

Evidence-based Practice Center Systematic Review Protocol

Project Title: Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

Amendment Date(s) if applicable: February 16, 2012

(Amendments Details—see Section VII)

I. Background and Objectives for the Systematic Review

Although ovarian cancer is only the eighth most common cancer in women (annual age-adjusted incidence 12.3/100,000), it is the fifth leading cause of cancer deaths (8.2/100,000).¹ Given current age-specific incidence data and U.S. Census demographic projections, we estimate that the annual number of new ovarian cancer cases will almost double (to 40,000) over the next 25 years as the baby boom generation reaches the ages of highest risk.² The high mortality rate has been largely attributed to the fact that ovarian cancer typically presents at a much later stage than other common cancers.¹ This in turn has led to intense interest in developing screening strategies, with disappointing results to date, especially in terms of mortality reduction.³⁻⁹ However, several factors limit the success of screening for this disease: the cause of ovarian cancer is unknown; there is no definitive preinvasive stage; and, most important, there is no physical barrier to impede rapid spread from the surface of the ovary (FIGO Stage I) to the upper abdomen (FIGO Stage III).¹⁰ The possibility of rapid spread from the ovary means that many 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. 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, as suggested by previous work from our group.¹¹

Given that the potential effectiveness of screening for reducing morbidity and mortality from ovarian cancer is limited by the underlying biology of the disease, alternative strategies, including both more efficacious and less toxic therapies after diagnosis and primary prevention, need to be considered and evaluated. Oral contraceptives (OCs) represent the most 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.^{12,13} OCs have both other noncontraceptive health benefits^{14,15} and harms, including premature death.¹⁶⁻¹⁹ The combination of a systematic review and decision analytic modeling will allow us to estimate the tradeoffs between these harms and benefits for the overall population and for individual women, accounting for the potential influence of other factors such as OC formulation and intervening pregnancies.

II. The Key Questions

The draft key questions (KQs) were distributed to the Technical Expert Panel (TEP) members for review and discussion during a teleconference held with the EPC research team, AHRQ Task Order Officers, and partner organization representatives on January 18, 2011. The TEP members accepted the key questions as written, with no suggestions for revision. KQ 6 was subsequently revised for clarity after further discussion with AHRQ. The TEP members recommended ranking the candidate outcomes for consideration according to the potential impact OC use might have on them. This process is described further in section IV F.

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 (e.g., reducing the risks of conditions such as benign ovarian cysts, endometriosis, endometrial hyperplasia, endometrial cancer or dysmenorrhea, acne, colorectal cancer, dysfunctional uterine bleeding, or premenstrual dysphoric disorder)?

KQ 5: What are the harms of OC use, including, but not necessarily limited to, breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, neurological conditions, stroke, or cardiovascular disease? 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 primary prevention of ovarian cancer?

Population(s):

All KQs: Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy

KQs 3 and 6: (1) Women with a strong family history of ovarian or premenopausal breast cancer

(2) Women with a known BRCA1/BRCA2 mutation

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Interventions:

KQs 1–7: OC use for varying time periods; OC use with different formulations

Comparators:

KQs 1–7: 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 [IUDs], injectable or implantable hormonal contraception)

Outcomes for each question:

KQs 1, 2, 3, 6:

- Intermediate outcomes: none
- Final outcomes: diagnosis of ovarian cancer, ovarian cancer mortality, overall mortality
- Adverse effects of intervention(s): see KQ 5

KQ 4:

- Intermediate outcomes: none
- Final outcomes: diagnosis of endometrial cancer, endometriosis, dysmenorrhea, dysfunctional uterine bleeding, acne, colorectal cancer, premenstrual dysphoric disorder, benign ovarian cysts, or endometrial hyperplasia
- Adverse effects of intervention(s): see KQ 5

KQ 5:

- Intermediate outcomes: none
- Final outcomes: diagnosis of breast cancer, cervical cancer, venous thromboembolic event (VTE), stroke, cardiovascular disease (including myocardial infarction; disease-specific mortality associated with these outcomes), meningioma, melanoma
- Adverse effects of intervention(s): Same as final outcomes

KQ 7: Not applicable

Timing:

All KQs: Minimum of 1 year of followup from the start of OC use to diagnosis of ovarian cancer to rule out prevalent cases at the time of starting OCs

Settings:

Studies will not be restricted based on setting.

III. Analytic Framework

Figure 1. Analytic Framework

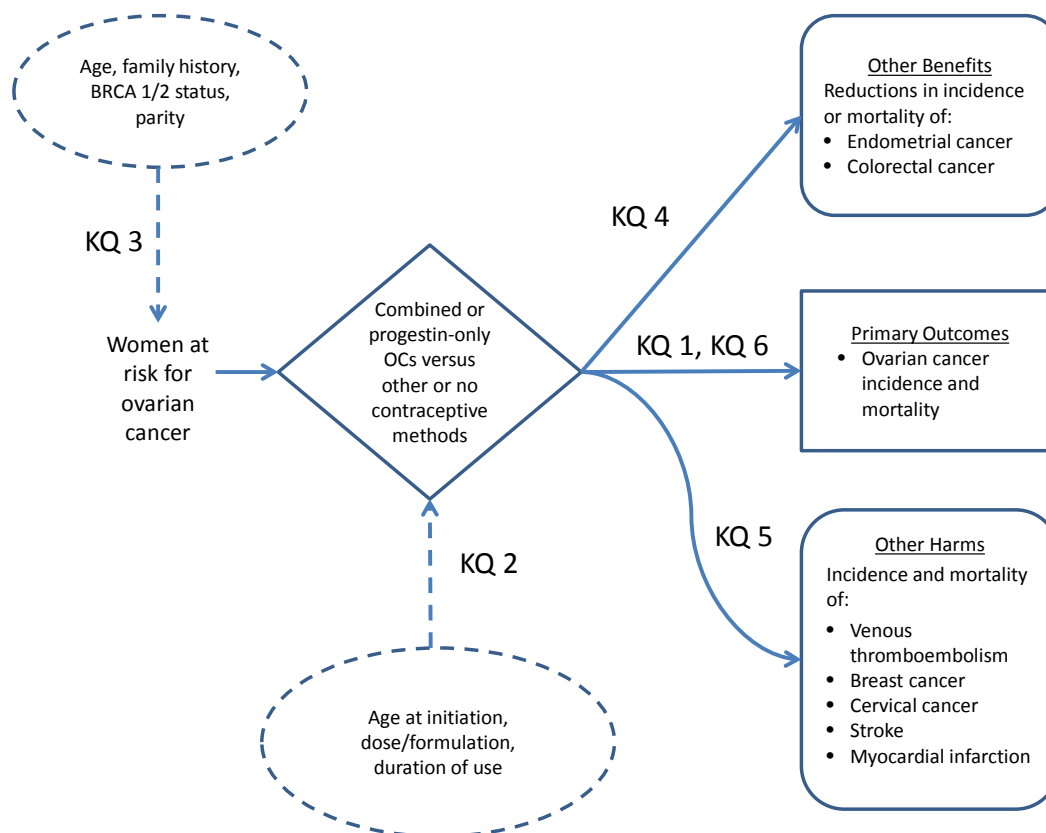


Figure 1 depicts the key questions within the context of the PICOTS (population, interventions, comparators, outcomes, timing, setting) described elsewhere in this document. Women at risk for ovarian cancer, by virtue of having at least one ovary, can use OCs for contraception or other indications at various points during their reproductive years, or use alternative methods of contraception (including no contraception). The difference in the incidence of ovarian cancer between OC users and nonusers provides an estimate of effectiveness of OCs in preventing ovarian cancer (KQ 1). Factors such as the age of starting and stopping OC use, the dose/formulation of OC, and the number and timing of intervening pregnancies (and possibly lactation) may modify this effect (KQ 2). Different subpopulations of women (e.g., based on age, family history, the presence of BRCA1/BRCA2 mutations, or parity) may have different underlying risks of ovarian cancer and/or different responses to OCs (KQ 3). OCs have other benefits, including reducing the risks of conditions such as endometrial hyperplasia, or dysfunctional uterine bleeding (KQ 4). Because these conditions can lead to hysterectomy and/or

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oophorectomy, they may affect ovarian cancer risk indirectly. OCs also increase the risk of certain short-term (e.g., venous thromboembolism) and long-term (e.g., breast cancer, cervical cancer) adverse outcomes (KQ 5). The model, by quantitatively estimating the balance of these benefits and risks, may suggest combinations of patient characteristics and OC usage that indicate a role for OCs in primary prevention of ovarian cancer (KQ 6). Both the systematic review and the model should provide insight into key evidence gaps needed to be filled in order to definitively characterize the potential role of OCs in ovarian cancer prevention (KQ 7, not shown in analytic framework).

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Given the scope of this project, the amount of literature to be reviewed is quite large—we anticipate the need to review at least 5000 abstracts. We plan several broad exclusion criteria:

- Studies published prior to January 1, 1990. Rationale:
 - A major methodological challenge facing this project is that, given the lag time between OC exposure and subsequent ovarian cancer development, much of the literature will be based on OC formulations that are no longer on the market. In particular, much of the literature in the 1970s and 1980s will be based on first-generation OCs, which had much higher estrogenic doses than more recent OCs. Therefore, in order to maximize the generalizability of the results, we plan on limiting the search to a time period where the likelihood that the types of OCs used by subjects were similar to those currently available.
 - Based on the EPC team's prior experience in conducting observational studies of the association between OCs and ovarian cancer, even more recent studies will include some women who developed cancer in their 70s and 80s who used higher dose OCs. Because of this, it will be difficult to exclude studies based on the age/cohort of the study. We believe that the (admittedly arbitrary) cutpoint of 1990 should maximize the probability that at least some members of the cohort used more contemporary OC formulations. Pre-1990 studies are likely to be included in meta-analyses that meet our inclusion criteria so that some data on the association between earlier formulations and ovarian cancer risk should be available. We would also note that, since one of the areas of focus of this project is other benefits and harms of OCs, many of which occur within several years of initial use, focusing on more recent literature (which will still be quite large) is more likely to provide clinically relevant information.

- Non-English language studies. Rationale:
 - OC formulations are not universally approved across countries. Non-English language studies may be more likely to include OCs not available in the U.S.
 - Based on prior experience with evidence reports and comparative effectiveness reviews (CERs) in women's health, the potential yield of high-quality studies published in non-English language journals has been quite small. Given the high volume of literature to search and abstract, we do not believe that the resources required for translation of non-English articles are justified by the low potential likelihood of ultimately including those articles.
- Nonhuman studies. Rationale:
 - Although studies with nonhuman subjects may provide some important background data about mechanisms of action, such studies, without some evidence from human studies, do not provide information for making clinical judgments.

We anticipate that articles will fall into three broad categories:

- Articles meeting inclusion criteria that specifically address one of the key questions but which may not provide data relevant to the model
- Articles that provide some data to inform the model but which due to either the study design (e.g., non-systematic reviews) or the questions considered (e.g., association between hysterectomy with ovarian preservation and ovarian cancer risk) are not directly applicable to the key questions
- Articles that are useful for both the systematic review and the model

We do not anticipate the need to search the grey literature since the high volume of peer-reviewed literature identified in our preliminary search makes it unlikely that a systematic search of the grey literature would substantially increase the chances of identifying relevant data that would meet inclusion criteria. Also, at this point we do not plan to directly contact authors. The one exception may be in the case where data on the distribution of key variables would be helpful for the model; in this case, we will contact the authors regarding the availability of summary statistics for those variables that would allow more precise distribution characterization.

For articles relevant to the systematic review, we will use these criteria:

Inclusion criteria:

- Controlled studies (randomized trials, cohort studies, or case-control studies), meta-analyses, or systematic reviews study-level will be,
- Study reports quantitative association between exposure to OC use and one of the relevant outcomes listed below:

For KQs 1, 2, 3, 6:

- Final outcomes: diagnosis of ovarian cancer, ovarian cancer mortality
- Adverse effects of intervention(s): see KQ 5

KQ 4:

- Final outcomes: diagnosis of endometrial cancer, endometriosis, dysmenorrhea, acne, colorectal cancer, or premenstrual dysphoric disorder
- Adverse effects of intervention(s): see KQ 5

KQ 5:

- Final outcomes: diagnosis of breast cancer, cervical cancer, venous thromboembolic event (VTE), stroke, coronary artery disease, myocardial infarction meningioma, melanoma
- Adverse effects of intervention(s): Same as final outcomes

KQ 7: Not applicable

- ❖ Study sample size ≥ 100 subjects for nonrandomized studies. The primary rationale for this criterion is that confidence intervals for outcomes of interest will generally be quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

Exclusion criteria:

- Editorials, letters to the editor, or exploratory studies with inadequate sample size
- Non-systematic reviews

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Our search strategy will use the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we will use

PubMed, EMBASE®, and the Cochrane Database of Systematic Reviews for our literature search. We will date-limit our search to articles published since January 1990. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library and additional manuscripts retrieved. All citations will be imported into an electronic database (DistillerSR).

In developing this comprehensive overview, we will apply the rules of evidence and formulation of strength of evidence recommended by AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *General Methods Guide*).²⁰ We will follow the methodology outlined in the *General Methods Guide* for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each key question.

The literature search will be updated concurrent with the peer and public review process. Any additional literature recommended during public and peer review or found during the updated literature search will be evaluated according to the established criteria for inclusion and exclusion, and incorporated if appropriate.

C. Data Abstraction and Data Management

The research team will create data abstraction forms and evidence table templates for abstracting data for the key questions. Based on clinical and methodological expertise, a pair of researchers will be assigned to the research questions to abstract data from the eligible articles. One of the pair will abstract the data, and the second researcher will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached between the first two researchers. Guidance documents will be drafted and provided to the researchers as reference material to perform this task, thus aiding in both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes will be framed to help identify adverse events as described in KQ 5. Data necessary for assessing quality and applicability, as described in the *General Methods Guide*,²⁰ will also be abstracted. Before they are used, abstraction form templates will be pilot tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles. Separate data abstraction forms may be developed for articles included for the systematic review versus those used for the model alone.

D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies using the approach described in AHRQ's *General Methods Guide*.²⁰ To assess quality, we will employ the strategy 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 will apply criteria for each study type derived from core elements described in the *General Methods Guide*. Criteria of interest for all studies will include similarity of groups at baseline, 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. Criteria specific to randomized studies will include methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding will be considered. To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, and poor. Included meta-analyses will be appraised according to criteria adapted from the PRISMA Statement.²¹

Grading will be outcome-specific; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. Study design will be considered when grading quality. RCTs will be graded as good, fair, or poor. Observational studies will be graded separately, also as good, fair, or poor. We anticipate that any included retrospective studies would fall into a grading of fair or poor.

E. Data Synthesis



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We will summarize the primary literature by abstracting relevant continuous (e.g., age and categorical data (e.g., BRCA 1/2 mutation status). We will then determine the feasibility of completing a quantitative synthesis. Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the results reporting. If a quantitative synthesis is judged feasible, we would then specify particular a priori subgroups, primarily based on age. For this project, we anticipate that quantitative evidence synthesis will take the form of the model, rather than a meta-analysis, because (1) the majority of the literature is likely to be observational, increasing the methodological complexity of the meta-analysis, and (2) there is likely to be substantial heterogeneity in the types of exposures (e.g, OC formulation), timing of exposures (intermittent use of OCs over the course of a reproductive lifetime), and how exposures are measured (ever- versus never-users, duration of use, intermittent use). The model will allow greater flexibility in exploring the potential effects of these issues on estimates of the association between OC use and the outcomes of interest.

F. Grading the Evidence for Each Key Question

The strength of evidence for each key question and outcome will be assessed using the approach described in AHRQ's *General Methods Guide*.²⁰ The evidence will be evaluated using the four required domains:

- Risk of bias (low, medium, or high), assessed primarily through study design (RCT versus observational study) and aggregate study quality
- Consistency (consistent, inconsistent, or 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 or 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 versus IUDs) or use of separate bodies of evidence (risk of stroke in OC users versus placebo, and risk of stroke in IUD users versus placebo)
- Precision (precise or imprecise), based primarily on the size of the confidence intervals of effect estimates

Additionally, when appropriate, the studies will be evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. The strength of evidence will also be 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 effect.

The final choice of which outcomes to grade will be based on rankings of the potential impact of OC use, at the individual and population level, on the candidate outcomes listed in the key questions, with input from the stakeholders as represented on the TEP. For each outcome, we will use currently available estimates of lifetime risk, prevalence of OC use, and relative risk (or relative risk reduction) for that outcome in OC users to generate estimates of the impact of OC use on the individual risk and population-level number of cases attributable to, or potentially prevented by,

OC use. We will tentatively exclude any outcome from grading if the potential impact of OC use was less than 50 percent of that of OCs on ovarian cancer risk; however, since there is no consensus for this proposed threshold, we will consult with the TEP before making a final decision on the threshold.

G. Assessing Applicability

To assess applicability, we will use the PICOTS (population, interventions, comparators, outcomes, timing, setting) format to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *General Methods Guide*.²⁰ We will use 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 *General Methods Guide*.

We anticipate that the single most important factor limiting the applicability of a finding of a protective effect of OC use on ovarian cancer will be the lack of randomized trial data; recent experience with hormone replacement therapy for prevention of cardiovascular disease has illustrated the risks of basing clinical practice primarily on observational studies. Beyond that general caveat, specific factors affecting applicability include (but are not necessarily limited to):

- **Population:** We anticipate that most of the literature will be 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 to 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 will use 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 will summarize issues of applicability qualitatively.

H. Modeling Component

We will adapt our existing ovarian cancer Markov model, which has been described in detail elsewhere,^{11,22,23} to incorporate exposure to OCs and outcomes other than ovarian cancer (see Figures 2 and 3). Specifically, we will incorporate pregnancy (which may affect ovarian cancer risk), bilateral tubal ligation, and hysterectomy. The latter two procedures, even with ovarian preservation, decrease ovarian cancer risk. In addition, OCs (by affecting the risk of gynecologic conditions such as abnormal uterine bleeding, endometrial hyperplasia, or endometriosis, which frequently lead to hysterectomy) can affect hysterectomy risk. The model is calibrated to the Surveillance, Epidemiology, and End Results (SEER) Program's incidence and mortality data and can be run either deterministically or stochastically.

Figure 2 depicts a schematic view of the flow of events to be considered in the proposed model. The model begins with a woman's reproductive history (shaded box, detailed in Figure 3) and proceeds through the subsequently available intermediate states: hysterectomy, bilateral oophorectomy, undetected ovarian cancer (stages I, II, III, and IV), detected ovarian cancer (stages I, II, III, and IV), and ovarian cancer survivor. The final outcomes of the model are death from ovarian cancer and death from other causes. Ovarian cancer can either be detected at a given stage or progress to the next stage prior to detection. Ovarian cancer risk may be modified by use of OCs or by hysterectomy or oophorectomy for another indication. Because OCs may affect the risk of these other indications, they may indirectly affect ovarian cancer risk.

Figure 2. Schematic of Proposed Model

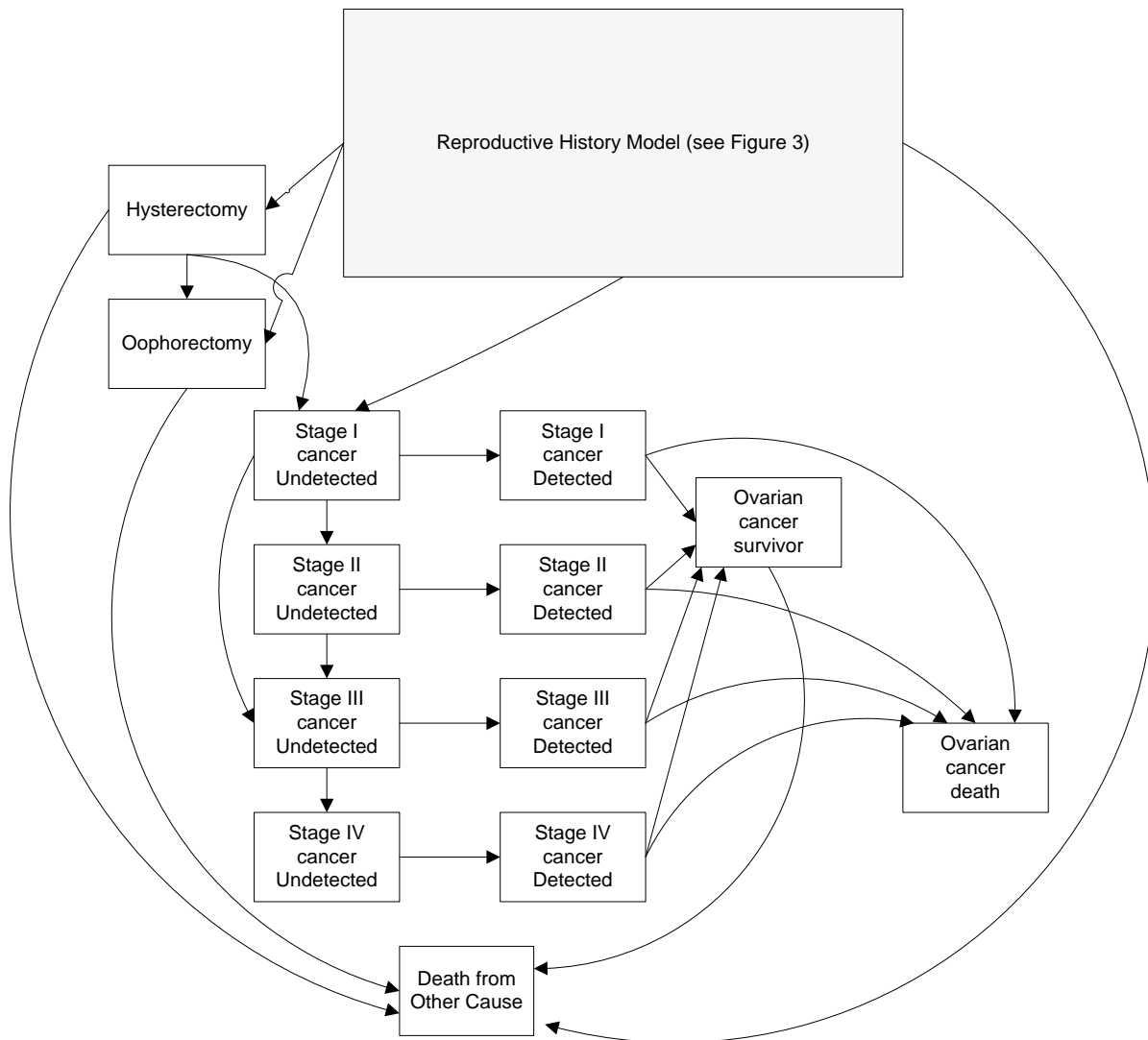
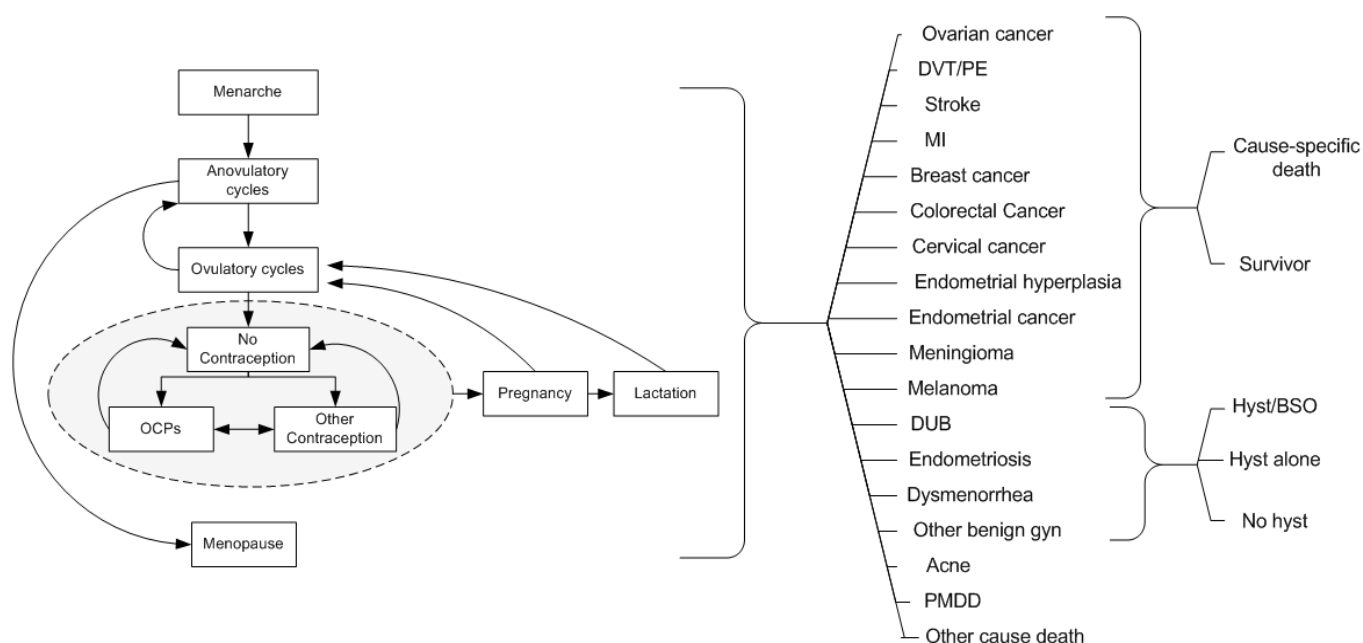


Figure 3 shows a detailed schematic of the reproductive history model that will be incorporated in the existing model. The reproductive history includes menarche, ovulatory or anovulatory cycles, contraception use, pregnancy, lactation, and menopause. While on OCs, women are at risk for both short- and long-term harms, some of which may be fatal. Possible OC-associated outcomes include ovarian cancer, deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, breast cancer, colorectal cancer, cervical cancer, endometrial cancer, endometrial hyperplasia, meningioma, melanoma, dysfunctional uterine bleeding (DUB), endometriosis, dysmenorrhea, other benign gynecological disorders, acne, and premenstrual dysphoric disorder (PMDD) as well as death from other causes. The final choice of specific outcomes included in the model will be determined by the initial estimate of lifetime risk of those outcomes in OC users and nonusers relative to the difference in ovarian cancer risk in OC users and nonusers.

Figure 3. Detail of Reproductive History Model



Although we will continue to explore different modeling approaches, given the need to incorporate factors such as age of starting OC use, duration of use, the potential intermittent nature of OC use over the course of a woman's lifetime, and the potential impact of pregnancy, our current plan is to use a microsimulation approach that incorporates individual variation in these and other factors. The primary limitation to this approach is that it is unlikely the distributions for many key parameters, as well as any correlations between them, will be well described. We will perform extensive sensitivity

analyses (including one-way, two-way, multi-way, and probabilistic sensitivity analysis) on all variables within the decision model to assess the sensitivity of the clinical implications of our findings to the data input. When possible, we will use ranges for inputs based on reported or calculated 95 percent confidence intervals from the original data sources. Otherwise, we will estimate ranges by adding or subtracting 25 percent from the base-case estimate.

We will estimate the expected number of clinical events for women in different populations who use OCs (either as prophylaxis or primarily for contraception) compared to nonusers. These clinical events include:

- Incidence and stage distribution of ovarian cancer
- Death from ovarian cancer
- Incidence of other conditions potentially affected by OC use, either through reduction in risk (e.g. endometriosis, endometrial cancer, colorectal cancer) or increase in risk (e.g., breast and cervical cancer, MI, stroke)
- Death from these other conditions

We will summarize these estimates in tables providing the number of expected outcomes per 100,000 women (stratified by OC use) over 5-, 10-, 25-year, and lifetime time horizons. The net effects of these outcomes will be compared using estimated life expectancy for these groups to summarize the overall mortality effects of these benefits and harms, and by using quality-adjusted life expectancy to additionally account for quality-of-life effects of these benefits and harms.

The final model will include only outcomes that also meet the threshold for inclusion for evidence grading as described above. We will use sensitivity analysis to assess the potential impact of OC side effects and effects on conditions affecting quality of life (such as acne and PMDD) on duration of OC use and quality-adjusted life expectancy.

Results will be presented based on the starting age of the cohort and may be stratified as well based on other factors such as family history. If one of the final outputs is a value-of-information analysis to assist with research prioritization, we would necessarily need to include some component of cost-effectiveness. Parameter values will be primarily from the systematic review. Additional data that did not meet inclusion criteria for the searches in support of the key questions will be used as necessary and appropriate. For example, data on relevant utilities for quality-adjusted life expectancy will likely be from studies that would not meet inclusion/exclusion criteria based on direct relevance to risk of development of ovarian cancer, and population-based incidence and prevalence data necessary for model calibration and/or validation may come from uncontrolled studies. In general, studies that provide any relevant data for model parameterization can be used to provide initial parameter estimates, with greater weight given to studies of higher quality and sensitivity analysis used to address the potential impact of issues such as small sample size or potential bias on model output.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Amendment 1, 30Jan2012:

Date	Section	Original Protocol	Revised Protocol	Rationale
16Feb 2012	II, III, IV	KQ 4 was worded as: Aside from pregnancy	KQ4 restated as: Aside from pregnancy prevention, are there	Candidate outcomes no longer under consideration for the

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		prevention, are there other benefits of OC use (e.g., reducing the risks of conditions such as benign ovarian cysts, endometriosis, endometrial hyperplasia, endometrial cancer, dysmenorrhea, acne, colorectal cancer, dysfunctional uterine bleeding, or premenstrual dysphoric disorder)?	other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?	<p>review (benign ovarian cysts, endometriosis, endometrial hyperplasia, dysmenorrhea, acne, dysfunctional uterine bleeding, and premenstrual dysphoric disorder) were removed from the KQ for clarity in the final report. These outcomes were de-prioritized following the ranking process described in Sections II and IV F.</p> <p>The candidate outcomes no longer under consideration were removed from the PICOTS listing in Section II, the analytic framework in Section III, and the outcomes inclusion criterion in Section IV.</p>
16Feb 2012	II, III, IV	KQ 5 was worded as: What are the harms of OC use, including, but not necessarily limited to, breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, neurological conditions, stroke, or cardiovascular disease? How do these harms vary by dose or formulation, duration of use, or specific population?	KQ5 restated as: 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?	<p>The reference to neurological conditions (an outcome no longer under consideration for the systematic review) was removed; cardiovascular disease was revised to myocardial infarction for clarity in the final report. These outcomes were de-prioritized following the ranking process described in Sections II and IV F.</p> <p>The candidate outcomes no longer under consideration were removed from the</p>

				PICOTS listing in Section II, the analytic framework in Section III, and the outcomes inclusion criterion in Section IV.
16Feb 2012	IV	None	<ul style="list-style-type: none"> • Study population is women taking OCs for contraception or women taking OCs as primary prevention for ovarian cancer • Study includes controls (i.e. an estimate of outcome(s) in women not using OCs); population estimates are acceptable • Article provides either a description of the OC formulation(s) used, or a description of the length of OC use 	Explicit clarification of criteria applied to ensure inclusion of articles with appropriate level of detail for the review.
16Feb 2012	IV	None	<p>Outcome reporting falls within the following publication ranges:</p> <ul style="list-style-type: none"> • Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published 01-Jan-2000 to present • Study reports venous thromboembolic event (VTE), stroke, or myocardial infarction outcome of interest and was published 01-Jan-1995 to present 	Date ranges for cancer outcomes selected to strike balance between generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10-30 years after typical use of oral contraceptives). Date range for acute complications of OC use restricted to more recent years to reflect currently available formulations.

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			<ul style="list-style-type: none"> • Study reports a ovarian cancer outcome of interest and was published 01-Jan-1990 to present 	
16Feb 2012	IV	<p>Inclusion criterion:</p> <p>Controlled studies (randomized trials, cohort studies, or case-control studies), meta-analyses, or systematic reviews</p>	<p>Inclusion criterion:</p> <p>Controlled studies (randomized trials, cohort studies, or case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses. Systematic reviews and study-level meta-analyses will be excluded from abstraction, but those representing key sources relevant to the topic will be hand-searched as potential sources of additional material.</p>	<p>Explicit clarification of the use of systematic reviews and meta-analyses in the review.</p>

VIII. Review of Key Questions

Key questions submitted by the CDC partner in this systematic review will be reviewed and refined as needed by the EPC with input from the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. The TEP will be drawn from individuals with expertise in ovarian cancer biology and epidemiology, hormonal contraception, and women's health. We anticipate that many of these experts will represent stakeholder organizations, including professional organizations, patient groups, advocacy groups, and Federal agencies.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches

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do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

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 are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.