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LONG-TERM EFFECTS OF ORAL CONTRACEPTIVES ON OVARIAN CANCER RISK

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Several epidemiologic studies have reported a protective effect of oral contraceptives (OCs) on ovarian cancer. However, there remain open issues, including better quantification of time-related factors such as time since last use, age at first use and time since first use. We performed a collaborative reanalysis of 6 case-control studies conducted between 1978 and 1999 in the United Kingdom, Greece and Italy, including a total of 2,768 incident, histologically confirmed cases of epithelial ovarian cancer and 6,274 hospital controls under age 70 years. A reduced risk of ovarian cancer was found for ever- compared to never-users [odds ratio (OR) = 0.66, 95% confidence interval (CI) 0.56–0.79], and a stronger reduction was observed for women who had used OCs for ≥5 years (OR = 0.50, 95% CI 0.33–0.76) compared to those who had used them for <5 years. The protective effect of OCs on ovarian cancer was consistent across strata of age, parity, menopausal status and family history of breast or ovarian cancer. After allowance for duration of use, no other time factor was related to ovarian cancer risk: the reduced risk was similar for women who stopped OC use ≥20 years before compared to <10 years; likewise, no significant modification of risk reduction was observed for age at first OC use and time since first OC use. The present analysis indicates that, after taking into account duration of OC use, the OC protection from ovarian cancer persists for a long time after stopping use.

Key words: *ovarian cancer; oral contraceptive; case-control study*

Epidemiologic studies conducted since the late 1970s have reported a protective effect of oral contraceptives (OCs) from ovarian cancer and a stronger reduction of risk for longer duration of use.[1–3] An indication of a favorable impact of OC on ovarian carcinogenesis comes also from descriptive epidemiology. In several developed countries, young women have shown substantial decreases in incidence of and mortality from ovarian cancer, and the downward trends are greater in countries where OCs are widely used.[4–7]

However, there remain open issues on the relation between OC use and ovarian cancer, including a better quantification of time-related factors, notably time since last use, age at first use and time since first use. Some of the studies that have considered time since last OC use have reported that the favorable effect of OCs on ovarian cancer risk persists for at least 15 years after stopping use.[2,8–11] A few studies, however, have assessed the risk with longer time since last use.[12–16] A cohort analysis of ovarian cancer incidence and mortality rates in U.S. women over the period 1970–1995[7] indicated that the relative decrease in incidence is greater before age 50. There is, therefore, a suggestion that the protection declines with time since last use, but the data are inconclusive.[2] In addition, few studies have simultaneously addressed all time factors, so the possibility of residual confounding in some of these studies cannot be excluded.

To clarify the time relation between OC use and ovarian cancer risk, we conducted a collaborative reanalysis of European case-control studies of epithelial ovarian cancer.

MATERIAL AND METHODS

In the present analysis, data from 6 case-control studies conducted in the United Kingdom, Greece and Italy were combined, *i.e.,* all studies on OC and ovarian cancer published from Europe. The study design and methods have already been described.[12] Briefly, the first was a hospital-based investigation conducted in London and Oxford, UK, between 1978 and 1983.[17] Cases were 235 women under 65 years of age with epithelial ovarian cancer; controls were 451 women of comparable age, hospitalized for gastrointestinal diseases (23%), bone or joint diseases including fractures (22%) and a large number of other diagnostic categories, each including <10% of the total number of controls.

The second study included 150 patients with malignant epithelial tumors of the ovary, admitted during 1980 and 1981 to 10 large hospitals of the Greater Athens area, Greece,[18] and 250 controls of similar age, hospitalized in the same time period in Athens hospitals for orthopedic conditions (among which 62% were traumas).

The third study included 189 cases of epithelial ovarian cancer admitted to 2 major hospitals in Athens between 1989 and 1991.[19] Controls were 200 women, resident in the Greater Athens area, visitors of patients hospitalized in the same ward as cases in the same time period. Both cases and controls were below 75 years of age.

The fourth study was a hospital-based investigation conducted in the Greater Milan area, northern Italy, comprising a total of 971 patients under 75 years of age with epithelial cancer of the ovary, admitted between 1983 and 1991 to the National Cancer Institute and the Ospedale Maggiore.[20] The control group included 2,578 women admitted to the same network of hospitals for acute conditions (34% traumas, 30% nontraumatic orthopedic disorders, 16% surgical conditions and 20% other miscellaneous diseases). Controls were comparable to cases in terms of age and area of residence.

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The fifth study was conducted between 1992 and 1999 in 4 Italian areas, including Greater Milan, the provinces of Pordenone, Padua and Gorizia (northern Italy), the province of Latina (central Italy), and the urban area of Naples (southern Italy).[21] Cases were 1,031 women under 79 years of age with incident ovarian cancer admitted to major teaching and general hospitals in the areas under study. Controls were 2,411 women resident in the same geographic areas and admitted to the same network of hospitals as cases for acute, non-neoplastic conditions unrelated to known or potential risk factors for ovarian cancer (26% traumas, 28% nontraumatic orthopedic disorders, 15% surgical conditions and 31% miscellaneous other illnesses).

The last study was another Italian investigation, including 440 women with a diagnosis of epithelial ovarian cancer admitted between 1988 and 1998 to the Department of Gynecologic Oncology of the Catholic University Hospital in Rome.[22] Controls were 868 women admitted to the same hospital for acute, nongynecologic, nonhormonal and non-neoplastic conditions (29% traumatic conditions, 21% nontraumatic orthopedic disorders, 17% acute abdominal diseases and 33% other miscellaneous disorders).

Only women under 70 years of age were considered in the present analysis, which thus includes a total 2,768 histologically confirmed epithelial ovarian cancer cases and 6,274 corresponding controls.

Data analysis

From the 6 original data sets, a single file was obtained, including comparable variables coded in a uniform format. These included age, an indicator of sociocultural level (based on social class[17–19] or education[20–22]), age at interview, parity, menopausal status, age at menopause and various indicators of OC use. Information on OC use (ever/never) was provided by all studies, whereas information on duration of OC use was provided by all except the first Greek study[18] and age at first OC use was given only in the UK[17] and the 3 Italian studies.[20–22] Data on family history of breast or ovarian cancer in first-degree relatives were available only in the 3 Italian studies.

Odds ratios (ORs) for various indicators of OC use and the corresponding 95% confidence intervals (CIs) were estimated using an unconditional logistic regression model,[23] including terms for study center, age, year of interview, sociocultural level, parity, menopausal status and age at menopause.

RESULTS

Table I gives the distribution of 2,768 ovarian cancer cases and 6,274 controls according to age and other selected variables. The age distribution was similar for cases and controls. Cases had a higher socioeducational level, were more frequently nulliparous, reported a later age at menopause and a more frequent history of breast or ovarian cancer in first-degree relatives.

The relation between various indicators of OC use and ovarian cancer risk is presented in Table II. Overall, 9.2% of ovarian cancer cases and 13.2% of controls were ever-users of OCs, corresponding to an OR of 0.66 (95% CI 0.56–0.79), compared to never-users.

The protective effect of OCs against ovarian cancer was consistent across study centers, though the proportion of ever-users ranged between 21.7% in the U.K. study and 4.6% in the 2 Greek studies combined. Furthermore, no meaningful or consistent differences in the apparent favorable effect were observed when strata of age, parity, menopausal status and family history of breast or ovarian cancer were considered (Fig. 1).

A stronger reduction of ovarian cancer risk was found for women who had used OCs for a longer period (OR = 0.83, 95% CI 0.69–1.01 for duration of use <5 years; OR = 0.42, 95% CI 0.30–0.59 for duration of use ≥5 years, with a significant trend of decreasing risk). The beneficial effect on ovarian cancer was observed for at least 20 years since last OC use (OR = 0.77, 95% CI 0.51–1.16 15–19 years after stopping OC use). Ovarian cancer risk was lower for women reporting first use before 25 years of age (OR = 0.59, 95% CI 0.42–0.83) and after 15 years from first OC use (OR = 0.66, 95% CI 0.51–0.86), though these estimates could partly confounded by duration of use.

TABLE I – DISTRIBUTION OF 2,768 OVARIAN CANCER CASES AND 6,274 CONTROLS ACCORDING TO AGE AND SELECTED VARIABLES

	Cases		Controls	
	Number	%	Number	%
Age (years)				
<40	318	11.5	933	14.9
40–49	637	23.0	1,495	23.8
50–59	1,015	36.7	1,983	31.6
60–69	798	28.8	1,863	29.7
Sociocultural level[1]				
Low	1,378	50.0	3,210	51.4
Medium	795	28.9	1,909	30.6
High	581	21.1	1,121	18.0
Parity[1]				
0	621	22.5	1,176	18.8
1	499	18.1	1,308	20.9
2	924	33.6	2,055	32.8
≥3	710	25.8	1,730	27.6
Menopausal status[1]				
Pre/peri	1,048	38.0	2,552	40.7
Post	1,708	62.0	3,717	59.3
Age at menopause[1] (year)				
<50	765	0.65	1,863	0.50
≥50	924	0.55	1,838	0.50
Family history[2]				
No	1,990	89.1	5,104	94.2
Yes	243	10.9	312	5.8

[1]The sum does not add up to the total because of some missing values.–[2]Family history of breast or ovarian cancer in first-degree relatives. Based only on Parazzini *et al.*,[20] Chiaffarino *et al.*,[21] and Greggi *et al.*[22]

When analyses were restricted to ever-users and allowance was made for duration of OC use (Table III), no other time factor was related to ovarian cancer risk: the reduced risk was similar for women who stopped OC use ≥20 years before compared to <10 years (OR = 0.81, 95% CI 0.40–1.66). Likewise, no significant pattern of risk was observed for age at first OC use (OR = 1.04, 95% CI 0.56–1.92 for age at first use ≥35 years compared to <25 years) and time since first OC use (OR = 0.67, 95% CI 0.41–1.09 for ≥15 years since first use compared to <10 years).

DISCUSSION

The present analysis, conducted on the largest data set to date of ovarian cancer, confirms the beneficial effect of OCs on ovarian cancer and the stronger protection provided by a long duration of use.[2,3] Inadequate information was, however, available on the possible role of other time-related factors, in particular the persistence of any reduced risk long after stopping OC use. Our study thus allows meaningful analyses of these time-related factors, with specific reference to the absence of any attenuation of protection with time since last OC use.

The protective effect of OCs was consistent in all studies included in the analysis, notwithstanding the differences in the prevalence of OC use, lifestyle and reproductive characteristics of women from the various countries. Moreover, the inverse relation between OC use and ovarian cancer was not confounded by age, education and other risk factors for ovarian cancer, including nulliparity, menopausal status and age at menopause. In particular, when we analyzed the effect of OC use separately among nulliparous and parous women, no significant difference in the magnitude of protection was observed. This indicates that OCs are unlikely to be simply an indirect marker of parity and fertility,[11,24] which are inversely related to the risk of ovarian cancer.[1,13] Furthermore, an inverse relation between OC use and ovarian cancer risk was present in women with and without a family history of breast or ovarian cancer.[25,26]

TABLE II – DISTRIBUTION OF OVARIAN CANCER CASES AND CONTROLS ACCORDING TO SELECTED INDICATORS OF OC USE AND CORRESPONDING OR AND 95% CI

	Cases	Controls	OR[1] (95% CI)
OC use[3]			
Never	2,476	5,444	1[2]
Ever	255	830	0.66 (0.56–0.79)
Duration of OC use[3,4] (months)			
Never	2,347	5,251	1[2]
<60	202	539	0.83 (0.69–1.01)
≥60	46	242	0.42 (0.30–0.59)
χ^2 trend (*p* value)			24.56 (<0.0001)
Time since last OC use[3,5] (years)			
Never	1,876	4,492	1[2]
<10	95	288	0.74 (0.57–0.98)
10–14	44	138	0.75 (0.52–1.08)
15–19	38	113	0.77 (0.51–1.16)
≥20	27	52	0.86 (0.50–1.47)
Age at first OC use[3,5] (years)			
Never	1,876	4,492	1[2]
<25	54	216	0.59 (0.42–0.83)
25–34	103	299	0.80 (0.61–1.03)
≥35	48	120	0.73 (0.51–1.07)
Time since first OC use[3,5] (years)			
Never	1,876	4,492	1[2]
<10	69	182	0.90 (0.65–1.25)
10–14	39	150	0.64 (0.44–0.94)
≥15	97	303	0.66 (0.51–0.86)

[1]Estimates from unconditional logistic regression models, including terms for age, study center, year of interview, sociocultural level, parity, menopausal status and age at menopause.–[2]Reference category.–[3]The sum does not add up to the total because of some missing values.–[4]Information not provided by Tzonou *et al.*[18]–[5]Information not provided by Tzonou *et al.,*[18] Polychronopoulous *et al.*[19] and Greggi *et al.*[22]

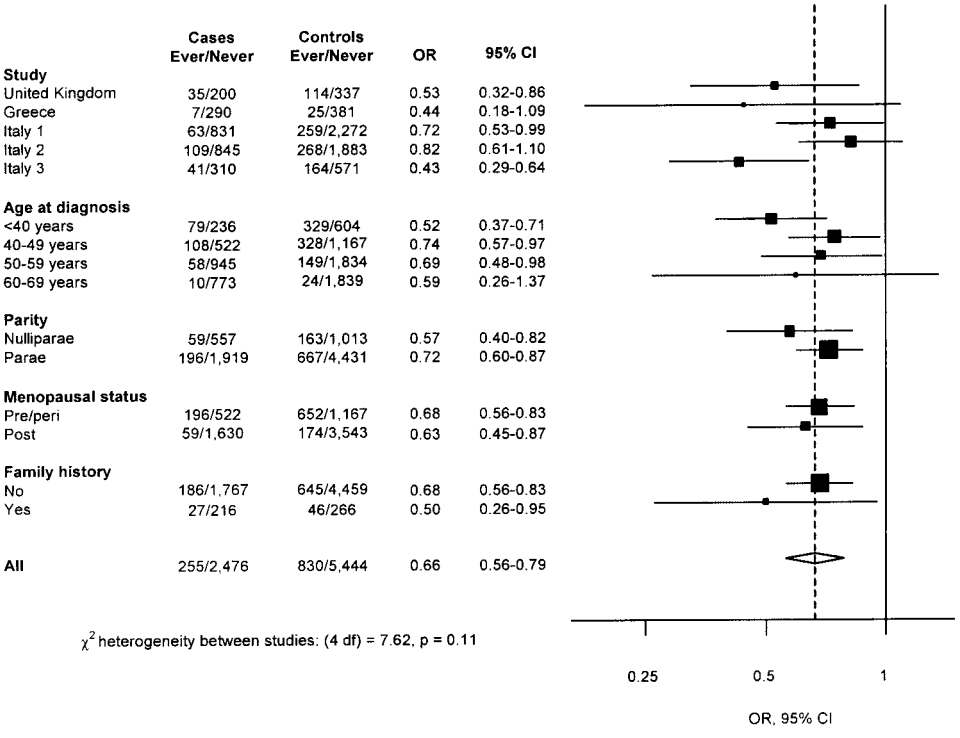

FIGURE 1 – ORs of ovarian cancer and 95% CIs for ever- compared to never-users of OCs in strata of study and selected covariates. Estimates from unconditional logistic regression models included terms for age, study center, year of interview, sociocultural level, parity, menopausal status and age at menopause.

With regard to time-related factors, the present analysis shows that OCs convey protection for a long time after stopping use (at least 20 years). An apparent leveling off of this effect after 20 years since last use was no more evident after taking into account duration of use. Long-term protection from OCs has been reported,[8–11] though only a few studies had the opportunity to observe long time intervals between OC use cessation and ovarian cancer occurrence.[12,13,15,16] Also, no attempt has previously been made to simultaneously control for duration of OC use and other time-related factors.

In our investigation, women who started using OCs at younger ages and reported a longer time since first use had an apparent stronger protection, which, however, appeared to be mainly attributable to a longer duration of use. Among the few studies that considered these time-related factors, 2 reported that age at first use was unrelated to ovarian cancer risk.[16,27]

TABLE III – OR AND 95% CI ACCORDING TO SELECTED INDICATORS OF OC USE IN EVER-USERS ONLY

	OR[1] (95% CI)
Duration of OC use[2] (months)	
<60	1[3]
≥60	0.50 (0.33–0.76)
Time since last OC use[4] (years)	
<10	1[3]
10–14	0.86 (0.54–1.37)
15–19	0.77 (0.45–1.33)
≥20	0.81 (0.40–1.66)
Age at first OC use[4] (years)	
<25	1[3]
25–34	1.12 (0.71–1.76)
≥35	1.04 (0.56–1.92)
Time since first OC use[4] (years)	
<10	1[3]
10–14	0.76 (0.46–1.25)
≥15	0.67 (0.41–1.09)

[1]Estimates from unconditional logistic regression models, including terms for age, study center, year of interview, sociocultural level, parity, menopausal status, age at menopause and duration of OC use. Numbers of cases and controls are given in Table II.–[2]Information not provided by Tzonou *et al.*[18]–[3]Reference category.–[4]Information not provided by Tzonou *et al.,*[18] Polychronopoulous *et al.*[19] and Greggi *et al.*[22]

Among the limitations of our analysis are the absence of information on the potency of progestin and estrogen[28] and the potential weaknesses of the original case-control studies, including a possible biased recall of past OC use and the possibility of more careful surveillance of ovarian diseases in OC users; these biases, however, were considered minor by the authors of the original studies. Moreover, the consistency of results across various study designs and populations weighs against the existence of major bias. The advantage of our study is the possibility of comparing and analyzing different data sets using a uniform format, while the large data set allows more precise estimates and simultaneous allowance of various time-related factors.

In conclusion, our study further quantifies the degree of protection conveyed by OCs on ovarian carcinogenesis and documents its inverse relation with longer duration of use. It also indicates that, after taking into account duration of OC use, the protection persists for a long time after stopping OC use, whereas other time-related factors appear to be unrelated to ovarian cancer risk. The persistence of long-term protection from OCs against ovarian cancer has major implications for individual risk assessment and for public health since the incidence of ovarian cancer rises with age and the disease is over 10-fold more frequent at age 60 than at age 30.[29]

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