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Relation between oral contraceptives and cervical cancer

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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). 12 Cervical cancers studies were included in this report . 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.

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 [4-7].

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 .

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. 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 cancer in cervical region , When possible,

Aim

This report was made in order to assess the risk of developing cervical cancers following oral contraceptive use.

Methods

The data of this report have been collected from 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, year-by-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.

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 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.Twelve studies (5 good, 4 fair, 4 poor quality) evaluated the association between oral contraceptive use and cervical cancer incidence, including 2 articles from an International Agency for Research on Cancer (IARC) study representing distinct populations. 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

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 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 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, both rated poor quality, also assessed the risk of cervical cancer associated with oral contraceptive use among HPV-positive women. One study 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 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 and 3 cohort studies representing 3,981,072 person-years met criteria for the meta-analysis examining ever versus never oral contraceptive use, 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 show a statistically significant increase in risk with ever use of oral contraceptives (OR, 2.7; CI, 1.2–5.8).

Six studies 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; 5 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.

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

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 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 .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 compared with HPV uncontrolled studies or among the subset of women with a confirmed HPV infection compared with populations not selected for HPV status .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.

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.

Future Work

More researches and data regarding the relation between these two diseases in order to prevent the risk of cancer and updating more treatment protocols while using oral contraceptives

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