Oral Contraceptives and Cervical Cancer Risk in Costa Rica

Detection Bias or Causal Association?

Kathleen L. Irwin, MD, Luis Rosero-Bixby, MD, Nancy C. Lee, MD, Anne S. Whanley, MS, Judith A. Forney, PhD, Michele G. Bonhomme, MSPH

To examine the relationship between cervical cancer and oral contraceptive (OC) use, we analyzed data from a population-based, case-control study in Costa Rica. Women aged 25 to 58 years in whom cervical cancer was diagnosed and reported to the National Tumor Registry were examined as two separate case groups: invasive cervical cancer and carcinoma in situ (CIS). Controls were women aged 20 to 58 years identified through a national survey. Women who had used OCs had no increased risk of invasive cervical cancer compared with women who had never used OCs (relative risk, 0.8; 95% confidence interval, 0.5 to 1.3). Women who had used OCs had an increased risk of CIS compared with those who had never used OCs (relative risk, 1.8; 95% confidence interval, 1.2 to 2.2). However, further analyses indicated that this increased risk was confined to those who had recently used OCs. Also, the risk of CIS was not elevated in subgroups in which a history of cervical smears was not strongly linked to OC use. The elevated risk of CIS among OC users may therefore reflect a bias caused by enhanced detection of disease rather than a causal association.

METHODS

A detailed review of the methods of this population-based case-control study of cervical and breast cancer has been previously published.7 The breast cancer cases are the subjects of a separate report.7 Here we describe the methods relevant to this analysis.

Study Participants

We selected cases from the Costa Rica National Tumor Registry. Since 1987, the registry has received reports on all inpatients and outpatients with a diagnosis of cancer from all hospitals and pathologists in Costa Rica. We enrolled 589 cases of CIS and 550 cases of invasive cervical cancer newly diagnosed between January 1, 1982 and March 31, 1984. The patients were between 25 and 59 years of age at diagnosis. Between September 1984 and February 1986 OCs were first introduced to Costa Rica in the early 1960s and are the most common contraceptive used today.11 In 1981, more than half of currently married women 15 to 44 years of age were using OCs at some time during their reproductive years.12 Costa Rica's primary care medical care services are among the most comprehensive in Central America; free cervical cancer screening is provided by the country's many hospitals, outpatient clinics, and rural health posts.7 In 1986, 70% of women aged 15 to 49 years reported having had at least one Papnicolau (Pap) smear.13

The relationship between oral contraceptives (OCs) and cervical cancer remains controversial, largely because of conflicting results from epidemiologic studies. In studies of carcinoma in situ (CIS) and invasive cervical cancer from both developed and developing countries, reported risk estimates have ranged from a low of 0.6 for all OC users to a high of 6.0 for long-term users.9 Methodologic problems such as confounding by sexual behavior and detection bias caused by the enhanced detection of cervical cancer among OC users have plagued nearly all studies to date.9

Costa Rica provides a unique opportunity to examine the relationship between OCs and cervical cancer. Costa Rica maintains a nationwide Tumor Registry,9 which recently reported an annual incidence of invasive cervical cancer of 36.2/100,000 women, one of the highest rates in the world.10 In 1985, cervical cancer was the most commonly reported cancer and the second leading cause of cancer mortality among Costa Rican women.7 In addition, combination OCs were first introduced to Costa Rica in the early 1960s and are the most common contraceptive used today.11 In 1981, more than half of currently married women 15 to 44 years of age were reported to be using OCs at some time during their reproductive years.12 Costa Rica's primary care medical care services are among the most comprehensive in Central America; free cervical cancer screening is provided by the country's many hospitals, outpatient clinics, and rural health posts.7 In 1986, 70% of women aged 15 to 49 years reported having had at least one Papnicolau (Pap) smear.13

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From the Division of Reproductive Health, Centers for Disease Control, Atlanta (K.L.I., A.S.W., and J.A.F.); the Division of Reproductive Health, Centers for Disease Control, Atlanta (K.L.I., A.S.W., and J.A.F.); the Division of Reproductive Health, Centers for Disease Control, Atlanta (K.L.I., A.S.W., and J.A.F.); and the University of Costa Rica, San José (L.R.-B. and F.M.H.) Research supported in part by US Agency for International Development Grants P-4327 and P-4299 and by the World Health Organization, and by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and by the National Institutes of Health, National Institutes of Health, and United States Department of State.}

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diagnosed, we used an index date to adjust for use variables and factors that might confound or modify the relationship of OCs and cervical cancer. The index date for each patient was the date of her diagnostic biopsy. The index date for all controls was Feb 15, 1980, the midpoint of the 27-month case enrollment period. Women who were between 25 to 58 years of age at the index date were excluded from the analysis (Table 1). We classified each woman's OC use before the index date, as follows: total months of use (interruption or continuous), years since last use, years since first use, and age at first use. Women who did not report all their dates of OC use were classified as unknown users; women who reported their first use after the index date were considered never users of OCs. The Ministry of Health and Social Security (MOH and CSSS) provide the vast majority of family planning services in Costa Rica. To estimate differences between patients and controls in the recall of OC use, we examined a sample of women from our study who had clinic visit records at the MOH or CSSS from 1974 through 1980. We estimated the proportion of women with false-negative reports of OC use by dividing the number of women who at interview reported no use of OCs from the MOH or CSSS but were identified as OC users by MOH or CSSS records by the number of women in the corresponding patient or control groups.

We used logistic regression models to evaluate the effects of OC use and age at index date as a categorical variable (25 to 29, 30 to 34, 35 to 39, 40 to 44 years, and 45 years) to screen individually for the following potentially confounding factors: gravidity; number of lifetime sex partners; age at first coitus; history of any STD or pelvic inflammatory disease (PID) in the history of Pap smears before 1980 (the beginning of the case enrollment period); education; region of residence; socioeconomic status (SES); use of douches; use of condoms; use of other barrier-method contraceptives; use of depomedroxy-progestrone acetate contraceptive; history of smoking; number of marriages or consensual unions; and positive serologic test for HSV-2, syphilis, or chlamydia. We included age and the first five listed variables in the final models because each study adequately distorted the risk estimates associated with OC use. All relative risk estimates presented here are odds ratios that were simultaneously adjusted for all the potential confounding factors. In all analyses, patients who had never used OCs served as the referent group; they are denoted as nonusers. Tests for linear trend with OC exposure variables were calculated using months as a continuous variable.

To assess if detection for cervical cancer differed between subjects who had used OCs compared with those who had never used OCs, we analyzed Pap smear screening before 1980 in the controls included in the analysis, because they represent the general population of Costa Rican women. To deter-
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carcinoma in Situ</th>
<th>Invasive Cancer</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry</td>
<td>35-69</td>
<td>70-95</td>
<td>&lt;= 29</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>Education</td>
<td>High school graduate</td>
<td>Less than high school graduate</td>
<td>High school graduate</td>
</tr>
<tr>
<td>Occupation</td>
<td>Blue collar</td>
<td>White collar</td>
<td>Blue collar</td>
</tr>
<tr>
<td>Family history</td>
<td>First degree relative</td>
<td>Second degree relative</td>
<td>First degree relative</td>
</tr>
<tr>
<td>Prior history</td>
<td>Previous diagnosis</td>
<td>Previous treatment</td>
<td>Previous diagnosis</td>
</tr>
</tbody>
</table>

**RESULTS**

**Characteristics**

On average, patients with CIS were younger than controls and patients with invasive cancer were older than controls. This was a consequence of the age-weighted control selection. As expected, patients with CIS and invasive cancer had a greater prevalence of controls of previously reported risk factors for cervical cancer. Including low SES, first contact at a young age, multiple sexual partners, high gravidity, a history of smoking, a history of any STD or HIV, and positive results in a serologic test for syphilis, chlamydia, and/or HSV-2 (Table 2). Compared with controls, patients with CIS were more likely and patients with invasive cancer were less likely to report having had a Pap smear before the study began in 1985 (Table 3).

**Carcinoma in Situ**

Subjects who had used OCs had an increased risk of risk compared with those who had never used OCs (SE = 1.96; confidence interval [CI], 1.2 to 2.2) (Table 3). Risks appeared to increase steadily with increasing duration of use, so that women who had used OCs for 10 years or more had twice the risk of those who had never used OCs (Table 3). However, when time since last use was considered, the elevated risk associated with long-term use was eliminated. Only recent users had an elevated risk regardless of age at first use, factors that were highly correlated with duration of use. When we restricted the analysis to patients and controls who had had at least one Pap smear before 1985, the risk estimates associated with OC use, duration of use, time since first use, time since last use, and age at first use did not differ appreciably from risk estimates in the unrestricted analysis.

Among controls, a history of a Pap smear was more common in those who had used OCs than in those who had never used OCs regardless of age, residence, or SES (Table 3). In Costa Rica, Pap smears are routinely offered by family planning providers. Differences in Pap smear history between OC users and nonusers were greatest among controls residing outside of San José and controls who had a low or medium SES. Despite Costa Rica's extensive national health system, access to medical care is more limited for women who live outside of San José or who have a low or medium SES.

The relationship between Pap smear screening and OC use in Costa Rica varied, and condom users were more common among controls residing outside of San José and controls who had a low or medium SES.
affected risk estimates in two subgroups: (1) Among women from San Jose, where Pap smear screening is less strongly linked with OC use than elsewhere in the country, OC use was associated with an elevated risk of CIS (Table 6). (2) Among women with high SES, for whom differences in Pap smear screening between OC users and nonusers were least pronounced, OC use was not associated with an elevated risk of CIS (Table 6). Thus, in two groups in which Pap smear screening and OC use were not closely linked, OC users had no elevated risk of CIS. In addition, among women with high SES, OC users had no elevated risk of CIS (Table 6). We observed no important interactions with the four measures of medical care utilization (including Pap smear history, attendance, and SES) or the seven cervical cancer risk factors studied. COMMENT

In this case-control study of cervical cancer in Costa Rica, OC use was not associated with risk of invasive cancer but was positively associated with risk of CIS. Although we cannot rule out a causal association as an explanation for

The elevated risk of CIS, we believe that the enhanced detection of CIS among OC users, ie, detection bias, best explains these results.

Evidence that OCs induce neoplasia in women as yet has not been conclusively demonstrated in animal studies. Conceivably, OCs could accelerate the progression of preneoplastic lesions or could promote the action of other suspected carcinogens such as human papillomavirus. In women, OCs increase the risk of CIS through either mechanism, there should be a dose-response effect, with long-term users showing the greatest cancer risk. The greatest CIS risk in our study, however, was found in the most recent OC users, including those who had used OCs for one year or less; the elevated risk of long-term OC users was eliminated when recent use was considered. Such a pattern of risk would be biologically plausible only if OCs had a short, lived carcinogenic effect on the cervix that diminished a few years after use. Such an effect, particularly one that could result in its maximal potency in less than one year, seems to be inconsistent with reports that short-term OC use does not adversely affect cervical tissue.

Detection bias provides a better explanation for the elevated risk of CIS observed in this study. Because CIS are the precursor stages of dysplasia and are usually asymptomatic, a Pap smear is required to detect these conditions. Women with CIS who had used OCs were more likely to have had a Pap smear, to have been referred to a diagnosis and biopsy, and to have been enrolled in our study than women with CIS who had never used OCs; a detection bias, if this were true, would introduce a spuriously elevated in the risk estimate associated with OC use. Such an overrepresentation of OC users among the patients with CIS in our study is likely, because OC users in Costa Rica are more likely than nonusers to have had a Pap smear.

An analysis of time since last OC use supports this detection bias argument. Women who had used OCs recently were more likely than women who had used OCs less than 10 years ago to have had a Pap smear and a recent Pap test, which might lead to the diagnosis of CIS. This enhanced detection of disease among recent OC users would explain why the risk of CIS was greater than zero in years of use.

Including Pap smear histories in our logistic regression models adjusted for the confounding effects of Pap smear utilization, but only among the patients and controls enrolled in our study. This adjustment factor could not duplicate the bias caused by not enrolling a
large group of patients with CIS who had never used OCs and thus, had never had a Pap smear that might have led to diagnosis. This bias can only be assessed indirectly, by analyzing subgroups in which detection for cervical cancer was equally applied, regardless of OC use. Among the groups from San Jose and those with high SES, OC users and nonusers had the smallest differences in screening practices, and the risk of CIS was not elevated. Detection bias should be least apparent in these three groups, and their risk estimates, which included 0.9 and 1.1, may best reflect the true association between OCs and CIS in Costa Rica. Among the group that reported saving ten or more Pap smears before 1983, we found no elevated risk of CIS. This was true despite the fact that OC users were more likely than nonusers to have had frequent Pap smears. Some women in this frequently screened group may have had cervical dysplasia, which was treated and followed up with repeated Pap smears, thus preventing progression to CIS. Unfortunately, we could not directly examine this possibility because we did not collect information on the results and treatment associated with each Pap smear. The risk estimate of 0.8 associated with OC use and invasive cervical cancer may also reflect a detection bias. Patients with invasive cancer in this region may have been less likely than other patients with CIS or controls to have had a Pap smear before 1983. Because OC users were more likely than nonusers to have had a Pap smear and to have their disease detected at the investigative stage of CIS, OC users should be less likely than nonusers to have disease that had progressed to the invasive stage. In contrast, nonusers were less likely to have had a Pap smear and, therefore, were less likely to have their invasive cancer diagnosed when they became symptomatic. Thus, OC users should be overrepresented among the CIS cases, resulting in an overall positive association, and underrepresented among the invasive cancer cases, resulting in an overall negative association. Moreover, among recent users of OCs (women who were likely to have had a recent Pap smear that might have led to the diagnosis of CIS), the risk of CIS is high and the risk of invasive can-

### Table 5 — Comparing Rates at Least One Pap Smear before 1983, %

<table>
<thead>
<tr>
<th>OC Users</th>
<th>OC Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>87.5%</td>
<td>77.2%</td>
</tr>
<tr>
<td>87.7</td>
<td>69.1</td>
</tr>
<tr>
<td>93.1</td>
<td>94.5</td>
</tr>
<tr>
<td>82.9</td>
<td>81.9</td>
</tr>
<tr>
<td>85.3</td>
<td>85.9</td>
</tr>
<tr>
<td>70.4</td>
<td>70.2</td>
</tr>
<tr>
<td>79.3</td>
<td>74.4</td>
</tr>
<tr>
<td>95.0</td>
<td>95.0</td>
</tr>
<tr>
<td>89.9</td>
<td>89.9</td>
</tr>
<tr>
<td>70.4</td>
<td>68.9</td>
</tr>
</tbody>
</table>

### Table 6 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
<thead>
<tr>
<th>OC Use</th>
<th>Patterns/Patterns Controls</th>
<th>RR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users</td>
<td>81.59</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Used</td>
<td>41200</td>
<td>0.95 (0.93-1.01)</td>
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</table>

### Table 7 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
<thead>
<tr>
<th>Duration of use, years</th>
<th>OC Use</th>
<th>Patterns/Patterns Controls</th>
<th>RR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>15.86</td>
<td>0.95 (0.85-1.05)</td>
<td></td>
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<tr>
<td>1-5</td>
<td>12126</td>
<td>1.00 (0.90-1.10)</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>2315</td>
<td>0.95 (0.85-1.05)</td>
<td></td>
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</table>

### Table 8 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
<thead>
<tr>
<th>Time since last use, years</th>
<th>OC Use</th>
<th>Patterns/Patterns Controls</th>
<th>RR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>13197</td>
<td>0.95 (0.85-1.05)</td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>2315</td>
<td>0.95 (0.85-1.05)</td>
<td></td>
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</tbody>
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### Table 9 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
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<tr>
<th>Time since last use, years</th>
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<tr>
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<td>2315</td>
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<thead>
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<tr>
<td>10+</td>
<td>2315</td>
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### Table 11 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

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### Table 12 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

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<td></td>
</tr>
<tr>
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<td>0.95 (0.85-1.05)</td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>2315</td>
<td>0.95 (0.85-1.05)</td>
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</table>

### Table 14 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
<thead>
<tr>
<th>Time since last use, years</th>
<th>OC Use</th>
<th>Patterns/Patterns Controls</th>
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<tbody>
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<td>13197</td>
<td>0.95 (0.85-1.05)</td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>2315</td>
<td>0.95 (0.85-1.05)</td>
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</table>

### Table 15 — Estimate of Relative Risk (RR) of Invasive Cervical Cancer in Relation to OC Use

<table>
<thead>
<tr>
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<th>OC Use</th>
<th>Patterns/Patterns Controls</th>
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<td>13197</td>
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<td></td>
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<td>2315</td>
<td>0.95 (0.85-1.05)</td>
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trois. (7.06). Although we could not ex-
amine false-positive reports of UC use or reports of UC use outside the public sector or before 1971, we believe that memory aids used during the inter-
views minimized differences between cases and controls in the recall of UC use.**

The fact that 19.1% of the eligible patients with invasive cancer died before they could be interviewed may have biased our results. Women who died shortly after diagnosis would, on average, have more advanced disease at diagnosis. Because UC use in Costa Rica is linked to access to Pay smugglers, which facilitate the detection of cervical can-
cer at its earliest stages, a smaller pro-
portion of patients with invasive cancer who would be expected to die of UC use compared with the patients with invasive cancer who were included in the analysis. Thus, if we could have included UC use information for the pa-
tients who died, the resulting risk esti-
mate might have been even lower than 0.8. We doubt that the exclusion of patients with cervical cancer who did not have their diagnostic biopsy results confirmed by the pathologist panel bi-
ased our results, because, in additional analyses that included these patients, risk estimates for UC use in associations with CIB or CIB or invasive cancer did not change appreciably. We controlled for confounding bias by including most of the established risk factors for cervical cancer in our logistic regression models and by screening for other po-
tentially confounding factors, which did not confound our data. Although we could not directly examine two poten-
tially confounding factors, the sexual histories of sex partners* and exposure to human papillomavirus, the three available STD serologic tests may have served as surrogates for these unexam-
ined factors, and none of these tests appreciably confounded our results.

Our results concur with those of the majority of the epidemiologic studies, which suggest no important causal asso-
ciation between UC and invasive cervical cancer. Investigators who have reported positive associations be-
 tween UC use and cervical cancer have suggested that positive associations may reflect confounding bias related to sexual behaviors or STD histories.** Although other researchers have con-
cluded that differential screening prac-
tices may also introduce confound-
ing and detection bias that distorts risk estimates in the positive direction, they have not suggested a possible role of disinhibition in their data.