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ORIGINAL PAPER

Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses

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Abstract
Purpose Endometriosis is associated with ovarian cancer, but the relation with endometrial cancer is unclear. Prior studies generally were retrospective and had potential limitations, including use of self-reported endometriosis, failure to account for delays between symptom onset and endometriosis diagnosis, and changes in risk factors post-endometriosis diagnosis. We evaluated whether these limitations obscured a weak association with endometrial cancer and the extent to which these limitations impacted associations with ovarian cancer.
Methods Cox proportional hazards regression models were used to assess associations between endometriosis and cancer risk, evaluating the impacts of self-reported vs. laparoscopically confirmed endometriosis, delayed diagnosis, and post-endometriosis diagnosis changes in risk factor exposures on relative risk estimates.
Results Over 18 years of follow-up, we identified 228 ovarian and 166 endometrial cancers among 102,025 and 97,109 eligible women, respectively. Self-reported endometriosis was associated with ovarian cancer [relative risk (RR): 1.81; 95% confidence interval (CI): 1.26–2.58]; this association was stronger for laparoscopically confirmed endometriosis (HR: 2.14; 95% CI 1.45–3.15). No association was observed with endometrial cancer (self-report RR: 0.78; 95% CI 0.42–1.44; laparoscopic-confirmation RR: 0.76; 95% CI 0.35–1.64). Accounting for diagnosis delays or post-endometriosis diagnosis changes in risk factors had a little impact.
Conclusions This study adds to the evidence that endometriosis is not strongly linked to endometrial cancer risk and that the association with ovarian cancer is robust to misclassification, diagnostic delay, and changes in exposures post-endometriosis diagnosis. Our analysis suggests that confounding and misclassification do not obscure a weak association for endometrial cancer risk, although our results should be replicated.

Keywords Endometriosis · Ovarian cancer · Endometrial cancer

Introduction

Endometriosis is defined as the presence of endometrial tissue outside the uterus and is associated with pelvic pain and infertility [1]. The causes of endometriosis are unknown, but several theories, including retrograde menstruation, coelomic metaplasia, and dissemination of endometrial cells through the blood or lymphatic system, have

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been proposed [2]. Because the gold-standard for diagnosing endometriosis is laparoscopic surgery and many women with endometriosis are asymptomatic [1], the prevalence of endometriosis is difficult to determine. Among women undergoing surgery for other indications, the prevalence can be as high as 60%; in the general population, the prevalence is estimated to be 6–10% [2, 3].

Endometriosis has been consistently linked to risk of ovarian cancer, particularly the endometrioid and clear cell histologies [4–11]. However, many of these studies relied on the self-report of endometriosis, which is substantially misreported [3, 12], and/or did not address the delay between symptom onset and clinical diagnosis. In our validation study among Nurses' Health Study II (NHSII) participants, this delay was 4 years [3], but is 7 years among the general population [13]. This difference is likely due to the greater access to healthcare and greater knowledge of health among nurses compared to the general population. Furthermore, many studies had limited ability to evaluate potential confounders or mediators [5, 6, 8, 10, 11, 14–16], such as use of oral contraceptives, which are commonly prescribed to treat endometriosis symptoms and are associated with decreased risk of ovarian cancer. Few studies have evaluated whether endometriosis is associated with risk of endometrial cancer [11, 17–19]; most reported weak positive associations, but case numbers were small and prospective data are scarce. However, because endometrioid ovarian cancers and endometrioid endometrial cancers, the most common type of endometrial cancers, share many molecular features [20–22], it is biologically plausible that endometriosis may also impact the risk of developing endometrial cancer.

To address potential limitations of previous studies, we compared the associations of self-reported vs. laparoscopically confirmed endometriosis and ovarian cancer, accounting for delays to endometriosis diagnosis, and evaluated the influence of post-endometriosis diagnosis factors (e.g., oral contraceptive use and parity). We further evaluated whether any of these factors obscured an association between endometriosis and risk of endometrial cancer in the NHSII.

Methods

The NHSII has been described previously [23]. Briefly, the NHSII was established in 1989 among 116,429 female registered nurses, residing in 14 US states and aged 25–42 years. Participants completed an initial questionnaire about their lifestyle factors, health behaviors, and medical history, and, since baseline, have been followed biennially by questionnaire to update exposure status and disease diagnoses.

Ascertainment of endometriosis

In 1993, women were asked if they had ever had physician-diagnosed endometriosis. If a yes response was given, women were asked to report the date of diagnosis and whether it had been confirmed by laparoscopy. These questions were repeated on each subsequent questionnaire. In March 1994, we conducted a validation study to assess the accuracy of self-reported endometriosis [3]. A supplementary questionnaire was mailed to 200 NHSII participants randomly selected from the 1766 women who had reported a new diagnosis of endometriosis after study enrollment. Among women who reported laparoscopic confirmation and for whom records were received and reviewed ($n=105$), the diagnosis was confirmed in 96%. However, among women who did not report laparoscopic confirmation ($n=26$), evidence of a clinical diagnosis was found in only 54%. Therefore, self-reported diagnosis of endometriosis without gathering details on laparoscopic confirmation is likely to be substantially misclassified.

Documentation of ovarian and endometrial cancer cases and deaths

We collected information about ovarian and endometrial cancer diagnoses on each questionnaire. For all reported cases and deaths due to ovarian or endometrial cancer identified by family members, the US National Death Index, or the US Postal Service, we requested medical records pertaining to the diagnosis; for cases whose records were unavailable, we confirmed diagnoses through state cancer registries. For both outcomes, a gynecologic pathologist reviewed the medical records to confirm the diagnosis and abstract stage, histology, and invasiveness.

Statistical analysis

NHSII participants who completed the 1993 questionnaire were eligible for this analysis ($n=107{,}721$). Women diagnosed with cancer (except non-melanoma skin cancer) prior to 1993 ($n=2051$), missing date of birth ($n=221$), who had menopause due to pelvic irradiation ($n=33$), or who died prior to 1993 ($n=1$) were excluded from all analyses. For the ovarian cancer analyses, we additionally excluded women who reported a bilateral oophorectomy ($n=3387$) or whose ovarian cancer was diagnosed prior to 1993 ($n=3$). For the endometrial cancer analyses, we excluded all women who reported a hysterectomy ($n=8302$) or whose endometrial cancer was diagnosed prior to 1993 ($n=4$). In total, there were 102,025 women for the ovarian cancer analyses and 97,109 women for the endometrial cancer analyses.

Participants accrued person-time from the time of the return of the 1993 questionnaire until the date of ovarian cancer diagnosis (for the ovarian cancer analyses) or invasive endometrial cancer diagnosis (for the endometrial cancer analyses), diagnosis of any other cancer (except non-melanoma skin cancer), bilateral oophorectomy (for the ovarian cancer analysis), hysterectomy (for the endometrial cancer analysis), pelvic irradiation, death, or the end of follow-up (1 June 2011), whichever occurred first. For the endometrial cancer analyses, non-invasive endometrial cancers were not considered as cases but were censored at diagnosis. For the ovarian cancer analyses, non-invasive cases were included as cases. Secondary analyses including only invasive ovarian cancer cases yielded similar results (data not shown.)

We used Cox proportional hazards regression to estimate the relative risks (RRs) and 95% confidence intervals (CIs) of ovarian or endometrial cancer in relation to endometriosis, adjusting for potential confounding factors; these factors were updated in models whenever we received updated information on biennial questionnaires. To compare self-reported endometriosis (SRE) vs. laparoscopically confirmed endometriosis (LCE), we ran separate models, using SRE as the exposure in one model and LCE as the exposure in the other. In the LCE analyses, women who reported SRE without laparoscopic confirmation were censored at the time SRE was reported. In the analyses accounting for the delay between onset of endometriosis symptoms and clinical diagnosis, we compared a model in which we moved the diagnosis date back 4 years to the main LCE model described above. To evaluate the potential impact of changes in post-diagnosis exposures that may mediate the relationship between endometriosis and ovarian/endometrial cancer, we compared the main LCE model described above to a model in which we fixed covariates to their pre-endometriosis diagnosis values. We restricted this analysis to women without endometriosis at inclusion, since covariate values prior to study enrollment were unknown. To evaluate differences by ovarian cancer histologic subtype, we used Cox proportional hazards competing risks regression; differences by subtype were evaluated using a likelihood ratio test comparing a model that allowed a different RR for each histologic subtype to one that forced a common RR across subtypes.

To finely adjust for age and calendar time differences, we used a stratified Cox model that allows for differing baseline hazards for groups defined by age (continuous) and calendar time (indicators for each 2-year time period) [24]. All models were adjusted for parity and duration of OC use, as these factors are associated both with endometriosis and with ovarian and endometrial cancer risk. We considered known and suspected endometrial and ovarian cancer risk factors, as well as known endometriosis-associated factors as potential confounders. Covariates were retained in models if they altered the age- and calendar time-adjusted RR by 10%. The ovarian cancer models were further adjusted for menopause status, tubal ligation, and family history of ovarian cancer; as a secondary analysis, we adjusted for endometriosis treatments, including use of menopausal hormone therapy (HT) or intrauterine devices (IUDs) and hysterectomy, as well as history of infertility (defined as the attempt to conceive for 12 months or more without success, with the exclusion of male factors) and menstrual cycle irregularity at ages 18–22. The endometrial cancer models were further adjusted for body mass index (BMI), age at menopause, duration of HT use (by type), age at menarche, menstrual cycle irregularity at ages 18–22, and infertility history. Additional variables that were considered, but not retained in final models, include smoking, duration of breastfeeding, oophorectomy (in endometrial cancer analyses only), and years of ovulation. p values <0.05 were considered statistically significant; all analyses were conducted in SAS v.9.3 (Cary, NC). This project was approved by the Partners Human Research Committee at Brigham and Women's Hospital.

Results

Over 1,635,947 person-years of follow-up for the ovarian cancer analysis and 1,501,378 for the endometrial cancer analysis, 228 ovarian cancer cases and 166 invasive endometrial cancer cases were documented. Women with self-reported endometriosis (SRE) were similar in age, BMI, and menopause status to women who reported no history of endometriosis. However, women with SRE were less likely to be parous (72%) compared to women with no SRE (83%); women with SRE were more likely to report a hysterectomy than women without SRE (17 vs. 7%). These differences were more striking among women who reported laparoscopic confirmation (Table 1).

Ovarian cancer

Women with SRE had an 81% increased risk of ovarian cancer compared to women with no history of endometriosis (95% CI 1.26–2.58); this association was stronger for LCE (RR: 2.14; 95% CI 1.45–3.15; Table 2). Associations were strengthened when adjusted for correlates of endometriosis (hysterectomy, HT use, IUD use, infertility history, menstrual cycle irregularity). Compared to the model with LCE diagnosis date as reported (RR: 2.14; 95% CI 1.45–3.15), the association with ovarian cancer was stronger in the model in which diagnosis date was moved back 4 years to account for delays in diagnosis (RR: 2.41; 95% CI 1.68–3.45; Table 3). When we fixed covariates to

Table 1 Age-standardized characteristics of NHSII participants at midpoint of follow-up (1999)

	No endometriosis ($n=86,930$)	All self-reported endometriosis ($n=8,226$)	Laparoscopically confirmed endometriosis ($n=5,910$)	Self-reported endometriosis without laparoscopic confirmation ($n=2,316$)
Means (SD)				
Age[a]	44.5 (4.6)	44.5 (4.5)	44.2 (4.4)	45.2 (4.6)
Duration of OC use	4.4 (4.8)	4.5 (4.6)	4.5 (4.5)	4.7 (4.8)
Number of children[b]	2.3 (1.0)	2.1 (0.9)	2.0 (0.9)	2.2 (0.9)
BMI (kg/m^2)	26.5 (6.2)	26.2 (6.0)	25.9 (5.7)	27.0 (6.7)
Percentages				
Ever parous	83	72	70	77
Tubal ligation	26	24	24	25
Family history of ovarian cancer	2	2	2	3
Post-menopausal	8	8	9	7
Infertility history	2	7	8	3
IUD use	1	0	0	0
Menstrual irregularity	23	25	24	27
Hysterectomy	7	17	17	19

Values are means (SD) or percentages and are standardized to the age distribution of the study population

BMI body mass index, *IUD* intrauterine device

[a]Value is not age adjusted

[b]Among parous women only

Table 2 Endometriosis and ovarian cancer risk—comparing self-reported vs. laparoscopy-confirmed endometriosis

	Self-reported	Laparoscopically confirmed
Cases with endometriosis/total cases	37/228	31/222
Person-time with endometriosis/total person-time	140,688/1,635,947	100,487/1,595,747
Relative risk[a]	1.81	2.14
95% Confidence interval	1.26–2.58	1.45–3.15
Adjusted for common endometriosis treatments and consequences[b]	1.94	2.28
	1.35–2.78	1.54–3.38

[a]The RR compares women who reported endometriosis to those who did not. Cox proportional hazards model stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopause status, tubal ligation, and family history of ovarian cancer

[b]Potential treatments for and consequences of endometriosis include post-menopausal hormone use, infertility history, IUD use, hysterectomy, and menstrual cycle irregularity

Table 3 Laparoscopically confirmed endometriosis and ovarian cancer risk—accounting for delay between symptom onset and diagnosis

	Diagnosis dateas reported	4-year delay between symptom onset and diagnosis
Cases with endometriosis/total cases	31/222	37/219
Person-time with endometriosis/total person-time	100,487/1,595,747	113,782/1,589,970
Relative risk[a]	2.14	2.41
95% Confidence interval	1.45–3.15	1.68–3.45

Stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopause status, tubal ligation, and family history of ovarian cancer

[a]The RR compares women who reported endometriosis to those who did not.

their pre-diagnosis values to account for changes in behavior and endometriosis treatment, there was a slight attenuation of the association (RR: 1.91; 95% CI 1.08–3.38; Table 4) compared to the model in which covariates were updated every 2 years (RR: 2.17; 95% CI 1.25–3.77).

We observed a stronger association with non-serous subtypes (RR: 2.44; 95% CI 1.48–4.01) than for serous tumors (RR: 1.69; 95% CI 0.92–3.11; Table 5). The association was strongest for mucinous tumors (RR: 2.90; 95% CI 0.97–8.68; Table 6), although the numbers were small ($n=62$ endometrioid or clear cell cases; $n=22$ mucinous cases) and the RR for endometrioid and clear cell tumors was also elevated (RR: 1.78; 95% CI 0.84–3.78). Although the case numbers are small, the associations were similar when we examined endometrioid and clear cell cases separately ($RR_{endometrioid}$: 2.07; 95% CI 0.80–5.40; $RR_{clear\ cell}$: 1.46; 95% CI 0.44–4.91).

Endometrial cancer

Endometriosis was not associated with invasive endometrial cancer risk. In the analyses, comparing SRE to

Table 4 Laparoscopically confirmed endometriosis and ovarian cancer risk—setting covariates to pre-endometriosis diagnosis values

	Updated covariates	Covariates set to pre-dx values
Cases with endometriosis/total cases	14/205	14/205
Person-time with endometriosis/total person-time	47,592/1,542,852	47,592/1,542,852
Relative risk[a]	2.17	1.91
95% confidence interval	1.25–3.77	1.08–3.38

This analysis can only be conducted among women whose endometriosis was diagnosed after the beginning of NHSII as covariates prior to study entry are unknown. Stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopause status, tubal ligation, and family history of ovarian cancer

[a]The RR compares women who reported endometriosis to those who did not

Table 5 Laparoscopically confirmed endometriosis and ovarian cancer risk by ovarian cancer histologic subtype

	Serous	Non-serous
Cases with endometriosis/total cases	12/107	12/84
Person-time with endometriosis/total person-time	100,494/1,595,771	100,494/1,595,771
Relative risk[a]	1.69	2.44
95% confidence interval	0.92–3.11	1.48–4.01
p–Heterogeneity[b]	0.36	

[a]The RR compares women who reported endometriosis to those who did not. Cox proportional hazards model stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopause status, tubal ligation, and family history of ovarian cancer

[b]p-heterogeneity was calculated via likelihood ratio test comparing a Cox proportional hazards competing risks model that allowed for different risk factor associations by histology to a similar model which held the association constant across the two ovarian cancer subtypes

Table 6 Laparoscopically confirmed endometriosis and ovarian cancer risk by ovarian cancer histologic subtype

	Serous	Endometrioid, clear cell	Mucinous
Cases with endometriosis/total cases	12/107	8/62	4/22
Person-time with endometriosis/total person-time	100,494/1,595,771	100,494/1,595,771	100,494/1,595,771
Relative risk[a]	1.70	1.78	2.90
95% confidence interval	0.93–3.12	0.84–3.78	0.97–8.68
p–Heterogeneity[b]		0.72	

[a]The RR compares women who reported endometriosis to those who did not. Cox proportional hazards model stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopause status, tubal ligation, and family history of ovarian cancer

[b]p-heterogeneity was calculated via likelihood ratio test comparing a Cox proportional hazards competing risks model that allowed for different risk factor associations by histology to a similar model which held the association constant across the three ovarian cancer subtypes

LCE, results were similar between the two definitions (SRE RR: 0.74; 95% CI 0.39–1.42; LCE RR: 0.68; 95% CI 0.30–1.56; Table 7). Accounting for delayed diagnosis attenuated the association (RR: 1.07; 95% CI 0.56–2.04; Table 8). There was a little impact of setting covariates to pre-endometriosis diagnosis levels. Compared to a model in which covariates were updated every 2 years (RR: 0.53; 95% CI 0.13–2.16), the association when covariates were set at pre-endometriosis diagnosis levels was very similar (RR: 0.45; 95% CI 0.10–1.96; Table 9).

Discussion

In this detailed analysis of the association between endometriosis and risk of ovarian or endometrial cancer, the association between endometriosis and ovarian cancer was strengthened by accounting for the manner of case confirmation (i.e., self-report only vs. laparoscopic confirmation) and somewhat attenuated when accounting for potential mediation by factors that frequently change post-endometriosis diagnosis and are known ovarian cancer risk factors (e.g., parity and OC use). However, we observed no association between endometriosis and endometrial cancer risk.

The previous studies of the association of endometriosis and endometrial cancer risk have been mixed: six observed

Table 7 Endometriosis and invasive endometrial cancer risk—comparing self-reported vs. laparoscopically confirmed endometriosis

	Self-reported	Laparoscopically confirmed
Cases with endometriosis/total cases	10/166	6/162
Person-time with endometriosis/total person-time	114,485/1,501,378	83,127/1,470,020
Relative risk[a]	0.74	0.68
95% Confidence interval	0.39–1.42	0.30–1.56

Stratified by age and time period; adjusted for BMI, parity, duration of post-menopausal hormones (by type), age at menopause, age at menarche, menstrual irregularity, infertility history, and duration of oral contraceptive use

[a]The RR compares women who reported endometriosis to those who did not

Table 8 Laparoscopically confirmed endometriosis and invasive endometrial cancer risk—moving diagnosis date backwards in time to account for delay between symptom onset and diagnosis

	Diagnosis dateas reported	4-year delay between symptom onset and diagnosis
Cases with endometriosis/total cases	6/162	10/161
Person-time with endometriosis/total person-time	83,127/1,470,020	95,023/1,464,444
Relative risk[a]	0.68	1.07
95% confidence interval	0.30–1.56	0.56–2.04

Stratified by age and time period; adjusted for BMI, parity, duration of post-menopausal hormones (by type), age at menopause, age at menarche, menstrual irregularity, infertility history, and duration of oral contraceptive use

[a]The RR compares women who reported endometriosis to those who did not

Table 9 Laparoscopically confirmed endometriosis and invasive endometrial cancer risk—setting covariates to pre-endometriosis diagnosis values**

	Updatedcovariates	Covariates set to pre-dx values
Cases with endometriosis/total cases	2/158	2/158
Person-time with endometriosis/total person-time	38,978/1,425,871	38,978/1,425,871
Relative risk[a]	0.53	0.45
95% confidence interval	0.13–2.16	0.10–1.96

This analysis can only be conducted among women whose endometriosis was diagnosed after the beginning of NHSII as covariates prior to study entry are unknown. Stratified by age and time period; adjusted for BMI, parity, duration of post-menopausal hormones (by type), age at menopause, age at menarche, menstrual irregularity, infertility history, and duration of oral contraceptive use

[a]The RR compares women who reported endometriosis to those who did not

statistically non-significant or marginally significant increases in risk [5, 15, 16, 18, 25, 26], two observed a statistically significant increase in risk [11, 19], two observed non-significant decreases in risk [4, 27], and one observed a significant decrease in risk [14], although most studies were small ($n = 12$–454 cases). The two largest studies, a case-cohort study using the Danish hospital discharge database ($n = 1398$ cases) [5] and an Australian case–control study ($n = 1399$ cases) [18], observed a suggested increased risk that was strongest in the first year after endometriosis diagnosis, indicating a potential for increased detection among women with endometriosis, rather than a true association. Together, these data demonstrate no clear association of endometriosis with endometrial cancer risk; our data are consistent with a lack of association between endometriosis and endometrial cancer risk. Better accounting for the limitations of the previous analyses had no impact on our conclusion, suggesting that these issues did not obscure a weak association between endometriosis and endometrial cancer in prior studies. These data suggest that, although endometrial and ovarian cancer subtypes may share molecular characteristics [20–22], including mutations in PTEN, PIK3CA, and ARID1A, they may have distinct etiologic pathways.

Most studies of endometriosis and ovarian cancer have reported positive associations, particularly for endometrioid and clear cell tumors [4–11, 14–16]. In the largest study, to date, from the Ovarian Cancer Association Consortium (OCAC; $n = 7911$ invasive ovarian cancer cases), the self-reported history of endometriosis was strongly associated with risk of endometrioid (odds ratio [OR]: 2.04; 95% CI 1.67–2.48) and clear cell tumors (OR: 3.05; 95% CI 2.43–3.84) [7]. Our findings were consistent with this report: although the number of non-serous ovarian tumors was low ($n = 84$), the association was stronger for non-serous tumors. Unexpectedly, the strongest association was for mucinous tumors, although this may be due to chance, as the p–heterogeneity between tumor types was not significant ($p = 0.72$) and the number of mucinous tumors was very small ($n = 22$).

Unlike the analysis for endometrial cancer, the association was stronger when we defined exposure as laparoscopically confirmed endometriosis, likely due to lower misclassification compared to simple self-report. Indeed, in the OCAC study reported above, the prevalence of self-reported endometriosis varied widely, ranging from 1.0 to 12.7% across studies [7]. However, the association between laparoscopically confirmed endometriosis and ovarian cancer was somewhat weakened when we accounted for changes after endometriosis diagnosis, such as use of OCs and parity. This suggests that some of the association between endometriosis and ovarian cancer may be mediated through these factors.

Endometriosis is complex and not fully understood; it is not clear whether the association of endometriosis with ovarian cancer is causal or whether some underlying mechanism leads to both. Evidence suggests that endometriosis may create a microenvironment that promotes cancer, even if the endometriosis itself is not carcinogenic. For example, both endometriosis [28] and ovarian cancer [29, 30] are characterized by high estrogen and low progesterone. In addition, immune and inflammatory responses are altered in both endometriosis [2, 29, 30] and ovarian cancer [29, 31], with high levels of pro-inflammatory cytokines, including TNFα, IL-6, and IL-1β [31], suggesting a potential inflammatory milieu that fosters both endometriosis and ovarian carcinogenesis. However, several studies suggest a causal relationship between endometriosis and ovarian cancer. For example, in a recent set of OCAC analyses, endometrioid and clear cell tumors had a high genetic correlation with endometriosis and many regions were associated with risk of both [32, 33]. Furthermore, inactivation of PTEN is a frequent occurrence in endometrioid and clear cell ovarian tumors; similar mutations have been found in isolated endometriosis cysts as well as in tumor-adjacent cysts [34]; in a mouse model of endometriosis, PTEN deletion resulted in the development of invasive endometrioid carcinomas [35]. In addition, mutations in ARID1A have been observed in endometrioid and clear cell carcinomas, as well as in adjacent endometriosis tissue, but not in high grade serous tumors [36]. Taken together, these studies suggest that endometriosis is a pre-cursor lesion to clear cell and endometrioid ovarian cancers.

A limitation of this study is that 39% of the women with endometriosis were diagnosed prior to study enrollment. For women who were diagnosed with endometriosis prior to enrolling in NHSII, we did not have access to the exact date of diagnosis (i.e., we only knew that the endometriosis was diagnosed prior to enrollment). Therefore, among these women, we could not account for delays between symptom onset and endometriosis diagnosis or deal with potential changes in behavior or exposures post-diagnosis, a key component of this analysis. In addition, because detailed information on endometriosis stage, location, and subtype was not consistently reported in medical records [3], we could not assess whether associations differ for ovarian endometriosis (i.e., endometriomas) vs. endometriosis in other locations, as was observed in other studies [8, 15], or by subtype of endometriosis (i.e., superficial peritoneal vs. endometrioma vs. deep infiltrating endometriosis). However, to date, no study has conclusively demonstrated that the endometriosis-ovarian cancer link is limited to a specific subtype or location of endometriosis. In addition, NHSII participants were not surgically evaluated for endometriosis; therefore, there is likely undiagnosed endometriosis in the cohort, leading to non-differential

misclassification and an attenuation of true associations. This is true for most prior analyses as well; however, the alternative is to examine the association between endometriosis and ovarian cancer among women who have been surgically evaluated for endometriosis. Given that women who have had laparoscopic surgery, but do not have endometriosis, are unlikely to represent the general population and that the prevalence of undiagnosed endometriosis in the general population is likely less than 2% [37], the potential impact of including undiagnosed endometriosis cases in the unexposed group is far less than that of using an inappropriate comparison group. Furthermore, in a study the size of the NHSII (102,023 women in the NHSII ovarian cancer analysis), the impact of undiagnosed endometriosis among the unexposed group is likely to be quite small [37]. Finally, although recent evidence suggests differences in epidemiologic risk factors for type I vs. type II endometrial cancers [38–43], we did not have the ability to determine endometrial cancer type in our study.

This study had several strengths. First, unlike many prior studies, we were able to account for false positive reports of endometriosis by considering laparoscopically confirmed endometriosis as the main exposure. As noted above [3], self-report of laparoscopically confirmed endometriosis was valid (101/105 were confirmed by medical record review), but self-report without laparoscopic confirmation was not (14/26 women had evidence of clinical diagnosis of endometriosis), suggesting that studies that use self-report underestimate the true association between endometriosis and ovarian cancer risk. Second, because the information from study participants was updated every 2 years, we could finely adjust for confounding and evaluate the impact of post-endometriosis changes in exposures in relation to ovarian and endometrial cancer risks. This is in contrast to the large registry studies conducted in Scandinavian countries [5, 8, 11, 14–16], which have a very good evaluation of exposure (i.e., a hospital discharge for endometriosis), but have limited ability to adjust for confounders or evaluate mediation. Third, the large sample size provided power to evaluate the association of endometriosis with ovarian and endometrial cancer: we had 228 cases of ovarian cancer and 166 cases of invasive endometrial cancer.

In summary, this analysis provided evidence that, by accounting for problems with self-reported endometriosis diagnosis, delays between symptom onset and endometriosis diagnosis, and changes in cancer-relevant exposures post-endometriosis diagnosis, the association with ovarian cancer was strengthened, suggesting that further efforts to treat and prevent endometriosis would be beneficial for ovarian cancer prevention. By contrast, this detailed analysis provided additional evidence that endometriosis is not associated with risk of endometrial cancer. This highlights the potential differences in etiology between non-serous ovarian tumors, particularly the endometrioid subtype, and endometrial cancer. Additional research should focus on the direct and indirect effects of endometriosis on ovarian carcinogenesis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or personal relationships that might influence this work.

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