

Oral contraceptives and cervical cancer: critique of a recent review

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Abstract

A recent review article by Smith et al. in *The Lancet* purports to find a causal relationship between long-term use of oral contraceptives (OCs) and cervical cancer. While we endorse the search for such a relationship, we felt it important to critically examine Smith et al.'s review process and, as a result, we have questions about the validity of their conclusions. In our view, the findings of published articles as presented by Smith et al. do not confirm a causal connection between long-term use of OCs and cervical cancer. Our goal is not to conduct another formal review of the evidence, but to evaluate whether Smith et al. have met the burden of proof for establishing a causal relationship. Given the importance of OCs to women the world over, we urge reproductive health professionals to consider this issue carefully before accepting that a causal relationship exists. © 2004 Elsevier Inc. All rights reserved.

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1. Introduction

The World Health Organization (WHO) recently commissioned a review of the published evidence of a possible link between oral contraceptive (OC) use and cervical cancer. The resulting review by Smith et al. [1] was published in *The Lancet* in April 2003. Given the prevalence of cervical cancer, especially in developing countries, as well as the social and medical importance of OCs, we applaud the attention to this topic. Smith et al. purport to find a causal relationship between long-term use of OCs and cervical cancer, and we expect this conclusion to be influential due to the origins and venue of their review. For this reason, their conclusion warrants careful scrutiny.

This article aims to examine Smith et al.'s review process and, if indicated, to raise questions about the validity of their conclusions. Our goal is not to re-review the literature regarding such a connection, but to question whether Smith et al. have met the burden of proof for establishing a causal relationship, given the articles they present. A brief letter printed in *The Lancet* in response to the Smith et al. review [2] also questioned their conclusions; we propose to examine the issue in more detail. In our view, the findings of

published articles as presented by Smith et al. do not positively confirm a causal connection between long-term use of OCs and cervical cancer.

Smith et al. reviewed 21 studies, but do not discuss possible behavioral or biological routes of causation. Three causal routes could have been investigated with the collected studies:

1. Use of OCs may be behaviorally related to increased risk of human papillomavirus (HPV) transmission. Compared to age-matched controls, women who use OCs may be more sexually active, more frequently screened for cervical cancer and less apt to use barrier methods. Increased exposure to and screening for HPV over time would lead to higher observed cancer rates among users. OCs themselves would be exonerated of any causal role in cervical cancer.
2. Use of hormonal contraception may increase the biological vulnerability of the cervix. Given the same exposure to HPV, hormone users may be at higher risk of transmission.
3. Use of OCs may increase the chances or speed with which HPV infection progresses to in situ or invasive cervical cancer.

Establishing the causal route has clinical and programmatic significance. If behavioral factors are most important,

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OC users should be counseled, along with all sexually active women, on protection from sexually transmitted infections. OCs themselves would play no role in cervical cancer risk except as a probable sign of sexual activity. If OCs increase the vulnerability of the cervix, then OC users should be targeted for additional counseling. If OCs increase the chances of cancer given HPV infection, then women with persistent HPV infection should be counseled against long-term hormone use until the relationship is better understood.

Smith et al. appear to be interested in causal routes (2) and (3), yet we question their interpretation of controls on the behavioral factors of (1). If behavioral factors are not properly addressed, it is impossible to evaluate (2) and (3). In short, behavioral factors present a strong risk of confounding in searching for a causal association between OCs and cervical cancer [3].

Smith et al. present relative risks from each study adjusted for whatever controls happened to be included in the original articles, with no accompanying discussion of how those controls sequentially mediate the risk. We question whether Smith et al.'s pooled estimates of these relative risks are appropriate because each study was designed and controlled differently. These pooled estimates are presented centrally in a large figure and discussed in the text, yet later the authors admit that these estimates "cannot be formally compared," and even suggest that their analysis is not a "proper evaluation" (p. 1165). The emphasis on the figure may mislead the reader to conclude that a causal relationship exists.

Here, we propose to sift through the studies presented in Smith et al. with an eye to the included controls, looking for evidence that OCs confer an increased risk of cervical cancer, net of behavioral controls.

2. Reconsideration of the research

The designs of the 21 included studies partly determine how their results should be evaluated. Four of the source studies have prospective cohort designs, which is one of the most valid designs for treatments that cannot be randomized. In this design, control variables such as sexual partners and condom use can be recorded as they occur, leading to more valid data. All of the remaining studies have case-control designs, which are expedient but weak in their ability to control for unobserved confounding variables, since cases and controls are never strictly comparable. Case-control studies are also retrospective, so their data are subject to recall bias, which increases with time. These observations lead to two overall caveats about the source papers for this review. First, Smith et al. note that the four cohort studies generally found greater relative risks than the case-control studies, "and the reason for this is unclear" (p. 1165). Yet, recall bias in case-control studies could easily prejudice these results relative to cohort studies, especially considering the daunting task of recalling sexual partners,

OC use, condom use and cervical screenings 10 years or more in the past. We regard the long-term results from case-control studies with skepticism. Second, the measurement of the behavioral variables is critical. For instance, do studies measure the number of sexual partners at the time of interview, before HPV diagnosis, at the time of hormonal contraception use, or over a lifetime? These and other approaches affect the meaning of the measurement in terms of controlling for exposure to HPV. Similar points can be made about the measurement of cervical screening and barrier method use. These measurement problems are further compounded by recall bias.

Next, we consider the studies and their controls. Our central concern is whether behavioral factors are adequately controlled in the source studies before attributing biological causes. The three behavioral controls considered by Smith et al. are number of sexual partners, use of barrier methods and cervical screening. Smith et al. do not report if any study had other behavioral controls. Moreover, for the purposes of this argument, we do not consider smoking a behavioral control because its relationship with cervical cancer would presumably be biological, not through increased exposure to HPV. We would not want to assume, for example, that women who smoke have more or fewer sexual partners than those who do not. Some studies also controlled for HPV status, which Smith et al. dismiss as an uninterpretable covariate because HPV is thought to be a necessary precondition for cervical cancer. We agree that this control is not useful.

Table 1, which is adapted from a table in Smith et al. (p. 1160), includes brief information on each study and its controls. Listed in Smith et al. by study design and year of publication, the studies are arranged here by successive controls for barrier method use, number of sexual partners and cervical screening. Only statistically significant relative risks are included.

The first three studies in Table 1 [4–6] include none of the three behavioral controls. Even before considering their results, we believe these studies will present the weakest evidence of a causal relationship between OCs and cervical cancer, since behavioral factors are completely uncontrolled. None of the three studies finds a statistically significant increased risk of cervical cancer among OC users relative to nonusers, at any duration of use. Because of the lack of behavioral controls, they tell us little about the relationship between OC use and cervical cancer.

We turn next to the studies that control for number of sexual partners or use of barrier methods, which we argue to be the most proximate behavioral controls. One study by Zondervan and colleagues [7] controls for barrier method use only. It finds a barely significant medium-term increased relative risk and has no information on the longer-term risk. The three subsequent studies in Table 1 control only for the number of sexual partners. Cuzick et al. [8] finds no significant relative risks, Ylitalo et al. [9] finds an increased risk with time, and Lazcano-Ponce et al. [10] finds a decreased

Table 1
Studies included in Smith et al., 2003 [1]

Study and year	Country	Design	Behavioral controls			Statistically significant RRs (95% CI)		
			No. of sexual partners	Use of barrier methods	Cervical screening	~<5 years of OC use	~5–9 years of OC use	~10+ years of OC use
Deacon et al., 2000 [4]	UK	Cohort						
Peters et al., 1986 [5]	USA	Case-control				No data		
Hildesheim et al., 2001 [6]	Costa Rica	Case-control						No data
Zondervan et al., 1996 [7]	UK	Cohort		✓			2.1 (1.2–3.6)	No data
Cuzick et al., 1996 [8]	UK	Case-control	✓				2.4 (1.3–4.3)	3.6 (2.0–6.7)
Ylitalo et al., 1999 [9]	Sweden	Cohort	✓					No data
Lazcano-Ponce et al., 1995 [10]	Mexico	Case-control	✓			.7 (.5–.9)		No data
Ursin et al., 1994 [11]	USA	Case-control	✓	✓				4.4 (1.8–10.8)
Beral et al., 1988 [12]	UK	Cohort			✓	2.1 (1.4–3.0)	3.1 (2.1–4.5)	4.7 (2.9–7.5)
WHO 1993 [13]	9 countries	Case-control			✓	1.2 (1.1–1.3)	1.7 (1.5–2.0)	2.2 (1.9–2.7)
Madeleine et al., 2001 [14]	USA	Case-control	✓		✓		3.4 (1.5–8.0)	5.5 (2.1–14.6)
Irwin et al., 1988 [15]	Costa Rica	Case-control	✓		✓		1.6 (1.1–2.3)	No data
Berrington et al., 2002 [16]	UK	Case-control	✓		✓			2.8 (1.2–6.6)
Moreno et al., 2002 [17]	8 studies	Case-control	✓		✓			1.9 (1.3–2.7)
Brinton et al., 1990 [18]	4 countries	Case-control	✓		✓			No data
Lacey et al., 1999 [19]	USA	Case-control	✓		✓			No data
Ebeling et al., 1987 [20]	Germany	Case-control	✓		✓			No data
Daling et al., 1996 [21]	USA	Case-control	✓		✓			No data
Parazzini et al., 1998 [22]	Italy	Case-control	✓		✓			No data
Brinton/Jones et al., 1986 [23,24]	USA	Case-control	✓	✓	✓		2.0 (1.3–3.0)	1.6 (1.1–2.5)
Kjaer et al., 1993 [25]	Denmark	Case-control	✓	✓	✓		1.7 (1.1–2.6)	No data

RR = relative risk; CI = confidence interval.

risk in the short term. These conflicting results do not inspire confidence in a strong association. A better approach would be to control both barrier use and sexual partners simultaneously. One study by Ursin et al. [11] controlled for both and found a somewhat heightened risk with long-term use. Yet, as a case-control study, its long-term results are suspect. This single article, the best-controlled study yet considered, gives, at best, weak support to a relationship between OCs and cervical cancer in the long term only. Yet, it does not control for cervical screening.

Beral et al. [12] and WHO [13] both control for screening only. These two studies appear to give some of the strongest evidence for an association between cervical cancer and long-term OC use. The relative risks are statistically significant and their magnitude increases with time. Beral has the stronger prospective cohort design, and WHO has a massive sample size (3848 cases and 13,644 controls). Here, Smith et al.'s conclusion seems bolstered, yet again we question the results because neither study controls simultaneously for sexual partners or barrier method use. Moreover, a large sample size can increase the chances of finding significant associations through sheer statistical power, but it cannot correct for excluded controls.

The next nine papers in Table 1 control for both cervical

screening and sexual partners simultaneously. Of these, only the first, Madeleine et al. [14], finds the kind of relationship that Smith et al. argue for, with increasing and statistically significant relative risks over time. Irwin et al. [15] finds a barely significant increased risk in the medium term and provides no information about the longer term. Berrington et al. [16] and Moreno et al. [17] show a slightly increased risk in the longer term, but as they are both case-control studies, these results are suspect. None of the next five articles [18–22] find any significant increased risk at all. Taken together, these studies do not argue for a strong association between OC use and cervical cancer. In fact, this group of studies suggests that the increased risks found by Beral et al. and WHO may well be an artifact of differences in number of sexual partners among OC users and nonusers.

The remaining two studies, Brinton et al., Jones et al. [23,24] and Kjaer et al. [25] are the only ones to control simultaneously for sexual partners, barrier method use and cervical screening. In our view, these are the best-controlled studies of the whole set, and their results should be given more weight than the others. Kjaer et al. finds a barely significant increased risk in the medium term and has no information about the long term. Brinton et al. and Jones et

al. find a modest short-term risk and a smaller and scarcely significant long-term risk.

At this point, Smith et al. might argue that Kjaer, Brinton, Jones and their colleagues have found a slight increased risk of cervical cancer with OC use over time, net of behavioral factors. These relative risks would presumably be attributed to the causal routes (2) or (3) listed above, since the behavioral factors of (1) have been controlled. Again, we question the strength of this conclusion. First, the Brinton/Jones results show a larger risk in the medium term than in the long term. How can this be explained? It may reflect the instability in long-term recall in case-control studies, calling into question the overall validity of the results over time. Arguing for the causal relationship that Smith et al. favor would be difficult given the larger medium-term association. Second, our caveats about measurement of control variables still stand. We do not know how these variables were measured in the source studies, but the size of the net relative risks are certainly small enough to have resulted from measurement error or any number of other design flaws. Based on these two studies, we question any biological association between OCs and cervical cancer, let alone a causal relationship.

3. Discussion

Smith et al. conclude that “the relative risk of cervical cancer increases with increasing duration of oral contraceptive use” (p. 1165) and elsewhere hint at a causal relationship with phrases such as “the effects of oral contraceptives on the risk of cervical cancer” (p. 1166). Considering the same evidence, we are not so convinced of a causal relationship, and we are concerned that healthcare providers may counsel women against long-term OC use due to a perceived risk of cervical cancer. Although we support a conservative approach to assessing medical risks, improperly assigning a risk of cervical cancer to OCs would also be damaging to women’s health.

Worldwide, OCs and other forms of hormonal contraception confer enormous health advantages to women. First, efficient hormonal contraception allows women to avoid pregnancies, which carry their own significant risks, particularly in the developing world. Second, thorough and consistent research results have shown that OC use protects against a range of serious health threats, such as ovarian cancer, endometrial cancer, ectopic pregnancy, colorectal cancer, rheumatoid arthritis and bone loss [26]. These known health benefits of OCs must be weighed against any possible association with cervical cancer. Moreover, if we assume for the moment that the results of Kjaer et al. and Brinton/Jones et al. are correct, the probable relative risk of cervical cancer with long-term OC use is estimated at 2.0 at the most. Yet other factors, such as educational level, number of sexual partners, age at sexual debut, immunosuppression and history of vaginal discharge have all been shown to have odds

ratios variously ranging from about 4 up to 17 in relation to cervical neoplasia [27–30]. If public health authorities are genuinely concerned with cervical cancer rates, they would achieve much better outcomes by targeting women with these risk factors for screening than by discouraging OC use. Cervical cancer can be detected early with effective screening tools, even in resource-poor settings where cytology-based screening is not practical. Recent research supports the usefulness of acetic acid wash in combination with clinical history screening, for example, where Pap smear technology is not feasible [31]. Given the health and contraceptive benefits of OC use, we argue that risks associated with cervical cancer can be best addressed by investing in accessible, low-cost screening tools and targeting women with substantial risk factors.

In closing, we suggest that Smith et al.’s review could have been more circumspect in its conclusions. We applaud the effort of sifting through a large literature but question whether the authors have met the burden of proof of establishing a causal relationship between long-term OC use and cervical cancer beyond confounding behavioral factors.

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