Oral Contraceptives and Cervical Cancer Risk in Costa Rica

Detection Bias or Causal Association?

Kathleen L. Irwin, MD; Luis Rosero-Bixby; Mark W. Oberle, MD; Nancy C. Lee, MD; Anne S. Whatley, MS; Judith A. Fortney, 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 25 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, 1.6; 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.

(*JAMA* 1988;259:59-64)

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.[1-4] 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.[1,5]

Costa Rica provides a unique opportunity to examine the relationship between OCs and cervical cancer. Costa Rica maintains a nationwide Tumor Registry,[6] which recently reported an annual incidence of invasive cervical cancer of 36.2/100 000 women, one of the highest rates in the world.[7] In 1983, 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.[8] In 1981, more than half of currently married women 15 to 49 years of age reported having used OCs at some time during their reproductive years.[8] Costa Rica's primary medical care services are among the most comprehensive in Central America[9]; free cervical cancer screening is provided by the country's many hospitals, outpatient clinics, and rural health posts.[10] In 1986, 70% of women aged 15 to 49 years reported having had at least one Papanicolaou (Pap) smear.[11]

From the Division of Reproductive Health, the Centers for Disease Control, Atlanta (Drs Irwin, Oberle, and Lee and Ms Whatley); Instituto de Investigaciones en Salud, University of Costa Rica, San José (Mr Rosero-Bixby); and Family Health International, Research Triangle Park, NC (Dr Fortney and Ms Bonhomme).

The opinions expressed in this article are the authors' and do not necessarily reflect the views of the US Agency for International Development.

Reprint requests to Division of Reproductive Health, Centers for Disease Control, Atlanta, GA 30333 (Dr Irwin).

METHODS

A detailed review of the methods of this population-based case-control study of cervical and breast cancer has been previously published.[12] The breast cancer cases are the subject of a separate report.[12] Here we describe the methods relevant to this analysis.

Study Participants

We selected cases from the Costa Rican National Tumor Registry. Since 1980, 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 583 cases of CIS and 293 cases of invasive cervical cancer newly diagnosed between Jan 1, 1982, and March 31, 1984; the patients were between 25 and 59 years of age at diagnosis. Between September 1984 and February

1985, we identified 938 eligible control women 25 to 58 years of age at the time of interview through a nationwide household survey. Women in certain five-year age groups were oversampled so that the age distribution of the controls would reflect the age distribution of the patients with breast and cervical cancer in the study.

Interviews and Serologic Procedures

At the time of the household survey, trained female interviewers questioned patients and controls about their reproductive, contraceptive, and sexual histories; 92.8% of eligible controls, 89.2% of eligible patients with CIS, and 66.9% of eligible patients with invasive cervical cancer completed an interview (Table 1). Interviewers constructed a calendar of each participant's reproductive events to enhance the subjects' recall of contraceptive use. After the interview, a technician obtained serum specimens from 88.1% of interviewed controls, 95.0% of patients with CIS, and 92.3% of patients with invasive cancer after receiving informed consent. Serum specimens were analyzed for antibodies to herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis*, and *Treponema pallidum* as a measure of previous exposure to sexually transmitted disease (STD).[13-15]

Analysis

We considered only cervical cancer of squamous-cell origin that was diagnosed by biopsy and subsequently confirmed by a panel of three Costa Rican pathologists. To assure that controls were at risk for cervical cancer but had no history of this cancer, we excluded those who reported a previous hysterectomy or cone biopsy of the cervix (Table 1). In a sample of 216 interviewed controls who provided the date and location of their last Pap smear, only 3.2% had evidence of dysplasia on that smear.

Carcinoma in situ and invasive cervical cancer differ in the way they are detected: CIS is typically asymptomatic and requires a Pap smear to initiate a diagnostic evaluation, whereas invasive cancer may present with symptoms and may be diagnosed without cytologic examination.[16] If OC use were associated with having a Pap smear, differences in disease detection related to OC use might bias the association of OCs with CIS more than the association with invasive cancer. Therefore, we compared the CIS and invasive cancer case groups with the control group in separate analyses.

Because interviews were conducted up to three years after the cases were diagnosed, we used an index date to adjust OC 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, 1983, the midpoint of the 27-month case enrollment period. Women who were not 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 (intermittent or continuous), years since last use, years since first use, and age at first use. Women who did not know all their dates of OC use were classified as unknown users; women who reported their first use after the index date were considered never to have used OCs.

The Ministry of Health (MOH) and social security system (CCSS) 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 CCSS 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 CCSS but were identified as OC users by MOH or CCSS records by the number of women in the corresponding patient or control groups.

We used logistic regression models[17,18] that included variables of OC use and age at index date as a categorical variable (25 to 29 years, 30 to 34 years, 35 to 39 years, 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); history of Pap smears before 1982 (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 depomedroxyprogesterone 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 appreciably distorted the risk estimates associated with OC use. All relative risk estimates presented here are odds ratios that were simultaneously adjusted for all six 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.[18]

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 practices before 1982 among the controls included in the analysis, because they represent the general population of Costa Rican women. To deter-

Table 1.—Status of Eligible Patients With Cervical Cancer and Controls at Interview and Analysis

	Patients		
	Carcinoma In Situ	Invasive Cancer	Controls
Eligible women, No.	583	293	938
Interview Status			
Completed interview, % (No.)	89.2 (520)	66.9 (196)	92.8 (870)
Did not complete interview, %			
Address unknown	8.9	11.2	...
Died	0.2	19.1	...
Absent	0.7	0.7	3.4
Refused	0.2	0.7	2.2
Other	0.8	1.4	1.6
Total, %	100.0	100.0	100.0
Analysis Status			
Included in analysis, % (No.)	79.8 (415)	76.0 (149)	87.8 (764)
Excluded,%			
Biopsy not confirmed	13.7	18.9	...
Nonsquamous type	0.8	4.6	...
Previous hysterectomy	...	...	6.7
Previous cone biopsy	...	...	0.7
Age at index date <25 y or > 58 y	4.4	0.5	4.6
Other	1.3	0.0	0.2
Total, %	100.0	100.0	100.0

mine if the relationship between OCs and cervical cancer was modified by four measures of access to cervical cancer screening or general medical care (number of Pap smears before 1982, age at first Pap smear, region of residence, and SES) and seven previously reported[16,19] risk factors for cervical cancer (high gravidity, early age at first coitus, multiple lifetime sex partners, history of any STD or PID, nonuse of condoms, nonuse of other barrier-method contraceptives, and history of smoking), we applied likelihood ratio tests to logistic regression models that included the relevant single-order interaction terms.[17,18]

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 than controls of previously reported risk factors for cervical cancer,[16] including low SES, first coitus at a young age, multiple sexual partners, high gravidity, a history of smoking, a history of any STD or PID, and positive results to 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 was begun in 1982 (Table 2).

Carcinoma In Situ

Subjects who had used OCs had an increased risk of CIS compared with those who had never used OCs (RR = 1.6; 95% confidence interval [CI], 1.2 to 2.2) (Table 3). Risk appeared to increase steadily with increasing duration of use, so that women who had used OCs for ten 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; long-term users did not have an elevated risk if the time since they had last used OCs was five years or more (Table 4). Furthermore, only recent users of OCs had an elevated risk regardless of the time since first use or 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 1982, 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.

Table 2.—Percentage Distribution of Selected Characteristics of Patients With Cervical Cancer and Controls

Characteristic	Patients: Carcinoma in Situ (n = 415), %	Patients: Invasive Cancer (n = 149), %	Controls (n = 764), %
Age at index date, y			
25-29	22.2	7.4	19.0
30-39	51.3	32.9	36.4
40-49	21.4	29.5	27.7
50-58	5.1	30.2	16.9
Residence			
Metropolitan San José	33.3	32.2	35.0
Nonmetropolitan Central Valley	34.5	23.5	33.1
Other urban areas	13.0	12.8	10.9
Other rural areas	19.3	31.5	21.1
Socioeconomic status			
Low	52.1	66.4	45.7
Medium	28.7	20.1	28.8
High	19.3	13.4	25.5
Age at first coitus			
Never had intercourse	0.2	0.0	5.6
< 16 y	24.6	28.2	13.9
16-21 y	58.1	61.0	50.2
≥22 y	16.9	10.1	29.8
Unknown	0.2	0.7	0.5
No. of lifetime sex partners			
0	0.2	0.0	5.6
1	48.7	41.6	64.7
2 or 3	36.4	36.9	24.5
≥4	13.7	19.5	4.5
Unknown	1.0	2.0	0.7
No. of pregnancies			
0	1.7	1.3	8.7
1 or 2	22.4	10.1	21.9
3 or 4	33.7	16.1	29.7
≥5	42.0	72.5	39.6
Unknown	0.2	0.0	0.1
Ever smoked			
Yes	25.5	26.2	20.8
No	74.3	73.8	79.1
Unknown	0.2	0.0	0.1
No. of Papanicolaou smears before 1982			
0	9.9	40.3	25.9
1-9	61.7	44.9	60.2
≥10	27.7	12.8	13.1
Unknown	0.7	2.0	0.8
History of sexually transmitted disease or pelvic inflammatory disease			
Yes	32.3	26.8	9.2
No	64.8	72.5	90.0
Unknown	2.9	0.7	0.8
Sexually transmitted disease serologic results			
Reactive for syphilis	9.1	17.5	6.5
Positive for chlamydia	68.9	73.0	57.3
Positive for herpes simplex virus type 2	57.5	62.8	41.5

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 5). 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.[10]

The relationship between Pap smear screening and OC use in Costa Rica

Table 3.—Estimate of Relative Risk (RR) of Carcinoma In Situ in Relation to OC* Use

OC Characteristic	Patients/Controls	RR (95% Confidence Interval)†
Use‡		
Never used	111/331	1.0 (Referent)
Used	256/300	1.6 (1.2-2.2)
Duration of use, y§‖		
<1	39/66	1.2 (0.7-2.0)
1-4	97/126	1.5 (1.0-2.2)
5-9	80/71	1.9 (1.3-3.0)
≥10	29/29	2.0 (1.1-3.6)
Time since last use, y§¶		
<1	118/102	2.3 (1.5-3.5)
1-4	68/62	2.1 (1.3-3.3)
≥5	59/128	0.9 (0.6-1.4)
Time since first use, y§#		
<5	41/45	2.1 (1.2-3.6)
5-9	90/92	1.8 (1.2-2.8)
≥10	114/155	1.4 (1.0-2.0)

*OC indicates oral contraceptive.
†All RR estimates are adjusted for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first coitus, number of sex partners, and history of Papanicolaou smears before 1982. Referent group consists of those who had never used OCs.
‡Excludes 48 patients and 133 controls with unknown values for OC use or confounding variables.
§Excludes 48 patients and 133 controls with unknown values for OC use or confounding variables and an additional 11 patients and eight controls who provided incomplete information about their dates of OC use.
‖$P = .04$, test for linear trend.
¶$P = .01$, test for linear trend.
#$P = .3$, test for linear trend.

Table 4.—Estimate of Relative Risk (RR) of Carcinoma In Situ in Relation to OC* Use

Duration of Use, y	RR (95% Confidence Interval)† by Time Since Last Use, y		
	<1	1-4	≥5
<5	2.2 (1.3-3.7)	2.6 (1.4-4.9)	0.9 (0.6-1.4)
≥5	2.5 (1.5-4.0)	1.8 (1.0-3.1)	0.9 (0.3-2.3)
Total	2.3 (1.5-3.5)	2.1 (1.3-3.3)	0.9 (0.6-1.4)

*OC indicates oral contraceptive.
†All RR estimates are adjusted for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first coitus, number of sex partners, and history of Papanicolaou smears before 1982. Referent group consists of those who had never used OCs. Excludes 59 patients and 141 controls with unknown values for OC use characteristics or confounding variables.

affected risk estimates in two subgroups: (1) Among women from San José, where Pap smear screening is less strongly linked with OC use than outside of San José, OC use was not 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 frequently screened women (≥10 Pap smears), OC users had no elevated risk of CIS (Table 6). We observed no additional important interactions with the seven cervical cancer risk factors studied, including history of STD and smoking.

Invasive Cervical Cancer

Subjects who had used OCs had no increased risk of invasive cancer compared with those who had never used OCs (RR = 0.8; 95% CI, 0.5 to 1.3) (Table 7). Recent users had the lowest risk; there were no clear patterns of risk by duration of use, time since last use, time since first use (Table 7), or age at first use. When we restricted the analysis to patients and controls who had had at least one Pap smear before 1982, 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 change appreciably. We observed no important interactions with the four measures of medical care utilization (including Pap smear history, residence, 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 tha the enhanced detection of CIS among OC users, ie, detection bias, best ex plains our data.

Evidence that OCs induce neoplasi in human cervical tissue remains incon clusive.[1] Conceivably, OCs could accel erate the progression of preinvasive le sions to invasive ones[20] or could promote the action of other suspected carcino gens such as human papillomavirus.[21] I 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, how ever, 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 elimi nated when recent use was considered Such a pattern of risk would be biologi cally 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 reach 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.[22-24]

Detection bias provides a better explanation for the elevated risk of CIS observed in this study. Because CIS and the precursor stages of dysplasia are usually asymptomatic, a Pap smear is required to detect these conditions.[16] I women with CIS who had used OCs were more likely to have had a Pap smear, to have been referred for a diagnostic biopsy, and to have been enrolled in our study than women with CIS who had never used OCs, a detection bias would be introduced, causing a spurious elevation 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 in the distant past to have had a recent Pap smear, which might lead to the diagnosis of CIS. This enhanced detection of disease among recent OC users would explain why their risk of CIS was greater than that of users in the distant past.

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, however, could not eliminate the bias caused by not enrolling a

Table 5.—Controls Reporting at Least One Papanicolaou Smear by OC* Use

Characteristic	Controls Reporting at Least 1 Papanicolaou Smear Before 1982, %†	
	OC Users (n=312)	OC Nonusers (n=387)
Age at index date, y		
25-29	87.7	60.0
30-39	93.7	58.1
40-49	85.9	61.6
50-58	92.0	55.7
Residence		
Metropolitan San José	94.2	70.4
Nonmetropolitan Central Valley	93.1	59.2
Other urban areas	86.5	56.4
Other rural areas	79.3	44.1
Socioeconomic status		
Low	87.9	46.5
Medium	90.3	66.1
High	94.9	74.7
Total	90.4	58.9

*OC indicates oral contraceptive.
†Excludes 65 controls with unknown history of OC use or unknown history of Papanicolaou smears before 1982.

Table 6.—Estimate of Relative Risk (RR) of Carcinoma In Situ in Relation to OC* Use in Selected Groups

Characteristic	Patients/Controls		RR (95% Confidence Interval)†
	OC Users	OC Nonusers	
Residence‡			
Metropolitan San José	79/114	44/107	0.9 (0.6-1.5)
Nonmetropolitan Central Valley	90/99	34/102	2.0 (1.2-3.3)
Other urban areas	37/37	9/37	2.3 (0.9-6.0)
Other rural areas	50/50	24/85	2.3 (1.2-4.4)
Socioeconomic status§			
High	44/75	24/77	1.1 (0.6-2.2)
Medium	79/90	31/94	1.7 (1.0-3.0)
Low	133/135	56/160	1.7 (1.1-2.7)
No. of Papanicolaou smears before 1982‖			
≥10	76/66	24/29	0.9 (0.4-1.8)
1-9	163/201	63/176	1.7 (1.2-2.5)
0	17/33	24/126	1.9 (0.9-4.1)

*OC indicates oral contraceptive.
†All RR estimates are adjusted for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first coitus, number of sex partners, and history of Papanicolaou smears before 1982. Referent groups consist of those who had never used OCs in each stratum. Excludes 48 patients and 133 controls with unknown values for OC use or confounding variables.
‡$\chi^2 = 7.03$, $P > .05$, test for heterogeneity.
§$\chi^2 = 1.27$, $P > .5$, test for heterogeneity.
‖$\chi^2 = 2.96$, $P > .2$, test for heterogeneity.

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

OC Characteristic	Patients/Controls	RR (95% Confidence Interval)†
Use‡		
Never used	81/331	1.0 (Referent)
Used	48/300	0.8 (0.5-1.3)
Duration of use, y§‖		
<1	15/66	1.2 (0.6-2.5)
1-4	12/126	0.5 (0.2-1.0)
≥5	20/100	0.9 (0.5-1.6)
Time since last use§¶		
<1	7/102	0.3 (0.1-0.8)
1-4	14/62	1.0 (0.5-2.1)
≥5	26/128	1.0 (0.6-1.7)
Time since first use§¶		
<10	13/137	0.5 (0.3-1.1)
10-14	23/103	1.0 (0.6-1.9)
≥15	11/52	0.8 (0.4-1.7)

*OC indicates oral contraceptive.
†All RR estimates are adjusted for age, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first coitus, number of sex partners, and history of Papanicolaou smears before 1982. Referent group consists of those who had never used OCs.
‡Excludes 20 patients and 133 controls with unknown values for OC use or confounding variables.
§Excludes 20 patients and 133 controls with unknown values for OC use or confounding variables and an additional patient and eight controls who provided incomplete information about their dates of OC use.
‖$P = .9$, test for linear trend.
¶$P = .2$, test for linear trend.

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 José 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 having ten or more Pap smears before 1982, 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/or 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 study were less likely than either patients with CIS or controls to have had a Pap smear before 1982. Because OC users were more likely than nonusers to have had a Pap smear and to have their disease detected at the preinvasive 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, should be more likely to have their invasive cancer diagnosed when they become 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 cancer is low (RR = 2.3 and 0.3, respectively). Among the long-term users (women who may have had numerous opportunities for a Pap smear while renewing their OC prescriptions), the risk of CIS is high and the risk of invasive cancer is low (RR = 2.0 and 0.9, respectively).

It is unlikely that differences between patients and controls in the recall of OC use substantially distorted our risk estimates, because the proportion of women with false-negative reports of OC use in the public sector was similar for patients with CIS (6.7%), patients with invasive cancer (6.0%), and con-

trols (7.0%). Although we could not examine false-positive reports of OC use or reports of OC use outside the public sector or before 1974, we believe that memory aids used during the interviews minimized differences between patients and controls in the recall of OC use.[25]

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 OC use in Costa Rica is linked to access to Pap smears, which facilitate the detection of cervical cancer at its earliest stages, a smaller proportion of patients with invasive cancer who died would be expected to be OC users compared with the patients with invasive cancer who were included in the analysis. Thus, if we could have included OC use information for the patients who died, the resulting risk estimate 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 biased our results, because, in additional analyses that included these patients, risk estimates for OC use in association with CIS 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 several other potentially confounding factors, which did not confound our data. Although we could not directly examine two potentially confounding factors, the sexual histories of sex partners[26] and exposure to human papillomavirus,[27] the three available STD serologic tests may have served as surrogates for these unexamined factors, and none of these tests appreciably confounded our results.

Our results concur with those of the majority of epidemiologic studies, which suggest no important causal association between OCs and CIS or invasive cervical cancer.[1] Investigators who have reported positive associations between OC use and cervical cancer have suggested that positive associations may reflect confounding bias related to sexual behaviors or STD histories.[28,29] Although other researchers have concluded that differential screening practices may also introduce both confounding and detection bias that distorts risk estimates in the positive direction, they have not quantified the magnitude of distortion in their data.[28-30] Our study demonstrates that when data are analyzed in ways that minimize both confounding and detection bias, no positive associations remain between OC use and CIS.

Our findings also emphasize that in developing countries such as Costa Rica, OC use provides not only important contraceptive benefits but also an opportunity to routinely screen women for cervical cancer who otherwise might not be screened; this allows detection of this cancer in its early, readily treated stages. Increasing the availability of Pap smears throughout Costa Rica's national health system, including its primary care, maternal-child health, STD, and family planning clinics, would in time decrease this cancer's toll.

Principal Investigators: Luis Rosero-Bixby, Mark W. Oberle, MD; *Project Coordinators:* Carmen Grimaldo, Lic; Martín Fallas; Daisy Fernández, MD; *Data Managers:* Anne S. Whatley, MS; Hernán Caamano; Elizabeth Z. Rovira, MStat; A. H. Rampey, Jr, MS; *Project Associates:* Oscar Fallas, MD; Nancy C. Lee, MD; Kathleen L. Irwin, MD; Judith A. Fortney, PhD; Gary S. Grubb, MD; Michele G. Bonhomme, MSPH; *Project Consultants:* Raimundo Riggioni, MD; Miguel Gómez, MS; Phyllis A. Wingo, MS; George L. Rubin, MBBS; Howard W. Ory, MD; Peter M. Layde, MD; Jacquelyn Arthur; Emilia Leon, MD; *Costa Rican National Tumor Registry:* Georgina Muñoz de Brenes; *Laboratory Consultants:* Mary E. Guinan, MD, PhD; Jorge Ramírez; Sandra Larson, PhD; Andre J. Nahmias, MD; Julius Schachter, PhD; *Pathology Consultants:* Saeed Mekbel, MD; Jorge Salas Cordero, MD; León Tropper, MD.

This study was supported in part by Family Health International, Research Triangle Park, NC, with funds from the US Agency for International Development.

We thank the Costa Rican women and interviewers who participated in this study; James Marks, MD, Herbert Peterson, MD, and Richard Steketee, MD, for their critical review of the manuscript; and Miriam Hunter, Cynthia Rowe, Judy Mast, and Valerie Vanhaltern for word processing.

References

1. Piper JM: Oral contraceptives and cervical cancer. *Gynecol Oncol* 1985;22:1-14.
2. Brinton LA, Huggins GR, Lehman HF, et al: Long-term use of oral contraceptives and risk of invasive cervical cancer. *Int J Cancer* 1986;38:339-344.
3. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. *Br Med J* 1985;290:961-965.
4. Reeves WC, Brinton LA, Brenes MM, et al: Case control study of cervical cancer in Herrera Province, Republic of Panama. *Int J Cancer* 1985;36:55-60.
5. Swan SH, Petitti DB: A review of problems of bias and confounding in epidemiologic studies of cervical neoplasia and oral contraceptive use. *Am J Epidemiol* 1982;115:10-18.
6. De Bermudez DG: The National Tumor Registry in Costa Rica. *Epidemiol Bull PAHO* 1985;6:10-13.
7. Rosero-Bixby L, Grimaldo-Vásquez C: Epidemiología descriptiva del cancer de mama y de cuello de útero en Costa Rica. *Bol Of Sanit Panam* 1987;102:483-493.
8. Rosero-Bixby L, Asociación Demográfica Costarricense: *Fecundidad y anticoncepción en Costa Rica 1981: Resultados de la segunda encuesta de prevalencia anticonceptiva*. Columbia, Md, Westinghouse Health Systems, 1981.
9. Garfield RM, Rodriguez PF: Health and health services in Central America. *JAMA* 1985;254:936-943.
10. Casas A, Vargas H: The health system in Costa Rica: Toward a National Health Service. *J Public Health Pol* 1980;1:258-279.
11. Oberle MW, Becker S, Morris L, et al: *The Costa Rican Fertility and Health Survey, 1986: Final English Language Report*. Atlanta, Centers for Disease Control, 1987.
12. Lee NC, Rosero-Bixby L, Oberle MW, et al: A case-control study of breast cancer and hormonal contraception in Costa Rica. *JNCI* 1987;79:1247-1254.
13. Lee FK, Coleman RM, Pereira L, et al: Detection of herpes simplex virus type 2–specific antibody with glycoprotein G. *J Clin Microbiol* 1985;22:641-644.
14. Wang SP, Grayston JT, Alexander ER, et al: Simplified microimmunofluorescence test with trachoma-lymphogranuloma venereum (*Chlamydia trachomatis*) antigens for use as a screening test for antibody. *J Clin Microbiol* 1975;1:250-255.
15. Cox PM, Logan LC, Norins LC: Automated, quantitative microhemagglutination assay for *Treponema pallidum* antibodies. *Appl Microbiol* 1969;18:485-489.
16. Cramer DW: Uterine cervix, in Schottenfeld D, Fraumeni JF (eds): *Cancer Epidemiology and Prevention*. Philadelphia, WB Saunders Co, 1982, pp 881-900.
17. Schlesselman JJ: *Case-Control Studies: Design, Conduct, Analysis*. New York, Oxford University Press, 1982, pp 227-290.
18. Harrel FE: *The Logist Procedure: SUGI Supplemental Library User's Guide*. Cary, NC, SAS Institute, 1983, pp 181-202.
19. LaVecchia C, Franceschi S, DeCarli A, et al: Cigarette smoking and the risk of cervical neoplasia. *Am J Epidemiol* 1986;123:22-29.
20. Stern E, Forsythe AB, Youkeles L, et al: Steroid contraceptive use and cervical dysplasia: Increased risk of progression. *Science* 1977;196:1460-1462.
21. Zur Hausen H: Human genital cancer: Synergism between two virus infections or synergism between a virus infection and initiating events? *Lancet* 1982;2:1370-1372.
22. Gall SA, Bourgeois CH, Maguire R: The morphologic effects of oral contraceptive agents on the cervix. *JAMA* 1969;207:2243-2247.
23. Maquero M, Azuela JC, Calderon JJ, et al: Morphology of the cervix in women treated with synthetic progestins. *Am J Obstet Gynecol* 1966;96:994-998.
24. Wied GL, Davis E, Frank R, et al: Statistical evaluation of the effect of hormonal contraceptives on the cytologic smear pattern. *Obstet Gynecol* 1966;27:327-334.
25. Coulter A, Vessey M, McPherson K: The ability of women to recall their oral contraceptive histories. *Contraception* 1986;33:127-137.
26. Skegg DCG, Corwin PA, Paul C, et al: Importance of the male factor in cancer of the cervix. *Lancet* 1982;2:581-583.
27. Reid R, Crum CP, Herschman BR, et al: Genital warts and cervical cancer: III. Subclinical papillomaviral infection and cervical neoplasia are linked by a spectrum of continuous morphologic and biologic change. *Cancer* 1984;53:943-953.
28. Swan SH, Brown WL: Oral contraceptive use, sexual activity, and cervical carcinoma. *Am J Obstet Gynecol* 1980;139:52-57.
29. Vessey MP, Lawless M, McPherson K, et al: Neoplasia of the cervix uteri and contraception: A possible adverse effect of the pill. *Lancet* 1983;2:930-934.
30. Harris RWC, Brinton LA, Cowdell RH, et al: Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer* 1980;42:359-369.