GYNECOLOGY

Pelvic inflammatory disease and risk of epithelial ovarian cancer: a national population-based case-control study in Sweden

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BACKGROUND: Epithelial ovarian cancer is an insidious disease, and women are often diagnosed when the disease is beyond curative treatment. Accordingly, identifying modifiable risk factors is of paramount importance. Inflammation predisposes an individual to cancer in various organs, but whether pelvic inflammatory disease is associated with an increased risk of epithelial ovarian cancer has not been fully determined.
OBJECTIVE: This study aimed to investigate a possible association between clinically verified pelvic inflammatory disease and the risk of epithelial ovarian cancer.
STUDY DESIGN: In this national population-based case-control study, all women in Sweden diagnosed with epithelial ovarian cancer between 1999 and 2020 and 10 controls for each were identified, matched for age and residential district. Using several Swedish nationwide registers, data on previous pelvic inflammatory disease and potential confounding factors (age, parity, educational level, and previous gynecologic surgery) were retrieved. Adjusted odds ratios and 95% confidence intervals were estimated using conditional logistic regression. Histotype-specific analyses were performed for the subgroup of women diagnosed with epithelial ovarian cancer between 2015 and 2020. Moreover, hormonal contraceptives and menopausal hormone therapy were adjusted in addition to the aforementioned confounders.
RESULTS: This study included 15,072 women with epithelial ovarian cancer and 141,322 controls. Most women (9102 [60.4%]) had serous carcinoma. In a subgroup of cases diagnosed between 2015 and 2020, high-grade serous carcinoma (2319 [60.0%]) was identified. A total of 168 cases (1.1%) and 1270 controls (0.9%) were diagnosed with pelvic inflammatory disease. Previous pelvic inflammatory disease was associated with an increased risk of epithelial ovarian cancer (adjusted odds ratio, 1.39; 95% confidence interval, 1.17—1.66) and serous carcinoma (adjusted odds ratio, 1.46; 95% confidence interval, 1.18—1.80) for the entire study population. For the subgroup of women diagnosed in 2015—2020, pelvic inflammatory disease was associated with high-grade serous carcinoma (adjusted odds ratio, 1.43; 95% confidence interval, 1.01—2.04). The odds ratios of the other histotypes were as follows: endometrioid (adjusted odds ratio, 0.13; 95% confidence interval, 0.02—1.06), mucinous (adjusted odds ratio, 1.55; 95% confidence interval, 0.56—4.29), and clear cell carcinoma (adjusted odds ratio, 2.30; 95% confidence interval, 0.90—5.86). A dose-response relationship was observed between the number of pelvic inflammatory disease episodes and the risk of epithelial ovarian cancer ($P_{trend}<.001$).
CONCLUSION: A history of pelvic inflammatory disease is associated with an increased risk of epithelial ovarian cancer and a dose-response relationship is evident. Histotype-specific analyses show an association with increased risk of serous epithelial ovarian cancer and high-grade serous carcinoma and potentially also with clear cell carcinoma, but there is no significant association with other histotypes. Infection and inflammation of the upper reproductive tract might have serious long-term consequences, including epithelial ovarian cancer.

Key words: epithelial ovarian cancer, high-grade serous carcinoma, ovarian cancer, pelvic inflammatory disease, population-based case-control study

Introduction

Pelvic inflammatory disease (PID) has gained interest as a modifiable factor that may potentially increase the risk of epithelial ovarian cancer (EOC), but the evidence so far is limited. EOC is an insidious disease, as, in its early stages, it is associated with few symptoms or no symptom, making it difficult for both patients and clinicians to detect. There is no validated screening method for EOC, and women are often diagnosed when tumors have already spread throughout the abdominal cavity and the disease is beyond curative treatment. Accordingly, identifying modifiable risk factors is of paramount importance.

PID is described as inflammation of the female reproductive organs, caused by ascending microorganisms from the lower genital tract. It involves a spectrum of conditions, including endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess. Chronic inflammation is increasingly studied as part of the oncogenic process and microorganisms are suggested to cause 15% to 20% of all cancers.[1] Chronic inflammation in the female reproductive tract has been suggested to be involved in EOC carcinogenesis. The association between PID and subsequent risk of EOC has been investigated by several authors with contradictory findings; some have found an increased risk of EOC to be associated with PID,[2−6] whereas others found no such association.[7−11]

Nulliparity and infertility are both potential consequences of PID and are associated with an increased risk of EOC.[12] In contrast, salpingectomy, hysterectomy, and tubal ligation have all been associated with a reduced risk of EOC.[13−15] In addition to removing organs with precursor potential as

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AJOG at a Glance

Why was this study conducted?

Pelvic inflammatory disease is suggested to increase the risk of epithelial ovarian cancer (EOC). This was examined in a population-based case-control study of Swedish registers.

Key findings

A history of pelvic inflammatory disease was associated with an increased risk of EOC. In histotype-specific analyses, this association was evident for serous and high-grade serous carcinoma, with extended definition of PID also for clear cell carcinoma, but was not for any other histotype. An increase in pelvic inflammatory disease episodes was associated with an increased risk of EOC.

What does this add to what is known?

The association of pelvic inflammatory disease with risk across EOC histotypes was described and adjusted for register-based information regarding potential confounding factors. A significant dose-response relationship was found.

suggested with salpingectomy, a possible explanation could be the inability of infectious agents to ascend to the upper reproductive tract and cause inflammation. The most consistently reported protective factors for EOC are related to parity and oral contraceptive use,[12,16,17] and the related mechanism is suggested to primarily be the reduction in the number of lifetime ovulations.[18] Both factors can also reduce the risk of ascending infections by modulating the cervical barrier.[19]

The number of population-based studies with well-defined participants and clinically verified PID is limited. Others include self-reported cases of PID with a risk of recall bias. Therefore, this study aimed to investigate a possible association between clinically verified and registered PID episodes and risk of EOC in a population-based case-control study using Swedish registers.

Materials and Methods

Study design

The cases in this national population-based case-control study consist of all women residing in Sweden diagnosed with EOC between January 1, 1999, and December 31, 2020. Cases were matched with 10 controls each at the date of diagnosis (index date), year of birth, and residential district using data from Statistics Sweden. Data on potential confounders were extracted from Swedish nationwide registers. With the help of the personal identification number, received by Sweden citizens at birth or upon immigration, correct linkages between different registers are possible.[20] Full descriptions of the Swedish national registries included in the study can be found in the Supplementary Methods. This study was approved by the Swedish Ethical Review Authority (Dnr 2020-03679) and conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting case-control studies (www.strobe-statement.org).

Cases

Women with EOC were selected from the Swedish National Cancer Register concerning tumor site using the International Classification of Diseases for Oncology, Second Edition (ICD-O-2): ovary (C56.9), fallopian tube (C57.0), and primary peritoneum (C48.1 and C48.2) (Supplemental Table 1). The aim was to study invasive ovarian cancer; thus, borderline ovarian tumors were excluded. Tumor histotypes were specified using the ICD-O-2 morphology codes (Supplemental Table 1). Registration of high-grade serous carcinoma (HGSC) was introduced in the Swedish National Cancer Register in 2014, following the World Health Organization guidelines, making it possible to discern HGSC from low-grade serous carcinoma (LGSC). In the subgroup of women diagnosed with EOC between 2015 and 2020, tumor morphology was specified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), morphology codes, in cases where the specific code for HGSC (84613) could be identified. For serous carcinomas not diagnosed with the specific code for HGSC (84613), we used data from the Swedish Quality Register of Gynecological Cancer regarding tumor grade to discern HGSC from LGSC and serous carcinomas not otherwise specified (NOS). Only invasive carcinomas were included for all histotypes. Information about tumor stage was retrieved for all cases from 2004 onward, when tumor stages were introduced into the Swedish National Cancer Register.

Controls

Control individuals were matched using the Swedish Register of the Total Population[21] and drawn without reversal; thus, a control individual could only be selected once.

Exclusion of cases and controls

Data requested from the Statistics Sweden and the National Board of Health and Welfare excluded women diagnosed with ovarian tumors before 1999 registered in the National Cancer Register (defined by International Classification of Disease, Seventh Revision: 158, 1750, 1751, 1758, 1759, 1769, 1974, 1993, and 1994). Women who had undergone bilateral oophorectomy, bilateral salpingo-oophorectomy, or major gynecologic surgery, including bilateral salpingo-oophorectomy before the index date, who were registered in the National Patient Register, were also excluded. Supplemental Table 1 provides details of the diagnostic codes. Furthermore, to increase the possibility of capturing exposure from the register, selected women had to have been residents in Sweden since the age of 18 years. If cases were excluded, the subsequent controls were also excluded. We

performed quality checks on data delivered from the National Board of Health and Welfare, based on the aforementioned description.

Exposure

Information regarding clinically verified PID was retrieved from the National Patient Register, including inpatient and specialized outpatient care by, for example, gynecologists. General practitioners were not reporting to the National Patient Register during the period of the study. Here, we defined PID as an inflammation of the female upper reproductive tract, including the diagnoses of salpingitis, oophoritis, and tubo-ovarian abscess in the International Classification of Diseases, Ninth Revision (ICD-9), and International Classification of Diseases, Tenth Revision (ICD-10; 614A-C and N70.0−9). In addition, we studied PID extended (PID_{ext}), including endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess defined by ICD-9 and ICD-10 (614A-X and 615 and N70.0−9, N71, and N73−4) (Supplemental Table 1). To avoid reversed causation and misclassification, exposures of <90 days before the index date were not included in the analyses.

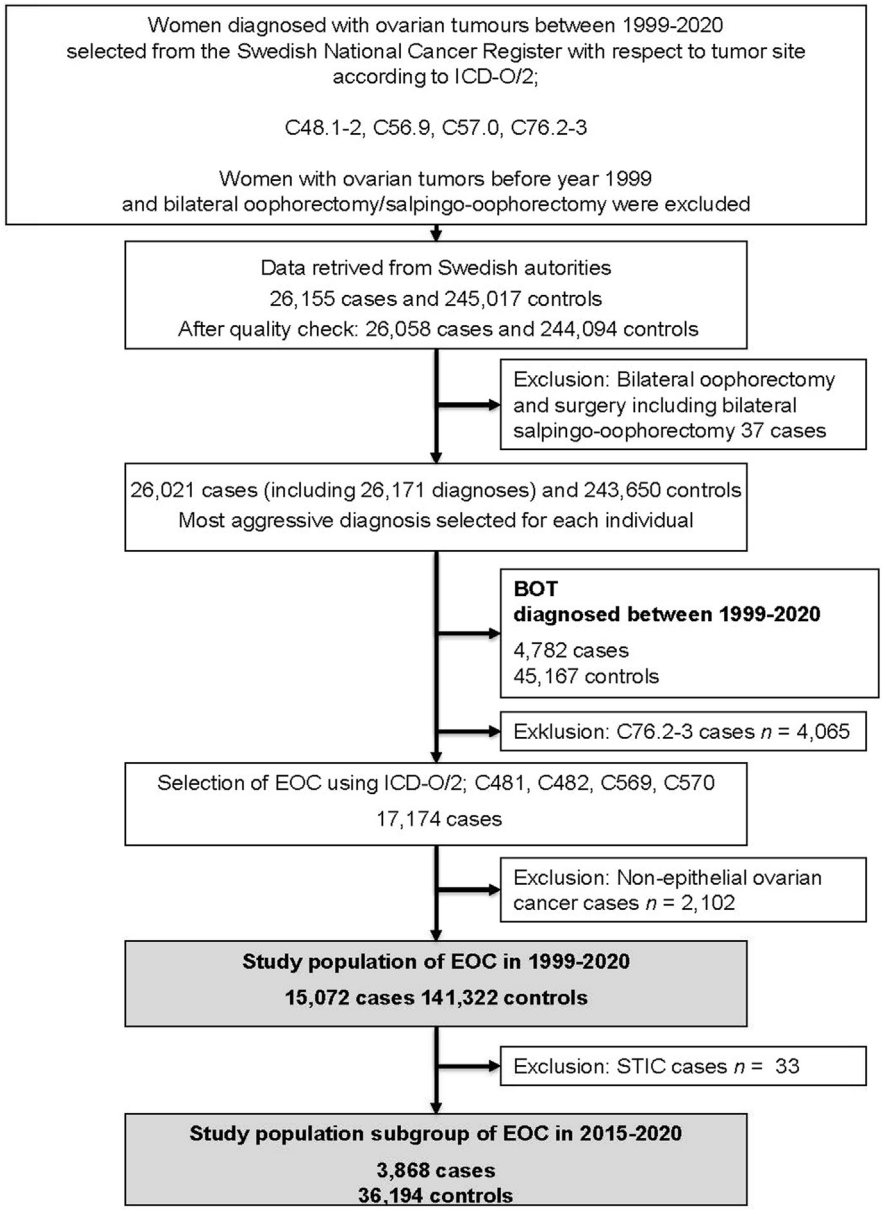
Potential confounders

Potential confounders were chosen a priori and include age, parity, educational level, previous gynecologic surgical procedures, hormonal contraceptives (oral, implants, injectables, patches, and the vaginal ring), and menopausal hormone therapy (MHT) (Supplemental Materials and Methods). Parity at the index date was extracted from the Multi-Generation Register. The highest educational level (1 year before index diagnosis year) was retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies. Previous gynecologic surgical procedures, such as salpingectomy, unilateral salpingo-oophorectomy, hysterectomy, and tubal ligation, were retrieved from the National Patient Register. Lateralization of salpingectomy was included for women who had a surgical procedure before 1997 or later if they had registered salpingectomy twice during the entire study period. Any gynecologic surgical procedures occurring within 90 days before the index date were not included in the analyses. Data on hormonal contraceptives and MHT were retrieved from the Swedish Prescribed Drug Register and were available from 2005. To allow for sufficient exposure and follow-up time, these were adjusted only in the subgroup of women with index dates between 2015 and 2020.

Data management

Exposures were categorized by the number of PID episodes (0, 1, 2, and ≥3), number of children (0, 1, 2, and ≥3), and educational level as mandatory

FIGURE 1
Flowchart of the study population



BOT, borderline ovarian tumor; *EOC*, epithelial ovarian cancer; *ICD-O-2*, International Classification of Diseases for Oncology, Second Edition; *STIC*, serous tubal intraepithelial carcinoma.

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TABLE 1
Baseline characteristics for cases with epithelial ovarian cancer and matched controls, separated by year of diagnosis

	EOC (1999–2020)		EOC (2015–2020)	
	Cases[a]	Controls[a]	Cases[a]	Controls[a]
Characteristic	n=15,072	n=141,322	n=3868	n=36,194
PID[b]				
Never	14,904 (98.9)	140,052 (99.1)	3804 (98.3)	35,701 (98.6)
Ever	168 (1.1)	1270 (0.9)	64 (1.7)	493 (1.4)
Age at first PID (y)[b]				
Mean (SD)	43.3 (12.7)	41.8 (11.5)	46.1 (14.5)	40.0 (11.8)
Range	18–80	15–85	18–78	16–79
Lead time at first PID (y)[b]				
Mean (SD)	13.9 (8.5)	16.0 (8.6)	15.6 (9.6)	20.2 (8.9)
Range	0–33	0–34	0–33	0–34
No. of PID episodes[b]				
0	14,904 (98.9)	140,052 (99.1)	3804 (98.3)	35,701 (98.6)
1	120 (0.8)	986 (0.7)	41 (1.1)	377 (1.0)
2	32 (0.2)	210 (0.1)	14 (0.4)	82 (0.2)
≥3	16 (0.1)	74 (0.1)	9 (0.2)	34 (0.1)
PID_{ext}[b]				
Never	14,760 (97.9)	138,922 (98.3)	3748 (96.8)	35,243 (97.4)
Ever	312 (2.1)	2400 (1.7)	120 (3.1)	951 (2.6)
Educational level				
Mandatory school	4824 (32.4)	44,706 (32.2)	862 (22.5)	7941 (22.2)
High school	6040 (40.6)	56,224 (40.5)	1661 (43.3)	15,375 (43.1)
University graduate or other	4010 (27.0)	37,834 (27.3)	1316 (34.3)	12,376 (34.7)
Parity				
0	3024 (20.1)	21,070 (14.9)	785 (20.3)	5239 (14.5)
1	2697 (17.9)	23,693 (16.8)	638 (16.5)	5669 (15.7)
2	5648 (37.5)	56,007 (39.6)	1505 (38.9)	15,083 (41.7)
≥3	3703 (24.6)	40,552 (28.7)	940 (24.3)	10,203 (28.2)
Previous gynecologic surgery[b]				
Ooporectomy, unilateral	26 (0.2)	381 (0.3)	8 (0.2)	126 (0.3)
Salpingectomy, unilateral	37 (0.2)	405 (0.3)	12 (0.3)	132 (0.4)
Salpingectomy, bilateral	3 (0.0)	111 (0.1)	0 (0)	42 (0.1)
Salpingectomy, unspecified	37 (0.2)	382 (0.3)	24 (0.6)	198 (0.5)
Unilateral salpingo-oophorectomy	136 (0.9)	1756 (1.2)	47 (1.2)	642 (1.8)
Hysterectomy	673 (4.5)	7414 (5.2)	244 (6.3)	2335 (6.5)
Tubal ligation	221 (1.5)	2711 (1.9)	96 (2.5)	992 (2.7)

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TABLE 1
Baseline characteristics for cases with epithelial ovarian cancer and matched controls, separated by year of diagnosis
(continued)

	EOC (1999–2020)		EOC (2015–2020)	
	Cases[a]	Controls[a]	Cases[a]	Controls[a]
Characteristic	n=15,072	n=141,322	n=3868	n=36,194
Drug use				
Hormonal contraceptives				
None	6527 (94.7)	59,977 (92.7)	3615 (93.5)	32,973 (91.1)
≤5 y	264 (3.8)	3070 (4.7)	171 (4.4)	1984 (5.5)
>5 y	103 (1.5)	1632 (2.5)	82 (2.1)	1237 (3.4)
MHT				
None	4226 (61.3)	41,290 (63.8)	2294 (59.3)	22,273 (61.5)
≤5 y	1405 (20.4)	13,058 (20.2)	737 (19.1)	7088 (19.6)
>5 y	1263 (18.3)	10,331 (16.0)	837 (21.6)	6833 (18.9)

Data are presented as number (percentage), unless otherwise indicated. PID includes salpingitis, oophoritis, and tubo-ovarian abscess. PID_{ext} indicates PID and endometritis and pelvic peritonitis.

EOC, epithelial ovarian cancer; *MHT*, menopausal hormone therapy; *PID*, pelvic inflammatory disease; *SD*, standard deviation.

[a] Numbers may not sum to total because of missing data; [b] PID and surgical procedures within 90 days before the index date were not accounted for in the analyses.

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school, high school, university graduate, or other. Previous gynecologic surgical procedures were categorized as follows: salpingectomy (unilateral, bilateral, or unspecified) (yes or no), unilateral salpingo-oophorectomy (yes or no), hysterectomy (yes or no), and/or tubal ligation (yes or no). Previous uses of hormonal contraceptives and MHT were categorized into none, ≤5 years, or >5 years.

Statistical methods

IBM SPSS Statistics software (version 26; IBM Corporation, Armonk, NY) was used for statistical analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression on matching factors and were adjusted for potential confounders (educational level, parity, salpingectomy, salpingo-oophorectomy, hysterectomy, and tubal ligation) (adjusted OR 1 [aOR1]). A test for trend was performed for the analysis of the ordinal "number of PID" by treating it as a continuous variable. In addition to previously described potential confounders, we performed sensitivity analyses for the last 6 years and added previous use of hormonal contraceptives or MHT as adjusting factors (adjusted OR 2 [aOR2]). We performed analyses stratified by histotype for the subgroup with index dates falling between 2015 and 2020.

Results

Participants

The final study population consisted of 15,072 women with EOC (ovarian cancer [12,565 (83.4%)], tubal [1725 (11.4%)], and primary peritoneal cancer [782 (5.2%)]) and 141,322 controls (Figure 1). Background characteristics, exposure data, and confounding factors of cases and controls are presented in Table 1. Additional background characteristics are presented in Supplemental Table 2.

Outcome data

Case characteristics are presented in Table 2. The mean age of women diagnosed with EOC was 65.5 years (standard deviation, 12.8; range, 18–97). Serous EOC was the most common histotype (9102 [60.4%]), and in descending order, serous EOC was followed by adenocarcinoma NOS (2011 [13.3%]), endometrioid (1542 [10.2%]), mucinous (1 167 [7.7%]), clear cell (786 [5.2%]), and unspecified carcinoma (464 [3.1%]) (Table 2). Among women diagnosed with EOC between 2015 and 2020, the most common histotype was HGSC (2319 [60.0%]) (Table 2).

Exposure data

Here, 168 of 15,072 cases (1.1%) and 1270 of 141,322 controls (0.9%) had ≥1 clinically verified PID episode (Table 1). Cases were slightly older than controls at first PID (mean: 43.3 vs 41.8 years, respectively) (Table 1). The highest number of PID episodes in any individual in the register was 9. Among those with previous PID, having had only 1 episode was most common in both cases and controls (71.4% vs 77.6%, respectively), followed by 2 registered PID episodes (19.0% vs 16.5%, respectively), and ≥3 registered PID episodes (9.5% vs 5.8%, respectively).

Main results

A history of PID was associated with an increased risk of EOC in the unadjusted model (OR, 1.25; 95% CI, 1.06–1.47) and when adjusting for potential confounders (aOR1, 1.39; 95% CI,

TABLE 2
Tumor characteristics of epithelial ovarian cancer cases in the study population

Characteristic	EOC (1999–2020) n=15,072	EOC (2015–2020) n=3868
Age at diagnosis (y)		
Mean (SD)	65.5 (12.8)	66.2 (12.6)
Range	18–97	18–97
Year of diagnosis		
1999–2003	3586 (23.8)	—
2004–2009	4189 (27.8)	—
2010–2014	3386 (22.5)	—
2015–2020	3911 (25.9)	3868 (100.0%)[a]
Histotype		
Serous	9102 (60.4)	485 (12.5)
HGSC[b]	—	2319 (60.0)
Endometrioid	1542 (10.2)	316 (8.2)
Mucinous	1167 (7.7)	271 (7.0)
Clear cell	786 (5.2)	261 (6.7)
Adenocarcinoma NOS	2011 (13.3)	163 (4.2)
Unspecified carcinomas	464 (3.1)	53 (1.4)
FIGO stage[c]		
I	2452 (16.3)	850 (22.0)
II	914 (6.1)	296 (7.7)
III	4980 (33.0)	1572 (40.6)
IV	1930 (12.8)	816 (21.1)
Unknown	4796 (31.8)	334 (8.6)

Data are presented as number (percentage), unless otherwise indicated.

EOC, epithelial ovarian cancer; *FIGO*, International Federation of Gynecology and Obstetrics; *HGSC*, high-grade serous ovarian carcinoma; *NOS*, not otherwise specified; *SD*, standard deviation.

[a] Cases defined by the International Classification of Diseases for Oncology, Third Edition; [b] HGSC was first introduced in the Swedish National Cancer Register 2014; [c] Clinical stage was first introduced in the Swedish National Cancer Register 2004.

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1.17–1.66) (Table 3). A dose-response relationship was observed between the number of PID episodes and the risk of EOC (P_{trend}<.001) (Figure 2). Histotype-specific analyses showed an association between an increased risk of serous carcinoma (aOR1, 1.46; 95% CI, 1.18–1.80) and clear cell carcinoma (aOR1, 1.83; 95% CI, 0.99–3.41), although a nonsignificant association (Table 4). No significant association was found for any of the other histotypes (Table 4).

In the subgroup of women diagnosed with EOC in 2015–2020, previous PID was associated with an increased risk of subsequent HGSC (aOR2, 1.43; 95% CI, 1.01–2.04) and a nonsignificant increased risk of clear cell carcinoma (aOR2, 2.30; 95% CI, 0.90–5.86) but no other histotypes (Table 5).

The results are similar when using the extended definition of PID, which includes endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess. Extended PID was associated with an increased risk of EOC (aOR1, 1.35; 95% CI, 1.19–1.53), and serous carcinoma (aOR1, 1.40; 95% CI, 1.20–1.64) and clear cell carcinoma (aOR1, 1.81; 95% CI, 1.15–2.87) (Table 4) for the entire study population. In histotype-specific analyses within the 2015–2020 subgroup, PID_{ext} was significantly associated with an increased risk of serous carcinoma (aOR2, 2.07; 95% CI, 1.20–3.59) and clear cell carcinoma (aOR2, 2.12; 95% CI, 1.08–4.13) (Table 5).

Discussion

Principal findings

In this nationwide register-based case-control study, a history of PID was associated with an increased risk of EOC. In histotype-specific analyses, an increased risk was found for serous EOC and HGSC, but no significant association was found for any other histotype. Moreover, we found a trend toward an increased risk of EOC associated with an increasing number of PID episodes. The association was seen when PID was defined as salpingitis, oophoritis, and tubo-ovarian abscess and was similar when using the extended definition of PID_{ext} with an additional significant association observed for clear cell carcinoma.

Results in the context of what is known

The results support our hypothesis that women with previous PID have an increased risk of EOC; particularly HGSC, which is in line with other studies.[3–5,14] In a Danish population-based cohort study using national health registers, PID was associated with a modest risk of serous EOC.[5] Our study demonstrates an association of PID with EOC overall and, similar to Rasmussen, discerns HGSC from the serous histotype.

When using the extended definition of PID, which also includes endometritis and pelvic peritonitis, our results were similar for all histotypes with an additional finding: an association with an increased risk of clear cell carcinoma became significant. Previous studies using this extended definition of PID have only shown significant associations with serous or HGSC but no other histotypes of invasive EOC.[5,8,22] Rasmussen et al[5] discussed a potential association with

TABLE 3
Crude OR and aOR for the association between clinically verified PID and risk of EOC in women diagnosed with EOC (1999–2020)

Variable	Cases/controls	OR	95% CI	aOR[a]	95% CI	aOR1[b]	95% CI
PID[c]							
Never	14,904/140,052	Ref		Ref		Ref	
Ever	168/1270	1.25	1.06–1.47	1.22	1.03–1.44	1.39	1.17–1.66
No. of PID episodes[c]							
0	14,904/140,052	Ref		Ref		Ref	
1	120/986	1.14	0.94–1.38	1.10	0.91–1.34	1.26	1.04–1.54
2	32/210	1.50	1.03–2.17	1.45	1.00–2.11	1.67	1.14–2.44
≥3	16/74	2.16	1.25–3.70	2.19	1.27–3.78	2.50	1.44–4.35

PID includes salpingitis, oophoritis, and tubo-ovarian abscess.

aOR, adjusted odds ratio; *aOR1*, adjusted odds ratio 1; *CI*, confidence interval; *EOC*, epithelial ovarian cancer; *OR*, odds ratio; *PID*, pelvic inflammatory disease; *Ref*, reference.

[a] Conditioned on matching factors (age and residential district) adjusted for educational level and parity; [b] Conditioned on matching factors (age and residential district) adjusted for educational level, parity, and previous surgery (salpingectomy, salpingo-oophorectomy, hysterectomy, and tubal ligation); [c] PID and surgical procedures within 90 days before the index date were not accounted for in the analyses.

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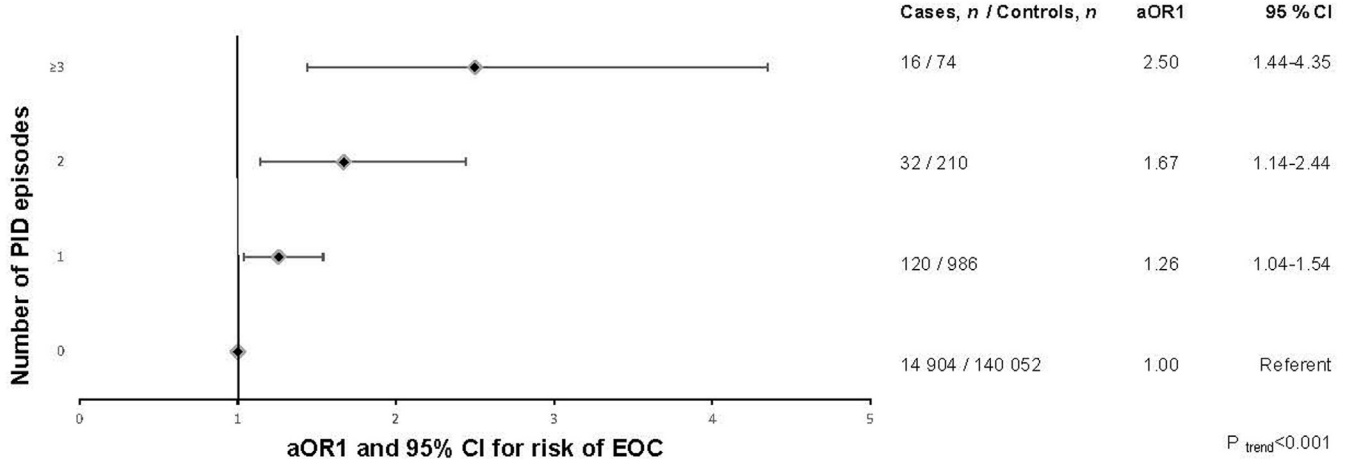
an increased risk of mucinous and clear cell ovarian carcinoma among women with PID aged ≥35 years, although the results were not significant.

Similar to our study, an increased risk of HGSC was evident after PID in an Australian population-based cohort study.[4] The risk estimates seem to increase when adjusting for confounders, including previous gynecologic surgery. Observational studies have demonstrated a reduced risk of EOC in women with previous gynecologic surgery.[13–15] PID, or a sequela thereof, is one of the primary indications for salpingectomy in benign indications. We adjusted for gynecologic surgical procedures, considering that women with previous PID are more likely to have undergone surgery. In a Swedish population-based cohort study, the protective effect of salpingectomy on EOC was not limited to women with previous PID but was also evident in women without previous PID.[14] This explains why the ORs in our study tended to increase when adjusting for this potential confounder.

The proportion of registered PID in our study was low (0.9%). Moreover, there is a reason to believe that it could be higher if there were more sensitive noninvasive diagnostic tests for PID aside from laparoscopy. In comparison, more than 42% of women in Nordic countries were seropositive for *Chlamydia trachomatis*–specific antibodies in 1 study.[23] Prospective serologic studies have demonstrated that *C trachomatis*–

FIGURE 2
Number of PID episodes and risk of EOC (1999–2020)



aOR1, adjusted odds ratio 1; *CI*, confidence interval; *EOC*, epithelial ovarian cancer; *PID*, pelvic inflammatory disease.

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TABLE 4
Association between clinically verified PID and EOC in women diagnosed in 1999–2020 by histotype

		PID[a]				PID_{ext}[a]			
		Cases	Controls			Cases	Controls		
Histotype	Cases/controls	n (%)	n (%)	aOR1[b]	95% CI	n (%)	n (%)	aOR1[b]	95% CI
EOC overall	15,072/141,322	168 (1.1)	1 270 (0.9)	1.39	1.17–1.66	312 (2.1)	2 400 (1.7)	1.35	1.19–1.53
Serous	9102/85,560	111 (1.2)	815 (1.0)	1.46	1.18–1.80	202 (2.2)	1 515 (1.8)	1.40	1.20–1.64
Endometrioid	1542/14,509	15 (1.0)	130 (0.9)	1.11	0.63–1.96	30 (1.9)	251 (1.7)	1.21	0.81–1.81
Mucinous	1167/10,921	11 (0.9)	99 (0.9)	1.38	0.72–2.64	17 (1.5)	202 (1.8)	0.94	0.56–1.56
Clear cell	786/7350	15 (1.9)	82 (1.1)	1.83	0.99–3.41	28 (3.6)	152 (2.1)	1.81	1.15–2.87

PID includes salpingitis, oophoritis, and tubo-ovarian abscess. PID_{ext} indicates PID and endometritis and pelvic peritonitis.

aOR1, adjusted odds ratio 1; *CI*, confidence interval; *EOC*, epithelial ovarian cancer; *PID*, pelvic inflammatory disease.

[a] PID and surgical procedures within 90 days before the index date were not accounted for in the analyses; [b] Conditioned on matching factors (age and residential district) adjusted for educational level, parity, and previous surgery (salpingectomy, salpingo-oophorectomy, hysterectomy, and tubal ligation).

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specific antibodies, indicating previous infection, are associated with an increased risk of EOC,[23–25] supporting the idea of PID as a risk factor for EOC.

Clinical implications

Women are rarely diagnosed with PID, but even so, this condition is associated with a subsequent risk of EOC. Women with multiple PIDs seem to be at greatest risk of subsequent EOC.

Research implications

The association between previous PID and EOC risk has been recognized, although much remains to be explored. To demonstrate causality, the temporal relationships between PID and EOC risk and the biological mechanisms behind the association need to be explored in more depth. PID precedes EOC; however, the lead time between inflammation and cancer development is unknown. It is not established whether it is the carcinogenic effect of a particular pathogen or the inflammatory process itself that increases risk. However, *C trachomatis*, the major cause of PID, may have carcinogenic effects.[26–28] It is likely that there are additional as-yet-unknown contributing factors that merit further investigation. Mechanisms of inflammation and tumor development could be studied more closely in experimental animal models. Moreover, a potential link between PID and borderline ovarian tumors deserves future exploration.

Strengths and limitations

The results of this study are based on data from the Swedish national registers, which have high population coverage, and offer large sample sizes in combination with consistently recorded

TABLE 5
Association between clinically verified PID and EOC in women diagnosed in 2015–2020 by histotype

		PID[a]				PID_{ext}[a]			
		Cases	Controls			Cases	Controls		
Histotype	Cases/controls	n (%)	n (%)	aOR2[b]	95% CI	n (%)	n (%)	aOR2[b]	95% CI
EOC overall	3872/36,194	64 (1.7)	493 (1.4)	1.33	1.01–1.76	120 (3.1)	951 (2.6)	1.29	1.06–1.58
HGSC	2319/21,731	40 (1.7)	308 (1.4)	1.43	1.01–2.04	64 (2.8)	589 (2.7)	1.12	0.85–1.47
Serous	485/4509	8 (1.6)	45 (1.0)	1.67	0.73–3.86	18 (3.7)	87 (1.9)	2.07	1.20–3.59
Endometrioid	316/2957	1 (0.3)	48 (1.6)	0.13	0.02–1.06	9 (2.8)	94 (3.2)	0.86	0.41–1.82
Mucinous	271/2559	5 (1.8)	36 (1.4)	1.55	0.56–4.29	8 (3.0)	68 (2.7)	1.26	0.57–2.77
Clear cell	261/2467	8 (3.1)	38 (1.5)	2.30	0.90–5.86	15 (5.7)	74 (3.0)	2.12	1.08–4.13

PID includes salpingitis, oophoritis, and tubo-ovarian abscess. PID_{ext} indicates PID and endometritis and pelvic peritonitis.

aOR2, adjusted odds ratio 2; *CI*, confidence interval; *EOC*, epithelial ovarian cancer; *HGSC*, high-grade serous carcinoma; *MHT*, menopausal hormone therapy; *PID*, pelvic inflammatory disease.

[a] PID and surgical procedures within 90 days before the index date were not accounted for in the analyses; [b] Conditioned on matching factors (age and residential district) adjusted for educational level, parity, previous surgery (salpingectomy, salpingo-oophorectomy, hysterectomy, and tubal ligation), and use of hormonal contraceptives or menopausal hormone therapy.

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details on exposure, outcome, and covariates (see the Supplemental Materials and Methods for details). Tumor morphology was available for the entire study population, as defined by ICD-O-2 criteria. For the 2015–2020 subgroup, tumor morphology was defined by ICD-O-3 criteria, and HGSC could be discerned from serous carcinomas.

Exposure data included diagnoses and surgical procedures occurring in inpatient care since 1987 and in specialized outpatient clinics since 2001. Diagnoses from general practitioners occurring in the outpatient setting are not available. Furthermore, PID is difficult to diagnose, and women might not seek medical care. Consequently, the proportion of women diagnosed with PID might be underestimated, leading to misclassification. However, this would lead to an underestimation of the association as the misclassification is considered nondifferential.

The Swedish Prescribed Drug Register was established in 2005, and consequently, hormonal therapy could not be adjusted in the whole study population. However, a sufficient follow-up time was available for the subgroup of women with index dates between 2015 and 2020.

Conclusions

A history of PID is associated with an increased risk of EOC, and a dose-response relationship is evident. Histotype-specific analyses show an association with an increased risk of particularly serous EOC and HGSC, including the use of a wider definition of PID with clear cell carcinoma; however, there is no significant association with other histotypes. Infection and inflammation of the upper reproductive tract might have serious long-term consequences, such as EOC, and future studies on biological explanations and temporal relations are required. ■

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Supplemental Materials and Methods

Descriptions of the Swedish national registers

The National Cancer Register

Here, cases were retrieved from the nationwide Swedish National Cancer Register, established in 1958. It is mandatory for clinicians and pathologists to report independently all patients with cancer, premalignant conditions, and certain benign tumors. The diagnoses are morphologically verified in 99% of enrollees, and the completeness of the registry exceeds 95%.[1] Moreover, we included ovarian, fallopian tube, and primary peritoneal cancer in our definition of epithelial ovarian cancer (EOC). Borderline ovarian tumors were excluded. Morphology was defined according to the International Classification of Diseases for Oncology, Second Edition (ICD-O-2), united for the whole cohort. In a subgroup analysis of women diagnosed with EOC from 2015 to 2020, we used the morphology classification according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). In this subgroup, we discerned high-grade serous carcinoma (HGSC) from other serous tumors either by the specific morphology code assigned HGSC or by using the tumor grade retrieved from the Swedish Quality Register of Gynecological Cancer.[2]

The Swedish Quality Register of Gynecological Cancer

For the subgroup of women diagnosed between 2015 and 2020, tumor grades were retrieved from the Swedish Quality Register of Gynecological Cancer.[2] The register can be divided into 4 parts, and the register covering ovarian cancer was established in 2008. The quality is assessed to be "good," and the register is a source of data used for research.[3] The register has an estimated completeness of 94% relative to the Swedish National Cancer Register, and coverage akin to other quality registers in Sweden is reported.[3]

The National Patient Register

The exposure to pelvic inflammatory disease (PID) and previous gynecologic surgical procedures were collected from the National Patient Register.[4] The register was established in 1964 and reached nationwide coverage in 1987.[4] It contains individual data on hospital admission, major interventions, discharge, and discharge diagnosis.[4] The register was supplemented in 1997 with outpatient surgery and from 2001 with specialized outpatient care records.[4] The diagnoses are coded according to the International Classification of Diseases, Ninth Revision, classifications from 1987 to 1996 and according to the International Classification of Diseases, Tenth Revision, classification from 1997 onward. Surgical interventions are coded according to the classifications of surgical procedures from 1963 to 1996 (K06) and the classifications of surgical procedures from 1997 to 2020. The quality of the register is considered high.[5]

The Multi-Generation Register

Parity was extracted from the Multi-Generation Register.[6] The register contains data on individuals born in 1932 or later and who were registered in the Swedish population register from 1960 onward.[6] For women born in Sweden from 1915 and later, parity data are of high quality.[6]

The Longitudinal Integration Database for Health Insurance and Labor Market Studies

The variable educational level was collected from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA).[7] LISA is one of the largest databases in Sweden. LISA was established in 1990. Moreover, the quality of data is generally high.[7] The register contains data from adult individuals in Sweden aged $\geq$16 years (and since 2010, from age $\geq$15 years).[7] It is updated annually. Data on the highest attained educational level is available in >98% of all individuals aged 25 to 64 years.[7]

The Swedish National Prescribed Drug Register

Information regarding prescription and expedition of hormonal contraceptives (oral, implants, injectables, patches, and the vaginal ring) and menopausal hormone therapy (MHT) were extracted from the Swedish Prescribed Drug Register.[8] The register started in July 2005. The register includes data on all prescribed drugs dispensed at pharmacies in the entire country.[8] Drugs administered in hospital settings, vaccines, and over-the-counter medicines are not included in the register. The register includes detailed information on the product (Anatomical Therapeutic Chemical code, drug name, pack size, etc.), prescription, and costs. The quality of the register is reported to be high.[9,10]

Selection and exclusions of cases

Cases were retrieved from the Swedish National Cancer Register and the same register was used to exclude women with previous EOC. This requirement was set out to assure that our cases were primary EOC and not recurrent EOC. Cases received their diagnosis between 1999 and 2020, and we chose to identify the histotypes using the morphology code defined in ICD-O-2, except for the subgroup of women diagnosed between 2015 and 2020, for whom we used ICD-O-3.

Of note, 1 diagnosis per individual was selected. In women with $\geq$1 diagnosis recorded at the same index date, the histotypes were ranked according to aggressiveness in the following descending order: serous, endometrioid, mucinous, and clear cell carcinoma. The diagnosis with the highest rank was chosen.

Selection of exposure

The symptoms of PID and EOC are similar. To avoid misclassification, exposures <90 days before the index diagnosis date were excluded from the analyses. Women should have been residing in Sweden since the age of 18 years. This requirement has been stated to ensure that a previous PID would have been registered and, therefore, would be possible to include in the analyses.

Rationale for adjusting factors

Here, we used educational level as a proxy for socioeconomic status, which was adjusted in the regression models.[11]

It is likely that sexual behavior varies among individuals, leading to an uneven distribution of PID risk for the women included in our study. A geographic variation in sexual behavior has been observed in a Swedish study between urban and rural areas.[12] In addition, families carrying gene alternations in breast cancer genes 1 and 2 (BRCA1 and BRCA2) or other hereditary genes increasing the risk of ovarian cancer may be unevenly distributed geographically. Therefore, residential districts were adjusted in our analyses.

Nulliparity is suggested to be a risk factor for EOC. During pregnancy, the cervical mucus plug isolates the uterus from the vaginal compartment and protects the fetus against vaginal pathogens, decreasing the risk of salpingitis and oophoritis, which is why nulliparity is potentially increasing the risk of PID and, therefore, is included as a confounding factor. Previous gynecologic surgical procedure reduces the risk of PID and has been suggested to reduce the risk of EOC. Surgical procedures within 90 days of the diagnosis date were censored to avoid misclassification of the procedure. We assumed that surgical procedures performed within 90 days before the index date were connected to the index diagnosis, and therefore, they were not adjusted.

Hormonal contraceptives were considered a confounding factor in our study. Hormonal contraceptives are shown to reduce the risk of EOC. Hormonal contraceptives affect the cervical mucosa and might reduce the risk of ascending infections and PID. MHT has been associated with an increased risk of EOC. Moreover, MHT use could be associated with sexual activity and, thus, the risk of PID. Therefore, MHT was chosen as a confounder. As the Swedish Prescribed Drug Register did not start until 2005, it is not possible to retrieve previous drug use for the entire study population. A Swedish register-based study showed a different drug use between groups of different educational levels,[13] and we used educational level as a proxy for previous drug use, in addition to socioeconomic status, and, therefore, included it as a confounding factor.

Data management

Birth date was defined as July 1 of the birth year, which was used to calculate age at the index date. If day of diagnosis in the National Cancer Register was missing or "0," it was replaced with the 15th of the month of diagnosis (3255 and 3). If it occurred during outpatient care, the date of diagnosis was set to the date of clinical diagnosis. If treated at the hospital, the date of admission to inpatient care was used as the date of diagnosis. If missing date of admission (n=49), the date was replaced with date of discharge (n=3). Individuals with no date available were excluded (n=46). Data on educational level were assessed the year before the index year, and if missing, the educational level from the closest previous year was used.

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SUPPLEMENTAL TABLE 1
Codes used to identify women with EOC, PID, and potential confounders

Outcome		
The Swedish National Cancer Register (1958–2020)		
	ICD-O-2 (1997–2020) topography	
EOC[a]	C48.1, C48.2, C56.9, C57.0	
	ICD-O-2 (1993 onward) morphology	ICD-O-3 (2005 onward) morphology
Serous carcinoma	8441–8462 90143	8441–8462[b] (84613) 90143
Endometrioid carcinoma	8380–8381 8560 8570	8380–8381 8560 8570
Mucinous carcinoma	8470–8490 90153	8470–8490 90153
Clear cell carcinoma	8310–8313	8310–8313
Adenocarcinoma NOS	8140–8190 8211–8231 8260, 8440	8140–8190 8211–8231 8260, 8440
Unspecified	8010–8034	8010–8034
Exclusion		
The Swedish National Cancer Register (1958–2020)		
	ICD-10 (1997–2020) topography	
BOT	C48.1, C48.2, C56.9, C57.0, C76.2, C76.3	
	ICD-O-2 (1993–2004) morphology	ICD-O-3 (2005 onward) morphology
Serous borderline	84411, 84421, 84423, 84513 84601, 84621, 84623	84421, 84511, 84602, 84621 90141
Endometrioid borderline	83801, 83802, 83811, 84623	83801, 83811
Mucinous borderline	84701, 84702, 84711, 84723 84733, 84801	84721, 84731, 84741 90151
Clear cell borderline	84623	83131, 84441
Brenner borderline	90001	90001
Exclusion		
The Swedish National Patient Register (1987–2020)		
	Classification of surgical procedures (1963–1996)	Classification of surgical procedures (1997–2020)
Bilateral oophorectomy and salpingo-oophorectomy	7021, 7022, 7031, 7032,	LAE20, LAE21, LAF10, LAF11, LAF30

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SUPPLEMENTAL TABLE 1
Codes used to identify women with EOC, PID, and potential confounders *(continued)*

Hysterectomy, including bilateral salpingo-oophorectomy	7221—7228, 7250—7252, 7259, 7263	LCE
Exposure		
	ICD-9 (1987—1996)	ICD-10 (1997—2020)
PID[c]	614A, 614B, 614C	N70.0, N70.1, N70.9
PID_{ext}[d]	614A, 614B, 614C, 614D—X, 615	N70.0, N70.1, N70.9, N71, N73, N74.3, N74.4
Potential confounders		
The Swedish National Patient Register (1987—2020)		
	Classification of surgical procedures (1963—1996)	Classification of surgical procedures (1997—2020)
Tubal ligation	7150—7152	LGA
Hysterectomy	7210, 7211, 7220, 7262, 7467	LCC, LCD
Unilateral oophorectomy	7020	LAE10—LAE11
Unilateral salpingectomy	7120	—
Bilateral salpingectomy	2 procedures of 7120 A combination (7120 + LBE) 7121	2 procedures of LBE — —
Salpingectomy unspecified	—	LBE
Unilateral salpingo-oophorectomy	7030	LAF00—LAF01, LAF20
The Swedish National Prescription Register (2005—2020)		
	ATC	
Hormonal contraceptives	G03A (G03AC01—05 excluded)	
Menopausal hormone therapy	G03C, G03F	
Longitudinal Integration Database for Health Insurance and Labor Market Studies (1990 onward)		
Educational level	Highest educational level 1 year before the index diagnosis year	
Multi-Generation Register (1961 onward)		
Parity	Number of children before the index date	

ATC, Anatomical Therapeutic Chemical; *BOT*, borderline ovarian tumor; *EOC*, epithelial ovarian cancer; *ICD-9*, International Classification of Diseases, Ninth Revision; *ICD-9*, International Classification of Diseases, Tenth Revision; *ICD-O-2*, International Classification of Diseases for Oncology, Second Edition; *ICD-O-3*, International Classification of Diseases for Oncology, Third Edition; *NOS*, not otherwise specified; *PID*, pelvic inflammatory disease.

[a] Excluding women with ovarian tumors before 1999 defined by International Classification of Diseases, Seventh Revision: 158, 1750, 1751, 1758, 1759, 1769, 1974, 1993, and 1994; [b] Registration of high-grade carcinoma was introduced in the Swedish National Cancer Register in 2014, according to the World Health Organization guidelines (ICD-O-3 code 84613); [c] Salpingitis, oophoritis, and tubo-ovarian abscess; [d] Endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess.

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SUPPLEMENTAL TABLE 2
Baseline characteristics of cases of EOC and matched controls, separated by year of diagnosis

	EOC (1999–2020)		EOC (2015–2020)	
	Cases[a]	Controls[a]	Cases[a]	Controls[a]
Characteristic	n=15,072	n=141,322	n=3868	n=36,194
Age at first PID_{ext}[b]				
Mean (SD)	42.5 (12.2)	42.6 (12.1)	44.1 (13.1)	41.5 (12.0)
Range	18–81	13–91	18–81	15–81
Lead time at first PID_{ext} (y)[b]				
Mean (SD)	14.1 (8.5)	15.1 (8.5)	16.1 (9.8)	17.9 (9.2)
Range	0–33	0–34	0–33	0–34
No. of PID_{ext} episodes[b]				
0	14,760 (97.9)	138,922 (98.3)	3748 (96.9)	35,243 (97.4)
1	229 (1.5)	1839 (1.3)	81 (2.1)	711 (2.0)
2	55 (0.4)	417 (0.3)	24 (0.6)	171 (0.5)
≥3	28 (0.2)	144 (0.1)	15 (0.4)	69 (0.2)
Country of birth				
Sweden	13,044 (86.5)	120,430 (85.2)	3251 (84.0)	30,186 (83.4)
Nordic country	835 (5.5)	7707 (5.5)	198 (5.1)	1724 (4.8)
Europe	789 (5.3)	7857 (5.6)	247 (6.4)	2197 (6.1)
World outside Europe	395 (2.6)	5323 (3.8)	172 (4.4)	2086 (5.8)
Infertility				
Never	14,794 (98.2)	139,876 (99.0)	3748 (96.9)	35,494 (98.1)
Ever	278 (1.8)	1446 (1.0)	120 (3.1)	700 (1.9)
Endometriosis				
Never	14,605 (96.9)	139,074 (98.4)	3679 (95.1)	35,392 (97.8)
Ever	467 (3.1)	2248 (1.6)	189 (4.9)	802 (2.2)

Data are presented as number (percentage), unless otherwise indicated. PID_{ext} indicates PID and endometritis, salpingitis, oophoritis, pelvic peritonitis and tubo-ovarian abscess.

EOC, epithelial ovarian cancer; *PID*, pelvic inflammatory disease; *SD*, standard deviation.

[a] Numbers may not sum to total because of missing data; [b] PID and surgical procedures within 90 days before the index date were not accounted for in the analyses.

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