Oral Contraceptive Pills as Primary Prevention for Ovarian Cancer
A Systematic Review and Meta-analysis

Laura J. Havrilesky, MD, MHS, Patricia G. Moorman, PhD, William J. Lowery, MD, Jennifer M. Gierisch, PhD, MPH, Remy R. Coeytaux, MD, PhD, Rachel Peragallo Urrutia, MD, Michaela Dinan, PhD, Amanda J. McBroom, PhD, Vic Hasselblad, PhD, Gillian D. Sanders, PhD, and Evan R. Myers, MD, MPH

OBJECTIVE: To estimate the overall reduction in ovarian cancer risk associated with the use of oral contraceptive pills (OCPs) and whether reduction in risk is affected by specifics of OCP use, such as formulation or duration of use.

DATA SOURCES: We searched PubMed, Embase, the Cochrane Database of Systematic Reviews, and Clinical-Trials.gov for studies published from January 1990 to June 2012, with primary analysis of studies published since January 2000.

METHODS OF STUDY SELECTION: We reviewed 6,476 citations. We included English-language controlled studies with human participants reporting a quantitative association between exposure to OCPs (in which the explicit or implicit indication for OCP use was prevention of pregnancy or ovarian cancer) compared with no use of OCPs. Two investigators independently reviewed the title and abstract and full-text of articles for inclusion or exclusion decision; discordant decisions were resolved by team review and consensus.

TABULATION, INTEGRATION, AND RESULTS: Fifty-five studies met inclusion criteria. A random-effects meta-analysis of 24 case-control and cohort studies showed significant reduction in ovarian cancer incidence in ever-users compared with never-users (odds ratio 0.73, 95% confidence interval 0.66–0.81). There was a significant duration–response relationship, with reduction in incidence of more than 50% among women using OCPs for 10 or more years. The lifetime reduction in ovarian cancer attributable to the use of OCPs is approximately 0.54% for a number-needed-to-treat of approximately 185 for a use period of 5 years.

CONCLUSION: Significant duration-dependent reductions in ovarian cancer incidence in the general population are associated with OCP use.

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Ovarian cancer is the eighth most common cancer in women (annual age-adjusted incidence 12.3/100,000) but is the fifth leading cause of cancer death (8.2/100,000).1 Despite advances in primary treatment, the mortality rate for ovarian cancer remains the highest among the gynecologic malignancies. Because ovarian cancer typically presents at a later stage (with concomitant higher mortality) than other common cancers,1 there has been intense interest in developing effective screening strategies. Unfortunately, screening studies to date have not demonstrated reductions in mortality and false-positive rates have been high,2–8 leading the U.S. Preventive Services Task Force to conclude that screening for ovarian cancer is not recommended (USPSTF-2012-08-4R1).9
Force to recommend against screening the general population for ovarian cancer (a “D” recommendation).  

Oral contraceptive pills (OCPs) represent a potentially promising primary prevention strategy for ovarian cancer. Several large pooled analyses suggest that OCPs confer a protective effect on ovarian cancer risk, with a risk reduction of up to 50% with long-term OCP use.  

The largest pooled analysis to date estimates that OCP use already has prevented 200,000 cases of ovarian cancer and 100,000 deaths from this disease worldwide.  

We performed a systematic review and meta-analysis, sponsored by the Agency for Healthcare and Research Quality and the Centers for Disease Control and Prevention, to quantify the potential benefits and risks of OCP use for the purpose of reducing the incidence of ovarian cancer.  

Although the current article deals with the use of OCPs for ovarian cancer prophylaxis in the general population, we also have examined the use of OCPs in subsets of women who are at elevated risk for development ovarian cancer (separate manuscript in preparation). In this article, we address the effect of OCPs on ovarian cancer risk in the general population and examine relationships between specific characteristics of OCP use and ovarian cancer incidence and mortality. Specifically, this article focuses on the following two key questions: 1) What is the effectiveness of combined (estrogen and progestin containing) and progestin-only OCPs for reducing the risk of ovarian cancer?; and 2) Do specifics of OCP use (eg, dose or formulation, age at initiation, duration of use) affect the relative risk of development of ovarian cancer?  

STUDY SELECTION  

Inclusion and exclusion criteria were developed based on population, intervention, comparators, outcomes, timing, and setting criteria. Study inclusion criteria were as follows: study includes women using OCPs for contraception or for primary prevention of ovarian cancer; study includes a comparison group consisting of no use of combination or progestin-only OCPs (either no contraceptive method or contraceptive methods other than combination or progestin-only OCPs); study reports a quantitative association between exposure to OCPs and ovarian cancer incidence or mortality; controlled studies (randomized trials, cohort studies, case-control studies) or pooled patient-level meta-analyses; sample size for nonrandomized studies was 100 or more participants; study is peer-reviewed and written in the English language; and study was published on or after January 1, 1990. Study exclusion criteria were as follows: study only reports outcomes related to the use of OCPs for postcoital contraception or in specialized populations such as women immediately after termination of pregnancy, or women receiving assisted reproductive technologies; or publication type is editorial, review, or letter to the editor.  

Two investigators independently reviewed the titles and abstracts of retrieved articles for potential relevance to the key questions. Articles included by either reviewer were promoted to full-text screening, and two investigators independently reviewed each article and indicated an include or exclude decision for data abstraction. Based on clinical and methodologic expertise, pairs of researchers were assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements at any stage were resolved by review and discussion among investigators.  

We evaluated the quality of individual studies using the approach described in Agency for Healthcare and Research Quality’s Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Summary ratings of good, fair, and poor were assigned to each study. Quality ratings for individual articles within study groupings could differ based on the quality of reporting, the evaluated outcomes, and the statistical and analytical methods used in the articles.  

We determined the feasibility of completing a quantitative synthesis for a given outcome based on the volume of relevant literature, the conceptual homogeneity of the studies, and the completeness of...
the reporting of results. Meta-analysis was particularly challenging because all of the literature was observational. There was substantial heterogeneity in the types of exposures (e.g., OCP formulation), timing of exposures (e.g., intermittent use of OCPs over the course of a reproductive lifetime), and how exposures were measured and reported (ever-users compared with never-users or current users compared with noncurrent users, duration of use as a continuous or categorical variable). Outcome measures considered for the meta-analyses were disease-specific incidence, disease-specific mortality, and disease-specific survival. We performed meta-analyses on the following relationships: ever use of OCPs, duration of OCP use, age at first OCP use, time since last OCP use, and OCP formulation (estrogen, progestin).

To meta-analyze a specific association, we required at least three comparable individual studies. Studies also were required to report odds ratios (ORs) and 95% confidence intervals (CIs) or to provide sufficient data to allow us to calculate the 95% CI. We performed meta-analyses using Comprehensive Meta-Analysis 2. All analyses were performed using a random-effects model. We included pooled analyses in our meta-analyses if all three of the following conditions were met: none of the individual studies included in the pooled analysis already had been included for meta-analysis; at least half of the studies in the pooled analysis were published on or after January 1, 2000; and data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

For the primary ever-use of OCP meta-analysis, we excluded studies that reported effects for only a particular subpopulation (e.g., studies reporting ORs only for women with a BRCA mutation) and not for the general population. Studies that reported ever-use of OCP ORs for mutually exclusive subpopulations (e.g., mucinous and nonmucinous tumors) were included in the meta-analysis, and results for the subpopulations were combined.

Evaluation of clinical relationships for which multiple temporal stratifications were possible, such as duration of OCP use, age at first OCP use, and time since last OCP use, required creation of the following additional simplifying assumptions: to facilitate identification of any existing duration–response effects, we included only studies that reported ORs for at least three different time intervals; and we required that the ORs were reported relative to no OCP use.

The challenge of performing a meta-analysis on duration of OCP use is that individual studies reported the ORs for different duration intervals. We assumed that the logarithm of each OR could be described by a linear model. The model included a random-effects term, sigma squared $(\sigma^2)$, as well as terms for the following time point intervals: 1–12 months; 13–60 months; 61–120 months; and more than 120 months. We then used independent variables to create the time period desired. For example, if the first interval had been from 1 to 36 months, the vector of independent variables would be (one third, two thirds, 0, 0, 0). This would reflect that one third of the patients in the interval were in the 1-month to 12-month interval and two thirds of the patients were in the 13-month to 60-month interval. Using this methodology, any interval could be described. The model was fitted using SAS PROC NLMIXED with “subject” set to the particular study.

Methods analogous to those used for the duration analyses were used for other temporal relationships. For age at first use, we assumed there were four different intervals: younger than 20 years of age; 20–24 years of age; 25–30 years of age; and older than 30 years of age. For time since last OCP use, we used intervals of 0–10 years, 10–20 years, 20–30 years, and more than 30 years.

Studies were included in the meta-analysis examining the effect of different estrogen formulations if they reported the effect of low-dose estrogen-containing OCPs, high-dose estrogen-containing OCPs, or both on ovarian cancer incidence and included the definition of low-dose and high-dose estrogen. For studies that presented estrogen dose results stratified by low or high progestin dose, ORs for groups with identical estrogen doses were combined across progestin arms using an inverse weighted meta-analysis. To compare high-dose with low-dose estrogen, we included those studies that had ORs for each with “never use” as a reference category and divided the high-dose OR by the low-dose OR. This has the effect of canceling out the never-use category. All analyses were performed using a random-effects model. Studies were included in the meta-analysis examining the effect of different progestin formulations if they reported the effect of low-dose progestin, high-dose progestin, or both on ovarian cancer incidence and presented an established reference for determination of progestin potency. These meta-analyses were analogous to those performed for estrogen dose.

To maximize the probability that members of the study populations used contemporary OCP formulations, we constrained the primary analyses to studies published from January 2000 to June 2012. We then conducted sensitivity analyses that included the older data from articles with publication dates beginning...
January 1990. This approach allowed us to compare the primary analysis results with those obtained from a longer date range and studies that may have included older formulations of OCPs. We conducted additional sensitivity analyses in which we repeated the meta-analyses excluding studies not conducted at least partially within the United States and excluding poor-quality studies.

We assessed the potential for publication bias using the following three methods: the funnel plot; which looks for an uneven number of studies falling to the left or right of the funnel; Begg and Mazumdar test based on the rank correlation between the observed effect sizes and observed standard errors; and Egger regression intercept, which is similar to that of Begg and Mazumdar but uses actual values instead of ranks. We performed the calculations using Biostat Comprehensive Meta-Analysis 2.

RESULTS

In the literature search (Fig. 1) conducted for the full Agency for Healthcare and Research Quality report, 6,476 unique citations were identified. After exclusions, 55 studies (92 articles) remained that reported ovarian cancer outcomes relevant to this article. The full list of included articles is provided in Appendix 2 available at http://links.lww.com/AOG/A381; relationships between articles are detailed in Appendix C of the Agency for Healthcare and Research Quality report.

Seventeen case-control studies (11 good quality, six fair quality, and one poor quality) representing 10,031 cases and 21,025 controls met criteria for the meta-analysis examining ever-use compared with never-use of OCPs (Appendix 3, available at http://links.lww.com/AOG/A382). See Appendix 4 available at http://links.lww.com/AOG/A382 for ever-use compared with never-use data from all studies. The OR for meta-analysis of the case-control studies was 0.72 (95% CI 0.64–0.81), which demonstrates an almost 28% reduction in ovarian cancer risk in women who have ever used OCPs (Fig. 2A). The cohort meta-analysis included seven studies (three good quality, three fair quality, one poor quality) (Appendix 3, available at http://links.lww.com/AOG/A382), of which four included 625,999 participants and the other three included 3,981,072 person-years of follow-up. The OR for the cohort meta-analysis was 0.75 (95% CI 0.62–0.92), indicating a 25% reduction in ovarian cancer risk in women who have ever used OCPs (Fig. 2B). In a combined meta-analysis of all 24 case-control and cohort studies, the OR for ever-use compared with never-use of OCPs was 0.73 (95% CI 0.66–0.81). Based on an estimated lifetime risk of ovarian cancer of 1.38%,16 an estimated lifetime prevalence of ever-use of OCPs of 83%,20 and the estimates from our meta-analysis, the lifetime reduction in ovarian cancer attributable to the use of OCPs is approximately 0.54% for a number needed to treat of approximately 185. The duration of exposure to OCPs among ever-users is, by definition, the mean duration of use, for which the best estimate is approximately 4.5 years.

Fifteen studies (seven good quality, seven fair quality, one poor quality) were included in a meta-analysis examining the effect of duration of OCP use on ovarian cancer incidence (Appendix 5, available at http://links.lww.com/AOG/A382). Of these, 10 were case-control studies (6,901 cases and 15,999 controls) and five were cohort studies (524,463 participants in

![Fig. 1. Literature flow diagram. *Description and length of oral contraceptive pill use not required for studies reporting ovarian cancer outcomes or conducted in a population using oral contraceptives for primary prevention of ovarian cancer. †Comparisons between oral contraceptive formulations acceptable for articles reporting venous thromboembolism, stroke, or myocardial infarction. Havrilesky. OCPs as Primary Prevention for Ovarian Cancer. Obstet Gynecol 2013.](http://links.lww.com/AOG/A382)
Table 1. Estimated Odds Ratios for Ovarian Cancer Incidence

<table>
<thead>
<tr>
<th>Duration Interval</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-user</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>By duration of use (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–12</td>
<td>0.91 (0.78–1.07)</td>
<td>.250</td>
</tr>
<tr>
<td>13–60</td>
<td>0.77 (0.66–0.89)</td>
<td>.001</td>
</tr>
<tr>
<td>61–120</td>
<td>0.65 (0.55–0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>More than 120</td>
<td>0.43 (0.37–0.51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>By age at first use (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 20</td>
<td>0.63 (0.45–0.89)</td>
<td>.018</td>
</tr>
<tr>
<td>20–24</td>
<td>0.71 (0.51–0.99)</td>
<td>.044</td>
</tr>
<tr>
<td>25–30</td>
<td>0.67 (0.46–0.99)</td>
<td>.045</td>
</tr>
<tr>
<td>Older than 30</td>
<td>0.89 (0.60–1.32)</td>
<td>.489</td>
</tr>
<tr>
<td>By time since last use (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>0.41 (0.34–0.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10–20</td>
<td>0.65 (0.56–0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20–30</td>
<td>0.92 (0.76–1.12)</td>
<td>.369</td>
</tr>
<tr>
<td>More than 30</td>
<td>0.79 (0.58–1.12)</td>
<td>.104</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Table 1 and Figure 3 show the ORs for the meta-analysis of duration of OCP use. These findings indicate a significant duration–response relationship between OCP use and ovarian cancer incidence, with a reduction in ovarian cancer incidence of more than 50% among women using OCPs for 10 or more years.

Six studies (four good quality, two fair quality) were included in the primary meta-analysis examining the effect of age at first OCP use on ovarian cancer incidence (Appendix 6, available at http://links.lww.com/AOG/A382). Of these, five were case-control studies (3,552 cases and 4,713 controls) and one was a cohort study (103,552 participants). The results show a relatively strong relationship between younger age at first use and lower ovarian cancer incidence, although CIs overlap (Table 1). Most studies examining age did not control for duration of use, which is a potential confounder and reduces the strength of this finding. Two pooled analyses reported on age at first use, with none reporting significant trends.

Eight studies (four good quality, four fair quality) were included in the meta-analysis examining the effect of time since last use on ovarian cancer incidence (Appendix 6, available at http://links.lww.com/AOG/A382). Of these, three were case-control studies (3,552 cases and 4,713 controls) and one was a cohort study (103,552 participants). The results show a relatively strong relationship between younger age at first use and lower ovarian cancer incidence, although CIs overlap (Table 1). Most studies examining age did not control for duration of use, which is a potential confounder and reduces the strength of this finding. Two pooled analyses reported on age at first use, with none reporting significant trends.

Fig. 3. Relationship between duration of oral contraceptive use (months) and ovarian cancer incidence. There is no evidence of heterogeneity. The estimated value of sigma (σ) is 0.15. Havrilisky. OCPs as Primary Prevention for Ovarian Cancer. Obstet Gynecol 2013.
ovarian cancer incidence (Appendix 7, available at http://links.lww.com/AOG/A382). Five were case-control studies (3,606 cases and 7,759 controls) and three were cohort studies (198,704 participants and 1,083,000 person years). None of the three pooled analyses reporting on time since last OCP use met inclusion criteria for meta-analysis.

Table 1 lists the ORs for the meta-analysis of time since last OCP use. The individual ORs show significant associations between OCP use and ovarian cancer incidence among women who used OCPs within the past 20 years, but not for those with a longer time since last use. A test for differences between the four ORs was significant ($P = .002$). We then used the midpoint of each interval as the estimate of the time since last use for each subgroup. The slope from this model was highly significant ($P = .001$), indicating a stronger protective effect with a shorter time since last OCP use.

Six studies (five good quality, one fair quality) were included in the meta-analysis examining the effect of estrogen formulation on ovarian cancer incidence (Appendix 8, available at http://links.lww.com/AOG/A382). All were case-control studies, representing 2,607 cases and 6,400 controls. The definition of a low-estrogen OCP formulation varied among the six studies included in the meta-analysis, with three studies using a cut-off of 35 micrograms of estradiol, two studies using a cut-off of 50 micrograms of estradiol, and one study reporting results for three separate doses of estradiol (20–34 micrograms, 35–44 micrograms, and 45 micrograms or more).

Five studies calculated ORs separately for high-dose or low-dose estrogen-containing OCPs compared with never use. Of these, two studies presented estrogen dose results stratified by low or high progestin dose. One study calculated a direct OR comparing high-dose with low-dose estrogen OCP use. When this was combined with the other five included studies, the OR comparing high-dose with low-dose estrogen OCP use was 1.25 (CI 0.95–1.64) (Fig. 4A). These results do not suggest a relationship between estrogen dose and ovarian cancer incidence.

Four studies (all good quality) were included in the meta-analysis examining the effect of progestin formulation on ovarian cancer incidence (Appendix 8, available at http://links.lww.com/AOG/A382). All were case-control studies, representing 2,049 cases and 5,479 controls. The four included studies classified progestosterone potency based on a subnuclear vacuolation assay and a delay of menses test, and defined low-dose progestin OCPs as those containing a relative potency cut-off of 0.2 mg norgestrel or less. Three of these studies also stratified progestin results based on low-estrogen or high-estrogen dose. One study calculated a direct OR comparing high-dose with low-dose progestin OCP use. The random-effects meta-analysis of all four studies reveals an OR for ovarian cancer incidence comparing high-dose progestin OCPs with low-dose progestin OCPs of 0.86 (95% CI 0.60–1.21) (Fig. 4B). These results do not support a relationship between OCP progestin dose and ovarian cancer incidence.

Three studies (all fair-quality cohort studies) were identified that examined the effect of OCP use on ovarian cancer mortality (Appendix 9, available at http://links.lww.com/AOG/A382). Two were population-based cohort studies (representing a total of 46,112 participants and 602,700 reported person-years) and assessed death from ovarian cancer as a primary outcome among ever-users compared with never-users of OCPs. Both reported a significant reduction in ovarian cancer mortality among OCP users that was similar in magnitude and direction to the reduction in incidence discussed previously. The third study identified a cohort of women with ovarian cancer and subsequently compared survival outcomes based on low-estrogen or high-estrogen dose. One study calculated a direct OR comparing high-dose with low-dose progestin OCP use. The random-effects meta-analysis of all four studies reveals an OR for ovarian cancer incidence comparing high-dose progestin OCPs with low-dose progestin OCPs of 0.86 (95% CI 0.60–1.21) (Fig. 4B). These results do not support a relationship between OCP progestin dose and ovarian cancer incidence.

![Fig. 4. Forest plots describing the relationship between high-dose compared with low-dose oral contraceptive pill formulations and ovarian cancer incidence. A. Estrogen formulations. There was some evidence of heterogeneity, with a Q-value of 10.611 for 5 degrees of freedom ($P = .06$). B. Progestin formulations. There was some evidence of heterogeneity, with a Q-value of 7.52 for 3 degrees of freedom ($P = .057$). CI, confidence interval.](http://links.lww.com/AOG/A382)
between OCP users (n=310) and nonusers (n=366), with nonsignificant findings.

We conducted sensitivity analyses in which we repeated the meta-analyses in three ways: including studies published from 1990 forward, excluding studies not conducted at least partially within the United States, and excluding poor-quality studies. None of our findings were changed substantively with these analyses.

The strength of evidence for each outcome is described in Appendix 10 (available at http://links.lww.com/AOG/A383). Because no randomized controlled trials were included in our analysis, the risk of bias was categorized as medium at best and high if other possible sources of bias were identified. With regard to directness of evidence, relationships between high and low steroid hormone doses and ovarian cancer incidence were considered to be indirect based on the use of “never use of OCP” as the reference category in those studies.

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

We performed publication bias analyses as described in the methods of study selection (Appendix 11, available at http://links.lww.com/AOG/A384). We found no evidence of publication bias for the Figure 2 meta-analyses assessing ever use compared with never use of OCPs and ovarian cancer incidence. For the meta-analyses examining the relationship between high-dose compared with low-dose OCP formulations and ovarian cancer incidence (Fig. 4), we identified a suggestion of publication bias for estrogen formulation and no evidence of publication bias for progestin formulation. The temporal analyses (age, duration, time since last use) are not amenable to these bias assessments.

CONCLUSION

In this systematic review and meta-analysis, we found that OCP use was associated with a decreased incidence of ovarian cancer (OR 0.73, 95% CI 0.66–0.81), with results from two large cohort studies showing a concomitant decrease in mortality. There is a positive relationship between the duration of OCP use and the degree of the protective effect. These findings are consistent with previous pooled analyses, which reported ORs for ever use compared with never use of OCP between 0.60 and 0.73; these previous analyses similarly identified a relationship between longer duration of OCP use and lower incidence of ovarian cancer. We estimate the lifetime reduction in ovarian cancer attributable to the use of OCPs to be approximately 0.54%.

The results of our meta-analysis show a strong relationship between duration of OCP use and ovarian cancer incidence (Fig. 3). Women who use OCPs for 10 or more years show a reduction in ovarian cancer incidence of more than 50%. Previous pooled analyses are consistent with these findings. Although our reported OR comparing OCP use for less than 12 months with never use was not statistically significant, our duration analysis suggests that there is no time threshold for OCP effectiveness, and the duration–response relationship likely starts as soon as a woman commences OCP use.

Regarding age at first OCP use, the ORs also appear to show a clearly positive relationship. This suggests that the earlier a woman begins using OCPs, the greater the reduction in ovarian cancer incidence. However, it is not possible to differentiate the effects of age at first use from the effects of duration of use. Our findings are consistent with the largest pooled analysis and are not unexpected, because the earlier a woman starts using OCPs, the longer the potential duration of use. The protective effect of OCPs appears to attenuate with increasing time since last use, again consistent with the findings of the Collaborative Group. Although the data available at the study level preclude estimation of the joint effect of duration and time since last use, stratified analysis of the pooled individual data by the Collaborative Group suggest that the magnitude of protection with increased duration is greater than the attenuation with time since last use.

In an effort to enhance the applicability of these findings to contemporary OCP formulations and dosages, we included only studies published since January 1, 2000, for the primary analysis and since 1990 for the sensitivity analysis. However, our primary meta-analysis produced an OR comparing ever use with never use (0.73) similar to ORs reported in the sensitivity analysis (0.72) and pooled analyses that included older studies. This suggests that current OCP formulations may have an effectiveness similar to older formulations in reducing the incidence of ovarian cancer. This is supported by our finding that the relative estrogen and progestin doses in OCPs do not appear to have an effect on ovarian cancer incidence. However, given that the age of peak incidence of ovarian cancer is in a woman’s early 60s, even more recent publications do not capture the potential long-term effect of formulations introduced in the past 20 years.
Another limitation of the current analysis is the degree of generalizability of the included studies to clinical decision-making. The included studies almost never specifically reported the reasons for OCP use. It is likely that most women used OCPs for contraception or to treat conditions such as dysmenorrhea, whereas few used them for ovarian cancer prophylaxis.

The main limitation of our analysis is the lack of randomized, prospective trials examining the preventive effect of OCPs on ovarian cancer, raising the potential for bias. The most common study design within our primary analyses (ever compared with never use) was case-control (71%), with a minority being cohort studies (29%). The point estimate for case-control studies (0.72) was lower than for cohort studies (0.75), suggesting that there may be some residual confounding in the case-control studies. Likewise, although the majority of studies were rated as being of good or fair quality (92%), there was marked inconsistency across studies, particularly in the methods for adjustment of confounding.

The observed association between OCP use and reduced ovarian cancer risk fulfills many of the classic criteria for causal inference in epidemiology, including strength of association, consistency across studies, temporality, a biological gradient, biological plausibility, and coherence. However, the potential for the limitations discussed to lead to biased estimates of the effects of OCP require considerable caution when using the results for clinical decision-making.

The current literature consistently shows a statistically significant reduction in ovarian cancer risk among women with a history of OCP use, with greater reductions in risk with longer duration of use. Although the overall body of evidence is supportive of the beneficial effects of OCPs on ovarian cancer, there remains potential for unmeasured bias. Continued evaluation of effects by dose of OCPs is warranted, especially because some of the older women included in studies published since 1990 would have used OCPs when higher doses were more commonly prescribed. Further research also is needed to sort out the relative importance of the duration and timing of use of OCPs. Understanding the combined effects of timing and duration is particularly important for making recommendations to women of mid-to-late reproductive age who are considering OCP use for ovarian cancer prevention but not necessarily for contraception. To facilitate future systematic reviews, one step would be to standardize the categories and descriptive statistics for reporting results. Although particular categorization choices may be best-suited for analyzing individual studies on the basis of study design and characteristics of a given population, reporting of standardized results—perhaps as an appendix to the main analysis—would greatly improve the ability to combine published results in meta-analysis.

This systematic review and meta-analysis confirms previous large studies in demonstrating a duration-dependent protective effect of OCP use on the incidence of ovarian cancer. The inherent limitations of our analysis prevent us from making recommendations regarding the preferred OCP formulation and dose or the optimal time period of use for ovarian cancer prevention. However, consideration of this benefit can be made along with careful consideration of the other known risks and benefits of OCP use.

REFERENCES


