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Risk Factors for Epithelial Ovarian Cancer in Women Under Age 45

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Risk factors for ovarian cancer in young women were investigated using data from a case–control study conducted between 1983 and 1992 in Milan, northern Italy, on 194 women below age 45 with histologically confirmed incident cancers of the ovary and 710 controls admitted to the same network of hospitals for acute non-gynecological, non-hormonal and non-neoplastic diseases. An elevated relative risk (RR) of ovarian cancer was found among women reporting 12 or more years of education [RR 1.6, 95% confidence intervals (CI) 1.0–2.03] and belonging to the highest social class (RR 1.8, 95% CI 1.1–3.0). Women whose mothers had had ovarian cancer had a multivariate RR of 2.7 (95% CI 0.7–10.5) compared to those with no family history. Menarche above age 13 and irregular menstrual cycles were significantly protective against ovarian cancer (RR 0.6 for both risk factors). There was a significant inverse relationship with abortions, the RR being 0.6 both for spontaneous and for induced abortions, while protection of parity was not significant. Higher risks of ovarian cancer were observed in women having first or last birth when older than 30 years (RR 2.0 and 2.4, respectively, compared to those delivering under age 25). A significant trend toward an increased risk of ovarian cancer was also observed with decreasing time since last birth. Compared with women whose last birth occurred 10 or more years before diagnosis, the RR was 2.1 (95% CI 1.1–3.9) for those reporting a birth during the last 5 years. The RR for oral contraceptive users was 0.7 (95% CI 0.5–1.0) and the protection increased with duration, with RR of 0.3 (95% CI 0.1–0.7) for 5 or more years of use. This study indicates that, although the incidence of ovarian cancer is higher in older women, recognised risk and protective factors are similar below age 45. An excess risk in the few years after a term delivery is also suggested. *Eur J Cancer*, Vol. 29A, No. 9, pp. 1297–1301, 1993.

INTRODUCTION

IN DEVELOPED areas of the world ovarian cancer is common, being among the five leading sites of incidence and mortality in most countries [1–3]. Several studies have assessed the role of menstrual, reproductive and hormonal factors on ovarian cancer and a few aspects of its epidemiology are now well understood [3]. Ovarian cancer has been inversely associated with parity [4] and oral contraceptive (OC) use [5, 6]. Early age at first pregnancy and abortions are also potential weak protective factors [4], while family history of ovarian cancer increases the risk [7–9]. A positive association of ovarian cancer with late age at menopause has been shown in several although not all studies [3], while evidence for a detrimental effect of early age at menarche is less consistent. [10, 11].

Information on the determinants of ovarian cancer in women below age 45 is scanty; trends over the past 20 years in developed countries show substantial declines in ovarian cancer mortality in young women, possibly because of the protection afforded by OC use [12, 13]. Only one study [14], to our knowledge, was restricted to ovarian cancer under age 50, and suggested that the number of live births, number of incomplete pregnancies and OC use were protective factors. However, only the combination of those factors in a total measure of "anovulatory" or "protected time" showed a significant inverse association. Thus, in the present study we investigated and quantified risk factors for ovarian cancer in young women, focusing on the role of family history of ovarian cancer, menstrual and reproductive factors and OC use, using data from a case–control study conducted in Milan, northern Italy.

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Table 1. Distribution of 194 cases of ovarian cancer and 710 controls according to age, education and social class. Milan, Italy, 1983–1992

	Ovarian cancer		Controls	
	No.	%	No.	%
Age (years)				
< 25	21	10.8	80	11.2
25–29	23	11.9	56	7.9
30–34	28	14.4	107	15.1
35–39	45	23.2	208	29.3
40–44	77	39.7	259	36.5
Education (years)				
< 7	53	27.3	231	32.5
7–11	69	35.6	262	36.9
≥ 12	72	37.1	217	30.6
Social class*				
Low	58	33.3	257	39.9
Medium	84	48.3	311	48.2
High	32	18.4	77	11.9

* Missing data: 20 in the case and 65 in the control group; based on the head of the household's occupation.

SUBJECTS AND METHODS

Data were derived from an ongoing case–control study of ovarian cancer, based on women admitted between January 1983 and April 1992 for the neoplasm under study (cases) and for a wide spectrum of other conditions (controls) to a network of teaching and general hospitals in the greater Milan area. On average, less than 2% of the eligible women (cases or controls) refused to be interviewed. Trained interviewers identified and questioned cases and controls using a structured questionnaire, including information on personal and family characteristics and habits, education and socioeconomic factors, gynaecological data, related medical history and history of lifetime use of OC, including time and duration of use. Questions on reproductive factors included number of full-term pregnancies and spontaneous and voluntary abortions (defined as any pregnancy terminated earlier than 28 weeks), age at first pregnancy and at first and last birth.

Cases

Cases were women with histologically confirmed epithelial cancers of the ovary, 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). There were 194 incident cases below the age of 45 (median age 38 years, range 16–44) diagnosed within the year preceding the interview.

Controls

Controls were women residing in a comparable geographical area and admitted for acute conditions to the same network of hospitals where cases had been identified. Women were not included if they had been admitted for gynaecological, hormonal or neoplastic disease, and had undergone hysterectomy and/or bilateral oophorectomy. A total of 710 controls below age 45 (median age 38 years, range 15–44) were interviewed. They were admitted to hospital for a wide spectrum of acute diseases (37% traumas, 13% other orthopedic disorders, 40% acute surgical conditions, 10% miscellaneous other diseases).

Data analysis

Relative risks (RR) of ovarian cancer and the corresponding 95% confidence intervals (CI) in relation to socioeconomic factors, family history of ovarian cancer, menstrual and reproductive factors and OC use were estimated, after adjustment for age, by the method described by Mantel and Haenszel [15]; for multiple levels of exposure, the significance of the linear trend in risk was assessed by the Mantel test [16]. Unconditional multiple logistic regression, fitted by the method of maximum likelihood, was used to allow for several possible confounding factors [16]. The regression models included terms for age, education, family history, number of births, number of abortions, OC use and, in turn, age at menarche, menstrual cycles, age at first and at last birth, time since last birth and duration of OC use.

RESULTS

Table 1 shows the distribution of cases of ovarian cancer and controls according to age group, educational level and social class. The risk was significantly higher among women reporting 12 or more years of education (RR 1.6, 95% CI 1.0–2.3) and was also higher among women from the highest social class (RR 1.8, 95% CI 1.1–3.0).

A tendency towards a positive association between family history of ovarian cancer and cancer risk was observed, although it did not reach statistical significance (Table 2). There were 4 cases whose mothers had had ovarian cancer compared with 5 controls, the corresponding RR being 2.7 (95% CI, 0.7–10.5).

The relationship between menstrual history and ovarian cancer is presented in Table 3. Compared to women whose menarche occurred below age 13, those having menarche at a later age showed significant protection (RR = 0.6) and the trend in risk was significant. Irregular menstrual cycles were also protective against ovarian cancer (RR = 0.6, 95% CI 0.3–1.0).

Table 2. Distribution of ovarian cancer cases and controls and relative risk estimates according to family history. Milan, Italy, 1983–1992

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M–H*	Multivariate†
Family history of ovarian cancer				
No	190	705	1‡	1‡
Mother	4	5	3.1 (0.9–10.7)	2.7 (0.7–10.5)

* Mantel–Haenszel estimates adjusted for age.

† Estimates from multiple logistic regression; allowance was made for age, education, family history, number of births, number of abortions and OC use.

‡ Reference category.

Table 3. Distribution of ovarian cancer cases and controls and relative risk estimates according to menstrual history. Milan, Italy, 1983–1992

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M–H*	Multivariate†
Age at menarche‡				
≤ 12	116	337	1§	1§
13–14	64	305	0.6 (0.4–0.9)	0.6 (0.4–0.9)
≥ 15	13	67	0.6 (0.3–1.1)	0.6 (0.3–1.1)
χ^2 (trend)			8.21 (P = 0.005)	8.04 (P = 0.005)
Menstrual cycles‖				
Regular	177	600	1§	1§
Irregular	17	109	0.5 (0.3–0.9)	0.6 (0.3–1.0)

* Mantel–Haenszel estimates adjusted for age.
† Estimates from multiple logistic regression; allowance was made for age, education, family history, number of births, number of abortions and OC use.
‡ Missing data: 1 in the case and 1 in the control groups.
§ Reference category.
‖ Missing data: 1 in the control group.

Obstetric history is considered in Tables 4 and 5. The RR was 0.8 (0.6–1.1, 95% CI) for women with one or more children compared to nulliparae, and RR of 0.7–0.8 were found considering separately one, two or three and more births. A significant trend towards higher risks was observed with increasing age at first and at last birth (Table 4), with statistically significant RR for age over 30 for both variables (RR 2.0 and 2.4 for ≥ 30 vs. < 25 years). Abortions proved significantly protective, the RR being 0.6 both for spontaneous and induced abortions, and there was a significant inverse trend in risk with total number of abortions. The risk estimates for abortions and full-term births were both modified towards unity in the multivariate analysis: only the trends for age at last birth and abortions remained significant.

Table 4. Distribution of ovarian cancer cases and controls and relative risk estimates according to obstetric history. Milan, Italy, 1983–1992

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M–H*	Multivariate†
No. of births				
0	70	216	1‡	1‡
1	46	184	0.8 (0.5–1.2)	0.9 (0.6–1.4)
2	54	213	0.7 (0.4–1.1)	1.0 (0.6–1.7)
≥ 3	24	97	0.7 (0.4–1.3)	1.1 (0.6–2.0)
χ^2 (trend)			1.01 (P = 0.300)	0.10 (P = 0.764)
Total no. of abortions				
0	156	493	1‡	1‡
1	20	122	0.5 (0.3–0.9)	0.6 (0.4–0.9)
≥ 2	18	95	0.6 (0.4–1.0)	0.6 (0.3–1.4)
χ^2 (trend)			6.67 (P = 0.012)	5.78 (P = 0.016)
Age at first birth§‖				
< 25	62	290	1‡	1‡
25–29	40	158	1.3 (0.8–2.0)	1.0 (0.6–1.7)
≥ 30	22	44	2.5 (1.4–4.5)	2.0 (1.1–3.7)
χ^2 (trend)			8.01 (P = 0.005)	3.00 (P = 0.084)
Age at last birth§¶				
< 25	23	135	1‡	1‡
25–29	48	214	1.4 (0.9–2.4)	1.3 (0.7–2.4)
≥ 30	52	143	2.0 (1.1–3.7)	2.4 (1.3–4.5)
χ^2 (trend)			12.06 (P < 0.001)	8.76 (P = 0.003)

* Mantel–Haenszel estimates adjusted for age.
† Estimates from multiple logistic regression; allowance was made for age, education, family history, number of births, number of abortions and OC use.
‡ Reference category.
§ Calculated omitting nulliparae.
‖ Missing data: 2 in the control group.
¶ Missing data: 1 in the case group and 2 in the control group.

Table 5. Distribution of ovarian cancer cases and controls and relative risk estimates, according to time since last birth in parous women only. Milan, Italy, 1983–1992

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M-H*	Multivariate†
Time since last birth (years)§				
> 10	51	263	1‡	1‡
> 5–10	35	139	1.3 (0.7–2.1)	1.4 (0.8–2.4)
≤ 5	37	90	2.5 (1.4–4.4)	2.1 (1.1–3.9)
χ^2 (trend)			7.00 (P = 0.008)	5.64 (P = 0.018)

* Mantel–Haenszel estimates adjusted for age.
† Estimates from multiple logistic regression; allowance was made for age, education, family history, number of births, number of abortions and OC use.
‡ Reference category.
§ Calculated omitting the nulliparae. Missing data: 1 in the case and 2 in the control groups.

Time since last birth in parous women only is considered in Table 5. A significant trend toward an increased risk of ovarian cancer was observed with decreasing time since last birth. Compared to women whose last birth was 10 or more years earlier, the RR was 1.3 for those reporting a birth from 5 to 10 years before diagnosis or interview and 2.5 for those reporting the last birth within the last 5 years. This association was not materially modified by multivariate analysis, including allowance for parity. Considering the two classes 0–1 and 2–4 years since last birth separately, the RR adjusted for age were, respectively, 3.3 (0.9–12.6, 95% CI) and 2.2 (1.2–4.3, 95% CI).

Measures of OC use are considered in Table 6. A total of 41 (21%) cases and 199 (28%) controls had used OC. The RR for OC users was 0.7 (95% CI 0.5–1.0) and the protection increased with duration, with RR of 0.1 for a use of ≥ 5 years. The trend in risk with duration was significant, although the longest category of use included only 2 cases and 46 controls. The inverse association with OC use remained significant after allowance for major identified covariates.

DISCUSSION

This study indicates that several risk and protective factors for epithelial ovarian cancer are similar in young women and in other age groups [3]. Risk factors were high educational and social status, later age at first and at last birth and, although based on a small number of subjects, family history of ovarian cancer; protective factors were older age at menarche, irregular menstrual cycles, abortions and OC use. Moreover, in this population of young women it was possible to study the relation between ovarian cancer and time since last birth, suggesting that the risk of ovarian cancer was elevated in the few years after a full-term birth.

A potential limitation of this study is its hospital-based design, with all the consequent implications, such as the use of hospital controls, which can be open to debate [15]. These results, however, could not be explained in terms of selection, information or confounding bias, since the catchment areas of cases and controls were well comparable, participation was almost complete, information is particularly reliable in young women, and allowance for several confounding factors did not notably modify the relative risk estimates.

The association between menstrual and reproductive factors and OC use and epithelial ovarian cancer has been extensively explored in aetiological terms [3] and there is a wide consensus that parity [4, 17, 18] and OC use [5, 6, 14, 19] are protective, and that a family history of ovarian cancer [3, 20] and late age at

Table 6. Distribution of ovarian cancer cases and controls and relative risk estimates according to oral contraceptive use. Milan, Italy, 1983–1992

	Ovarian cancer	Controls	Relative risk estimates (95% CI) M-H*	Multivariate†
Oral contraceptive use				
Never	153	511	1‡	1‡
Ever	41	199	0.7 (0.5–1.0)	0.7 (0.5–1.0)
Duration of use (years) §				
≤ 2	27	107	0.8 (0.5–1.3)	0.9 (0.5–1.4)
> 2–< 5	12	43	0.9 (0.5–1.8)	1.1 (0.5–2.4)
≥ 5	2	46	0.1 (0.04–0.5)	0.3 (0.1–0.7)
χ^2 (trend)			6.83 (P = 0.009)	6.48 (P = 0.012)

* Mantel–Haenszel estimates adjusted for age.
† Estimates from multiple logistic regression; allowance was made for age, education, family history, number of births, number of abortions and OC use.
‡ Reference category.
§ Missing data: 3 in the control group.

menopause [11] increase risk, while evidence is less consistent and weak, at most, on the effects of age at menarche [11] and first birth [21, 22].

In terms of mechanisms of ovarian carcinogenesis, menstrual and reproductive factors and OC use were suggested to act on ovarian cancer risk by affecting lifetime number of ovulations, according to the hypothesis of Fathalla [21] subsequently formalised by Casagrande *et al.* [14], who proposed that ovulation could be the relevant exposure that defines the incidence of the neoplasm. This study confirmed the association of some protection of abortion (both spontaneous and induced) and parity, but the absence of linear trend in risk, and the observation that age at first or last birth and time since last birth may have a role on ovarian carcinogenesis in young women suggest a more complex mechanism.

The elevated risk in the few years following a full-term birth probably cannot be explained by allowance in the age distribution of cases and controls or by a closer surveillance in the period following pregnancy and birth, as shown considering separately 0–1 and 2–4 years since last birth, and has, therefore, no simple explanation. It may possibly indicate, however, that some (hormonal) modification induced by pregnancy and birth is associated with some short-term (perinatal) effect on ovarian carcinogenesis. Although of little relevance on a public health scale, this finding, if confirmed, could have interesting implications on an aetiological level, since it could shed light on some more complex aspects of ovarian carcinogenesis.

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