

Oral Contraceptive Use and Invasive Cervical Cancer

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The relationship between oral contraceptive use and the risk of invasive cervical cancer was investigated using data from a hospital-based case-control study conducted in the greater Milan area, Northern Italy. A total of 367 women under 60 years of age with a histologically confirmed diagnosis of invasive cervical cancer was compared with a group of 323 controls admitted for a spectrum of acute conditions, non-gynaecological, hormonal or neoplastic and apparently unrelated to oral contraceptive use. Cases had used oral contraceptives more frequently than controls, the age-adjusted relative risk (RR) being 1.53 (95% confidence interval 0.99–2.36). The risk increased with duration of use: compared with never users the age-adjusted RR was 1.48 for up to two years and 1.83 for more than two years ($\chi^2_1 = 5.28$, $p = 0.02$). Allowing for major identified potential confounding factors, including sexual and reproductive habits, by means of multiple logistic regression, did not explain the association (multivariate RR 1.85 for ever use, 1.05 for up to two years and 2.47 for more than two years). When the interaction between oral contraceptive use and parity or sexual habits was analysed, the effects of various factors appeared independent: the point estimate for multiparous oral contraceptive users versus nulliparous never users was 8.01. There was no consistent influence on risk of invasive cervical cancer of age at first use, whereas the RRs were slightly greater for women who had first used oral contraceptives less than ten years before or had last used them less than five years before diagnosis: these findings, however, were far from significant.

A large number of investigations, including those based on cytology screening programmes, cohort and case-control studies have suggested that the incidence of cervical neoplasms is higher in women who have used oral contraceptives (OC). The estimated relative risks, however, were only moderately increased, and most studies could not adequately allow for major risk factors for cervical neoplasia, chiefly indicators of sexual habits.^{1–3}

Several studies have focused on pre-invasive abnormalities^{4–10} which are particularly prone to identification and classification bias, whereas the evidence from studies of invasive cancer is still inconsistent.^{1,2} A cohort study from Britain¹¹ as well as two case-control studies (one from US¹² and one from eight different countries¹³) have shown significantly elevated risks among long-term oral contraceptive users, but no noticeable association emerged from other studies conducted in the US¹⁴ and Central America.¹⁵

To provide further information on the issue, we

present here the updated results from a case-control study conducted in Northern Italy. The availability of information on major recognized risk factors for cervical cancer permitted careful examination of their confounding, modifying effects and interactions.

SUBJECTS AND METHODS

Since 1981 we have conducted a case-control study of cervical neoplasia. The design of this investigation has already been described.^{16,17} Briefly, trained interviewers identified subjects from hospital logs and clinical records and questioned cases and controls using a standard questionnaire.

Information was obtained on personal characteristics and habits, gynaecological and obstetric data, related medical history, general indicators of sexual habits (age at first intercourse, total number of sexual partners), and a detailed history of lifetime use of oral contraceptives and other female hormones. Despite the rather sensitive nature of the interview, less than 2% of cases and controls refused to be interviewed, reflecting a particularly favourable attitude towards epidemiological data collection among patients in Italy.

Cases were women younger than 60 years with a histologically confirmed diagnosis of invasive cervical

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cancer (367 subjects: median age 47 years, range 22–59) made in the year prior to interview, admitted to the Obstetrics and Gynaecology Clinics of the University of Milan, to the National Cancer Institute and the 'Ospedale Maggiore' of Milan (including the four largest teaching and general hospitals in Milan).

Controls were patients admitted for acute conditions to the 'Ospedale Maggiore' in Milan and several specialized University Clinics. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic disease or had undergone hysterectomy. A total of 323 controls aged 20–59 (median age 47 years) were included in the analysis; of these, 25% were admitted for traumatic conditions (mostly fractures and sprains), 28% for non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 20% for surgical conditions (mostly abdominal, such as appendicitis or strangulated hernia), and 27% for other illnesses such as ear, nose, throat and dental disorders. They were blind for the purpose and goals of the study (specifically the relation between OC use and cervical cancer).

The current report is based on data obtained before December 1987.

Data Analysis

We computed the relative risks (RR) of invasive cervical cancer, together with their 95% confidence intervals (CI),¹⁸ from data stratified for quinquennia of age by the Mantel-Haenszel procedure.¹⁹ When a factor could be classified in more than two levels, the significance of the linear trend was assessed by the Mantel test.²⁰

In order to allow simultaneously for the effects of several potential confounding factors, unconditional logistic regression, with maximum likelihood fitting,²¹ was used. Included in the regression equations were terms for age, marital status, education, parity, number of sexual partners, age at first intercourse, cigarette smoking, history of Pap smears and use of barrier contraceptive methods.

RESULTS

The distribution of cases and controls according to age, socio-demographic indicators, parity, sexual habits, lifetime frequency of Pap smears and use of barrier contraceptive methods is presented in Table 1.

Women with invasive cervical cancer were more frequently married, parous and less educated, had a greater number of sexual partners, earlier age at first intercourse, reported less frequent and less recent Pap smears and less frequent use of barrier methods of contraception.

The relation of various measures of OC use with invasive cervical cancer is considered in Table 2. Cases had used OC more frequently than controls, the age-adjusted RR being 1.53. The risk increased with duration of use: compared with never users, the age-adjusted RRs were 1.48 and 1.83 respectively for less than two years and two years or more. This trend in risk was statistically significant.

There was no consistent influence on risk of invasive cervical cancer of age at first use, whereas the RRs were slightly greater for women who had first used OC less than ten years before diagnosis or had last used them less than five years before diagnosis; these differences, however, were far from significant.

The multivariate RR values tended to be higher than

TABLE 1 Distribution of 367 cases of invasive cervical cancer and 323 controls* according to age and selected covariates.* Milan, Italy, 1981–87

Covariates	Cervical cancer		Controls	
	Number	%	Number	%
Age (years)				
<40	86	23.4	92	28.5
40–49	117	31.9	90	27.9
50–59	164	44.7	141	43.7
Marital status				
Never married	28	7.6	45	13.9
Ever married	339	92.4	278	86.1
Education (years)				
<7	263	71.7	175	54.2
7–11	72	19.6	94	29.1
≥12	32	8.7	54	16.7
Parity				
0	28	7.6	69	21.4
1–2	181	49.3	189	58.5
≥3	158	43.1	65	20.1
Number of sexual partners				
0–1	271	73.8	267	82.7
≥2	91	24.8	46	14.2
unreported	5	1.4	10	3.1
Age at first intercourse (years)				
<18	70	19.1	25	7.8
18–20	139	37.9	100	31.3
≥21 or never	158	43.1	195	60.9
Number of Pap smears				
0	241	65.7	98	30.3
≥1	126	34.3	225	69.7
Time since last smear				
<5 years	80	21.8	185	57.3
≥5 or never	287	78.2	138	42.7
Use of barrier contraceptive methods				
Never used	344	93.7	286	88.5
Ever used	23	6.3	37	11.5

*In some cases the number of various strata do not add to the total owing to a few missing values.

TABLE 2 Relative risk of invasive cervical cancer in relation to various measures of oral contraceptive use. Milan, Italy, 1981-87

	Cervical cancer	Controls	Relative risk estimates (95% CI)	
			M-H*	MLR**
Ever use				
No	298	276	1†	1†
Yes	69	47	1.53 (0.99-2.36)	1.85 (1.00-3.14)
Duration of use (years)‡				
≤2	36	27	1.48 (0.87-2.69)	1.05 (0.84-3.24)
>2	33	20	1.83 (1.00-3.34)	2.47 (1.19-5.13)
Age at first use (years)				
<25	17	13	1.49 (0.68-3.26)	2.41 (0.98-5.93)
25-29	21	14	1.72 (0.92-3.60)	1.67 (0.74-3.77)
≥30	31	20	1.43 (0.79-2.60)	1.23 (0.62-2.44)
Time since first use (years)				
<10	39	25	1.86 (1.02-3.39)	1.98 (1.01-3.89)
≥10	30	22	1.28 (0.72-2.29)	1.28 (0.67-2.45)
Time since last use (years)				
<5	22	12	2.06 (0.96-4.42)	1.69 (0.78-3.68)
≥5	47	35	1.47 (0.86-2.51)	1.53 (0.86-2.73)

*Mantel-Haenszel estimates adjusted for age.

**Estimates from multiple logistic regression equations including terms for age, marital status, education, parity, number of sexual partners, age at first intercourse, cigarette smoking, history of Pap smears and use of barrier methods of contraception.

†Reference category.

‡Test for trend age adjusted $\chi^2_1=5.28$ $p=0.02$; multivariate $\chi^2_1=7.24$ $p=0.007$.

the ones adjusted for age only. The point estimate for ever use was 1.85, and 2.47 for more than two years, both being statistically significant. The multivariate risks in relation to age at first use tended to decrease with later age. This, however, should be considered within the context of the complex interaction between various temporal factors (age, time since first and last use).

The interaction between OC use and the other major risk factors for cervical cancer in this study (ie parity and number of sexual partners) is considered in Table 3. The RR for OC use was elevated in subsequent strata of parity and number of sexual partners. Consequently, the effect of the factors considered appeared

independent. Compared with never user nulliparous women, the point estimate rose to 8.01 for OC users with three births or more.

Finally, the relative risks were not significantly heterogeneous in various strata of age, socioeconomic factors, parity, sexual habits, time since last Pap smear and use of barrier methods of contraception, most of the estimated values being above unity (Table 4).

DISCUSSION

According to these results, women who had used OCs more frequently experienced invasive cervical cancer. The risk increased with duration of use and was about double in OC users for more than two years.

Diagnostic bias (OC users tend to be more frequently screened by Pap smear and consequently more easily diagnosed for cervical neoplasia) has been claimed as a major problem in the interpretation of the association between OCs and cervical pre-invasive neoplasms.³ However, it is conceivable that if OC users preferentially attended screening clinics, they would be more likely to be diagnosed in an early stage of the process of carcinogenesis, thus artificially lowering the frequency of OC users among invasive cases.

Likewise, separate analyses or simultaneously allowing for lifetime Pap smear frequency, time from last Pap and several other potential confounding factors (including socioeconomic status, sexual habits and reproductive variables) did not show any appreciable interaction or materially change the risk estimates. Indeed the relative risks, if any, tended to increase after multiple adjustment. Plausible explanation for this finding is the effect of social class, which is inversely related with invasive cervical cancer, but directly with OC use in this population²² and the more frequent use of screening by OC users.

Finally, selection bias should not influence these

TABLE 3 Interaction between parity, number of sexual partners and oral contraceptive use of cervical cancer. Milan, Italy, 1981-87

	Relative risks* (95% CI) for oral contraceptive use	
	Never	Ever
Parity		
0	1†	2.27 (0.60-8.58)
1-2	2.42 (1.44-4.06)	3.62 (1.69-7.75)
≥3	5.66 (3.26-9.80)	8.01 (3.55-18.06)
Number of sexual partners		
0-1	1†	1.20 (0.72-1.99)
2	1.55 (0.90-2.67)	2.41 (0.78-7.45)
≥3	2.52 (1.26-5.05)	4.29 (1.45-12.69)

*Mantel-Haenszel estimates adjusted for age.

†Reference category.

TABLE 4 Relative risk of invasive cervical cancer according to ever use of oral contraceptives and selected covariates. Milan, Italy, 1981-87

Covariates	Relative risk estimates (95% CI)*
Age (years)	
<40	1.49 (0.80-2.79)
40-49	1.77 (0.84-3.73)
50-59	3.04 (0.40-3.49)
Marital status	
Never married	0.78 (0.22-2.85)
Ever married	1.54 (0.97-2.44)
Education (years)	
<7	1.53 (0.84-2.78)
7-11	2.67 (1.07-6.65)
≥12	1.06 (0.36-3.06)
Parity	
0	2.27 (0.60-8.58)
1-2	1.24 (0.68-2.27)
≥3	1.11 (0.47-2.62)
Number of sexual partners	
0-1	1.20 (0.72-1.99)
2	2.29 (0.49-10.59)
≥3	2.13 (0.53-8.62)
Age at first intercourse (years)	
<18	1.10 (0.33-3.60)
18-20	1.36 (0.66-2.77)
≥21 or never	1.28 (0.63-2.61)
Time since last Pap smear	
<5 years	1.75 (0.89-3.47)
≥5 years	2.49 (1.20-5.17)
Ever use of barrier contraceptive methods	
Yes	1.04 (0.29-3.73)
No	1.66 (1.03-2.66)

*Mantel-Haenszel estimates adjusted for age.

results, since cases and controls were identified in institutions covering a broadly comparable catchment area and, despite the sensitive nature of the interview, participation in the study was almost complete.

Thus, the present study adds further evidence to the hypothesis of a positive association between cervical cancer and oral contraceptives. Although the evidence is not totally consistent, the two largest studies, conducted in the US¹² and eight different countries,¹³ reported an approximately 50% higher risk of invasive cervical cancer among long-term OC users, which was not explained by allowing for the potential effects of major covariates, including indicators of sexual habits, which were suspected to exert a major confounding effect.

Interpretation of these findings in biological terms is largely tentative. There is some suggestion in the present as well as in previous work that the relative risk is higher in the short term, and decreases with time since first and last use. Within the framework of the multi-stage theory of carcinogenesis this would suggest a later stage effect, which is common to other hormonal-

related factors, for example the role of oestrogens in endometrial carcinogenesis.²³ This also agrees with the observation that oral contraceptives may accelerate the evolution of the pre-invasive condition to invasive neoplasia.²⁴

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