Gynecology Journal Club

Pelvic Inflammatory Disease and Risk of Epithelial Ovarian Cancer: A National Population-based Case-Control Study in Sweden

Supervising Professor:
Dr. Esalat Manesh

Presenter:
Dr. Shaghayegh Karami

August, 2024

Introduction

Epithelial Ovarian Cancer (EOC)

- Insidious Disease
- Few/ No symptoms in early stages
- No validated screening method
- Often diagnosed when beyond curative

Introduction

Pelvic Inflammatory Disease (PID)

- Female reproductive organ inflammation
- Ascending microorganisms
- Endometriosis, Salpingitis, Oophoritis, Pelvic peritonitis, Tubo-ovarian abscess

Introduction

Chronic Inflammation

- Microorganisms ⇨ 15-20% of cancer
- Involved in EOC carcinogenesis
- Contradictory findings around association between PID and EOC

Introduction

Protective Factors of EOC

- **Inability of infectious disease to ascend**

  Salpingectomy, Hysterectomy, Tubal ligation

- **Reduced lifetime ovulations**

  Parity, Oral Contraceptive Use

Introduction

Risk Factors of EOC

- Nulliparity
- Infertility
- Both are potential consequences of PID
- Possible association between PID and EOC

Materials and Methods

Study Design

- National (Sweden)
- Population based

  Women diagnosed with EOC (1999-2020)
- Case-control

  10 matched controls (diagnosis and birth date, residential district)

Materials and Methods

Cases

- Swedish National Cancer Register
- ICD-O-2 Classification (ovary-fallopian tube-primary peritoneum)
- Histotypes ⇨ Invasive Carcinoma
- Exclusion of borderline ovarian tumors
- 2015-2020 ⇨ICD-O-3 ⇨ HGSC and LGSC
- Tumor Stages ⇨ Introduced in 2004

Materials and Methods

Controls

- Swedish Register of the Total Population
- Could only be selected once
- Without reversal

Materials and Methods

Exclusion

- Before 1999
- Major gynecologic surgery
- Bilateral oophorectomy & Bilateral Salpingo-oophorectomy
- Not resident of Sweden since 18
- Exclusion of matched control

Materials and Methods

Exposure

- Clinically verified PID (National Patient Register)
- Inflammation of upper reproductive tract
- ICD9/ ICD10 ⇨ salpingitis, oophoritis, tubo-ovarian abscess
- PID extended ⇨ + endometritis, salpingitis
- Exposure of < 90 days were excluded

Materials and Methods

Potential Confounders

- Age
- Parity

  multi-generation register
- Educational level

  longitudinal Integration database

Materials and Methods

Potential Confounders

- Previous gynecological surgery

  national patient register, ≥ 90 days

- Hormonal contraceptives

- Menopausal Hormone Therapy

  Swedish prescribed drug register

Materials and Methods

Data Management

- Number of PID episodes

  0, 1, 2 and ≥ 3

- Number of Children

  0, 1, 2 and ≥ 3

- Education level

  mandatory, high school, university graduate

Materials and Methods

Data Management

- Previous gynecological surgery

  salpingectomy (unilateral, bilateral, unspecified)

  unilateral salpingo-oophorectomy

  Hysterectomy

  Tubal ligation

Materials and Methods

Data Management

- Hormonal contraceptive and MHT

  none

  ≤ 5 years

  > 5 years

Results

Participants

- Final population of 15,072 women (EOC)
- Ovarian cancer 12,565 (83.4%)
- Tubal cancer 1,725 (11.4%)
- Primary peritoneal cancer 782 (5.2%)
- 141,322 controls

Results

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]

Results

Tumor characteristics of epithelial ovarian cancer cases in the study population

Characteristic	EOC (1999–2020) n=15,072	EOC (2015–2020) n=3868
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)

Results

Exposure Data

- Highest PID episodes in any individual was 9
- In case and control patients with PID :

  1 PID episode was most common (71.4% & 77.6%)

  2 registered PID (19.0% & 16.5%)

  ≥ 3 episodes of PID (9.5% & 5.8%)

Results

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

(continued)

Characteristic	EOC (1999–2020) Cases[a] n=15,072	EOC (1999–2020) Controls[a] n=141,322	EOC (2015–2020) Cases[a] n=3868	EOC (2015–2020) Controls[a] 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)

Results

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

(continued)

Characteristic	EOC (1999–2020) Cases[a] n=15,072	EOC (1999–2020) Controls[a] n=141,322	EOC (2015–2020) Cases[a] n=3868	EOC (2015–2020) Controls[a] n=36,194
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)

Results

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

Characteristic	EOC (1999–2020) Cases[a] n=15,072	EOC (1999–2020) Controls[a] n=141,322	EOC (2015–2020) Cases[a] n=3868	EOC (2015–2020) Controls[a] 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.

Jonsson. Pelvic inflammatory disease and risk of epithelial ovarian cancer. Am J Obstet Gynecol 2024.

Results

Main Results

- With/ without adjustment for potential confounders, history of PID was associated with ⇧ risk of EOC
- Dose-response relationship between PID episodes and EOC risk ($p < 0.001$)

Results

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.

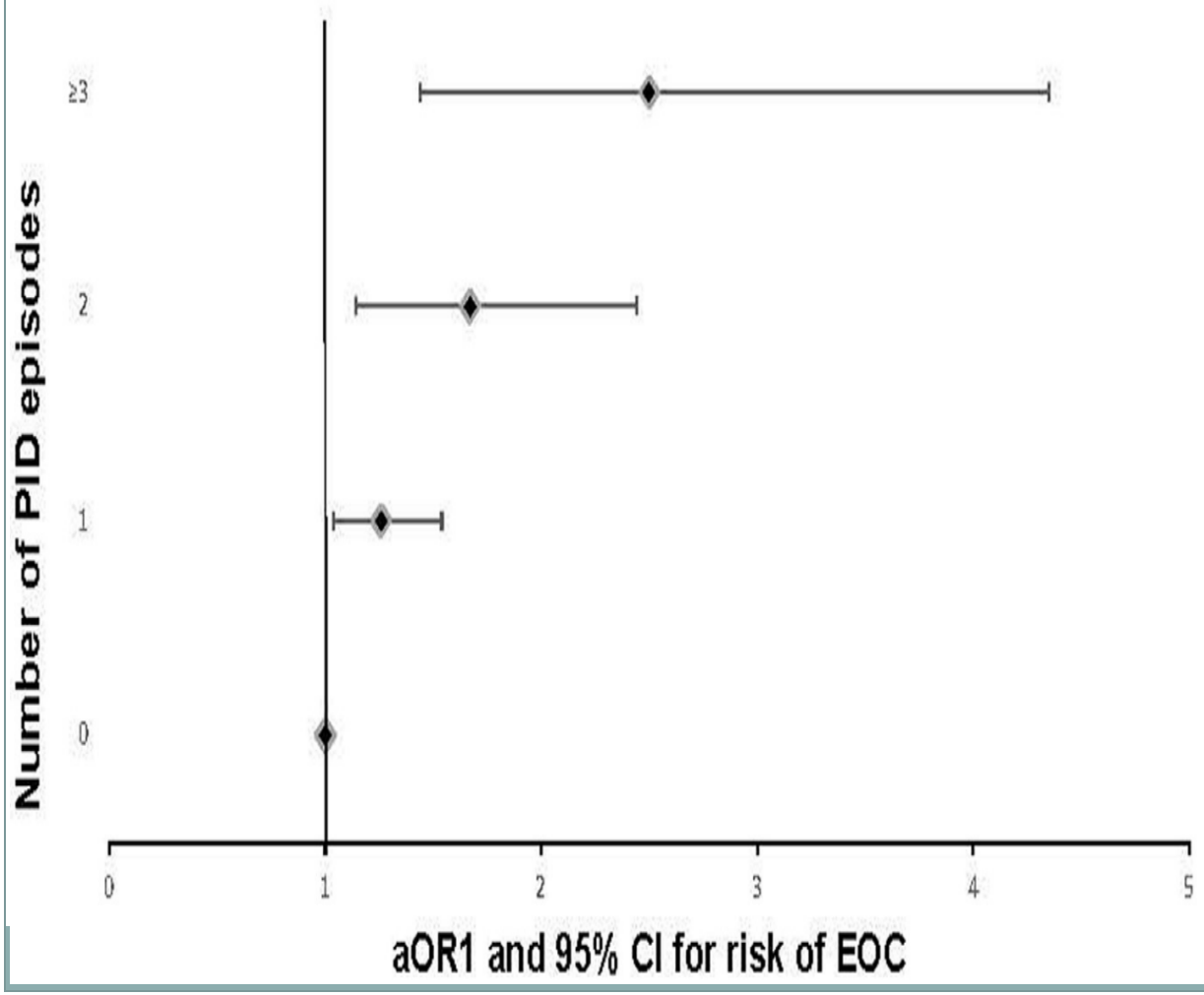
aOR, adjusted odds ratio; *aOR1*, adjusted odds ratio 1; *CI*, confidence interval; *EOC*, epithelial ovarian cancer; *OR*, odds ratio; *PID*, pelvic inflammatory disease; *Ref*, reference.

[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.

Jonsson. Pelvic inflammatory disease and risk of epithelial ovarian cancer. Am J Obstet Gynecol 2024.

Results

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



Number of PID episodes	Cases, *n* / Controls, *n*	aOR1	95 % CI
≥3	16 / 74	2.50	1.44-4.35
2	32 / 210	1.67	1.14-2.44
1	120 / 986	1.26	1.04-1.54
0	14 904 / 140 052	1.00	Referent

$P_{trend}<0.001$

Results

Main Results

- Nonsignificant association between ⇧ risk of serous carcinoma and clear cell carcinoma
- PID was associated with ⇧ risk of subsequent HGSC and nonsignificant ⇧ risk of clear cell carcinoma

Results

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).

Jonsson. Pelvic inflammatory disease and risk of epithelial ovarian cancer. Am J Obstet Gynecol 2024.

Results

Main Results (PID extended)

- Extended PID was associated with ⇧ risk of EOC, serous carcinoma, and clear cell carcinoma
- Extended PID was significantly associated with ⇧ risk of serous carcinoma and clear cell carcinoma

Results

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.

Jonsson. Pelvic inflammatory disease and risk of epithelial ovarian cancer. Am J Obstet Gynecol 2024.

Discussion

Principal Findings

- History of PID ⇨ ⇧ risk of EOC
- Histotype specific analysis ⇨ ⇧ risk for serous EOC and HGSC

  no association for any other histotype
- ⇧ risk of EOC with increasing number of PID episodes

  (salpingitis, oophoritis, tubo-ovarian abscess, clear cell carcinoma [PID ext])

Discussion

- Women with previous PID have ⇧ risk of EOC (HGSC)

➢ similar to a Danish population-based cohort study (PID and ⇧ risk of serous EOC)

Discussion

In PID extended:

- Similar results for all histotypes
- ⇧ risk of clear cell carcinoma

➢ Previous studies have shown significant association with serous or HGSC histotypes

➢ Rasmussen et al. ⇨ potential ⇧ in risk of mucinous and clear cell carcinoma with no significant result (PID and ≥ 35 age)

Discussion

- ⇧ risk of HGSC after PID in an Australian population-based cohort
- Observational studies ⇨ ⇩ risk of EOC in women with previous gynecologic surgery
- PID ⇨ primary indication of salpingectomy in benign condition

Discussion

- In a Swedish population based cohort study:

  protective effect of salpingectomy on EOC

  not limited to women with previous PID

  OR increase in current study when adjusting to

  potential cofounders

Discussion

- Low proportion of registered PID in this study (0.9%)
- Higher if there is noninvasive test other aside from laparoscopy
- ≥ 42% of women in Nordic countries were seropositive for Chlamydia trachomatis specific Ab in a study
- C. trichomonas specific Ab ⇨ ⇧ risk of EOC

Discussion

Clinical Implications

- Women are rarely diagnosed with PID
- PID is associated with ⇧ risk of EOC
- Women with multiple PIDs have greater risk of PID

Discussion

Research Implications

- Temporal relationship between PID and EOC
- Biological mechanism behind this association
- The lead time between inflammation and cancer
- Particular pathogen or inflammatory process
- Additional/ unknown contributing factors

Discussion

Strength and limitation

- High population coverage
- Consistently recorded detail on exposure, outcome and covariates
- Tumor morphology was available for entire study population
- Diagnosis from general practitioners in outpatient settings were unavailable

Discussion

Strength and limitation

- PID is difficult to diagnose
- Patient with PID might not seek medical care
- The proportion of women with PID might be underestimated
- Hormonal therapy records ⇨ after 2005

Conclusion

- A history of PID is associated with ⇧ risk of EOC(with dose-response relationship)
- Increased risk of serous EOC and HGSC, and clear cell carcinoma [PID ext]
- Infection and inflammation of upper reproductive tract might have serious long-term consequences such as EOC