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Original Paper

Ovarian Cancer Risk and History of Selected Medical Conditions Linked with Female Hormones

F. Parazzini,[1,2] S. Moroni,[2] C. La Vecchia,[1,3] E. Negri,[1] D. dal Pino[4] and G. Bolis[2,4]

[1]Istituto di Ricerche Farmacologiche 'Mario Negri', via Eritrea, 62-20157 Milan; [2]Clinica Ostetrico-Ginecologica, Università degli Studi di Milano, 20129 Milan; [3]Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, 20133 Milan; and [4]Divisione di Oncologica Ginecologica, Istituto Nazionale Tumori, Milan, Italy

To investigate the role of selected medical conditions on the risk of ovarian cancer, we analysed data from a case-control study. Cases were 971 women below the age of 75 years with histologically confirmed epithelial ovarian cancer, admitted to a network of hospitals including the major teaching and general hospitals in the greater Milan area. Controls were 2758 women admitted to the same network of hospitals for acute, non-gynaecological, non-hormone related, non-neoplastic conditions. Obesity/severe overweight were inversely associated with the risk of ovarian cancer (multivariate relative risk, RR, 0.66, 95% confidence interval, CI, 0.52–0.85). Hyperlipidaemia was also inversely related to ovarian cancer risk, (RR 0.64, 95% CI 0.45–0.89). No relationship emerged between ovarian cancer risk and diabetes (RR 0.80, 95% CI 0.54–1.19), hypertension (RR 0.85, 95% CI 0.68–1.06), thyroid diseases (RR 0.89, 95% CI 0.63–1.13) and cholelithiasis (RR 0.86, 95% CI 0.66–1.12). A decreased frequency of ovarian cancer was seen in women with a history of uterine leiomyomas (RR 0.66, 95% CI 0.47–0.92) and benign ovarian cysts (RR 0.69, 95% CI 0.41–1.13). © **1997 Elsevier Science Ltd.**

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INTRODUCTION

SEVERAL STUDIES have analysed the relationship between various medical conditions and the risk of ovarian cancer [1–7]. An increased frequency of ovarian cancer in women with a history of uterine myomas has been reported in a case-control study conducted in China [6]. Hypertension was reported to be less frequent in ovarian cancer cases in a study conducted in the late 1960s in the U.S. [1], but inconsistent results emerged from other studies [4, 8]. A Polish study reported an increased risk of endometrioid ovarian cancer in hypertensive women [8]. Obesity and overweight have also been associated with an increased risk of ovarian cancer [1, 9]. The standardised mortality ratio (SMR) of ovarian cancer was 1.6 for obese women in the American Cancer Society (ACS) cohort study [9]. However, findings from other studies are limited and inconsistent [1, 10].

Despite this scattered evidence, there are biological considerations that might explain an association between several medical conditions and the risk of ovarian cancer. Female hormones may be related to ovarian carcinogenesis [7] and hormonal levels are altered in several medical conditions, including diabetes, hypertension and disease of the female genital tract, thyroid, liver and gall bladder [11, 12]. Further, these conditions are related to age, sex, and variables such as parity and age at first birth and at menopause, that are recognised risk factors for ovarian cancer [7].

In order to understand better the role of several medical conditions on the risk of ovarian cancer, we analysed the findings of a large case-control study of ovarian cancer where cases and controls were specifically asked about any history of medical conditions potentially related to female hormones and about a large number of covariates.

PATIENTS AND METHODS

Between 1983 and 1991, we conducted a case-control study of ovarian cancer [13]. Briefly, cases were women

Correspondence to F. Parazzini.
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below the age of 75 years with histologically confirmed epithelial ovarian cancer diagnosed within the year before the interview. They were admitted to the Milan University Obstetrics and Gynaecology Clinics, to the National Cancer Institute and to the Ospedale Maggiore of Milan (including the major teaching and general hospitals in the greater Milan area). All cases with these characteristics were eligible for the study. A total of 971 cases (median age 54 years, range 22–74) entered the study.

Controls were women admitted to the same network of hospitals, where cases had been identified, for acute, non-gynaecological, non-hormone-related, non-neoplastic conditions. A total of 2758 controls (median age 52 years, range 23–74) was included in the present analysis. Of these, 34% were admitted for traumatic conditions, 30% for non-traumatic orthopaedic disorders (such as lower back pain or disc disorders), 16% for acute surgical conditions (mostly abdominal) and 20% for other illnesses, such as ear, nose, throat or dental disorders. Controls were identified on randomly selected days. All women with the characteristics indicated above were eligible; the protocol only indicated that the age distribution in quinquennia of cases and controls had to be checked every six months to maintain a similar distribution.

A standard questionnaire was used to obtain information on socio-demographic factors, general characteristics and habits, gynaecological and obstetric data. Information was specifically elicited, using a structured questionnaire, on history of 11 medical conditions or procedures, selected on the basis of their known or suspected relationship to female hormones. Severe overweight included only clinically relevant overweight. Diabetes, hypertension, thyroid diseases and hyperlipidaemia included treated conditions only. History of benign female conditions was based on clinical diagnosis. Whenever useful, information given by the patient was checked with the medical records. Overall participants was over 95% for *identified* cases and controls.

Data analysis

Odds ratios, as estimators of relative risks (RR), of ovarian cancer, together with their 95% confidence intervals (CI), were computed using unconditional multiple logistic regression, fitted by the method of maximum likelihood [14]. Included in the regression equations were terms for (i) age only and (ii) age, education, parity, menopausal status and, in turn, the various medical conditions considered.

RESULTS

The distribution of cases and controls according to age and selected covariates is given in Table 1. Cases were more frequently nulliparae and less frequently in post-menopause than controls. These variables, therefore, were included in the regression equations.

The effects of selected diseases on ovarian cancer risk are given in Table 2. Clinical history of severe obesity or overweight was inversely associated with the risk of ovarian cancer (multivariate RR 0.66, 95% CI 0.52-0.85, $P = 0.001$). In consideration of the potential association between obesity, overweight and traumatic/orthopaedic disorders, we also analysed the association between severe obesity/overweight after exclusion from the control groups of those with traumatic/orthopaedic disorders: the estimated multivariate RR was 0.6 (95% CI 0.5–0.8).

Hyperlipidaemia was also inversely related to ovarian cancer risk. No relationship emerged between ovarian cancer risk and diabetes, hypertension, thyroid diseases and cholelithiasis.

A decrease in the frequency of ovarian cancer was seen in women with a history of uterine leiomyomas (RR 0.66, 95% CI 0.47–0.92 $P = 0.002$) and benign ovarian cysts (RR

Table 1. Distribution of 971 cases of ovarian cancer and 2758 controls according to age and selected factors. Milan, Italy, 1983–1991

	Ovarian cancer	Controls	RR (95% CI) Age adjusted	RR (95% CI) MLV*
Age (years)				
<45	200	727		
45–54	305	739		
55–64	312	751		
≥65	154	541		
Education (years)				
<7	558	1591	1†	1†
7–11	233	686	1.01 (0.84–1.21)	1.03 (0.85–1.25)
≥12	178	479	1.08 (0.87 1.35)	1.09 (0.87–1.36)
Unknown	2	2		
Parity				
0	237	590	1†	1†
1	204	660	0.77 (0.61–0.96)	0.78 (0.62–0.99)
2	301	836	0.87 (0.71–1.10)	0.89 (0.72–1.11)
≥3	226	666	0.80 (0.66–1.00)	0.81 (0.64–1.03)
Unknown	3	6		
Menopausal status				
Pre-menopausal	384	1084	1†	1†
Post-menopausal	584	1673	0.67 (0.51–0.89)	0.90 (0.68–1.21)
Unknown	3	1		

*RR, odds ratio from a multiple logistic model including terms for age, education, parity and menopausal status, CI, confidence interval. †reference category

Table 2. Relation between history of selected diseases and ovarian cancer risk. Italy, 1983–1991

Diagnosis	No. (%) with diagnosis		RR (95% CI)	
	Ovarian cancer	Controls	Age-adjusted	Multivariate*
Diabetes	35 (3.6)	126 (4.6)	0.78 (0.53–1.16)	0.80 (0.54–1.19)
Thyroid disease	69 (7.1)	210 (7.6)	0.83 (0.63–1.12)	0.84 (0.63–1.13)
Severe overweight	91 (9.4)	369 (13.4)	0.66 (0.51–0.84)	0.66 (0.52–0.85)
Hypertension (treated)	143 (14.7)	474 (17.2)	0.81 (0.66–1.01)	0.85 (0.68–1.06)
Cholelithiasis	82 (8.4)	268 (9.7)	0.85 (0.65–1.11)	0.86 (0.66–1.12)
Hyperlipidaemia	45 (4.6)	200 (7.3)	0.63 (0.45–0.89)	0.64 (0.45–0.89)
Benign female conditions				
Uterine leiomyomas	67 (6.9)	292 (10.6)	0.60 (0.44–0.78)	0.66 (0.47–0.92)
Ovarian cysts/benign tumours	35 (3.6)	139 (5.0)	0.70 (0.40–1.26)	0.69 (0.41–1.13)
Benign breast disease	85 (8.8)	240 (8.7)	1.01 (0.77–1.31)	1.00 (0.76–1.31)
Previous breast biopsies	32 (3.3)	37 (1.3)	2.53 (1.52–4.19)	2.48 (1.50–4.13)

RR, relative risk; CI, confidence interval. *RR estimates from a multiple logistic model including terms for age, education, parity, menopausal status and in turn the above variables

0.69, 95% CI 0.41–1.13), but the latter finding was not statistically significant. No association emerged between ovarian cancer risk and history of benign breast disease. The multivariate RR estimate of ovarian cancer was 2.48 (95% CI 1.50–4.13) in women reporting previous breast biopsies.

DISCUSSION

In this analysis, severe overweight and hyperlipidaemia were inversely related to ovarian cancer. Further, cases less frequently reported a history of fibroids, and more frequently a history of breast biopsies. No other medical condition considered was significantly related to ovarian cancer risk. In particular, no association emerged between ovarian cancer risk and diabetes, thyroid disease, hypertension and cholelithiasiis.

These results provide the opportunity of re-assessing and quantifying, in a large dataset, the role of several medical conditions that have been only anecdoctally associated with ovarian cancer.

The study was hospital-based, with subjects collected from the main general teaching hospitals in the greater Milan area. Although the study protocol indicated that all new consecutive cases observed during the study period in the surveyed hospitals should be interviewed, it is likely that some subjects did not enter the study (for instance, simply because they were not present in the ward at the time of the interviewer's visit). However, it is unlikely that a selective mechanism could have been introduced.

Other potential strengths and limitations of this analysis should be considered. With regard to recall bias and data reliability and validity, interviews in a hospital setting probably assured more accurate ascertainment of medical history and a closer similarity between cancer cases and controls than in a community setting [15]. Cases and controls should, in fact, be similarly sensitised to recalling medical conditions and procedures. Among other strengths of the present study, we were able to supplement interview information with medical record data, thus reducing the risk of misclassification.

Furthermore, selection should not represent a major problem. Cases and controls, in fact, were identified in institutions covering broadly comparable catchment areas, participation was almost complete and exclusion was made of any chronic gynaecological or hormonal condition as admission diagnoses for controls. The analysis presented in this paper included several significant tests. It is well known that when simultaneous tests of association are carried out, the possibility of obtaining at least one that is statistically significant at $P = 0.05$ should be taken into account. However, the P value for the association between ovarian cancer risk and severe overweight obesity and history of uterine fibroids, the main findings of the analysis, were less than 0.005. The uniquely large dataset, moreover, gives reasonable statistical power and hence stable estimates even for rare exposures. However, caution should be taken in the interpretation of these findings. Overweight/obesity may be associated with low back pain or other orthopaedic disorders, and it may, therefore be of concern that the comparison group included women with orthopaedic disease or trauma. However, no difference emerged in the estimated RR for overweight when the analysis considered only controls with surgical conditions or other illnesses.

Oestrogen levels are inversely related to cholesterol levels [16]. Assuming that oestrogens are related to ovarian cancer [7], this helps explain the negative association between hyperlipidaemia and risk of ovarian cancer observed in this study.

Hypertension has been associated with the risk of ovarian [1] and also endometrial cancer [17]. In general, hypertension is an indicator of 'Western' lifestyle habits [17], and ovarian cancer is considered a disease of developed countries [7]. However, in the present, as well as in previous studies [4, 8], no association emerged between hypertension and the risk of ovarian cancer. Likewise, no relationship was observed in this study between diabetes, another indicator of 'Western' lifestyle habits, and the risk of ovarian cancer.

Women with a history of uterine leiomyomas tended to be at a lower risk of ovarian cancer. This contrasts with the results from a study conducted in China, showing an increased risk of ovarian cancer in women reporting a history of myomas, as well as ovarian cysts [6]. More interesting, a history of benign ovarian cysts was inversely related, although not significantly, to ovarian cancer. This finding is not easy to explain, since ovarian cysts included in this analysis were of several histological types (functional, seromucinous or endometroid cysts), which only partially share

risk factors for ovarian cancer [18–21]. Interpretation of the inverse association between uterine fibroids, ovarian cysts and ovarian cancer is further complicated by potential diagnostic bias and selective mechanisms related to the diagnosis of benign conditions and by the possible confounding or modifying effect of education, a correlate of ovarian cancer risk [7], as well as diagnosis of several benign gynaecological conditions in various populations [18, 21–23]. However, adequate allowance for education was possible in the analysis. Further, women with fibroids and benign ovarian cysts are more likely to undergo pelvic surgery, that may be related to a reduced risk of ovarian cancer [13]. The RR estimates were, however, not significantly modified when allowance was made for pelvic surgery (data not shown) and no association emerged when the analysis was restricted to ovarian cysts which did not undergo surgery. An increased risk of ovarian cancer was observed in women with previous breast biopsy, but not in those with a history of benign breast disease.

A protective effect of overweight on ovarian cancer was observed. Diagnostic bias must, however, be considered, since diagnosis of early, less aggressive ovarian cancer may be more difficult in overweight women. Previous findings on the relationship between overweight or obesity and risk of ovarian cancer are not consistent. For example, an inverse relationship emerged between obesity at age 20 years and risk of ovarian cancer in a study conducted in Japan [5]; no relationship emerged in two studies conducted in the U.S. in the 1960s [1, 2], and a non-significant, moderate direct effect was observed in the ACS cohort study [9]. We considered only a history of severe, clinically relevant obesity, but the findings do not support any major role of obesity in ovarian cancer risk.

In conclusion, from this large dataset, it appears that medical conditions known or likely to be related to female hormones are not important determinants of the risk of ovarian cancer. Minor effects remain possible, but are unlikely to be of major clinical or public health relevance.

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