Oral Contraceptive Use and Risk of Breast, Cervical, Colorectal, and Endometrial Cancers: A Systematic Review

Jennifer M. Gierisch1,2,3, Remy R. Coeytaux2,4, Rachel Peragallo Urrutia5, Laura J. Havrilesky6,7, Patricia G. Moorman3, William J. Lowery5, Michaela Dinan8, Amanda J. McBroom2, Vic Hasselblad6, Gillian D. Sanders2,3, and Evan R. Myers5

Abstract

Oral contraceptives may influence the risk of certain cancers. As part of the AHRQ Evidence Report, Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer, we conducted a systematic review to estimate associations between oral contraceptive use and breast, cervical, colorectal, and endometrial cancer incidence. We searched PubMed, Embase, and Cochrane Database of Systematic Reviews. Study inclusion criteria were women taking oral contraceptives for contraception or ovarian cancer prevention; includes comparison group with no oral contraceptive use; study reports quantitative associations between oral contraceptive exposure and relevant cancers; controlled study or pooled patient-level meta-analyses; sample size for nonrandomized studies ≥100; peer-reviewed, English-language; published from January 1, 2000 forward. Random-effects meta-analyses were conducted by estimating pooled ORs with 95% confidence intervals (CIs). We included 44 breast, 12 cervical, 11 colorectal, and 9 endometrial cancers studies. Breast cancer incidence was slightly but significantly increased in users (OR, 1.08; CI, 1.00–1.17); results show a higher risk associated with more recent use of oral contraceptives. Risk of cervical cancer was increased with duration of oral contraceptive use in women with human papillomavirus infection; heterogeneity prevented meta-analysis. Colorectal cancer (OR, 0.86; CI, 0.79–0.95) and endometrial cancer incidences (OR, 0.57; CI, 0.43–0.77) were significantly reduced by oral contraceptive use. Compared with never use, ever use of oral contraceptives is significantly associated with decreases in colorectal and endometrial cancers and increases in breast cancers. Although elevated breast cancer risk was small, relatively high incidence of breast cancers means that oral contraceptives may contribute to a substantial number of cases. Cancer Epidemiol Biomarkers Prev; 22(11); 1931–43. ©2013 AACR.

Introduction

Oral contraceptives, the most common form of effective and reversible contraception in the United States (1), significantly decrease the personal and societal burdens associated with unintended or unwanted pregnancy (2, 3). Oral contraceptives also have significant noncontraceptive health benefits such as improving acne and regulating dysmenorrhea (4–7). However, oral contraceptive use is not without risks. Many studies show serious adverse events associated with oral contraceptive use including venous thromboembolic disease, myocardial infarction, and stroke (8–10).

In addition to the risk of acute harms, the use of oral contraceptives may influence the risk of certain cancers (11). Oral contraceptive use may promote or initiate tumors of the breast or cervix (12–14). For breast cancer, these risks may be even greater for women at elevated risk due to family history of cancer or genetic mutation carrier status (e.g., BRCA1/2); however, results from studies are inconclusive (15, 16). Oral contraceptive use has also been associated with a greater risk of certain clinically challenging types of breast tumors (17). Conversely, oral contraceptive use is associated with significant reductions in colorectal, endometrial, and ovarian cancers (11, 18–20). A recent systematic review and meta-analysis supports a significant risk reduction for ovarian cancer incidence and mortality associated with the use of oral contraceptives (20).

Assessing the risk of cancer associated with oral contraceptive use is fraught with difficulties. For example, cancer is a disease with a long latency period, and the time...
between exposure to oral contraceptives and diagnosis of cancer may span decades. Also, temporal variations in oral contraceptive formulations available on the market and used over a woman’s lifetime may influence associations between cancer risk and oral contraceptive use. Furthermore, patterns of oral contraceptive use over a lifetime may be influenced by factors that also affect cancer risks (e.g., gravidity, parity, breastfeeding). Duration of oral contraceptive use or length of time since ceasing use (i.e., recency) may also modify the risk of cancers associated with oral contraceptives (13, 21).

We conducted a systematic review and meta-analysis, sponsored by the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), to inform the use of oral contraceptives to reduce the risk of ovarian cancer (20). In addition to the primary question regarding ovarian cancer, we also addressed other harms and benefits of oral contraceptive use. In this article, we examine the evidence for associations between oral contraceptive use and the risks of developing 4 cancers: breast, cervical, colorectal, and endometrial. When possible, we conducted meta-analyses of the literature to assess the risk of developing these cancers following oral contraceptive use; we also examined risk by duration of oral contraceptive use and time since last oral contraceptive use (20).

Materials and Methods

We followed the methodology recommended in AHRQ’s “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (22). Methods are summarized here, with complete details provided in the full AHRQ report (20).

Search strategy

In collaboration with an experienced librarian, we conducted searches of PubMed, Embase, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov to identify relevant published literature. Our searches were date-limited to articles published from January 1, 1990 to June 29, 2012. For the outcomes presented in this article, we restricted the results to 2000 forward for the following reason. Formulations of oral contraceptives have been changed and updated almost continuously since their introduction to the U.S. market in 1957; such changes have not occurred at discrete time points. Also, yearly-year market share, duration of use, and patterns of use are not readily available and would vary based on the country in which a given study was conducted. Realizing the inaccuracy of any discrete cutoff date with regard to current oral contraceptive formulations, we limited the publication years of included studies to those published from 2000 forward to try to maximize the proportion of subjects who used oral contraceptive formulations similar to those currently on the market. We supplemented electronic searches with a manual search of citations from key review articles. Exact search strings are provided in Appendix A of the full AHRQ report (20).

Selection criteria

Inclusion criteria for studies relevant to this article were: (i) study includes women taking oral contraceptives for contraception or primary prevention of ovarian cancer; (ii) study includes comparison group with no use of combination or progestin-only oral contraceptives (either no contraceptive method at all or contraceptive methods other than combination or progestin-only oral contraceptives); (iii) study reports quantitative associations between exposure to oral contraceptives and breast, cervical, colorectal, or endometrial cancer incidence; (iv) controlled study (randomized trials, cohort studies, case–control studies) or pooled patient-level meta-analyses; (v) sample size for nonrandomized studies ≥100 subjects; (vi) study is peer-reviewed and English-language; and (vii) published on or after January 1, 2000. Exclusion criteria were: (i) study reports outcomes related to the use of oral contraceptives only for contraception, or in specialized populations such as women immediately post-termination of pregnancy, or women receiving assisted reproductive technologies; (ii) study does not provide a description of the oral contraceptive formulation(s) or length of oral contraceptive use; or (iii) publication type is editorial, review, or letter to the editor.

Reviewer pairs used prespecified criteria to assess titles and abstracts. Full-text articles included by either reviewer underwent further evaluation. Eligibility decisions and disagreements were reconciled through discussion or by a third reviewer. For included studies, we abstracted data on study populations, interventions, outcomes, quality, and applicability. We used criteria developed by AHRQ to assess study quality, summarized as good, fair, or poor (22). Quality ratings for individual articles within study groupings could differ based on articles’ reporting quality, evaluated outcomes, and statistical and analytical methods used. We screened and abstracted data using DistillerSR software (Evidence Partners Inc.).

Data synthesis

When at least 3 studies were available with comparable study designs and outcomes, we conducted random-effects meta-analyses grouped by study design (case–control or cohort study) and estimated pooled ORs with 95% confidence intervals (CI). As there were no significant differences by design, we used a random-effects model to combine subgroups and estimate the overall effect. When studies reported multiple models, we used the most adjusted model. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold $P < 0.10$. We included pooled analyses in our meta-analyses if all these conditions were met by the pooled analysis: none of the individual articles were already included in the meta-analysis, at least half of the studies were published on or after January 1, 2000, and data were presented such that their inclusion in meta-analysis was feasible.

Not all studies meeting criteria for inclusion in the review were included in meta-analyses. The reasons for
exclusion from meta-analysis were (i) study populations that represented specialized subgroups (e.g., BRCA mutation, family history, age at diagnosis ≤ 45 years, cancer subtype); (ii) studies that reported a subset of results from the same study as another article already included in the analysis; and (iii) studies that did not report an OR for ever oral contraceptive use versus never oral contraceptive use. When studies gave results only by subgroup (premenopausal, postmenopausal), we combined subgroups to generate an estimate only when the combined group represented a broad population. When possible, we conducted sensitivity analyses by including only U.S.-based studies. These analyses were conducted using Comprehensive Meta-Analysis Version 2 (23).

We estimated the increase or decrease in absolute risk of cancer from estimates of the lifetime incidence of malignant cases for women beginning at age 45 years generated using the National Cancer Institute’s DevCan software (24), estimated lifetime ever use of oral contraceptives from the National Survey of Family Growth (25), and the ORs (with 95% CIs) produced in our meta-analyses. We then calculated the number needed to treat (NNT) or number needed to harm (NNH) by taking the inverse of the absolute risk. Because we were unable to conduct meta-analysis of the association of oral contraceptive use and cervical cancer among populations that were selected for HPV-positive status, we were unable to generate estimates of change in absolute risk.
When we had sufficient studies to assess the effect of duration of oral contraceptive use, we used a random-effects model to compute ORs. We required that the ORs were given relative to no oral contraceptive use and that the population studied was not restricted to a particular subpopulation. The challenge of conducting a meta-analysis on duration of oral contraceptive use is that individual studies reported 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, $\sigma^2$, as well as terms for time point intervals. We then used independent variables to create the time period desired. The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; 2009) with "subject" set to the particular study.

We evaluated strength of evidence using the approach described in AHRQ’s "Methods Guide" (22, 26).

**Results**

Of the 6,476 unique citations screened, we identified 44 studies relevant to breast, 12 to cervical, 11 to colorectal, and 9 to endometrial cancers (Fig. 1). Several included studies were relevant to more than one outcome of interest. All studies were observational; we did not identify any eligible randomized controlled trials. We did not identify any qualitative difference between breast, cervical, colorectal, or endometrial cancers and oral contraceptive use based on probable dates of exposure when examined by study recruitment date versus publication date.

**Breast cancer incidence**

Forty-four studies (19 good quality, 25 fair, and 3 poor) evaluated the association between oral contraceptive use and breast cancer incidence (16, 17, 27–78). Of these, 29 were case-control studies, 14 were cohort studies, and 1 was a pooled analysis (Supplementary Table S1). Fifteen case-control studies (38,682 women; refs. 16, 27–30, 33, 37, 48, 49, 51, 54, 56, 73, 74, 78) and 8 cohort studies (317,341 women across 5 studies and 3,981,072 person-years across 3 studies; refs. 59–61, 63, 65, 67–69) met criteria for meta-analysis examining ever versus never oral contraceptive use. Figure 2 shows the results suggesting that a history of oral contraceptive use slightly but significantly increases breast cancer incidence compared with never oral contraceptive use (OR, 1.08; 95% CI, 1.00–1.17), with a Q value of 73.35 for 21 degrees of freedom (DF); $P < 0.001$. In a sensitivity analysis of only U.S.-based studies, effect sizes were smaller and no longer statistically significant (OR, 1.03; CI, 0.93–1.14). On the basis of the point estimates of the meta-analyses, the approximate increase in estimated lifetime absolute risk of breast cancer incidence is shown in Figure 2.
cancer from ever use of oral contraceptives is 0.89% (NNH, 113).

Fourteen studies (16, 27, 30, 36, 37, 44, 48, 49, 54, 59–61, 63, 69, 78) met criteria for the meta-analysis examining duration of oral contraceptive use. We found no time-dependent relationship as a function of duration of use: 1–12 months (OR, 0.95; CI, 0.83–1.09); 13–60 months (OR, 1.03; CI, 0.92–1.15); 61–120 months (OR, 1.01; CI, 0.90–1.13); and >120 months (OR, 1.04; CI, 0.93–1.17). Heterogeneity was significant (t = 5.84, 19 DF, P < 0.0001).

Eleven studies (16, 27, 30, 33, 37, 38, 46, 49, 51, 53, 59, 61) met criteria for the meta-analysis examining time since last oral contraceptive use. Results show a time-dependent relationship as a function of time since last oral contraceptive use, with higher risk associated with more recent use of oral contraceptives and ORs that approach 1 (no effect) by >20 years of use: 0–5 years (OR, 1.21; CI, 1.04–1.41); 5–10 years (OR, 1.17; CI, 0.98–1.38); 10–20 years (OR, 1.13; CI, 0.97–1.31); >20 years (OR, 1.02; CI, 0.88–1.18). Heterogeneity was significant (σ = 0.12; t = 4.95, 11 DF, P = 0.0004).

The strength of evidence for the effect of ever oral contraceptive use on breast cancer incidence was moderate. Most studies were of good or fair quality, exhibited consistent findings, and confidence interval for summary estimate were precise. However, all included studies were observational; thus there may be some risk of bias due to limitations of the study designs. The strength of evidence was low for both duration of use and time since last use for risk of breast cancer incidence; results were inconsistent with a high level of heterogeneity across studies.

Cervical cancer incidence

Twelve studies (5 good, 4 fair, 4 poor quality) evaluated the association between oral contraceptive use and cervical cancer incidence (63, 65, 66, 69, 70, 73, 79–87), including 2 articles from an International Agency for Research on Cancer (IARC) study representing distinct populations (86, 87). Of these, 9 were case–control studies, 3 were cohort studies, and 1 was a pooled analysis. Only 2 studies were conducted with U.S.-based populations (Supplementary Table S2).

Persistent infection with one or more oncogenic HPV types is required for cervical carcinogenesis; thus, women who are HPV-positive represent the most relevant population to assess the risks for cervical cancer associated with oral contraceptive use. Only 3 studies (80, 83, 86) assessed the association between oral contraceptive use and cervical cancer among women who are HPV-positive. Limited studies across comparisons precluded quantitative synthesis; we summarize each study below.

One fair-quality study (86) pooled data from 8 case–control studies of HPV-positive patients with cervical cancer. Ever use of oral contraceptives was associated with a statistically nonsignificant increase in invasive cervical cancer (OR, 1.29; CI, 0.88–1.91) and cervical cancer in situ (OR, 2.54; CI, 0.95–6.78). However, duration of use was significantly associated with cancer incidence such that HPV-positive women who used oral contraceptives for 5 to 9 years (OR, 2.82; CI, 1.46–5.42) and ≥10 years (OR, 4.03; CI, 2.09–8.02) experienced a significant increase in the risk of cervical cancers compared with never users. This estimate did not vary by time since first or last use; the trend was not observed for women who used oral contraceptives for <5 years.

Two case–control studies (80, 83), both rated poor quality, also assessed the risk of cervical cancer associated with oral contraceptive use among HPV-positive women. One study (80) recruited hospital-based HPV-positive cases and controls in Lima, Peru. Results of this study were included in the pooled analysis above and, thus, could not be combined again. Compared with HPV-positive controls, HPV-positive women who had ever used oral contraceptives were at elevated risk of cervical cancer compared with women who had never used oral contraceptives (OR, 2.7; CI, 0.90–8.4), but the contrast was not significant. This study did not compute any analysis by duration of use.

The other case–control study (83) assessed the association between oral contraceptive use and cervical cancer among hospital-based HPV-positive cases and HPV-positive community controls in the United States. This study assessed duration of oral contraceptive use; ever use versus never use was not calculated. Increasing the duration of oral contraceptive use—categorized as <5, 5–10, and >10 years—was associated with a decrease in cervical cancers. This trend was significant only in women with ≥5 years of use compared with never users (OR, 0.6; CI, 0.4–0.9).

In populations that were not selected for HPV-positive status, 6 case–control studies representing 5,436 women (73, 79, 81, 82, 84, 85) and 3 cohort studies (63, 65, 69) representing 3,981,072 person-years met criteria for the meta-analysis examining ever versus never oral contraceptive use. Figure 3 shows results indicating increased odds of cervical cancer for women who had ever used oral contraceptives compared with women who never used oral contraceptives (OR, 1.21; CI, 0.91–1.61), but the comparison was not significant. There was a large amount of heterogeneity (Q = 25.52, 7 DF, P < 0.001), possibly due to differences in HPV status among studies, which made the estimates unstable. We could not conduct sensitivity analysis by U.S.-based studies because only one study was conducted within the United States. Results from this case–control study (79) show a statistically significant increase in risk with ever use of oral contraceptives (OR, 2.7; CI, 1.2–5.8).

Six studies (63, 79, 81, 82, 85, 87) met criteria for the meta-analysis examining duration of oral contraceptive use. Results show no time-dependent relationship as a function of duration: 1–60 months (OR, 0.99; CI, 0.58–1.70) and >60 months (OR, 1.47; CI, 0.91–2.38). Heterogeneity was significant (t = 4.72, 6 DF, P = 0.0033).
The strength of evidence for the effect of ever oral contraceptive use on cervical cancer incidence among HPV-positive women was insufficient. Only 3 studies assessed risk in HPV-positive women, and most were of poor quality. Results were inconsistent, sensitivity analysis yielded qualitatively different estimates of effects, and CIs were wide. Studies did not control for factors that may influence risk such as age at first use by duration or age at sexual debut, which is likely highly correlated with age at first use. Future studies could influence magnitude and, possibly, direction of effect.

Colorectal cancer incidence

Eleven studies (4 good, 6 fair, 1 poor quality) evaluated the association between oral contraceptive use and colorectal cancer incidence (63, 65, 66, 68–95). Of these, 3 were case–control studies, 7 were cohort studies, and 1 was a pooled analysis. Nine studies were conducted in Western countries and 2 in China (Supplementary Table S3).

Three case–control studies (88–90), 1 pooled analysis (94), and 7 cohort studies (63, 65, 68, 91–93, 95) representing 503,816 women across 8 studies and 2,969,189 person-years across 3 studies met criteria for the meta-analysis examining ever versus never oral contraceptive use. Figure 4 shows the results showing a decrease in the risk of colorectal cancers among women who ever used oral contraceptives compared with women who never used oral contraceptives (OR, 0.86; CI, 0.79–0.95; Q = 17.17, P < 0.046). We conducted sensitivity analyses of studies that included only patients from the United States; results were similar to analyses containing all studies, but the confidence interval eclipsed 1 (OR, 0.83; CI, 0.69–1.01). On the basis of the point estimates of the meta-analyses, the approximate decrease in absolute risk of colorectal cancer is 0.76% (NNT 132).

Ten studies (63, 65, 68, 88–92, 94, 95) met criteria for the meta-analysis examining duration of oral contraceptive use. We categorized duration of use into 2 intervals and found no time-dependent relationship as a function of duration: 1–60 months (OR, 0.88; CI, 0.77–1.01) and >60 months (OR, 0.88; CI, 0.76–1.01). There was no significant heterogeneity (t = 1.52; 9 DF, P = 0.164).

The strength of evidence for the effect of oral contraceptive use on colorectal cancer incidence was moderate. Results were consistent across studies, and the summary estimate showed high precision with a tight CI. Future studies will not likely have an impact on the direction of effect but may slightly influence the magnitude of the effect. The strength of evidence for duration was insufficient; the test was underpowered and we found significant heterogeneity.

Endometrial cancer incidence

Nine studies (6 good, 2 fair, 1 poor quality) evaluated the association between oral contraceptive use and endometrial cancer incidence (63, 65, 66, 69, 70, 73, 96–100). Of these, 4 were case–control studies and 5 were cohort studies. Only 2 studies were conducted in the United States (Supplementary Table S4).

Three case–control studies (73, 97, 100) and 4 cohort studies (63, 65, 69, 98) representing 308,198 women (within 4 studies) and an additional 3,981,072 person-years (within the other 3 studies) were included in this meta-analysis examining ever versus never oral contraceptive use. Figure 5 shows results indicating a protective effect for endometrial cancer associated with ever oral contraceptive use (OR, 0.57; CI, 0.43–0.77). Heterogeneity was significant (Q = 26.11, 6 DF, P < 0.001). We also explored how our findings changed when including only
U.S.-based studies. Only one study was conducted with patients from the United States and reported a somewhat greater protective effect than summary estimates for all studies (OR, 0.34; CI, 0.25–0.47). On the basis of the point estimates of the meta-analyses, the approximate decrease in absolute risk of endometrial cancer is 1.77% (NNT 60).

**Discussion**

Our results are confirmatory of initial analyses and reviews, including those which included studies published before 2000. This evidence synthesis highlights some of the tradeoffs about nonreproductive outcomes that patients and providers need to consider with the use of oral contraceptives: increased risk for some cancers (breast and cervical) but decreased risk for others (colorectal and endometrial). Other considerations include decreased risk of ovarian cancer (101) and increased risk for thromboembolic events (102). Estimating the overall balance of benefit and harm is difficult from a technical sense and because the timing of the outcomes affected by oral contraceptive use is variable—some risks and benefits are seen only during use, whereas others occur 20 to 30 years in the future. Moreover, different patients may well have different values for those outcomes.

We found that the risk of breast cancer was slightly—but significantly—elevated for women who have ever used oral contraceptives compared with women who have never used oral contraceptives. Although the...
relative increase in risk was small (OR, 1.08), the relatively high incidence of breast cancer diagnosis means that oral contraceptive use may contribute to a substantial number of cases. We found no time-dependent relationship as a function of duration of oral contraceptive use. Duration results should be interpreted with caution; there was significant heterogeneity, and the test was underpowered—which is not surprising, given that breast cancer is relatively uncommon during the ages when women are most likely to be using oral contraceptives. We also found that women with more recent use had an elevated risk of breast cancer, with decreasing risk over time, so that by 10 years since last use, the risk among users was equivalent to never users.

Our results are consistent with results of other meta-analyses and pooled analyses that identified a small increase in the relative risk of breast cancer associated with having ever used oral contraceptives—a risk that diminishes over time since last use (12, 103). The Collaborative Group on Hormonal Factors in Breast Cancer, a collaborative reanalysis of individual data in 153,536 women, found a small but significant increase in the relative risk of breast cancer (OR, 1.07 ± 0.02; ref. 12). Similar to our results, the Collaborative Group did not identify an increase in risk with increasing duration of use or after discontinuation of use for ≥10 years. Another recent meta-analysis of premenopausal breast cancer across 37 studies found a somewhat larger increase in the risk (OR, 1.19; CI, 1.09–1.29), with the greatest risk associated with oral contraceptive use before first full-term pregnancy (OR, 1.44; CI, 1.28–1.62; ref. 104). These results support our finding that recent use (≤5 years) is associated with an increased risk of breast cancer. Women who delay first full-term pregnancies may also be more likely to be recent users of oral contraceptives relative to a breast cancer diagnosis. These results cannot be directly compared with ours, as this meta-analysis was restricted to premenopausal women or women <50 years who may be at elevated risk due to other factors (e.g., genetic mutations) or represent cancer subtypes that differentially affect younger women. An alternative explanation of an association between oral contraceptive use and increased incidence may also be more surveillance in women who use oral contraceptives. Women who use oral contraceptives must come in contact with the healthcare system on a regular basis, thus increasing their chances of receiving referrals for preventive screenings such as mammography.

We found no significant increase in the risk of cervical cancer among ever oral contraceptive users compared with never users across 9 pooled studies. We also found no time-dependent relationship as a function of duration of oral contraceptive use. It is important to note that this contrast was underpowered with only 5 included studies. However, women having long-term use of oral contraceptives (≥5 years) were at an elevated but not statistically significant risk of cervical cancer compared with never users.

Three studies (2,592 women) assessed oral contraceptive use and cervical cancer incidence among HPV-positive women. Results were similar to those of women not selected for HPV status. Many studies did not control for factors that may influence risk, such as age at first oral contraceptive use by duration or age at sexual debut, which is likely highly correlated with age at first use. Future research is needed to assess the additional cervical cancer risk associated with oral contraceptive use among HPV-positive women. However, both studies reported statistically significant increased risk of death with ≥8 years of oral contraceptive use compared with never use.

Our cervical cancer results differ in some ways from other evidence syntheses published over the last 10 years. Smith and colleagues (13) pooled study-level data across 28 studies and found an overall significant increase in the risk of cervical cancer when comparing ever versus never users of hormonal contraceptives [relative risk (RR), 1.2; CI, 1.1–1.3]. We found a similar increase in the risk of cervical cancers, but our summary estimate was not significant. Both our review and the Smith study found the risk of cervical cancer increased with prolonged exposure. This effect weakened but remained significant when stratifying duration by time since use. For our review, this effect was significant only for women who used oral contraceptives for ≥5 years compared with never users; we did not have sufficient studies to stratify by time since last use. The International Collaborative of Epidemiological Studies of Cervical Cancer undertook a collaborative patient-level reanalysis of 24 observational studies (105). Results expand the duration by recency effect. The analysis found that excess risk of cervical cancers increases with duration of use, but this effect declined after discontinuing oral contraceptives and was equivalent to the risk of nonusers after 10 years of nonuse.

Key methodological differences between our study and the 2 recent syntheses preclude drawing exact comparisons. First, we included only studies of invasive cervical cancers; other studies also included carcinoma in situ and cervical intraepithelial neoplasia grade 3. It is likely that effects differ between invasive cancers and cancer precursor lesions. In fact, a case–case comparison in the collaborative reanalysis showed significant differences in the risks for in situ and invasive cervical cancers for nearly every category of time since last use by duration of use. Second, we included studies that assessed only the effects of oral contraceptives; the 2 other recent syntheses included all forms of hormonal contraceptives. It is possible that formulation differences contribute to some of the differences between our results and their findings. However, the collaborative reanalysis reported separate findings for progestin-only injectable contraceptives and found a similar pattern to those reported for oral contraceptives. Third, we did not include the 3 studies conducted with women selected for HPV infection status. The effects of this decision appear to be negligible; both prior reviews...
noted similar patterns of findings when controlling for HPV status as a covariate (13) compared with HPV uncontrolled studies or among the subset of women with a confirmed HPV infection compared with populations not selected for HPV status (105). Last, we date-limited our search from 2000 forward to minimize the effect of older formulations; other studies had no such date restrictions. Despite these differences, we found similar patterns of increased risk by duration of use. There is no direct evidence to suggest that cervical cancer screening recommendations should be different based on duration of oral contraceptive use.

We found that the risk of colorectal cancer was significantly decreased for women who have ever used oral contraceptives compared with women who have never used oral contraceptives. However, we found no evidence of a time-dependent relationship as a function of duration. Duration results should be interpreted with caution; the test was underpowered.

Our results are similar to 2 other evidence syntheses that also assessed the risk of colorectal cancers associated with oral contraceptive use (11, 106). These meta-analyses both found a pooled relative risk of approximately 0.82, which is comparable to our pooled findings. These reviews also found no increase in the protective effect by duration of use. The similarity between our findings and those of the other 2 reviews is noteworthy. We limited our studies from January 2000 forward so that we had a greater probability of capturing a set of studies with newer oral contraceptive formulations that may confer differential effects. Thus, we shared no studies in common with the study by Fernandez and colleagues (106), and we excluded 12 older or non-English studies and included 5 newer studies (63, 68, 90, 93, 95) compared with the systematic review by Bosetti and colleagues (11). Similarity in our findings with these earlier evidence syntheses suggests that oral contraceptives confer a significant protective effect for colorectal cancer, and future research could investigate oral contraceptives potential as a beneficial therapy for chemoprevention.

We identified 9 studies that evaluated the association between oral contraceptive use and the incidence of endometrial cancers; 7 were included in our meta-analysis to assess ever versus never oral contraceptive use. We found a significant protective effect with ever oral contraceptive use and a time-dependent relationship as a function of duration categorized as <60 and ≥60 months of total use.

Our study is one of the few systematic reviews and meta-analyses to summarize the evidence on the effects of oral contraceptives on endometrial cancers; Grimes and colleagues (107) conducted a systematic review and qualitative synthesis of studies up to 1993. They identified 13 case–control studies with protective ORs ranging from 0.1 to 0.6, with most effects clustering around 0.5. Two of the 3 cohort studies identified also found protective effects of oral contraceptive use. Schlesselman and colleagues (108) conducted a meta-analysis of 11 case–control studies. A significant duration trend was reported such that longer durations of use conferred greater protection (RR, 0.44 for 4 years of use; RR, 0.33 for 8 years of use; RR, 0.28 for 12 years of use; \( P < 0.0001 \)). We found a similar trend but used a different analytic approach; direct comparisons are difficult to draw. This meta-analysis also reported on time since last use and found that the protective effect of oral contraceptives is diminished after they are discontinued but still persists even 20 years after cessation. We did not have sufficient studies to assess the effect of time since last use. Protective effects of oral contraceptives may vary with formulation. However, our results are similar to other studies conducted in the 1990s that may have included different formulations based on market availability. Unfortunately, there are limited data on the formulations used in the majority of the studies reviewed, and it is likely that the distribution of formulations in the studies included in this review is different compared to contemporary oral contraceptive formulation distribution. If the association between oral contraceptive use and cancer varies based on formulation, particularly estrogen dosage, and type of progestin, then estimates of reduction or increases in future cancer risk among current pill users are subject to considerable additional uncertainty. Our results—in combination with other evidence reviews—confirm that oral contraceptives confer a significant protective effect on the risk of endometrial cancers.

Limitations

While we conducted a comprehensive systematic review and evidence synthesis of the current research on oral contraceptive use and the incidence of breast, cervical, colorectal, and endometrial cancers, there are limitations to our approach and findings. As expected, we identified no randomized trials; such studies are not likely feasible. Thus, we included only observational studies in our meta-analyses. Even the highest quality observational studies are susceptible to multiple forms of bias (e.g., confounding). Most included studies adjusted for multiple likely sources of cofounding; when possible, we used the most adjusted point estimates in our meta-analyses. Recall bias is also a common source of diminished quality in observational studies. Our findings were remarkably similar across case–control studies and cohort studies, which suggests a lack of evidence for recall bias of oral contraceptive use across study types. Also, we found significant heterogeneity across many of our comparisons. We included a diverse group of studies conducted across the world; differences in study populations and geographic variability in other risk factors not routinely assessed (e.g., access to health care) likely contributed to this heterogeneity. This may be particularly true for cancers such as breast, cervical, and colorectal, where screening can affect both incidence and mortality and where there may be associations between oral contraceptive use and screening behaviors. Sensitivity analyses using only U.S.-based studies (or with patients from the United States) could investigate oral contraceptives potential as a beneficial therapy for chemoprevention.
States) showed similar patterns to unrestricted analyses. Also, studies varied considerably in the type and specification of covariates, which may be a likely source of heterogeneity. To try to maximize the proportion of subjects who used oral contraceptive formulations similar to those currently on the market, we included only studies published in 2000 and later. However, study publication date is a gross estimate of oral contraceptive formulation exposure because observational studies published since 2000 still represent some cohorts exposed to earlier formulations. It may have been preferable to limit studies by year of diagnosis instead of publication date. Yet many of our findings are consistent with other meta-analyses without date restrictions, which suggest that current oral contraceptive formulations may have similar carcinogenic or protective effects compared with older formulations. Still, given the long latent period between exposure and tumor development, it is likely that recent publications may not fully assess the effect of formulations introduced in the past 20 years.

Conclusion

This systematic review of the literature identified several gaps in the evidence that warrant future investigation. Several subgroups deserve further attention; there are limited data on the effects of oral contraceptives on cancer risk in women at elevated risk of malignancy due to behavioral risk factors such as smoking, heavy alcohol consumption, obesity, or physical inactivity. These factors are known to be associated with cancer development, and so behavioral risk factors may modify the association between oral contraceptives and cancers. We found that duration of use conferred a different pattern of risk, but we found limited support of a time-dependent relationship. Because the benefits and risks associated with oral contraceptive use differ by pattern of use, more research is needed on the interaction of different patterns of use (e.g., duration by time since last use, age at initiation by duration) on the risk of breast, cervical, colorectal, and endometrial cancers to optimize the risks and benefits of oral contraceptive use.

Quantifying the potential impact of changes in oral contraceptive formulations is difficult. Although our analyses were based on more recently published data, and we did not identify an obvious association based on probable dates of exposure within these studies, the long lag time between "typical" exposure to oral contraceptives and incident cancers means that the distribution of formulations among subjects in even the most recent literature is likely to be different than the distribution among current oral contraceptive users. This uncertainty affects both estimated harms (increased risk of breast cancer) and benefits (decreased risk of endometrial and colorectal cancer).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.M. Gierisch, R.M. Coeytaux, R.P. Urrutia, L.J. Havrilesky, P.G. Moorman, W.J. Lowery, A.J. McBroom, G.D. Sanders


Writing, review, and/or revision of the manuscript: J.M. Gierisch, R.M. Coeytaux, R.P. Urrutia, L.J. Havrilesky, P.G. Moorman, W.J. Lowery, M. Dinan, A.J. McBroom, G.D. Sanders, E.R. Myers

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Gierisch, A.J. McBroom

Study supervision: G.D. Sanders

Acknowledgments

The authors thank Liz Wing, for editorial assistance; Kathryn Roth, Lallinger and Michael Musty, for project coordination; and Megan von Itshagen, for help with the literature search and retrieval.

Grant Support

All authors received support and this project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services.

Received March 19, 2013; revised August 21, 2013; accepted August 27, 2013; published OnlineFirst September 6, 2013.

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37. Published OnlineFirst September 6, 2013; DOI: 10.1158/1055-9965.EPI-13-0298
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