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Oral Contraceptives and Cervical Carcinoma *in Situ* in Chile[1]

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ABSTRACT

A case-control study of cervical carcinoma *in situ* was conducted in Santiago, Chile, to determine whether risk of this condition is altered by use of oral contraceptives. Responses to a standardized questionnaire were compared in 133 hospitalized cases and 254 age-matched controls selected from the same screening program through which the cases were detected. After controlling for the possible confounding influence of a variety of indices of sexual behavior, socioeconomic status, and prior cytological smears, no increase in risk was found in women who ever used oral contraceptives. No trend of increasing or decreasing risk was seen in relation to duration of use, up to more than 6 years of exposure, or with the passage of time from either initial or most recent exposure. An observed increase in risk in current users of oral contraceptives was not considered likely to represent a causal relationship.

INTRODUCTION

Both case-control and cohort studies of cervical intraepithelial neoplasia have tended to show increased risks of squamous dysplasia in women who have ever used oral contraceptives (1–7) and evidence of an increase in risk with duration of use (2–6). Results for carcinoma *in situ* are much less consistent. Three cohort studies (5–7), but only one case-control study (2), showed an increase in risk in ever-users, and four case-control studies (1, 3, 8, 9) did not. Two of the cohort studies (5, 6), and one case-control study (2) reported risk to increase with duration of use, but such a trend was not found in two other case-control studies (3, 9) that assessed risk in relation to length of exposure. One cohort study of women with dysplasia found risk of progression to carcinoma *in situ* to be greater in users of oral contraceptives than in nonusers (10). Three case-control studies of invasive cervical cancer have found elevated risks in users of oral contraceptives and increasing risks with duration of use (11–13), and three cohort studies have found incidence rates of invasive disease to be greater in users than nonusers (6, 7, 14). Results among studies thus appear to be fairly consistent for squamous dysplasia and invasive carcinoma of the cervix in relation to use of oral contraceptives, but inconsistent for carcinoma *in situ*.

Many of the studies cited have not provided estimates of relative risks in relation to oral contraceptive use that have been adequately controlled for the potentially confounding influences of prior cytological screening and sexual practices, and variations in the degree of such confounding may be one reason for the inconsistent results for carcinoma *in situ*. Incomplete or lack of control for confounding may also be one explanation for the observed associations of oral contraceptives with cervical dysplasia and invasive carcinoma, and it cannot be stated with confidence that oral contraceptives enhance risk of cervical neoplasia. Additional studies of rigorous design in which sexual behavior and prior Pap[3] smears are assessed are thus needed, particularly of carcinoma *in situ*. This is a report of the results from an investigation in Santiago, Chile, that was conducted to further evaluate the role that use of oral contraceptives may play in altering the risk of cervical carcinoma *in situ*.

MATERIALS AND METHODS

Cases for this study were recruited from one university hospital (J. J. Aguirre) and two health ministry hospitals (Salvador and San Jose) in Santiago, Chile. The Ministry of Health operates a cervical cancer screening program in Santiago. Cases eligible for inclusion in this study were all women between the ages of 15 and 50 years who were referred by this program to one of the above three hospitals, and who subsequently were found to have histological evidence of carcinoma *in situ* between October 1979 and October 1985. Slides from all cases were reviewed by a single local pathologist (A. D.) to confirm the diagnosis.

Two controls were selected for each eligible case from the cytological records of the screening program. The controls were the two women in the same 5-year age group as the corresponding case, who had a normal Pap smear closest in time to the abnormal smear that led to the diagnosis of carcinoma *in situ* in the case.

A standardized Spanish-language questionnaire was used to obtain information on the known and suspected risk factors for cervical cancer, as well as a complete obstetric and contraceptive history. The three interviewers were nurse-midwives, specially trained and not involved in the case or control selection. The cases were interviewed at hospitals or occasionally at home. All controls were interviewed at home. Pictures of different oral contraceptives available in Chile were shown to cases and controls to help identify specific products. A calendar was incorporated into the questionnaire to help establish dates of use. Attempts were made to validate selected items in the questionnaire by reviewing medical records. These items included previous Papanicolaou smears and use of oral or injectable contraceptives and intrauterine devices.

Data from Spanish questionnaires were transcribed onto an identically formatted English version of the questionnaire. All original English questionnaires were sent to the Coordinating Center in Seattle, WA. A copy of the English form was kept in Santiago. Computerized editing was performed at the Coordinating Center to detect inadmissible codes and inconsistencies between variables. Information on errors that could not be corrected at the Coordinating Center were sent back to Santiago for clarification.

This report is based on analyses of data on cases and controls with complete information available at the Coordinating Center as of October 30, 1985. Since this is a matched study, all relative risks were estimated using conditional logistic regression (15).

RESULTS

Of the 152 cases identified as eligible for inclusion in the study, three could not be interviewed, two were excluded because data on them were incomplete, and 14 had no controls matched to them with complete data at the time the analyses were begun, leaving 133 cases included in the analyses. Of the 266 controls that were matched to these 133 cases, 2 could not be interviewed, and data on 10 were incomplete, leaving 254 controls in the analyses.

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[3] The abbreviation used is: Pap, Papanicolaou.

The control selection process insured that cases and controls were of comparable age (Table 1). Approximately equal proportions of cases and controls gave a prior history of high blood pressure, heart disease, thromboembolism, stomach ulcer, diabetes, gallbladder disease, jaundice during pregnancy or at any other time, tubal ligation, prior treatment for vaginal discharge, use of injectable contraceptives, work outside the home, and use of female hormones for menopausal, menstrual, or ovarian conditions.

As shown in Table 2, several sexual variables were associated with an increased risk of carcinoma *in situ*. These include history of prior miscarriages, any prior aborted pregnancy (including spontaneous and induced abortions), total number of pregnancies, number of sexual partners, and age at first sexual intercourse. Use of condoms for contraception was associated with a reduced risk and, unexpectedly, so was the use of an intrauterine device. There were too few users of diaphragms to evaluate the influence of these devices on risk. Also unexpectedly, women of relatively high socioeconomic status, as judged by their method of payment for medical services, constituted a higher proportion of the cases than controls.

A history of one or more Papanicolaou smears, 6 or more months prior to the smear that resulted in the subject's inclusion in the study, was associated with a reduced risk, but no trends of decreasing risk with number of prior smears (Table 3) or with frequency of smears (not shown) were observed.

Estimates of relative risks of carcinoma *in* situ in women who ever used various types of oral contraceptives are shown in Table 4. These estimates are controlled for the potentially confounding effects of the other types of oral contraceptives shown in Table 4, number of pregnancies, history of any type of abortion, pay status, age of first sexual intercourse, number of sexual partners, prior Pap smears, and prior treatment for vaginal discharge. All but the last variable (an indicator of prior pelvic inflammatory disease) were significantly associated with carcinoma *in situ* in our data (Table 2), and all were found to either exert independent effects on the estimates of the relative risks, or were identified as confounders in previous analyses of data on invasive cervical cancer from Chile and elsewhere (11). The relative risks shown in Table 4 were not appreciably altered by controlling for any of the other variables considered as possible confounders (Table 2). The relative risks in women who ever used combined or sequential oral contraceptives, or products of unknown type, were not significantly different from one, and the relative risk in users of any type of oral contraceptives was 0.95. However, power to detect an altered risk in users of sequential preparations was low. Too few women had used continuous products to provide meaningful information on the influence of these preparations on risk.

Since most oral contraceptives used in Chile are of the combined type, it is reasonable to assume that most users of oral contraceptives of unknown type had used combined products. Therefore, known users of combined oral contraceptives and users of unknown type oral contraceptives were grouped and considered users of combined preparations. Relative risks of cervical carcinoma *in situ* in relation to various features of use of combined oral contraceptives, as defined in this manner, are shown in Table 5. No increase in risk in women who ever used these products was found, and no increase in risk with duration of use was observed. Risk was also not found to increase after over 10 years since initial exposure (latency). Although based on small numbers of exposed individuals, the upper portion of Table 6 shows no consistent evidence for an increase in risk in long-term users (more than 6 years), even after a potential latency period of more than a decade. The lower portion of Table 5 shows an increase in risk in current users of oral contraceptives, but not in ex-users; and there is no consistent decline in risk with time since cessation of use (recency). As shown in the lower portion of Table 6, the enhanced risk in current users is confined to women who used oral contraceptives for less than 6 years. Results similar to those in Tables 5 and 6 were obtained when users of unknown type oral contraceptives were omitted from the analyses (not shown).

Table 1 *Age distribution of cases and controls*

Age (yr)	Cases ($N = 133$)	Controls ($N = 254$)
15–29	25.6	26.4
30–34	21.0	22.4
35–39	20.3	18.9
40–54	33.1	31.1
55–60		1.2
Total	100.0	100.0

DISCUSSION

This study provides little evidence that use of oral contraceptives enhances risk of cervical carcinoma *in situ*. The relative risk in women who ever used these products was not increased, no trend of an increase in risk with duration of use was observed, and the estimate of the relative risk in women who were exposed for more than 6 years is actually less than one. Risk also did not increase with years since initial or most recent use, and relative risks in women first or last exposed over 10 years previously were not significantly greater than one.

The only subgroup of users in which an increased risk was observed was current users. A spurious increase in risk in current users could occur if users with carcinoma *in situ* were more likely to be screened than users with normal cervices. This is an unlikely explanation in this study because only 12 of the 133 cases were symptomatic (9 with vaginal bleeding), and none of the women with symptoms was a current user. Another possible reason for the observed increase in risk in current users is overdiagnosis among current users, but this is not a likely explanation in this instance because all slides were read by a single pathologist without knowledge of the womens' contraceptive history, and the pathologist has sufficient experience that he would not likely have mistaken any acute steriod induced changes in the histological appearance of the cervical epithelium for neoplastic changes. Finally, the observed increase in relative risk in current users could be causal. Evidence against this interpretation, however, is the observation that the elevated risk in current users was restricted to women who used oral contraceptives for less than 6 years. Also, for the enhanced risk to be restricted to current users, the resultant lesions would either have to regress soon after cessation of exposure or progress rapidly to invasive disease. Neither possibility is in accordance with the generally accepted perception that carcinoma *in situ* is a chronic condition that progresses slowly. We conclude that the observed increase in relative risk in current users is most likely due to chance.

The absence of an overall association between carcinoma *in situ* and oral contraceptives in this study is in accordance with most previous case-control studies of carcinoma *in situ* (1, 3, 8, 9), although one such investigation (2) found an increase in risk with duration of use, as did two cohort studies (5, 6). Reasons for these discrepant findings are unknown. Studies of squamous

Table 2 *Relative risks of cervical carcinoma in situ in relation to several sexual and social variables*

Variable	Level	No. of Subjects		Relative risk	95% confidence interval
		Cases	Controls		
Number of live births	None	6	15	0.65	0.22, 1.94
	1	25	43	1.0	
	2–3	67	125	0.91	0.49, 1.68
	≥4	35	71	0.81	0.40, 1.65
Stillbirths	No	127	239	1.0	
	Yes	4	5	1.60	0.43, 5.96
	Never pregnant	2	10	0.37	0.08, 1.78
Miscarriage	No	76	177	1.0	
	Yes	55	67	1.94	1.22, 3.08
	Never pregnant	2	10	0.47	0.10, 2.29
Induced abortion	No	97	196	1.0	
	Yes	34	48	1.38	0.84, 2.27
	Never pregnant	2	10	0.59	0.08, 1.87
Any abortion	No	56	143	1.0	
	Yes	75	101	1.85	1.20, 2.86
	Never pregnant	2	10	0.47	0.10, 2.34
Total number of pregnancies	None	2	10	0.62	0.11, 3.44
	1	13	36	1.0	
	2–3	48	98	1.57	0.72, 3.44
	≥4	70	110	2.16	0.96, 4.88
Female hormones for pregnancy test or abortion	No	105	207	1.0	
	Pills	5	14	0.72	0.25, 2.13
	Injections	19	29	1.27	0.68, 2.37
	Both	4	4	2.08	0.44, 9.72
Use of condom	No	125	217	1.0	
	Yes	8	37	0.39	0.18, 0.87
Use of an intrauterine device	No	54	58	1.0	
	Yes	79	196	0.38	0.23, 0.64
Pay status	Low	101	224	1.0	
	High	32	29	2.33	1.35, 4.02
	Unknown	0	1		
Martial status	Single	8	17	1.0	
	Married	112	219	1.11	0.45, 2.73
	Divorced	12	15	1.75	0.55, 5.54
	Widowed	1	3	0.60	0.05, 6.75
Number of sexual partners	None	0	1	0.0	
	1	62	177	1.0	
	2	48	57	2.17	1.36, 3.48
	≥3	22	18	3.39	1.65, 6.96
	Unknown	1	1		
Age at first intercourse	Never	0	1	0.0	
	≤16	42	58	1.0	
	17–19	49	77	0.87	0.52, 1.47
	≥20	42	118	0.44	0.25, 0.78
Venereal disease	No	127	247	1.0	
	Yes	5	6	1.67	0.51, 5.46
	Unknown	1	1		

Table 3 *Relative risks of cervical carcinoma in situ cancer in relation to number of Papanicolaou smears 6 or more months prior to inclusion in the study*

No. of prior smears	No. of Subjects		Relative risk	95% confidence interval
	Cases	Controls		
None	34	40	1.0	
1	21	51	0.44	0.21, 0.91
>1	74	148	0.52	0.27, 1.00
Unknown	4	15		

dysplasia (1–7) and invasive cervical cancer (6, 7, 11–14) are more consistent in showing associations with use of oral contraceptives. No good biological explanation has been proposed for an association between oral contraceptives and both dysplasia and invasive cervical cancer, but not between oral contraceptives and carcinoma *in situ*. Strong consideration should therefore be given to the possibility that the studies of carcinoma *in situ* that show an association with oral contractives are correct, and that the studies that do not, including this investigation, are in error.

Possible reasons for this study failing to detect a true increase in risk of carcinoma *in situ* in users of oral contraceptives include lack of statistical power, negative confounding, ascertainment bias, and selection bias. Relative risks of carcinoma *in situ* in users of oral contraceptives of 4 or more years duration had an average relative risk of 2.5 in two cohort studies (16) and a relative risk of 4.7 in the case-control study of Ory *et al.* (2). The present study had a power of 80% of detecting a relative risk of 2.3 or greater in users of 4 or more years duration. If oral contraceptives enhance risk by the amount observed in the studies showing an association between oral

Table 4 *Relative risks of cervical carcinoma in situ in women who ever used various types of oral contraceptives*

Type of oral contraceptive	Ever used	No. of Subjects		Relative risk[a]	95% confidence interval
		Cases	Controls		
Combined	No	74	164	1.0	
	Yes	59	90	1.21	0.71, 2.07
Sequential	No	129	248	1.0	
	Yes	4	6	0.68	0.14, 3.27
Continuous	No	133	250	1.0	
	Yes	0	4	0.0	
Unknown type	No	123	228	1.0	
	Yes	10	26	0.69	0.27, 1.80
Any type	No	65	134	1.0	
	Yes	68	120	0.95	0.56, 1.59

[a] Adjusted for total pregnancies, any abortions, pay status, age at first intercourse, number of sexual partners, history of vaginal discharge, frequency of prior Pap smears, and use of the other types of oral contraceptives shown in the table.

Table 5 *Relative risk of cervical carcinoma in situ in relation to various features of use of combined oral contraceptives*

Category of use	No. of Subjects[a]		Relative risk[b] (95% confidence interval)
	Cases	Controls	
Nonuser	65	130	1.0
Any use[a]	64	106	0.97 (0.57, 1.66)
Months of use			
≤12	28	52	0.87 (0.44, 1.72)
13–72	28	37	1.26 (0.63, 2.54)
>72	8	17	0.65 (0.22, 1.95)
Months since first use[c]			
≤60	20	29	1.34 (0.57, 3.14)
61–120	15	27	1.03 (0.41, 2.58)
>120	29	49	0.81 (0.40, 1.64)
Months since last use[c]			
Current user	12	10	3.23 (1.06, 9.82)
≤60	24	46	0.93 (0.45, 1.94)
61–120	8	26	0.39 (0.14, 1.10)
>120	20	23	1.19 (0.51, 2.78)

[a] Excluding 3 cases and 8 controls who had used only sequential or continuous oral contraceptives.

[b] Adjusted for total pregnancies, any abortions, pay status, age at first intercourse, number of sexual partners, history or vaginal discharge, and frequency of prior Pap smears.

[c] Excluding 1 control with unknown months since first and last use.

Table 6 *Relative risks of cervical carcinoma in situ in relation to months of use of combined oral contraceptives and months since first and last exposures*

Risks are relative to nonusers (65 cases and 129 controls) and are adjusted for total pregnancies, any abortions, pay status, age at first intercourse, number of sexual partners, history of vaginal discharge, and frequency of Pap smears. The 95% confidence limits for all relative risks include 1.0.

Category of use	Months of use		
	≤12	13–72	>72
Months since first use			
≤60	0.80 (11, 23)[a]	3.63 (9, 6)	(0, 0)
61–120	0.57 (4, 8)	0.73 (6, 15)	3.16 (5, 3)
>120	1.13 (13, 20)	0.87 (13, 16)	0.25 (3, 13)
Months since last use			
Current user	4.82 (4, 2)	4.67 (6, 3)	1.05 (2, 5)
≤60	0.51 (7, 22)	1.38 (11, 7)	1.39 (6, 6)
>60	0.93 (17, 27)	0.76 (11, 17)	(0, 5)

[a] Numbers in parentheses, number of cases and controls. Subjects with unknown values for any of the features of use or control variables were omitted.

contraceptives and carcinoma *in situ*, it is unlikely that this study would have failed to detect such an enhancement by chance alone.

For negative confounding to explain the findings, either variables that were considered would have to be imprecise measures of underlying negative confounders or there was negative confounding by factors that were not considered. For the sexual behavior of the women to be a negative confounder, women with behavior conducive to acquisition of sexually transmitted agents would have to less frequently be users of oral contraceptives than other women. This seems unlikely. However, if this were true, then incomplete control for female sexual behavior could explain the findings if our information on sexual behavior was imprecise. Although this possibility cannot be confidently ruled out, the demonstration in our data that enhanced risk was associated with a number of previously observed indices of sexual behavior suggests that the sexual information is reasonably accurate. Furthermore, other studies of sexual behavior in Chile (17–19) elicited sensitive sexual information when the interviews were conducted in private by well trained personnel, as was done in this investigation.

Two potentially important confounders that were not considered in this study are male sexual behavior and smoking. For smoking to be a negative confounder, smoking would have to be causally related to carcinoma *in situ*, and smokers would have to be less likely to use oral contraceptives than nonsmokers. The converse of the latter criteria is more likely to be true. Also, the association between smoking and cervical cancer that has been observed in several studies may itself be a result of confounding by sexual variables; and if it is, then smoking would not be a confounder that should be controlled for. Furthermore, unpublished preliminary analyses of data from both Chile and Mexico from the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (11), do not show an association between smoking and invasive cervical cancer. We conclude that negative confounding by smoking is an unlikely explanation for our results.

For the sexual behavior of male partners to be a negative confounder in this study, women married to men with multiple partners would have to less frequently be users of oral contraceptives than women married to men with few or no pre- or extramarital relationships. This seems unlikely, although no information on this issue is currently available.

Ascertainment bias could have obscured a true association between use of oral contraceptives and cervical carcinoma *in situ*, if the proportion of users who gave a history of use was lower for cases than controls. The interviewers were highly skilled and it is unlikely that they frequently failed to elicit a correct contraceptive history from cases or controls. However, if this were to occur, under ascertainment of use would have been more likely in the controls, who were interviewed at home, than in the cases, who were interviewed in a hospital setting. It is therefore unlikely that biased ascertainment of prior oral contraceptive use from the study subjects can explain the results of this investigation.

Biased ascertainment of information from medical records also is an unlikely explanation for our results. Since attempts were made to validate from medical records only positive histories of oral contraceptive use, the estimate of the relative risk in women who ever used oral contraceptives could not have been appreciably altered by this potential source of error. We could, however, have failed to detect true trends of increasing relative risk with duration of use or times since first or last use if such use had been recorded as being longer for women whose use was validated than for those whose use was not validated, and if a higher proportion of control users than case users had their use validated. The proportion of users with validated use

was slightly higher for the controls (41%) than for the cases (37%). However, compared to women whose use was not validated, those with validated oral contraceptive histories tended more frequently to be users of shorter duration, and recent or current users. These tendencies would have resulted in a slightly spurious increase in risk in long-term users and a somewhat spuriously low risk in current or recent users. The observed relative risks in long-term and current users were actually in the opposite directions from those predicted if this potential source of bias had been operative.

Selection bias is also not a likely explanation for the observed results. For selection bias to inhibit the demonstration of a true association between carcinoma *in situ* and use of oral contraceptives, cases included in the study would have to less frequently be users of oral contraceptives than cases not included in the study. This is unlikely. On the contrary, one might expect women with cervical cancer to be more, rather than less, likely to have a Pap smear if they had used oral contraceptives. Also, there is no reason to suspect that women with cervical cancer are referred from the screening program to the three study hospitals preferentially if they have not used oral contraceptives. Such referrals are made on the basis of proximity of the woman's residence to the hospital, and without regard to methods of contraception.

We conclude that this study provides reasonable assurance that women who have used oral contraceptives for up to 6 or more years are not at increased risk of cervical carcinoma *in situ* and that women who ever used oral contraceptives are not at increased risk for at least a decade after exposure.

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