cost or side effects, and so the formulation identified may not have been the one that should have been associated with the event. In addition, estrogen dose is not independent of progestin generation. Most higher dose estrogens are only found in combination with earlier generation progestins. We were unable to control for this in the analysis. Even if there were enough data to compare risks across formulations, the sheer volume of formulation combinations would cause a problem with multiple testing. Finally, current OC prescribing patterns in the United States involve mostly "very low dose" estrogen (e.g., 20 mcg or less); this dose of estrogen was infrequently reported in the included studies, and the risk associated could not be analyzed separately.

For each of the outcomes of interest, increasing age is associated with increased risk in the general population. Although every study corrected for age of the participant in the analysis, there were few studies that assessed the risk of each outcome in current OC users stratified by age. This information would be clinically meaningful when counseling patients. The age of participants is very integral to the risk–benefit calculation of using OCs to prevent ovarian cancer. For example, very few women over age 35 use OCs for contraception; therefore, this age group is probably underrepresented in the current data. However, this is the very age group that may be interested in using OCs for prevention of ovarian cancer.

Future Research

Given the increased risk of VTE and stroke among OC users, future randomized controlled trials (RCTs) are unlikely. However, it would be useful if women who participated in RCTs of OC use investigating other outcomes could be followed to determine long-term risk of VTE, stroke, and MI. Future observational research into the risk of acute vascular complications associated with OC use should (1) clearly define the outcome of interest (e.g., ischemic vs. hemorrhagic stroke, not including transient ischemic attacks), (2) define the exposure as current versus never use and former versus never use and clearly define "current use," (3) adjust for all known risk factors of the outcome (e.g., hypertension), (4) collect duration data according to years of use instead of categories so that more detailed analysis could be undertaken, (5) collect data on contemporary OCs such as very low dose estrogen pills, and (6) prioritize longitudinal cohort data. Studies addressing the risk of MI among current users of OCs are needed most.

Applicability

The most important applicability issues are the time period of study for some of the large studies (going all the way back to the 1960s, with subsequent problems around dissimilar OCs used then vs. used now) and that very few of the included studies were conducted in the United States. Inadequate or incomplete reporting of age-related variables (e.g., age at first use of OCs, age at time of outcome event, and age at time of study participation) also contribute to the difficulty in applying these findings to specific age-groups of women in the United States.

Section 5. Overall Benefits and Harms of Oral Contraceptives for Prevention of Ovarian Cancer

Background

Our systematic review and evidence synthesis found significant protective effects of oral contraceptives (OCs) against ovarian cancer, in both the general population and in high-risk groups such as BRCA1 and BRCA2 carriers, with risk decreasing as the duration of use increases. We also found significant decreases in the risk of colorectal and endometrial cancers. Increased risks were significant for breast cancer (with risk declining with time since last use), deep venous thrombosis (DVT), pulmonary embolism (PE), and ischemic stroke. The incidences of myocardial infarction (MI) and cervical cancer were also increased, although the confidence interval for these two associations included 1.0.

There has long been recognition that OC use has important noncontraceptive implications for health.[349] Previous studies using formal methods to synthesize the available data in order to estimate net effects have generally shown either no overall effect, or a small positive effect, particularly for younger women.[66,350,351]

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 5, we have developed a new simulation model to generate estimates of the net harms and benefits of OC use in order to examine the following KQs:

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure 40 shows the analytic framework that guided this section of the review.

Figure 40. Analytic framework for overall benefits and harms of OCs
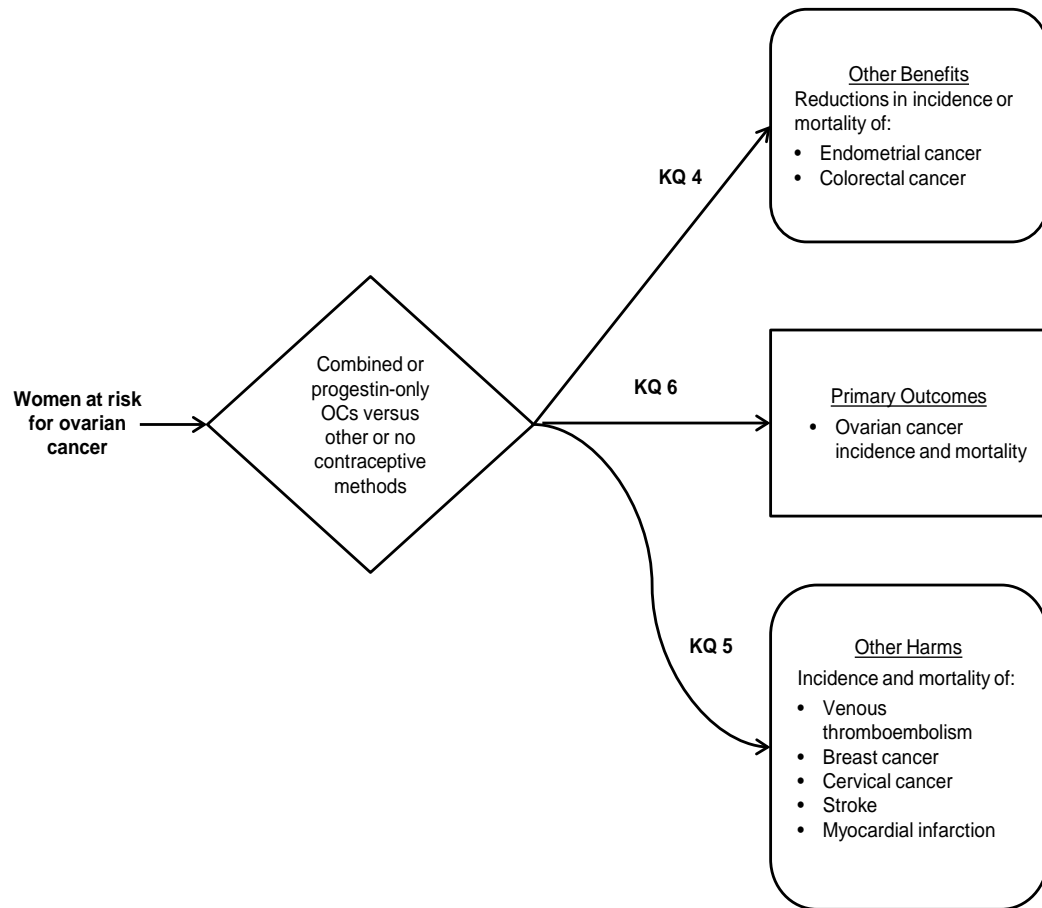
KQ = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

Methods

A detailed description of the simulation model structure, data sources, and parameters is provided in Appendix F. Section 5 summarizes those aspects most relevant to the presented results. Unless otherwise noted, we used national estimates from 2007—the most recently available at the start of the model-construction process.

Age-Specific Incidence of Relevant Outcomes With and Without OC Use

We obtained estimates of the age-specific (in 5-year age groups) incidence of ovarian, breast, cervical, colorectal, and endometrial cancers from two sources: (1) the Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute (http://seer.cancer.gov/canques/index.html) and (2) the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (http://wonder.cdc.gov/wonder/help/cancernpcr-v2009.html). Estimates were derived for all women as well as for four mutually exclusive race/ethnicity classifications: non-Hispanic white, non-Hispanic black, non-Hispanic other, and Hispanic. For the simulation model, we used age-specific and race/ethnicity-specific estimates of the number of cases and the total number of women in each strata from U.S. Census estimates (www.census.gov/popest/data/intercensal/national/nat2010.html) to generate beta distributions for incidence.

Estimates for the age-specific and race/ethnicity-specific incidence of DVT, PE, stroke, and acute MI were derived from the 2007 Nationwide Inpatient Sample (NIS), using specific International Classification of Disease-9 (ICD-9) codes as detailed in Appendix F. Again, distributions for stochastic modeling were derived by generating gamma distributions based on point estimates and standard errors and dividing by the estimated number of females in each strata based on Census estimates.

Estimates for the usage history of OCs were obtained from the National Survey of Family Growth (NSFG) data for 2002[352] and 2006 (www.cdc.gov/nchs/nsfg/nsfg_2006_2010_puf.htm).

For current exposure to OCs, we estimated age-specific and race/ethnicity-specific prevalence of current use of OCs as reported by survey respondents; for ever OC use, we used the cumulative estimate of race/ethnicity-specific self-reported ever use by age 44 in the 2006 NSFG. We derived estimates of the age-specific probability of beginning OC use for the first time from the age-specific prevalence of ever use within each racial/ethnic group.

We then estimated the impact of current OC use and ever OC use on the five cancers and four vascular events from the age-specific incidence estimates, the age-specific exposure estimates for OCs, and the derived odds ratios from the meta-analyses reported earlier. For any outcome,

Overall Incidence = (Incidence in OC users) * (Prevalence OC use) + (Incidence in nonusers) * (Prevalence nonuse).

since

Incidence in OC users = (Incidence in nonusers) * (Relative risk in OC users),

and

Prevalence nonuse = 1 – (Prevalence OC use),

separate estimates for age-specific incidence in users and nonusers can be derived from the overall incidence (converted to probabilities as described in Appendix F), the prevalence of OC use, and the relative risks (estimated here from the odds ratios from the respective meta-analyses).

Table 60 shows the relative risk estimates for the association between OC use and incidence of outcomes of interest (relative risks estimated based on odds ratios). All estimates except for the joint effect of duration of OC use and time since last use are derived from the meta-analyses

described in Sections 2–4 of this report. These estimates reflect the results of our initial analyses completed for the initial version of the report; as described in the methods, these analyses were updated during peer review. Because the estimates and confidence intervals are essentially unchanged, we present the results of the more extensive analyses completed with the original estimates. The one substantive change was that time since last use was found to have a significant effect on the protective association between OC use and ovarian cancer risk, with protection decreasing with increasing time since last use. Because the study-level meta-analyses did not allow for estimating the distribution of duration of OC use and time since last use, we used stratified data from a single published pooled analysis.[21] Because the pooled analysis had insufficient observations to generate estimates for risks for durations of use greater than 5 years with last use 30 or more years previously, we used the estimates for 20 to 29 years. We assumed that OC use had no effect on survival after diagnosis of cancer or a vascular event since the literature review did not identify a significant effect of OCs on postdiagnosis survival. Therefore, any effects of OC use on cancer-specific or vascular event-specific mortality generated by the model are due only to effects on incidence.

Table 60. Relative risk estimates for association between OC use and incidence of outcomes of interest

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Specified)	Distribution Type
Cancers (Ever vs. Never OC Use)			
Ovarian			
General population	0.71	0.64 to 0.79	Lognormal
BRCA1 carrier	0.54	0.45 to 0.65	Lognormal
BRCA2 carrier	0.60	0.29 to 1.54	Lognormal
Breast			
General population	1.08	1.01 to 1.15	Lognormal
BRCA1 carrier	1.18	0.92 to 1.50	Lognormal
BRCA2 carrier	1.18	0.92 to 1.50	Lognormal
Cervical	1.28	0.89 to 1.86	Lognormal
Colorectal	0.86	0.79 to 0.95	Lognormal
Endometrial	0.55	0.42 to 0.70	Lognormal
Cancers (Other Exposure Types)			
Duration of OC use and ovarian cancer risk	$1 - 1 / (1 + 7.43 / \text{duration (years)})^{**}1.239$		Function
Time since last OC use and breast cancer risk	$1 + (0.2711 * EXP(-0.06551 * \text{years})$		Function

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Table 60. Relative risk estimates for association between OC use and incidence of outcomes of interest (continued)

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Specified)	Distribution Type
Joint Effect of Duration of OC Use and Time Since Last Use and Ovarian Cancer Risk			
Current or <10 Years Since Last Use			
Duration of use <5 years	0.88	0.75 to 1.04*	Lognormal
Duration of use 5–9 years	0.52	0.43 to 0.64*	Lognormal
Duration of use ≥10 years	0.39	0.33 to 0.47*	Lognormal
Last use 10–19 Years Previously			
Duration of use <5 years	0.85	0.62 to 0.73*	Lognormal
Duration of use 5–9 years	0.62	0.53 to 0.73*	Lognormal
Duration of use ≥10 years	0.51	0.44 to 0.59*	Lognormal
Last Use 20–29 Years Previously			
Duration of use <5 years	0.81	0.74 to 0.89*	Lognormal
Duration of use 5–9 years	0.69	0.60 to 0.78*	Lognormal
Duration of use ≥10 years	0.60	0.51 to 0.72*	Lognormal
Last Use ≥30 Years Previously			
Duration of use <5 years	0.83	0.73 to 0.95*	Lognormal
Duration of use 5–9 years	0.69	0.60 to 0.78*	Lognormal
Duration of use ≥10 years	0.60	0.51 to 0.72*	Lognormal
Vascular Events (Noncurrent vs. Current OC Use)			
Deep vein thrombosis	3.01	2.47 to 3.68	Lognormal
Pulmonary embolism	1.61	1.26 to 2.05	Lognormal
Stroke	2.02	1.11 to 3.65	Lognormal
Myocardial infarction	1.24	0.75 to 2.04	Lognormal

BRCA = breast cancer genetic mutation; CI = confidence interval; OC = oral contraceptive
*99% confidence interval.

Impact of Current Use Patterns of OCs on Overall Life Expectancy and Disease-Specific Incidence and Mortality

We developed a semi-Markov state-transition model using TreeAge Pro (Williamstown, MA: TreeAge, Inc.) to simulate the effects of use and nonuse of OCs on incidence and mortality from ovarian cancer and the other outcomes of interest (Appendix F). The model is run as a microsimulation, starting at age 10. During each iteration of the simulation, individual "subject" characteristics, including race/ethnicity and BRCA status are drawn from distributions (second-order Monte Carlo simulation). Depending on the simulation, the values of other parameters are either the base case estimate or a value drawn from the appropriate distributions described in Tables 60 and 61 (first-order Monte Carlo simulation). Cycle lengths are 1 month.

Table 61. Key parameter values, ranges, and distributions

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Indicated)	Distribution Type	Reference
Demographics/Natural History				
Race/ethnicity at age 10	Non-Hispanic: White: 56.9% Black: 14.9% Other: 7.9% Hispanic: 20.3%	Census data—assumed to have negligible uncertainty	Fixed	Census
BRCA1				
Prevalence	0.22%	0.15-0.33%	Beta	John, 2007[353] Anonymous 2000[354]
RR Ovarian cancer	41.7	30.1-53.3	Lognormal	Anonymous 2000[354]
RR Breast cancer	Age-dependent 20–39: 58.6 40–49: 14.4 50–99: 1.0	Age-dependent 20–39: 49.9-67.2 40–49: 0.9-28.0) 50–99: 1.0	Lognormal	Anonymous 2000[354]
BRCA2				
Prevalence	0.15%	0.08-0.23%	Beta	John, 2007[353] Anonymous 2000[354]
RR Ovarian cancer	9.9	2.3-17.4	Lognormal	Anonymous 2000[354]
RR Breast cancer	Age-dependent 20–39: 17.1 40–49: 11.2 50–99: 22.4	Age-dependent 20–39: 17.1 (9.7-24.5) 40–49: 7.5-15.0 50–99: 18.1-26.8	Lognormal	Anonymous 2000[354]
Age-Specific Incidence				
Hysterectomy	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Oophorectomy	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Bilateral tubal ligation	Age- and race/ethnicity-dependent	See Appendix F	Beta	Chan, 2010[355] Whiteman, 2012[356]
Cancers	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Vascular events	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Mortality				
All-cause mortality	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NCHS[a]
Cancers	Age- and race-dependent (white/black only)	See Appendix F	Beta	SEER
Vascular events	Age- and race/ethnicity-dependent	See Appendix F	Beta	NIS

Table 61. Key parameter values, ranges, and distributions (continued)

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Indicated)	Distribution Type	Reference
Oral Contraceptive Use				
Age At First Use				
Natural history	Age- and race/ethnicity-dependent	See Appendix F	Dirichlet	NSFG
Prescription	Randomly assigned	15–45	Uniform	
Duration of Use				
Natural history	Mean 54.8 months	Standard deviation 41 months, range 1–240	Gamma	Chasan-Taber, 1996[357]
Prescription	Randomly assigned	1–240 months, partly dependent on age of starting (not continued past age 45)	Uniform	
Reduction in ovarian cancer incidence after tubal ligation	0.69 for 15 years, then 1.0	0.64 to 0.75	Lognormal	Cibula, 2011[17]

NCHS = National Center for Health Statistics; NIS = Nationwide Inpatient Sample; NSFG = National Survey of Family Growth; RR = risk ratio; SEER = Surveillance, Epidemiology, and End Results

[a]http://wonder.cdc.gov/wonder/help/cmf.html#Compressed%20Mortality%20File:%20ICD%20Revision

The use of probabilistic analysis and microsimulation offer two main advantages over a deterministic approach. First, probabilistic analysis allows the model to incorporate both the range of uncertainty in parameter estimates (e.g., the width of a 95% confidence interval) as well as the distribution of that uncertainty. For example, for a given mean parameter value with a normal distribution around that mean, the model can be run multiple times, drawing from the distribution with most of the values lying close to the mean value, but 2.5 percent would be drawn from below the lower 95-percent confidence bound and 2.5 percent from above the upper 95-percent confidence bound). Using distributions can be particularly helpful for parameters that are not "statistically significant" using conventional criteria, but where the weight of the existing evidence suggests a trend. For example, if a point estimate for a relative risk is 1.6 with a 95-percent confidence interval of 0.99 to 2.3, the traditional interpretation is that the observed increased risk is not statistically significant. However, because it is only the lower tail of the distribution that is below 1.0, the probability that the risk is greater than 1.0 is more than 95 percent. From a decisionmaking perspective, quantifying these effects can be quite helpful—in some situations, a patient, clinician, or policymaker might want to consider the potential effects of an increased risk of harm if the probability of the harm truly being increased was more than 80 or 90 percent (depending on the absolute risk of harm and the consequences of that harm), even though a threshold based on "not statistically significant" would preclude consideration of that harm.

The main advantage of microsimulation for this specific application is that it allows the model to have "memory" so that the probability of the outcomes of interests can be conditioned not only on the current state but also on past events, such as past use of OCs or duration of OCs.

OC Use Scenarios

We modeled OC use under five scenarios; all scenarios began at age 10 and continued until death or age 100. Table 62 illustrates the main differences in the four OC-use scenarios. The

initial scenario included the full range of available contraceptive options as well as varying contraceptive effectiveness, pregnancy outcomes (including duration of pregnancy), and lactation. However, because of the paucity of data on the dynamics of contraceptive choice over a woman's lifetime, particularly in the United States, and because pregnancy is a potential competing risk for some outcomes, we elected to model "No OC use" by fixing the risk of the outcomes of interest to that of nonusers, based on the equations above. This allowed us to focus only on the potential tradeoffs between harms and benefits of OC use as a potential preventive agent.

Table 62. Five OC use scenarios used in model

Parameter/ Assumption	OC Use Scenario				
	Ever/Never	**Duration**	**No OC**	**Prescribed Duration and Age at First Use and Duration**	**Joint Effects of Duration and Time Since Last Use**
Age at first use	Age- and race-specific probability	Age- and race-specific probability	Age- and race-specific probability	Uniform distribution, assigned in sensitivity analysis	Age- and race-specific probability
Duration of OC use	Population distribution, constrained to stop by age 50	Population distribution, constrained to stop by age 50	Population distribution, constrained to stop by age 50	Uniform distribution, assigned in sensitivity analysis, constrained to stop by age 50	Population distribution, constrained to stop by age 50
Association between OC use and cancers	Relative risk based on ever vs. never use for all	Relative risk based on duration of use for ovarian cancer, time since last use for breast cancer, ever vs. never for others	No reduction or increase in risk associated with OCs; incidence assumed to be that of nonusers in general population	Relative risk based on duration of use for ovarian cancer, time since last use for breast cancer, ever vs. never for others	Relative risk based on duration of use and time since last use for ovarian cancer, time since last use for breast cancer, ever vs. never for others
Association between OC use and vascular events	Relative risk based on current vs. noncurrent use for all	Relative risk based on current vs. noncurrent use for all	No reduction or increase in risk associated with OCs; incidence assumed to be that of noncurrent users in general population	Relative risk based on current vs. noncurrent use for all	Relative risk based on current vs. noncurrent use for all

OC = oral contraceptive

Model Assumptions

We made a number of simplifying assumptions as described below. If an assumption could possibly bias the analysis for or against the potential benefits of OC use, we chose the more conservative assumptions that biased against potential benefits of OC use whenever feasible.

Excluded Other Potential Benefits and Harms

We did not include other potential benefits (e.g., prevention of pregnancy, effects on menstrual flow and discomfort, effects on other reproductive outcomes such as endometriosis or benign ovarian cysts, effects on acne or premenstrual syndrome) or harms (e.g., neoplasms of the liver, gallbladder disease). Although including the full range of potential benefits and harms is ultimately of great interest, the scope of this analysis was specifically restricted to the potential noncontraceptive preventive benefits of OCs. Therefore, we restricted our analysis to relatively common, potentially fatal cancers or vascular events for which a preliminary literature review suggested consistent evidence of an association with OC use.

Excluded Quality-of-Life Measures

We did not include quality-of-life measures. Although we originally intended to include quality-adjusted life expectancy, expressed as quality-adjusted life years (QALYs) as one of the outcomes, we were limited by a lack of available data on preferences for OC use. Although we identified several economic analyses of OC use for contraception—some of which included other outcomes,[350,358,359] or prophylaxis against ovarian cancer in BRCA1 and BRCA2 mutation carriers[360,361] which included utility values for outcomes relevant to our analysis—none included any values for OC use itself. There is a relatively high discontinuation rate of OC use within the first 12 months after starting, some of which is attributable to side effects.[362-366] Conversely, there are other potentially positive effects on quality-of-life, including effects on menstruation, reassurance against unwanted pregnancy, or reduced acne. Including only the effect of cancers and vascular events on QALYs could substantially bias overall estimates of the impact of OCs on quality-adjusted life expectancy. Therefore, we focused primarily on the specific balance between benefits (in terms of reduced cancers) and harms (in terms of increased cancers or acute vascular events); further work to integrate the effect of OCs, either as contraceptives or as prevention against other diseases, is a major research need.

Continuous OC Use for Duration

We assumed that, once "assigned" an age at first use and duration of use by the model, OC use would be continuous for that duration, then stopped. This is clearly not the case for most women, but because the available literature on duration of use does not distinguish between continuous and intermittent use, and data to inform patterns of use were not available, we used this simplifying assumption.

This assumption creates the potential for bias in both directions. In the case of breast cancer and vascular events, where incidence increases with age, an assumption of continuous use may underestimate the upper tail of the age distribution of current OC users, and therefore underestimate the potential increased risk associated with OC use. On the other hand, to the extent that time since last use potentially decreases protection for ovarian, colorectal, and endometrial cancers, underestimating the upper tail may lead to underestimating the protective effect, since the continuous use assumption results in longer average duration between last use and the time of highest cancer risk.

Point Estimates in Base-Case Analysis

For the purposes of the base-case analysis, we used the point estimates from the meta-analyses; since two of these (MI and cervical cancer) were not statistically significant using conventional criteria, this is a potential bias against OC use.

Analysis of Temporal Relationships

We included an analysis of temporal relationships such as age at first or last use, duration of use, or time since last use only for those found to be significant in the meta-analyses (duration of use and time since last use for ovarian cancer, and time since last use for breast cancer). Because the data available for meta-analysis did not allow for estimation of the joint effect of duration of use and time since last use, we used estimates for ovarian cancer risk stratified by both duration and time since last use from the pooled analysis of the Collaborative Group on Epidemiological Studies of Ovarian Cancer.[21] As discussed in Section 2, these estimates are quite similar to the results of the study-level meta-analyses. This was done primarily for tractability of modeling, and because estimates of relative risk were most commonly reported as ever vs never use. This assumption of lifetime effects for any duration exposure could result in overestimation of both benefits and harms.

Constant Risk of Vascular Events

We assumed that the risk of vascular events among current users was constant across time; i.e., that the degree of risk associated with OCs was the same during a woman's first and last month of use no matter how long. As discussed in Section 4, there is some evidence that the risk is highest early during use for some outcomes, particularly DVT,[281] presumably because women with an increased underlying risk such as inherited thrombophilias develop the outcome quickly. If this is the case, the assumption of constant risk may overestimate the likelihood of these events among all OC users.

We also assumed that there was no increased risk in vascular events after discontinuation of OCs. This was consistent with the findings for venous thromboembolism and stroke discussed in Section 4. Although we did not explicitly consider ever vs never use for myocardial infarction, another meta-analysis found no difference in risk between past users and never users.[47]

Survival After Cancer Diagnosis

We modeled survival after diagnosis for each cancer up to 5 years; after 5 years, we assumed cure (women with breast cancer were at risk for a second primary, although this was not conditioned on previous history). We limited followup for five years primarily because there is variability in reported length of followup between the different cancers. Particularly for breast cancer, where late recurrences are not uncommon, this may result in an underestimate of cause-specific mortality.

As described in Appendix F, survival after diagnosis was conditional on age at diagnosis and race (black vs. white only, with the assumption that survival for Hispanic and other-race women was identical to white women). Also as described in Appendix F, the model predictions for overall lifetime incidence when incorporating patterns of OC use and the derived estimates for the association between OC use and cancers showed good agreement with estimates of lifetime incidence derived from the SEER DevCan software. (http://surveillance.cancer.gov/devcan/).

Patterns of OC Use Over Lifetime

We found surprisingly few data on patterns of use of OCs over a woman's lifetime. Although we were able to generate an estimate of the distribution based on one study that reported a mean and standard deviation for duration,[357] the available literature does not provide any data to correlate duration of use with age of starting, and so we modeled these as independent

probabilities for those analyses where the values for these parameters were drawn from distributions.

We assumed no one would start OCs after age 45, (i.e., age at first use ranged from 12 to 44) age of first use to 44, based on data from the NSFG that showed almost no increase in the proportion of "ever users" after age 35, and the lack of available data for women over age 45 (since the NSFG only includes women aged 15 to 44 years). We also constrained duration of use so that all women stopped OC use at age 50, regardless of assigned age at first use and duration. Assuming that there is, in fact, a correlation between age at first use and duration of use, this assumption of independence may underestimate duration of use in younger women and overestimate it in older women. Particularly for vascular events, where overall risk increases with age and there is an assumption of constant risk with time among current users, this may result in an overestimate of the number of events in OC users.

Tubal Ligation

Because there is a consistent association between tubal ligation and reduced ovarian cancer risk, even after controlling for contraceptive use,[17,19,123,367] we included tubal ligation (based on age-specific and race/ethnicity-specific incidence and prevalence) in the model, and used the estimate for reduction in risk from a recent meta-analysis.[17] Because most studies of the association between ovarian cancer and OCs controlled for tubal ligation (and vice versa), we assumed that the risks were independent such that the risk of ovarian cancer in a woman with a history of OC use was further reduced if she subsequently underwent tubal ligation. We also assumed that the probability of tubal ligation was not conditioned on prior OC use.

Effect of Other Contraceptive Methods

Because the overwhelming majority of the literature classified OC use as some variant of ever versus never, we assumed that contraceptive methods other than tubal ligation that were used whenever OCs were not being used did not affect ovarian cancer risk, although one recent study suggests this may not be the case.[123]

Effect of Hysterectomy or Oophorectomy

Because removal of the potentially cancerous organ obviously affects the likelihood of developing cancer, we included age-specific and race/ethnicity-specific probabilities of hysterectomy and oophorectomy (in various combinations) in the model. We assumed that the risk of cervical and endometrial cancer was zero after hysterectomy and that the risk of ovarian cancer was zero after bilateral oophorectomy. Although there are fairly consistent data showing that women who undergo hysterectomy alone, without removal of the ovaries, have a reduced risk for ovarian cancer,[19,368] we assumed hysterectomy alone did not affect ovarian cancer risk, primarily because of uncertainty about potential interactions with OC use. Because OCs may reduce the incidence of both benign and malignant indications for hysterectomy, they could potentially decrease hysterectomy rates.

Conversely, because OCs may be prescribed for many conditions that can lead to hysterectomy, use of OCs may be associated with increased hysterectomy rates. This is consistent with data from two observational studies; in Denmark, a country with high overall use of OCs, long-term OC use was associated with decreased hysterectomy rates, while short-term use was associated with increased rates,[369] and in Ireland, where OC use for contraception was historically quite low, a history of OC use was associated with an increased hysterectomy rate.[370]

Three Types of Simulations

With the above assumptions and base-case estimates, we ran three types of simulations:

1. *Simple simulations,* where the mean value of the relative risks associated with OC use was used for all iterations. These included:

    a. A series of 60,000 simulations for the general population (all women including BRCA1 and BRCA 2 carriers) and 20,000 each for BRCA1 and BRCA2 carriers where the effect of OC use based on current use patterns was compared with no use.

    b. A series of 50,000 simulations for the general population and 20,000 each for BRCA1 and BRCA2 carriers where OC use was based on current use patterns. After the simulations, the "population" dataset was divided into ever and never users. Differences in outcomes were compared and 50,000 simulations were run for the general population and for BRCA1 and BRCA2 carriers.

2. *Age and duration analyses,* where sets of 20,000 simulations were run varying both age at first OC use (15, 20, 25, 30, 35, and 40 years) and duration of use (1, 2, 5, and 10 years). A total of 24 combinations were simulated (we did not model 10 years' duration starting at age 40). These simulations also indirectly captured the effect of recency of use on breast cancer since "recency" relative to age-specific breast cancer risk is a direct function of age at first use and duration of use.

3. *Two-dimensional simulations,* where individual values of the OC-associated relative risks were drawn from the distribution (n=200), followed by 10,000 simulations for each relative risk value, for a total of 2,000,000 simulations.

Modeled Outcomes

We used the model to estimate overall life expectancy and lifetime incidence and mortality from the five cancers and four acute vascular events; for the "direct" comparison of ever vs never users, we also estimated the absolute number of harms and benefits attributable to OC use per 100,000, and the number needed to harm or prevent (defined as 1 divided by the risk difference)

Sensitivity Analyses

We assessed the effect of uncertainty in the model structure and parameter values in several ways. First, for each set of simulations, we modeled the association between OC use and outcomes based on current use in two different ways: (1) where all cancer relative risks were based solely on ever versus never use and (2) where the risks for ovarian cancer were modeled on the basis of duration of use and the risks for breast cancer were modeled on ever vs never use and time since last use.

Second, we focused on age of starting use and duration of use by fixing the value of these across a wide range and then comparing the results. Third, we conducted a series of two-dimensional simulations, where the values for the relative risks of events were first drawn from the distributions described in Table 60, followed by a series of microsimulations, drawing "individual" values for BRCA status, race/ethnicity, and disease incidence and mortality from their appropriate distributions described in Table 61. For each outcome, we then generated the equivalent of "acceptability curves,"[371] where the proportion of sets of simulations where one strategy was "optimal" compared with another are illustrated at different thresholds for "optimality."

For outcome incidence and mortality, we used a net benefits approach.[371] In health economics, net monetary benefits (NMB) are defined as a function of willingness-to-pay (WTP) as follows:

NMB = (WTP * Effectiveness) – Costs

If WTP is measured in dollars per QALY, then NMB reduces to a single dollar figure. At any given WTP, the strategy with the highest NMB is preferred. Alternatively, the same approach can be applied using net health benefits (NHB):

NHB = (Costs/WTP) – Effectiveness

In a growing number of economic analyses, probabilistic analysis is used to estimate the effect of uncertainty in parameter values on the likelihood of making an optimal decision.[372] However, for those settings where costs are not explicitly being considered, this approach still has value. Harms can be considered "costs"—especially in the setting of preventive interventions.

For this analysis, we estimated separate harm/benefit ratios for incidence and mortality, with harms defined as the difference in incidence or mortality for breast and cervical cancer, and DVT, PE, MI, and stroke, and benefits as the difference in incidence or mortality for ovarian, colorectal, and endometrial cancers. For the incidence ratio, we varied the WTP from 0 net (no harms with some benefit) to 5.0 (5 extra incident cases for each case prevented) and benefits equivalent). For the mortality ratio, we varied the WTP from 0 (no excess mortality relative to deaths prevented) to 1.0 (excess mortality attributable to OC use exactly equivalent to prevented deaths attributable to OC use) We assumed that the harms and benefits compared here—all of which are associated with potential long-term morbidity and mortality—were roughly equivalent; obviously, this may not be the case, and appropriate weighting using validated preference measures is needed. Although this approach has been described,[373] it has not gained wide acceptance in the health economics literature. However, the simple comparison of net harms and benefits is frequently used in guidelines development,[374,375] and this approach may be particularly helpful in illustrating the effects of uncertainty on specific harms and benefits when developing practice or policy recommendations.

Results

Age-Specific Incidence of Relevant Outcomes With and Without OC Use

Estimated age-specific incidences of cancers among ever and never users of OCs are shown in Figures 41 to 45. At the ages of peak incidence, ever use is associated with an absolute reduction in ovarian cancer incidence of approximately 20 per 100,000 (Figure 41). For other cancers, peak incidence was increased by approximately 20 per 100,000 for breast cancer (Figure 42) and 4 per 100,000 for cervical cancer (Figure 43), and peak incidence decreased by approximately 50 per 100,000 for colorectal cancer (Figure 44) and 55 per 100,000 for endometrial cancer (Figure 45).
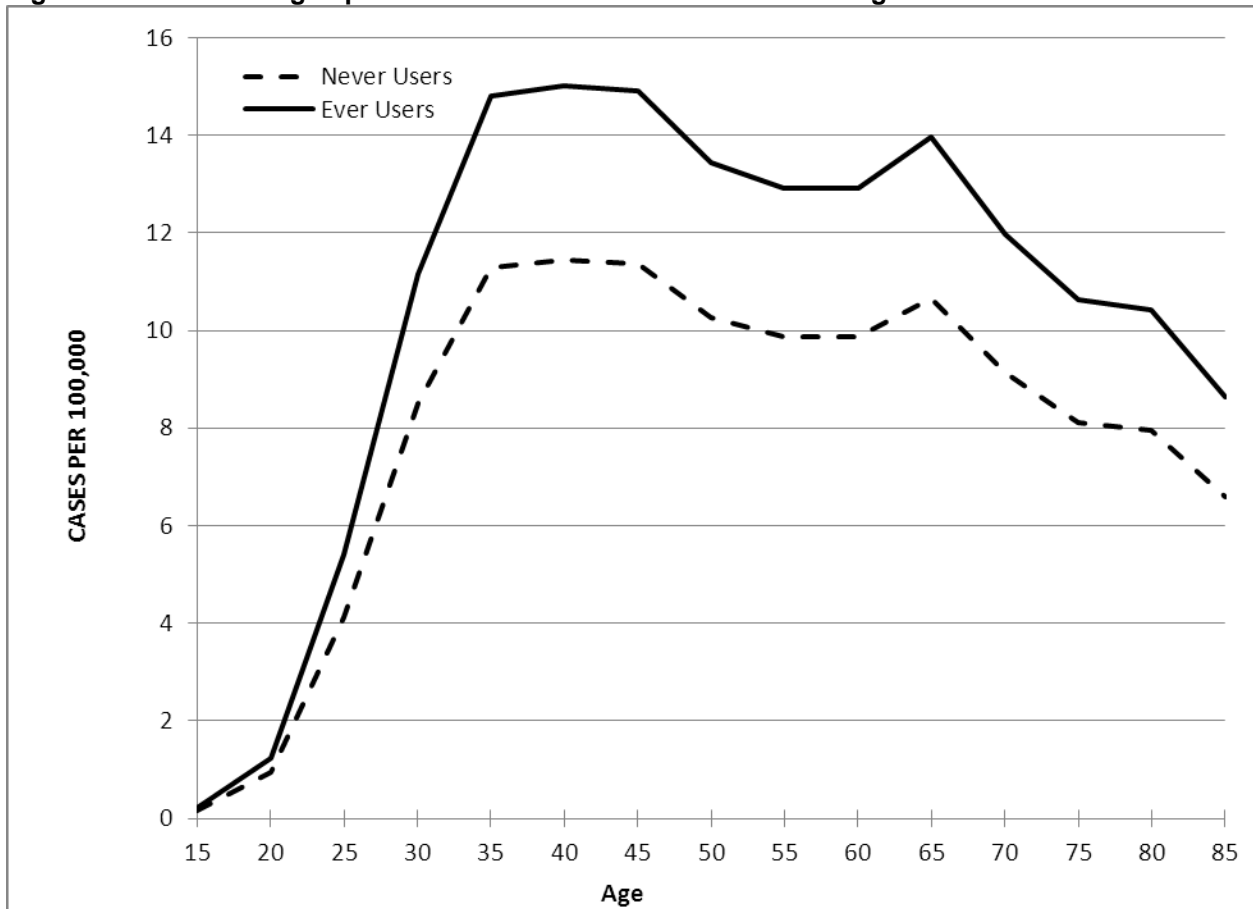
Figure 41. Estimated age-specific incidence of ovarian cancer among ever versus never OC users
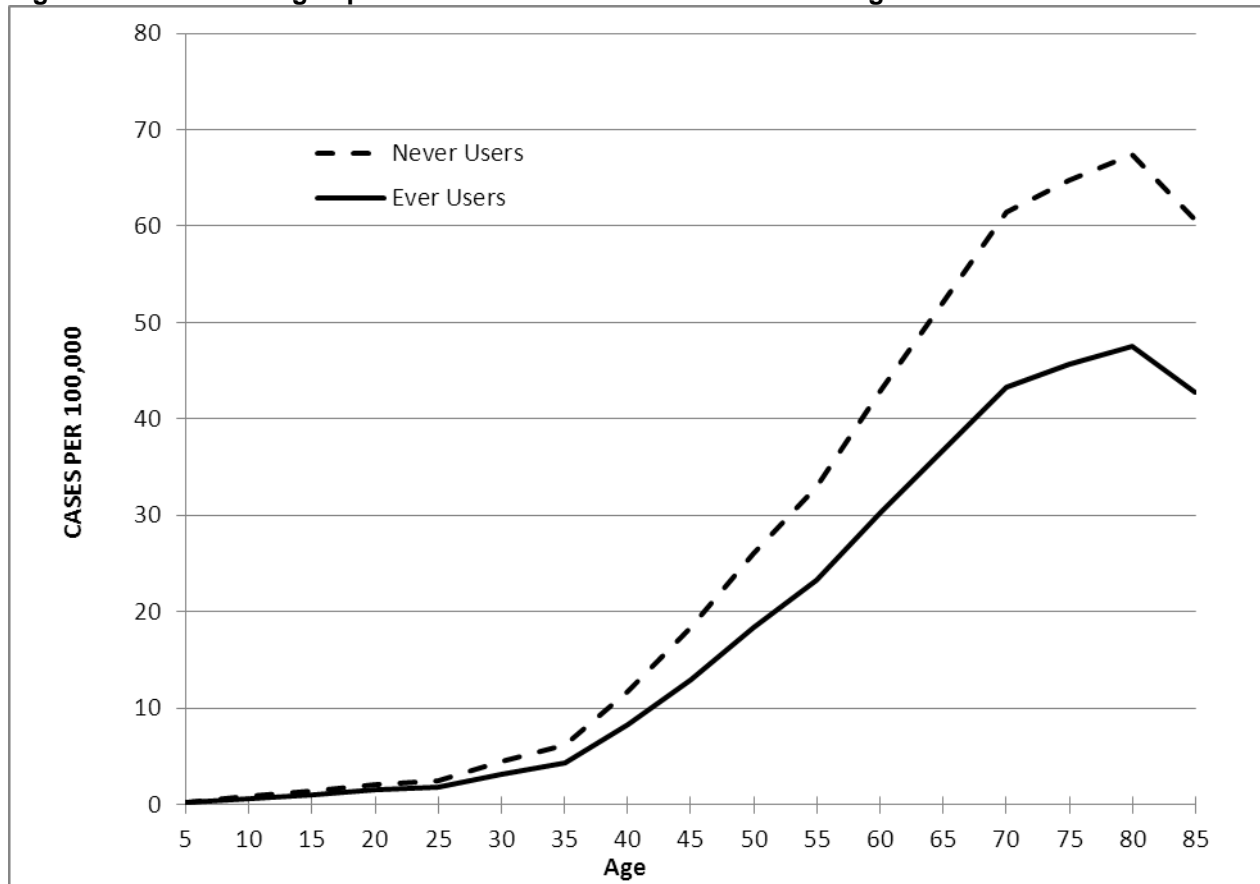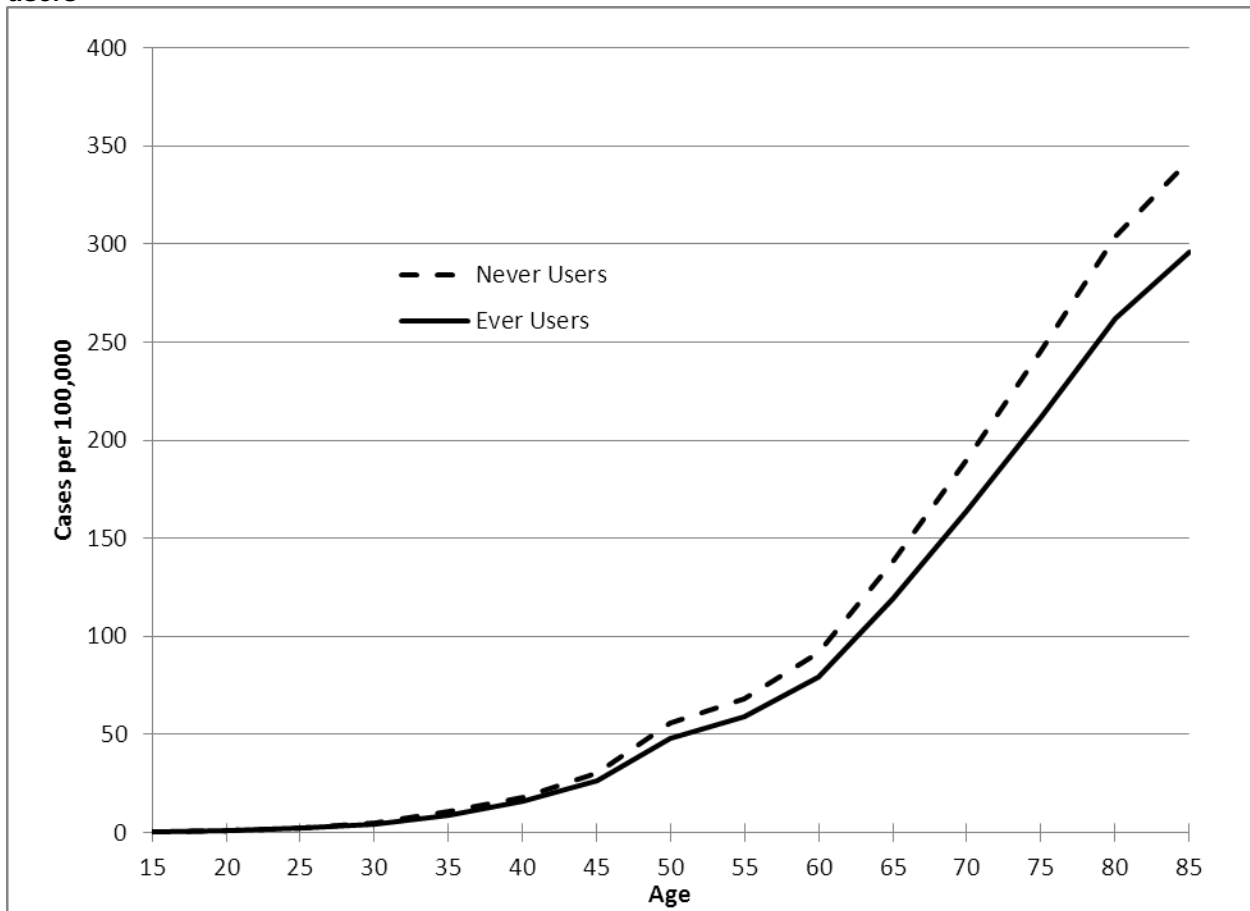
Figure 42. Estimated age-specific incidence of breast cancer among ever versus never OC users
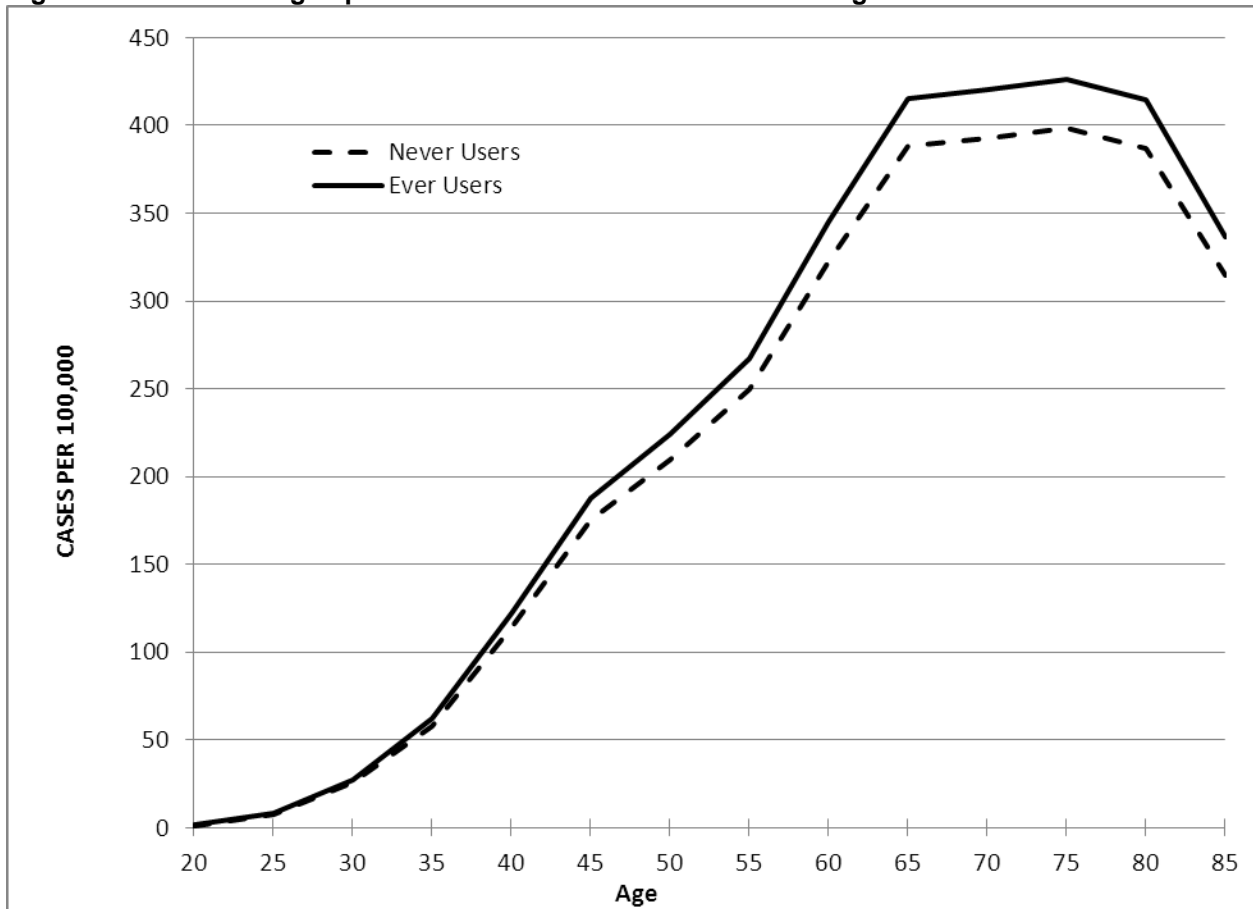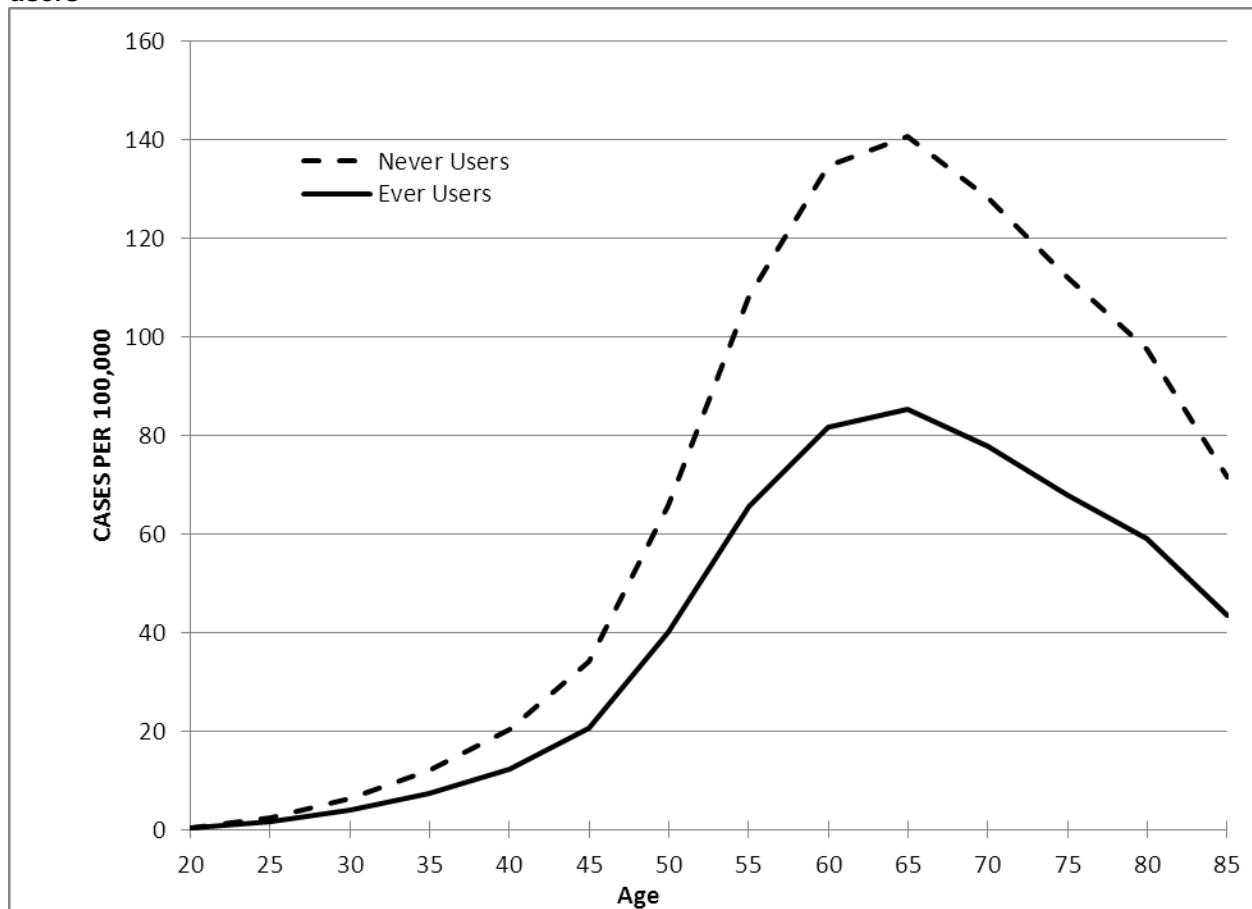
Figure 43. Estimated age-specific incidence of cervical cancer among ever versus never OC users

Figure 44. Estimated age-specific incidence of colorectal cancer among ever versus never OC users
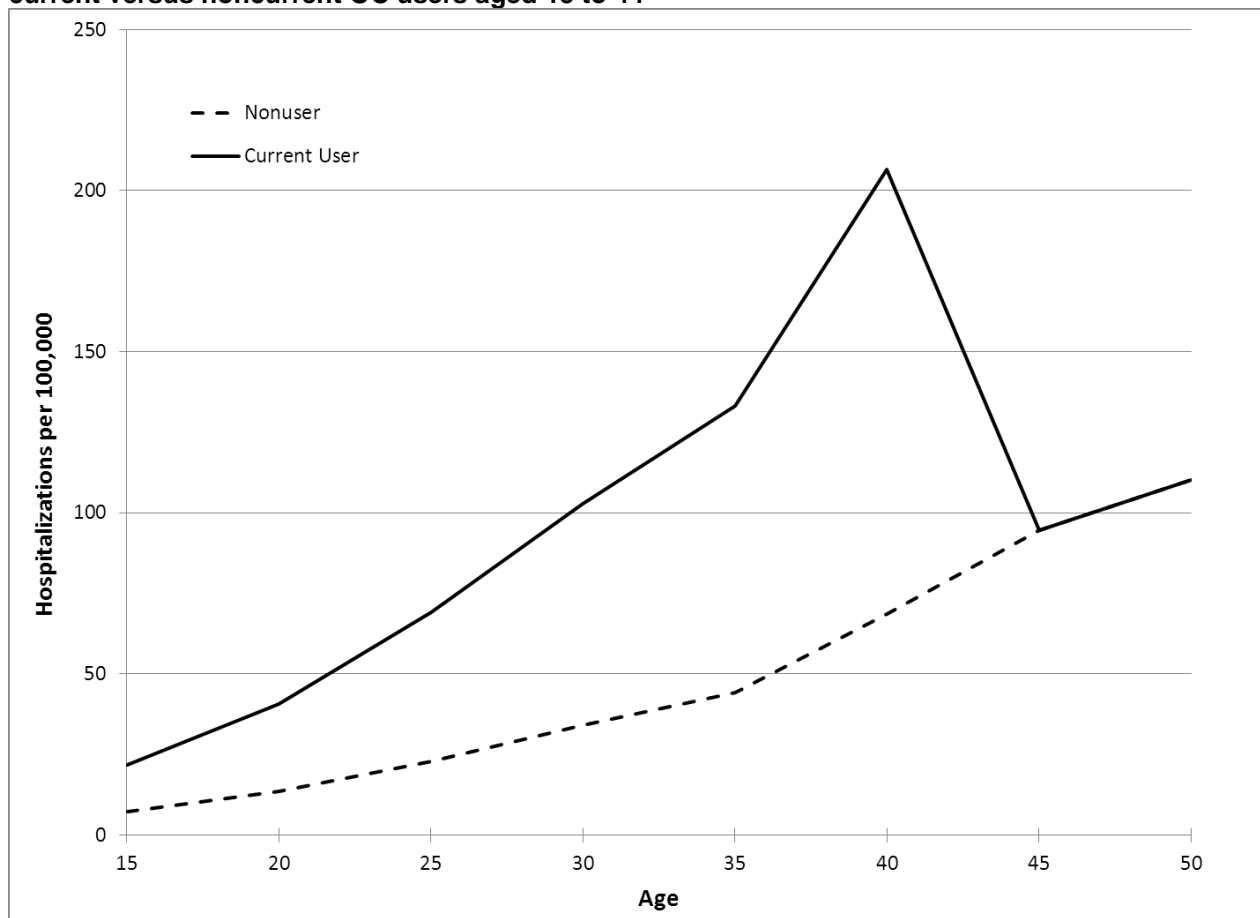
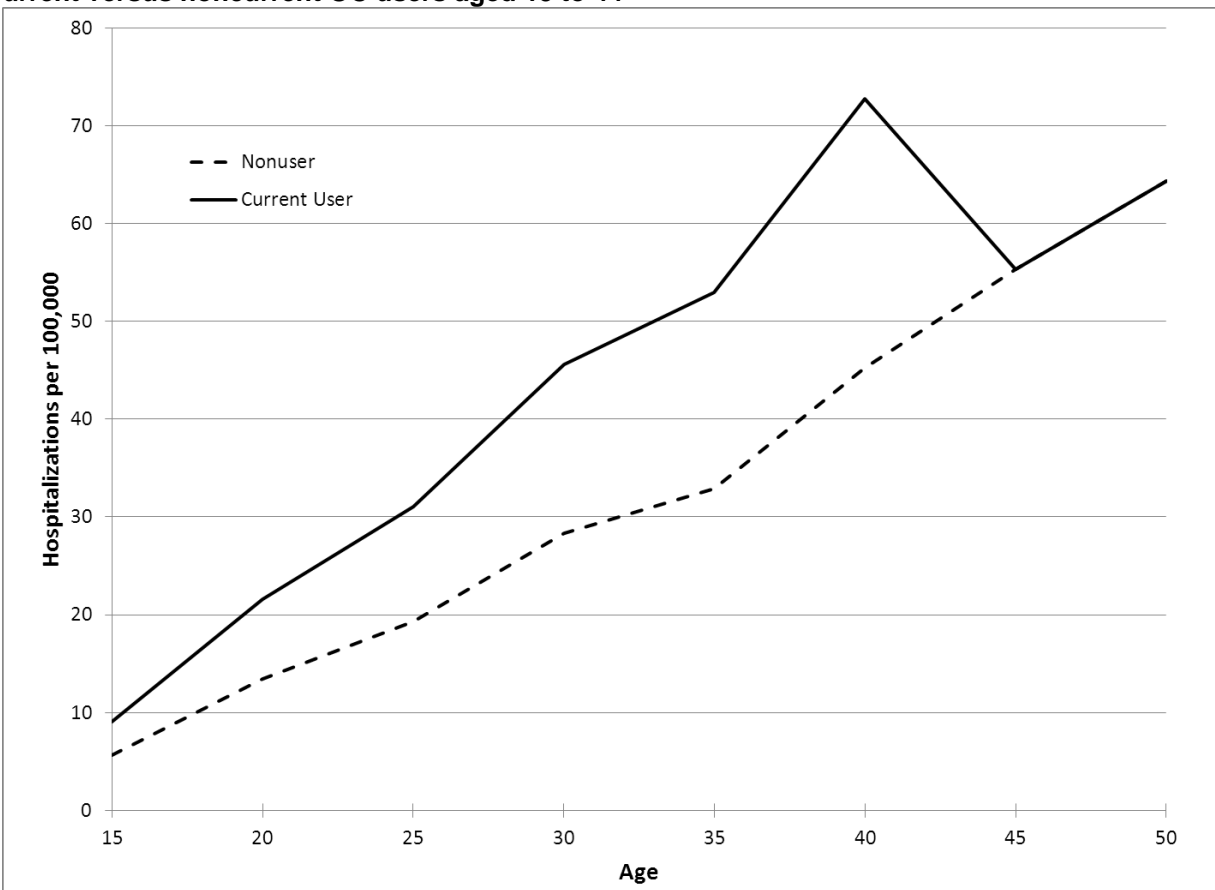**Figure 45. Estimated age-specific incidence of endometrial cancer among ever versus never OC users**

Estimates for vascular events among current versus noncurrent users of OCs are shown in Figures 46 to 49. Peak increases in incidence were approximately 150 per 100,000 for DVT (Figure 46), 30 per 100,000 for PE (Figure 47), 30 per 100,000 for stroke (Figure 48), and 12 per 100,000 for acute MI (Figure 49); all of these were in women between the ages of 35 and 44. Note that the rates for all events merge at age 45. This is due to the lack of data on the prevalence of OC use in women over 45 years of age, since the best available data source, the NSFG, is limited to women aged 15 to 44. Because the formula for estimating incidence of an outcome based on exposure status subjects is derived from relative risk, overall incidence, and prevalence of exposure, there is no way to estimate the incidence in OC users over age 45, but it is certainly likely to be greater than for nonusers.

Figure 46. Estimated age-specific incidence of hospitalizations for deep vein thrombosis among current versus noncurrent OC users aged 15 to 44
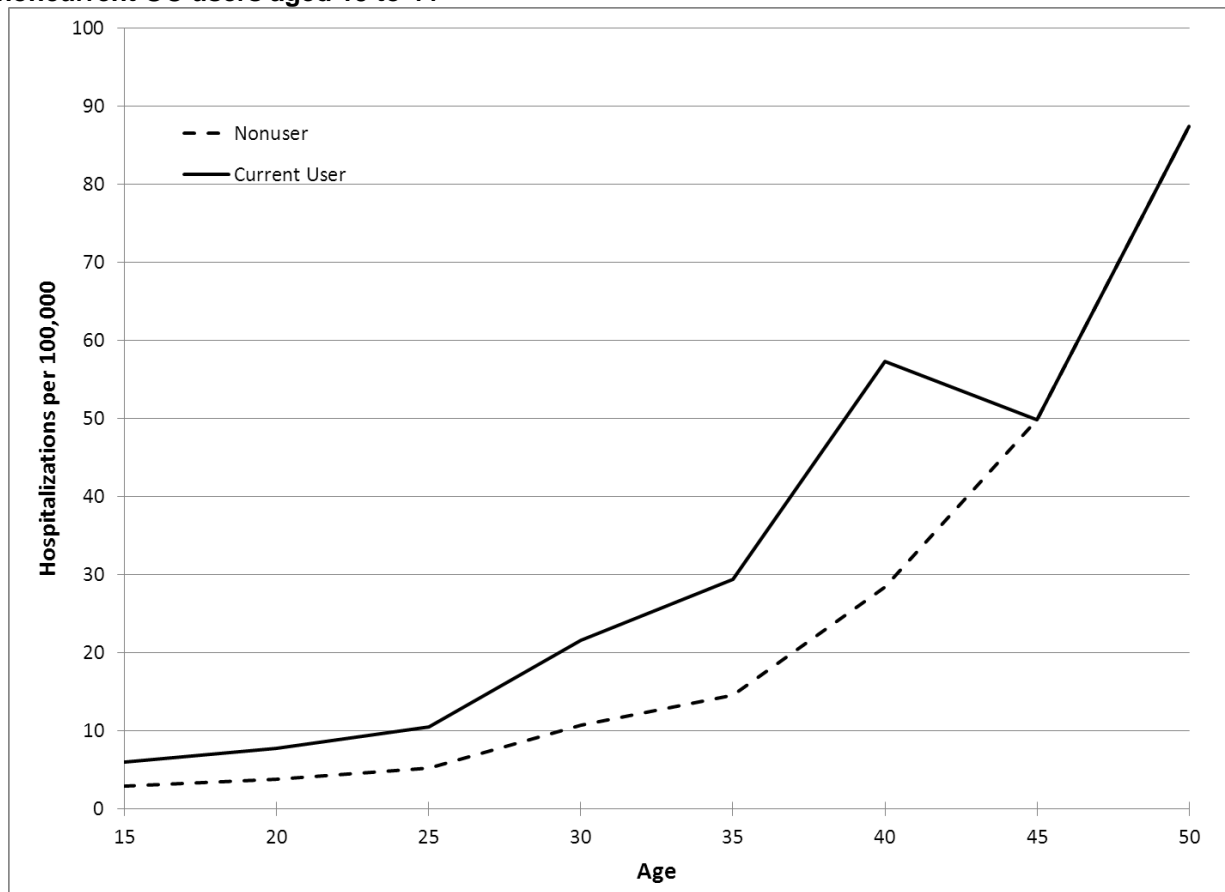
Figure 47. Estimated age-specific incidence of hospitalizations for pulmonary embolism among current versus noncurrent OC users aged 15 to 44

Figure 48. Estimated age-specific incidence of hospitalizations for stroke among current versus noncurrent OC users aged 15 to 44

Figure 49. Estimated age-specific incidence of hospitalizations for acute myocardial infarction among current versus noncurrent OC users aged 15 to 44
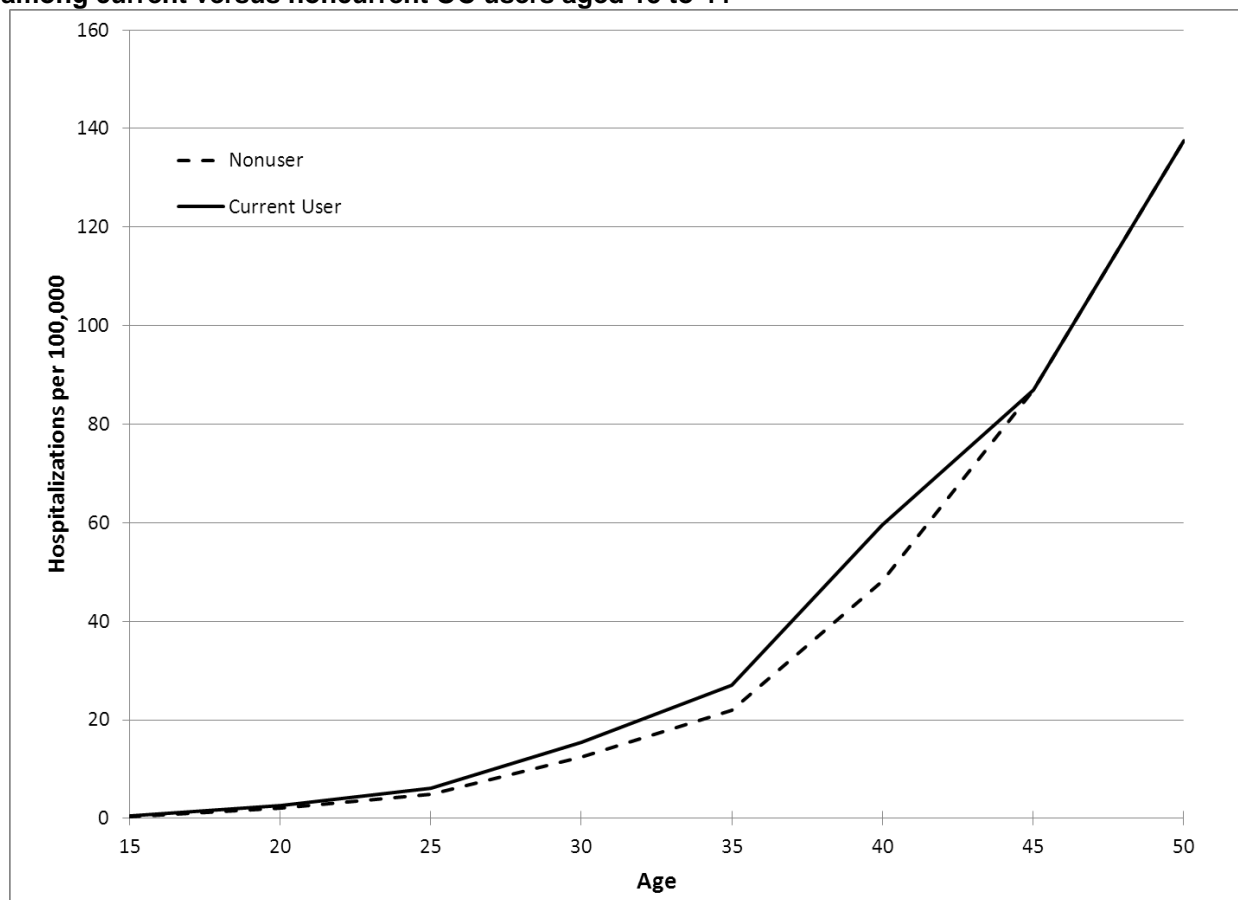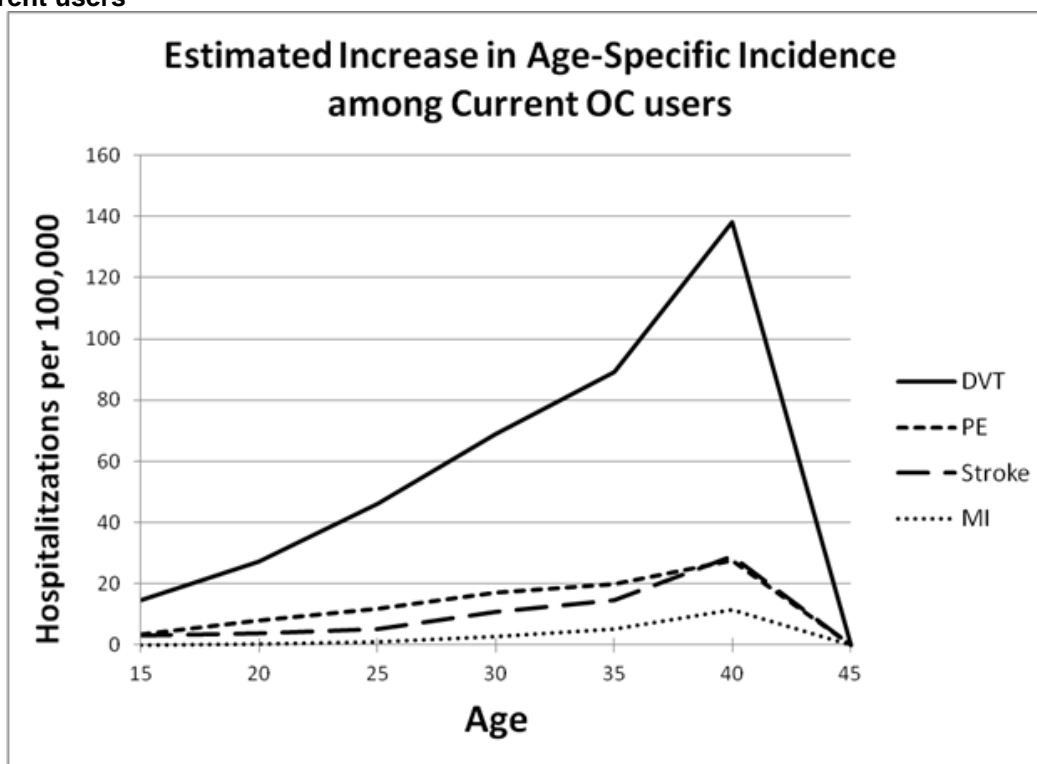
Figure 50 (for cancers) and Figure 51 (for vascular events) summarize the effects of OC use on age-specific incidence on a common scale. Each graph represents the estimated net difference in cases or hospitalizations per 100,000 in OC users compared with nonusers at each age. It is important to note that these estimates are for each individual outcome only and are not adjusted for competing risks such as hysterectomy or oophorectomy, or the occurrence of other outcomes, and effects of duration of use or time since last use are not incorporated.

Figure 50. Increase or decrease in age-specific incidence of cancers in ever OC users versus never users

Estimated Difference in Age-Specific Incidence in Ever Users of OCs compared to Never Users
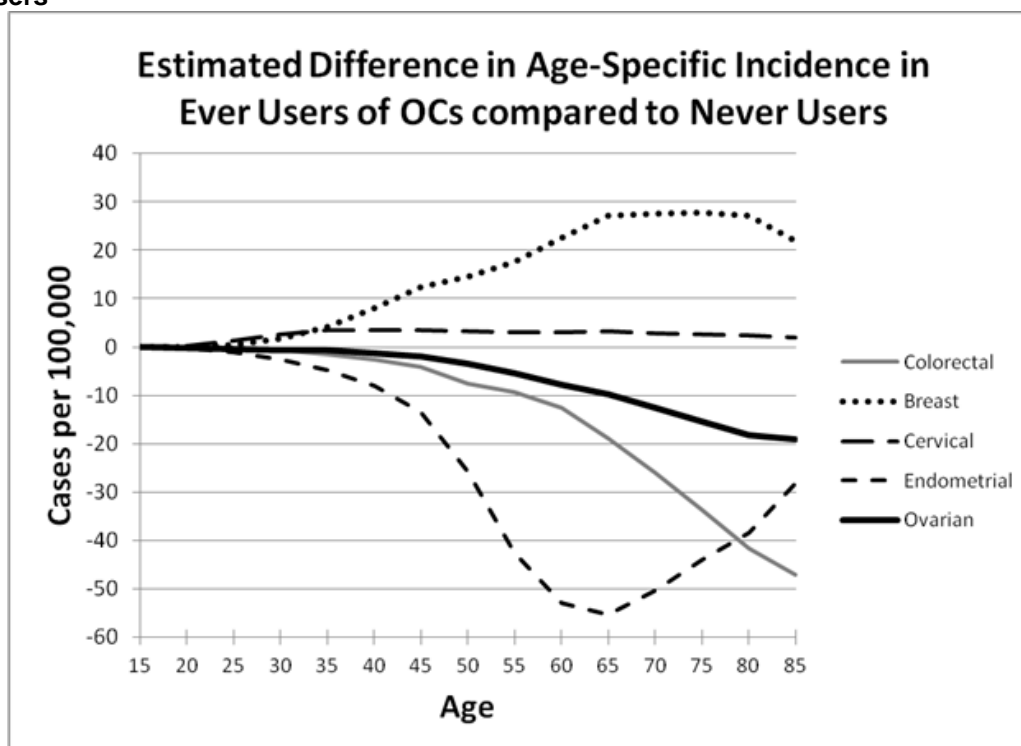
Figure 51. Increase in age-specific incidence of vascular events in current OC users versus noncurrent users

Estimated Increase in Age-Specific Incidence among Current OC users

DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism

Effect of OC Use on Lifetime Incidence and Mortality

Table 63 shows the results of 60,000 simulations for the general population, along with 20,000 simulations each for BRCA1 and BRCA2 carriers; results were not qualitatively different by race or ethnicity. In this analysis, we estimate the overall effects of OC use based on current population patterns of use (including some women who never use OCs), and compare it to a simulated population that has the same patterns of pill us, but without any harms or benefits attributable to the pill (i.e., the risk of events in pill users is assumed to be identical to nonusers estimated base on relative risk estimates). Current patterns of OC use resulted in an increase in life expectancy of 1 to 2 months in the general population (with larger gains when modeled on the basis of duration), 10.5 months in BRCA1 carriers, and 1 month in BRCA2 carriers. Estimated ovarian cancer incidence and mortality, and overall mortality, in the model incorporating the joint effects of duration of use and time since last use was intermediate between estimates resulting from the ever/never and duration-only models. For clarity, we present only ever/never and duration only. Because there were no data on effects of duration of use or time since last use on outcomes in BRCA1 or BRCA2 carriers, effects of OCs were based on ever versus never use. Again, for the purposes of clarity, we omit confidence intervals but note that, even with this large number of simulations, the confidence intervals between different models overlapped.

Table 63. Estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events

Outcome	All Women (n=60,000)			BRCA1 Only (n=20,000)		BRCA2 Only (n=20,000)	
	No Effect of OCs	OC-Attributable Effects		No Effect of OCs	OC- Attributable Effects	No Effect of OCs	OC- Attributable Effects
		Ever/Never[a]	Time-Dependent[b]		Ever/Never[a]		Ever/Never[a]
Life expectancy	71.26	71.37	71.42	63.81	64.76	65.31	65.41
Lifetime Risks of Cancers							
Ovarian							
Developing	1.76%	1.42%	1.00%	48.92%	36.21%	14.15%	9.97%
Dying	0.99%	0.78%	0.55%	25.55%	19.33%	7.80%	5.63%
Breast							
Developing	10.52%	11.04%	11.14%	48.45%	54.09%	82.92%	85.89%
Dying	0.92%	0.98%	0.97%	5.11%	5.58%	8.14%	8.45%
Cervical							
Developing	0.54%	0.63%	0.60%	0.39%	0.61%	0.28%	0.47%
Dying	0.01%	0.01%	0.01%	0.00%	0.01%	0.00%	0.01%
Colorectal							
Developing	5.16%	4.70%	4.78%	3.42%	3.33%	3.44%	3.22%
Dying	1.72%	1.57%	1.64%	1.09%	1.05%	1.00%	1.03%
Endometrial							
Developing	3.21%	2.13%	2.15%	2.19%	1.63%	2.71%	1.50%
Dying	0.60%	0.41%	0.38%	0.42%	0.26%	0.52%	0.27%

Table 63. Estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events (continued)

Outcome	All Women (n=60,000)			BRCA1 Only (n=20,000)		BRCA2 Only (n=20,000)	
	No Effect of OCs	OC-Attributable Effects		No Effect of OCs	OC- Attributable Effects	No Effect of OCs	OC- Attributable Effects
		Ever/ Never[a]	No Effect of OCs		Ever/ Never[a]		Ever/ Never[a]
Life expectancy	71.26	71.37	71.42	63.81	64.76	65.31	65.41
Lifetime Risks of Other Outcomes							
DVT							
Cases	8.54%	8.74%	8.77%	5.77%	6.30%	5.79%	5.47%
Deaths	0.45%	0.50%	0.50%	0.34%	0.38%	0.40%	0.34%
PE							
Cases	4.89%	4.89%	4.89%	3.46%	3.19%	3.13%	3.14%
Deaths	0.43%	0.40%	0.39%	0.27%	0.29%	0.27%	0.23%
Stroke							
Cases	10.53%	10.38%	10.36%	7.31%	7.44%	6.26%	6.45%
Deaths	0.87%	0.79%	0.79%	0.48%	0.58%	0.53%	0.48%
MI							
Cases	15.62%	15.66%	15.68%	11.10%	11.27%	9.02%	9.42%
Deaths	1.99%	1.98%	2.01%	1.48%	1.51%	1.07%	1.04%

BRCA = breast cancer genetic mutation; DVT = deep venous thrombosis; MI = acute myocardial infarction; OC = oral contraceptive; PE = pulmonary embolism
[a]Association between OC use and ovarian and breast cancers modeled as ever versus never users.
[b]Association between OC use and ovarian cancer dependent on duration of use, and between OC use and breast cancer on time since last use.

This gain was largely attributable to decreases in ovarian cancer (which, while uncommon, has a high mortality rate), and colorectal cancer, which is common and has an intermediate mortality rate. While OC use did increase breast cancer cases, the relative increase in mortality from breast cancer was lower than the decrease from ovarian and colorectal cancer. This outcome is likely due to two factors. First, the overall case mortality rate for breast cancer is lower than for ovarian or colorectal cancer, even without adjusting for any effect of OCs on mortality through screening and/or biological changes. Second, by increasing age-specific incidence, cases are diagnosed at an earlier age—because we used age-specific survival in the model, this will lead to lower expected mortality. Finally, we assumed that 5-year survivors were no longer at risk for cancer death (although breast cancer survivors were at risk for a contralateral new cancer), which may also be contributing to lower overall mortality (other than BRCA carriers, who were at increased risk for both breast and ovarian cancers, we assumed the risk of different cancers was independent—women with a history of breast cancer were as likely to develop ovarian or other cancers as women who did not). The effect on mortality of cases occurring at younger ages is also seen for vascular events; in some iterations of the model, mortality was even reduced among users compared with nonusers, although some of this is also because of the large variance around the probability estimates due to the small number of cases. The prevalence of ever use in the models averaged approximately 75 percent across all iterations, which is somewhat lower than the 84 percent reported in the NSFG. However, given the relative magnitudes of the different effects, this likely leads to underestimation of overall net benefit.

The relative effects of incidence and disease-specific mortality are particularly clear in the results for BRCA1 and BRCA2 carriers. For BRCA1 carriers—where the relative increases in risk of breast and ovarian cancer are similar and result in similar lifetime risks of close to 50

percent in this model—the absolute reduction in ovarian cancer mortality is approximately 6 percent, while the absolute increase in breast cancer mortality is less than 1 percent, resulting in a gain in life expectancy of over 10 months. Conversely, for BRCA2 carriers—where the increased risk of breast cancer is much larger than for ovarian cancer (83% vs. 14%)—resulted in a smaller absolute reduction in mortality. The estimated number of other cancers and vascular events is also smaller for the BRCA carriers, largely due to the large competing risks associated with breast and ovarian cancers. As with the general population, the combination of small probabilities and earlier diagnosis lead to some paradoxical results in terms of the effect of OC use on incidence and mortality.

These results reflect estimates of the population-level impact of associations between OC use and these outcomes based on current patterns of OC use—in other words, the weighted average based on estimates of the population distribution of ever use, age at first use, and duration of use. Because the "OC use" model includes "subjects" who never use OCs, the absolute difference in outcomes at the population level will be lower than it will be when directly comparing ever users to never users.

Effect of OC Use on Lifetime Incidence and Mortality in Ever Versus Never Users

To estimate absolute differences in outcomes between ever users and never users, we generated a "population" of women who had used OCs based on reported patterns, then calculated life expectancy and incidence and mortality from cancers and vascular events for "subjects" who had "taken" OCs during the simulation versus those who had not. We performed 50,000 iterations for the general population and 20,000 each for BRCA1 and BRCA2 carriers.

In Table 64, the estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events is compared between ever versus never users. The results are qualitatively similar but somewhat larger in scale than seen when modeled as a general population effect, where the effect is the weighted average of incidence in users and nonusers. Estimated gains in life expectancy ranged from 5 months for BRCA2 carriers to 11.5 to 12.5 months for the general population, to 16 months for BRCA1 carriers. The incidence estimates for never users are also somewhat higher than in the population model, which is likely due to differences resulting from the effect of actually modeling no use, which may slightly modify the effects of differences in possible state transition compared with the general population model, which assumes similar patterns of pill use but no pill effects on cancers or vascular events.

Table 64 presents these results as the absolute number of case or deaths caused or prevented by OC use per 100,000 women over a lifetime starting at age 10. We also present the number needed to harm (NNH) or number need to prevent (NNP), which is the reciprocal of the absolute risk associated with OC use. For the general population, modeling the effects of exposure as time-dependent compared with ever vs never has an impact on the magnitude of the effect of OC use on both harms and benefits, increasing the number of breast cancer cases but decreasing the number of ovarian cancer. Although the qualitative effects are similar, and the absolute difference between the two different modeling approaches is quite small, the fact that they are different illustrates the potential importance of better data about the relationship between duration of use, time since last use, and the risk of developing specific cancers. There are also some paradoxical results for BRCA carriers (for example, decreased incidence but increased mortality for colorectal cancer among both BRCA1 and BRCA2 carriers), but it is unclear whether this represents the instability of relatively small numbers, or perhaps a competing risk

effect because of the high background risk of mortality from ovarian cancer which is reduced by OC use. This series of simulations also resulted in lower estimated mortality, despite increased incidence, from breast cancer when OC effects are modeled based on time or in BRCA1 carriers. As noted in the meta-analysis, breast cancer incidence is increased by OC use, but mortality was not significantly increased. These model results, which are based only on modeling an increased incidence, suggest that some of the effect observed in the studies may be the result of shifts in age-specific incidence resulting in better overall survival. As noted below, we observed similar effects for stroke, which are almost entirely explained by differences in age distribution of cases. Some of this may also be related to a relatively small number of "subjects" with no history of OC use in the simulated data set. Finally, there are structural differences in competing risks depending on how the effects of OC use on the outcomes considered here are modeled, which may also contribute to this effect.

Table 64. Estimated lifetime excess cases and deaths (harms) and prevented cases (benefits) per 100,000 women

Outcome	General Population				BRCA1		BRCA2	
	Ever/Never[a]		Duration[b]					
	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)
Harms								
Breast Cancer								
Cases	1021	98	(345)	(290)	2080	48	2268	44
Deaths	(170)	(588)	(263)	(380)	(48)	(2078)	318	315
Cervical Cancer								
Cases	7	14154	74	1356	149	671	217	461
Deaths	0	4513455	11	9369	7	14899	7	15029
DVT								
Cases	1226	82	1277	78	1059	94	45	2215
Deaths	4	24208	20	4959	46	2184	(77)	(1297)
PE								
Cases	524	191	530	189	575	174	451	222
Deaths	484	207	468	214	432	232	317	315
Stroke								
Cases	1329	75	1177	85	1819	55	1461	68
Deaths	77	1300	37	2706	138	726	(105)	(949)
MI								
Cases	1253	80	1645	61	1823	55	1396	72
Deaths	378	264	448	223	(33)	(3009)	149	671
Total harms								
Cases	5361	19	4357	23	7505	13	5840	17
Deaths	773	129	720	139	541	185	608	164
Benefits								
Ovarian cancer								
Cases	(806)	(124)	(1076)	(93)	(9701)	(10)	(4300)	(23)
Deaths	(389)	(257)	(566)	(177)	(4478)	(22)	(1845)	(54)
Colorectal Cancer								
Cases	(802)	(125)	(717)	(139)	(810)	(123)	(682)	(147)
Deaths	(374)	(267)	(321)	(312)	50	2017	49	2021
Endometrial Cancer								
Cases	(1344)	(74)	(1421)	(70)	(1553)	(64)	(1996)	(50)
Deaths	(145)	(690)	(160)	(625)	(71)	(1402)	(85)	(1181)

Table 64. Estimated lifetime excess cases and deaths (harms) and prevented cases (benefits) per 100,000 women (continued)

Outcome	General Population				BRCA1		BRCA2	
	Ever/Never[a]		Duration[b]					
	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)
Total Benefits								
Cases	(2952)	(34)	(3215)	(31)	(12064)	(8)	(6978)	(14)
Deaths	(908)	(110)	(1046)	(96)	(4500)	(22)	(1880)	(53)

BRCA = breast cancer genetic mutation; DVT = deep venous thrombosis; MI = acute myocardial infarction; OC = oral contraceptive; PE = pulmonary embolism

[a] Association between OC use and ovarian and breast cancers modeled as ever versus never users.

[b] Association between OC use and ovarian cancer dependent on duration of use, and between OC use and breast cancer on time since last use.

Effect of Age at First Use and Duration of OC Use

Figures 52 to 76 present the results of simulations at varying ages of starting OCs (15, 20, 25, 30, 35, and 40 years) and duration of use (1, 2, 5, and 10 years) for cancer incidence and mortality, vascular event incidence and mortality, overall life expectancy and combined benefits and harms, and harm to benefit ratio. For all except life expectancy and the harm/benefit ratios, results are presented as changes in absolute incidence or mortality relative to no OC use—values above 0 reflect an increase relative to no OC use, while values below 0 reflect a decrease relative to OC use. Life expectancy is presented as absolute difference in fractions of years. For the harm/benefit ratio, values less than 0 indicate that total harms are reduced relative to no use; values between 0 and 1 indicate that harms are increased but that benefits exceed harms; and values greater than 1 indicate that harms exceed benefits.

Not surprisingly, the relationship between duration of use and outcome is strongest for ovarian cancer, since the effect of OC use on ovarian cancer incidence is directly modeled as a function of duration. There may be an interaction between age at first use and duration for breast cancer. The effect of OC use on breast cancer is modeled as a constant risk until stopping, with a subsequent decline over time. Therefore, women who start at later ages for longer periods of time may be at greater risk because breast cancer incidence increases with age. However, the results of the simulations do not show a clear relationship between age at first use and duration, which may be a function of the relatively small number of simulations for each age/duration combination. There do not appear to be any age/duration effects for the remaining cancers (again, likely due to exposure being modeled simply as ever vs. never use).

For vascular events, there was no clear relationship between age at first use and risk, but estimates for incidence and mortality tended to converge at 10 years of use for all ages of first use. This likely due to the assumption of constant risk—at longer durations of use, there is more opportunity for any effect of OC use on the event to occur, and the estimates are more stable.

For several of the outcomes, particularly breast cancer and stroke, overall lifetime incidence is decreased but overall lifetime cause-specific mortality is decreased for some groups, even though we do not model a separate effect of OC use on cause-specific mortality. There are several possible explanations for this, including random "noise" for rare events, the effects of competing risks, and structural factors in the model (for example, although "women" remain at risk for subsequent events such as a second VTE, this probability is not conditioned on experiencing a previous VTE while on OCs). However, some of the reductions in cause specific mortality may also be related to changes in age-specific mortality from specific conditions—increasing age-specific incidence while on OCs will by definition lead to a shift in the overall incidence to younger ages. Because survival after diagnosis for these conditions is better for younger women (because of lower prevalence of comorbid diseases and, in the case of cancers, potential shifts in stage distribution because of screening), it is possible to have increased incidence along with decreased mortality. We tested this hypothesis for stroke by fixing in-hospital stroke mortality in the model to the national average (9.8%) rather than to age-specific values, which vary from 7.8% in women under 45 years of age to 12.8% in women 85 years and older. Lifetime stroke mortality was 0.9 percent for no OC use, 0.83 percent when modeled as age-specific mortality, and 1.1 percent when modeled at the fixed overall rate, demonstrating the effect of changes in age-specific incidence on overall mortality if mortality is variable across age.

Similar convergences with longer duration of use were observed for combined harms and benefits, with an overall greater reduction in mortality from ovarian, colorectal, and endometrial cancer compared with the increased mortality from other causes (note that the trend was not perfect, which may be due to unstable estimates resulting from too few simulations).

Use of OCs for 5 years or less was associated with net increase in life expectancy except for women 35 years and older. Longer durations were associated with gains in life expectancy in younger women but not women 30 years and older. This is largely explained by the impact of deaths occurring at younger age on overall life expectancy—more potential years lost has a greater impact. These results are consistent with the results showing net gains in life expectancy in Tables 63 and 64: if, as the age of first use versus duration effects suggest, net benefit is optimized by 5 years of use, then one would expect net increases in life expectancy in a population that has a mean duration of use of 5 years, which is the value used in the model.

Note that for each figure, the different shapes 15, 20, 25, 30, 35, and 40 represent the age of starting OC use, while the y-axis represents the absolute change in lifetime incidence or mortality due to the estimated association between OC use and the outcome.

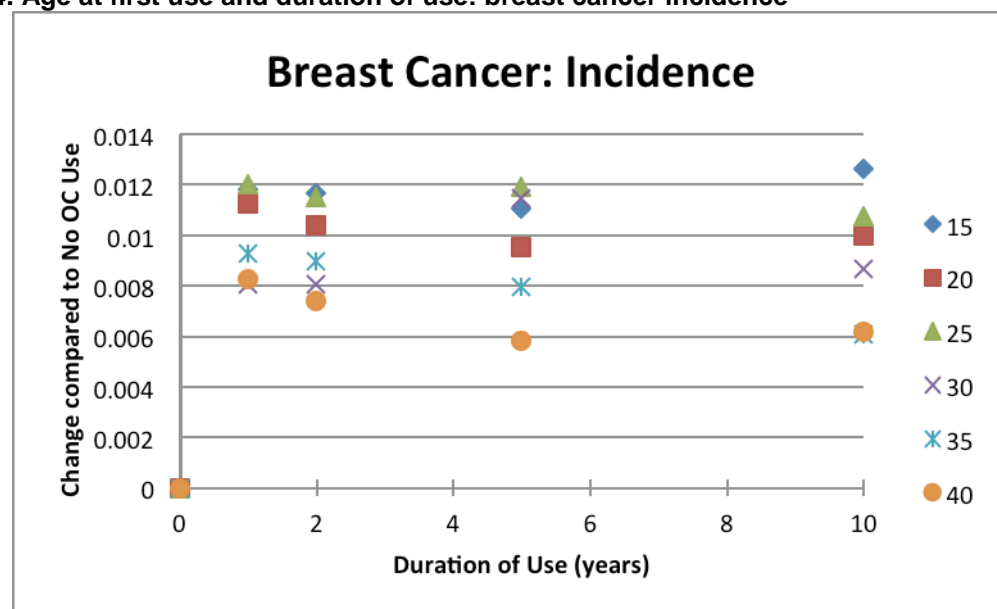**Figure 52. Age at first use and duration of use: ovarian cancer incidence**
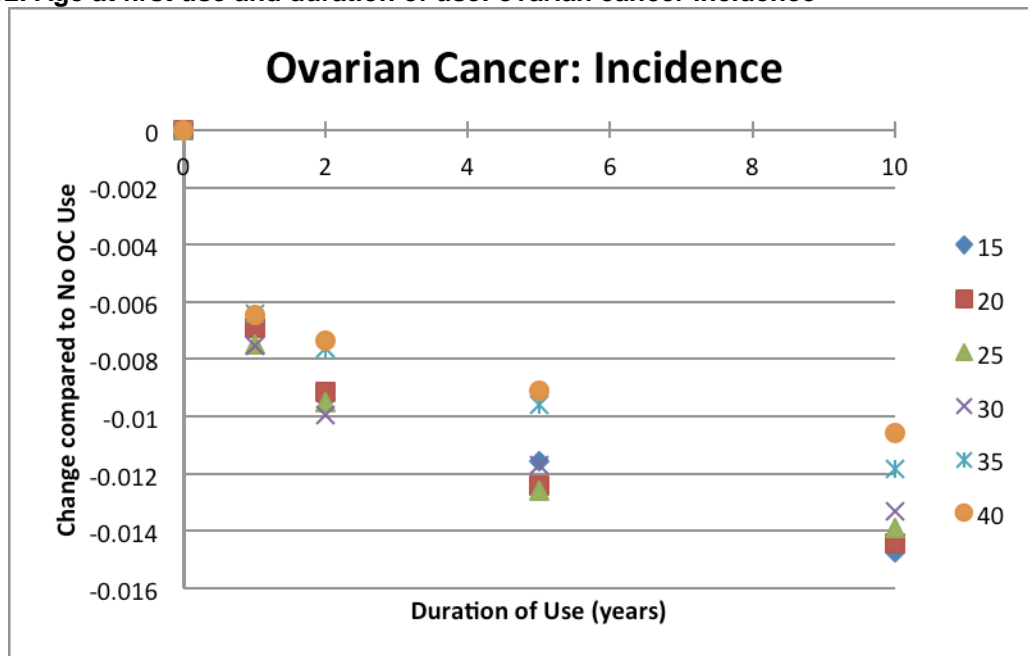
OC = oral contraceptive

Figure 53. Age at first use and duration of use: ovarian cancer mortality
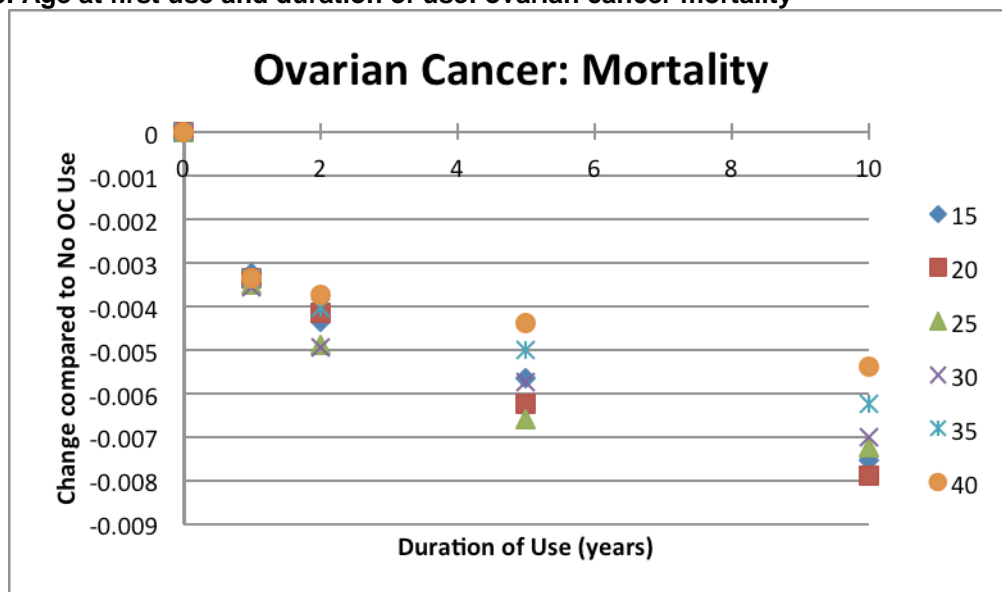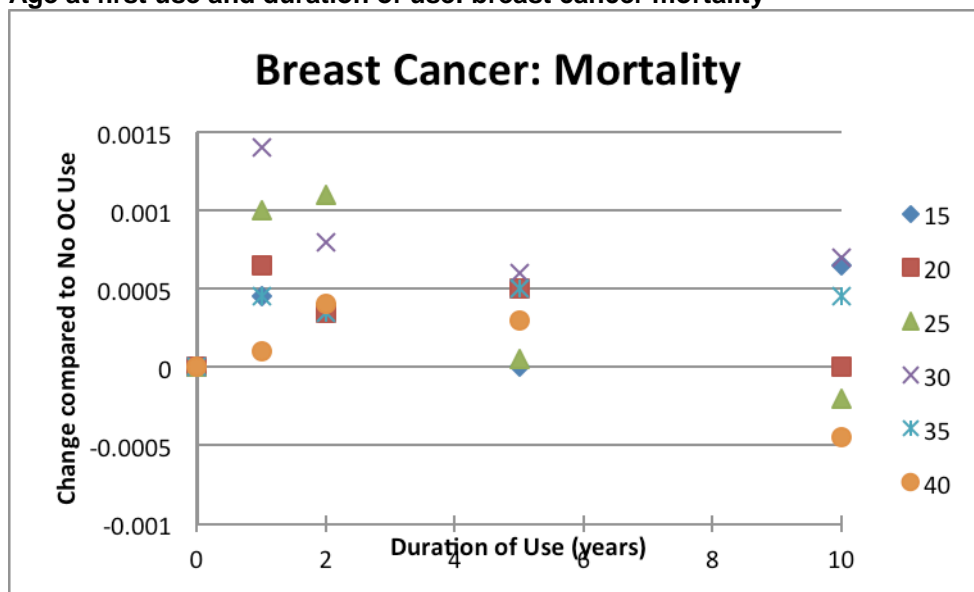

OC = oral contraceptive

Figure 54. Age at first use and duration of use: breast cancer incidence

OC = oral contraceptive

Figure 55. Age at first use and duration of use: breast cancer mortality

OC = oral contraceptive

Figure 56. Age at first use and duration of use: cervical cancer incidence

OC = oral contraceptive

Figure 57. Age at first use and duration of use: cervical cancer mortality

OC = oral contraceptive

Figure 58. Age at first use and duration of use: colorectal cancer incidence

OC = oral contraceptive

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Figure 59. Age at first use and duration of use: colorectal cancer mortality

OC = oral contraceptive

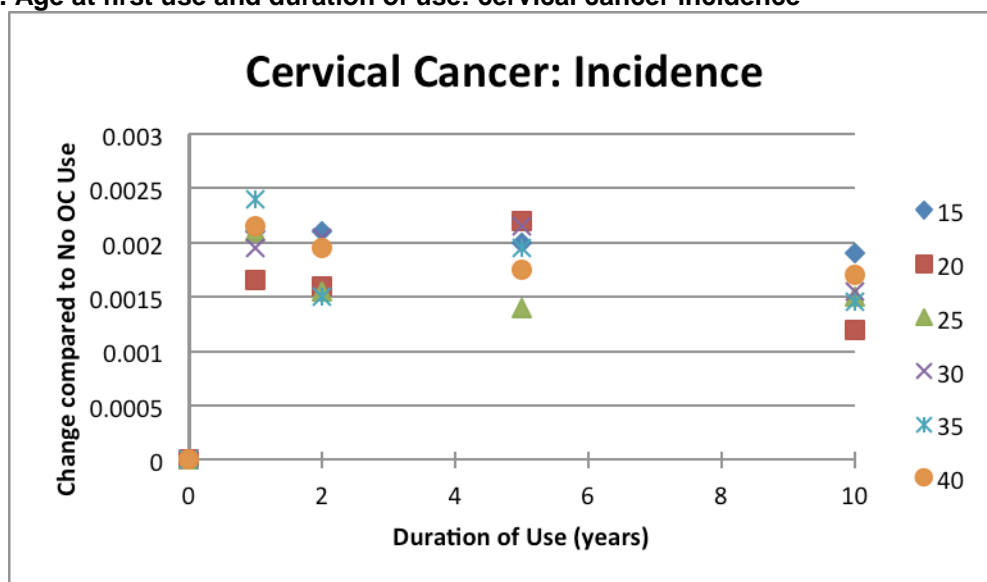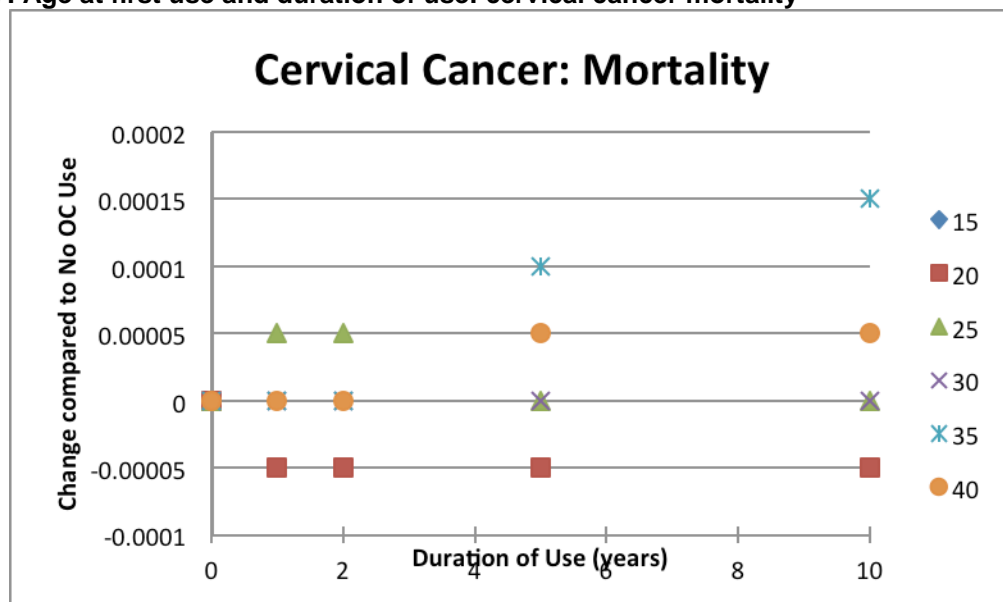**Figure 60. Age at first use and duration of use: endometrial cancer incidence**

OC = oral contraceptive

Figure 61. Age at first use and duration of use: endometrial cancer mortality

OC = oral contraceptive

Figure 62. Age at first use and duration of use: deep vein thrombosis incidence

DVT = deep vein thrombosis; OC = oral contraceptive
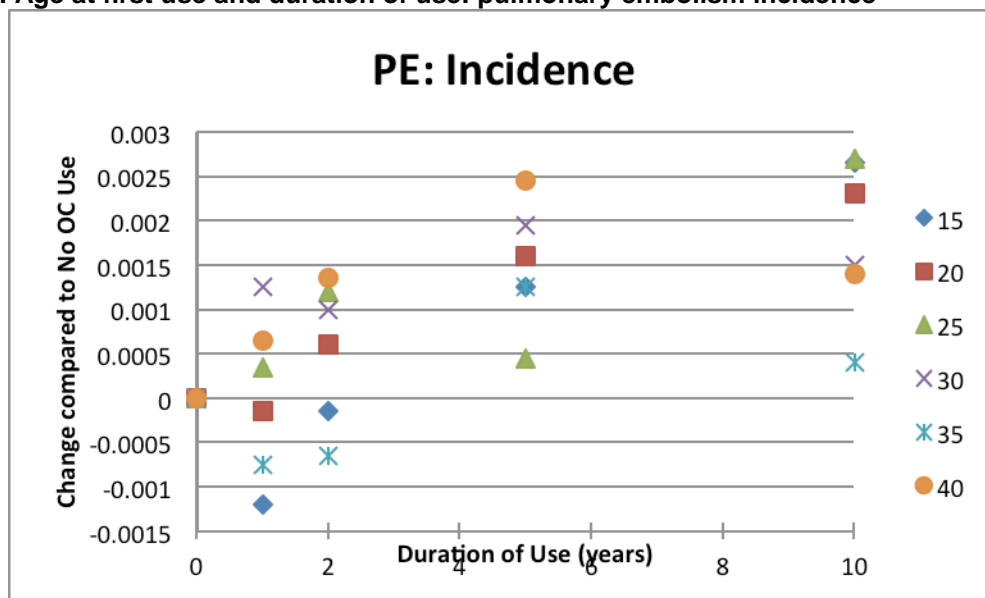
Figure 63. Age at first use and duration of use: deep vein thrombosis mortality

DVT = deep vein thrombosis; OC = oral contraceptive

Figure 64. Age at first use and duration of use: pulmonary embolism incidence

OC = oral contraceptive; PE = pulmonary embolism

Figure 65. Age at first use and duration of use: pulmonary embolism mortality
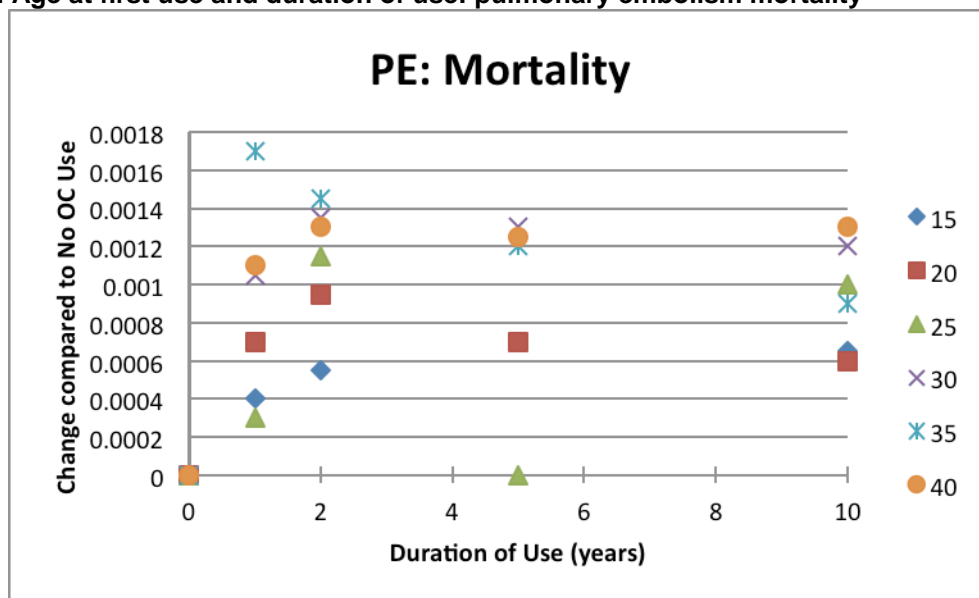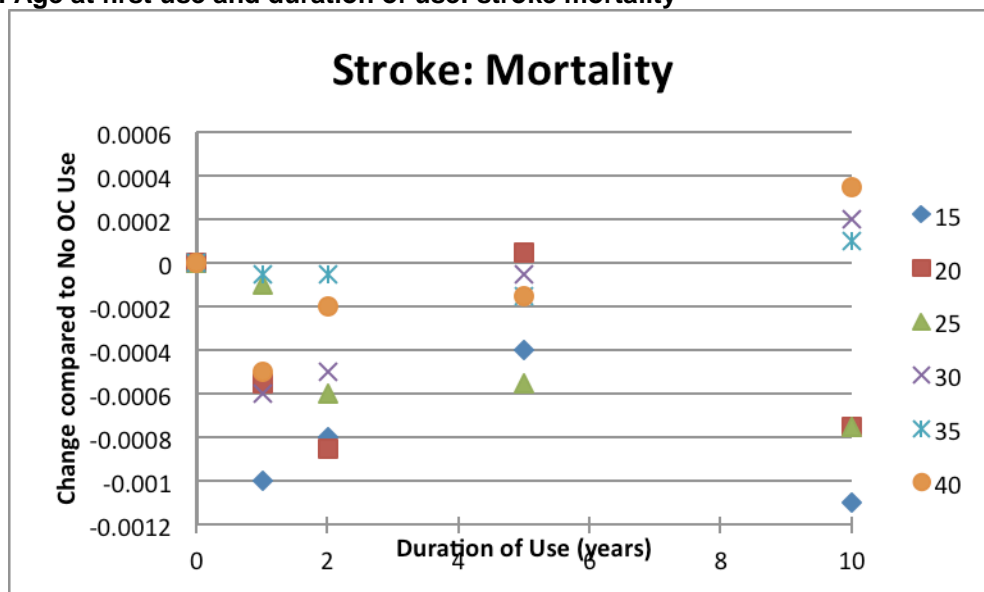
OC = oral contraceptive; PE = pulmonary embolism

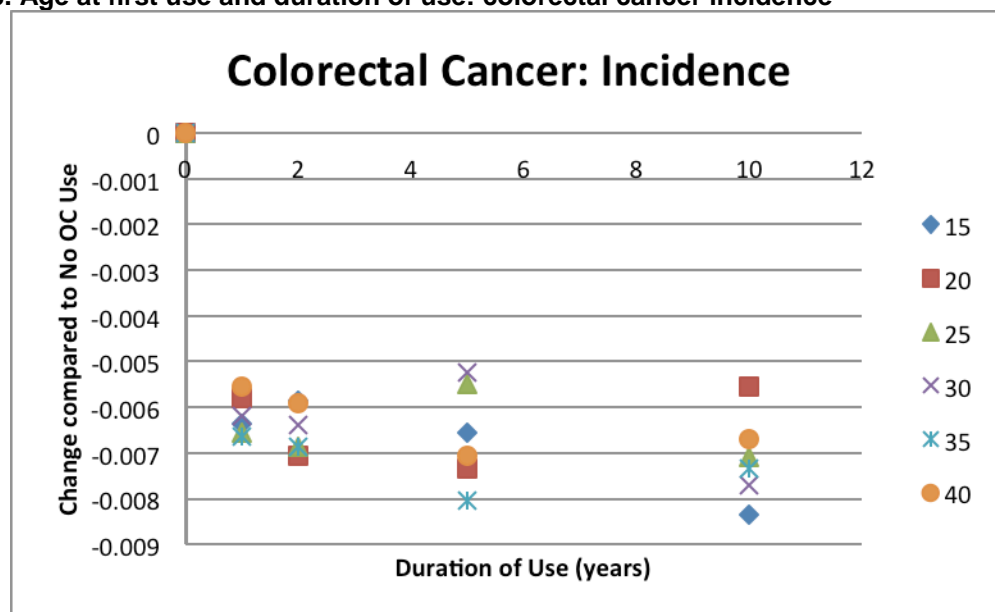**Figure 66. Age at first use and duration of use: stroke incidence**
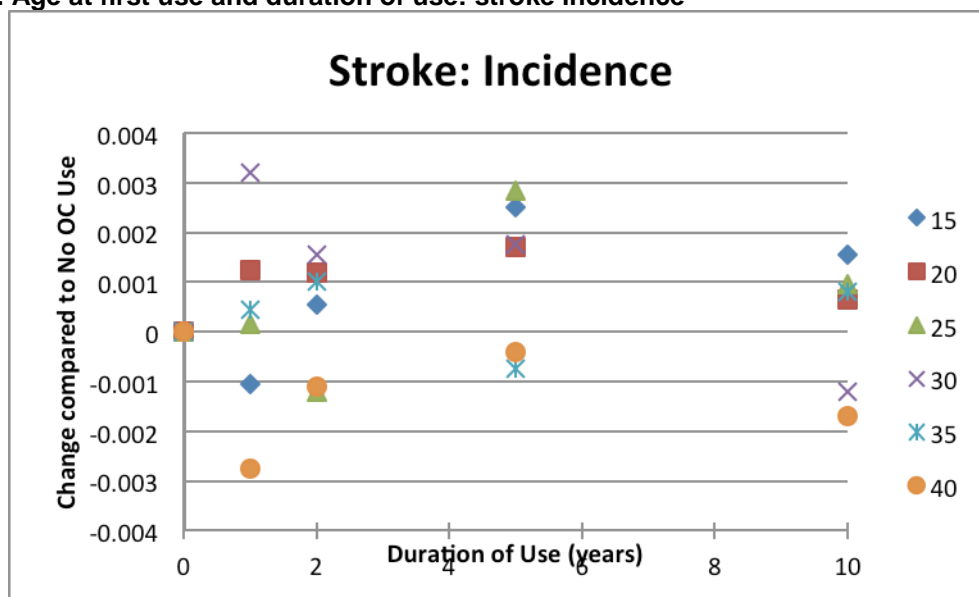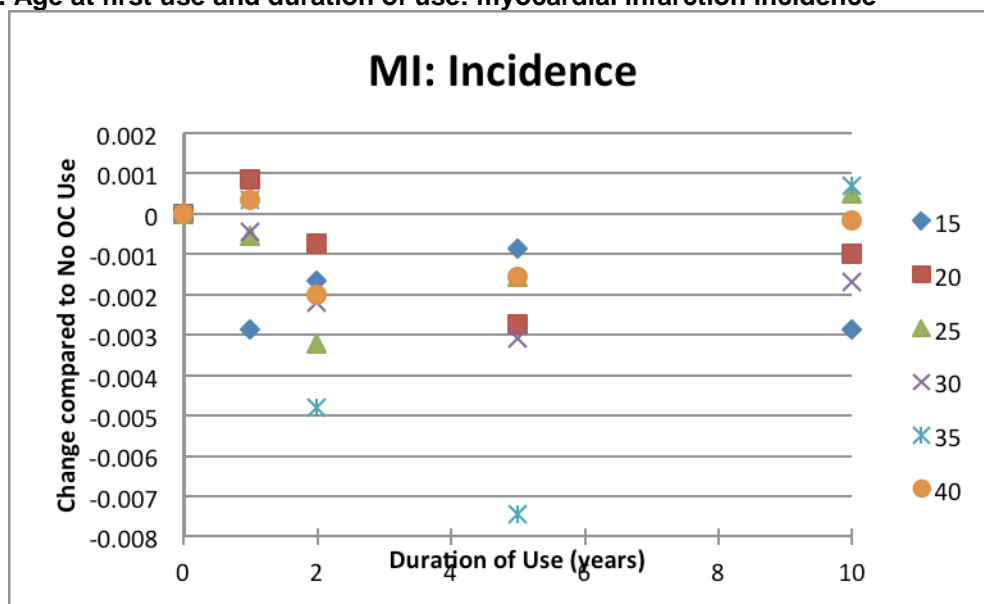
OC = oral contraceptive

Figure 67. Age at first use and duration of use: stroke mortality

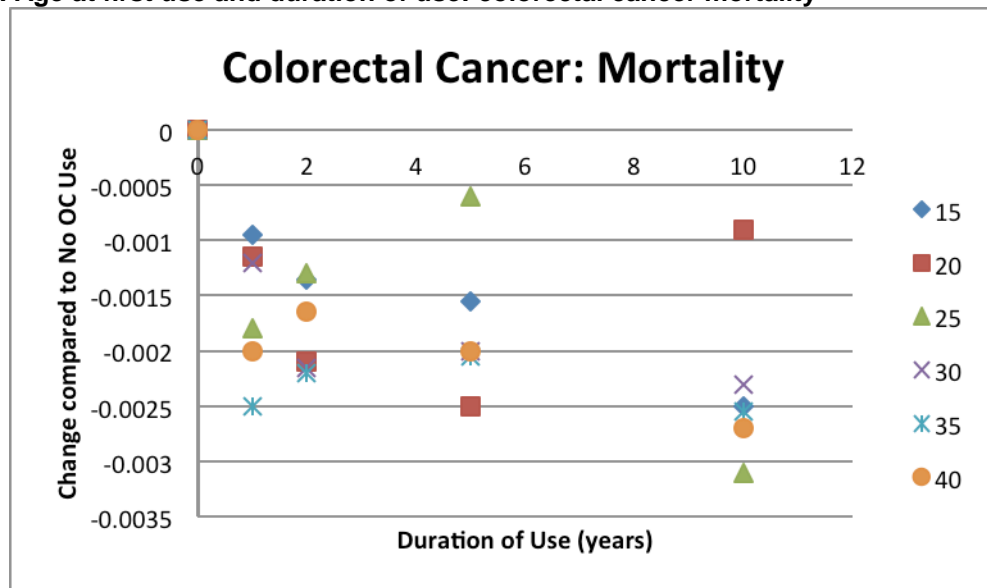OC = oral contraceptive

Figure 68. Age at first use and duration of use: myocardial infarction incidence

MI = myocardial infarction; OC = oral contraceptive

Figure 69. Age at first use and duration of use: myocardial infarction mortality
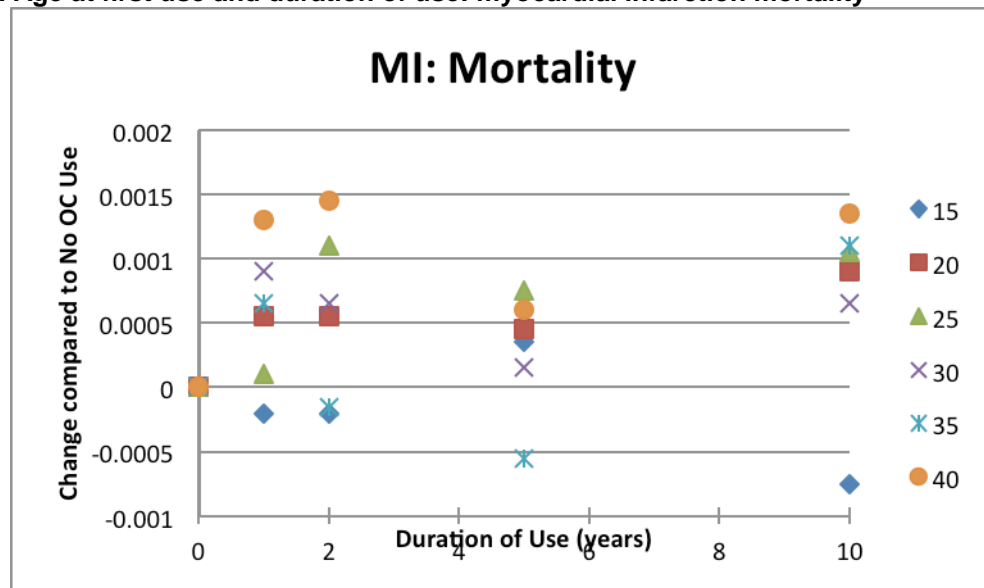
MI = myocardial infarction; OC = oral contraceptive

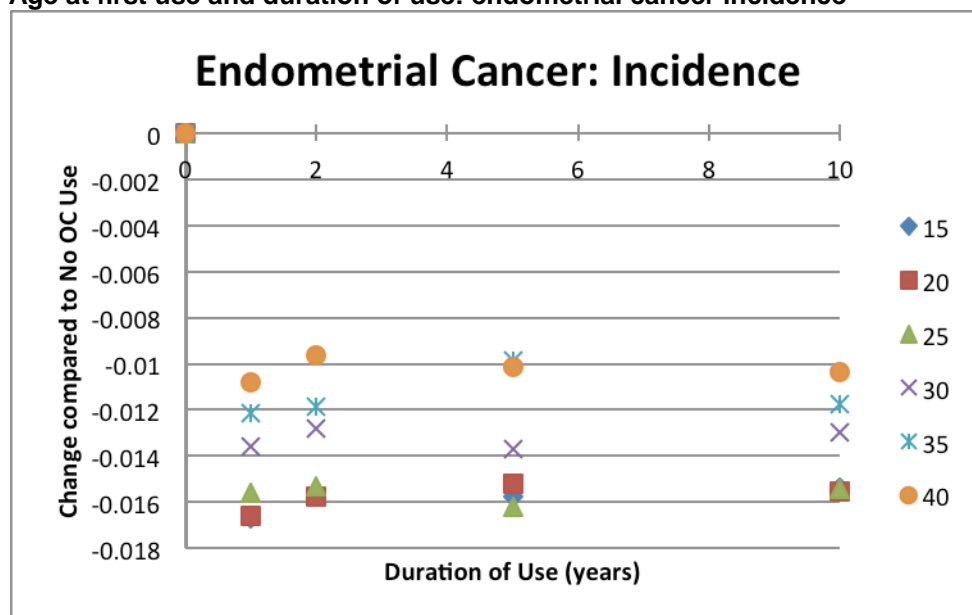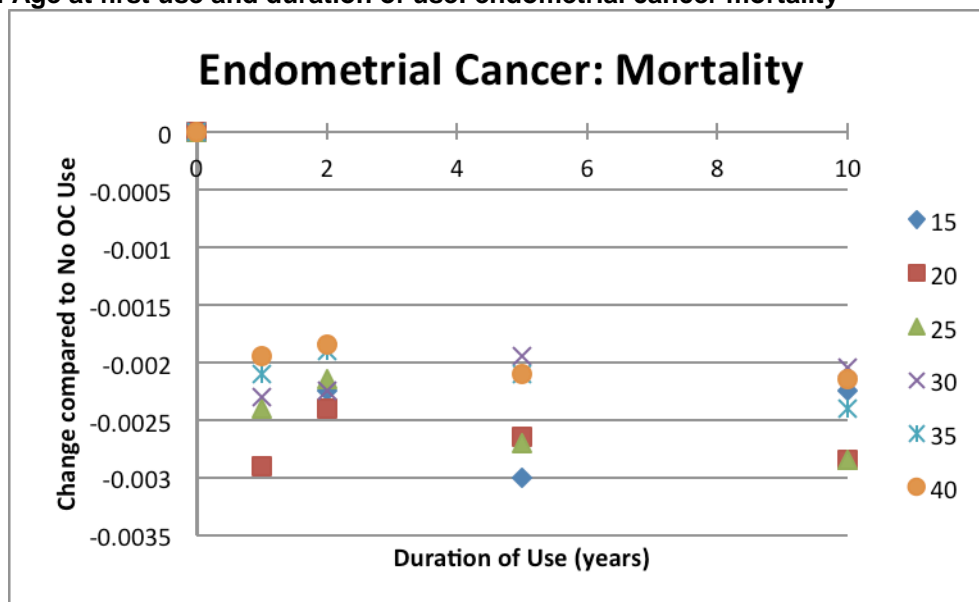**Figure 70. Age at first use and duration of use: life expectancy**
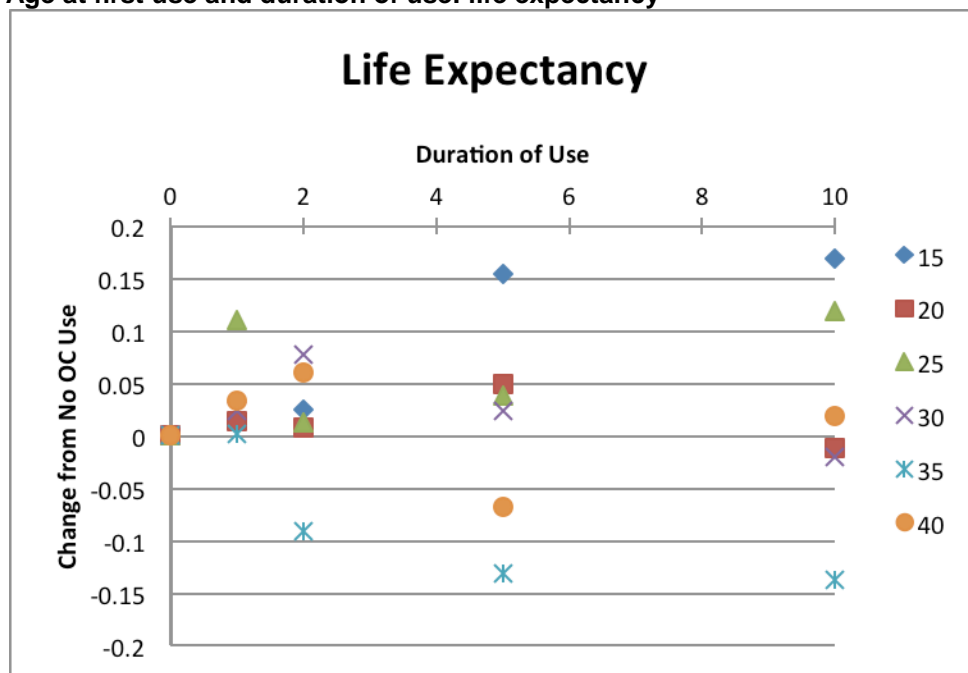
OC = oral contraceptive

Figure 71. Age at first use and duration of use: total harms incidence
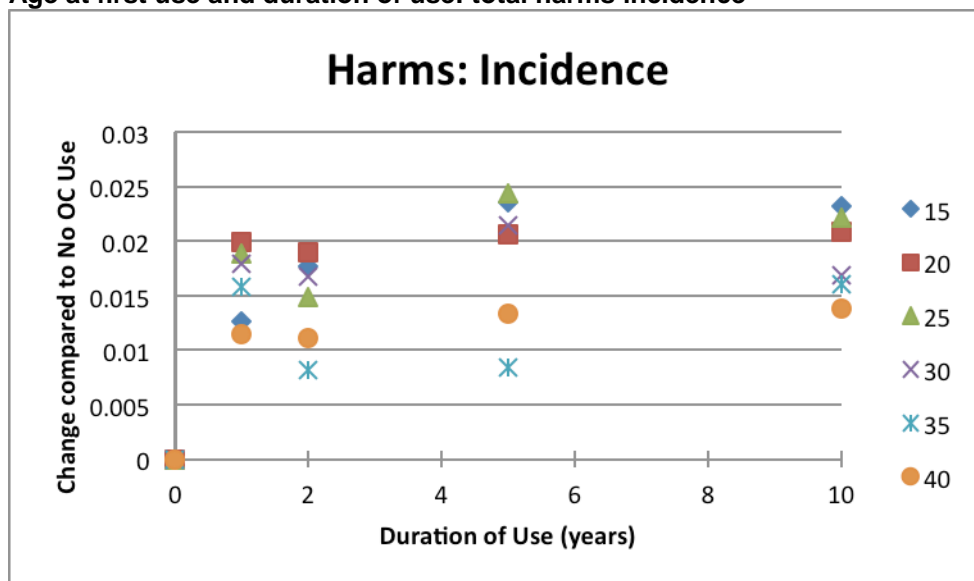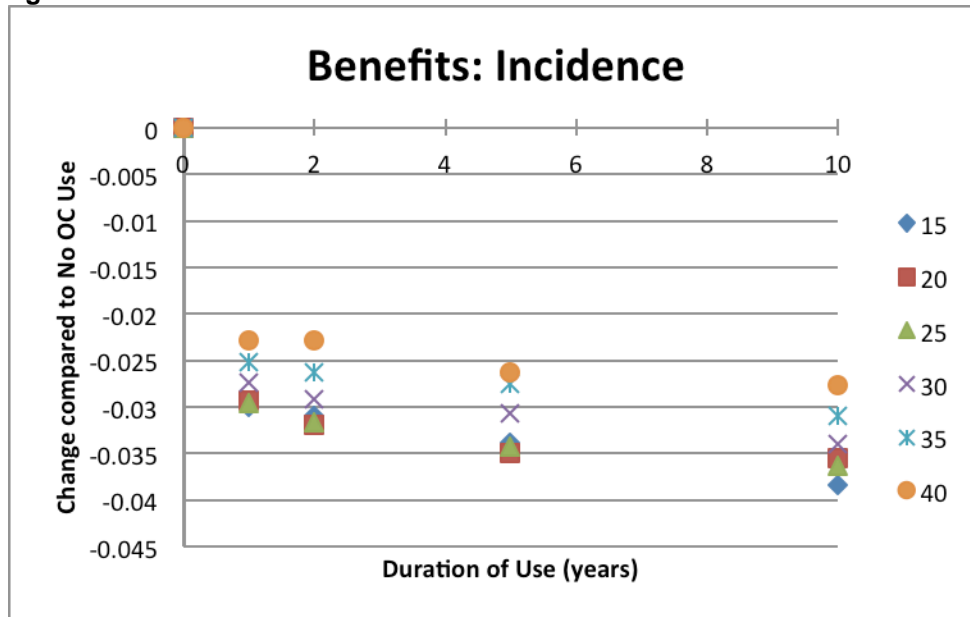
OC = oral contraceptive

Figure 72. Age at first use and duration of use: total harms mortality
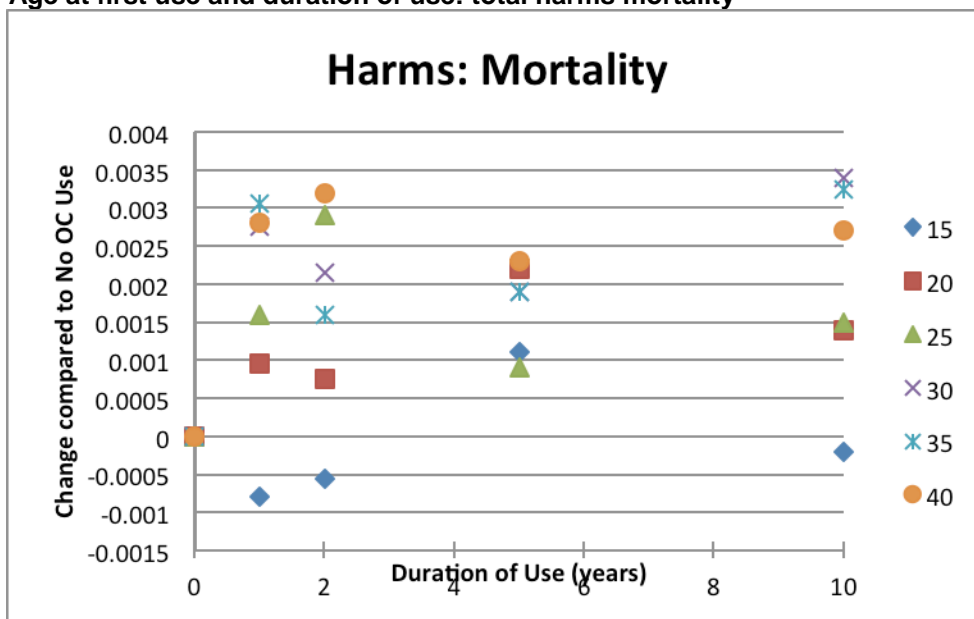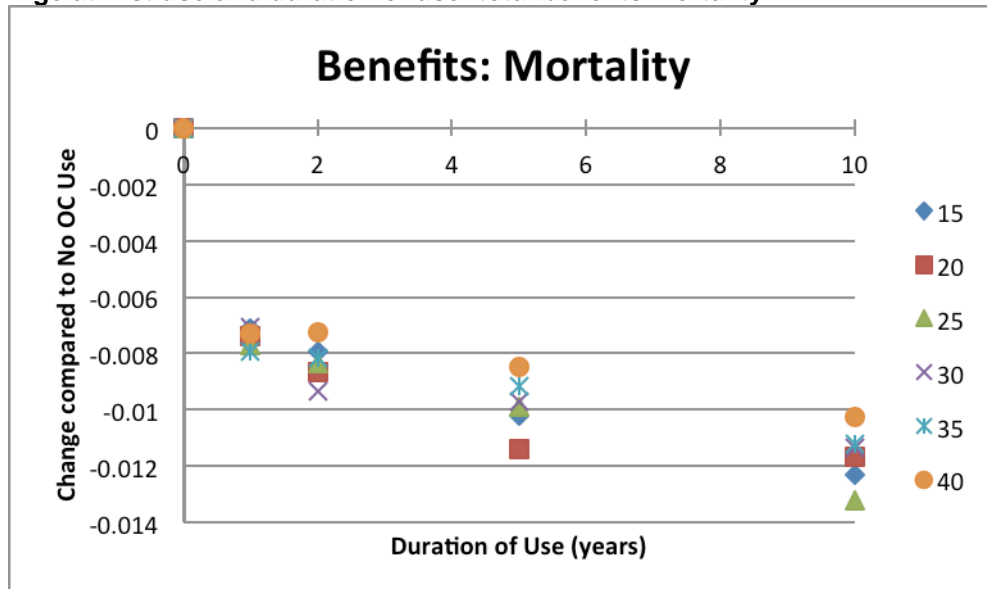
OC = oral contraceptive

Figure 73. Age at first use and duration of use: total benefits incidence
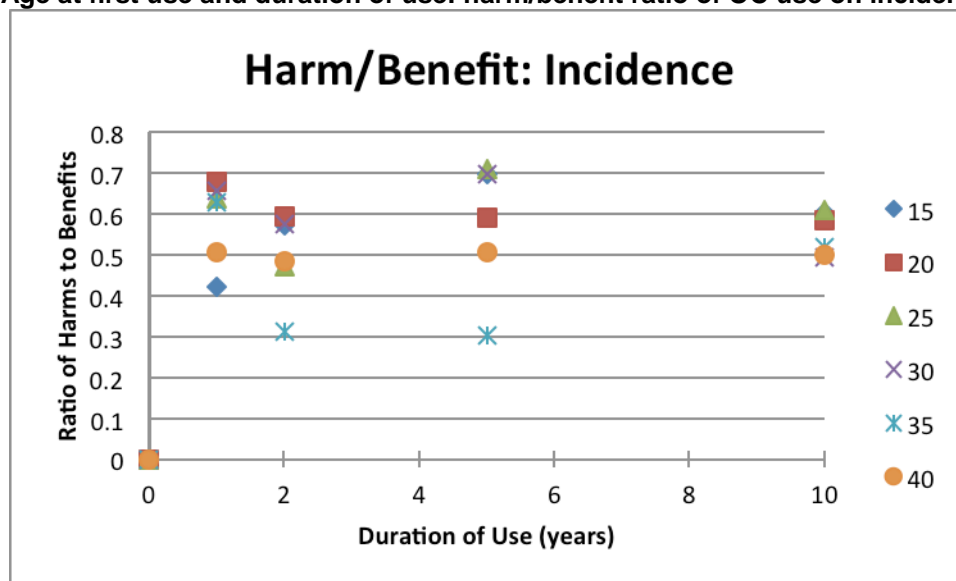
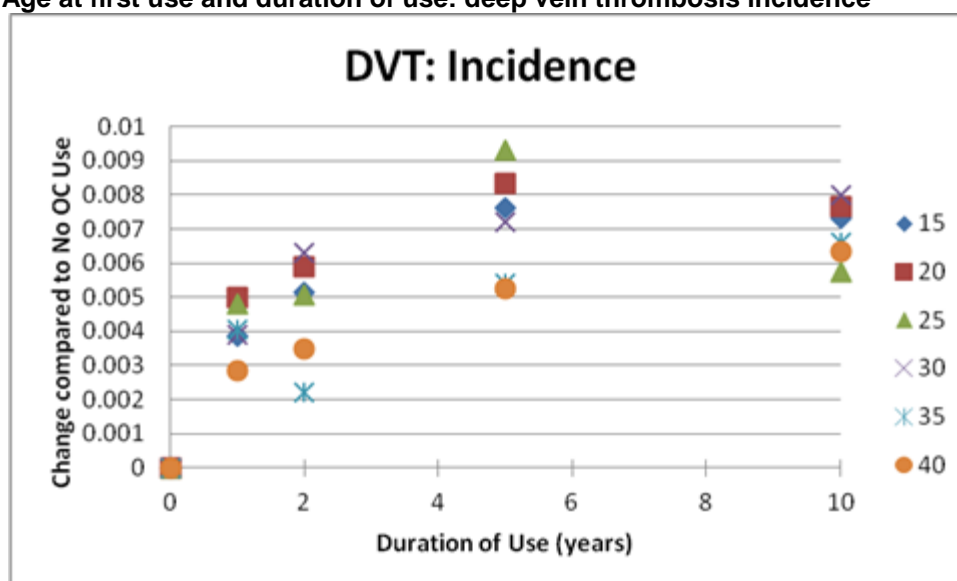OC = oral contraceptive

Figure 74. Age at first use and duration of use: total benefits mortality
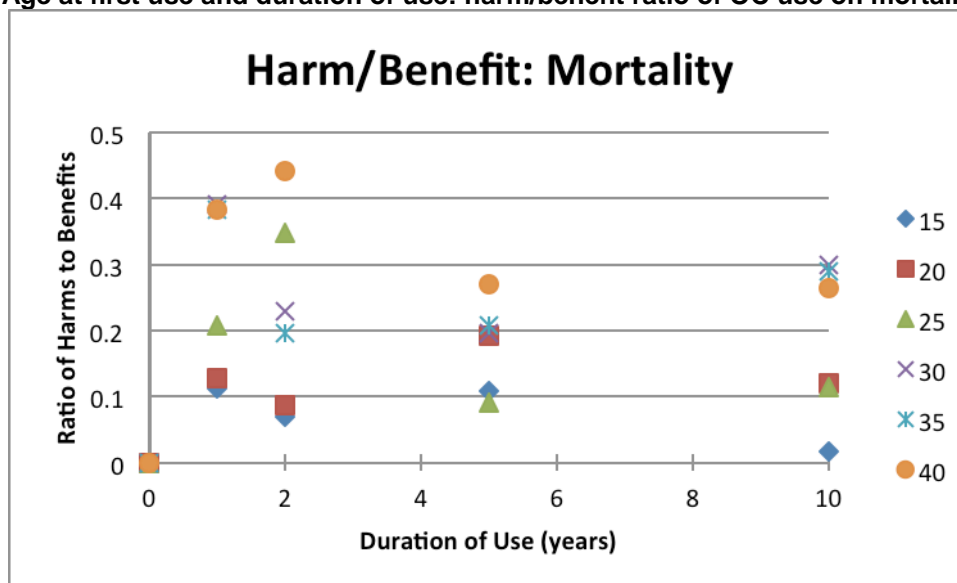
OC = oral contraceptive
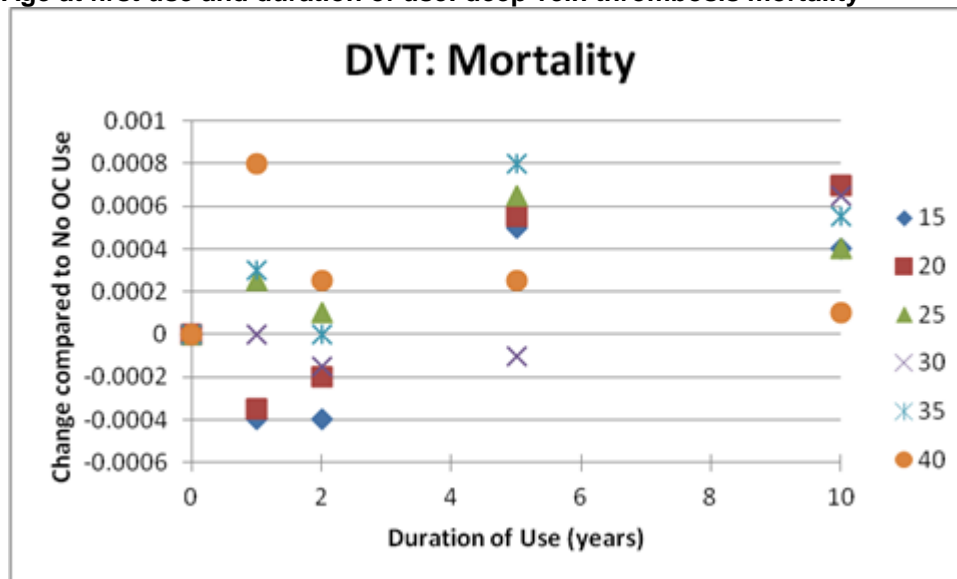
Figure 75. Age at first use and duration of use: harm/benefit ratio of OC use on incidence

OC = oral contraceptive

Figure 76. Age at first use and duration of use: harm/benefit ratio of OC use on mortality

OC = oral contraceptive

Harm/Benefit Acceptability

To assess the impact of uncertainty of the estimates of the relative risks associated with OC use on the tradeoffs between benefits and harms, we ran a series of simulations where the value for each relative risk was drawn from the distributions described in Table 60 (200 draws from these distributions, with 10,000 "subjects" per draw, for a total of 2 million simulations).This method allows us to generate estimates of the effect of uncertainty in the parameter estimates on the uncertainty in the output. For example, Figure 77 compares the distribution of the difference in life expectancy in the general population model between modeling OC effects as ever versus

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never, versus dependent on duration of exposure for ovarian cancer and time since last use for breast cancer. Consistent with the results presented earlier, modeling OC effects based on time results in a greater mean gain in life expectancy. The probabilistic analysis shows this clearly, and also shows the distribution of outcomes, including the small proportion of simulations using ever versus never use which results in net loss of life expectancy.

Figure 77. Distribution of net life expectancy difference due to OC effects[a]
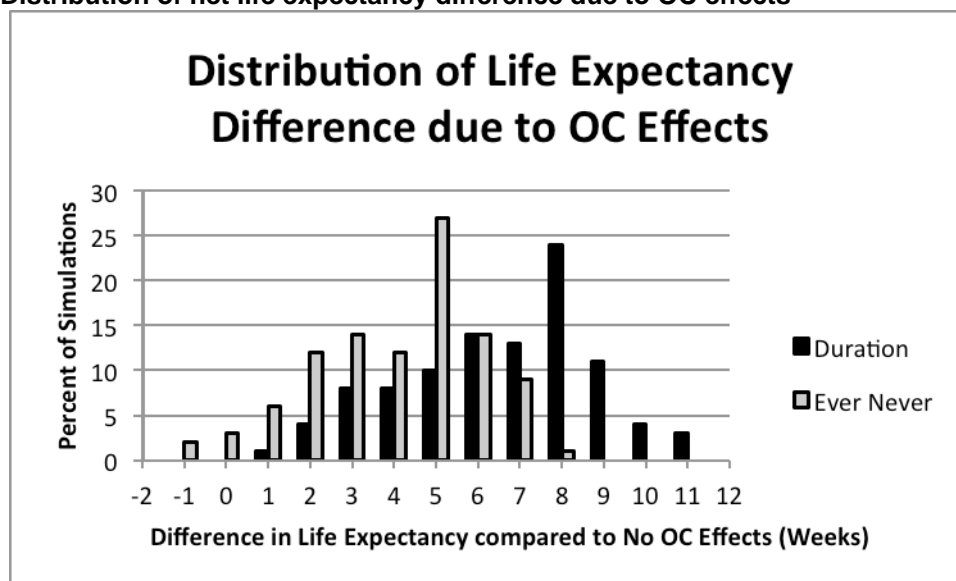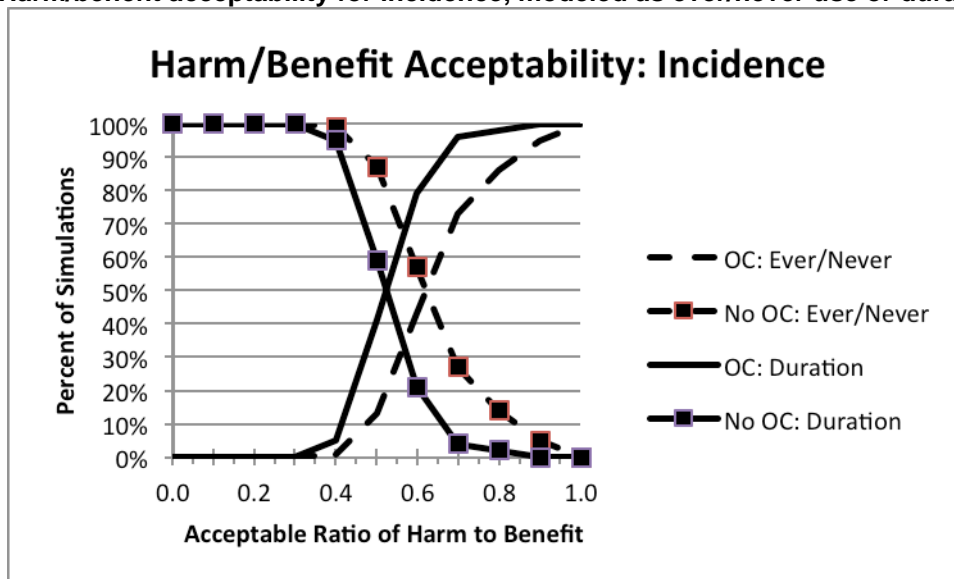
OC = oral contraceptive
[a]Based on OC use in the general population for 100 simulations, where OC effects are either time-dependent for breast and ovarian cancer, or modeled simply as ever versus never.

For the analysis of net benefits, we present the results as acceptability curves—the y-axis represents the proportion of simulations where a given scenario was optimal at a given "willingness-to-pay" (WTP) in terms of harms incurred versus benefits gained; in other words, the sum of all adverse outcomes divided by the sum of all desired outcomes. The point where the lines cross represents the point where half of the simulations favor OC use and half favor nonuse. At a WTP threshold below the point on the x-axis where the lines cross, the majority of simulations favor not using OCs, and, above that point, OC use is favored. The ratio of harms to benefits ranges from 0 (no excess harms) to 1 (harms equal to benefits).

Figures 78 and 79 show the curves for incidence cases and mortality, respectively. The acceptability threshold where OC use is favored is lower for mortality then for incidence, but for both it is below 0.5. For mortality, the model is based on duration of use results in a slightly, more favorable threshold for OC use: the proportion of simulations where a given acceptability threshold was reached was consistently higher because of the higher estimate of ovarian cancers prevented and the lower number of excess breast cancers.
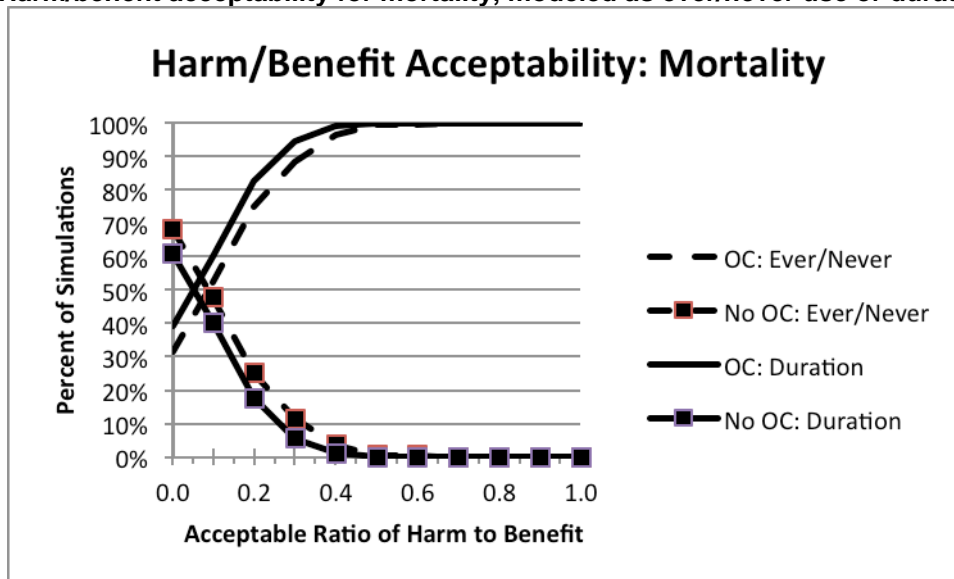
Figure 78. Harm/benefit acceptability for incidence, modeled as ever/never use or duration of use

OC = oral contraceptive

Figure 79. Harm/benefit acceptability for mortality, modeled as ever/never use or duration of use

OC = oral contraceptive

We then explored the relative impact of different components of harm and benefit on acceptability by systematically removing different conditions from the numerator or denominator of the harm/benefit ratio and comparing the proportion of simulations where OC use was favored at a given WTP threshold. For ease of visualization, we present only the proportion of simulations where OC use was acceptable for each combination of harms and benefits at a given WTP threshold; implicitly, the proportion of simulations where OC use was not acceptable at that threshold is 100 percent minus the value for OC use.

In these figures, we sequentially remove groups of harms from the numerator, leaving all benefits, then sequentially remove benefits, leaving all harms. The lines represent the following outcomes:

- Harms (incident cases and mortality)
  - "All combined": breast and cervical cancer, DVT, PE, stroke, MI
  - "No vascular events": breast and cervical cancer only
  - "No cancers": DVT, PE, stroke, MI only
- Benefits (prevented incident cases and deaths)
  - "All combined": ovarian, colorectal, and endometrial cancers
  - "Ovarian and colorectal": ovarian and colorectal cancers only
  - "Ovarian only": ovarian cancer only

Removing vascular events from the harms results in a shift to the left of the acceptability curve for incidence. An even greater shift is seen with removal of breast cancer and cervical cancer (Figure 80). Given the very low absolute increase in cervical cancer incidence associated with OCs, this effect is almost entirely due to breast cancer. This is due to several factors. First, although the relative risk of breast cancer attributable to OC use is relatively small, the absolute number of cases is larger than for vascular events. Second, the degree of uncertainty around the risk estimate for breast cancer is larger than it is for vascular events, with a lower bound very close to 1, so that removing the effect of this uncertainty leads to a greater number of simulations favoring OCs at a given threshold. Conversely, removing colorectal and endometrial cancer resulted in a marked shift of the curve to the right—40 percent of the simulations resulted in a harm/benefit ratio (number of harms incurred per case of ovarian cancer prevented) of 1.0 (Figure 81). This suggests that it is more likely that, for OC use solely for ovarian cancer prevention, the number of harms in terms of incident cases is likely to exceed the benefit (of course, the case might be different if patient preferences for the specific harms and benefits were included). Adding colorectal cancer improved the threshold somewhat, but the major effect was seen by replacing endometrial cancer into the equation. These results are consistent with the tables presented above, where the number needed to prevent one endometrial cancer case is substantially lower than for colorectal or ovarian cancer.

Figure 80. Effect of specific harms on harm/benefit acceptability for incidence (duration model only)
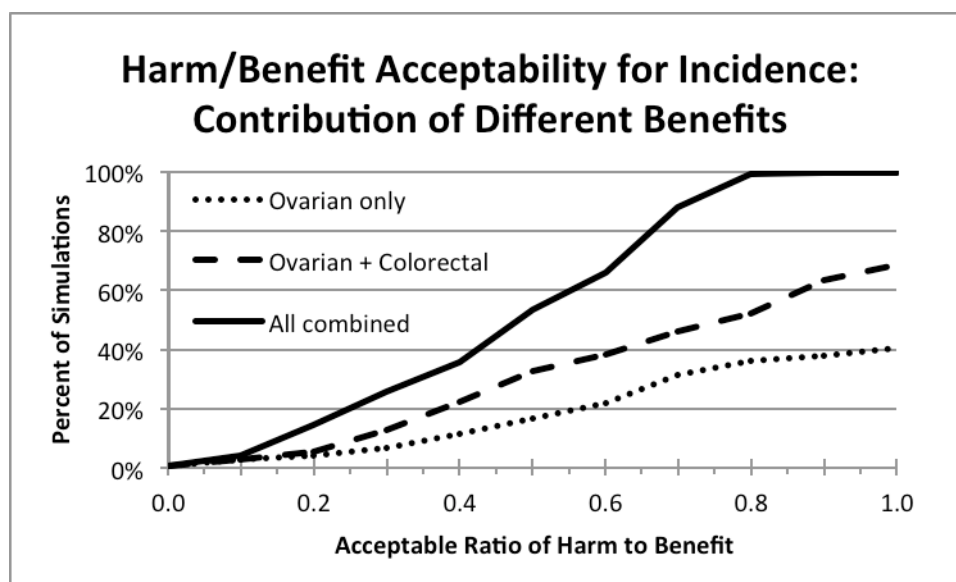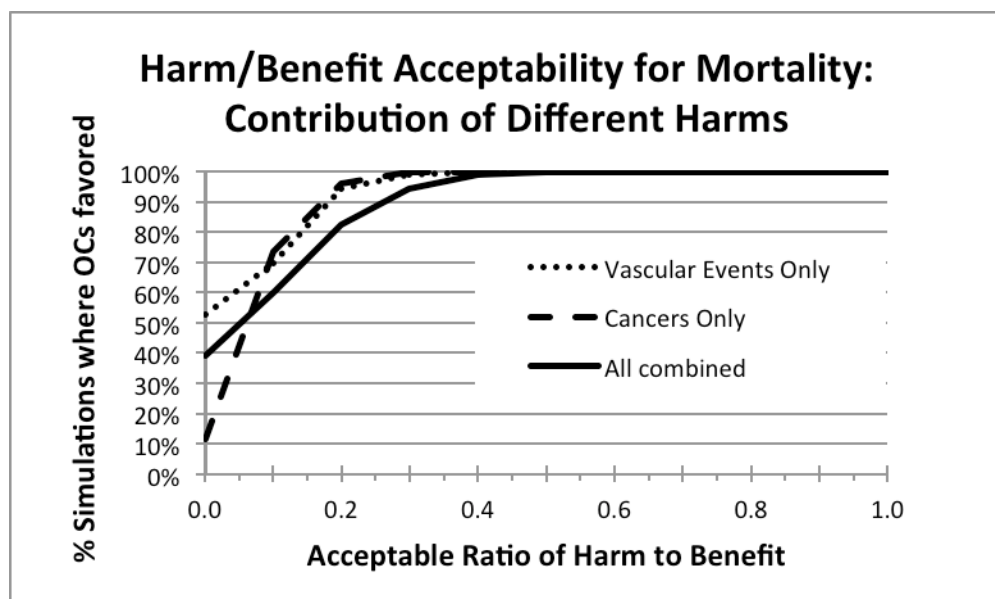
Figure 81. Effect of specific benefits on harm/benefit acceptability for incidence (duration model only)
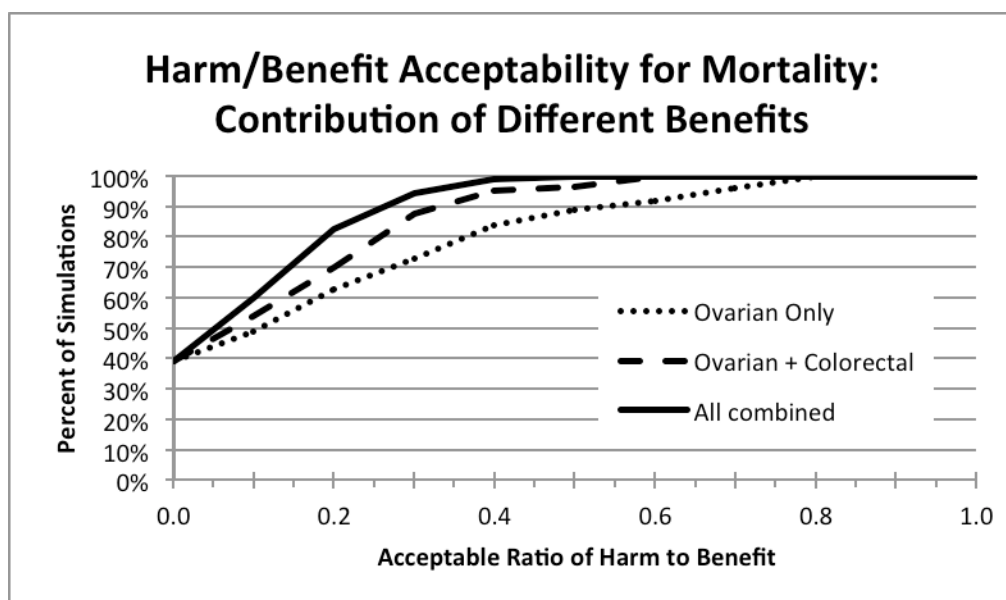
Results for harms related to mortality were qualitatively similar, but showed an interesting pattern (Figure 82). Removing vascular events actually resulted in decrease in the acceptability threshold at WTO values below 0.1. This is due to the consistent model prediction of increased incidence but decreased mortality from stroke in OC users discussed above: because strokes are included as harms, the net harm in terms of lifetime deaths is smaller when vascular events are included then when they are not. As discussed, these results are due to modeled changes in age-specific incidence leading to changes in age-specific mortality. Taken at face value, these results raise an important point about the limitations of simply counting harms and benefits—clearly,

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the potential morbidity from a stroke at a young age is substantial, even if mortality is lower, and this needs to be taken into account by decisionmakers at every level, whether through an informal weighting process or formal methods such as quality-adjusted life expectancy. On the benefit side, the pattern was similar to that seen for incident benefits, although the relative contribution of ovarian cancer alone was much greater (Figure 83).

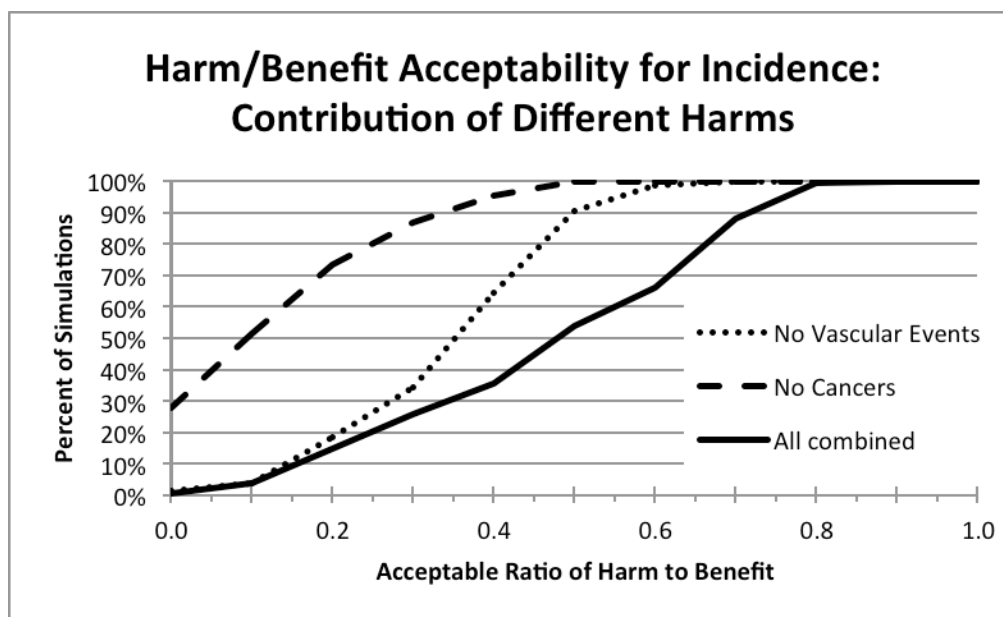**Figure 82. Effect of specific harms on harm/benefit acceptability for mortality (duration model only)**

Figure 83. Effect of specific benefits on harm/benefit acceptability for mortality (duration model only)

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Discussion

Previous sections of this report have provided discussion of the findings, limitations, and clinical and public health implications of the detailed analyses of OC use and ovarian cancer (Section 2), OC use and other cancers (Section 3), and OC use and vascular events (Section 4). In Section 5, we used mathematical modeling methods to integrate the results of the systematic reviews and meta-analyses of these individual outcomes to better understand the combined effects. In Section 5, we also:

- Summarize the findings of the evidence synthesis
- Compare the results with previous studies
- Discuss the uncertainties, limitations, and subsequent future research needs
- Discuss the clinical and public health implications of the findings, given the uncertainties and limitations

Summary of the Evidence Synthesis

The following are key points from our systematic review and meta-analyses:

- The incidences of ovarian cancer, colorectal cancer, and endometrial cancer were significantly reduced among women who used OCs, with the magnitude of reduction in ovarian cancer risk significantly associated with duration of use (risk declined with longer duration of use, with no evidence of a threshold effect); endometrial cancer risk was also reduced by longer duration of use. The meta-analysis also found a statistically significant effect of time since last use (protective effect decreased as time since last use increased) but not for other characteristics of OC use including ages at use or formulation.
- The reduction in ovarian cancer risk was consistent in different subgroups of women, including BRCA1 and BRCA2 carriers.
- The incidence of breast cancer was significantly increased among women who used OCs, with the magnitude of the increase significantly associated with time since last use (risk decreased with increasing time since last use). The meta-analyses did not find statistically significant effects of other characteristics of OC use including ages at use or formulation.
- The increase in breast cancer risk was consistent in different subgroups of women, including BRCA1 and BRCA2 carriers.
- The incidence of cervical cancer was increased among women who used OCs, although this result was not statistically significant in the meta-analysis.
- The incidences of DVT (including PE) and ischemic stroke were significantly increased among current users of OCs. Risk was associated with increasing estrogen dose, but the meta-analyses did not identify a significant effect of progestin formulation.
- The incidence of MI was increased among women who use OCs, although the results were not statistically significant in the meta-analysis. Again, risk was associated with increasing estrogen dose and, potentially, progestin formulation.
- All of these results are derived from observational studies and may be affected by unmeasured or uncorrected biases.

Modeling Analysis

Key points from our modeling analysis are:

- Using the point estimates for the odds ratios from the meta-analyses (including MI and cervical cancer, where confidence intervals included 1) and adjusting for the age-specific prevalence of OC use, we found the following differences in peak incidence between ever users and never users (for cancers) and current users versus nonusers (for vascular events):
- There was a relatively large absolute increase (maximum increase in annual age-specific incidence 22 per 100,000) in breast cancer risk despite a small relative risk.
- The largest reduction in incidence was in endometrial cancer (maximum decrease in annual age-specific incidence of 55 per 100,000), followed by colorectal cancer (maximum decrease in annual age-specific incidence of 50 per 100,000), and finally ovarian cancer (maximum decrease in annual age-specific incidence of 20 per 100,000), reflecting their relative frequency in women.
- By far the largest absolute increase for any harm was for venous thromboembolism, particularly deep venous thrombosis (maximum increase in annual age-specific incidence of 120 per 100,000); maximum increases in the annual age-specific incidence of PE, stroke, and acute MI were all 30 per 100,000 or less.
- Using a simulation model and these point estimates as well as probabilistic sampling of the age-specific incidence of relevant other events (including hysterectomy, oophorectomy, tubal ligation, and other-cause mortality) to model estimated patterns of OC use in terms of age of starting and duration of use in the general population, we found that:
  - The net effect of OC use on these outcomes was to extend mean life expectancy by approximately 1 month, which is consistent with other cancer prevention strategies in the general population.[376]
  - Modeling the association between OC use and ovarian cancer as a function of duration of use, and between OC use and breast cancer as a function of time since last use, resulted in slightly greater gains in life expectancy compared with modeling these results as a function of ever versus never use, due to a greater reduction in ovarian cancer incidence combined with a lower increase in breast cancer incidence when compared with a model where OC effects were solely based on ever versus never use.
  - Incorporating the joint effects of duration of use and time since last use decreased the population-level effects of OC use on ovarian cancer incidence and overall mortality slightly compared with duration of use alone, but higher than a simple ever/never model.
  - The largest population effect of OC use on incidence of benefits was on colorectal and endometrial cancers rather than ovarian cancers, while reductions in mortality were similar across all three cancers. The largest effect of OC use on both incidence and mortality due to increased risk was seen in breast cancer.
  - For all harms, increases in mortality were much smaller than increases in incidence (and, in some simulations, actually lower with OC use), likely due to a shift in incidence to younger ages, when age-specific mortality from all harms (including cancer) is lower.
  - Assuming a pattern of use similar to the general population, estimated increases in life expectancy were greatest for BRCA1 carriers (approximately 10 months), due to the much higher incidence of ovarian cancer. Estimates for BRCA2 carriers

were approximately equivalent to those for the general population, due to the much larger increase in breast cancer risk relative to the increased ovarian cancer risk.
- o Directly modeling ever versus never use results in larger positive effects of OCs compared with alternative methods to simulate lower exposure to OC use.
- When age at first OC use and duration of use were systematically varied, we found that:
  - o Estimates of the effect on life expectancy were positive for durations of use of 2 years or less and positive for women under age 35 for 5 years of use. Longer duration of use led to either lower life expectancy (women 30 and older) or smaller increases in life expectancy for all except women who started at age 15.
  - o Estimates for both incidence and mortality for harms (particularly vascular events) were unstable for shorter duration of use across all ages, converging with increasing duration; this is a function of the very low probability of events at younger ages and the assumption of constant risk during use.
  - o The total reduction in ovarian, colorectal, and endometrial cancer incidence and mortality was directly related to increased duration, which is largely due to the explicitly modeled association between duration and ovarian cancer incidence.
- Using a probabilistic analysis incorporating the range of uncertainty around the relative risk estimates, we found that:
  - o When the association between OC use and ovarian cancer risk was modeled as a function of duration of use, 45 percent of simulations resulted in a life expectancy gain of 1 and 2 months, while 44 percent resulted in gains of 2 to 3 months. When modeled as a function of ever versus never use, 62 percent of gains were between 1 and 2 months, while only 1 percent was greater than 2 months; 2 percent had a net loss of life expectancy of 1 week.
  - o For incident harms, breast cancer was the largest contributor. Conversely, for incident benefits, ovarian cancer had almost no effect relative to colorectal and endometrial cancers.
  - o For mortality, breast cancer was by far the biggest contributor to uncertainty; removing deaths from vascular events had minimal effect. On the benefit side, the contributions of ovarian, colorectal, and endometrial cancers were roughly equivalent.

Comparison With Previous Modeling Studies

Comparison of the results of the individual meta-analyses with other studies is provided in previous sections of this report. In general, our results were largely consistent with the recent literature, with most of the difference attributable to different inclusion/exclusion criteria.

Our modeling results are roughly consistent with previous U.S.-based studies, which have generally found minimal harms and small-to-moderate net noncontraceptive benefits of OC use—although our overall estimate suggests somewhat larger net benefits, especially in terms of mortality. We briefly describe the main differences in outcomes and approach here.

Fortney et al.[351] used a life table approach to estimate net effects on life expectancy, assuming 5 years of use and varying age at first use from 15 to 44 years of age in 5-year increments, and concluded that there was essentially no net effect, with gains of 4 days for women under age 0, and losses of 18 days for women in their 30s up to 80 days for women over age 45. In contrast, we found an overall net increase of 1 to 2 months across all age groups. The following are possible reasons for this discrepancy:

- The paper by Fortney et al. was published in 1986, so we were able to include subsequently published papers. We also used a more formal set of inclusion/exclusion criteria; the authors excluded a condition if there were less than two papers with a significant association, which eliminated breast cancer for consideration, and used formal meta-analysis methods to synthesize the results.
- Fortney et al. did not include breast or colorectal cancer, DVT, or PE, but did include complications of pregnancy, benign gallbladder disease, pelvic inflammatory disease, and rheumatoid arthritis.
- We used different methods for estimating incidence. Although the baseline estimates presented in Table 1 of the paper are reported as those for women not using OCs, it is unclear from either the table or the paper whether these results were adjusted for the prevalence of OC use or simply the overall rates that were subsequently multiplied by the relative risk estimate. Given the high prevalence of a history of OC use, population-based rates—which are the weighted average of the rates in exposed and unexposed—will be much closer to the rates in ever users compared with never users, all else (such as a history of smoking or an inherited thrombophilia) being equal. Thus, simply multiplying the population rate by the relative risk will overestimate the magnitude of the effect of the exposure in users. We estimated expected incidence based both relative risk and prevalence of exposure.
- We modeled competing risks.
- Fortney et al. applied relative risks derived from incidence to mortality. As shown in our results, the increase in mortality for a given outcome resulting from increased incidence in younger ages attributable to OC use may not result in equivalent increases in mortality because of the effect of age on outcome-specific mortality.

Schlesselman[66] used meta-analytic methods to estimate relative risks related to duration of use and time since last use and applied these estimates using life-table methods and durations of use of 4, 8, and 12 years to estimate the effect of OCs on ovarian, endometrial, cervical, breast, and liver cancers for women 20 to 54 years of age. The estimated mean number of breast and cervical cancers per 100,000 were similar to ours, but the estimates for ovarian and endometrial cancers were significantly lower.

Differences in approach include:

- As with the paper by Fortney et al., we were able to include papers published subsequent to this 1995 analysis. It is also possible that there were differences in inclusion/exclusion criteria and potential differences in the meta-analytic approach, although this is difficult to ascertain from the paper.
- Schlesselman included estimates of duration of use and time since last use effects for all cancers; we included only those which were statistically significant in the meta-analysis (duration for ovarian cancer, time since last use for breast cancer). As seen in our analysis, this had a noticeable effect on outcomes, and, accumulated across multiple cancers, could result in even greater difference.
- We used a different time horizon of 10 to 100 years compared with Schlesselman's 20 to 54 year range. Depending on the size of any effect of time since last use, this could have a substantial effect. This is likely one of the reasons for the similar results for cervical and breast cancers, which have higher incidences when women are in their 40s and 50s compared with ovarian and endometrial cancers.
- We included different nonreproductive cancers. Schlesselman included liver cancer, which is much less common than colorectal cancer; our analysis shows that a protective effect against colorectal cancer would have a marked impact on overall benefits. It is not clear from the paper how competing risks were modeled.

Sonnenberg et al.[350] used a Monte Carlo simulation model to estimate the cost-effectiveness, in dollars per QALY, for a wide range of contraceptive methods. Although the modeling approach is similar to the one we used, the results cannot be directly compared primarily because the results are presented as net effects in terms of QALYs without estimates of individual event rates. The following are other differences:

- Sonnenberg et al. included contraceptive effects, and other contraceptive methods, some of which were assumed to have similar vascular effects as OCs.
- We included papers published subsequent to this 2000 analysis, used different inclusion/exclusion criteria, and used formal meta-analytic methods to derive risk estimates.
- Sonnenberg et al. adjusted for smoking prevalence and the potential interaction between smoking and OC use on relevant outcomes
- They did not include effects on colorectal cancer.
- Data are not provided on the ranges and distributions used in the Monte Carlo simulation.
- The time horizon was very short, only 2 to 5 years, and did not extend past age 50.

Limitations and Uncertainties

The single most important limitation of this analysis is that it is "synthetic"—it is a synthesis of observational data using statistical and mathematical modeling techniques, rather than a directly observed controlled trial designed to minimize potential biases and optimized to detect a clinically significant effect. Women who use OCs are likely to be different from women who never use OCs in a variety of ways that may affect estimates of the association between OCs and a given outcome. For example, concerns about an increased risk for vascular events among obese women may make providers less likely to prescribe oral contraceptives; to the extent that obesity is associated with increased risk for many cancers, this would lead to an overestimation of a protective effect or an underestimation of an increased risk. Although the effect of these differences on the estimate can be mitigated by appropriate study design and analytic methods, they cannot be eliminated.

The majority of evidence we identified was consistent in both direction and magnitude of effect size, showed some evidence of a duration relationship and was adjusted for known confounders. However, this was also the case for hormone replacement therapy as primary prevention for cardiovascular disease. When synthesized into high-quality models, the results strongly suggested a beneficial effect for most women,[377,378] which were subsequently disproven by a randomized trial.[379]

For most women who are considering OCs for contraception, or who have OCs recommended for indications for which there is strong evidence of effectiveness, the lack of RCT data on OCs and potentially fatal outcomes is important, especially if an increased baseline risk of a particular outcome would affect the decision whether or not to use OCs. Given recent evidence on the comparative effectiveness of OCs and long-acting, reversible contraceptives in terms of pregnancy prevention,[380] consideration of the noncontraceptive benefits and harms of OC use relative to other contraceptive methods may become an even greater factor for helping women choose appropriate contraceptive methods. However, quite appropriately, the ultimate decision about using OCs for contraception or as treatment for other conditions should primarily be based on consideration of evidence for their effectiveness for *that indication*, weighed against the potential harms and other relevant attributes (convenience, duration of effectiveness, etc.).

The considerations are somewhat different when the question being considered is whether to recommend OCs primarily to prevent ovarian cancer; here, the potential for bias in the estimates of both benefits and harms also is particularly critical. As noted in the introduction, ovarian cancer has a high mortality rate; there are no effective screening interventions (and, given the biology of the disease, the prospect of effective screening for most women is poor); and surgical removal of the tubes and ovaries carries risks of operative morbidity and the potential effects of early menopause. (We note that the observed reduction in OC risk with tubal ligation is roughly equivalent to that seen with OC use, even with adjustment of OC use among women with tubal ligation—further evaluation of the potential role of tubal ligation as primary prevention for ovarian cancer for women who have completed childbearing is an important area for future research). Approximately 15 percent of women have never used OCs by age 44,[172] and based on the distribution reported in the Nurses' Health Study,[357] another 10 percent of users have taken OCs for less than 12 months. Given the high mortality of ovarian cancer and the lack of proven alternative strategies for prevention that do not involve removal of the ovaries, a course of OCs as primary prevention is potentially a reasonable strategy but one which warrants further research. Even without the potential for biased estimates from the observational studies in the review, the modeling results indicate substantial remaining uncertainty about the balance of harms and benefits of OC use solely for the prevention of ovarian cancer.

Despite the desirability of an unbiased estimate of risk, a formal prospective trial would face numerous, perhaps insurmountable, challenges, as described below.

Sample size and duration of followup, particularly if ovarian cancer is the primary outcome. For example, in a trial targeting women aged 35 to 39 for prevention of ovarian cancer incidence, the expected incidence ovarian cancer by age 55 would be 0.2 percent; assuming a 70-percent reduction in incidence, a trial would require 20 years of followup of over 70,000 subjects *per arm* using an alpha of 0.05 and a beta of 0.2. For mortality to be the endpoint, the trial would need to be extended an additional 5 years. Even if endometrial and colorectal cancer were added as trial outcomes, sample sizes would be over 5,000 per arm for a 20-year study to detect differences in incidence and 25,000 for a 25-year study to detect differences in mortality. None

of these estimates includes correction for loss to followup or hysterectomy or oophorectomy for other causes.

Although alternative statistical analyses or composite outcomes might reduce sample size somewhat, a trial of OCs versus placebo or another method would still require, at the very least, a similar sample size to the Women's Health Initiative with at least twice the length of followup. Maintaining followup in a study of that size for that duration would be challenging, to say the least. Another issue with a study of such long duration would be the inherent problem of applicability: by the time the study was done, alternative methods of contraception (including OC formulations) may well be available and preferred to the formulations tested in the trial.

Recruitment and inclusion/exclusion criteria. In addition to the normal difficulties of recruitment, a substantial proportion of women who are either never users of OCs or used OCs for less than 12 months would be women who had medical contraindications, religious or other objections to OC use, or who stopped OC use because of side effects. Recruitment is always an issue for any randomized trial; one that uses a daily oral medication with known side effects and potential serious short- and long-term harms for primary prevention of a relatively rare cancer would face more difficulty than usual.

Choice of comparator. For reproductive-age women not using another contraceptive method, placebo alone would not be acceptable, further complicating trial logistics if women in both arms would be required to use an alternative contraceptive method. If some of those methods are also effective against ovarian cancer, or increase risk of vascular events, sample size would need to be increased even more. Given the recognizable effects of OCs on menstrual symptoms, blinding would be difficult.

Safety monitoring. The Women's Health Initiative used a complex composite endpoint that included both benefits and harms; a trial of OCs for primary prevention of ovarian cancer would likely require a similar design. However, establishing appropriate safety monitoring, particularly rules for stopping, would be even more complex since the majority of the vascular harms would occur during treatment, while benefits would not be seen for 15 to 25 years.

These daunting challenges create a dilemma. Ovarian cancer is a disease with high mortality where both the disease itself and the treatments have a profound negative impact on quality-of-life in the time between diagnosis and death—and there are no effective preventive strategies. On one hand, the current evidence, while highly suggestive, has inherent limitations that may be leading to incorrect estimates of OC effectiveness. Even ignoring those limitations, there is a high degree of remaining uncertainty about harm/benefit tradeoffs. Future research to fill in the evidence gaps discussed below should improve the ability of researchers to synthesize the available evidence from observational studies, but ultimately the inherent biases associated with observational studies means that some uncertainty will remain even if all the evidence gaps related to observational studies are filled. On the other hand, a definitive trial to address the question would be, in the best-case scenario, hugely expensive and complex. One option might be a trial in a high-risk population, such as BRCA1 and BRCA 2 carriers, where higher incidence rates would substantially reduce sample size. However, there are different challenges with a study in this population, particularly the choice of appropriate comparator; given the known high risk of these conditions and the availability of other treatment options, a placebo-controlled study might face substantial recruitment challenges, and, without a placebo group, it would be very difficult to draw any inferences about the potential applicability of results in BRCA carriers to the general population.

One important next step in developing a research agenda is to formally identify the situations where a decision to start or continue OCs would be done primarily for the purpose of preventing ovarian cancer (and potentially other cancers) and assess how much certainty would be required to make a recommendation for or against this use. One potential future application of the microsimulation model developed for this review is to address some of these issues quantitatively, to help determine the ultimate feasibility of a definitive trial. A first step might be to apply value-of-information analysis to further quantitate the relative contribution of the uncertainties about the tradeoffs between harms and benefits and evaluate the efficiency of potential study designs and sample sizes.[381-383]

Model Limitations and Evidence Gaps

The limitations of the model and its results can be divided into limitations of the model *structure*—the type of model, the methods for converting the available literature into probabilities that the model can use, the assumptions about the relationship between different parameters, the methods for analysis—and of the model *parameters*, which derive from the availability and quality of the data. Because both of these types of limitations are ultimately driven by the data, we discuss how future research can address these limitations in each section.

Model Structure Limitations

Design

We used a semi-Markov state-transition model, which reflects current practice. Instead of running the model as a cohort analysis, where the model provided estimates of the probability of the events of interest based on the parameter values, we ran the model as a microsimulation, where multiple simulations of a series of "individual" subjects with characteristics drawn from appropriate distributions are performed. The main advantage of this approach is that the conditional probability of a transition from one state to another can be conditioned on the underlying state, the time spent in the simulation, and events in past states in a tractable model structure. The main disadvantage is the computational time required to perform the simulations. Some of this time may be due to the specific software package used, which we chose primarily for its ease of programming; using an alternative program would increase the efficiency of calculations, but would be more difficult to program. Because of the computational time required for some of the analyses, we limited the number of "subjects" for a particular analysis (for example, 5000 per each age at first use and duration of use combination). This resulted in unstable results, especially for rare events. However, even this limitation is helpful, since it reinforces the importance of adequate sample size in achieving stable estimates of rare events, which certainly fits the description of vascular events in young women. More iterations would narrow the confidence intervals for the model-based estimates further—but it is worth considering that if the effect size is small enough to require a very large number of simulations, the individual clinical risk, and public health impact, is likely to be relatively small.

Independence of Risks

We assumed that the risk estimates obtained from the meta-analyses, most of which were derived from individual studies with multivariate analyses, were independent of each other—in other words, the estimate for the relative risk for ovarian cancer associated with OC use was independent of any other patient characteristics, such as parity. However, this may not be the case. This may be particularly important for hysterectomy, which is a competing risk for ovarian,

cervical, and endometrial cancer, and which may be affected by OC use. We also modeled individual cancer risks independently, but this is clearly not the case, for both familial cancer syndromes and sporadic cancers, which may share risk factors. Ideally, the model would be run using parameter estimates that incorporated correlations where appropriate.

The model-predicted lifetime incidence for cancers, adjusted for population-level estimates of OC use and relative risks estimated from the meta-analyses, closely approximates estimates based directly on age-specific incidence (Appendix F), which provides some reassurance that the assumption of independence is not resulting in substantial bias.

Other States and Other Contraceptive Methods

We originally included other relevant health states, including menarche and pregnancy, and the range of other contraceptive methods with their effectiveness against pregnancy. For the purposes of this analysis, we excluded these states and other methods for several reasons. First, there is a lack of data on the dynamics of contraceptive method switching; because the majority of the data on OC use and the outcomes of interest was based on comparisons between OC users and all other methods combined, the assumptions and extra work required to derive reasonable estimates would not have added any extra reliability or precision to our analysis.

Second, during early model runs, it became apparent that pregnancy was also a potential competing risk, one which had different probabilities based on age and contraceptive method. Because parity was almost universally adjusted for in the studies included in the meta-analyses, we elected to eliminate pregnancy as a state. However, for a more comprehensive analysis of the combined harms and benefits of OCs, adding pregnancy (including pregnancy-specific vascular event rates) is an important next step. Including other reproductive states, such as menarche and lactation, would also allow modeling the effect of reduction in ovulation, rather than OC use alone, as a modifier of ovarian cancer risk. However, incorporating these into the model will be facilitated by more standardized reporting, as discussed further below.

Finally, the model, which estimates mortality based on age- and race-specific survival after detection of an incidence case, consistently underestimates lifetime mortality risk compared with estimates derived from death certificate data. This is consistent with other "incidence-based mortality" models, where overall mortality estimates are derived from specific survival functions based on patient or tumor characteristics.[384,385] There are multiple explanations for this, including (1) the effect of competing risks for other cause mortality within the model after diagnosis, (2) age/period/cohort effects in the death certificate data that are not reflected in the model estimates, (3) the fact that SEER incidence and survival data represent a sample of the population, while the mortality data are derived from the entire population, and (4) inadequate modeling of mortality more than 5 years after survival (particularly for breast cancer). Since the potential underestimation of cancer mortality affects both potential harms of OC use (breast and cervical cancer) and benefits (ovarian, endometrial, and colorectal), the net effect on the overall balance of mortality harm and benefit is likely to be small but is clearly worthy of further exploration.

Other Potential Confounders and Effect Modifiers

We did not model the potential effect of other characteristics, particularly smoking and obesity, which could plausibly affect contraceptive method choice, risk of different cancers or vascular events, or the association between OC use and these outcomes. The potential impact of smoking status and obesity on estimated risks, both at the individual patient level and at the population level, should be incorporated in future modeling studies.

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Ever Versus Never Exposure Versus Time-Dependent Effects

Although the qualitative results were similar whether ovarian and breast cancer risks were modeled as ever/never exposure versus time dependent, the time-dependent approach resulted in better outcomes (greater life expectancy, lower threshold for acceptable harm/benefit ratios), suggesting that how exposure is modeled (and, implicitly, how exposure is measured in studies) could have a more substantial impact on model predictions if it held for additional outcomes. Conversely, because the increased risk of vascular events during current OC use was assumed to be constant over time, longer duration of OC use resulted in greater risk of a vascular event. If, as some of the studies reviewed suggest, risk is highest in early use, then this assumption overestimates the harms associated with longer duration.

Model Structure Evidence Gaps

The following are key future research needs for a model structure:
- Needed are better estimates of correlations between parameters; for example, using the covariate estimates from logistic regression models derived from pooled analyses for all relevant variables instead of the adjusted odds ratios. This would require publication (perhaps in an online appendix), or access to, the actual models used rather than the summary odds ratios and confidence limits typically reported.
- One advantage of microsimulation is that it can generate simulated data sets of individuals, with characteristics such as age of events, history of past events, and so on. These data sets could be used to explore some of these issues related to correlation as well as issues related to study design, sample size, etc. For example, one could simulate a large number of individuals using a fixed estimate of relative risk, then sample the data set using different study designs and sample sizes to identify any systematic effects on bias or precision.
- Incorporate additional reproductive history into models; again, use of simulated data sets could be helpful in exploring the relationship between ovulatory cycles, OC use, and ovarian cancer risk.
- To the extent possible, observational studies should report associations as functions both of ever versus never, or current versus noncurrent use, and duration of use. Pooled analyses, such as those of the Collaborative Group on Epidemiological Studies of Ovarian Cancer,[21] are an excellent way to address some of these limitations. Although access to the raw data is extremely useful, the ability to overcome inconsistencies in reporting is ultimately dependent on how consistently the data was collected. As noted below, some standardization of how duration of use and other potentially relevant parameters are both recorded and reported would also be extremely helpful.

Model Parameter Limitations

Data Reporting/Quality

Data limitations for specific outcomes are noted in the individual sections, but there are general issues that apply to most of the data, particularly for the risk data.

Imprecision and bias. Using a stochastic modeling approach—where data values are drawn from appropriate distributions describing the data—is one way to incorporate the effects of imprecision in estimates resulting from small studies, particularly for rare events, since the effects of the imprecision in the input values are reflected in the distribution of output values. However, even the most precise estimates are not helpful if they are biased in some way;

although models can potentially be used to evaluate a possible effect of bias, and to potentially correct for it, there are no clear standards for this.

Data structure. One limitation common to many simulations where age is an important factor affecting probabilities is that available data on age-specific event probabilities are cross-sectional and may represent cohort effects that are not captured in the model. As the figures in Section 1 show, there is some suggestion of a cohort effect in ovarian cancer incidence due to increasing use of OCs; if this is the case, then the reduction in risk predicted by any model that uses these data to generate age-specific probabilities will overestimate the impact of OC use in the future. Some of this effect may also be seen even with harms from vascular events—for example, age-specific probabilities may decrease with time, as awareness of the possibility of complications leads to more selective use of OCs, or increase with time, especially for less severe cases, where a higher index of suspicion on the part of clinicians would lead to a lower threshold for testing to make a definitive diagnosis.

Inconsistency in reporting. As noted in the individual sections, there was wide disparity in how various potential confounders or effect modifiers, such as parity, duration of OC use, time since last use, woman's age, etc., were described in published papers. While we recognize that the needs of specific studies or the idiosyncrasies of particular data sets may require different categorization of relevant parameters during analysis, it would be extremely helpful for meta-analysis and simulation modeling if there were reporting standards that allowed consistent comparison across studies, which could be presented as an alternate to the categorization selected for the main analysis. Again, this could be presented online.

Data Choices and Available Data

There were minimal data available for some important potential parameters. For others, available data sources may have inherent biases that affect the model.

Data Sources. We used hospitalization rates, and in-hospital mortality, to derive age-specific probabilities of vascular events. To the extent that these outcomes, in particular DVT, may be managed on an outpatient basis, this will underestimate the rates. Similarly, hysterectomy is increasingly being performed in outpatient settings, and hospital-based data may underestimate true population rates. Use of in-hospital mortality may underestimate longer term mortality due to vascular events, although, to the extent the risk of recurrence is reduced by stopping pills, long-term mortality after OC-associated vascular events may be lower than after events associated with other causes. For cancers, we assumed cure after 5 years and did not incorporate the risk of longer term recurrence, which may underestimate total mortality, particularly for breast cancer.

Utilities/Preferences. Quality-adjusted life expectancy is a generally well-accepted method among health policy researchers for integrating the effects of interventions on both quality-of-life and life expectancy. Although estimates for utilities for all of the relevant outcomes were available, we did not identify any utilities for the use of OCs. The studies that incorporated QALYs in their analyses implicitly assumed that OC use has a utility of 1.0; given that a substantial proportion of women who start OCs discontinue due to side effects, this is clearly not the case.

On the other hand, many women may have improvement in quality of life because of OC effects on menstrual symptoms. Some estimate of the effect of OC use on quality of life in the context of use for prevention purposes is needed. Although groups making recommendations typically focus on a semiquantitative assessment of harms versus benefits with some consideration of quality of life, appropriately capturing patient preferences is especially

important for primary prevention. Our acceptability analysis shows that the different harms and benefits contribute differently to incidence (where quality of life is a major factor) compared with mortality. Given that vascular events contribute much more to incidence than mortality (because of the lower age-specific mortality), the potential impact of long-term morbidity from stroke and MI, in particular, should ultimately be considered.

Another factor that needs to be incorporated in any preference/quality-of-life study is time preference. In the setting of OCs for primary prevention of cancer, the benefits occur much later in the future than the potential risks. Deriving empirically-driven discount rates is an important component of future research.

Progestin-only pills. Because the risk of vascular events appears to primarily be related to the estrogen component of combined OCs (Section 4), and because there is evidence from both basic science[170] and observational studies (Section 2) that the progestational component of OCs is the primary factor affecting reduction in ovarian cancer risk, use of progestin-only pills as the OC of choice for reducing OC risk seems attractive. However, largely because there is little use of progestin-only pills, there is a paucity of evidence regarding their effects, particularly on long-term outcomes.

Other patterns of use. Although there is no biological reason to suspect that continuous OC use (i.e., no week without pills to allow menses) would have differential effects on any of these outcomes, data to confirm this would be useful. In addition, more data on both the frequency of use and the outcomes of use for OCs in women over 45 would be extremely helpful.

Model Parameters Evidence Gaps

The following evidence gaps for model parameters should be addressed:

- Consensus among researchers and editors on standardized reporting of key variables would be extremely helpful. One approach would be through the development of consensus data collection and reporting standards under the sponsorship of one or more organizations with an interest in the area, such as the American Cancer Society, NIH, WHO, etc.
- More precise estimates of longer term outcomes are needed.
- Patient preferences for relevant outcomes, as well as for the use of OCs, need to be incorporated into models used for estimating the outcomes of OC use. Ideally, these would include both utilities derived from standard methods of utility elicitation, as well as by methods such as conjoint analysis which allow elicitation of preferences for multiple attributes.[386]
- More data are needed on the potential effects of progestin-only pills on long-term outcomes. However, given our findings that vascular events make a minimal contribution to the harm/benefit ratio in terms of mortality, the value of further research into the potential of progestin-only pills for primary prevention should be assessed first. This could be facilitated by better data on the long-term quality-of-life impact of vascular events in young women.

Potential Next Steps

Although we did not perform a formal value-of-information analysis, the results of our evidence synthesis and modeling do suggest that addressing certain research needs first would have a greater impact in reducing uncertainty about the relative harms and benefits of OCs for

primary prevention of ovarian cancer. Within the context of specific issues discussed above, we would suggest the following broad areas be given priority.

Assessing patient preferences, including those related to regular use of OCs for noncontraceptive purposes. Given the finding that vascular events contribute little to uncertainty about the harm/benefit ratio in terms of mortality, a better understanding of how long-term morbidity associated with these events in younger women, would be extremely helpful. This research area also has the advantage of requiring considerably fewer resources than, for example, a 20-year randomized trial of more than 140,000 subjects.

Achieving greater certainty about the importance of time-related effects relative to ever-never exposure. This could be facilitated by consensus on reporting standards. In terms of cancers, we would suggest prioritizing colorectal cancer and breast cancer because (a) there is greater certainty regarding the time-dependent effects of ovarian cancer, (b) although endometrial cancer is an important contributor to the mortality harm/benefit ratio, there is less uncertainty about the benefits of OC use, and (c) increased cervical cancer risk has almost no contribution to the overall mortality risk (note that this is not likely to be true in settings where adequate screening, or widespread population coverage with vaccination against oncogenic human papillomavirus, is unavailable). In terms of vascular events, the most important uncertainty is the extent to which risk may or may not decrease with increasing duration of use.

Another need is for better understanding of the potential effects of OC formulation on breast and colorectal cancer risks. Again, these two contribute substantially to the harm/benefit ratio in terms of mortality. Particularly in the context of the potential use of progestin-only pills, greater certainty about the potential effects relative to combination OCs on these two cancers would be particularly helpful.

Clinical and Public Health Implications of the Findings

The overall strength of evidence for the literature review was moderate to low with applicability for current practice affected by two major factors. First, there was a large number of studies (many of higher quality) performed outside of the United States, where several differences may affect observed associations—differences in available OC formulations; in population patterns of contraceptive use; in genetic factors (e.g., inherited thrombophilias) and acquired factors (e.g., prevalence of smoking) that interact with OC effects; and in health system attributes, particularly regarding population coverage for screen-detectable cancers. Second, particularly for cancers, the long period between exposure to OCs and development of the cancer means that much of the available literature is based on exposure to OC formulations that are no longer on the market—which has implications for both harms and benefits.

Although there are published guidelines for assessing the quality of modeling studies,[387] there is no consensus on how to consider the "strength of evidence" of the results of modeling studies. In most cases, modeling is done because randomized trials are not available and, even in the best-case scenario, will be based on evidence from lesser quality studies. Given the inherent limitations of modeling, many of which are discussed above and in Appendix F, the strength of evidence for even the most sophisticated model will be at best moderate and, realistically, low in most cases. That is certainly the case with these results, which are based on low-moderate quality evidence for the most important parameters of interest.

With these caveats, based on our synthesis of the best available literature, the clinical and public health implications of our review include the following:

- Assuming that the general estimates of increased or decreased risk are not overly biased by observational studies, the net effects on cancers and vascular events of current patterns of OC use in the general population likely result in a net increase in life expectancy of 1-2 months, which is comparable to many other preventive interventions.[376] This is in addition to any effects from prevention of unwanted pregnancy. In our probabilistic analysis, OC use resulted in net loss in life expectancy in less than 5 percent of simulations.
- The model predicts similar net gains in BRCA1 and BRCA2 carriers; in BRCA1 carriers, who have marked elevation in ovarian cancer risk, the gain may be as high as 10 months.
- These results should be reassuring to women who are considering OC use for contraceptive purposes or who are prescribed OCs for treatment of other conditions.
- Other than for ovarian cancer, the effects of increasing duration of use for individual outcomes is unclear. The modeling results suggest that the net benefits of OC use decrease between 5 years of use (the approximate mean duration of use in the population) when they are generally positive, especially at younger ages, and 10 years of use for all but the youngest women. This may be a function of a conservative assumption about constant risk over time for exposed women, but based on the available data, there is less confidence in the net benefits of duration of use longer than 5 years for women at average risk of ovarian cancer. For a woman who has used OCs for 5 years and is considering other contraceptive methods, there is insufficient evidence to suggest continuing to use OCs solely for their effect on ovarian cancer risk—particularly since there is consistent evidence that at least one other method (tubal sterilization) reduces risk by a similar order of magnitude and recent evidence that other nonpermanent methods may also reduce risk.[123]
- For a woman who has never used OCs for contraception, and who otherwise does not have a contraindication to their use, there is insufficient evidence to recommend for or against a course of OCs solely for ovarian cancer prevention, regardless of her age or the potential duration of use. The estimated net benefits of OC use on mortality are equally distributed between prevention of ovarian cancer (relatively low incidence but high mortality), colorectal cancer (intermediate incidence and mortality), and endometrial cancer (high incidence but low mortality), while the net harms are driven by breast cancer (high incidence but relatively low mortality). In terms of incidence, the net benefits of OC use are largely driven by endometrial and colorectal cancer, while the net harms are largely due to the increased incidence of breast cancer. We did not include the potential impact of specific harms on quality of life—for example, a stroke at an early age, even if less likely to be fatal, may have a profound negative impact on quality of life.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
BRCA	breast cancer genetic mutation
BSO	bilateral salpingo-oophorectomy
BTL	bilateral tubal ligation
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DMV	Department of Motor Vehicles
DVT	deep venous thrombosis
ER	estrogen receptor
FIGO	International Federation of Gynecology and Obstetrics
GCT	granulosa cell tumor
HPV	human papilloma virus
HR	hazard ratio
HRT	hormone replacement therapy
IRR	incidence rate ratio
IUD	intrauterine device
KQ	Key Question
MI	myocardial infarction
mo	month/months
NA	not applicable
NCHS	National Center for Health Statistics
NHB	net health benefits
NIS	Nationwide Inpatient Sample
NMB	net monetary benefits
NNH	number needed to harm
NNP	number needed to prevent
NR	not reported
NS	nonsignificant
NSFG	National Survey of Family Growth
NZ	New Zealand
OC	oral contraceptive
OR	odds ratio
PE	pulmonary embolism
PICOTS	population, interventions, comparators, outcomes, timing, settings
PR	progesterone receptor
QALY	quality-adjusted life year
RR	risk ratio
SEER	Surveillance, Epidemiology, and End Results registry
SOE	strength of evidence
TEP	Technical Expert Panel
UK	United Kingdom
VTE	venous thromboembolism

WHO	World Health Organization
WTP	willingness to pay
yr	year/years

Appendix A. Exact Search Strings

PubMed® search strategy (June 29, 2012)

(((("contraceptive agents, female"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields] AND "female"[All Fields]) OR "female contraceptive agents"[All Fields] OR ("female"[All Fields] AND "contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents, female"[Pharmacological Action]) OR ("contraceptives, oral"[MeSH Terms] OR ("contraceptives"[All Fields] AND "oral"[All Fields]) OR "oral contraceptives"[All Fields] OR ("oral"[All Fields] AND "contraceptives"[All Fields]) OR "contraceptives, oral"[Pharmacological Action])) AND (("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields]) OR ("granulosa cell tumour"[All Fields] OR "granulosa cell tumor"[MeSH Terms] OR ("granulosa"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields]) OR "granulosa cell tumor"[All Fields]) OR ("luteoma"[MeSH Terms] OR "luteoma"[All Fields]) OR ("meigs syndrome"[MeSH Terms] OR ("meigs"[All Fields] AND "syndrome"[All Fields]) OR "meigs syndrome"[All Fields]) OR ("sertoli leydig cell tumour"[All Fields] OR "sertoli-leydig cell tumor"[MeSH Terms] OR ("sertoli-leydig"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields]) OR "sertoli-leydig cell tumor"[All Fields] OR ("sertoli"[All Fields] AND "leydig"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields]) OR "sertoli leydig cell tumor"[All Fields] OR "Sertoli-Leydig Cell Tumor"[MeSH Terms] OR ("Sertoli-Leydig"[All Fields] AND "Cell"[All Fields] AND "Tumor"[All Fields]) OR "Sertoli-Leydig Cell Tumor"[All Fields] OR ("sertoli"[All Fields] AND "leydig"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields]) OR "sertoli leydig cell tumor"[All Fields] OR "Sertoli Leydig Cell Tumor"[MeSH Terms] OR ("Sertoli"[All Fields] AND "Leydig"[All Fields] AND "Cell"[All Fields] AND "Tumor"[All Fields]) OR "Sertoli Leydig Cell Tumor"[All Fields] OR ("sertoli"[All Fields] AND "leydig"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields])) OR ("thecoma"[MeSH Terms] OR "thecoma"[All Fields]) OR "ovarian cysts"[MeSH Terms:noexp] OR ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) OR ("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields] OR ("deep"[All Fields] AND "vein"[All Fields] AND "thrombosis"[All Fields]) OR "deep vein thrombosis"[All Fields]) OR DVT[All Fields] OR ("budd-chiari syndrome"[MeSH Terms] OR ("budd-chiari"[All Fields] AND "syndrome"[All Fields]) OR "budd-chiari syndrome"[All Fields] OR ("budd"[All Fields] AND "chiari"[All Fields] AND "syndrome"[All Fields]) OR "budd chiari syndrome"[All Fields]) OR ("retinal vein occlusion"[MeSH Terms] OR ("retinal"[All Fields] AND "vein"[All Fields] AND "occlusion"[All Fields]) OR "retinal vein occlusion"[All Fields]) OR ("thrombophlebitis"[MeSH Terms] OR "thrombophlebitis"[All Fields]) OR ("venous thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "venous thromboembolism"[All Fields]) OR (("veins"[MeSH Terms] OR "veins"[All Fields] OR "venous"[All Fields]) AND ("thromboembolism"[MeSH Terms] OR "thromboembolism"[All Fields] OR ("thromboembolic"[All Fields] AND "event"[All Fields]) OR "thromboembolic event"[All Fields])) OR VTE[All Fields] OR ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR ((("brain"[MeSH Terms] OR "brain"[All Fields]) OR ("cerebrum"[MeSH Terms] OR "cerebrum"[All Fields] OR "cerebral"[All Fields] OR "brain"[MeSH Terms] OR "brain"[All Fields])) AND (("infarction"[MeSH Terms] OR "infarction"[All Fields]) OR ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields]) OR ("embolism"[MeSH Terms] OR "embolism"[All Fields]) OR ("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields]))) OR ("meningioma"[MeSH Terms] OR "meningioma"[All Fields]) OR ("melanoma"[MeSH Terms] OR "melanoma"[All Fields]) OR ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) OR ("uterine neoplasms"[MeSH Terms] OR ("uterine"[All Fields] AND "neoplasms"[All Fields]) OR "uterine neoplasms"[All Fields]) OR ("uterine cervical neoplasms"[MeSH Terms] OR ("uterine"[All Fields] AND "cervical"[All Fields] AND "neoplasms"[All Fields]) OR "uterine cervical neoplasms"[All Fields] OR ("cervical"[All Fields] AND "cancer"[All Fields]) OR "cervical cancer"[All Fields]) OR ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrial"[All Fields] AND "cancer"[All Fields]))

OR "endometrial cancer"[All Fields]) OR ("endometriosis"[MeSH Terms] OR "endometriosis"[All Fields]) OR ("endometrial hyperplasia"[MeSH Terms] OR ("endometrial"[All Fields] AND "hyperplasia"[All Fields]) OR "endometrial hyperplasia"[All Fields]) OR ("metrorrhagia"[MeSH Terms] OR "metrorrhagia"[All Fields] OR ("dysfunctional"[All Fields] AND "uterine"[All Fields] AND "bleeding"[All Fields]) OR "dysfunctional uterine bleeding"[All Fields]) OR ("metrorrhagia"[MeSH Terms] OR "metrorrhagia"[All Fields]) OR ("menorrhagia"[MeSH Terms] OR "menorrhagia"[All Fields]) OR ("hypermenorrhoea"[All Fields] OR "menorrhagia"[MeSH Terms] OR "menorrhagia"[All Fields] OR "hypermenorrhea"[All Fields]) OR ("menstruation disturbances"[MeSH Terms] OR ("menstruation"[All Fields] AND "disturbances"[All Fields]) OR "menstruation disturbances"[All Fields]) OR ("amenorrhoea"[All Fields] OR "amenorrhea"[MeSH Terms] OR "amenorrhea"[All Fields]) OR ("dysmenorrhoea"[All Fields] OR "dysmenorrhea"[MeSH Terms] OR "dysmenorrhea"[All Fields]) OR "painful menstruation"[All Fields] OR "menstrual pain"[All Fields] OR ("oligomenorrhoea"[All Fields] OR "oligomenorrhea"[MeSH Terms] OR "oligomenorrhea"[All Fields]) OR ("premenstrual syndrome"[MeSH Terms] OR ("premenstrual"[All Fields] AND "syndrome"[All Fields]) OR "premenstrual syndrome"[All Fields]) OR PMS[All Fields] OR "premenstrual dysphoric disorder"[All Fields] OR PMDD[All Fields] OR ("uterine haemorrhage"[All Fields] OR "uterine hemorrhage"[MeSH Terms] OR ("uterine"[All Fields] AND "hemorrhage"[All Fields]) OR "uterine hemorrhage"[All Fields]) OR "uterine bleeding"[All Fields] OR ("acne vulgaris"[MeSH Terms] OR ("acne"[All Fields] AND "vulgaris"[All Fields]) OR "acne vulgaris"[All Fields] OR "acne"[All Fields]) OR ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) OR ("colonic 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Letter[ptyp] OR Case Reports[ptyp])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) AND (English[lang] AND ("1990"[PDAT] : "3000"[PDAT]))

Embase® search strategy (June 29, 2012)

Platform: Embase.com

[embase]/lim NOT [medline]/lim AND ('oral contraceptive agent'/exp OR 'oral contraceptives') AND ('ovary tumor'/exp OR 'ovarian cancer':ti OR 'ovarian cancer':ab OR 'granulosa cell tumor':ti OR 'granulosa cell tumor':ab OR dysgerminoma:ti OR dysgerminoma:ab OR 'meigs syndrome':ti OR 'meigs syndrome':ab OR luteoma:ti OR luteoma:ab OR 'androblastoma'/exp OR 'sertoli-leydig cell tumor':ti OR 'sertoli-leydig cell tumor':ab OR thecoma:ti OR thecoma:ab OR 'ovary cyst'/de OR 'ovarian cyst':ti OR 'ovarian cyst':ab OR 'pregnancy'/exp OR pregnancy:ti OR pregnancy:ab OR 'vein thrombosis'/exp OR 'venous thrombosis':ti OR 'venous thrombosis':ab OR 'deep vein thrombosis':ti OR 'deep vein thrombosis':ab OR dvt:ti OR dvt:ab OR 'budd chiari syndrome'/exp OR 'budd chiari syndrome':ti OR 'budd chiari syndrome':ab OR 'vein occlusion'/exp OR 'retinal vein occlusion':ti OR 'retinal vein occlusion':ab OR thrombophlebitis:ti OR thrombophelbitis:ab OR 'venous thromboembolism'/exp OR 'venous thromboembolism':ti OR 'venous thromboembolism':ab OR 'venous thromboembolic event':ti OR 'venous thromboembolic event':ab OR vte:ti OR vte:ab OR 'cerebrovascular disease'/exp OR stroke:ti OR stroke:ab OR (brain:ti OR brain:ab OR cerebral:ti OR cerebral:ab AND (infarction:ti OR infarction:ab OR ischemia:ti OR ischemia:ab OR embolism:ti OR embolism:ab OR thrombosis:ti OR thrombosis:ab OR hemorrhage:ti OR hemorrhage:ab OR hematoma:ti OR hematoma:ab)) OR 'meningioma'/exp OR meningioma:ti OR meningioma:ab OR 'melanoma'/exp OR melanoma:ti OR melanoma:ab OR 'breast cancer'/exp OR 'breast cancer':ti OR 'breast cancer':ab OR 'uterus cancer'/exp OR 'uterine cancer':ti OR 'uterine cancer':ab OR 'uterine cervix cancer'/exp OR 'cervical cancer':ti OR 'cervical cancer':ab OR 'endometrium cancer'/exp OR 'endometrial cancer':ti OR 'endometrial cancer':ab OR 'endometriosis'/exp OR endometriosis:ti OR endometriosis:ab OR 'endometrium hyperplasia'/exp OR 'endometrial hyperplasia':ti OR 'endometrial hyperplasia':ab OR menorrhagia:ti OR menorrhagia:ab OR metrorrhagia:ti OR metrorrhagia:ab OR hypermenorrhea:ti OR hypermenorrhea:ab OR 'dysfunctional uterine bleeding':ti OR 'dysfunctional uterine bleeding':ab OR 'menstruation disorder'/exp OR amenorrhea:ti OR amenorrhea:ab OR oligomenorrhea:ti OR oligomenorrhea:ab OR dysmenorrhea:ti OR dysmenorrhea:ab OR 'premenstrual dysphoric disorder':ti OR 'premenstrual dysphoric disorder':ab OR pmdd:ti OR pmdd:ab OR 'premenstrual syndrome':ti OR 'premenstrual syndrome':ab OR pms:ti OR pms:ab OR 'painful menstruation':ti OR 'painful menstruation':ab OR 'menstrual pain':ti OR 'menstrual pain':ab OR 'uterus bleeding'/exp OR 'uterine hemorrhage':ti OR 'uterine hemorrhage':ab OR 'uterine bleeding':ti OR 'uterine bleeding':ab OR 'acne'/exp OR acne:ti OR acne:ab OR 'colon cancer'/exp OR 'colon cancer':ti OR 'colon cancer':ab OR 'colorectal cancer':ti OR 'colorectal cancer':ab OR 'rectum cancer'/exp OR 'rectal cancer':ti OR 'rectal cancer':ab OR 'anus cancer'/exp OR 'anus cancer':ti OR 'anus cancer':ab OR 'anal cancer':ti OR 'anal cancer':ab OR 'heart infarction'/exp OR 'heart attack':ti OR 'heart attack':ab OR 'myocardial infarction':ti OR 'myocardial infarction':ab OR 'liver cancer'/exp OR 'liver cancer':ti OR 'liver cancer':ab OR 'mortality'/exp OR mortality:ti OR mortality:ab OR 'death rate':ti OR 'death rate':ab OR 'survival'/exp OR survival:ti OR survival:ab OR 'fatality'/exp OR fatality:ti OR fatality:ab OR 'life expectancy':ti OR 'life expectancy':ab OR 'life expectancy'/exp) AND ('controlled study'/exp OR 'randomized controlled trial':ti OR 'randomized controlled trial':ab OR randomized:ti OR randomized:ab OR placebo:ti OR placebo:ab OR randomly:ti OR randomly:ab OR trial:ti OR 'cohort analysis'/exp OR 'controlled clinical trial'/exp OR 'case control study'/exp OR 'intervention study'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'cohort study':ti OR 'cohort study':ab OR longitudinal:ti OR longitudinal:ab OR 'follow up':ti OR 'follow up':ab OR prospective:ti OR prospective:ab OR 'case control':ti OR 'case control':ab OR 'systematic review'/exp OR 'meta analysis'/exp) NOT 'case report'/exp AND [humans]/lim AND [english]/lim AND [1990-2011]/py

Cochrane search strategy (June 29, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

Oral contraceptives [in title-abstract-keywords]

ClinicalTrials.gov search strategy (December 15, 2012)

Platform: www.clinicaltrials.gov

Search #1:
>   Intervention: oral contraceptive
>   Outcome Measures: ovarian cancer OR myocardial infarction OR MI OR
>   thromboembolism OR VTE OR PE OR DVT OR pulmonary embolism OR stroke OR
>   cervical cancer OR endometrial cancer OR breast cancer OR colorectal cancer

Search #2:
>   General search terms (all fields): oral contraceptive AND ovarian cancer

Appendix B. Data Abstraction Elements

I. Study Characteristics
- Other articles used in this abstraction
- Last Name of First Author
- Publication Year
- Study dates
  - Date enrollment started
  - Date follow-up ended
- Study site information
  - Single center, multicenter, or pooled analysis
  - If single center, city and state (U.S.) or city and country (outside U.S.)
  - If multicenter
    - Number of sites
    - Location/ geographic region(s) (Select all that apply)
      - U.S.
      - Canada
      - U.K.
      - Europe
      - S. America
      - Asia
      - Africa
      - Australia/New Zealand
      - Unclear/Not reported
      - Other (specify)
  - If pooled analysis, number of studies included
- Funding (Select all that apply)
  - Government
  - Private
  - Foundation
  - Industry
  - Unclear/Not reported
  - Other (specify)
- Indications for OCs (Select all that apply, assume contraception if not otherwise stated)
  - Contraception
  - Prevention of ovarian cancer
  - Other stated indication (specify)
- Outcomes Assessed (Select all that apply)
  - Ovarian cancer (Select all that apply)
    - Invasive
    - Borderline/Low Malignant Potential
    - Unclear/Not reported
  - Breast cancer
  - Colorectal cancer
  - Cervical cancer
  - Endometrial cancer
  - Other cancer (specify)

- o Stroke (Select all that apply)
  - ▪ Hemorrhagic stroke
  - ▪ Thrombotic stroke
  - ▪ Unclear/Not reported
- o Myocardial infarction
- o Deep venous thrombosis
- o Pulmonary embolism
- Study design
  - o Randomized controlled trial (RCT)
  - o Cohort
  - o Case-control
  - o Patient-level pooled analysis (Select design of component studies)
    - ▪ Case-control
    - ▪ Cohort
- Comments

II. Cohort Study Details
- Total number of subjects (Enter total N for each category, NR for not reported, or NA for not applicable)
  - o Number reported as (Select one): Subjects/Person-years
  - o Record the following for both OCP exposed and OCP non-exposed groups:
    - ▪ Initially screened
    - ▪ Enrolled
    - ▪ Excluded for other specified reason
    - ▪ Lost to follow-up
    - ▪ N for analysis
    - ▪ Source of subjects reported (Yes/NR)
      - If yes, select source
        - o Hospital
        - o Population
        - o Other (specify)
- Subject Age Reported (Yes/NR)
  - o Record age in years for both OCP exposed and OCP non-exposed groups
    - ▪ Mean
    - ▪ Median
    - ▪ SD
    - ▪ Min. age
    - ▪ Max. age
    - ▪ 25% IQR
    - ▪ 75% IQR
    - ▪ Categorical reporting (specify)
    - ▪ Other (specify)
  - o p-value between groups
- Subject Race Reported (Yes/NR)
  - o Record the following for both OCP exposed and OCP non-exposed groups
    - ▪ American Indian or Alaska Native (N or %)
    - ▪ Asian (N or %)
    - ▪ Black or African American (N or %)
    - ▪ Hispanic (N or %)
    - ▪ Native Hawaiian or other Pacific Islander (N or %)

- White (N or %)
- Multiracial (N or %)
  - p-values between groups
- Medical History
  - Record the following for both OCP exposed and OCP non-exposed groups
    - Age at menarche reported (Yes/NR)
      - Mean
      - SD
      - Min age
      - Max age
      - Median
      - 25% IQR
      - 75% IQR
      - Categorical reporting (specify)
      - Other (specify)
    - Gravidity reported (Yes/NR)
      - Mean
      - SD
      - Min age
      - Max age
      - Median
      - 25% IQR
      - 75% IQR
      - Categorical reporting (specify)
      - Other (specify)
    - Parity reported (Yes/NR)
      - Mean
      - SD
      - Min age
      - Max age
      - Median
      - 25% IQR
      - 75% IQR
      - Categorical reporting (specify)
      - Other (specify)
    - Menopausal status reported (Yes/NR)
      - Premenopausal (%)
      - Postmenopausal (%)
      - Perimenopausal (%)
      - Unknown
    - Breastfeeding reported (Yes/NR)
      - Yes (%)
      - No (%)
    - Hysterectomy reported (Yes/NR)
      - Yes
      - No
    - Oophorectomy reported (Yes/NR)
      - Yes

- No
- Excluded
  - Family history of ovarian cancer reported (Yes/NR)
    - Yes
    - No
  - BrCA1 status reported (Yes/NR)
    - Positive
    - Negative
  - BrCA2 status reported (Yes/NR)
    - Positive
    - Negative
  - Other genetic risk factor reported (Yes/NR)
    - Family history of primary outcome
    - Factor V Leiden
    - Other thrombogenic genotype
    - Other genetic risk factor (specify)
  - p-values between groups
- Contraception data reported (Yes/NR)
  - Non-Oral Contraceptive Group(s)
    - Record N and % for the following:
      - Barrier method
      - IUD
      - Injectable/implantable hormones
      - Female sterilization
      - Male sterilization
  - Oral Contraceptives
    - For each OC type reported, record the following:
      - Estrogen formulation (Select one)
        - Estradiol valerate
        - Ethinyl estradiol
        - Mestranol
        - None
      - Estrogen Dose (Select one)
        - High
        - Low
        - Not applicable
      - Progestin formulation (Select one)
        - Desogestrel
        - Dienogest
        - Drospirenone
        - Ethynodiol diacetate
        - Levonorgestrel
        - Norethindrone
        - Norethindrone diacetate
        - Norgestimate
        - Norgestrel
      - Progestin Generation (Select one)
        - 1
        - 2

- o 3
- o 4
- o Unclear/Not Reported
- Progestin Dose (Select one)
  - o High
  - o Low
  - o Not applicable
- N and % of subjects using this type of OC
  - Duration of OC use (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Ages OCs used (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Time since last OC use & assessment of outcome status (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Pattern of OC use (record the following, if reported):
    - Number of episodes of use
    - Number of continuous months
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Number of months between OC uses (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median

- SD
- p-value
- Categorical reporting (specify)
  - Comments

III. Case-Control Study Details
- Total number of subjects (Enter total N for each category, NR for not reported, or NA for not applicable)
  - Number reported as (Select one): Subjects/Person-years
  - Record the following for both cases and controls:
    - Initially screened
    - Declined to participate
    - Excluded based on criteria
    - N for analysis
    - Source of subjects reported (Yes/NR)
      - If yes, select source
        - Hospital
        - Population
        - Other (specify)
- Subject Age Reported (Yes/NR)
  - Record age in years for both cases and controls
    - Mean
    - Median
    - SD
    - Min. age
    - Max. age
    - 25% IQR
    - 75% IQR
    - Categorical reporting (specify)
    - Other (specify)
  - p-value between groups
- Subject Race Reported (Yes/NR)
  - Record the following for both cases and controls
    - American Indian or Alaska Native (N or %)
    - Asian (N or %)
    - Black or African American (N or %)
    - Hispanic (N or %)
    - Native Hawaiian or other Pacific Islander (N or %)
    - White (N or %)
    - Multiracial (N or %)
  - p-values between groups
- Medical History
  - Record the following for both cases and controls
    - Age at menarche reported (Yes/NR)
      - Mean
      - SD
      - Min age
      - Max age
      - Median
      - 25% IQR

- 75% IQR
- Categorical reporting (specify)
- Other (specify)
  - Gravidity reported (Yes/NR)
    - Mean
    - SD
    - Min age
    - Max age
    - Median
    - 25% IQR
    - 75% IQR
    - Categorical reporting (specify)
    - Other (specify)
  - Parity reported (Yes/NR)
    - Mean
    - SD
    - Min age
    - Max age
    - Median
    - 25% IQR
    - 75% IQR
    - Categorical reporting (specify)
    - Other (specify)
  - Menopausal status reported (Yes/NR)
    - Premenopausal (%)
    - Postmenopausal (%)
    - Perimenopausal (%)
    - Unknown
  - Breastfeeding reported (Yes/NR)
    - Yes (%)
    - No (%)
  - Hysterectomy reported (Yes/NR)
    - Yes
    - No
  - Oophorectomy reported (Yes/NR)
    - Yes
    - No
    - Excluded
  - Family history of ovarian cancer reported (Yes/NR)
    - Yes
    - No
  - BrCA1 status reported (Yes/NR)
    - Positive
    - Negative
  - BrCA2 status reported (Yes/NR)
    - Positive
    - Negative
  - Other genetic risk factor reported (Yes/NR)

- Family history of primary outcome
- Factor V Leiden
- Other thrombogenic genotype
- Other genetic risk factor (specify)
  - o p-values between groups
- Contraception data reported (Yes/NR)
  - o Record the following for both cases and controls:
    - ▪ Record N and % of subjects utilizing the following non-OC contraceptive methods:
      - Barrier method
      - IUD
      - Injectable/implantable hormones
      - Female sterilization
      - Male sterilization
    - ▪ Oral Contraceptives
      - For each OC type reported, record the following:
        - o Estrogen formulation (Select one)
          - ▪ Estradiol valerate
          - ▪ Ethinyl estradiol
          - ▪ Mestranol
          - ▪ None
        - o Estrogen Dose (Select one)
          - ▪ High
          - ▪ Low
          - ▪ Not applicable
        - o Progestin formulation (Select one)
          - ▪ Desogestrel
          - ▪ Dienogest
          - ▪ Drospirenone
          - ▪ Ethynodiol diacetate
          - ▪ Levonorgestrel
          - ▪ Norethindrone
          - ▪ Norethindrone diacetate
          - ▪ Norgestimate
          - ▪ Norgestrel
        - o Progestin Generation (Select one)
          - ▪ 1
          - ▪ 2
          - ▪ 3
          - ▪ 4
          - ▪ Unclear/Not Reported
        - o Progestin Dose (Select one)
          - ▪ High
          - ▪ Low
          - ▪ Not applicable
        - o N and % of subjects using this type of OC
    - ▪ Duration of OC use (record the following, if reported):
      - Minimum
      - Maximum
      - Mean

- Median
- SD
- p-value
- Categorical reporting (specify)
  - Ages OCs used (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Time since last OC use & assessment of outcome status (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Pattern of OC use (record the following, if reported):
    - Number of episodes of use
    - Number of continuous months
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
  - Number of months between OC uses (record the following, if reported):
    - Minimum
    - Maximum
    - Mean
    - Median
    - SD
    - p-value
    - Categorical reporting (specify)
- Comments

IV. Outcomes Reporting Form
- Select outcome being reported
  - Ovarian Cancer
  - Breast Cancer
  - Colorectal Cancer
  - Cervical Cancer
  - Endometrial Cancer

- o Deep venous thrombosis
- o Pulmonary embolus
- o Stroke
- o Myocardial infarction
- o Is this data for disease incidence or disease-specific mortality?
  - ▪ Incidence
  - ▪ Disease-specific mortality
- o Is this data for a special population (Yes/No)
  - ▪ If yes, indicate the population
- o Is this data for a subgroup of the overall study population (Yes/No)
  - ▪ If yes, indicate the subgroup population
- For this outcome
  - o Enter N analyzed for cases or OC exposed group
  - o Enter N analyzed for controls or OC non-exposed group
  - o Record the following data for OC ever use
    - ▪ Crude OR and 95% CI
    - ▪ Adjusted OR and 95% CI
      - Indicate adjustment factors:
        - o Age
        - o Race
        - o Parity
        - o Menopausal status
        - o BMI
        - o Family History
        - o Age at menarche
        - o Smoking
        - o Breastfeeding
        - o Other (specify)
  - o Data reported by OC duration (Yes/NR)
    - ▪ Does this data represent recency of use (Yes/No)
    - ▪ Record the following for all duration categories reported:
      - Crude OR and 95% CI
      - Adjusted OR and 95% CI
        - o Indicate adjustment factors:
          - ▪ Age
          - ▪ Race
          - ▪ Parity
          - ▪ Menopausal status
          - ▪ BMI
          - ▪ Family History
          - ▪ Age at menarche
          - ▪ Smoking
          - ▪ Breastfeeding
          - ▪ Other (specify)
  - o Data reported by age at first use (Yes/NR)
    - ▪ Record the following for all categories reported:
      - Crude OR and 95% CI
      - Adjusted OR and 95% CI
        - o Indicate adjustment factors:
          - ▪ Age

- - - Race
      - Parity
      - Menopausal status
      - BMI
      - Family History
      - Age at menarche
      - Smoking
      - Breastfeeding
      - Other (specify)
  - Data reported by age at last use (Yes/NR)
    - Record the following for all categories reported:
      - Crude OR and 95% CI
      - Adjusted OR and 95% CI
        - Indicate adjustment factors:
          - Age
          - Race
          - Parity
          - Menopausal status
          - BMI
          - Family History
          - Age at menarche
          - Smoking
          - Breastfeeding
          - Other (specify)
  - Data reported by formulation (Yes/NR)
    - Record the following for all categories reported:
      - Crude OR and 95% CI
      - Adjusted OR and 95% CI
        - Indicate adjustment factors:
          - Age
          - Race
          - Parity
          - Menopausal status
          - BMI
          - Family History
          - Age at menarche
          - Smoking
          - Breastfeeding
          - Other (specify)
  - Subgroup/Stratified Analyses performed? (Yes/No)
  - Stratification Variables
    - Age
    - Race
    - Parity
    - Menopausal status
    - BMI
    - Family history
    - Other (specify)
- Comments

V. Cohort Studies Quality Assessment

- Selection Bias
  - Was there any attempt to balance the allocation between the groups? (Yes/No/Unclear)
  - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/No/Unclear)
  - Is the selection of the comparison group appropriate? (Yes/No/Unclear)
  - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Unclear)
  - Are baseline characteristics similar between groups? If not, did the analysis control for differences? (Yes/No/Unclear)
  - Does the design or analysis control account for important confounding and modifying variables? (Yes/No/Unclear)
- Performance Bias
  - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - Did variation from the study protocol compromise the conclusions of the study?
- Attrition Bias
  - Is the length of follow-up different between the groups?
  - Was there a high rate of differential or overall attrition?
  - Is the analysis conducted on an intention-to-treat (ITT) basis?
- Detection Bias
  - Were the outcome assessors blinded to the intervention or exposure status of participants?
  - Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
  - Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
  - Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
  - Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
- Reporting Bias
  - Are the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?
- Record any additional comments relating to potential sources of bias or other study limitations.
- Summary Quality Rating
  - Good
  - Fair
  - Poor
  - If the study is rated as "Fair" or "Poor," provide rationale for decision.

VI. Case-Control Studies Quality Assessment

- Selection Bias
  - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/No/Unclear)
  - Is the selection of the comparison group appropriate? (Yes/No/Unclear)
  - Does the design or analysis control account for important confounding and modifying variables? (Yes/No/Unclear)
- Performance Bias

- o Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - o Did variation from the study protocol compromise the conclusions of the study?
- Detection Bias
  - o Were the outcome assessors blinded to the intervention or exposure status of participants?
  - o Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
  - o Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
  - o Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
  - o Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
- Reporting Bias
  - o Are the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?
- Record any additional comments relating to potential sources of bias or other study limitations.
- Summary Quality Rating
  - o Good
  - o Fair
  - o Poor
  - o If the study is rated as "Fair" or "Poor," provide rationale for decision.

VII. Cohort Applicability Assessment
- Population (P)
  - o Age at OC use
    - ▪ At least 25% of study population age 35 years or older
    - ▪ <25% of study population age 35 or older
  - o Baseline risk for ovarian cancer
    - ▪ Risk factors described (e.g., family history)
    - ▪ Risk factors not described
- Intervention (I)
  - o OC formulation
    - ▪ Currently available in U.S.
    - ▪ Not currently available in U.S.
    - ▪ NR
- Comparator (C)
  - o Other contraceptive
    - ▪ Currently available in U.S.
    - ▪ Not currently available in U.S.
    - ▪ NR
- Setting (S)
  - o Location
    - ▪ U.S.
    - ▪ Non-U.S.

VIII. Case-Control Applicability Assessment
- Population (P)
  - o Age at OC use
    - ▪ At least 25% of study population age 35 years or older

- ▪ <25% of study population age 35 or older
    - o Baseline risk for ovarian cancer
        - ▪ Risk factors described (e.g., family history)
        - ▪ Risk factors not described
- Intervention (I)
    - o OC formulation
        - ▪ Currently available in U.S.
        - ▪ Not currently available in U.S.
        - ▪ NR
- Comparator (C)
    - o Other contraceptive
        - ▪ Currently available in U.S.
        - ▪ Not currently available in U.S.
        - ▪ NR
- Setting (S)
    - o Location
        - ▪ U.S.
        - ▪ Non-U.S.

Appendix C. Included Studies

Althuis MD, Brogan DD, Coates RJ, et al. Breast cancers among very young premenopausal women (United States). Cancer Causes Control. 2003;14(2):151-60. PMID: 12749720.

Althuis MD, Brogan DR, Coates RJ, et al. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. Br J Cancer. 2003;88(1):50-7. PMID: 12556959.

Andersen BS, Olsen J, Nielsen GL, et al. Third generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism. Thromb Haemost. 1998;79(1):28-31. PMID: 9459317.

Anonymous. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1997;349(9060):1202-9. PMID: 9130941.

Anonymous. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception. 1998;57(5):315-24. PMID: 9673838.

Anonymous. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995;346(8990):1582-8. PMID: 7500749.

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Anonymous. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1996;348(9026):498-505. PMID: 8757151.

Anonymous. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995;346(8990):1575-82. PMID: 7500748.

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Austin H, Lally C, Benson JM, et al. Hormonal contraception, sickle cell trait, and risk for venous thromboembolism among African American women. Am J Obstet Gynecol. 2009;200(6):620 e1-3. PMID: 19306959.

Badawy YA and Bayoumi DM. An epidemiologic study of ovarian cancer. Part 11: Oral contraceptive use and menstrual events. J Egypt Public Health Assoc. 1992;67(5-6):579-91. PMID: 1294683.

Barinagarrementeria F, Gonzalez-Duarte A, Miranda L, et al. Cerebral infarction in young women: analysis of 130 cases. Eur Neurol. 1998;40(4):228-33. PMID: 9813407.

Barnett GC, Shah M, Redman K, et al. Risk factors for the incidence of breast cancer: do they affect survival from the disease?. J Clin Oncol. 2008;26(20):3310-6. PMID: 18612147.

Barsoum MK, Heit JA, Ashrani AA, et al. Is progestin an independent risk factor for incident venous thromboembolism? A population-based case-control study. Thromb Res. 2010;126(5):373-8. PMID: 20833412.

Beard CM, Hartmann LC, Atkinson EJ, et al. The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935-1991. Ann Epidemiol. 2000;10(1):14-23. PMID: 10658685.

Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303-14. PMID: 18294997.

Beral V, Hermon C, Kay C, et al. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. BMJ. 1999;318(7176):96-100. PMID: 9880284.

Bernholtz S, Laitman Y, Kaufman B, et al. Cancer risk in Jewish BRCA1 and BRCA2 mutation carriers:

Effects of oral contraceptive use and parental origin of mutation. Breast Cancer Research and Treatment. 2011;129(2):557-563. PMID: 2011504819.

Bloemenkamp KW, Rosendaal FR, Buller HR, et al. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. Arch Intern Med. 1999;159(1):65-70. PMID: 9892332.

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Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol. 2007;25(25):3831-6. PMID: 17635951.

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Figueiredo JC, Bernstein L, Capanu M, et al. Oral contraceptives, postmenopausal hormones, and risk of asynchronous bilateral breast cancer: the WECARE Study Group. J Clin Oncol. 2008;26(9):1411-8. PMID: 18250348.

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Study Groupings

Table C-1. Primary articles and companion articles grouped by study name (alphabetical)

Study Name	Primary Abstracted Article	Companion Articles*
Cancer and Steroid Hormone (CASH) Study	Gross, 1992[1]	
	Gwinn, 1990[2]	
	Maxwell, 2006[3]	
	Schildkraut, 2002[4]	
Collaborative Ovarian Cancer Group Study	Harris, 1992[5]	Steinberg, 1997[6]
	Hartge, 1994[10]	Whittemore, 1992[7]
	Horn-Ross, 1992[11]	Whittemore, 1992[8]*
	John, 1993[12]	Whittemore, 1992[9]*
European Prospective Investigation Into Cancer and Nutrition	Dossus, 2010[13]	
	Tsilidis, 2010[14]	
	Tsilidis, 2011[15]	
International Agency for Research on Cancer (IARC) Multicentric Case-Control Study	Moreno, 2002[16]	
	Hammouda, 2005[17]	
International BRCA1/2 Carrier Cohort Study	Antoniou, 2009[18]	
	Brohet, 2007[19]	
Leiden Thrombophilia Study	Bloemenkamp, 1995[20]	
	Bloemenkamp, 2000[21]	
Malignant Ovarian (MALOVA) Cancer Study	Huusom, 2006[22]	
	Soegaard, 2007[23]	
Myocardial Infarction Causality (MICA) Study	Dunn, 1999[24]	
	Dunn, 1999[25]	
	Dunn, 2001[26]	
Norwegian-Swedish Women's Lifestyle and Health Cohort Study	Kumle, 2004[27]	
	Kumle, 2004[28]	
Nurses' Health Study	Hankinson, 1995[29]	Colditz, 1994[30]
	Grodstein, 1996[31]	
	Tworoger, 2007[32]	
Oxford Family Planning Association (Oxford-FPA) Contraceptive Study	Mant, 1998[33]	
	Vessey, 1995[34]	
	Vessey, 2006[35]	
	Vessey, 2010[36]	Vessey, 2003[37]
Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) Study	Kemmeren, 2002[38]	
	Tanis, 2001[39]	
Royal College of General Practitioners' Oral Contraceptive Study	Hannaford, 1998[40]	
	Hannaford, 2007[41]	Hannaford, 2005[42]
	Hannaford, 2010[43]	Beral, 1999[44]
Shanghai Breast Cancer Study	Fowke, 2004[45]	
	Xu, 2011[46]	
Shanghai Textile Workers Study	Rosenblatt, 2004[47]	
	Rosenblatt, 2009[48]	Wernli, 2006[49]
	Gallagher, 2011[50]	

Study Name	Primary Abstracted Article	Companion Articles*
Study of Health and Reproduction (SHARE)	Greer, 2005[51]	
	Greer, 2005[52]	
	Modugno, 2001[53]	Ness, 2000[54] Ness, 2000[55] Ness, 2001[56]
	Ness, 2000[55]	Ness, 2000[54] Ness, 2001[56] Modugno, 2001[53]
	Ness, 2001[56]	Ness, 2000[55] Modugno, 2001[53] Ness, 2000[54]
	Walker, 2002[57]	
Transnational Study on Oral Contraceptives and the Health of Young Women	Heinemann, 1997[58]	Heinemann, 1998[59] Spitzer, 1993[60]*
	Heinemann, 1999[61]	
	Lewis, 1999[62]	Lewis, 1996[63] Lewis, 1996[64] Lewis, 1997[65] Lewis, 1999[66]
	Suissa, 1997[67]	Spitzer, 1996[68]
	Suissa, 2000[69]	
Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study	Figueiredo, 2008[70]	
	Figueiredo, 2010[71]	
Women's Contraceptive and Reproductive Experiences (CARE) Study	Folger, 2007[72]	
	Ma, 2010[73]	
	Marchbanks, 2002[74]	Marchbanks, 2002[75]*
	Norman, 2003[76]	
	Marchbanks, 2012[77]	Marchbanks, 2002[74]
	Lu, 2011[78] (Presents data from both CARE and the California Teachers Study [CTS], analyzed separately)	
Women's Learning the Influence of Family and Environment (LIFE) Study	Lee, 2008[79]	
	Ma, 2006[80]	
World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception	Anonymous, 1995[81]	Anonymous, 1995[82]*
	Anonymous, 1995[83]	
	Anonymous, 1996[84]	
	Anonymous, 1996[85]	
	Anonymous, 1997[86]	
	Anonymous, 1998[87]	
	Chang, 1999[88]	
World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives	Rosenblatt, 1992[89]	
	Thomas, 1991[90]	

*Companion articles marked with an asterisk did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

Table C-2. Primary articles and companion articles grouped by author (study name not applicable)

Author	Primary Abstracted Article	Companion Articles*
Althuis, 2003	Althuis, 2003[91]	Brinton, 1995[92]*
	Althuis, 2003[93]	
Badawy, 1992	Badawy, 1992[94]	Badawy, 1992[95]*
Chiaffarino, 2001	Chiaffarino, 2001[96]	
	Tavani, 2004[97]	
Jick, 2000	Jick, 2000[98]	Jick,1995[99]
	Farmer, 2000[100]	
Le Gal, 2010	Le Gal, 2010[101]	Rodger, 2008[102]*
Legnani, 2002	Legnani, 2002[103]	
	Legnani, 2004[104]	
Lidegaard, 2012	Lidegaard, 2012[105]	Lidegaard, 2002[106] Lidegaard, 1998[107]
	Lidegaard, 2011[108]	Lidegaard, 2009[109]
	Lidegaard, 2002[110]	Lidegaard, 1998[111]
	Lidegaard, 1998[112]	Lidegaard, 1999[113] Lidegaard, 1995[114] Lidegaard, 1998[107]
Newcomer, 2003	Newcomer, 2003[115]	Newcomb, 1994[116]*
Parazzini, 1991	Parazzini, 1991[117]	
	Parazzini, 2000[118]	
	Tavani, 2000[119]	
Riman, 2001	Riman, 2001[120]	
	Riman, 2002[121]	
Risch, 1996	Risch, 1996[122]	Risch, 1994[123] Risch, 1994[124]*
Sanderson, 2000	Sanderson, 2000[125]	
	Wittenberg, 1999[126]	
Siskind, 2000	Nagle, 2008[127]	
	Siskind, 2000[128]	Purdie, 2001[129]
Tryggvadóttir, 2002	Tryggvadóttir, 2002[130]	Tryggvadóttir, 2001[131]*
Tung, 2003	Lurie, 2007[132]	Goodman, 2005[133] Goodman, 2002[134]
	Lurie, 2008[135]	
	Tung, 2003[136]	
	Tung, 2005[137]	
van Vlijmen, 2007	van Vlijmen, 2007[138]	Brouwer, 2006[139]*
Wang, 2012	Wang, 2012[140]	Li, 2006[141]
	Li, 2010[142]	

*Companion articles marked with an asterisk did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

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6. Steinberg KK, Smith SJ, Stroup DF, et al. Comparison of effect estimates from a meta-analysis of summary data from published studies and from a meta-analysis using individual patient data for ovarian cancer studies. Am J Epidemiol. 1997;145(10):917-25. PMID: 9149663.

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Appendix D. Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in bold. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Abstract only or full text unobtainable

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Appendix E. Analyses of Potential Publication Bias

We used Comprehensive Meta-Analysis Version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ [2005]) to test for potential publication bias for the outcomes described below. Figures E-1 to E-5 show the resulting funnel plot for each outcome. Note that there is no asymmetry in any of the plots.

Ovarian Cancer Incidence

Figure E-1. Funnel plot for ovarian cancer incidence
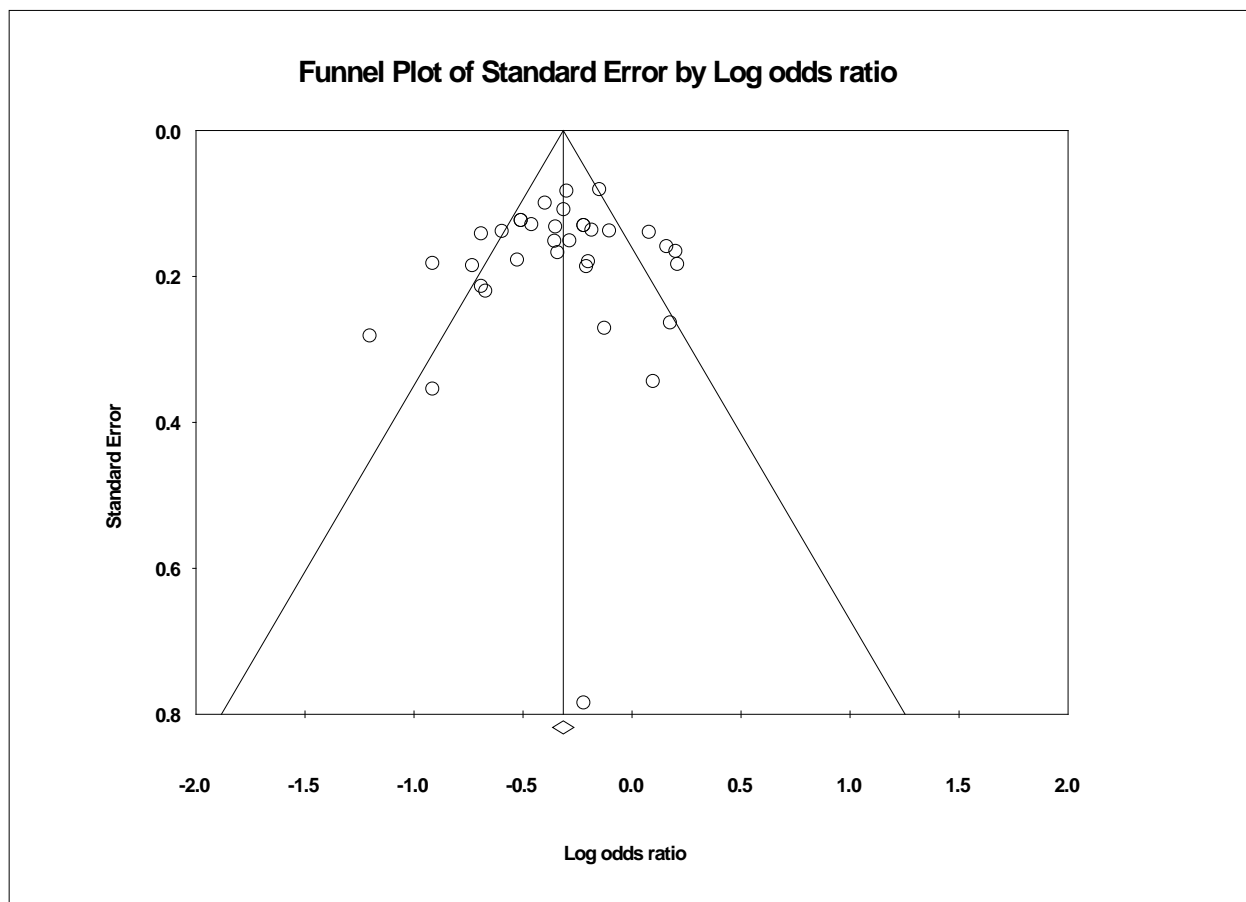
Breast Cancer Incidence
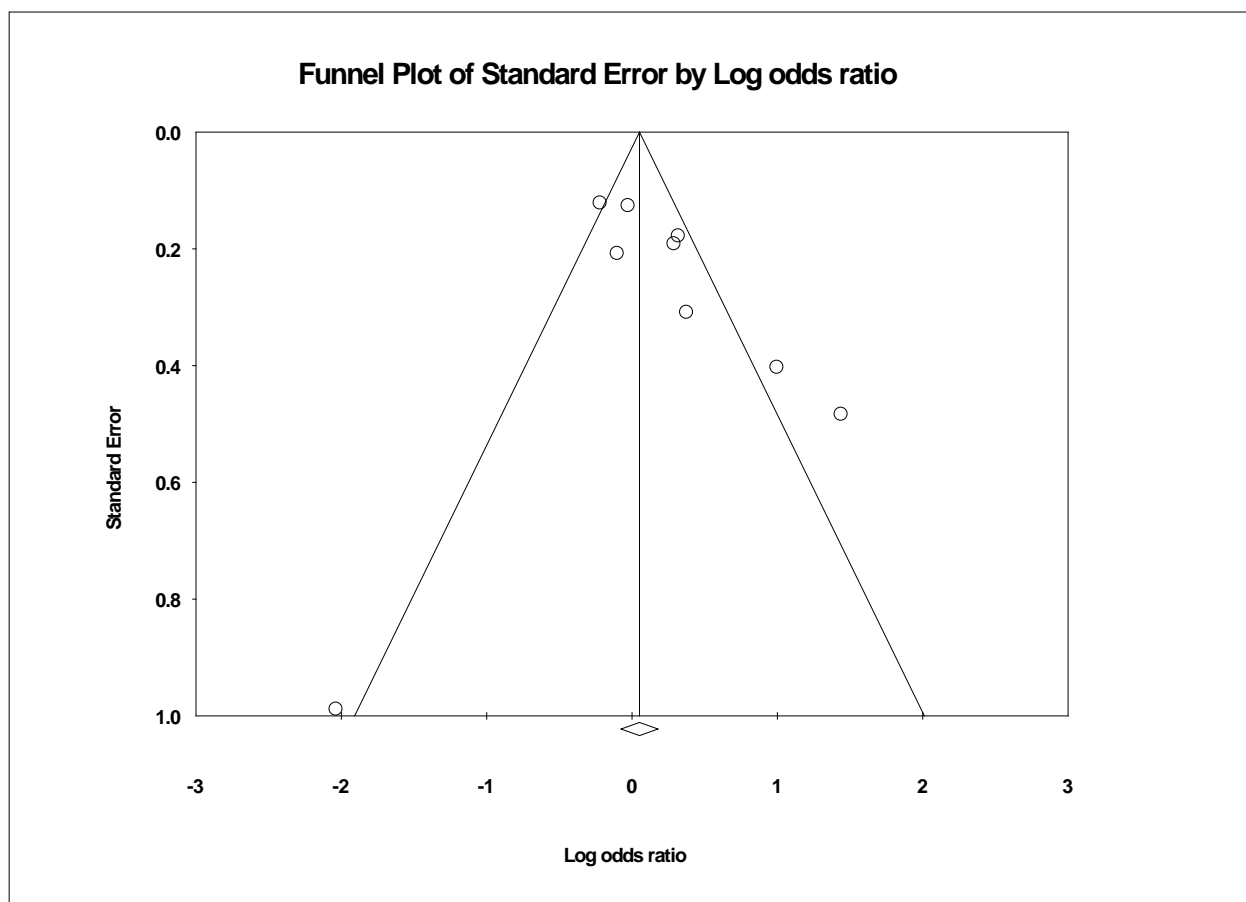
Figure E-2. Funnel plot for breast cancer incidence
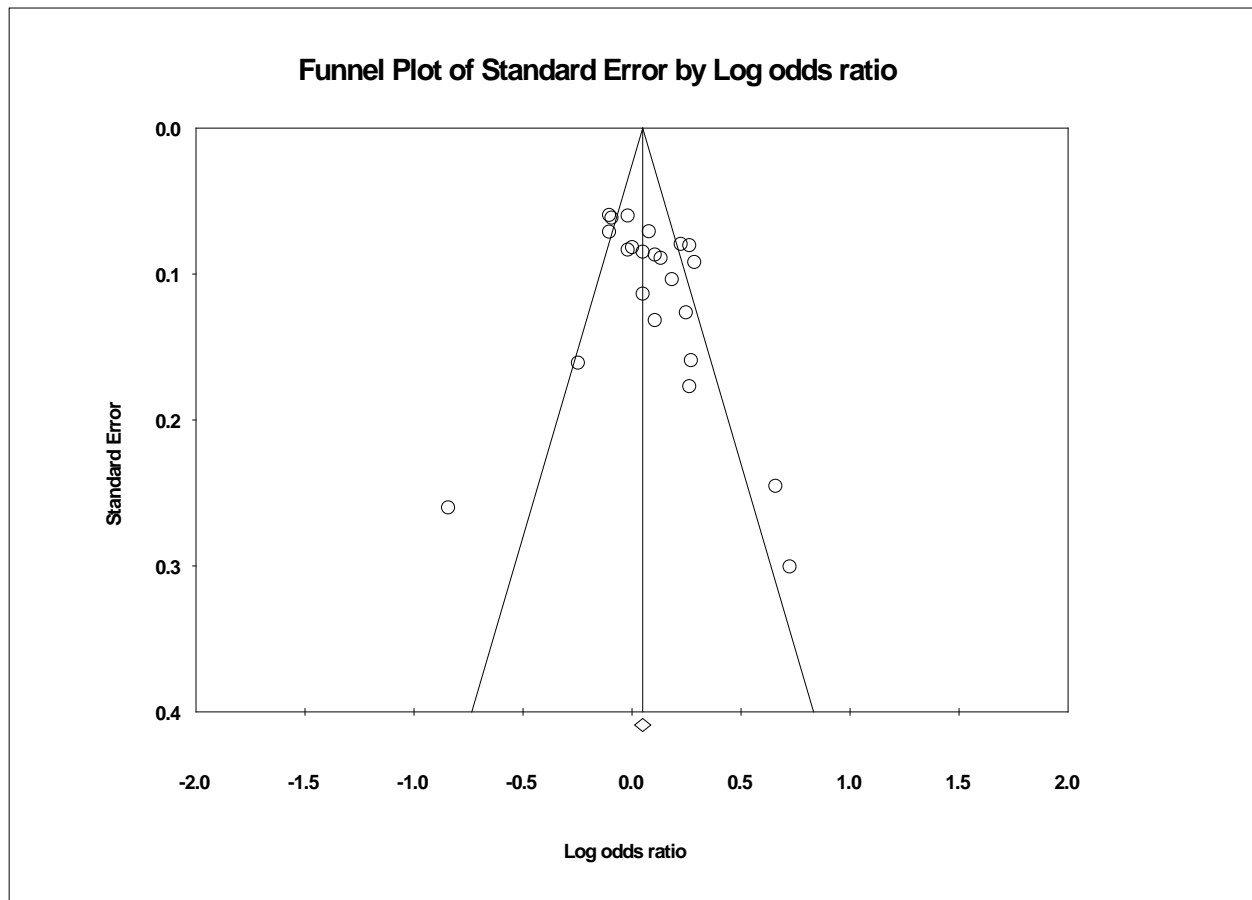
Cervical Cancer Incidence

Figure E-3. Funnel plot for cervical cancer incidence

Funnel Plot of Standard Error by Log odds ratio

Colorectal Cancer Incidence

Figure E-4. Funnel plot for colorectal cancer incidence
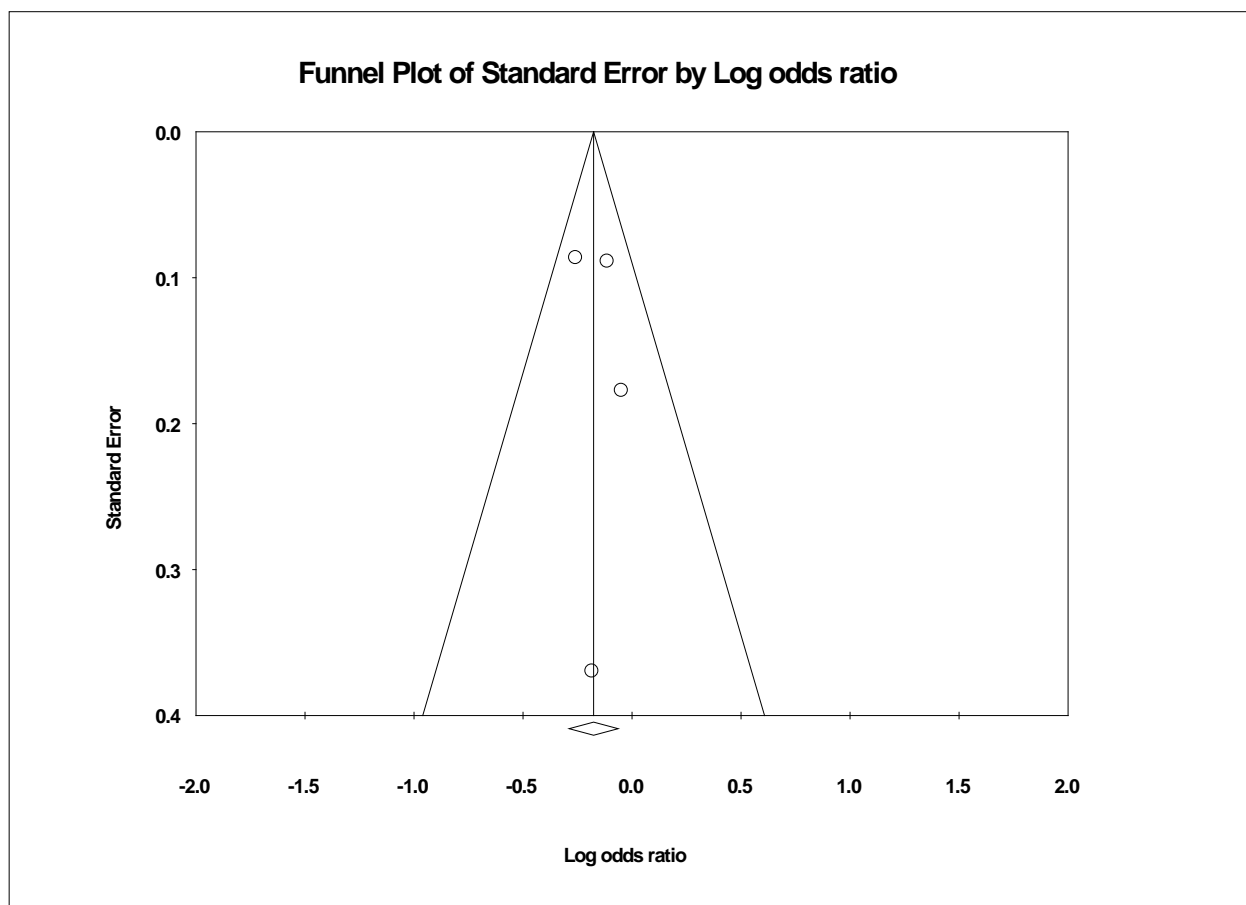
Endometrial Cancer Incidence

Figure E-5. Funnel plot for endometrial cancer incidence
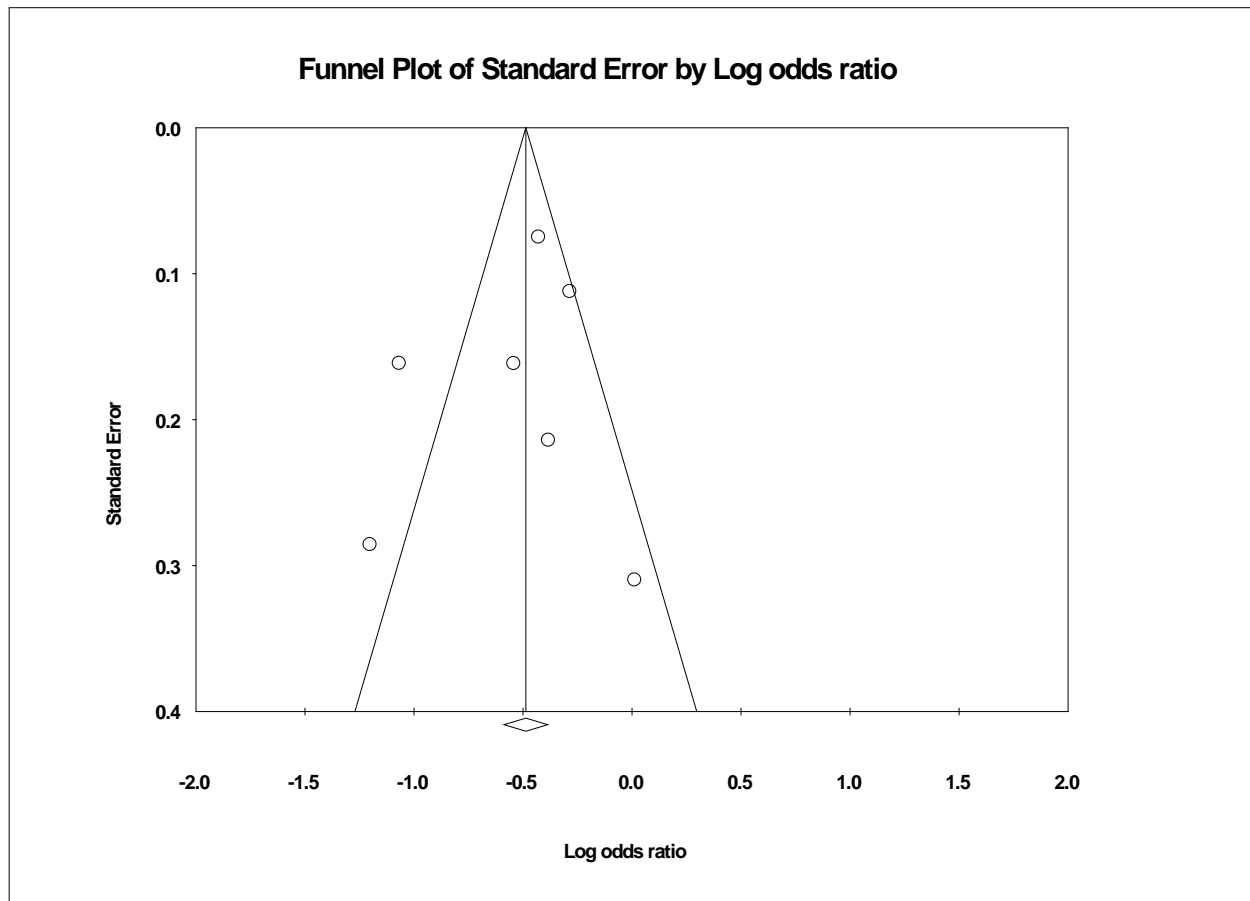
We also computed Begg and Mazumdar's correlation test for publication bias for each cancer incidence (Table E-1). None of the correlations were significant although breast cancer incidence was marginal.

Table 1. Begg and Mazumdar's correlation test for publication bias

Cancer Incidence	Correlation	p-value
Ovarian	-0.055	0.6458
Breast	0.289	0.0539
Cervical	0.278	0.2972
Colorectal	0.000	1.0000
Endometrial	-0.048	0.8806

Overall, there was no evidence of publication bias in the meta-analyses.

Appendix F. Model Description and Parameters

General Considerations

We previously developed a simulation model for the natural history of ovarian cancer at the population level, which has provided insights into the potential effectiveness of screening as a strategy for reducing ovarian cancer morbidity and mortality,[1,2] and many of the basic parameters and model structure used in that model are used here. However, the ovarian cancer screening model—while including such relevant parameters as age-specific oophorectomy rates, age-specific ovarian cancer incidence, stage-specific survival, between-stage transition rates derived from the observed incidence and survival data, and the potential effect of known risk factors such as BRCA mutation status—focuses primarily on ovarian cancer mortality. For the purposes of quantifying the potential tradeoffs of benefits and harms for primary prevention of ovarian cancer through the use of oral contraceptives (OCs), there were three additional major considerations for the model:

1. The eight additional outcomes (breast, cervical, colorectal, endometrial cancers; and DVT, PE, MI, and stroke) needed to be included.

2. Specific characteristics of OC use, including ages at first and last use and duration of use, may affect the association between OCs and any of the relevant outcomes; so the model needed to incorporate a mechanism for including as many aspects of OC use as possible.

3. Many aspects of reproductive history—age at menarche, age at first pregnancy, numbers of pregnancies, breast feeding history, age at menarche, number of ovulatory cycles—are related to both OC use and the risk of ovarian cancer and many of the other outcomes of interest, either as confounders or effect modifiers. The balance of benefits and harms of OC use for primary prevention of ovarian cancer for specific women may well vary based on these other factors. Therefore, ultimately, a model that incorporates a mechanism for including relevant reproductive factors and their effect on ovarian cancer risk independent of OC use may prove quite useful (as well as have applications for other areas of reproductive health).

We initially developed a model that starts at age 10 and runs through age 100, and which includes age-specific and race/ethnicity-specific probabilities of menarche (including postmenarchal anovulatory cycles), age at sexual debut, contraceptive method prevalence, age-specific fecundity, contraceptive method-specific effectiveness, pregnancy (including age-specific miscarriage rates and race/ethnicity-specific probabilities of delivery by gestational age), lactation, and hysterectomy and oophorectomy rates as well as incidence and mortality from the nine conditions of interest. Although the model generated estimates of incidence and mortality that were consistent with observed data, we ultimately opted to simplify the reproductive components of the model for the following reasons:

- The studies included in the meta-analyses almost always provided risk estimates for the association of OC use and outcomes, particularly for reproductive cancers that were adjusted for most, if not all, of the potentially relevant factors such as age at menarche and menopause. Without data on the separate parameter estimates (for example, the odds ratio for parity derived from a logistic regression model that also included OC use), modeling the joint effects was impossible.

- Even if these separate estimates were reported, there was wide disparity in how the parameters were described (categorical versus continuous, choice of categories, etc.), again making modeling difficult.

- The review of those studies which did assess joint effects of other reproductive factors did not detect significant differences.

- Although there are population-based data on the age- , race/ethnicity-, and parity-specific prevalence of the use of different contraceptive methods, as well as reasonable data on short-term method discontinuation rates, there are almost no data available for estimating the dynamics of contraceptive method switching. Because the only available data on duration of OC use did not provide data on patterns of intermittent use, we, like others, assumed that, once OC use began, women used it continuously for the specified duration (either assigned by the model or drawn from a distribution).

- Therefore,

  o We needed to assume continuous use of OCs.

  o The majority of the literature reviewed compared OC users with nonusers who used a mix of other available contraceptive methods (including no methods).

  o We found a paucity of data on the effect of contraceptive methods other than OCs and tubal ligation on ovarian cancer, our primary outcome of interest.

  o There were relatively small but noticeable effects of differential pregnancy rates (resulting from different contraceptive effectiveness) on outcome rates in early versions of the model, likely due to a competing risk effect; while further exploration of the implications of this effect of model structural assumptions on model output is definitely worthwhile, it was well outside the scope of work for this project.

We elected to simplify the model to just three "reproductive" states—OC users, OC nonusers, and tubal ligation for the purposes of this report. We plan further work on integrating a more detailed reproductive history into the model in future versions.

Model Structure

The model is a semi-Markov state-transition model (Figure F-1); transition probabilities are conditioned on both the current state and time (i.e., age).

Figure F-1. Model structure

Transition probabilities modified by hysterectomy and oophorectomy status
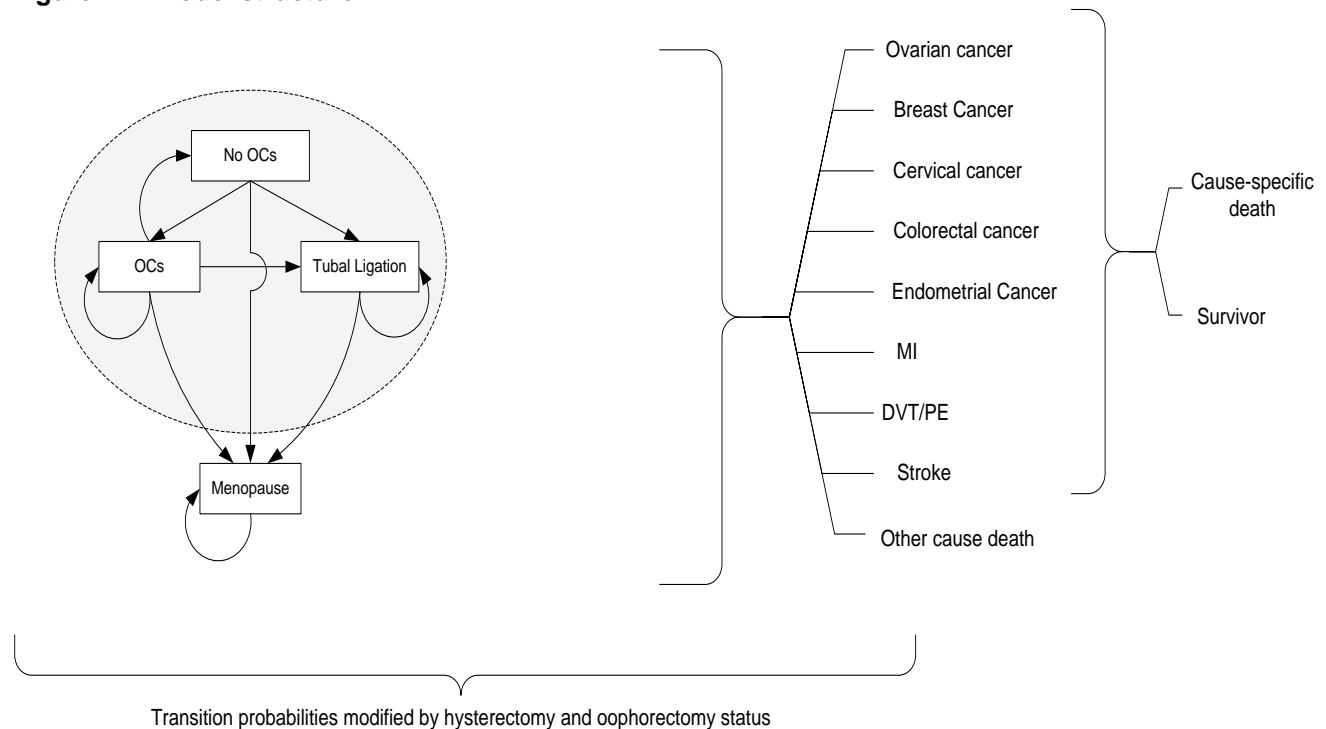
We have used Markov models extensively for analysis of clinical and policy decisions involving ovarian and cervical cancer, pregnancy, and other reproductive conditions, with transition probabilities modified by time (including age and time in state for cancer diagnoses) and current state. One limitation of the "standard" Markov model, particularly when run as a deterministic model, is the inability to readily modify transition probabilities based on past events (for example, number of prior pregnancies). Because the ability to modify the probability of the relevant outcomes based on past events is a critical requirement of the model, we used microsimulation, which allows further conditioning of transition probabilities on events prior to the current cycle.

Software

The model was built in TreeAge Pro 2012 (Williamstown, MA: TreeAge, Inc.). Our decision to use TreeAge was based on our familiarity with it; most of our previous models were built using this program, which facilitated incorporating major portions of the relevant models. Iterative model building and modification, tree structure, updating parameters, using distributions, and model debugging are all relatively easy, and, given its widespread use among decision analysts, sharing of the model for purposes of review or collaboration is also straightforward. The major disadvantage of TreeAge is the relatively high computing resource requirements for complex stochastic simulations—some of the longer, more complex simulation

took more than 48 hours, even on a computer optimized for simulations. Given many of the uncertainties involved in this project, we prioritized flexibility in model building and revision over computational time. Ultimately, after a "final" structure has been identified, efficiency could be gained by recreating the model in a more efficient computing language.

Simulation Method

The model is run as a microsimulation of U.S. females, starting at a uniform age of 10 and drawing from the current U.S. racial/ethnic distribution (defined as non-Hispanic white, African-American, Hispanic, and other). By performing a microsimulation, we can use TreeAge's "tracker variable" capacity to allow the model to have "memory" of past events (e.g., time since last use of OCs, or age at menarche) in order to modify appropriate transition probabilities. Microsimulation also facilitates techniques such as value-of-information analysis for identifying future research priorities.

Cycle Length

The model has cycles of 1 month duration, with all transition probabilities adjusted appropriately (e.g., annual cancer incidences are converted to monthly probabilities).

Model States, Allowed Transitions, and Probabilities

Through the descriptions below, we refer to sources for parameter estimates, such as age- and race-specific rates, race-specific distributions of age, etc. In general, wherever possible, these data were used to define specific conditional probabilities based on age, race, or other relevant factors. For example, we used data on age- and race-specific prevalence of ever use of OCs to generate estimates of the monthly probability of starting OCs, given no prior use for each age and racial/ethnic category.

At the time of initial model building, the most recent available population data for many of our parameters at the time of initial model construction was from 2007. Unless otherwise noted, all values reflect estimates from that year. Subsequent versions of the model can be readily updated. When possible, we used point estimates and distributions defined by the data as described below.

The main report describes methods and sources for estimates of the relative risk of outcomes conditional on OC exposure, as well as the methods used to estimate incidence in exposed and unexposed women based on relative risk, prevalence of exposure, and overall incidence.

Demographic Variables

Race/ethnicity. We used U.S. Census estimates of the 10- to 14-year-old female population in 2007 (http://www.census.gov/popest/data/intercensal/national/nat2010.html), divided into 4 mutually exclusive categories: non-Hispanic whites (56.9%), non-Hispanic blacks (14.9%), Hispanic (20.3%), and non-Hispanic other race (7.9%). Because the errors around these estimates are so small, we did not model these as distributions.

*General states***:** For the purpose of estimating the overall balance of benefits and harms, nine health states potentially affected by OC use are included, in addition to other-cause mortality.

Other-cause mortality. During every cycle, individuals are at risk for age- and race-specific mortality for females. Once any of the potentially fatal states related to OCs become possible, other cause mortality is defined as age- and race-specific mortality for females minus cause-specific mortality for the five cancers, the four acute vascular events (DVT, PE, MI, and stroke), and pregnancy-related mortality.

Age-specific and race/ethnicity-specific all-cause mortality for females for 2007 was obtained from death certificate data maintained by the National Center for Health Statistics, accessed through the CDC's WONDER Web portal. We then subtracted the number of deaths attributed to malignancies of the ovary (C56), breast (C50), cervix (ICD-10 code C53), colon and rectum (C18-20), and uterine corpus (C54-55) as well as deep venous thrombosi (I82.8-I82.9), pulmonary embolism (I26), ischemic stroke (I63), and acute myocardial infarction (I21) from the total.

The monthly age- and race-specific probability of other cause mortality was then estimated by dividing the annual number of deaths in a given age/race/ethnicity stratum by the total number of women in that stratum in the Census data; this annual rate was then converted to a monthly probability by using the following formula:

$$Probability = 1 - e^{Rate*Time}$$

In order to facilitate simulations, we elected not to model these probabilities as a distribution for the purposes of the analyses presented here, but they could readily be transformed into beta distributions.

Table F-1. Deaths from causes other than ovarian, breast, cervical, colorectal, or endometrial cancers, or deep venous thrombosis, pulmonary embolism, stroke, or acute myocardial infarction, by age and race/ethnicity, U.S. females, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
5-9	647	235	251	49
10-14	760	291	239	63
15-19	2404	630	485	163
20-24	2985	926	665	223
25-29	3315	1216	698	237
30-34	3744	1415	721	280
35-39	5845	2154	916	357
40-44	9954	3111	1175	548
45-49	16489	4772	1583	738
50-54	22347	6047	2003	885
55-59	29258	6469	2405	1198
60-64	39267	6051	2726	1376
65-69	48550	6658	3271	1649
70-74	66511	7427	4245	2076
75-79	102413	7466	5855	2764
80-84	149152	6942	7016	3460
85-89	174304	4268	6319	3184
90-94	137341	2321	4433	2294
95-99	61555	1623	2030	854

Cancers: Ovarian, breast, cervical, colorectal, endometrial. For each cancer, the probability of transitioning from one of the noncancer states is the age- and race-specific incidence for women (based on national registry data), adjusted for reproductive history and use of OCs using adjusted odds ratios and/or hazard ratios obtained from the literature review. Key assumptions include:

- For all nongynecologic cancers, we assume cancer incidences are independent and non-mutually exclusive—for example, an endometrial cancer survivor will still be at risk for breast cancer at the appropriate age- and race-specific value. Other than BRCA carriers, we assume that development of one type of cancer implies an increased risk for certain other types.

- We include only invasive cancers, not *in situ* or preinvasive lesions.

- We assume that definitive therapies for ovarian, cervical, and endometrial cancer eliminate the possibility of developing another cancer of the female genital tract.

- Cancer incidences are not adjusted for screening behaviors—SEER incidence statistics, for example, represent the weighted average of cancer incidence and stage distribution among screened and unscreened populations. Although reproductive history, including contraceptive use, may affect screening behavior, we did not attempt to adjust for this.

- Cancer survival reflects the weighted age- and race-specific stage distribution—we do not separate cancers by stage at this level of the simulation. Although incorporating stage distribution in subsequent versions of the model may have value for comparing the potential effects of primary prevention of ovarian cancer with OCs to screening, modeling stage-specific outcomes would increase the complexity of the model without providing significant benefit in terms of the primary questions of interest.

- We do not separate specific cancers by histologic subtype (e.g., epithelial versus germ cell tumors of the ovary, or squamous versus adenocarcinomas of the cervix).

- After cancer diagnosis, individuals are at risk for cancer-specific mortality for 5 years, then assumed to be cured, primarily because of variable data on longer term recurrence risk. This may underestimate lifetime mortality for some cancers, particularly breast cancer.

Allowed transitions: Cancer-specific death, cancer survivor, other cancers, other cause mortality, menopause

We obtained estimates of the age-specific (in 5-year age groups) incidence of ovarian, breast, cervical, colorectal, and endometrial cancers from two sources: (1) the Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute (http://seer.cancer.gov/canques/index.html) and (2) the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (http://wonder.cdc.gov/wonder/help/cancernpcr-v2009.html). Cancer incidence was modeled in a similar fashion to other cause mortality, using the estimated number of cases. We converted incidence (a rate), to probabilities as described above, and assumed that the pooled odds ratios from the meta-analyses were reasonable estimates of the relative risk. For cancer, we used these

numbers and the Census population estimates to beta distributions (which are bounded between 0 and 1) for probabilistic analyses.

Table F-2. Number of ovarian cancers by age and race/ethnicity, United States, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	30	0	21	0
15-19	62	27	26	0
20-24	114	17	38	0
25-29	131	26	40	0
30-34	191	22	41	26
35-39	369	44	74	38
40-44	676	98	132	50
45-49	1263	139	156	82
50-54	1740	201	172	107
55-59	1948	188	200	81
60-64	2084	210	140	81
65-69	1885	196	135	51
70-74	1759	165	110	53
75-79	1716	148	107	31
80-85	1593	103	74	27
85+	1521	108	57	22

Table F-3. Number of breast cancers by age and race/ethnicity, United States, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	0	0	0
20-24	83	38	32	0
25-29	514	160	125	0
30-34	1485	414	364	46
35-39	4072	994	760	171
40-44	9202	1843	1393	336
45-49	15407	2659	1788	714
50-54	17534	2965	1741	998
55-59	19690	2913	1576	973
60-64	20700	2536	1484	854
65-69	19000	2250	1285	688
70-74	16115	1776	960	497
75-79	15172	1387	764	355
80-85	12543	1072	513	264
85+	10698	874	360	156

Table F-4. Number of cervical cancers by age and race/ethnicity, United States, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	16	0	0
20-24	81	66	26	0
25-29	326	145	103	0
30-34	597	170	197	21
35-39	952	225	295	72
40-44	999	265	294	51
45-49	1013	218	254	73
50-54	843	198	197	68
55-59	739	161	157	72
60-64	600	135	125	62
65-69	478	112	86	26
70-74	349	94	64	23
75-79	301	63	55	19
80-85	252	60	34	21
85+	219	0	24	0

Table F-5. Number of colorectal cancers by age and race/ethnicity, United States, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	23	0	0	0
20-24	49	0	0	0
25-29	131	36	26	0
30-34	245	56	51	24
35-39	562	150	120	40
40-44	1213	312	177	67
45-49	2185	582	276	151
50-54	3498	943	452	261
55-59	4220	953	437	281
60-64	4901	888	447	254
65-69	5792	945	475	270
70-74	6504	1015	429	289
75-79	7935	950	504	286
80-85	8240	815	411	233
85+	9799	768	351	208

Table F-6. Number of endometrial cancers by age and race/ethnicity, United States, 2007

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	0	0	0
20-24	0	0	0	0
25-29	73	17	55	0
30-34	224	42	92	24
35-39	539	64	151	46
40-44	1010	129	205	96
45-49	2107	219	211	149
50-54	3945	348	311	250
55-59	5401	555	399	236
60-64	5491	683	382	197
65-69	4273	649	294	135
70-74	3276	494	212	92
75-79	2762	352	141	75
80-85	2191	199	98	25
85+	1759	154	57	0

We converted incidence (a rate), to probabilities as described above, and assumed that the pooled odds ratios from the meta-analyses were reasonable estimates of the relative risk. We modeled the conditional probability of dying from each cancer for the first 5 years after diagnosis by using SEER relative survival data, stratified by age group and race. Survival data are stratified only as white versus black, without adjustment for ethnicity. We assumed that survival for Hispanics and non-Hispanic other races was identical to whites, and applied the estimates for blacks to non-Black Hispanics.

We used the number of cases at the start of the followup period and the reported relative survival rates for each year shown in the tables to generate estimates of the number of patients alive and dead at the start of each interval. These numbers were then used to create beta distributions for the annual probability of death, which were subsequently converted to monthly probabilities.

Table F-7. 5-year relative survival by age and race for ovarian cancer

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	1106	93.90%	87.80%	83.30%	79.50%	74.40%
45-45	1805	91.00%	80.80%	71.60%	65.00%	59.20%
55-64	2197	86.10%	73.70%	61.70%	52.50%	46.10%
65-74	1829	76.00%	60.90%	50.40%	41.70%	34.00%
75+	2568	1.00%	1.20%	1.30%	1.40%	1.50%
Black						
Age						
0-44	171	50.80%	38.70%	31.60%	25.60%	21.70%
45-45	195	87.20%	77.70%	69.70%	66.30%	62.90%
55-64	207	76.90%	62.80%	52.60%	44.70%	38.60%
65-74	174	67.90%	55.70%	41.20%	38.20%	33.10%
75+	169	40.80%	30.40%	22.20%	15.20%	14.40%

Table F-8. 5-year relative survival by age and race for breast cancer

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	11,155	99.00%	96.40%	94.10%	91.90%	89.60%
45-45	21,053	99.00%	97.20%	95.20%	93.60%	92.20%
55-64	21,814	98.30%	96.70%	95.00%	93.40%	91.90%
65-74	16,933	98.10%	96.90%	95.10%	93.40%	92.20%
75+	18,574	0.10%	0.20%	0.30%	0.30%	0.40%
Black						
Age						
0-44	2090	96.40%	94.40%	92.90%	91.90%	90.50%
45-45	2943	96.70%	90.00%	83.90%	79.70%	75.90%
55-64	2476	96.60%	90.20%	85.10%	81.10%	77.90%
65-74	1599	95.50%	91.00%	87.00%	82.60%	79.60%
75+	1411	88.40%	83.80%	80.10%	74.50%	72.30%

Table F-9. 5-year relative survival by age and race for cervical cancer

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Follow-up	1 year	2 years	3 years	4 years	5 years
0-44	2,160	95.90%	90.00%	87.00%	85.60%	84.80%
45-45	1,059	88.40%	79.10%	73.70%	70.10%	66.30%
55-64	686	83.10%	71.40%	66.80%	63.90%	61.00%
65-74	456	77.60%	69.50%	61.60%	57.80%	53.30%
75+	378	2.00%	2.30%	2.60%	2.70%	3.00%
Black						
Age						
0-44	369	59.00%	45.50%	41.00%	36.00%	30.30%
45-45	218	90.30%	79.70%	75.70%	74.10%	73.30%
55-64	171	85.70%	75.90%	71.60%	65.30%	60.00%
65-74	105	82.10%	71.00%	67.80%	62.50%	59.40%
75+	94	60.00%	43.90%	42.00%	35.60%	28.70%

Table F-10. 5-year relative survival by age and race for colorectal cancer

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	1,384	93.10%	85.60%	79.30%	75.70%	72.50%
45-45	3,150	92.70%	85.80%	80.90%	76.40%	73.70%
55-64	4,574	90.00%	82.40%	77.30%	73.50%	70.40%
65-74	6,334	85.40%	78.80%	74.30%	71.10%	68.90%
75+	13,107	0.50%	0.60%	0.60%	0.70%	0.80%
Black						
Age						
0-44	323	74.90%	68.50%	64.60%	62.70%	61.30%
45-45	764	89.00%	76.20%	69.00%	63.80%	63.20%
55-64	952	88.30%	79.90%	73.60%	68.60%	65.70%
65-74	948	85.00%	74.90%	68.80%	65.10%	61.30%
75+	1246	67.10%	58.50%	52.60%	50.00%	46.80%

Table F-11. 5-year relative survival by age and race for endometrial cancer

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	1,271	97.60%	94.90%	93.80%	92.40%	91.70%
45-45	3,571	96.40%	94.40%	92.50%	91.40%	90.10%
55-64	5,719	96.10%	93.30%	91.00%	89.50%	89.10%
65-74	4,007	94.00%	89.70%	87.20%	85.60%	83.90%
75+	3,606	0.40%	0.60%	0.70%	0.70%	0.90%
Black						
Age						
0-44	226	86.80%	80.70%	76.90%	74.70%	73.90%
45-45	309	90.40%	84.30%	80.00%	76.20%	74.70%
55-64	538	84.90%	76.50%	69.90%	67.30%	66.50%
65-74	470	86.50%	75.70%	71.00%	64.70%	63.40%
75+	269	70.50%	58.40%	49.80%	49.00%	46.40%

Vascular events: Deep venous thrombosis, pulmonary embolus, stroke, myocardial infarction. As with cancer, age- and race-specific incidences for these states are adjusted for OC use status as described below. Other key assumptions:

- Women who experience one of these events while on OCs will not use OCs afterwards.

- For women under the age of 65, the best population-level data for estimating both incidence and mortality is hospital discharge data. This may underestimate incidence by missing cases that are diagnosed and managed completely as outpatients, and underestimate mortality by missing postdischarge deaths.

Allowed transitions: Condition-specific mortality, survivor, cancers, other acute complications

Estimates of admissions for women by age and race/ethnicity were generated using the Nationwide Inpatient Sample (NIS) dataset from 2000 to 2007, a publicly available survey of a mix of community hospital inpatient settings that surveys diagnoses, procedures, length of stay, and costs associated with approximately 20 percent of all U.S. inpatient discharges (http://www.hcup-us.ahrq.gov/nisoverview.jsp).

Discharges within the NIS data were used to estimate national numbers of admissions for the vascular events of interest, using ICD-9 diagnosis codes, specifically acute myocardial infarction (410.x), pulmonary embolus (415.1), stroke (430.x, 431.x, 432.x, 434.x) and DVT (453.x). Estimates were weighted using available survey weights and subset into mutually exclusive categories comprised of 5-year age groups (15–85+) and race/ethnicity categories (white, black, Hispanic, other).

Hospital admission probabilities were estimated by using the point estimate and standard errors to generate gamma distributions (bounded by 0 at the lower end) for the annual number of admissions. During the simulations, the probability was calculated by drawing a number from the gamma distribution, dividing this number by the total number of women in a given age and race/ethnicity stratum and converting the rate to a probability.

We present only point estimates here—the standard errors used to generate the gamma distributions are available from the authors.

Table F-12. Annual admissions for deep venous thrombosis by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	678	210	125	25
20-24	1320	577	253	70
25-29	1813	928	499	198
30-34	2359	1292	617	215
35-39	3159	1687	747	250
40-44	4914	2529	874	339
45-49	6373	2955	1086	486
50-54	7330	2794	1132	630
55-59	8443	3008	1280	704
60-64	10024	3167	1225	692
65-69	11163	3127	1350	817
70-74	13111	3560	1405	964
75-79	16762	3206	1603	937
80-85	18656	2918	1444	1106
85+	24442	3645	1658	1218

Table F-13. Annual admissions for pulmonary embolism by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	448	127	56	35
20-24	1020	417	148	45
25-29	1315	622	226	86
30-34	1758	840	233	183
35-39	1957	1296	329	143
40-44	3014	1472	484	225
45-49	4150	1476	486	268
50-54	4804	1394	449	299
55-59	5688	1458	479	393
60-64	6406	1340	522	345
65-69	7582	1631	576	437
70-74	8532	1782	616	394
75-79	10044	1655	646	490
80-85	9954	1338	594	475
85+	10793	1368	624	349

Table F-14. Annual admissions for stroke by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	158	104	76	37
20-24	211	112	121	71
25-29	302	180	126	53
30-34	555	312	209	144
35-39	831	446	279	180
40-44	1906	765	389	301
45-49	3348	1398	643	358
50-54	5930	2035	909	555
55-59	8452	1878	1054	790
60-64	13234	1986	1402	910
65-69	17362	2699	1419	1199
70-74	21758	2468	1903	1542
75-79	27856	2821	1796	1708
80-85	29142	2384	1423	1572
85+	31688	2416	1247	1725

Table F-15. Annual admissions for acute myocardial infarction by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	37	5	3	0
20-24	120	64	42	10
25-29	259	204	57	15
30-34	606	446	132	58
35-39	1472	567	194	134
40-44	3297	1169	524	389
45-49	6388	2155	872	617
50-54	9631	3034	1280	912
55-59	13318	3374	1774	1243
60-64	18156	3552	1979	1329
65-69	20389	3720	2310	1985
70-74	24600	4162	2365	1973
75-79	31846	4013	2733	2298
80-85	37194	3768	2392	2480
85+	58620	4883	2690	3046

Mortality for each event was estimated using the number of patients in a given age/race stratum in the NIS with each diagnosis who had a discharge status of "death," together with the total number of admissions within a given diagnosis/age/race stratum, to generate beta distributions for the conditional probability of death given the occurrence of the event. We assumed all deaths occurred during the same cycle as the event.

Table F-16. Annual deaths during hospitalization for deep venous thrombosis by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	8	3	0	0
20-24	10	5	9	5
25-29	21	11	10	0
30-34	47	9	19	10
35-39	54	44	47	10
40-44	92	45	18	10
45-49	140	120	42	20
50-54	296	111	50	48
55-59	405	139	72	36
60-64	444	194	79	55
65-69	629	156	54	63
70-74	816	212	64	76
75-79	1136	186	145	57
80-85	1081	194	96	117
85+	1686	297	139	77

Table F-17. Annual deaths during hospitalization for pulmonary embolism by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5	0	0	5
20-24	20	14	9	0
25-29	15	16	10	5
30-34	26	10	14	10
35-39	30	61	21	5
40-44	87	69	44	5
45-49	145	119	30	10
50-54	354	106	13	37
55-59	347	115	45	26
60-64	521	170	89	43
65-69	618	114	33	55
70-74	723	158	50	30
75-79	811	140	88	56
80-85	907	105	42	50
85+	1225	176	85	59

Table F-18. Annual deaths during hospitalization for stroke by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	39	15	0	0
20-24	14	10	14	15
25-29	38	25	5	8
30-34	34	55	24	0
35-39	154	77	37	9
40-44	216	137	47	42
45-49	285	177	81	48
50-54	474	250	133	66
55-59	539	203	123	96
60-64	683	172	110	131
65-69	793	274	99	87
70-74	1148	177	171	160
75-79	1491	292	165	201
80-85	2096	232	143	185
85+	2992	329	175	221

Table F-19. Annual deaths during hospitalization for myocardial infarction by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	13	0	0	0
20-24	10	5	0	4
25-29	15	10	9	0
30-34	31	24	19	0
35-39	69	57	5	10
40-44	132	76	32	6
45-49	244	155	51	36
50-54	519	166	60	44
55-59	834	232	169	71
60-64	1235	334	164	84
65-69	1574	378	179	167
70-74	2359	410	203	246
75-79	3595	447	337	289
80-85	4892	504	391	328
85+	9507	803	502	463

Surgical removal of pelvic organs—hysterectomy and/or oophorectomy. Removal of the organ at risk eliminates the probability of developing cancer in that organ, and there is some evidence that removal of the uterus reduces ovarian cancer risk even if the ovaries are preserved. Because hysterectomy is performed for a variety of indications, often with removal of the ovaries, and is quite common in the U.S. (with up to 30% of women undergoing hysterectomy by age 65), we incorporated age- and race-specific hysterectomy and oophorectomy rates for

conditions other than cancers of the pelvic organs into the model, and adjusted probabilities for cancer development accordingly. We assumed the following:

- The probability of hysterectomy and/or oophorectomy is independent of OC use. Because OCs may reduce the risk of some conditions such as endometriosis which are common indications for hysterectomy, this may not be the case.

- These procedures are increasing being done on an outpatient basis; relying on discharge data may underestimate the rates.

Estimates were again derived from the NIS, excluding women with a diagnosis of any cancer of the cervix (180.x), uterus (182.x), or ovary (183.x). ICD-9 procedural codes were used to identify hysterectomy alone (68.4x, 68.5x, 68.9x), and with either bilateral (65.5x, 65.6x) or unilateral (65.3x, 65.4x) oophorectomy. Unilateral and bilateral oophorectomy without hysterectomy were also included. As with vascular event hospitalizations, we used point estimates and standard errors to generate gamma distributions, which in turn provided the numerator for estimating age- and race/ethnicity-specific probabilities.

Table F-20. Annual hospitalizations for hysterectomy alone by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	25	6	24	0
20-24	714	108	122	49
25-29	4002	634	482	146
30-34	8491	1902	1702	621
35-39	15776	4940	3920	1177
40-44	20735	7021	5494	2251
45-49	15636	4261	3401	1645
50-54	6093	970	1074	514
55-59	3002	198	534	205
60-64	2718	149	367	217
65-69	2545	108	413	198
70-74	2056	104	239	185
75-79	1753	52	152	85
80-85	864	11	64	40
85+	206	37	4	4

Table F-21. Annual hospitalizations for hysterectomy with unilateral oophorectomy by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5	0	6	0
20-24	149	10	5	11
25-29	743	86	68	44
30-34	1786	373	245	90
35-39	3235	951	704	250
40-44	4616	1448	956	353
45-49	3749	1137	760	460
50-54	1332	308	200	126
55-59	489	84	76	59
60-64	391	25	56	22
65-69	286	15	38	48
70-74	285	10	18	9
75-79	112	11	38	11
80-85	108	0	9	8
85+	30	0	5	0

Table F-22. Annual hospitalizations for hysterectomy with bilateral oophorectomy by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	23	0	5	0
20-24	271	24	16	9
25-29	1735	175	121	98
30-34	4125	494	316	190
35-39	7284	1208	813	465
40-44	15616	2885	2084	1200
45-49	24673	5260	3907	2450
50-54	17672	3307	2420	1760
55-59	8733	1052	1089	739
60-64	5847	723	705	413
65-69	4438	402	519	344
70-74	2644	244	317	238
75-79	1859	142	196	180
80-85	993	63	49	46
85+	507	52	43	14

Table F-23. Annual hospitalizations for unilateral oophorectomy alone by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5463	1904	1950	687
20-24	10375	3427	3351	1243
25-29	17637	5439	4719	2273
30-34	25214	7276	6309	3143
35-39	32831	9368	6856	3604
40-44	34752	9753	6658	4054
45-49	25178	6270	4215	2605
50-54	12685	2130	1465	1070
55-59	8212	1123	788	456
60-64	6798	879	659	293
65-69	6914	638	618	384
70-74	7135	593	470	341
75-79	6949	560	382	288
80-85	5161	291	235	150
85+	3865	193	155	118

Table F-24. Annual hospitalizations for bilateral oophorectomy alone by age and race/ethnicity for U.S. females

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	149	34	49	24
20-24	859	140	151	71
25-29	3819	645	483	204
30-34	9314	2026	1179	536
35-39	17836	4083	2461	1165
40-44	31852	7904	4411	2315
45-49	43168	9786	5895	4124
50-54	33232	5858	3512	2399
55-59	21266	2267	1717	1327
60-64	17005	1460	1258	819
65-69	15796	1270	1117	711
70-74	13198	672	808	639
75-79	10171	463	548	465
80-85	5990	286	283	194
85+	3048	104	126	163

Reproductive States

Menopause. We used published data to generate conditional probabilities of natural menopause by age.[3] Although the paper by Gold et al. found some differences in menopause probabilities by race and ethnicity, hazard ratios included 1, and we elected to model only age-specific probabilities. We assumed that women undergoing bilateral oophorectomy with or without hysterectomy, as well as women receiving definitive treatment for gynecologic cancers, were menopausal. We did not adjust menopausal probabilities in women who had undergone hysterectomy with ovarian preservation. We assumed that no woman underwent nonsurgical menopause prior to age 41, and all women had undergone menopause by age 55.

Table F-25. Conditional probability of natural menopause by age

Age	Conditional Probability
15-40	0.00%
41	1.02%
42	1.03%
43	1.04%
44	1.05%
45	2.15%
46	4.49%
47	4.71%
48	11.84%
49	11.76%
50	23.64%
51	37.50%
52	60.00%
53	66.67%
54	100.00%

*Allowed transitions***:** Other cause mortality, cancers, acute complications

Probability of contraceptive use. Estimates of contraception use were generated using the National Survey of Family Growth (NSFG) 2002 and 2006 to 2010 data sets. The NSFG is a survey conducted by the Centers for Disease control that gathers information on family life, marriage and divorce, pregnancy, infertility, use of contraception, and men's and women's health (http://www.cdc.gov/nchs/nsfg.htm), and supplemented with the literature as needed.

Estimates of national female contraception prevalence rates and accompanying standard deviations were generated using the NSFG dataset. All estimates were subset by age, race, and prior pregnancy/birth status distribution and were weighted to generate national-level estimates. Survey data was limited to women aged 15 to 44 and excluded women pregnant at the time of the survey. All other women were included. Total survey weights reflected 59 million women aged 15 to 44. Subset analysis was performed by creating several mutually exclusive categories. Age was analyzed by categorizing patients into 5-year age groups (6 groups total); race/ethnicity as white, black, Hispanic, or other; and prior birth and pregnancy status as never pregnant, pregnant with no live births, one live birth, two live births, or more than two live births. For each of these groups, estimates were for the following contraception categories:

1. Female sterilization

2. Male sterilization

3. OCs

4. Other hormonal methods (Norplant or Implanon implant, Lunelle (injectable), Depo-Provera (injectable), contraceptive patch, contraceptive ring, morning-after pill)

5. IUD

6. Barrier methods (diaphragm with or without jelly or cream, male condom, foam, Today sponge, suppository or insert, jelly or cream without diaphragm)

7. Periodic abstinence (NFP, cervical mucus test or temperature rhythm, calendar rhythm)

8. No method (withdrawal, other method, other nonuser—had intercourse in the 3 months prior to interview)

9. Not sexually active (other nonuser—never had intercourse since first period, other nonuser—has had intercourse but not in the 3 months prior to interview)

10. Other not at risk (pregnant; seeking pregnancy; postpartum; sterile-nonsurgical, female; sterile-nonsurgical, male; sterile-surgical, female noncontraceptive; sterile-surgical, male noncontraceptive; sterile-unknown reasons, male)

For the purposes of this analysis, we categorized contraceptive methods as oral contraceptives, female sterilization, and all others (including nonuse).

Age at first use of OCs. We used age-specific prevalences from the NSFG to generate conditional probabilities of use by age and race/ethnicity.

Table F-26. Conditional probability of oral contraceptive use by age and race/ethnicity

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	11.45%	21.82%	5.62%	5.62%
15-19	24.03%	14.37%	12.98%	29.06%
20-24	50.29%	29.86%	46.91%	28.05%
25-29	37.40%	32.34%	22.38%	34.04%
30-34	22.63%	5.58%	22.98%	21.31%
35-39	4.88%	12.80%	14.75%	37.19%
40	0	0	0	0

Duration of use. We found only one study which provided data to generate distributions for duration of use,[4] which reported a mean of 54.8 months with a standard deviation of 41 months. We used these to generate a gamma distribution, with a range of 1-308 months, 10th percentile of 13 months, 50th percentile of 45 months, and 90th percentile of 110 months.

Age-specific probability of tubal ligation. We used published estimates of the number of procedures by age and race/ethnicity, along with the total number of women in each stratum, to generate beta distributions for the probability of tubal ligation.

Table F-27. Conditional probability of oral contraceptive use by age and race/ethnicity

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	0	0	3083	3591
20-24	74769	40201	29260	22458
25-29	670855	155335	125356	66347
30-34	408671	223174	346754	102707
35-39	401060	114853	139134	655
40-44	486188	255996	273579	87172

Model Predictions Compared With SEER Estimates

Table F-28 compares mean predicted lifetime cancer incidence and mortality from age 10 to 100 for a 60,000-iteration simulation of our "base-case" model, where the effects of OC use on age- and race-specific incidence are modeled based on "ever/never" status and population-level estimates of patterns of OC use, and cancer-specific mortality is modeled as age- and race-specific post-diagnosis survival, to estimates for lifetime incidence and mortality from age 10 through 100 derived from the SEER DevCan Program (http://surveillance.cancer.gov/devcan/). DevCan models overall incidence using the same SEER datasets used for the model, but mortality estimates are independently derived based on death certificate data reported to the National Center for Health Statistics.

Table F-28. Model predictions compared with SEER estimates

Cancer Type	Lifetime Incidence		Lifetime Mortality	
	SEER DevCan	Model	SEER DevCan (Death Certificate)	Model (Incidence-based)
Ovarian cancer	1.37%	1.40%	1.98%	0.78%
Breast cancer	12.51%	11.0%	2.8%	0.98%
Cervical cancer	0.69%	0.63%	0.24%	0.01%
Colorectal cancer	4.83%	4.7%	1.98%	1.57%
Endometrial cancer	2.67%	2.1%	0.55%	0.41%

Lifetime incidence estimates—which in both our model and DevCan are based on the same age- and race-specific incidences and competing risks—are quite similar, providing some validation of the estimates of relative risk conditional on OC use used in the model and our underlying structural assumptions. The model-derived mortality estimates, which are independent of OC use and are based on age- and race-specific (black/white only) conditional survivals, are consistently lower than the DevCan estimates, which are derived from death certificate data. This is consistent with other "incidence-based mortality" models, where overall mortality estimates are derived from specific survival functions based on patient or tumor characteristics.[5,6] There are multiple possible explanations for this, including (1) the effect of competing risks for other cause mortality within the model after diagnosis, (2) age/period/cohort effects in the death certificate data that are not reflected in the model estimates, (3) the fact that SEER incidence and survival data represent a sample of the population, while the mortality data are derived from the entire population, and (4) inadequate modeling of mortality more than 5 years after survival (particularly for breast cancer). Since the potential underestimation of mortality affects both potential harms of OC use (breast and cervical cancer) and benefits (ovarian, endometrial, colorectal), the net effect on the overall balance of mortality harm and benefit is unclear—but is clearly worthy of further exploration.

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