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Endometriosis Typology and Ovarian Cancer Risk

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IMPORTANCE Endometriosis has been associated with an increased risk of ovarian cancer; however, the associations between endometriosis subtypes and ovarian cancer histotypes have not been well-described.

OBJECTIVE To evaluate the associations of endometriosis subtypes with incidence of ovarian cancer, both overall and by histotype.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study using data from the Utah Population Database. The cohort was assembled by matching 78 893 women with endometriosis in a 1:5 ratio to women without endometriosis.

EXPOSURES Endometriosis cases were identified via electronic health records and categorized as superficial endometriosis, ovarian endometriomas, deep infiltrating endometriosis, or other.

MAIN OUTCOMES AND MEASURES Estimated adjusted hazard ratios (aHRs), adjusted risk differences (aRDs) per 10 000 women, and 95% CIs for overall ovarian cancer, type I ovarian cancer, and type II ovarian cancer comparing women with each type of endometriosis with women without endometriosis. Models accounted for sociodemographic factors, reproductive history, and past gynecologic operations.

RESULTS In this Utah-based cohort, the mean (SD) age at first endometriosis diagnosis was 36 (10) years. There were 597 women with ovarian cancer. Ovarian cancer risk was higher among women with endometriosis compared with women without endometriosis (aHR, 4.20 [95% CI, 3.59-4.91]; aRD, 9.90 [95% CI, 7.22-12.57]), and risk of type I ovarian cancer was especially high (aHR, 7.48 [95% CI, 5.80-9.65]; aRD, 7.53 [95% CI, 5.46-9.61]). Ovarian cancer risk was highest in women with deep infiltrating endometriosis and/or ovarian endometriomas for all ovarian cancers (aHR, 9.66 [95% CI, 7.77-12.00]; aRD, 26.71 [95% CI, 20.01-33.41]), type I ovarian cancer (aHR, 18.96 [95% CI, 13.78-26.08]; aRD, 19.57 [95% CI, 13.80-25.35]), and type II ovarian cancer (aHR, 3.72 [95% CI, 2.31-5.98]; aRD, 2.42 [95% CI, −0.01 to 4.85]).

CONCLUSIONS AND RELEVANCE Ovarian cancer risk was markedly increased among women with ovarian endometriomas and/or deep infiltrating endometriosis. This population may benefit from counseling regarding ovarian cancer risk and prevention and could be an important population for targeted screening and prevention studies.

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Endometriosis is thought to affect approximately 11% of reproductive-aged women,[1] including 50% to 60% of women and teenage girls with pelvic pain and up to 50% of women with infertility.[2] Although pelvic pain and infertility are the most well-known comorbidities of endometriosis, ovarian, breast, and endometrial cancers are also purported to be associated with endometriosis. A 2021 systematic review and meta-analysis reported that women with endometriosis have nearly 2 times the risk of ovarian cancer (summary relative risk [SRR], 1.93 [95% CI, 1.68-2.22]; n = 24 studies) compared with those without, although associations varied by ovarian cancer histotype.[3] There was strong evidence to support associations between endometriosis and clear cell (SRR, 3.44 [95% CI, 2.82-4.20]; n = 5 studies), endometrioid (SRR, 2.33 [95% CI, 1.82-2.98]; n = 5 studies), and low-grade serous (SRR, 2.33 [95% CI, 1.64-3.31]; n = 2 studies) ovarian cancer.[3] However, associations were not consistently detected for high-grade serous (SRR, 1.08 [95% CI, 0.88-1.32]; n = 3 studies) or mucinous (SRR, 0.98 [95% CI, 0.74-1.29]; n = 5 studies) tumors.[3]

Although multiple studies have assessed heterogeneity in associations between endometriosis and ovarian cancer histotypes, associations between endometriosis macrophenotypic subtypes—superficial peritoneal endometriosis, ovarian endometriomas, and deep infiltrating endometriosis[3,4]—and ovarian cancer have not been adequately explored. Only 1 prior study incorporated information on both endometriosis subtypes and ovarian cancer histotypes, finding that women with ovarian endometriomas have an increased risk of endometrioid and clear cell ovarian cancer 5 to 10 years after index surgery.[5] A better understanding of the associations between endometriosis subtypes and ovarian cancer histotypes may inform novel etiologic pathways to both diseases and influence clinical decision-making for individuals with endometriosis. This study evaluated the associations of endometriosis and endometriosis subtypes with incidence of ovarian cancer, both overall and by histotype.

Key Points

Question How do endometriosis subtypes influence ovarian cancer risk?

Findings Women with endometriosis had 4.2-fold higher ovarian cancer risk than those without endometriosis. Women with ovarian endometriomas and/or deep infiltrating endometriosis, compared with no endometriosis, had 9.7-fold higher risk. Associations between endometriosis subtypes and ovarian cancer histotypes were much greater for type I (endometrioid, clear cell, mucinous, and low-grade serous) compared with type II (high-grade serous) ovarian cancers.

Meaning Women with endometriosis, especially more severe subtypes, have a markedly increased ovarian cancer risk and may be an important population for targeted cancer screening and prevention studies.

Methods

Study Population

The Utah Population Database (UPDB) is a comprehensive, population-based data resource that includes information on more than 11 million individuals.[6] The UPDB uses probabilistic record linking based on multiple identifiers to link vital records, health facility records (statewide inpatient, ambulatory surgery, and emergency department), Utah Cancer Registry records, and University of Utah and Intermountain Health electronic health records (EHRs).[7] Our study protocol was approved by the Resource for Genetic and Epidemiologic Research, the University of Utah Institutional Review Board (IRB), and the Intermountain Health IRB. All research was conducted under a waiver of informed consent designated by the University of Utah IRB. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Exposure: Endometriosis

We created a retrospective cohort (1992-2019) within the UPDB (eFigure in Supplement 1). First, we identified all women, aged 18 to 55 years, with 1 or more endometriosis diagnosis (72.1% with 1, 14.3% with 2, and 13.6% with 3 diagnostic records). The observed prevalence of endometriosis was 6.3%, which is in line with previous estimates.[8] Endometriosis diagnoses (defined by 617* or N80* *International Classification of Diseases* [*ICD*] *9/10* codes; eTable 1 in Supplement 1) were obtained from statewide inpatient records (1996-2019), statewide ambulatory surgery records (1996-2019), University of Utah EHRs (1994-2019), and Intermountain Health EHRs (1992-2019), and subtyped using *ICD 9/10* codes. In line with prior research,[5] we defined 5 categories: superficial peritoneal endometriosis (n = 39 277 [49.8%]), ovarian endometriomas (n = 18 977 [24.1%]), deep infiltrating endometriosis (n = 1028 [1.3%]), ovarian endometriomas and concurrent deep infiltrating endometriosis (n = 1374 [1.7%]), and other (n = 18 237 [23.1%]) (**Table 1**).

Consistent with prior UPDB-based cancer research,[9,10] we chose a matched cohort design to improve efficiency.[11] Women with a history of endometriosis (n = 78 893; "exposed") were matched in a 1:5 ratio to women without known endometriosis (n = 379 043; "unexposed") by birth year and birthplace (Utah/other). All unexposed women were living in Utah as of their matched endometriosis case's diagnosis date.

Outcome: Epithelial Ovarian Cancer

Ovarian cancers diagnosed from 1992 to 2019 (n = 597) were identified via the Utah Cancer Registry, a statewide cancer surveillance program. Cases were defined as those with *ICD-O-3* codes C56.9, C57.0, C48.1, C48.2, and C48.8. As has been done previously,[12,13] we used Surveillance, Epidemiology, and End Results Program morphology codes to assign cases to histotypes consistent with the 2020 World Health Organization ovarian cancer histotyping guidelines (eTable 2 in Supplement 1).[14] Assignments included high-grade serous, low-grade serous, endometrioid, mucinous, clear cell, carcinosarcoma, and other (ie, *ICD-O-3* codes for "carcinoma, not otherwise specified" or "mixed").[12,13,15] Among women without

Table 1. Assignment of Different Combinations of Endometriosis Diagnoses to Analytic Subtypes (N = 78 893)[a]

Deep infiltrating (n = 2402)	Ovarian endometriomas (n = 20 351)	Superficial (n = 62 721)	Other (n = 26 318)	Count, No. (%)	Final subtype assignment
		Yes		39 277 (49.8)	Superficial endometriosis (n = 39 277)
Yes				209 (0.3)	Deep infiltrating endometriosis (n = 1028)
Yes			Yes	92 (0.1)	
Yes		Yes		369 (0.5)	
Yes		Yes	Yes	358 (0.5)	
	Yes			4064 (5.2)	Ovarian endometriomas (n = 18 977)
	Yes		Yes	1154 (1.5)	
	Yes	Yes		8149 (10.3)	
	Yes	Yes	Yes	5610 (7.1)	
Yes	Yes			62 (0.1)	Deep infiltrating endometriosis and ovarian endometriomas (n = 1374)
Yes	Yes		Yes	41 (0.1)	
Yes	Yes	Yes		445 (0.6)	
Yes	Yes	Yes	Yes	826 (1.1)	
			Yes	10 550 (13.4)	Other (n = 18 237)
		Yes	Yes	7687 (9.7)	

[a] Women could have multiple endometriosis diagnoses. The most severe diagnosis was prioritized.

Table 2. Risk of Ovarian Cancer Histotypes Among Women With vs Without Endometriosis (N = 450 906)

Ovarian cancer diagnosis	No. of ovarian cancer cases in women		Multivariable-adjusted, RD (95% CI)[a,b]	HR (95% CI)	
	With endometriosis (n = 78 476)	Without endometriosis (n = 372 430)		Unadjusted	Multivariable-adjusted[a]
All epithelial ovarian cancers	225	372	9.90 (7.22 to 12.57)	3.64 (3.10 to 4.26)	4.20 (3.59 to 4.91)
High-grade serous[c]	71	222	1.35 (0.08 to 2.63)	2.02 (1.56 to 2.62)	2.70 (2.09 to 3.49)
Low-grade serous[c]	<11	<11	0.28 (−0.17 to 0.73)	7.33 (2.18 to 24.63)	8.12 (2.67 to 24.73)
Endometrioid	67	48	3.89 (2.45 to 5.33)	7.87 (5.52 to 11.22)	7.96 (5.59 to 11.34)
Mucinous	21	28	1.42 (0.42 to 2.43)	4.42 (2.56 to 7.62)	4.56 (2.64 to 7.90)
Clear cell	30	15	1.39 (0.56 to 2.21)	10.90 (6.02 to 19.74)	11.15 (6.19 to 20.10)
Carcinosarcoma	<11	<11	0.44 (−0.03 to 0.91)	5.69 (2.25 to 14.38)	6.24 (2.62 to 14.89)
Other epithelial[d]	23	47	0.89 (0.06 to 1.73)	2.96 (1.84 to 4.79)	3.34 (2.05 to 5.44)

Abbreviations: HR, hazard ratio; RD, risk difference.

[a] Multivariable-adjusted models are adjusted for birth state, birth year, age at first endometriosis diagnosis, and parity. None of these variables had missing values.

[b] RD is reported as the number of cases per 10 000 people.

[c] Per Utah Department of Health and Human Services confidentiality requirements, counts less than 11 are not reported and any counts that could be used to calculate those less than 11 for another category are not provided.

[d] Other epithelial ovarian cancer includes those with histology codes 8010, 8032, 8046, 8140, 8230, 8290, 8440, 8560, 9111, 8255, 8323, and 9000.

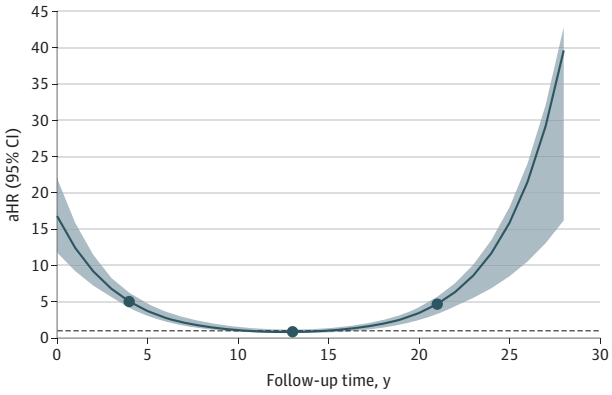
endometriosis, the distribution of the 5 most commonly evaluated histotypes (ie, high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous; **Table 2**) was consistent with distributions reported previously.[13] Due to small case counts for less common histotypes, we grouped cases into the commonly used classifications of type I (endometrioid, clear cell, mucinous, and low-grade serous) and type II (high-grade serous) for our main analyses.[12,15]

Covariate Information

Demographic data, obtained from the UPDB, included sex, race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, multiple races), ethnicity (non-Hispanic/Hispanic), birth month and year, birth location (Utah/other), birth residence (urban, rural, frontier),[16] death month and year, and last month and year known to be a resident of Utah. Race and ethnicity, collected via vital records from self-report, were used to consider generalizability to other US-based populations. Health data focused on reproductive and surgical histories.[12] Parity was derived from birth records. Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was captured via linked driver license records.[17] Smoking was captured using *ICD* codes for tobacco and/or nicotine use.[18] Surgical histories (including oophorectomy and hysterectomy) were obtained from inpatient and ambulatory surgery records (1996-2019).

Potential confounders were informed by the existing literature.[19,20] In addition to adjusting for matching factors, we adjusted for age at endometriosis diagnosis (or index date for the unexposed) and parity in our main analyses and age at endometriosis alone in a sensitivity analysis.

Figure 1. Time-Dependent Association of Endometriosis and Ovarian Cancer, Adjusted for Birth State, Birth Year, Age at First Endometriosis Diagnosis, and Parity



For this model, 3 knots (x-axis values of the join points) were chosen based on percentiles from the whole cohort (20% [n = 94 813], 50% [n = 236 475], and 85% [n = 393 530]). The plot and corresponding time-specific adjusted hazard ratios (aHRs) indicate a possible U-shaped relationship. At 5 years, the aHR was 3.72 (95% CI, 3.07-4.76), at 10 years the aHR was 1.09 (95% CI, 0.88-1.55), and at 20 years the aHR was 3.45 (95% CI, 2.50-4.26).

Statistical Analysis

From our initial cohort of 457 936 (n = 78 893 with endometriosis and n = 379 043 without endometriosis), we removed those with prevalent cancers (n = 2458), who died (n = 11), had a bilateral oophorectomy (n = 4482), or had ovarian cancer (n = 79) prior to their own, or their matched endometriosis case's, index date. Our final analytic cohort included 450 906 women (n = 78 476 with endometriosis and n = 372 430 without endometriosis) (eFigure in Supplement 1). We used Cox proportional hazards models, with robust variance estimation, to estimate unadjusted hazard ratios (HRs), adjusted HRs (aHRs), and 95% CIs for the associations between endometriosis subtypes and ovarian cancer histotypes.[21] We used a Kolmogorov-type supremum test based on a standardized pseudo-score process (1000 simulated datasets) to check for proportional hazards. The proportional hazards assumption was violated for endometriosis. Therefore, consistent with 2020 recommendations,[22] we interpreted the results of our Cox proportional hazards models as weighted averages of the true HRs over the entire follow-up period, used robust variance estimation, and estimated adjusted risk differences via generalized linear models.[22] We also employed a model that used restricted cubic splines to resolve the proportional hazards violation and reported those results for comparison (**Figure 1**).

Our main analyses assessed (1) deep infiltrating endometriosis and/or ovarian endometriomas, (2) superficial peritoneal endometriosis, and (3) other endometriosis. However, we also conducted analyses assessing all subtypes separately. Exposed women were followed up from their endometriosis index date, whereas unexposed women were followed up from the endometriosis index date of the woman to whom they were matched. The population was followed up until bilateral oophorectomy, ovarian cancer diagnosis, death, or December 31, 2019, whichever came first. Given the mean delay of 7 years from endometriosis symptoms to diagnosis, in instances when a woman was diagnosed with ovarian cancer on their observed index date, we assumed that the true index date occurred prior to cancer onset and follow-up duration was set to 0.5 years.[23]

To account for potential misclassification of endometriosis, we performed a probabilistic bias analysis.[24,25] The bias parameters came from an internal validation study (n = 412) that compared record-based endometriosis diagnoses with criterion standard laparoscopy clinical diagnoses. We converted the sensitivity (0.86) and specificity (0.83) from the validation study to positive and negative predictive values (PPVs and NPVs, respectively) within strata of ovarian cancer (yes/no). Then the PPVs and NPVs were converted to beta distributions to incorporate uncertainty in the estimates. Random draws from the beta distributions were conducted to reassign individuals probabilistically to an endometriosis diagnosis or not. This step was repeated 1000 times for each outcome, simultaneously adjusting for confounding and misclassification of exposure. We reported the bias-adjusted measures and 95% simulation intervals that account for both random and systematic errors.

All analyses were completed in SAS version 9.4 (SAS Institute).

Results

The study participants were a mean (SD) age at first endometriosis diagnosis of 36 (10) years and had a mean (SD) follow-up time of 12 (7) years (**Table 3**). The majority of women were parous (75%) and 6% underwent a bilateral oophorectomy during follow-up. Women with endometriosis vs those without were more likely to be nulliparous (31% vs 24%) and to have undergone a hysterectomy (39% vs 6%) during follow-up.

Women with endometriosis had a higher risk of all ovarian cancer histotypes (aHRs ranging from 2.70 [95% CI, 2.09-3.49] for high-grade serous ovarian cancer to 11.15 [95% CI, 6.19-20.10] for clear cell carcinoma) (Table 2) relative to women without endometriosis, with an overall risk of 4.20 (95% CI, 3.59-4.91). Ovarian cancer risk was highest for women with deep infiltrating endometriosis and/or ovarian endometriomas (aHR, 9.66 [95% CI, 7.77-12.00]) (**Figure 2**; eTable 3 in Supplement 1). Women with deep infiltrating endometriosis had the highest risk of ovarian cancer overall (aHR, 18.76 [95% CI, 10.78-32.66]) and women with deep infiltrating endometriosis and concurrent ovarian endometriomas had the second-highest ovarian cancer risk (aHR, 13.04 [95% CI, 6.43-26.47]), although precision was low (eTable 4 in Supplement 1). When endometriosis subtypes and ovarian cancer histotypes were evaluated together, the strongest association was between deep infiltrating endometriosis and/or ovarian endometriomas and type I ovarian cancer (aHR, 18.96 [95% CI, 13.78-26.08]), although risks were elevated for all endometriosis subtypes for both type I and type II ovarian cancer (Figure 2; eTable 3 in Supplement 1). Risk differences indicated that excess risk of ovarian cancer among women with endometriosis was 9.90 cases (95% CI, 7.22-12.57) per 10 000 women over a mean of

Table 3. Characteristics of Endometriosis Cases and Matched Controls From the Utah Population Database, 1992-2019 (N = 450 906)

Participant characteristics	No. (%)[a]	
	With endometriosis (n = 78 476)	Without endometriosis[a] (n = 372 430)
Baseline		
Birth year, mean (SD)[b]	1971.4 (11.6)	1971.4 (11.8)
Born in Utah[b]	43 270 (55.1)	213 911 (57.4)
Race		
American Indian or Alaska Native	127 (0.2)	2349 (0.7)
Asian	587 (0.8)	3488 (1.0)
Black or African American	322 (0.4)	1286 (0.4)
Native Hawaiian or Other Pacific Islander	171 (0.2)	1118 (0.3)
White	69 977 (94.9)	335 969 (93.9)
Multiple races	2582 (3.5)	13 478 (3.8)
Hispanic ethnicity	8496 (11.5)	38 096 (11.1)
Maximum educational attainment		
Less than high school	3774 (6.3)	20 095 (6.5)
High school graduate	18 800 (31.2)	87 226 (28.2)
Some college	22 754 (37.8)	111 681 (36.1)
College graduate	8894 (14.8)	54 027 (17.5)
Post college	5464 (9.1)	33 301 (10.8)
Marital status		
Married or partnered	51 579 (73.7)	241 661 (72.2)
Divorced or separated	8548 (12.2)	36 766 (11.0)
Single/never married	7959 (11.4)	46 027 (13.8)
Widowed	1942 (2.8)	10 188 (3.0)
Residential setting		
Urban	55 319 (80.3)	256 117 (80.0)
Rural	11 351 (16.5)	52 128 (16.3)
Frontier	2248 (3.3)	11 787 (3.7)
Smoking history (ever)	4592 (8.6)	21 078 (7.5)
BMI, median (IQR)	23.7 (21.1-27.5)	23.4 (21.0-27.4)
Nulliparous	24 341 (31.0)	87 433 (23.5)
No. of live births, mean (SD)[c]	2.6 (1.3)	2.8 (1.4)
Ever had a stillbirth	789 (1.0)	3989 (1.1)
No. of stillbirths, mean (SD)[d]	1.1 (0.3)	1.1 (0.2)
Over course of study		
Endometriosis index year, mean (SD)[e]	2006.9 (7.1)	NA
Age at index year, mean (SD), y[e]	35.5 (9.5)	NA
Total follow-up of at least 1 y	65 149 (83.0)	371 752 (99.7)
Total follow-up, median (IQR), y	8.0 (2.0-17.0)	14.0 (6.0-19.0)
Underwent hysterectomy during follow-up	30 380 (38.7)	22 341 (6.0)
Underwent bilateral oophorectomy during follow-up	17 547 (22.4)	8737 (2.4)

Abbreviation: NA, not applicable.

[a] Unless otherwise indicated.

[b] Birth year and birth state were matching factors.

[c] Number of live births among parous women.

[d] Number of stillbirths among women who ever had a stillbirth.

[e] Index year is defined as the year of first endometriosis diagnosis.

12 years (eTable 3 in Supplement 1). Models using cubic splines indicated a possible U-shaped relationship between endometriosis and ovarian cancer across follow-up time, with risk being elevated at less than 5 years and more than 20 years of follow-up (Figure 1). In a sensitivity analysis that removed parity from the model, results were further from the null (eTable 5 in Supplement 1).

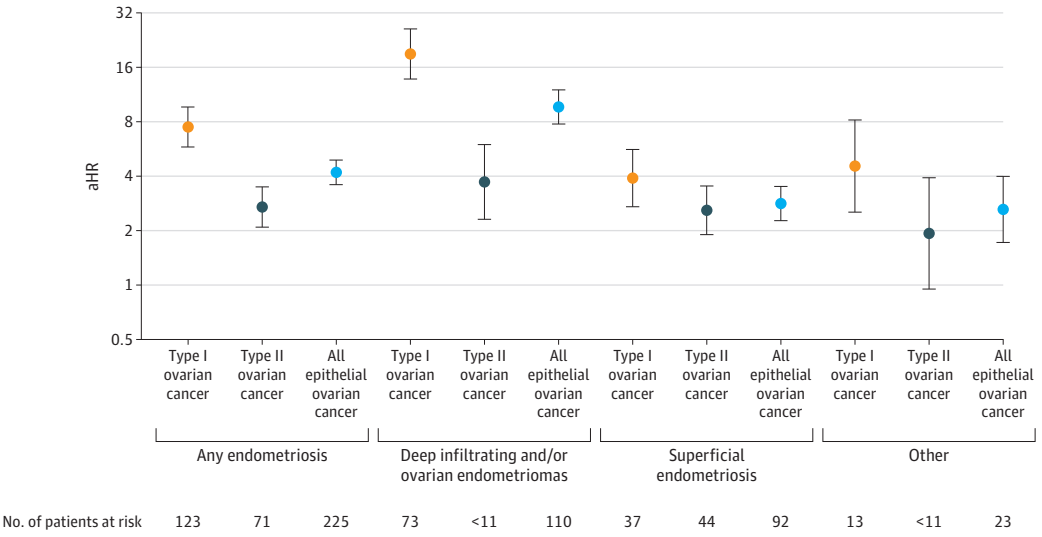
The results from the quantitative bias analysis to address potential misclassification of endometriosis consistently indicated bias toward the null. For the overall association, the bias-adjusted HR was 8.29 with the 95% simulation interval (4.9-112.5). Bias-adjusted HR estimates for type I and type II ovarian cancers were 20.2 (95% simulation interval, 10.1-219.9) and 3.9 (95% simulation interval, 2.2-30.8), respectively.

Discussion

In this large, population-based study, those with incident endometriosis were 4.20 times more likely to develop ovarian cancer (95% CI, 3.59-4.91), 7.48 times more likely to develop type I ovarian cancer (95% CI, 5.80-9.65), and 2.70 times more likely to develop type II ovarian cancer (95% CI, 2.09-3.49) compared with those without endometriosis. Magnitudes of these associations varied by endometriosis subtype. Individuals diagnosed with deep infiltrating endometriosis and/or ovarian endometriomas had 9.66 times the risk of ovarian cancer when compared with individuals without endometriosis (95% CI, 7.77-12.00), although diagnoses of superficial peritoneal endometriosis and other endometriosis were associated with 2.82-fold (95% CI, 2.27-3.51) and 2.62-fold (95% CI, 1.72-3.99) higher ovarian cancer risk, respectively.

Many prior studies of endometriosis and ovarian cancer relied on self-report of endometriosis and were unable to account for gynecologic operations.[26] Here, using medical record-confirmed diagnoses of endometriosis and accounting for oophorectomy, stronger associations between endometriosis and both endometrioid and clear cell ovarian cancer than have been reported previously were observed.[26] For example, Ovarian Cancer Cohort Consortium (OC3) and Ovarian Cancer Association Consortium (OCAC) analyses comparing individuals with endometriosis with those without reported 2.32 (95% CI, 1.36-3.95 [OC3]) and 2.04 (95% CI, 1.67-2.48 [OCAC]) times the risk of endometrioid ovarian cancer, and 2.87 (95% CI, 1.53-5.39 [OC3]) and 3.05 (95% CI, 2.43-3.84 [OCAC]) times the risk of clear cell ovarian cancer.[26,27] Results from the Finnish Hospital Discharge Register, which also used medical record-confirmed diagnoses of endometriosis, were slightly more comparable to this study, with a 3.12-fold (95% CI, 2.15-4.38) increased risk of endometrioid ovarian cancer and a 5.17-fold (95% CI, 3.20-7.89) increased risk of clear cell ovarian cancer among those with endometriosis vs without endometriosis.[5] Modest, but statistically significant, associations with serous ovarian cancer (particularly low-grade serous) had been reported in some, but not all, prior studies, although positive associations with mucinous ovarian cancer were unexpected.[5,26-28]

Figure 2. Adjusted Hazard Ratios (aHRs) Comparing Risk of Ovarian Cancer Among Women With vs Without Endometriosis



Results for each endometriosis subtype are presented separately for all histotypes of ovarian cancer: type I (endometrioid, clear cell, mucinous, and low-grade serous) and type II (high-grade serous). Although a positive association was observed for all possible combinations of endometriosis subtypes and ovarian cancer histotypes, the association between deep infiltrating and/or ovarian endometriomas and type I ovarian cancer was greatest in magnitude. Per Utah Department of Health and Human Services confidentiality requirements, counts less than 11 are not reported and any counts that could be used to calculate those less than 11 for another category are not provided. Whiskers indicate 95% CIs.

This study also estimated associations between endometriosis subtypes and ovarian cancer histotypes. The Swedish National Patient Register (n = 64 492) observed that ovarian endometriomas (Standardized Incidence Ratio [SIR], 1.77) and nonovarian endometriomas (SIR, 1.47) were both associated with greater ovarian cancer risk but did not consider associations by histotype. To our knowledge, the Finnish Hospital Discharge Register (n = 49 933) is the only other study that has investigated endometriosis subtypes in relation to ovarian cancer histotypes. The study observed associations between ovarian endometriomas and all ovarian cancer (SIR, 2.56), endometrioid ovarian cancer (SIR, 4.72), and clear cell ovarian cancer (SIR, 10.1). The study also observed an association between peritoneal endometriosis and endometrioid ovarian cancer (SIR, 2.03). No statistically significant associations were observed between deep infiltrating endometriosis and ovarian cancer, but there were only 3 ovarian cancer cases in this group. Within the larger UPDB study population, deep infiltrating endometriosis and/or ovarian endometriomas were associated with a 19-fold increased risk of type I ovarian cancer and a 4-fold increased risk of type II ovarian cancer. By quantifying the strong associations between deep infiltrating endometriosis and/or ovarian endometriomas subtypes and ovarian cancer risk, this study identified a population that may benefit from ovarian cancer screening or more aggressive prevention strategies. Further, because endometriosis subtypes have different etiology and risk factors, study observations of how endometriosis subtypes are differentially associated with risk of ovarian cancer could lead to novel hypotheses regarding ovarian cancer etiology.

A number of mechanisms may underlie the associations between endometriosis subtypes and ovarian cancer histotypes.[29] As mentioned previously, endometriosis is thought to be a tissue of origin for both endometrioid and clear cell ovarian cancer, potentially explaining the high magnitude of association for these histotypes.[30] Additionally, there is emerging evidence of an overlapping genetic predisposition for both endometriosis and endometrioid and clear cell ovarian cancer.[31-34] There are also overlapping endogenous hormonal, immunological, and inflammatory markers associated with both endometriosis and ovarian cancer.[5] For example, the number of lifetime ovulatory cycles is a risk factor for both endometriosis and ovarian cancer.[35] Conversely, oral contraceptive use, a common first-line treatment for endometriosis, and hysterectomy may protect against ovarian cancer among women with endometriosis,[27] although the extent to which these factors mediate the associations between endometriosis subtypes and ovarian cancer histotypes has not been established. Studies of endometriosis lesion excision and ovarian cancer risk have produced mixed findings[36-38] indicating possible heterogeneity in the impact of excision depending on both endometriosis lesion location and ovarian cancer histotype.

A key strength of the study was use of the UPDB, which allowed the accurate and comprehensive capture of endometriosis and ovarian cancer diagnoses and evaluated endometriosis and ovarian cancer typologies.

Limitations

This study has limitations. First, given the lack of a biomarker for diagnosing endometriosis, temporal changes in the procedures available to diagnose subtypes (ie, operation vs magnetic resonance imaging), and the difficulty in diagnosing endometriosis among women without symptoms or access to care, misclassification of endometriosis was possible. However, in a subanalysis comparing criterion standard laparoscopy clinical diagnoses captured as part of the NICHD ENDO

Study (2007-2009) to the administrative health care data used in this study, relatively high agreement was found: area under the curve was 0.84 (95% CI, 0.81-0.88); sensitivity was 0.86 (95% CI, 0.80-0.92); specificity was 0.83 (95% CI, 0.78-0.87); and κ was 0.75 (95% CI, 0.68-0.81). Further, when these estimates of sensitivity and specificity were used to run a quantitative bias analysis, a bias toward the null was observed, suggesting that the true associations between endometriosis and ovarian cancer may be stronger than observed. Second, misclassification of ovarian cancer histotypes was also possible, but prior research has shown relatively high agreement between expert pathology histotype review and record-based histotyping,[39] and the observed distribution of ovarian cancer subtypes was similar to the existing literature.[13]

Third, misclassification of BMI and smoking was possible due to the study's reliance on driver license data for BMI and *ICD* codes for smoking; however, prior reports show strong agreement with standard measures.[17,40] Fourth, hysterectomies and oophorectomies were measured from Utah facility data only, so procedures completed elsewhere were not included. Fifth, exact information on the time and duration of study participants' travel outside of Utah was unavailable, which could have biased results if participants with endometriosis systematically left the state for treatment. This risk was mitigated by matching endometriosis-exposed women to unexposed women by birth year and birth state and requiring Utah residency as of their matched endometriosis case's index date. Sixth, data on 2 medication types commonly used among women with endometriosis was unavailable: oral contraceptives (OCPs) and gonadotropin-releasing hormone (GnRH) agonists. The influence of GnRH agonists on ovarian cancer risk has not been well-studied in human populations; however, OCPs are associated with a lower risk of ovarian cancer, especially nonserous histotypes.[27] By not incorporating OCPs into the analyses, the true associations between endometriosis subtypes and ovarian cancer histotypes may have been underestimated.

Conclusions

This study observed that endometriosis is associated with a 4.20-fold increased risk of ovarian cancer and a 7.48-fold increased risk of type I ovarian cancer. Women with deep infiltrating endometriosis and/or ovarian endometriomas had the greatest increased risk of type I ovarian cancer, with nearly 19 times the risk of ovarian cancer when compared with women without endometriosis. Studies that can better characterize the biology underlying these associations are urgently needed to guide improved ovarian cancer screening and prevention strategies among women with severe endometriosis, with or without other important ovarian cancer risk factors (eg, *BRCA1/2* variations) and to inform novel molecular targets for ovarian cancer treatments.

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REFERENCES

1. Buck Louis GM, Hediger ML, Peterson CM, et al; ENDO Study Working Group. Incidence of endometriosis by study population and diagnostic method: the ENDO study. *Fertil Steril*. 2011;96(2):360-365. doi:10.1016/j.fertnstert.2011.05.087

2. Giudice LC. Endometriosis. *N Engl J Med*. 2010;362(25):2389-2398. doi:10.1056/NEJMcp1000274

3. Kvaskoff M, Mahamat-Saleh Y, Farland LV, et al. Endometriosis and cancer: a systematic review and meta-analysis. *Hum Reprod Update*. 2021;27(2):393-420. doi:10.1093/humupd/dmaa045

4. Sorbi F, Capezzuoli T, Saso S, et al. The relation between endometrioma and ovarian cancer. *Minerva Obstet Gynecol*. 2021;73(3):347-353. doi:10.23736/S2724-606X.21.04757-2

5. Saavalainen L, Lassus H, But A, et al. Risk of gynecologic cancer according to the type of endometriosis. *Obstet Gynecol*. 2018;131(6):1095-1102. doi:10.1097/AOG.0000000000002624

6. Huntsman Cancer Institute. Utah Population Database. Accessed April 7, 2024. https://uofuhealth.utah.edu/huntsman/utah-population-database

7. Prahalad S, Zeft AS, Pimentel R, et al. Quantification of the familial contribution to juvenile idiopathic arthritis. *Arthritis Rheum*. 2010;62(8):2525-2529. doi:10.1002/art.27516

8. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020;382(13):1244-1256. doi:10.1056/NEJMra1810764

9. Patel DP, Meeks HT, Pastuszak AW, et al. Lower female partner live birth rate in male cancer survivors: an age-matched cohort analysis of the Utah Population Database. *Andrologia*. 2022;54(1):e14293. doi:10.1111/and.14293

10. Oakley GM, Curtin K, Pimentel R, Buchmann L, Hunt J. Establishing a familial basis for papillary thyroid carcinoma using the Utah Population Database. *JAMA Otolaryngol Head Neck Surg*. 2013;139(11):1171-1174. doi:10.1001/jamaoto.2013.4987

11. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. *Modern Epidemiology*. 4th ed. Wolters Kluwer; 2021.

12. Barnard ME, Meeks H, Jarboe EA, Albro J, Camp NJ, Doherty JA. Familial risk of epithelial ovarian cancer after accounting for gynaecological surgery: a population-based study. *J Med Genet*. 2023;60(2):119-127. doi:10.1136/jmedgenet-2021-108402

13. Peres LC, Cushing-Haugen KL, Köbel M, et al Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst*. 2019;111(1):60-68. doi:10.1093/jnci/djy071

14. McCluggage WG, Singh N, Gilks CB. Key changes to the World Health Organization (WHO) classification of female genital tumours introduced in the 5th edition (2020). *Histopathology*. 2022;80(5):762-778. doi:10.1111/his.14609

15. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J Pathol*. 2016;186(4):733-747. doi:10.1016/j.ajpath.2015.11.011

16. Health Resources and Services Administration. Methodology for designation of frontier and remote areas. *Federal Register*. Published May 5, 2014. Accessed May 30, 2024. https://www.federalregister.gov/documents/2014/05/05/2014-10193/methodology-for-designation-of-frontier-and-remote-areas

17. Chernenko A, Meeks H, Smith KR. Examining validity of body mass index calculated using height and weight data from the US driver license. *BMC Public Health*. 2019;19(1):100. doi:10.1186/s12889-019-6391-3

18. Gill AS, Meeks H, Curtin K, Kelly K, Alt JA. Tobacco use increases the risk of chronic rhinosinusitis among patients undergoing endoscopic sinus surgery. *Clin Otolaryngol*. 2023;48(3):414-422. doi:10.1111/coa.14013

19. Poole EM, Lin WT, Kvaskoff M, De Vivo I, Terry KL, Missmer SA. Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses. *Cancer Causes Control*. 2017;28(5):437-445. doi:10.1007/s10552-017-0856-4

20. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22(5):745. doi:10.1097/EDE.0b013e318225c2be

21. Wang M, Spiegelman D, Kuchiba A, et al. Statistical methods for studying disease subtype heterogeneity. *Stat Med*. 2016;35(5):782-800. doi:10.1002/sim.6793

22. Stensrud MJ, Hernán MA. Why test for proportional hazards? *JAMA*. 2020;323(14):1401-1402. doi:10.1001/jama.2020.1267

23. Nnoaham KE, Hummelshoj L, Webster P, et al; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. 2011;96(2):366-373.e8. doi:10.1016/j.fertnstert.2011.05.090

24. Troeschel AN, Liu Y, Collin LJ, et al. Race differences in cardiovascular disease and breast cancer mortality among US women diagnosed with invasive breast cancer. *Int J Epidemiol*. 2019;48(6):1897-1905. doi:10.1093/ije/dyz108

25. Fox MP, MacLehose RF, Lash TL. *Applying Quantitative Bias Analysis to Epidemiologic Data*. Springer; 2021. doi:10.1007/978-3-030-82673-4

26. Pearce CL, Templeman C, Rossing MA, et al; Ovarian Cancer Association Consortium. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol*. 2012;13(4):385-394. doi:10.1016/S1470-2045(11)70404-1

27. Wentzensen N, Poole EM, Trabert B, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. *J Clin Oncol*. 2016;34(24):2888-2898. doi:10.1200/JCO.2016.66.8178

28. Mogensen JB, Kjær SK, Mellemkjær L, Jensen A. Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study. *Gynecol Oncol*. 2016;143(1):87-92. doi:10.1016/j.ygyno.2016.07.095

29. Farland LV, Davidson S, Sasamoto N, Horne AW, Missmer SA. Adverse pregnancy outcomes in endometriosis—myths and realities. *Curr Obstet Gynecol Rep*. 2020;9(1):27-35. doi:10.1007/s13669-020-00281-1

30. Committee on the State of the Science in Ovarian Cancer Research; Board on Health Care Services; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine. *Ovarian Cancers: Evolving Paradigms in Research and Care*. 2016.

31. Lee AW, Templeman C, Stram DA, et al Evidence of a genetic link between endometriosis and ovarian cancer. *Fertil Steril*. 2016;105(1):35-43 e1-10. doi:10.1016/j.fertnstert.2015.09.023

32. Sato N, Tsunoda H, Nishida M, et al. Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res*. 2000;60(24):7052-7056.

33. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med*. 2010;363(16):1532-1543. doi:10.1056/NEJMoa1008433

34. Lu Y, Cuellar-Partida G, Painter JN, et al; Australian Ovarian Cancer Study; International Endogene Consortium (IEC). Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum Mol Genet*. 2015;24(20):5955-5964. doi:10.1093/hmg/ddv306

35. Shafrir AL, Farland LV, Shah DK, et al. Risk for and consequences of endometriosis: a critical epidemiologic review. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:1-15. doi:10.1016/j.bpobgyn.2018.06.001

36. Melin AS, Lundholm C, Malki N, Swahn ML, Sparèn P, Bergqvist A. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand*. 2013;92(5):546-554. doi:10.1111/aogs.12123

37. Haraguchi H, Koga K, Takamura M, et al. Development of ovarian cancer after excision of endometrioma. *Fertil Steril*. 2016;106(6):1432-1437.e2. doi:10.1016/j.fertnstert.2016.07.1077

38. Chang WH, Wang KC, Lee WL, et al. Endometriosis and the subsequent risk of epithelial ovarian cancer. *Taiwan J Obstet Gynecol*. 2014;53(4):530-535. doi:10.1016/j.tjog.2014.04.025

39. Barnard ME, Pyden A, Rice MS, et al. Inter-pathologist and pathology report agreement for ovarian tumor characteristics in the Nurses' Health Studies. *Gynecol Oncol*. 2018;150(3):521-526. doi:10.1016/j.ygyno.2018.07.003

40. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. *J Am Med Inform Assoc*. 2013;20(4):652-658. doi:10.1136/amiajnl-2012-001557