Pelvic Inflammatory Disease and the Risk of Epithelial Ovarian Cancer[1]

Harvey A. Risch[2] and Geoffrey R. Howe

Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510 [H. A. R.], and National Cancer Institute of Canada Epidemiology Unit, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario M5S 1A8, Canada [G. R. H.]

Abstract

Infertility is a common complication of pelvic inflammatory disease (PID) and may result in decreased parity. Low parity and possibly infertility are risk factors for ovarian cancer. We therefore examined the association between ovarian cancer and history of PID in a case-control study conducted during 1989–1992 in metropolitan Toronto and nearby areas of Southern Ontario, Canada. In total, 450 histologically verified new primary epithelial ovarian cancer cases ages 35–79 years were interviewed concerning their reproduction history. Over the same time period, 564 randomly selected population controls, frequency matched to the cases according to three 15-year age groups, were interviewed similarly. Continuous unconditional logistic regression methods were used for analysis. It was found that cases were more likely than controls to report having had one or more episodes of PID; adjusted for age, parity, duration of oral contraceptive use, and other factors the odds ratio (OR) was 1.53 [95% confidence interval (CI), 1.10–2.13; $P = 0.012$]. Higher risk was present for women with recurrent PID (OR, 1.88; 95% CI, 1.13–3.12; $P = 0.014$). The elevated risk associated with PID was seen particularly among women <60 years of age at interview (OR, 1.60; 95% CI, 1.09–2.35; $P = 0.016$), for women of parity 0 or 1 (OR, 2.40; 95% CI, 1.39–4.15; $P = 0.0017$), among women who had ever had infertility (OR, 3.74; 95% CI, 1.28–10.9; $P = 0.016$), and for the small number of women who reported having PID before age 20 (OR, 3.08; 95% CI, 1.17–8.13; $P = 0.023$). After age 20 years, no case-control differences were seen in age at first PID episode. This study, based on self-reported PID history, supports an association with subsequent ovarian cancer. Because this appears to be a new finding, further studies of this association are warranted.

Introduction

PID[3] is a significant complication of sexually transmitted infections and of infections following childbirth, abortions, and gynecological instrumentation. It is estimated that over 1 million cases occur annually in the United States (1, 2) and that by the end of the reproductive years, at least 1 woman in 7 has been affected (3). Salpingitis, tubal obstruction, tubo-ovarian abscesses, and inflammatory residua and adhesions occur frequently in PID (4, 5), and infertility follows in 10–20% of cases (6). Low parity and possibly infertility are risk factors for ovarian cancer (7), and the cystic changes of the ovary seen in PID (5), as well as the involvement of ovarian surface epithelium in the PID inflammatory process, may enhance the likelihood of entrapment and malignant transformation of ovarian epithelium (8). We therefore examined the relationship between history of PID and the occurrence of epithelial ovarian cancer within a case-control study carried out to investigate reproduction and infertility factors and ovarian cancer risk (9).

Subjects and Methods

Study Population. Details of the selection of cases and controls have been given in a previous paper reporting parity and contraception results from the current study (9). In brief, the cases consisted of all women between the ages of 35 and 79 years residing within the highly populated area surrounding the western end of Lake Ontario and having confirmed (histologically) primary, malignant, or borderline malignant epithelial ovarian tumors newly diagnosed between November 1, 1989 and October 31, 1992. Regular review by us of all relevant hospital and laboratory pathology reports received in the province-wide operations of the Ontario Cancer Registry enabled ascertainment of the population-based sample. In total, 631 eligible cases were identified and 450 were interviewed (71.3%). Of the remainder, 55 (8.7%) cases had died, 29 (4.6%) had physicians who refused consent for case contact, 30 (4.8%) were too sick to interview, 17 (2.7%) were lost to follow-up, and 50 (7.9%) refused to participate.

A sample of population controls was obtained from the Ontario Ministry of Finance, with the use of the Enumeration Composite Record listings, which include all homeowners, tenants, and their family members and contain information such as name, address, age, and sex. From the listings, we selected a random sample of women resident in the study area during the same 3-year period, frequency matched by age within three 15-year groups, to the expected case distribution based on incidence tabulations of the Ontario Cancer Registry. Controls were contacted initially by letter with telephone follow-up to confirm suitability for the study, and arrangements were then made for interview. Control women found to have had bilateral oophorectomy performed 1 year or more in the past were considered ineligible and were excluded. In total, 873 eligible controls were identified, 564 (64.6%) of whom were interviewed. The remainder either refused (30.2%), were too sick (1.9%), or were lost to follow-up (3.2%).

Questionnaire and Interviewing. A questionnaire was developed for the recording of medical and reproduction history. Detailed information was sought regarding menstrual characteristics, pregnancies, hormone and contraceptive usage, and

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[2] To whom requests for reprints should be addressed, at the Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College Street, P.O. Box 3333, New Haven, CT 06510.

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

various infertility factors. In the interview, a life events calendar was used to help organize the reproduction-related behaviors and outcomes; thus, the ages at occurrence and durations of time applicable to these factors were obtained. To ascertain history of PID, subjects were asked the following: "Could you tell me whether you have ever had an internal pelvic infection, sometimes called PID or pelvic inflammatory disease? We are not including vaginal infections or bladder infections." The ages (or calendar years) for up to the first two episodes were recorded. For the entire interview, the questions were identical for cases and controls, and for both subject groups, information pertaining to events or exposures within 1 year of interview was excluded from analysis. Interviews were conducted in person in the home of the subject after explaining the study to the subject and obtaining verbal agreement to proceed. The study, using these procedures, was approved by the Human Subjects Review Board of the Office of Research Administration at the University of Toronto.

Statistical Analysis. Multivariate unconditional continuous logistic regression methods were used to estimate the relative odds (OR) of ovarian cancer associated with particular exposure factors. The GLIM computer program (10) was used for the calculations. All tests of statistical significance have been based on differences in log likelihood, with two-sided P values given. All confidence intervals were calculated at the 95% level by exponentiating the parameter estimate $\pm$ 1.96 SEs. Comparison of PID odds ratios across categories of a modifying factor was based on statistical significance of the model interaction term(s). Each of the models in this work includes indicator terms for the age categories of the frequency matching (35–49, 50–64, and 65–79 years); age as a continuous variable has also been included in order to adjust for residual age effects. Total years of oral contraceptive usage, number of full-term pregnancies, total duration of breast-feeding, and ever having a tubal ligation, a hysterectomy, or a mother or sister with ovarian or breast cancer have been included in all models as well.

Results

Table 1 shows descriptive characteristics of the 450 cases and 564 controls. As reported previously (9), case subjects had fewer full-term pregnancies and used oral contraceptives less than control subjects. Length of schooling was similar for the two groups; however, somewhat more controls than cases had been born in Canada or the United States. Because adjustment for country of birth, race, or years of schooling in the regression models left the associations with PID and the other reproduction-related variables unchanged, these terms were not included in the analyses presented here. A similar lack of confounding with PID was seen among both nulliparous and parous women for having ever had a period of 2 years or more during which pregnancy was attempted without success. This term, representing infertility, was therefore also omitted as an adjustment factor from our analyses, although we do consider its interaction with PID. Associations with ovarian cancer risk were seen for a family history of breast or ovarian cancer and for having had a tubal ligation or hysterectomy (Table 1), and these variables were included in the models. More detailed discussion of these associations has been presented elsewhere (9).

Overall, 23.1% of cases and 18.1% of controls reported that they had had PID (OR, 1.53; 95% CI, 1.10–2.13; P = 0.012). Considered according to number of PID episodes, an increasing trend in risk was present, with relative odds of 1.88 for a history of 2 or more episodes (Table 2). The mean age at

Table 1 Descriptive characteristics of 450 ovarian cancer cases and 564 randomly selected population controls, Southern Ontario, Canada, 1989–1992

	Cases	Controls	P value
Age at interview (yr)	57.2	57.5	—[a]
Born in Canada or US[b] (%)	59.1	64.7	0.066
Race (% black)	1.56	1.95	0.48
Length of schooling (yr)	12.3	12.5	0.51
No. of full-term pregnancies	1.90	2.45	$<10^{-7}$
Ever used oral contraceptives (%)	38.7	49.6	$<10^{-4}$
Ever had tubal ligation (%)	18.0	24.3	0.10
Ever had hysterectomy (%)	13.8	24.8	$<10^{-4}$
Ever had abortion (%)	8.67	8.16	0.68
Ever had miscarriage (%)	20.9	23.4	0.80
Ever had endometriosis (%)	2.44	2.13	0.89
Ever had infertility[c] (%)	8.22	6.91	0.64
Used contraception at age $\leq$20 (%)	12.7	15.8	0.79
Ever smoked cigarettes regularly (%)	45.1	47.9	0.56
Mother/sister with ovarian cancer (%)	4.22	1.95	0.013
Mother/sister with breast cancer (%)	12.9	7.98	0.0059

[a] Matching variable.
[b] US, United States.
[c] Infertility is defined as a time period of 2 years or more during which pregnancy was attempted without success.

Table 2 Relative odds of epithelial ovarian cancer according to number of reported episodes of PID, Southern Ontario, Canada, 1989–1992

	No. of PID episodes			P value for trend
	0	1	2+	
Cases (%)	76.9	13.6	9.6	
Controls (%)	81.9	12.1	6.0	
All subjects				
Adjusted OR (95% CI)[a]	1.00	1.36 (0.91–2.02)	1.88 (1.13–3.12)	0.0065
Parous subjects				
Adjusted OR (95% CI)[a]	1.00	1.23 (0.80–1.90)	1.59 (0.92–2.75)	0.071
Nulliparous subjects				
Adjusted OR (95% CI)[b]	1.00	2.84 (0.84–9.62)	9.92 (1.61–61.3)	0.0019
Nulligravid subjects				
Adjusted OR (95% CI)[b]	1.00	1.94 (0.52–7.17)	4.90 (0.73–33.0)	0.049

[a] OR adjusted for age at interview (3 groups plus continuous term), number of full-term pregnancies, total duration of breast-feeding, years of oral contraceptive usage, ever had tubal ligation, ever had hysterectomy, mother or sister with ovarian cancer, and mother or sister with breast cancer.
[b] Odds ratio adjusted as for models with parous subjects but omitting number of pregnancies and duration of breast-feeding.

Table 3 Relative odds of epithelial ovarian cancer for having had PID according to categories of age and time before interview, and with respect to oral contraceptive use and infertility, Southern Ontario, Canada, 1989–1992

Timing of PID	% of cases with PID in category	% of controls with PID in category	PID OR (95% CI)[a]
Age (yr)			
≤20	3.1	1.4	3.08 (1.17–8.13)
>20, ≤30	9.6	8.3	1.27 (0.79–2.05)
>30	14.9	10.8	1.49 (1.00–2.23)
Time before interview (yr)			
≤10	6.0	4.6	1.36 (0.75–2.46)
>10, ≤20	9.8	7.1	1.49 (0.92–2.42)
>20	11.1	9.6	1.29 (0.83–2.01)
Among ever users of oral contraceptives (174 cases, 280 controls)			
During OC[b] use	14.9	12.1	1.48 (0.81–2.72)
Not during OC use	25.3	16.1	1.63 (1.00–2.68)
Among women reporting infertility[c] (37 cases, 39 controls)			
During infertility[d]	32.4	5.1	26.0 (2.29–294.)
Not during infertility[e]	8.1	7.7	2.11 (0.24–18.3)

[a] OR for ever *versus* never having had PID in category, adjusted as in Table 2 for all subjects.
[b] OC, oral contraceptive.
[c] Infertility is defined as a time period of 2 years or more during which pregnancy was attempted without success.
[d] PID occurring prior to 1 year past the end of infertility interval.
[e] PID occurring more than 1 year after the end of infertility interval.

first PID episode was 32.5 years among cases and 31.2 years among controls ($P = 0.78$). However, the occurrence of PID at age ≤20 years was associated with an appreciably higher relative odds of 3.08 (Table 3), although only 14 cases and 8 controls were so affected. After age 20, little difference was seen in risk of ovarian cancer according to reported age at PID occurrence. Also, the risk did not change substantially according to years before interview. There was no difference in risk with PID when considering only cases of invasive histology (OR, 1.48; 95% CI, 1.04–2.12; $P = 0.031$) or of borderline histology (OR, 1.69; 95% CI, 0.97–2.95; $P = 0.065$). Using the overall odds ratio of 1.53 and the estimated lifetime prevalence (among controls) of 18.1% for a history of PID, we calculate that 8.8% (95% CI, 1.8%-17%) of ovarian cancer cases in the population could be due to PID.

In Table 4, we present the relative odds of ovarian cancer associated with a history of PID according to various potentially modifying factors. PID was much more common among younger women at interview (<60 years) than older women, among ever users compared to never users of oral contraceptives or intrauterine devices, for women who reported having had an abortion or who had used contraceptives at age less than or equal to 20 years, and among current or past cigarette smokers compared to never smokers (columns "% with PID" in Table 4). While some variation appeared in the magnitude of PID odds ratios across these particular categories, none of the different odds ratios could be distinguished at the 5% level of significance; the most significant difference was for women with a history of infertility (PID OR, 3.74) compared to no history (PID OR, 1.40; $P = 0.067$ for difference between these two ORs). However, among nulliparous women, the relative odds of ovarian cancer associated with a history of PID was 3.89 (95% CI, 1.62–9.29; $P = 0.0023$); this result differed significantly from the odds ratios seen at nonzero parities ($P = 0.024$). An increasing trend in risk with number of episodes

Table 4 Relative odds of epithelial ovarian cancer for having ever had PID, by categories of various factors, Southern Ontario, Canada, 1989–1992

Category	Cases		Controls		PID OR (95% CI)[a]
	No.	% with PID	No.	% with PID	
Age at interview (yr)					
<60	259	30.9	313	24.0	1.60 (1.09–2.35)
≥60	191	12.6	251	10.8	1.35 (0.73–2.49)
No. of full-term pregnancies					
0	105	24.8	63	14.3	3.89 (1.62–9.29)
1	79	30.4	74	25.7	1.86 (0.95–3.63)
2	123	24.4	186	16.7	1.42 (0.82–2.47)
3	88	18.2	124	16.9	1.19 (0.59–2.40)
4+	55	14.5	117	18.8	0.76 (0.31–1.84)
Oral contraceptive use (yr)					
0	276	15.2	284	10.2	1.60 (0.95–2.70)
>0, <6	125	34.4	175	25.1	1.31 (0.82–2.10)
≥6	49	38.8	105	27.6	2.02 (0.96–4.28)
Oral contraceptive use among parous women (yr)					
0	204	15.2	252	10.7	1.49 (0.85–2.62)
>0	141	33.3	249	26.5	1.27 (0.81–1.99)
Oral contraceptive use among nulliparous women (yr)					
0	72	15.3	32	6.2	2.69 (0.55–13.2)
>0	33	45.5	31	22.6	5.83 (1.41–24.1)
Oral contraceptive use among nulligravid women (yr)					
0	66	15.2	32	6.2	3.07 (0.60–15.8)
>0	21	42.9	23	26.1	2.33 (0.50–10.8)
Used contraceptive intrauterine device regularly					
Never	402	22.9	506	16.8	1.58 (1.11–2.24)
Ever	48	25.0	58	29.3	1.25 (0.56–2.77)
Had abortion					
Never	411	20.9	518	17.2	1.46 (1.02–2.07)
Ever	39	46.2	46	28.3	2.03 (0.94–4.36)
Had tubal ligation or hysterectomy					
Never	319	21.3	315	16.8	1.51 (0.99–2.31)
Ever	131	27.5	249	19.7	1.55 (0.92–2.61)
Had infertility[b]					
Never	413	21.5	525	18.5	1.40 (1.00–1.98)
Ever	37	40.5	39	12.8	3.74 (1.28–10.9)
Used contraceptives at age ≤20 yr					
Never	393	21.1	475	15.4	1.57 (1.09–2.27)
Ever	57	36.8	89	32.6	1.38 (0.73–2.63)
Smoked cigarettes regularly					
Never	247	20.6	294	13.3	1.76 (1.11–2.79)
Past[c]	101	25.7	133	20.3	1.46 (0.81–2.63)
Current[c]	102	26.5	137	26.3	1.28 (0.72–2.25)
Country of birth					
Canada or US[d]	266	22.6	365	17.8	1.42 (0.94–2.13)
Other	184	23.9	199	18.6	1.72 (1.05–2.82)

[a] Odds ratio for ever *versus* never having had PID, stratified by category; adjusted as in Table 2.
[b] Infertility is defined as a time period of 2 years or more during which pregnancy was attempted without success.
[c] Past smoker refers to having quit more than 1 year; current smoker to having quit ≤1 year.
[d] US, United States.

was present for both nulliparous and parous women (Table 2), although the risks were appreciably greater for the nulliparous. For women who reported ever having intervals of infertility, PID associated with the infertility appeared to convey much higher risk than PID at other times (Table 3).

Discussion

This study was designed to investigate, among ovarian cancer cases and controls, a number of reproduction- and infertility-related factors, including history of PID. Discussion of parity, contraception, and some of the infertility factors, as well as of the representativeness of our case and control samples, has been presented elsewhere (9). In the current study, subjects were asked whether they had ever had PID and at what ages but were not asked whether they had been treated for it in a doctor's office, clinic, or emergency room, or whether they had been hospitalized for it. Extensive histories related to sexual behavior and PID were not obtained, nor were corroborating medical records sought. Thus, the self-reports of our subjects could be inaccurate for several reasons. Subjects may have chosen intentionally not to reveal the occurrence of PID or may have forgotten about it. Some PID may have been asymptomatic (6) and, therefore, unknown to the women. Finally, although in the interview we clarified that vaginal or bladder infections were not to be considered PID, some subjects nevertheless may have been confused and may have described episodes that they thought were PID but which were, in fact, urinary tract or yeast infections. Most of these types of errors are generally nondifferential between cases and controls; thus, our results may tend conservatively toward the null. Of greater concern is the possibility that women with a serious disease like ovarian cancer may be relatively more likely to self-report a potentially stigmatizing condition such as PID than controls without such a cancer history. However, for the women in our study population, a history of having had an abortion appears at least as stigmatizing as a history of PID, yet cases and controls reported it by similar fractions (Table 1). Likewise, teenage sexual experience (here considered in terms of contraception use prior to age 20 years) may be stigmatizing, but no case-control difference in this factor was present. Cases with borderline malignant tumors who at diagnosis are generally less ill and who have much better prognoses than cases with invasive cancers had just as great an association with PID as did the women with invasive tumors. Finally, an ovarian cancer study that ascertained self-reported history of vaginal infections, also possibly stigmatizing, did not find a case excess (11).

In addition, our data are in general agreement with other estimates of lifetime PID prevalence. In total, 18.1% of controls in the present study reported ever having PID. Among women interviewed in the (United States) National Survey of Family Growth Cycle III in 1982, 16–20% of those over age 30 years reported that they had been treated for PID (12). For our controls <60 years of age at interview, 24.0% described having had PID; we estimate that about 21% would have had it based on age- and calendar year-specific Canadian hospital separation rates (13) and a 3.4 ratio for (reported) ever had PID:ever hospitalized for PID (12).

We also observed greater proportions of subjects who had had PID, within categories of exposures found in other studies, to be associated with increased risk of PID occurrence. Both teenage sexual experience and usage of an intrauterine contraceptive device are associated with higher incidence of PID in this work and elsewhere (6). Cigarette smokers are at greater risk of PID (14, 15), although reasons for this are uncertain. In the present study, women who had used oral contraceptives were also more likely overall to have had PID; this may be due to the greater sexual activity of these women and the higher chances for acquiring sexually transmitted infections rather than to an effect of the oral contraceptives *per se*. Women with greater sexual activity, such as those with higher numbers of sexual partners, are at increased PID risk (16). Among our subjects who used them, the oral contraceptives were used on average for about only 5 years, in contrast to a total reproductive life of perhaps 30 years at risk for PID. Women who used oral contraceptives also used other methods of contraception 41% more than women in our study who never used oral contraceptives. Thus, potential benefits of oral contraceptive use in terms of decreased acquisition of sexually transmitted diseases (14) may be outweighed by risks from greater sexual activity during use, as well as before and after use. This is borne out in our data, which show the percentage of oral contraceptive users who had an episode of PID during their oral contraceptive use (Table 3) to be similar to the percentage of nonusers who ever had PID (Table 4); the percentage of oral contraceptive users who had PID not during their oral contraceptive use was appreciably higher.

Among our subjects, the average age at first PID episode was about 5 years greater than that seen in studies in the United States (15, 16) and about 3 years greater than the average age estimated from PID hospitalizations in 1974 in Alberta, Canada (17). Women in our study were on average 57 years of age at interview in 1990–1992; thus, the majority were already in their late 20s or older at the beginning of the "sexual revolution" era in the 1960s when PID incidence began rising (6).

The present work suggests that PID may increase risk for developing ovarian cancer. Current theories for the etiology of ovarian cancer propose that tumors arise due to repeated formation of inclusion cysts, in which ovarian surface epithelium becomes entrapped in the ovarian stroma and differentiates, proliferates, and undergoes malignant transformation (8). Oral contraceptive usage reduces the risk of ovarian cancer (7–9) and is associated with decreased incidence of follicular and corpus luteum cysts (18). PID appears to increase the likelihood of occurrence of these types of cysts, although not necessarily of inclusion cysts (5). The inflammatory process may stimulate proliferation of ovarian surface epithelium. Surface papillomas are seen on ovaries with PID (5). To our knowledge, only one study has examined directly the possible association between PID and ovarian cancer. That study, conducted in Shanghai, China, found an odds ratio of 3.0 (95% CI, 0.30–30.2) for the 8 cases and 1 control who reported having had a pelvic infection (19). In our data, the increasing trend in risk with the number of PID episodes may reflect an association with severity similar to the association seen for PID-related infertility (6). Likewise, the decreasing trend in ovarian cancer risk associated with PID according to categories of increasing parity may be consistent with an effect of fertility reduction seen among PID cases of greater severity. The highest risk seen in this study was for women reporting PID temporally associated with infertility. It is also possible that some factors related to the occurrence of PID, rather than the PID itself, may be responsible for the associations observed here. Our findings should therefore be considered preliminary, and further ovarian cancer studies with extensive ascertainment of sexual practices, including more careful documentation of the PID episodes, are warranted.

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H A Risch and G R Howe

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