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Original Paper

Time Since Last Use of Oral Contraceptives and Risk of Invasive Cervical Cancer

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The time–risk relationship for the association between cervical cancer and oral contraceptives (OC) was examined using data on 592 cases of invasive cervical cancer aged 60 years or less and 616 controls with acute, non-gynaecological, non-hormone-related, non-neoplastic diseases. A total of 125 cases and 114 controls reported ever using OC and the multivariate odds ratio (OR) for ever versus never users was 1.21 (95% confidence interval (CI) 0.82–1.74). The risk of invasive cervical cancer was above unity in current users (OR 1.23) and in women who had stopped OC use less than 10 years before diagnosis, but not in those who had stopped their OC use $\geq$10 years before (OR 0.85). Similarly, the OR was less for women who had started OC use 15 years or more previously than for more recent users. These data suggest that OCs may have a late stage (promoter) effect on cervical carcinogenesis and thus have public health implications, since the incidence of invasive cervical cancers is low at young ages, when OC use is more common and increases during middle age. The absence of a persisting risk is therefore of interest both for assessing individual risk and for its public health implications. **© 1998 Elsevier Science Ltd. All rights reserved.**

Key words: cervical cancer, oral contraceptives, risk factors
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INTRODUCTION

SEVERAL EPIDEMIOLOGICAL studies have suggested that parous women and oral contraceptive (OC) users are at increased risk of invasive cervical cancer [1–4]. In biological terms, it has been postulated that oestrogen–progestin stimulation can favour, or promote, cervical carcinogenesis, possibly through glucocorticoid-dependent oncogenic transformation by selected papilloma virus types [5]. This suggests that hormonal stimulation may act on one of the latter stages of the process of cervical carcinogenesis.

A detailed analysis of the risk relationship over time of any association between cervical cancer and OCs may, therefore, help elucidate the role of hormonal correlates of cervical carcinogenesis, as well as define the benefit/risk profile of OCs. For example, an update of the Oxford Family Planning Association cohort study indicated that the elevated risk of cervical cancer associated with OC use was essentially confined to current or recent long-term users [6].

To provide further information on these issues, we considered data collected in a large case–control study of cervical neoplasia conducted in Italy.

MATERIALS AND METHODS

This was a hospital-based case–control investigation conducted in the greater Milan area, northern Italy between 1981 and 1993. Its general design has been described in previous papers including a subset of subjects considered in this report [4, 7].

Cases were 592 histologically confirmed invasive cervical cancers below the age of 61 years (range 17–60 years, median 48 years) admitted to a network of Obstetrics and Gynaecology Departments in the great Milan area.

The comparison group consisted of 616 women aged 60 years or less (range 16–60 years, median 48 years),

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Table 1. *Distribution of* 592 *invasive cervical cancer cases and* 616 *controls according to age and selected factors, Milan, Italy* 1981–1993

	Number of cases (%)	Number of controls (%)	Multivariate odds ratio (95% CI)*
Age (years)			
< 40	151 (25.5)	170 (27.6)	–
40–49	182 (30.7)	161 (26.1)	–
50–60	259 (43.7)	285 (46.2)	–
Education (years)			
< 7	373 (63.0)	310 (50.3)	1†
7–11	127 (21.5)	185 (30.0)	0.71 (0.53–0.98)
≥ 12	92 (15.5)	121 (19.6)	0.78 (0.54–1.16)
Smoking habits			
Never smokers	380 (64.2)	398 (64.6)	1†
Ever smokers	212 (35.8)	218 (35.4)	1.06 (0.80–1.42)
Parity			
0	54 (9.1)	130 (21.1)	1†
1–2	310 (52.4)	346 (56.2)	3.11 (2.08–4.69)
≥ 3	228 (38.5)	140 (22.7)	5.42 (3.48–8.56)
Lifelong number of sexual partners			
0	4 (0.7)	35 (5.7)	0.22 (0.07–0.67)
1	413 (69.8)	457 (74.2)	1†
2	81 (13.7)	62 (10.1)	1.80 (1.20–2.70)
≥ 3	86 (14.5)	49 (7.9)	3.85 (1.91–4.32)
Unreported	8 (1.4)	13 (2.1)	–
Lifelong number of normal Pap smears			
0	338 (57.1)	161 (26.1)	1†
1	90 (15.2)	89 (14.4)	0.39 (0.27–0.57)
2	91 (15.4)	63 (10.2)	0.26 (0.16–0.41)
≥ 3	70 (11.8)	296 (48.1)	0.15 (0.11–0.21)
Unreported	3 (0.5)	7 (1.1)	
Abnormal Pap smears‡			
Never	240 (94.5)	441 (96.9)	1†
Ever	14 (5.5)	14 (3.1)	1.49 (0.61–3.20)

CI, confidence interval. *Multivariate estimates including terms for age, education, calendar year at interview, smoking habits, parity, lifelong number of sexual partners and of Pap smears, and oral contraceptive use. †Reference categories. ‡One year before interview or more.

Table 2. *Distribution of* 592 *invasive cervical cancer cases and* 616 *controls according to selected measures of oral contraceptive (OC) use, corresponding odds ratios (OR) and* 95% *confidence intervals (CI), Milan, Italy* 1981–1993

			OR (95% CI)*	
	Number of cases (%)	Number of controls (%)	Age-adjusted	Multivariate
OC use				
Never users	467 (78.9)	502 (81.5)	1†	1†
Ever use	125 (21.1)	114 (18.5)	1.21 (0.89–1.64)	1.21 (0.82–1.74)
Duration of OC use (months)				
Never users	467 (78.9)	502 (81.5)	1†	1†
≤ 24	62 (10.5)	56 (9.1)	1.23 (0.82–1.83)	1.17 (0.75–1.82)
> 24	63 (10.6)	56 (9.1)	1.32 (0.81–2.15)	1.31 (0.72–2.39)
Unknown	–	2 (0.4)	–	–
χ^2_1 trend			1.33 ($P = 0.25$)	3.05 ($P = 0.08$)
Time since last use (years)				
Never users	467 (78.9)	502 (81.5)	1†	1†
Current	19 (3.2)	23 (3.7)	1.01 (0.53–1.94)	1.33 (0.65–2.70)
1– < 3	23 (3.9)	17 (2.8)	1.61 (0.82–3.13)	1.56 (0.74–3.29)
3– < 6	22 (3.7)	16 (2.6)	1.60 (0.81–3.17)	1.47 (0.69–3.14)
6– < 10	26 (4.4)	17 (2.8)	1.63 (0.86–3.09)	1.66 (0.83–3.34)
≥ 10	35 (5.9)	41 (6.7)	0.90 (0.56–6.45)	0.85 (0.51–1.43)
Time since first use (years)				
Never users	467 (78.9)	502 (81.5)	1†	1†
≤ 5	26 (4.4)	25 (4.1)	1.33 (0.72–2.45)	1.49 (0.76–2.94)
6– < 11	36 (6.1)	22 (3.6)	1.89 (1.06–3.35)	1.77 (0.93–3.37)
11– < 15	30 (5.1)	32 (5.2)	1.02 (0.60–1.74)	1.07 (0.60–1.90)
≥ 15	33 (5.6)	35 (5.7)	0.98 (0.60–1.61)	0.96 (0.55–1.65)
Age at first OC use				
Never users	467 (78.9)	502 (81.5)	1†	1†
< 25	38 (6.4)	40 (6.5)	1.12 (0.68–1.86)	1.12 (0.63–1.97)
25–29	35 (5.9)	35 (5.7)	1.10 (0.66–1.83)	1.10 (0.63–1.92)
≥ 30	52 (8.8)	39 (6.3)	1.35 (0.87–2.10)	1.36 (0.83–2.23)

*Multivariate estimates including terms for age, education, calendar year at interview, parity, number of sexual partners, smoking habits and number of Pap smears. †Reference category.

with acute, non-gynaecological, non-hormone-related, non-neoplastic diseases and who had not undergone total hysterectomy, admitted to the same network of hospitals where the cases had been identified, and from comparable catchment areas. Of these, 26% were admitted for traumatic conditions (mostly fractures and sprains), 35% had non-traumatic orthopaedic disorders (mostly lower back pain and disc disorders), 14% surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 24% had other illnesses, such as ear, nose and throat or dental disorders. Less than 2% of eligible women (cases and controls) refused to be interviewed.

A structured questionnaire was used to collect information on personal characteristics and habits, education and other socio-economic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, frequency of consumption of a few indicator foods, selected indicators of sexual habits, menstrual and reproductive history, related medical history, and history of lifelong use of OCs and female hormone preparations for any other indication, including time and duration of each episode of use and the brand name, whenever available. In addition, information on the lifetime number of Pap smears was collected.

Odds ratios (OR) of cervical cancer, and the corresponding 95% confidence intervals (CI) for various measures of OC use were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood [8], including terms for age in quinquennia, education (<7, 7–11, ≥ 12 years), calendar year and interview, smoking habits (ever, never), parity (0, 1–2, ≥ 3), number of partners (0, 1, ≥ 2) and of Pap smears (0, 1, 2, ≥ 3).

RESULTS

Table 1 shows the distribution of cases and controls according to age and selected covariates. Cases were less educated, more frequently multiparous, reported a lifelong larger number of sexual partners and less frequently underwent Pap smears.

In Table 2, different measures of OC use are considered. A total of 125 cases and 114 controls reported ever using OCs. The corresponding OR was 1.21 (95% CI 0.82–1.74, multivariate). The ORs were 1.17 in users for 24 months or less and 1.31 in users for >24 months (multivariate; χ^2_1 trend 3.05, $P=0.08$).

The risk of invasive cervical cancer was above unity for current users or in women who had stopped use less than 10 years before they were interviewed, but not in those who stopped their OC use ≥ 10 years before, whose OR was 0.85 (95% CI 0.51–1.43, multivariate). Likewise, in comparison with never users, the OR was 0.96 (95% CI 0.55–1.65, multivariate) for women who had started OC use 15 or more years previously. There was no clear relationship between age at first OC use and risk of cervical cancer.

Table 3 shows the analyses of the relationship between the time since last OC use and the risk of invasive cervical cancer in strata of selected covariates. The ORs were systematically higher in current OC users or ex-users from less than 10 years before, than in those who had stopped OC use for 10 years or more. The association with recent use was apparently stronger in less educated, multiparous women, who had never undergone a Pap smear (i.e. at baseline high risk). For example, the OR of cervical cancer in women reporting the time since last OC use as <10 years was 2.22 in women

Table 3. Multivariate odds ratios (ORs) of invasive epithelial cervical cancer [and corresponding confidence intervals (CI)] according to time since last oral contraceptive (OC) use in strata of selected covariates, Milan, Italy* 1981–1993

			Time since last OC use	
Never OC use		Current (no. cases:controls)	<10 years (no. cases:controls)	≥ 10 years (no. cases:controls)
Total	1†	1.23 [0.60–2.44]‡ (19:23)	1.57 [0.99–2.49] (71:50)	0.85 [0.51–1.43] (35:41)
Age (years)				
<45	1†	1.26 [0.59–2.71] (17:21)	1.42 [0.83–2.41] (60:42)	0.67 [0.29–1.55] (14:18)
45–60	1†	0.64 [0.08–5.07] (2:2)	1.53 [0.55–4.23] (11:8)	0.99 [0.51–1.93] (21:23)
Number of sexual partners				
0–1	1†	1.38 [0.49–3.87] (8:11)	1.41 [0.80–2.50] (36:33)	1.10 [0.59–2.05] (26:26)
≥ 2	1†	0.94 [0.35–2.47] (11:12)	1.74 [0.80–3.79] (35:17)	0.51 [0.19–1.60] (9:15)
Education (years)				
<7	1†	0.70 [0.16–2.99] (4:6)	2.22 [1.10–4.50] (39:17)	1.13 [0.54–2.35] (21:18)
≥ 7	1†	1.24 [0.55–2.80] (15:17)	1.12 [0.60–2.09] (32:33)	0.62 [0.27–1.37] (14:23)
Parity				
0–1	1†	1.25 [0.44–2.51] (13:15)	1.24 [0.61–2.54] (20:27)	1.10 [0.44–3.07] (9:12)
>2	1†	0.95 [0.30–3.07] (6:8)	1.97 [1.07–3.62] (51:23)	0.89 [0.48–1.66] (26:29)
Lifetime number of Pap smears				
0–1	1†	0.65 [0.22–1.86] (8:10)	2.30 [1.06–4.97] (45:10)	1.32 [0.56–3.07] (24:8)
≥ 2	1†	1.28 [0.50–3.29] (10:12)	1.10 [0.60–2.01] (26:40)	0.59 [0.28–1.24] (11:33)

*Multivariate estimates including terms for age, education, calendar year at interview, parity, number of partners, smoking habits and number of Pap smears. †Reference category. ‡95% confidence interval.

Table 4. Main results from selected studies on recency and duration of oral contraceptive use and risk of invasive cervical cancer

Author, year [ref.]	Type of study	Number of cases	Years of use	Relative risk*	Years since last use	Relative risk*
Peters and associates, 1986 [11]	Case–control	200	< 2	1.0	–	–
			2–9	1.0		
			≥ 10	1.1		
Brinton and associates, 1986 [12]	Case–control	479	< 5	1.3	≤ 1	2.0
			5–9	2.0	> 1	1.4
			≥ 10	1.8	–	–
Ebeling and associates, 1987 [13]	Case–control	129	1–3	1.1	Previous use	1.2
			4–6	1.2	Present use	2.0
			≥ 7	1.8		
Irwin and associates, 1988 [14]	Case-control	149	< 1	1.2	< 1	0.3
			1–4	0.5	1–4	1.0
			≥ 5	0.9	≥ 5	1.0
Beral and associates, 1988 [15]	Cohort	65	< 5	1.3 †		
			5–9	2.0		
			≥ 10	4.4		
Cuzick and associates, 1989 [16]	Case–control	135 (including 55 CIN III, 7 micro-invasive, 7 invasive cancers)	< 1	0.5		
			1–3	2.6		
			> 3–5	0.9		
			> 5	5.6		
Brinton and associates, 1990 [17]	Case–control	667	< 5	1.0	≤ 3	1.3
			5–9	1.3	> 3	1.0
			≥ 10	1.1		
Bosch and associates, 1992 [18]	Case–control	436	1–9‡	0.8		
			≥ 10	0.9		
			1–9§	3.0		
			≥ 10	8.9		
WHO, 1993 [19]	Case–control	4456	≤ 0.5	1.0	< 1	3.3
			0.5–1	1.2	> 1–3	1.6
			> 1–2	1.1	> 3–8	1.2
			> 2–3	1.2	> 8–13	1.1
			> 3–5	1.4	> 13	1.1
			> 5–8	1.5		
			> 8	2.2		
Eluf-Neto and associates, 1994 [20]	Case–control	199	1–4	1.3		
			≥ 5	2.7		
Zonderwan and associates, 1996 [6] (Oxford FPA)	Cohort	33	1–2	5.4	≤ 2	6.8
			> 2–6	2.8	> 2–6	2.6
			> 6	4.6	> 6	1.3

*Reference category: never users. †Rate ratio. ‡Human papillomavirus negative cases. §Human papillomavirus positive cases.

reporting < 7 years of education and 2.30 in those reporting 0–1 lifetime Pap smears.

DISCUSSION

In this study, the risk of invasive epithelial cervical cancer tended to be elevated in ever-users of OC and to increase with duration of use, but the trend in risk was not significant. The risk seems to be similar to that among current users, up to 10 years since last use, before decreasing for women who had last used OCs more than 10 years ago. These findings agree with the suggestion [6] that the excess risk of cervical cancer is largely restricted to current or recent long-term OC users and tends to decline with time since last use. Consequently, the present data suggest that the effect of oestro-progestins would be on one of the late stages of the process of cervical carcinogenesis (i.e. promotion).

Potential limitations of this study should be considered. OC users may tend to be more frequently screened by Pap smear [9]. This potential selection mechanism should lead to an underestimate of the role of OCs, particularly in the short term and in the present analysis the effect of OCs on cervical cancer risk was larger in women who did not report any Pap smear during their life. With regard to other covariates (chiefly education and sexual habits), their inclusion in the multivariate analysis did not drastically change any of the ORs. With reference to information bias, the similar clinical setting should favour a comparable recalling of drug use (including OCs) among cases and controls [10]. The questions regarding OC use were derived from a questionnaire including more than 100 questions, analysing general characteristics, reproductive and medical history and general lifestyle habits. Further, the analysis of the relationship between OC use and cervical cancer risk was not the main objective of the study and the interviewers, as well as the women interviewed, were not aware of the potential association between OC use and the risk of invasive cervical cancer. This association, moreover, had not gained widespread attention in the lay press in Italy. Selection bias should also not be a major problem in the study, since cases and controls were identified in institutions covering broadly comparable catchment areas and participation was almost complete. It is unlikely that any possible source of bias had specifically influenced the time–risk relationship of any OC–cervical cancer risk.

The results of the study are in general agreement with a recent update of the Oxford Family Planning Association contraceptive study [6], in that ever users of OCs had an elevated OR of cervical invasive neoplasm. In that study, the separate effects of time since last use and duration of use were examined and the risk was largely confined to current or recent (< 2 years), long-term users of OCs. The potential confounding by number of sexual partners and of cervical smears could not be taken into account, but it was thought that this was unlikely to have introduced major bias. Similar findings also emerged in other studies. Table 4 shows the results of selected published papers on the relationship between recency and duration of OC use and risk of invasive cervical cancer.

In biological terms, the effect of OC use in cervical carcinogenesis may be attributed to the progestin component of the pill. HPV-16, the most important cause of cervical cancer, contains a progesterone/glucocorticoid response element upstream to the common E6-E7 promoter [21] and progesterone enhances the transferring effect of HPV-16 DNA [22]. In fact, papillomavirus lesions are exacerbated during pregnancy [23], and cervical cancer risk is enhanced by OCs and pregnancy, when progestogen levels are relatively high. Otherwise, oestrogen (prolonged by local 16a-hydroxylation) increases human papillomavirus expression via upregulation of the progesterone receptor [24].

This line of reasoning indicates that, in terms of clinical and public health implications, OC use should be critically reconsidered for women with a diagnosis of cervical intraepithelial neoplasia. However, little association between OC use and cervical cancer emerged in screened women, suggesting that, from a public health perspective, any potential impact of OC on cervical cancer risk use would be largely controlled by Pap screening.

The major public health implications of this study, however, are the reassuring evidence on the absence of persisting cervical cancer risk in the medium–long term after stopping OC use. This is of particular interest, since the incidence of invasive cervical cancer is low at a younger age (i.e. below age 35 years), when OC use is most common and increases throughout middle age. Specific attention to screening for cervical neoplasia, in contrast, would be recommended for OC users above the age of 40 or 45 years.

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