Evidence Report/Technology Assessment
Number 212

Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

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

Evidence-based Practice Program

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 reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. 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.

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.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Evidence-Based Practice

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?

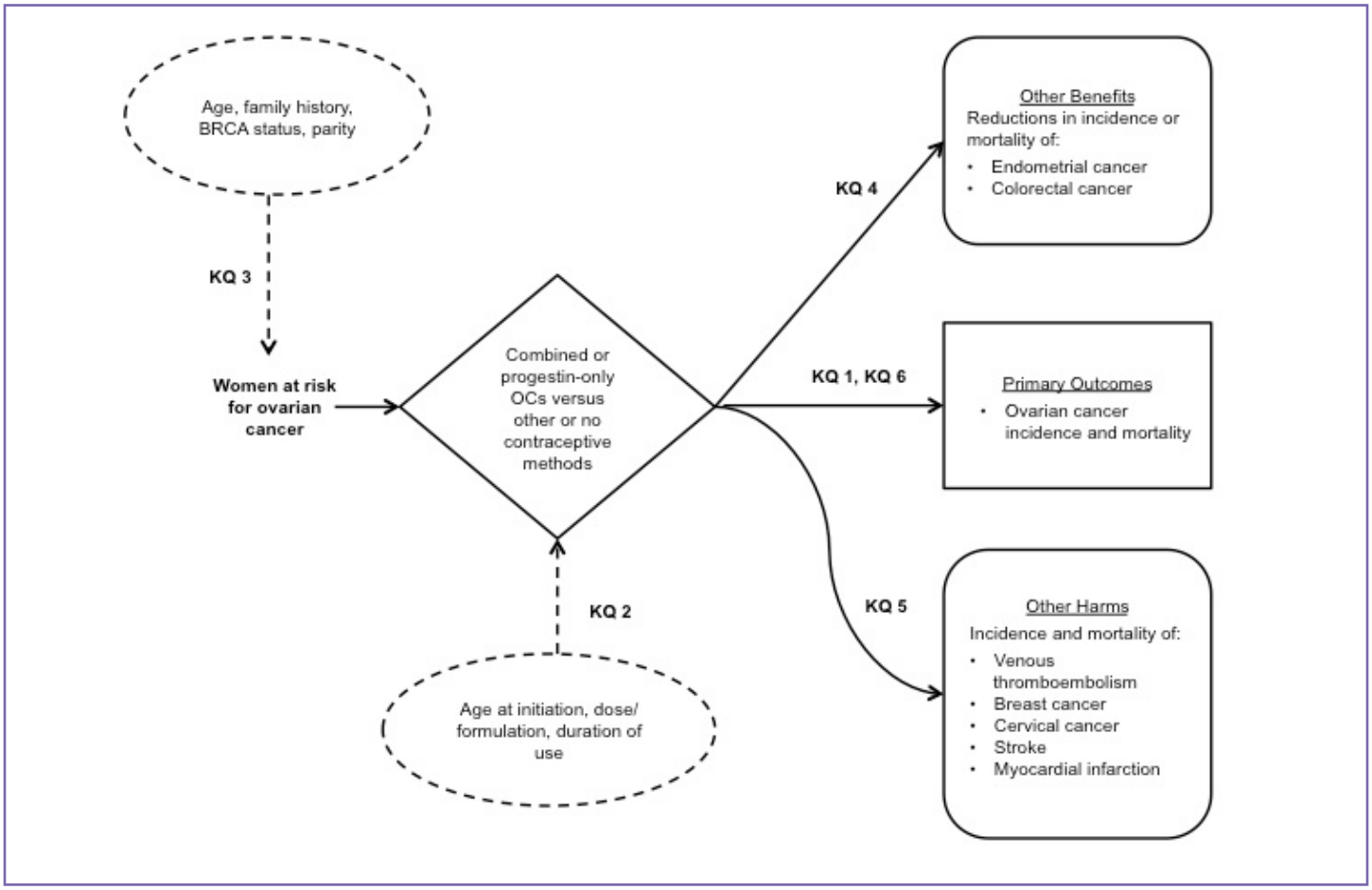
KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life 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: – 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 • KQs 3 and 6: – Women with a family history of ovarian or premenopausal breast cancer, suggesting increased risk according to current recommendations – 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: – 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

Table A. Summary of inclusion and exclusion criteria (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, 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: – Study reports an ovarian cancer outcome of interest and was published on or after Jan. 1,1990[d] – Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after Jan. 1, 2000[e] – 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)	Risk of Bias	Consistency	Directness	Precision	SOE and Magnitude of Effect (95% CI)
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)

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	
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) 5–30 yr: 0.67 (0.46 to 0.99) > 30 yr: 0.89 (0.60 to 1.32)
Time since last use	8 (210,069 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) 2 0–30 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 nulligravid/nulliparous women						
Ever vs. never use	2 (4,732 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient**

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	
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, 0.58; 95% CI, 0.45 to 0.73).

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** 0.58 (0.45 to 0.73)
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

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

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	
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)
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

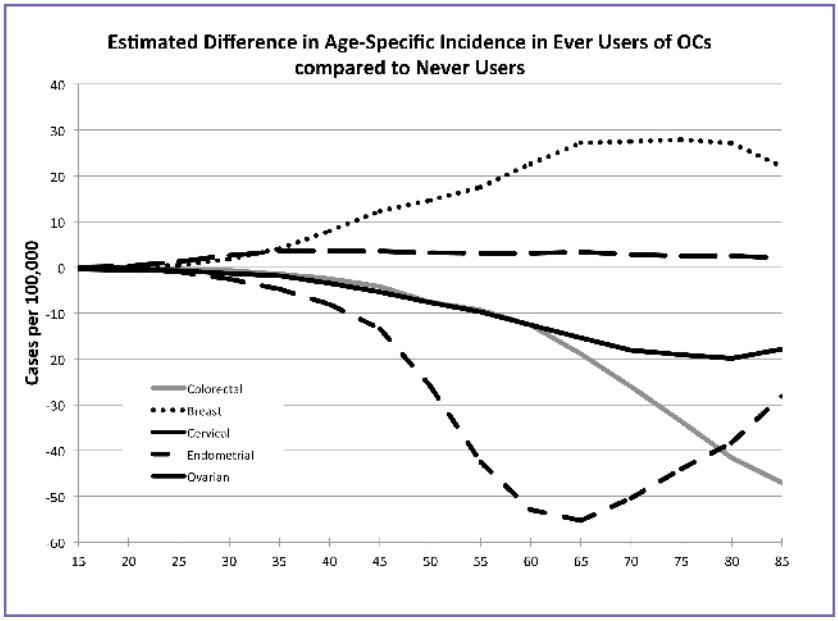
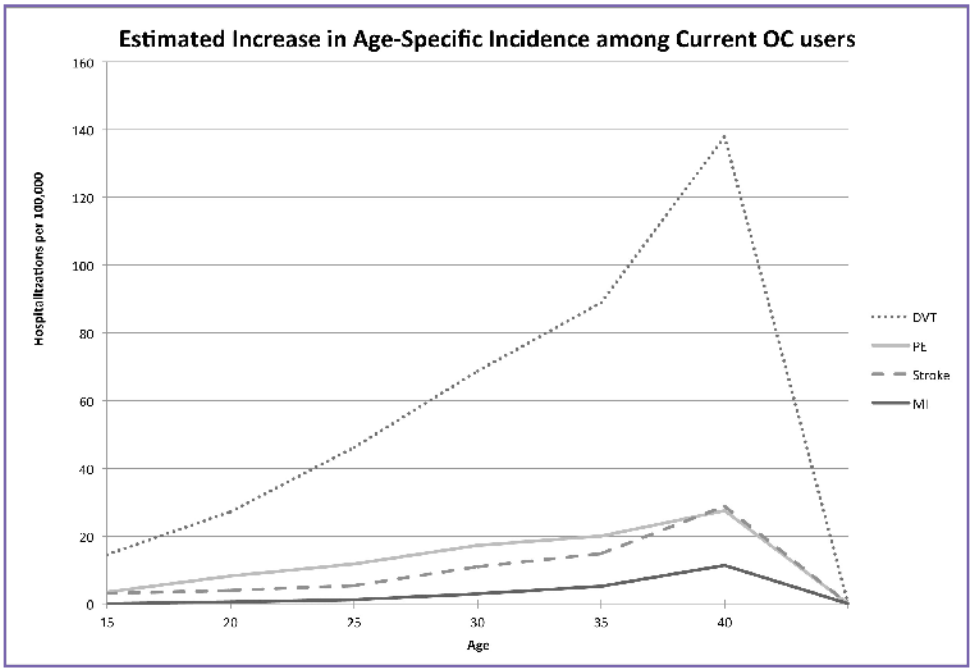


Figure C. Increase in age-specific incidence of vascular events in current OC users versus noncurrent users



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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Full Report

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