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Oral Contraceptive Use and the Risk of Ovarian Cancer: an Italian Case-Control Study

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The association between oral contraceptive (OC) use and the risk of ovarian cancer was analysed in a case-control study, conducted between 1985 and 1989 on 505 epithelial ovarian cancer cases under 60 years of age, and 1375 controls in hospitals for a spectrum of acute conditions, not gynaecological, hormonal or neoplastic, apparently unrelated to OC use. 41 (8.1%) women with epithelial ovarian cancer and 192 (14.0%) controls reported OC use. The multivariate relative risk (RR) for ever use was 0.7 (95% confidence interval (CI) = 0.5–1.0). The risk decreased with duration of use: compared with never users the multivariate RRs were 0.9 and 0.5 respectively for less than 2 years and 2 years or more users (χ^2_1 trend = 6.17, P = 0.01). The risk of ovarian cancer decreased with recency and latency of use: the estimated RR were 0.5 and 0.9 in women reporting last OC use less than 10 or 10 years or more from the diagnosis of the disease, and 0.6 and 0.8 in those reporting first OC use less than 10 or 15 or more years before. The protective effect of OC was consistent in separate strata of selected covariates, including parity and other major known or suspected risk factors for ovarian cancer. There was some indication that the protection declines with advancing age, but the risk estimates were similar in premenopause and postmenopause.
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INTRODUCTION

SINCE THE late 1970s, several epidemiological investigations have shown that oral contraceptive (OC) use lowers the risk of ovarian cancer [1–19].

An overview of published case-control studies indicated that the protection amounts to about 40% for women who used OC compared with never users and that this protection increases with duration of use. The reduced risk seems to persist in the medium period after pill use (at least 10 years), but the data did not provide definite relative risk estimates for longer periods or in relation to latency or recency of use, and for the potential interaction between pill use and the main risk factors for

ovarian cancer [18]. For example, some findings suggest that the protective effect of oral contraceptives may be greater in, or even restricted to, nulliparous women [4, 11], but the data are scanty and largely controversial in quantitative and qualitative terms [7, 8, 10, 16]. Further, published studies have been generally conducted on English-speaking populations, and few papers have considered the relation between OC and ovarian cancer in other areas of the world [9, 10, 15, 17], where the incidence and the baseline distribution of other determinants of ovarian cancer are different.

In this article we report the results of a case-control study conducted in Italy on the relation between OC use and ovarian cancer risk. A previous study conducted with a comparable design in the same area not including the subjects considered in this paper has been reported [10], while part of these data were included in a general analysis of oral contraceptive use and risk of cancers of the breast and female genital tract [19].

MATERIAL AND METHODS

Between 1983 and 1989 trained interviewers identified and questioned women admitted for ovarian cancer and for a wide spectrum of other conditions to a network of teaching and general hospitals in the greater Milan area. The design of this investigation has already been described [19].

A standard questionnaire was used to obtain information on personal characteristics and habits, gynaecological and obstetric data, related medical history, dietary habits and a detailed history of lifetime use of OC and other female hormones. The time and duration of OC use were recorded, as well as the brand name. Photographs of packages of the most common brands were provided to assist recall, whenever useful.

Less than 2% of eligible cases and controls refused to be interviewed.

Cases. The cases considered in this report were women below the age of 60, residing in the greater Milan area, with histologically confirmed epithelial ovarian cancer (505 subjects, median age 50 years, range 22–59) diagnosed within the year preceding the interview, who had been admitted to the Obstetric and Gynecology Clinics of the University of Milan, the National Cancer Institute and the Ospedale Maggiore (which includes the four largest teaching and general hospitals in the greater Milan area).

Controls. Patients aged 59 years or less, residing in the same geographical area and admitted for acute conditions to the same network of hospitals where cases had been identified were eligible as controls. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic disease or had undergone hysterectomy and/or bilateral oophorectomy.

A total of 1375 controls (median age 48 years, range 25–59) were interviewed. Of these, 31% were admitted for traumatic conditions (mostly fractures and sprains), 26% for non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 18% for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 25% for other illnesses such as ear, nose, throat and dental disorders.

Data analysis. For all analysis purposes, we considered only the combined OC use, which represents almost the totality of OC use in Italy. We computed the relative risks (RR) of epithelial ovarian cancer, according to various indications of OC use together with their 95% confidence intervals (CI), from data stratified for quinquennia of age by the Mantel–Haenszel procedure [20]. When a factor could be classified in more than two levels, the significance of the linear trend was assessed by the Mantel test [21].

In order to allow simultaneously for the effects of several potential confounding factors, unconditional logistic regression, with maximum likelihood fitting, was used [22]. Included in the regression equations were terms for age, education, marital status, parity, age at menarche, lifelong menstrual pattern, menopausal status, age at menopause and, in turn, various indicators of OC use.

RESULTS

The distribution of cases and controls according to age and the major identified ovarian cancer risk factors is shown in Table 1. Cases tended to be more frequently nulliparous, in postmenopause and to report a lifelong regular menstrual pattern. No difference emerged between cases and controls in relation to the use of barrier methods of contraception (RR adjusted for age, ever vs. never users = 1.0, 95% CI = 0.6–1.6), but cases tended less frequently to be IUD users, although this difference was not statistically significant (RR = 0.7, 95% CI = 0.3–1.2).

The relation of various measures of OC use with ovarian cancer risk is presented in Table 2. 41 (8.1%) cases and 192 (14.0%) controls reported OC use. Compared with never users the age-adjusted RR for ever users was 0.6. The risk decreased with duration of use: the age-adjusted RRs were 0.8 and 0.5 respectively for less than 2 years and 2 or more years. The trend in risk was statistically significant ($\chi^2_1 = 6.88$; $P < 0.01$). The risk of ovarian cancer tended to decrease with shorter recency and latency of use. The estimated RRs were 0.5 and 0.8 in women reporting last OC use less than 10 years or 10 years or more before diagnosis of the disease, and 0.5 and 0.8 in those reporting their first use less than 10 or 15 or more years before. The multivariate RRs were largely comparable to the age-adjusted ones (Table 2).

The risk of ovarian cancer in short-term (< 2 years) and medium/long-term (≥ 2 years) users was further examined in strata of time since last use. The only significant estimated RR was for long duration–short recency users, while no consistent pattern was observed in other strata (Table 3).

The effect of OC in separate strata of age and other selected covariates is shown in Table 4. There was no noteworthy interaction with any of the variables considered; all the estimated RRs were below unity and the variations observed were within the limits of random fluctuation. In particular, although there was some indication for the protection to decline with advancing age, the risks were similar in premenopause (RR = 0.6) and postmenopause (RR = 0.5). The latter estimate, however, was based on 5 OC user cases and 20 user controls, and, consequently, was not significant.

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Table 1. Distribution of 505 cases of ovarian cancer and 1375 controls according to age and selected covariates, Milan, Italy, 1983–1989

	Ovarian cancer		Controls	
	No.	%	No.	%
Age (years)				
<35	55	11	166	12
35–44	89	18	392	29
45–54	245	49	542	39
55–59	116	23	275	20
Marital status				
Never married	83	16	201	15
Ever married	422	84	1174	85
Education (years)				
<7	269	53	705	51
7–11	135	27	397	29
≥12	101	20	273	20
Parity				
0	137	27	273	20
1–2	266	53	795	58
>3	102	20	307	22
Age at menarche				
<13	215	43	555	40
≥13	290	57	820	60
Lifelong menstrual pattern*				
Regular	472	93	1191	87
Irregular	33	7	184	13
Menopausal status				
Pre/in menopause	290	57	868	63
Postmenopause	215	43	507	37
Age at menopause (years)				
<45	39	18	100	20
45–49	67	31	165	33
50–53	93	43	207	41
≥54	16	7	35	7
IUD use				
Never users	493	98	1316	96
Ever users	12	2	59	4
Use of barrier methods of contraception†				
Never users	486	96	1316	96
Ever users	19	4	59	4

In some cases the sum of cases and controls does not add up to the total because some values are missing.
*Irregular menses are defined as frequent menstrual-like episodes of bleeding less than 21 or more than 35 days apart.
†Condom and diaphragm as main contraceptive device (excluding occasional use).
IUD = intrauterine device.

Table 2. Relative risk of ovarian cancer in relation to various measures of oral contraceptive use

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M–H*	MLR†
Oral contraceptive use				
Never users	464	1183	1‡	1‡
Ever users	41	192	0.6 (0.4–0.9)	0.7 (0.5–1.0)
Duration of use (years)				
<2	22	78	0.8 (0.5–1.4)	0.9 (0.5–1.5)
≥2	19	111	0.5 (0.3–0.8)	0.5 (0.3–0.9)
χ^2_1 trend			6.88§	6.17§
Time since last use (years)				
<10	18	113	0.5 (0.3–0.8)	0.5 (0.3–0.8)
≥10	21	73	0.8 (0.5–1.4)	0.9 (0.5–1.5)
Time since first use (years)				
<10	13	70	0.5 (0.3–1.0)	0.6 (0.3–1.0)
10–14	12	65	0.6 (0.3–1.1)	0.6 (0.3–1.1)
≥15	15	55	0.8 (0.4–1.4)	0.8 (0.4–1.4)

In some cases the sum of cases and controls does not add up to the total because some values are missing.
*Adjusted for age. M–H = Mantel-Haenszel.
†Estimate from multiple logistic regression (MLR) equations including terms for age, education, marital status, parity, age at menarche, lifelong menstrual pattern, menopausal status, age at menopause, and, in turn, the above variables.
‡Reference category.
§$P = 0.01$.

DISCUSSION

This study provides further quantitative evidence of the protective effect of OC (in contrast to other contraceptive methods) against invasive epithelial ovarian cancer. The risk decreased with duration of use and was about halved in OC users for more than 2 years.

These relative risks compare well with the results of a case-control study conducted in the same area and with a similar design in the early 1980s [10], and agree with those of more than a dozen earlier epidemiological investigations from European and US areas [1–14, 16]. The present Italian data, based on a population with a low prevalence of OC use [23], are nonetheless of particular interest since the evidence from other areas of the world is less consistent. In the WHO Collaborative Study of Neoplasia and Steroid Contraceptives a protective effect of OC use was observed in five out of eight surveyed areas [15], but a case-control study conducted in China reported a not

Table 3. Relative risks (95% CI) of ovarian cancer in separate strata of duration and time since last oral contraceptive use*

	Duration of use (years)	
	<2	≥2
Time since last use (years)		
<10	0.8 (0.4–1.6)	0.3 (0.2–0.7)
≥10	0.9 (0.5–1.8)	1.0 (0.5–2.0)

*Estimate from multiple logistic regression equation including terms for age, education, marital status, parity, age at menarche, lifelong menstrual pattern, menopausal status, age at menopause and, in turn, the above variables.
Reference category: never OC users.

Table 4. Relative risks of ovarian cancer according to ever use of oral contraceptives and selected covariates*

	Relative risk (95% CI)
Age (years)	
<35	0.4 (0.2–0.9)
35–44	0.8 (0.4–1.4)
45–54	0.7 (0.4–1.3)
55–59	0.8 (0.1–7.6)
Marital status	
Never married	0.6 (0.3–1.5)
Ever married	0.6 (0.4–0.9)
Education (years)	
<7	0.5 (0.2–1.0)
7–11	0.4 (0.2–0.9)
≥12	0.8 (0.4–1.4)
Parity	
0	0.6 (0.3–1.3)
1–2	0.5 (0.3–0.9)
≥3	0.8 (0.3–1.7)
Age at menarche	
<13	0.5 (0.3–0.8)
≥13	0.7 (0.4–1.1)
Lifelong menstrual pattern	
Regular	0.6 (0.4–0.9)
Irregular	0.8 (0.3–2.2)
Menopausal status	
Pre/in menopause	0.6 (0.4–0.9)
Post menopause	0.5 (0.2–1.4)
Age at menopause	
<50	0.7 (0.2–2.3)
≥50	0.3 (0.03–1.9)

*Adjusted for age.
Reference category: never OC users.

Table 5. Relative risk of ovarian carcinoma in relation to oral contraceptive use in selected studies

	Relative risk	
Ref.	Ever use	Long term use (yrs)
1	0.6	n.r.
2	0.7	0.6 (≥7)
3	0.7	n.r.
4	0.8	0.8 (≥3)
5	0.5	n.r.
6	0.6	0.4 (≥9)
7	0.4	0.6 (>5)
8	0.6	0.3 (≥5)
9	0.4	n.r.
10	0.6	0.4 (≥2)
11	0.6	0.2 (≥10)
12	0.3	n.r.
13*	0.4	0.4 (>4)
14	0.7	0.5 (>3)
15	0.8	0.5 (≥5)
16	0.5	0.1 (>10)
17	1.8	1.9 (>5)
24	1.0	0.8 (>5)

*Borderline malignancy neoplasms.
n.r. = not reported.

significantly increased risk of the disease in OC users [17]. A general review of published relative risk estimates [1–17, 24] is shown in Table 5; since the term "ever use" aggregates relative risks over several patterns of duration of use, we have presented whenever available the estimates for long term use, too. Although the definition of long-term use is also based on different definitions, there is general evidence of greater protection associated with longer pill use.

Selection bias should not represent a major problem in this study, since cases and controls were identified in institutions covering broadly comparable catchment areas and participation was almost complete. Likewise, separate analyses or simultaneous allowance for several potential confounding factors did not show any appreciable interaction or materially change the risk estimates.

Nulliparity (and perhaps infertility) increases the risk of ovarian cancer [25, 26]. Hence the possibility that non-users tend to be more frequently infertile than OC users has been claimed as a potential bias in the interpretation of the negative association between OC use and ovarian cancer [18]. Along this line, OC use was reported to have a more limited (or no) protective effect in parous than in nulliparous women in three reports [4, 14, 15]. However in our analysis, as well as in five other studies [7, 8, 10, 16, 24], no relation emerged between the magnitude of the protective effect of OC use and strata of parity or marital status. Further, in this and previous reports [16, 17], no significant association emerged between ovarian cancer and barrier methods of contraception or IUD use (although a non-significantly reduced risk in IUD users was also reported in a Chinese study [17]).

The protective effect of OC use on ovarian cancer risk has been tentatively interpreted in the general framework of the "incessant ovulation theory", which implies that ovulatory cycles are the exposure which defines the incidence of the neoplasm [2]. In biological terms, Zajicek postulated that epithelial inclusions of the surface epithelium, which occur in association with ovulation, may be the relevant aetiological agent [27]. Animal data have shown that ovarian epithelium proliferates rapidly after ovulation and mitotic figures are concentrated near the site of ovulation [28]. Alternatively the reduced secretion of pituitary gonadotropin (which stimulates growth of cell lines derived from human ovarian carcinomas [29]) in itself might contribute to explain the inverse association between OC use and ovarian cancer risk.

In our study, the protective effect of OC use apparently had a later stage effect in the multistage process of ovarian carcinogenesis [30]. In fact, the reduction in risk was greater in younger women and long-term users reporting their last use less than 10 years before diagnosis. The protection, however, was evident in postmenopausal women too, although the estimate was based on small absolute numbers. Other published data, however, showed a reduced risk of the disease in the medium period after pill use (at least 10 years) [8, 11, 15, 16], although these differences can be at least in part due to heterogeneities in the prevalence and duration of OC use in subsequent cohorts of women and in various populations.

A more precise understanding of the time-relationship

between OC use and ovarian cancer risk will help in better defining the aetiopathogeneic mechanism(s) underlying the well recognised protective effect of OC in ovarian carcinogenesis, and its long-term public health impact. While, in fact, this study provides further quantitative evidence of the protection of OC against ovarian carcinogenesis in younger and middle-aged women (and this protection, together with the pill/breast cancer issue, is the key question for any cancer risk-benefit evaluation in women below age 50 or 55 [31]), little is known of the long-term effects and, probably, on the impact of OC on postmenopause ovarian cancers. Thus, any further elucidation of the timing of the OC–ovarian cancer relationship will be useful in defining the long-term implications of OC in ovarian cancer risk, and hence ultimately for quantifying any risk-benefit analysis of OC use and disease [18, 32].

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