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Cancer Epidemiology, Biomarkers & Prevention

Letter to the Editor

Oral Contraceptive Use and Risk of Cancer—Response

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We thank Dr. Weiss (1) for his thoughtful reading of our article (2). This review was part of a larger project (3) in which the main issue was whether there is sufficient evidence to justify a recommendation for the use of oral contraceptives for primary prevention of ovarian cancer in the United States, based on the available evidence on associations of oral contraceptive use with ovarian cancer, acute thrombotic events, and the four cancers discussed in this article. That project was intended to inform the question, "What is the likelihood that a recommendation to use oral contraceptives for primary prevention of ovarian cancer will result in overall net benefits?" rather than the question, "What is the likelihood that women who used oral contraceptives at some point in the past will develop one of the outcomes of interest?"

Oral contraceptive formulations have been continuously revised since their introduction to the U.S. market in 1957. Although the introduction date of a particular formulation can be identified from reviewing U.S. Food and Drug Administration (FDA) approvals, there are very limited data for estimating year-by-year market share, duration of use, and patterns of use, and details of the type of oral contraceptive used are inconsistently reported across studies. Because the underlying purpose was to inform current and future practice in the United States, and given the large number of outcomes to review within time and budget constraints, we prioritized more recent literature not only to increase the likelihood that oral contraceptives used by subjects were similar to currently available forms, but also to minimize the effect of secular trends in unmeasured confounders, screening behavior, or competing risks (such as hysterectomy rates). We agree with Dr. Weiss that even more recently published literature for some outcomes is likely to reflect use patterns from 15 to 30 years ago, which increases the uncertainty around inferences about the risk of future harms and benefits among women currently using, or considering using, oral contraceptives, and that our choice of the year 2000 as a cutpoint is arbitrary. We note that this decision was made in consultation with the sponsors of the project, Centers for Disease Control and Prevention (CDC) and Agency for Healthcare Research and Quality (AHRQ), as well as with a technical expert panel.

This issue was also raised during peer review of the article and in analyses performed in response to reviewer suggestions; we did not find any obvious temporal trend in point estimates for individual studies when stratified by decade when women were likely to be using oral contraceptives. This suggests that including older studies might have increased the precision of effect sizes; however, there would still be uncertainty about applicability to current practice. Many of our findings are qualitatively consistent with meta-analyses without date restrictions, suggesting that oral contraceptive formulations used by women in the more recent publications may have similar effects on breast, cervical, colorectal, and endometrial cancers when compared with older formulations. However, as we state in our article, because of the long latent period between exposure and tumor development, even more recent publications may not fully capture any changes in the direction or magnitude of association due to changes in formulation or changes in the distribution of different formulations among the population of oral contraceptive–using women. Ultimately, we believe that including older studies would not resolve the uncertainty about the noncontraceptive effects of currently available oral contraceptives on other cancers enough to inform clinical decision making.

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