Short Communication

Pelvic Inflammatory Disease and Risk of Ovarian Cancer[1]

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Abstract

We analyzed the association between history of pelvic inflammatory disease (PID) and the risk of subsequent epithelial ovarian cancer, using data from a large case-control study conducted between 1983–1991 in Italy. Data were collected from a network of hospitals, including the main teaching and general hospitals in the greater Milan area, Northern Italy. The cases studied were 971 women below the age of 75 years (median age, 54 years) with histologically confirmed epithelial ovarian cancer, diagnosed within 1 year before the interview. Control subjects were 2758 women admitted to the same hospitals where cases were identified for acute, nonmalignant, nonhormone-related conditions, who had not undergone bilateral oophorectomy. The median age of the control group was 52 years (range, 23–74). A total of 14 (1.4%) cases and 72 (2.6%) controls reported a history of PID/salpingitis, the corresponding multivariate relative risk being 0.7 (95% confidence interval, 0.4–1.3). A separate analysis of the association between history of PID/salpingitis and risk of ovarian cancer in strata of parity and education confirmed the results based on the whole series. In conclusion, although based on limited numbers of cases and controls with PID, this studies was able to exclude, at the conventional 95% confidence limit, an increased risk of ovarian cancer of over 30% in women with previous PID in this population.

Introduction

A study conducted in Ontario recently suggested that PID[3] increased the risk of subsequent epithelial ovarian cancer (1). In that study, 104 of 450 cases and 102 of 565 controls reported one or more episodes of PID, corresponding to a relative risk of 1.5 and of 1.8 for recurrent PID. The association was particularly strong for women below 60 years of age, for nulliparae or uniparae, for women with a history of infertility, and for those reporting PID before age 20. An increase in risk of ovarian cancer among women reporting a history of PID was also found in a study conducted in China (2) in which the relative risk was 3.0 based, however, only on eight cases with previous PID.

This association has been interpreted in terms of inflammatory changes of the ovarian surface epithelium associated with PID. This process may cause proliferation of epithelial cells or cyst formation (1, 3, 4). Furthermore, PID is associated with infertility and low parity (5) and a history of difficulty in conception, all of which may increase the risk of ovarian cancer (6).

We analyzed the relationship between a history of PID and the risk of ovarian cancer using data from a case-control study on risk factors of ovarian neoplasm conducted in Italy, where information was available on a large number of covariates (7).

Materials and Methods

Between 1983 and 1991, we conducted a case-control study on risk factors for ovarian cancer (7). Data were collected from a network of hospitals, including the major teaching and general hospitals in the greater Milan area, Northern Italy. Approximately 3% of cases and 4% of controls refused to participate.

The cases studied were women below the age of 75 years with histologically confirmed epithelial ovarian cancer, diagnosed within the year before the interview. The present analysis is based on a total of 971 women (median age, 54 years; range, 22–74 years).

Controls were women admitted to the same hospitals where cases were identified for acute, other than malignant, hormonal or gynecological conditions, who had not undergone bilateral oophorectomy. The median age of the control group was 52 years (range, 23–74 years). Among the 2758 controls interviewed, 34% were admitted for traumas, 30% for other orthopedic conditions (such as low back pain or disc disorders), 16% for surgical conditions (mostly abdominal problems, such as acute appendicitis or strangulated hernia), and 20% for other illnesses, such as ear, nose, throat, or dental disorders.

Trained interviewers used a standard questionnaire to obtain information on personal characteristics and habits and gynecological and obstetric history. Information was collected on episodes of PID that required medical consultation or treatment. Positive or negative history of PID was further checked with clinical records and, in case of inconsistencies, the interviewer was invited to question the subject again regarding this point to confirm the information. Cases and controls were specifically warned not to consider vaginal or bladder infections as an episode of PID.

ORs, together with their 95% confidence interval (8), were derived from unconditional multiple logistic regression equations (9), including terms for age and potential confounding variables (education, parity, family history of ovarian cancer, menopausal status, and use of oral contracep-

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[3] The abbreviations used are: PID, pelvic inflammatory disease; OR, odds ratio.

Table 1 Distribution of 971 cases of ovarian cancer and 2758 controls[a] according to age and selected factors in Milan Italy, 1983–1992

	Ovarian cancer	Controls	OR (95% CI)[b]
Age (yr)			
<45	200	727	
45–54	305	739	
55–64	312	751	
≥65	154	541	
Education (yr)			
<7	558	1591	1+
7–11	233	686	1.1 (0.8–1.4)
≥12	178	479	1.1 (0.9–1.4)
Parity			
0	237	590	1+
1	204	660	0.8 (0.6–1.0)
2	301	836	0.9 (0.7–1.1)
≥3	226	666	0.7 (0.4–1.1)
Family history of ovarian cancer			
No	928	2653	1+
Yes	43	105	1.3 (0.8–1.7)
Menopausal status			
Pre- or in menopause	384	1084	1+
Postmenopause	584	1637	0.9 (0.8–1.1)
Oral contraceptive use			
Never	908	2499	1+
Ever	63	259	0.7 (0.5–1.1)
Pelvic surgery			
No pelvic surgery	891	2503	1+
Hysterectomy	44	177	0.7 (0.5–0.9)
Hysterectomy plus unilateral oophorectomy	8	38	0.7 (0.3–1.4)
Unilateral oophorectomy alone	10	40	0.8 (0.3–1.7)

[a] In some cases, the sum does not add up to the total because of missing values.
[b] OR, odds ratio estimated from a multiple logistic model including terms for the above variables. CI, confidence interval; +, reference category.

Table 2 ORs of ovarian cancer according to history of PID/salpingitis in the overall data set and in separate strata of selected factors in Milan, 1983–1991

	History of PID/salpingitis	Ovarian cancer	Controls	OR (95% CI)[a]
Total	No	957	2686	1+
	Yes	14	72	0.7 (0.4–1.3)
Parity				
0	No	232	574	1+
	Yes	5	16	0.6 (0.2–1.9)
1	No	201	635	1+
	Yes	3	25	0.3 (0.1–1.2)
≥2	No	521	1471	1+
	Yes	6	31	0.6 (0.2–1.4)
Education (yr)				
<7	No	550	1557	1+
	Yes	8	34	0.7 (0.3–1.4)
≥7	No	405	1127	1+
	Yes	6	38	0.4 (0.2–1.0)

[a] OR, odds ratios estimated from a multiple logistic model including terms for history of PID plus age, education, parity, family history of ovarian cancer, menopausal status, oral contraceptive use, and any pelvic surgery; +, reference category.

tives, and history of pelvic surgery). Inclusion of terms for other potential confounding factors (such as smoking, or hormonal treatment for menstrual problems) did not materially modify any of the ORs.

Results

Table 1 shows the distribution of cases and controls, according to selected covariates, and the corresponding ORs. Cases did not differ from controls in respect to education but were slightly older, more frequently nulliparous, and postmenopausal. Oral contraceptive users tended to be more frequent among controls than ovarian cancer cases.

A total of 14 cases (1.4%) and 72 controls (2.6%) reported a history of PID/salpingitis, the corresponding OR being 0.7 (95% confidence interval, 0.4–1.3; Table 2). A separate analysis of the association between history of PID/salpingitis and risk of ovarian cancer in strata of parity and education confirmed the results based on the whole series.

Discussion

Potential limitations of this analysis should be considered. With regard to recall bias and data reliability and validity, the interviews in a hospital setting probably assured more accurate ascertainment of medical history, including PID, and a closer similarity between cases and controls than in a community setting (10). Cases and controls should, in fact, be in a similar way sensitized toward recalling medical conditions and procedures. More in general, it is difficult to evaluate potential selective bias of controls with reference to diagnosis of PID. We had the possibility of supplementing interview information with medical record data, with a consequent reduction of any potential misclassification (11). Furthermore, if cases tended to report their history of PID more accurately than controls, the relative risk should, if anything, be overestimated. With reference to selection bias, the catchment areas of cases and controls were comparable: 88% of cases and 82% of controls came from the same region, Lombardy, and the participation rate was practically complete. Finally, the distribution of education and other risk factors for PID/salpingitis was comparable for cases and controls; and in any case, these covariates were taken into account in the logistic regression models.

The absence of an association between history of PID and risk of ovarian cancer observed in this study does not confirm the findings from Canadian and Chinese studies (1, 2). This might be interpreted in terms of variable determinants of PID in different populations and/or of variable prevalence of the disease in the various areas. For example, the prevalence of PID/salpingitis was about 18% in controls interviewed in the North American study but less than 1% in the Chinese one (2). The low prevalence of PID observed in this study may reflect less diagnostic attention to minor episodes in Italy than in North America, although there are no data on the pattern of diagnosis of PID in Italy and in North America. Likewise, there is no information on the prevalence of PID in the Italian population, but the prevalence of PID among controls of the the present study is in agreement with prevalence estimates reported in an epidemiological study conducted in the same population (12), giving a prevalence of PID of about 3% in women aged 30–40 years. Nevertheless, it is likely that this refers essentially to severe disease, which, however, should be, if anything, more strongly related to ovarian carcinogenesis.

In conclusion, although based on a limited number of cases and controls with PID, this study was able to exclude, at the conventional 95% confidence limit, an increased risk of ovarian cancer of clinical relevance in women with previous clinically relevant PID.

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References

1. Risch H. A., and Howe, J. R. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. Cancer Epidemiol., Biomarkers & Prev., *4:* 447–451, 1995.

2. Shu, X. O., Brinton, L. A., Gao, Y. T., and Yuan, J. M. Population-based case-control study of ovarian cancer in Shanghai. Cancer Res., *49:* 3670–3674, 1989.

3. Bychkov, V. Ovarian pathology in chronic pelvic inflammatory disease. Gynecol. Obstet. Invest., *30:* 31–33, 1990.

4. Cramer, D. W., and Welch, W. R. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J. Natl. Cancer Inst., *71:* 717–721, 1983.

5. Cates, W., Jr., Rolf, R. T., Jr., and Aral, S. O. Sexually transmitted diseases, pelvic inflammatory disease, and infertility: an epidemiologic update. Epidemiol. Rev., *12:* 199–220, 1990.

6. Parazzini F., Franceschi S., La Vecchia, C., and Fasoli, M. The epidemiology of ovarian cancer. Gynecol. Oncol., *43:* 9–23, 1991.

7. Parazzini, F., Negri, E., La Vecchia, C., Restelli, C., and Franceschi, S. Family history of reproductive cancers and ovarian cancer risk: an Italian case-control study. Am. J. Epidemiol., *135:* 35–40, 1992.

8. Breslow, N. E., and Day, N. E. Statistical methods in cancer research. The Analysis of Case-Control Studies, Vol. 1. IARC Scientific Publications no. 32. Lyon, France: IARC.

9. Baker, R. J., and Nelder, J. A. The GLIM system, Release 3. Oxford, United Kingdom: Numerical Algorithms Group, 1978.

10. Kelly, J. P., Rosenberg, L., Kaufman, D. W., and Shapiro, S. Reliability of personal interview data in a hospital-based case-control study. Am. J. Epidemiol., *131:* 79–90, 1990.

11. Linet, M. S., Harlow, S. D., McLaughlin, J. K., and McCaffrey, L. D. A comparison of interview data and medical records for previous medical conditions and surgery. J. Clin. Epidemiol., *42:* 1207–1213, 1989.

12. Parazzini, F., Ferraroni, M., Tozzi, L., Ricci, E., Mezzopane, R. and La Vecchia, C. Induced abortions and risk of ectopic pregnancy. Hum. Reprod., *10:* 1841–1844, 1995.

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