

## LONG-TERM USE OF ORAL CONTRACEPTIVES AND RISK OF INVASIVE CERVICAL CANCER

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To evaluate the relationship between use of oral contraceptives and risk of invasive cervical cancer, a case-control study involving 479 patients and 789 population controls was undertaken in 5 geographic regions of the US. Initially, the relationship was obscured by confounding variables, particularly the interval since last Pap smear. Control for this variable as well as for sexual and sociodemographic factors revealed an RR of 1.5 overall, with long-term users (5 or more years) being at a 2-fold higher risk than non-users. Pill associations prevailed for both adenocarcinomas and squamous-cell tumors, and risks were highest for those using pills containing high estrogen potencies. In addition, there was some evidence that pill associations were most pronounced among women who had never used barrier methods of contraception or who had histories of genital infections, suggesting that oral contraceptives may act as co-carcinogens with transmissible agents. Our findings provide further evidence that long-term use of oral contraceptives may have a carcinogenic effect on cervical epithelium, but emphasize the need for careful evaluation of confounding influences.

Although the relationship between oral contraceptives and cervical neoplasia has received considerable attention, the nature of the association remains unclear. Several case-control (Boyce *et al.*, 1972; Worth and Boyes, 1972; Ory *et al.*, 1977; Harris *et al.*, 1980) as well as prospective studies (Peritz *et al.*, 1977; Stern *et al.*, 1977) have shown an increased risk of non-invasive cervical abnormalities for long-term pill users, but results have been questioned because of inability to control for sexual behavior as well as other sources of confounding (Swan and Petitti, 1982). However, two studies (Harris *et al.*, 1980; Swan and Brown, 1981) were able to account for sexual patterns and found that the excess risk for long-term pill users persisted. Further complicating the issue is the fact that most studies have focused on pre-invasive abnormalities, which are prone to pathologic classification difficulties (Editorial, 1975) and which may in fact be easier to detect among pill users (Editorial, 1977). This raises interest in the relationship of oral contraceptives to risk of invasive neoplasms, particularly since two recent studies (Vessey *et al.*, 1983a, b; Vessey *et al.*, 1985) have suggested that long-term use of the pill increases the risk of invasive cervical cancer.

In order to clarify the relationship of oral contraceptive use to risk of invasive cervical cancer, we undertook a case-control study in 5 metropolitan areas of the US. The large numbers of study subjects, combined with the collection of extensive information on a variety of potential confounding variables, enabled many

methodological issues raised by previous studies to be addressed.

### MATERIAL AND METHODS

This case-control study included as study sites 5 areas reporting to the Comprehensive Cancer Patient Data System—Birmingham, Chicago, Denver, Miami, and Philadelphia. In each of these areas, incident cases of invasive cervical cancer occurring among women aged 20 to 74 years were accrued over the period April, 1982 to January, 1984 at 24 participating hospitals (chosen on the basis of their diagnosing or treating a sufficiently large number of cases).

Controls for the study were ascertained through random digit dialling techniques (Waksberg, 1978; Hartge *et al.*, 1984), which involved individual matching to the cases for age ( $\pm 5$  years, whenever possible), ethnic origin and telephone exchange. Four waves of control selection were conducted during the course of the study, with the process involving (1) a generation of random numbers within the telephone exchanges of eligible cases; (2) interviewers calling each household to obtain an enumeration, by ethnic origin, of females aged 20-69 within each household and (3) a random selection of two appropriate matched controls for each eligible case in the study. A total of 23,404 telephone numbers were sampled, of which 13,561 (57.9%) were eligible for control selection. An enumeration of female members was successfully obtained for 84.1% of numbers assumed to be working and residential. Following the selection, whenever possible, of two appropriately matched controls for every case, a brief telephone interview was conducted to ascertain histories of prior hospitalization. Approximately 25% of the initially selected controls were found to have had a hysterectomy (therefore not being at risk for cervical cancer), and were replaced, when possible, by other eligible controls. A total of 1,114 controls were ascertained by these methods for the 658 eligible cases.

Home interviews with both cases and controls were conducted by trained interviewers. The majority (74%) of the cases were interviewed within 6 months of diagnosis, and 35% were interviewed within 3 months of diagnosis. Interviews lasted slightly more than one hour (mean = 76 min) and elicited detailed information

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on contraceptive usage as well as on demographics, pregnancy history, menstrual history and hygiene practices, sexual behavior, medical events, smoking, diet, marital history and family history. The contraceptive information involved use of a lifetime calendar, with behavior recorded on a monthly basis in the context of other life events, such as age at menarche, age at first sexual intercourse, pregnancies, etc. To aid in the recall of specific brands of oral contraceptives, color photographs of all pills ever marketed were shown.

Interviews were obtained from 481 of 658 eligible cases (73.1%) and from 801 of 1,114 controls (71.9%). The reasons for non-response included refusals (9.7% of cases vs. 21.9% of controls), subjects having moved or being unlocatable (3.8% vs. 3.4%), death (5.0% vs. 0.5%), being ill (2.1% vs. 1.1%), and other problems (1.7% vs. 1.1%). In addition, for 4.6% of cases, it was not possible to obtain physician consent to perform the interviews.

In the current analyses, 11 women who reported never having had sexual intercourse (and thus not questioned regarding their use of oral contraceptives) have been eliminated, as well as 3 subjects who could not provide information on whether they had ever used oral contraceptives. The final study groups consisted of 479 cases and 789 controls.

The relative risk (RR) as estimated by the odds ratio was the measure of association used for evaluating effects of oral contraceptive use on the risk of cervical cancer. Unmatched logistic regression analyses (Prentice and Pyke, 1979) using all cases and controls were done to obtain maximum likelihood estimates of the odds ratios and 95% confidence intervals (CI), while adjusting for confounding variables. Tests for trend in the logistic analyses were obtained by categorizing the exposure variable, assigning the score  $j$  to the  $j$ th exposure level of the categorical variable, and treating the scored variable as a continuous variable. Logistic regression was also used to test for the statistical significance of interactions. Since matching was employed in the study design, multivariate analyses, which included only the interviewed cases with at least one matched interviewed control, were undertaken (Lubin, 1981). However, this resulted in considerable loss in power, since the case and control populations

were reduced by 17% and 35%, respectively. After determining that any differences between matched and unmatched results were likely to be due to differences in the study populations rather than to true analytic discrepancies, it was decided that unmatched estimates only would be presented.

## RESULTS

Table I presents basic demographic information on cases and controls. There was a fairly even accumulation of cases from the 5 study sites, although the largest percentage (27.6%) came from Chicago. Despite attempts to obtain a close age-match, cases tended to be somewhat older than controls (mean of 46.7 vs. 43.7), necessitating control for age in all analyses. A total of 56.2% of the cases were white, 32.4% black, 9.2% hispanic, and 2.2% of other or unknown ethnic origin.

A total of 210 cases (43.8%) and 404 controls (51.1%) reported ever having used oral contraceptives, resulting in a crude RR of 0.8. This estimate, however, was found to be substantially confounded given that a number of other risk factors were significantly correlated with the probability of exposure to oral contraceptives. Most notably, there was confounding by the interval since last Pap smear. This variable exerted substantial negative confounding, since those with a limited screening history were at an extremely high risk of invasive cervical cancer (5- to 6-fold excess risk for never having had a Pap smear in the 10 years preceding diagnosis), but a low probability of having been exposed to oral contraceptives. A number of other variables were also found to affect the association between oral contraceptives and cervical cancer risk. In addition to interval since last Pap smear, education exerted some negative confounding, while number of sexual partners, age at first intercourse, and history of a non-specific genital infection or sore acted as positive confounders. Although years of smoking had a relation to cervical cancer risk, this variable did not significantly confound the oral contraceptive associations, and was therefore not included in the final models. Other variables, including study site, number of pregnancies, use of other methods of contraception

TABLE I - DISTRIBUTION OF CASES AND CONTROLS BY SELECTED DEMOGRAPHIC VARIABLES

	Cases		Controls	
	N	%	N	%
Study site				
Birmingham	96	20.0	151	19.1
Chicago	132	27.6	221	28.0
Denver	91	19.0	153	19.4
Miami	79	16.5	117	14.8
Philadelphia	81	16.9	147	18.6
Age				
<35	95	19.8	214	27.1
35-44	133	27.8	228	28.9
45-54	116	24.2	169	21.4
55+	135	28.2	178	22.6
Ethnic origin				
White, non-Hispanic	269	56.2	490	62.1
White, Hispanic	44	9.2	59	7.5
Black	155	32.4	238	30.2
Asian	5	1.0	1	0.1
American Indian	5	1.0	1	0.1
Unknown	1	0.2	0	—
Total	479	100.0	789	100.0

(including barrier methods), and history of abnormal Pap smears, were also not found to be substantial confounders.

After adjusting for pertinent confounding variables, it was found that the risk associated with ever using oral contraceptives was 1.5 (95% CI 1.1-2.1) (Table II). In addition, there was a significant linear increase in risk ( $p=0.003$ ) with increasing duration of pill use, the RRs being 1.3, 2.0, and 1.8 for users of <5, 5-9 and 10+ years, respectively. Both of these latter estimates were statistically significant. A significant linear trend ( $p=0.02$ ) was observed when "years of use" was also entered as a continuous variable. Those reporting recent use (within 1 year of diagnosis) were at a higher risk (RR=2.0) than those discontinuing use earlier (RR=1.4). No significant relationships of risk were observed according to either years since initial use or age at first use of the pill.

Long-term use and recent use, however, were correlated variables. Thus, analyses were restricted to oral contraceptive users and each variable controlled for the other. The duration effect remained essentially unchanged, but seemed to explain the apparent association with recency, with recent users being at no excess risk compared to non-recent users (RR=1.1).

Analyses further pursued the relationship of duration of use according to differing histologies of the invasive tumors. A total of 417 (87.1%) of the cancers were classified as squamous-cell, while 62 (12.9%) were adenocarcinomas or adenosquamous carcinomas. Long-term use of oral contraceptives was associated with elevated risks of both types of tumors, the RRs associated with use for 10 or more years being 1.6 for squamous-cell tumors and 3.0 for adenocarcinomas and adenosquamous carcinomas (Table III).

Associations were also examined by specific brands of pill, types of pill (combination vs. sequential), and total dosages of estrogen, progestogen, or subcategories of constituents (e.g., total dose of ethinyl estradiol, mestranol), but no significant differences were detected. Since these analyses resulted in categorization of a substantial number of pill users as unknowns,

analyses also considered risk according to the estrogen "potency" (Pike *et al.*, 1983) of the pill used longest in relation to total years of pill use. As seen in Table IV, among women having used the pill for 5 or more years, those reporting use of high-potency pills were at highest risk (RR=2.1-2.2 compared to non-users). When examined by histology, a significant excess risk of adenocarcinoma (RR=3.9) was associated with long-term, high-potency pill use, but this was based on only 6 exposed cases. No trends were observed according to months of pill use by 5-year calendar time periods (an additional manner of evaluating changes in pill content).

Effects of pill usage were examined according to a variety of other risk factors. Associations with pill use were similar for whites and non-whites. In addition, there was no evidence that pill association varied according to number of sexual partners, age at first intercourse, or years of smoking. There was also no interaction of pill use with years since last Pap smear, the adjusted RRs exceeding 1.2 for every interval stratum; the pill associations ranged from 1.4 for those with a recent Pap smear to 1.9 for those reporting 10 or more years since last Pap. There was, however, some indication that effects of oral contraceptive use were modified by several factors (Table V), although none of the interactions achieved statistical significance. Pill effects, however, were most profound among women under the age of 35 (RR=1.7, 95% CI 0.7-4.1), subjects who had never used barrier methods of contraception (RR=1.8, 1.1-3.0), those with a history of an abnormal Pap smear (RR=2.6, 0.7-9.0), and women with a history of a non-specific genital infection or sore (RR=2.1, 1.5-3.0).

#### DISCUSSION

This study initially revealed no increased risk of cervical cancer associated with use of oral contraceptives. However, associations were obscured by a variety of confounding factors, most notably by the interval since last Pap smear. This variable acted as a strong negative confounder since women who failed to have

TABLE II - RELATIVE RISKS<sup>1</sup> OF INVASIVE CERVICAL CANCER ASSOCIATED WITH VARYING PARAMETERS OF ORAL CONTRACEPTIVE USAGE

	Cases	Controls	RR	(95% CI)
Ever used				
No	269	386	1.00	—
Yes	210	403	1.49	(1.1-2.1)
Years of use				
<5	114	260	1.27	(0.9-1.9)
5-9	58	83	1.98	(1.2-3.2)
10+	38	60	1.82	(1.1-3.1)
Age at first use				
<20	67	122	1.28	(0.8-2.1)
20-24	82	167	1.71	(1.1-2.7)
25-29	36	56	1.92	(1.1-3.2)
30+	25	58	1.14	(0.7-2.0)
Years since first use				
<10	40	86	1.57	(0.9-2.8)
10-14	75	151	1.41	(0.9-2.2)
15-19	68	126	1.62	(1.1-2.5)
20+	27	40	1.35	(0.8-2.4)
Years since last use				
≤1	47	78	2.00	(1.2-3.4)
>1	163	325	1.44	(1.0-2.0)

<sup>1</sup>Relative risks are adjusted for age, ethnic origin, number of sexual partners, age at first intercourse, education, interval since last Pap smear, history of a non-specific genital infection or sore.

TABLE III - RELATIVE RISKS OF HISTOLOGIC SPECIFIC INVASIVE CERVICAL CANCERS ASSOCIATED WITH YEARS OF USE OF ORAL CONTRACEPTIVES

Years of use	Squamous-cell tumors (n = 417) <sup>1</sup>	Adenocarcinomas/ adenosquamous carcinomas (n = 62) <sup>2</sup>
Non-user	1.00 (237) <sup>3</sup>	1.00 (32)
<5	1.23 (98) (0.8-1.8)	1.41 (16) (0.6-3.3)
5-9	2.12 (51) (1.3-3.5)	1.43 (7) (0.5-4.1)
10+	1.63 (31) (0.9-2.9)	2.95 (7) (1.1-8.2)

<sup>1</sup>Relative risks are adjusted for the same variables as in Table II. <sup>2</sup>Relative risks are adjusted for age, ethnic origin, age at first intercourse, and interval since last Pap smear. <sup>3</sup>Numbers of cases are shown in parentheses.

regular Pap smears also had a low probability of having been prescribed oral contraceptives. However, when pill associations were examined according to varying intervals since last Pap smear, excess risks were observed for every interval since last Pap smear stratum, the pill-associated risks ranging from 1.4 for women with a recent Pap to 1.9 for those with 10 or more years since last Pap.

Thus, adjustment for interval since last Pap smear as well as other pertinent confounding variables resulted in a 50% excess risk of invasive cervical cancer among users of oral contraceptives compared to non-users. In addition, risk increased with years of pill use, those having used the pill for 5 or more years being at a significant 2-fold excess risk. These results raise concern, particularly in view of their consistency with two recent studies (Vessey *et al.*, 1983a; WHO, 1985), which showed an increased risk of invasive cervical cancer among long-term users of oral contraceptives. In the prospective study of Vessey *et al.* (1983a), the incidence of cervical neoplasia (preinvasive and invasive) rose from 0.9 per 1,000 woman-years among women with up to 2 years of pill use to 2.2 among those reporting more than 8 years of use. Of particular concern was the fact that all 13 cases of invasive cancer occurred among oral contraceptive users, and 9 had used the pill more than 6 years. Although this study was not able to control completely for various confounding variables, a substudy (Vessey *et al.*, 1983b) showed that the oral contraceptive users and the comparison group (IUD users) had similar sexual histories. In a large case-control study of invasive cervical can-

cer conducted by the World Health Organization (1985), it was possible to control extensively for confounding variables. The adjusted relative risk associated with ever having used oral contraceptives was 1.2, which increased with duration of use to 1.5 for those with 5 or more years of use. This pattern of increased risk for users, with further enhancement for long-term users, is comparable to our findings.

However, the issue is complicated, since not all investigations have shown a positive association (Thomas, 1972; Boyce *et al.*, 1977; Clarke *et al.*, 1985); and positive studies have been questioned on a number of methodologic grounds. Foremost among the questions raised is whether effects are merely reflecting confounding by sexual practices. It was of interest that we did not find the sexual variables to substantially confound the pill associations, which persisted even when analyses were restricted to women reporting only one sexual partner. Instead, the more important confounder was the interval since last Pap smear. Although the possible confounding effects of this variable have not been given extensive attention in previous studies, it is of interest that the WHO study also found that adjustment for screening histories increased the risks associated with pill use. In the WHO study, however, a substantial proportion of pill users had never been screened, and effects were adjusted for the presence or absence of screening rather than for the interval since last Pap smear.

A number of other confounding effects were considered as explanations for the increased risk among long-term oral contraceptive users. Since previous studies

TABLE IV - RELATIVE RISKS<sup>1,2</sup> OF HISTOLOGIC SPECIFIC INVASIVE CERVICAL CANCERS BY ESTROGEN POTENCY OF THE ORAL CONTRACEPTIVE USED LONGEST AND TOTAL YEARS OF ORAL CONTRACEPTIVE USE

	Total years of oral contraceptive use		
	<5	5-9	10+
Squamous-cell tumors			
Potency ≤ 50	1.29 (41) <sup>3</sup>	2.08* (24)	1.24 (8)
Potency > 50	1.09 (34)	2.35* (22)	1.70 (19)
Adenocarcinomas/ adenosquamous carcinomas			
Potency ≤ 50	1.75 (8)	1.25 (3)	1.09 (1)
Potency > 50	1.01 (5)	1.43 (3)	3.86* (6)
All cancers			
Potency ≤ 50	1.39 (49)	1.99* (27)	1.24 (9)
Potency > 50	1.09 (39)	2.18* (25)	2.10* (25)

<sup>1</sup>All risks are relative to non-users of oral contraceptives; unknowns are excluded from analyses. <sup>2</sup>Relative risks are adjusted for the same variables as in Table II. <sup>3</sup>Numbers of exposed cases are shown in parentheses.

\*p < .05.

TABLE V - RELATIVE RISKS<sup>1</sup> OF INVASIVE CERVICAL CANCER ASSOCIATED WITH ORAL CONTRACEPTIVE USE BY VARYING LEVELS OF OTHER SELECTED RISK FACTORS

	Exposed cases	Exposed controls	RR (95% CI)
Age			
<35	82	170	1.73 (0.7-4.1)
35-44	90	163	1.33 (0.7-2.5)
45+	38	70	1.17 (0.7-1.9)
Use of barrier methods of contraception			
No	106	177	1.84 (1.1-3.0)
Yes	104	226	1.22 (0.7-2.1)
History of an abnormal Pap smear			
No	179	374	1.40 (0.9-2.0)
Yes	31	29	2.55 (0.7-9.0)
History of a non-specific genital infection or sore			
No	179	374	1.66 (0.9-3.2)
Yes	31	29	2.13 (1.5-3.0)

<sup>1</sup>Relative risks are adjusted for the same variables as in Table II.

have shown that users of barrier methods are at a decreased risk of developing cervical abnormalities (Boyce *et al.*, 1977; Wright *et al.*, 1978), we were concerned that inclusion of these women among the unexposed might erroneously inflate risks. However, exclusion of both diaphragm users and partners of condom users from analyses failed to alter levels of risk. In addition, the elimination of women who reported never having used any contraceptives (and who were at a slightly elevated risk) resulted in no substantial differences in the risk estimates. Thus, it did not appear that our findings resulted from the use of inappropriate comparison groups. An additional concern related to the possibility that oral contraceptive users had a higher probability of having their diseases detected. Although it would have been desirable for analyses to be conducted separately for those presenting with the usual symptom of vaginal bleeding versus those without symptoms (in whom detection bias would be more likely), we failed to collect information on presenting symptoms. However, the WHO study found that exclusion of women who presented without vaginal bleeding did not substantially alter their results. Finally, we were concerned that our results might be affected by the relatively high non-response rate, particularly among controls. Although we have no information on contraceptive use among non-respondents, it seems unlikely that differential usage rates between the non-respondent cases and controls could account for observed effects, especially those related to duration of use and estrogen potency. Furthermore, analyses restricted to subgroups with the highest response rates (younger subjects, white women, and those from Philadelphia or Miami) yielded results similar to those based on the entire data set.

Although our results support a direct relationship between extended use of the pill and increased risk of cervical cancer, the mechanisms by which oral contraceptives might exert adverse effects on the cervical epithelium are unclear. There is evidence that cervical tissue has hormone receptor sites (Ford *et al.*, 1983) and that administration of hormones can result in histologic alterations (Gall *et al.*, 1969). Furthermore, Stern *et al.* (1977) have suggested that oral contraceptives may alter progression rates of preinvasive lesions

to more serious neoplastic states. Our finding of a higher pill-associated risk among those with abnormal Pap smears (RR=2.6) than in those without previous abnormalities (RR=1.4) is consistent with this possibility, although the difference was not statistically significant. In addition, oral contraceptives might influence cervical cancer risk by acting as promoters for other risk factors, including smoking and herpesvirus or papillomavirus infections (zur Hausen, 1982). Although we found no interactive effects of oral contraceptives and smoking on risk, it is noteworthy that pill associations were strongest among women who had never used barrier methods as well as among subjects who reported a history of a non-specific genital infection or sore, a finding consistent with results of the WHO study. If not due to chance, these interactions suggest that oral contraceptives may act as cocarcinogens with transmissible agents.

In summary, our findings of an increased risk of invasive cervical cancer among long-term oral contraceptive users are of concern, particularly given their consistency with recent observations. Although the issue is complicated because of potential confounding and bias from a number of sources, the elevated risks could not be readily explained on the basis of extraneous factors. We are currently obtaining additional data, including validation of Pap smear screening histories and serologic measures of micronutrient status and history of infections, and plan further analyses to assess the biologic plausibility of relationships observed in this study.

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