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Laparoscopically Confirmed Endometriosis and Breast Cancer in the Nurses' Health Study II

Leslie V. Farland, ScD^{1,5,*}, Rulla M. Tamimi, ScD^{1,2}, A. Heather Eliassen, ScD^{1,2}, Donna Spiegelman, ScD^{1,2,3}, Susan E. Hankinson, ScD^{1,2,4}, Wendy Y. Chen, MD, MPH^{2,6}, and Stacey A. Missmer, ScD^{1,2,5}

¹Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

²Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

³Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

⁴Department of Biostatistics and Epidemiology, University of Massachusetts, Amherst, Massachusetts

⁵Department of Obstetrics, Gynecology, and Reproductive Biology; Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

⁶Department of Medical Oncology, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA

Abstract

Objective—To investigate the association between laparoscopically confirmed endometriosis and risk of breast cancer. Previous research on endometriosis and breast cancer has found mixed findings.

Methods—Our prospective cohort study included 116,430 women from the Nurses' Health Study II cohort followed from 1989 until 2013. Our primary analysis investigated the association between self-reported laparoscopically confirmed endometriosis and risk of breast cancer. Breast cancer diagnosis was verified through medical records. Multivariable adjusted Cox proportional hazard models were used to calculate hazard ratios (aHR) and 95% confidence intervals (CI). Breast cancer was further classified by menopausal status at time of diagnosis and tumor hormone receptor status verified through tissue microarrays when available and medical records.

Results—At baseline, 5,389 (5%) women reported laparoscopically confirmed endometriosis. Over 24 years of follow-up, 4,979 (3%) incident breast cancer cases were diagnosed. Women with endometriosis were not at higher risk for overall (aHR:0.96 [0.88–1.06]), premenopausal (aHR: 1.05 [0.89–1.23] or postmenopausal breast cancer (aHR:0.93 [0.80–1.07]). However, associations varied by tumor hormone receptor status (P-value, test for heterogeneity: 0.001). While women with endometriosis were not at increased risk of estrogen/progesterone receptor positive (ER+/PR

*Corresponding Author: Leslie V. Farland, Harvard T.H. Chan School of Public Health, Department of Epidemiology, 677 Huntington Ave, Boston, MA 02115, lfarland@mail.harvard.edu, Phone: 563-940-1579, Fax: 617 - 566 - 7805.

+) tumors (aHR:1.00 [0.87–1.14]) or ER–/PR– tumors (aHR:0.90 [0.67–1.21]). Women with endometriosis reported 2.87 ER+/PR– breast cancer cases per 10,000 person-years compared to women without endometriosis (1.32/10,000 person-years) which resulted in nearly a twofold increased risk of ER+/PR– breast cancers (aHR:1.90 [1.44–2.50]).

Conclusion—Endometriosis was not found to be associated with overall risk of breast cancer in this study, however endometriosis was significantly associated with ER+/PR– breast tumors, which should be interpreted cautiously.

Introduction

Endometriosis is a painful and debilitating gynecologic condition defined by the presence of endometrial-like tissue outside the uterus. This chronic disorder affects 6–10% of women of reproductive age in the United States and is the third leading cause of gynecologic hospitalization(1). Yet its etiology and relationship to the risk of other diseases, including breast cancer, remain unclear (2).

The potential association between endometriosis and breast cancer is complex. Both diseases have been hypothesized to be associated with an abnormal hormonal environment (1, 3) and increased inflammation (4–6). Endometriosis and breast cancer also share many risk factors such as body size, age at menarche, and parity (7–9). Additionally, many of the treatments for endometriosis, including oral contraceptives, analgesic use, and oophorectomy, may alter breast cancer risk (7, 10, 11). The literature are mixed regarding the relationship between endometriosis and breast cancer (2):Ten studies suggested modest positive associations between endometriosis and the risk of breast cancer with effect estimates ranging from 1.08 to 3.20 (2, 12–21), four studies showed no clear association (22–25), and five studies reported an inverse relationship (26–30). However, the studies conducted to date are limited by minimal control for confounding and differences in definitions of endometriosis diagnoses. Additionally, it is now recognized for breast cancer that risk factor relationships differ by tumor hormone receptors and menopausal status at time of diagnosis.

To address these limitations, we investigated the relationship between endometriosis and subsequent breast cancer risk in the Nurses' Health Study II, a prospective cohort with detailed information on endometriosis, breast cancer, and potential confounders. We investigated whether results differed by hormone receptor and menopausal status at diagnosis of breast cancer.

Materials and Methods

The Nurses' Health Study II is a prospective cohort study that began in 1989 when 116,430 registered nurses, 25–42 years old, returned a mailed questionnaire on their health and lifestyle. Follow-up questionnaires, that collect information on environmental, dietary, and lifestyle risk factors, have been sent biennially. The cumulative follow-up rate from the original cohort is 90%. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

On the 1993 questionnaire, women were first asked if they had ever had “physician diagnosed endometriosis.” If they answered “yes,” they were asked to report when the diagnosis had occurred and if their disease had been confirmed by laparoscopy. Endometriosis diagnosis has been assessed on every questionnaire subsequently allowing women to become exposed through follow-up. In validation with medical records, we found a high concordance (96%) with self-reported laparoscopically confirmed endometriosis, but lower concordance (54%) with self-reported diagnosis without laparoscopic confirmation(8). Therefore, the primary exposure definition was restricted to women reporting endometriosis with laparoscopic confirmation. In sensitivity analyses, we included all self-reported endometriosis to see if results would differ with our more restrictive definition.

Participants have reported new cancer diagnoses have on every questionnaire. Women who reported a new breast cancer diagnosis were asked the diagnosis date and permission to obtain the pertinent medical records. Repeat mailings and telephone outreach were used for non-respondents. For deceased respondents, next-of-kin were contacted for permission to review medical records or data were linked from the state cancer registries. Information on histopathology, size, grade, node status, and hormone receptor status was recorded. For our primary analysis, we combined in situ and invasive breast cancers.

For our analyses of hormone receptors status, we combined information on estrogen and progesterone status of the tumor from tissue microarrays and medical records to create three categories: estrogen /progesterone receptor positive (ER+/PR+) breast cancer, ER+/PR– breast cancer, and ER–/PR– breast cancer, since previous work has indicated that ER–/PR+ is not a reproducible subtype (31). As described in detail previously (32), tissue blocks were obtained from approximately 60% of cases reported through 2006. Tissue microarray sections were evaluated for a panel of immunohistochemical markers including ER/PR. ER/PR by tissue microarrays were used as the primary categorization of hormone receptor status and medical/pathology reports were used to determine values for women without this information.

Women who reported a diagnosis of breast or other cancer (other than non-melanoma skin cancer) prior to June 1989 were excluded from our analysis. Women were followed from 1989 until return of the 2013 questionnaire. Cox proportional hazard models stratified by calendar time with age (months) as the time metameter were used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer. Known *a priori* risk factors for endometriosis and breast cancer were adjusted for and time-varying covariates were updated biennially at every questionnaire cycle. For analyses of tumor hormone receptor status, we accounted for competing risks in Cox regression by using the Lunn and McNeil approach (33). Subsequent analyses were further stratified by menopausal status and among postmenopausal women, type of menopause (natural vs. surgical).

Several additional *a priori* sensitivity analyses were conducted to investigate potential biases. Specifically, we evaluated the impact of delays in diagnosis, timing of diagnoses, different diagnostic criteria for endometriosis, exclusion of in situ breast cancer cases, and the effect of variables that are associated with endometriosis and breast cancer risk including history of infertility, hysterectomy, oophorectomy, menopausal hormone therapy, and analgesic use.

Results

Over 24 years of follow-up, 4,979 incident breast cancer cases were observed. At baseline 5% of women reported laparoscopically confirmed endometriosis. Across follow-up, an additional 5.5% of women were diagnosed with endometriosis. Of the endometriosis cases, 33.2% were excluded from the primary analysis because they lacked report of laparoscopic confirmation, these cases were later included in sensitivity analyses. At baseline, compared to women without endometriosis, women with endometriosis had lower BMI in adulthood and at age 18, were more likely to be nulliparous, have biopsy confirmed benign breast disease and earlier age at menarche (Table 1). Women with endometriosis were also more likely to be current or past users of oral contraceptives (OCs), to use analgesics regularly, have had a hysterectomy or oophorectomy, and to have used menopausal hormone therapy.

In multivariate models, no association was found between endometriosis and risk of breast cancer overall (aHR:0.96 95% Confidence Interval: [0.88–1.06]) (Table 2) or invasive breast cancer (aHR:0.96 [0.86–1.06]). Women with endometriosis reported 2.32 breast cancer cases per 1,000 person-years compared to women without endometriosis (1.92/1,000 person-years). Results were similar for premenopausal (aHR:1.05 [0.89–1.23]) and postmenopausal breast cancer (aHR:0.93 [0.80–1.07]). Among postmenopausal women, results did not change by type of menopause (natural menopause aHR:1.06 [0.80–1.36]; surgical menopause aHR:0.90 [0.75–1.09]).

In contrast, the association between endometriosis and breast cancer varied by tumor hormone receptor status (P-value, test for heterogeneity: 0.001) (Table 3). Women with endometriosis were not at increased risk of ER+/PR+ tumors (aHR:1.00 [0.87–1.14]) or ER–/PR– tumors (aHR:0.90 [0.67–1.21]) (P-value, test for heterogeneity for pair-wise comparison between ER+/PR+ and ER–/PR–: 0.53). However, women with endometriosis had an increased risk for ER+/PR– breast cancer (aHR: 1.90 [1.44–2.50]). Women with endometriosis reported 2.87 ER+/PR– breast cancer cases per 10,000 person-years compared to women without endometriosis (1.32/10,000 person-years). The strongest confounding factors of this relationship were parity, age at first birth, and history of benign breast disease.

In sensitivity analyses we sought to investigate potential biases introduced by our restriction of endometriosis diagnosis to those that were laparoscopically defined, our inclusion of endometriosis cases diagnosed before 1989, and the potential delay from symptom onset to disease diagnosis. Regardless of the definition or predating of the endometriosis diagnosis (by 4, 6, and 8 years), we saw no significant difference in the reported relationships. To better understand the biologic relationship between endometriosis and breast cancer, we restricted the outcome definition to only invasive breast cancer and again had similar results. Since infertility may be linked with breast cancer, we stratified by infertility history which did not change aHRs. Since hysterectomy, oophorectomy, menopausal hormone therapy, and analgesic use may impact breast cancer risk, we performed mediation analyses and saw no substantial effect.

Discussion

We found that endometriosis was not associated with overall breast cancer risk, nor risk of pre-menopausal or post-menopausal breast cancer. We observed differences in the association of endometriosis with breast cancer by hormone receptor status. While endometriosis was not found to be associated with ER+/PR+ or ER-/PR- tumors, endometriosis was associated with approximately a twofold increased risk of ER+/PR- breast cancer tumors.

We did not observe differential associations with breast cancer risk by menopausal status. Previous studies that have investigated breast cancer by menopausal status have reported mixed results. One small case-control study among premenopausal women reported an increased risk of breast cancer in women with endometriosis (OR 1.99; 95% CI: 1.0–4.0) (12). However, subsequent studies have not replicated this finding (16) nor does ours. Our study is consistent with results in previous work that endometriosis does not appear to be associated with overall breast cancer risk in naturally postmenopausal women (16, 24). Since treatment for endometriosis may involve surgical menopause, the relationship between endometriosis and surgically postmenopausal women is more complex. While one small study found increased risk of breast cancer among women who underwent hysterectomy or oophorectomy as treatment for endometriosis (RR: 3.2 [1.2–2.8]) (17), they lacked information on exogenous hormone usage -- which is common among these women and may alter breast cancer risk. In our analyses we had detailed information on hysterectomy, oophorectomy, and menopausal hormone therapy and controlled for these in the model without any change in the associations.

Our finding that results differ by breast cancer tumor type supports the mounting evidence that ER+/PR- tumors differ biologically (7, 34–36), however these results should be interpreted cautiously given the small number of ER+/PR cases. Previous research has reported stronger relationships with ER+/PR- tumors for some other risk factors, including adult BMI (7, 35, 37, 38), age at menarche (37), and time between menarche and first birth (7). Interestingly, these risk factors have also been found to be consistently related to endometriosis risk (8). Unlike other studies, we only saw an association with ER+/PR- tumors, but not with other tumors.

There are several potential mechanisms behind an association between endometriosis and breast cancer. An environment high in estrogen is hypothesized to be associated with both endometriosis and breast cancer development, with varying degrees of evidence for pre vs. post-menopausal breast cancer (1, 3). Additionally, women with endometriosis have increased levels of inflammatory markers in both their peritoneal fluid and peripheral blood (4, 5) and chronic inflammation may be associated with breast cancer (6, 39). Thus, a shared altered hormonal and/or inflammatory environment may be consistent with an environment in which both endometriosis and breast cancer tumors may develop.

Our study has several limitations. Due to the possible delay in endometriosis diagnosis, some members of our cohort may have asymptomatic endometriosis and may have been incorrectly included in the group without endometriosis. The inclusion of a few undiagnosed

endometriosis cases in the unexposed group would have minimal effect given the large number of women in this group (~80,000) (40). The impact of diagnostic delay did not alter results. Finally, results did not change using self-reported endometriosis with or without laparoscopy confirmation.

While the participants are not a random sample of all US women, it is unlikely that the biologic relationships that we analyzed would differ between this cohort of female nurses and women in general. The level of health education in this cohort allows for high quality information to be collected by self-report (as has been consistently demonstrated in validation studies) and reduces confounding by education and socio-economic status. Our tumor receptor findings were restricted to those women who we had collected tissue microarray information or who had pertinent information in their medical record (71% of cases). Given the small sample size among the ER+/PR– group these results should be interpreted cautiously.

In summary, endometriosis was not found to be associated with risk of overall breast cancer. However, we found that endometriosis was associated with an increased risk for a specific type of tumor, ER+/PR– breast cancer.

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Table 1

Characteristics of women in the Nurses' Health Study II at baseline in 1989 by endometriosis status (%), adjusted for age

Demographic characteristics	Laparoscopically Confirmed Endometriosis	
	No (n=109,936)	Yes (n=5,389)
Age in 1989 [†]	34.3 ± 4.7	35.6 ± 4.2
Height (meters) [†]	1.65 ± 0.07	1.65 ± 0.07
Body Mass Index (kg/m ²) [†]	24.1 ± 5.1	23.7 ± 4.6
BMI at age 18 (kg/m ²) [†]	21.3 ± 3.4	20.8 ± 3.2
Alcohol Intake (gms/day) [†]	3.1 ± 6.1	2.9 ± 5.8
Number of pregnancies among parous women [†]	2.1 ± 0.9	1.8 ± 0.8
Family history of breast cancer	6	7
Biopsy confirmed benign breast disease	8	11
Caucasian	92	94
Age at first menstrual period		
- <12 years	24	29
- 12 years	30	30
- 13 years	28	26
- 14 years	10	9
- >14 years	8	7
Nulliparous	30	42
Current oral contraceptive use		
- Never	17	11
- Past	70	80
- Current	13	10
Smoking history		
- Never	65	64
- Past	21	21
- Current	13	14
Recent health seeking behavior ^{**}	95	98
Analgesic 2+ times per week	41	52
Hysterectomy	4	22
Oophorectomy		
- No procedure	98	83
- Unilateral	1	4
- Bilateral	1	14
Postmenopausal hormone use		
- Never User	90	68
- Past User	7	16
- Current User	3	17

[†]Mean (SD)

Values are means (SD) or percentages and are standardized to the age distribution of the study population in 1989 women were between the ages of 25 and 42

Values of polytomous variables may not sum to 100% due to rounding

** health seeking behavior defined by whether participant sought recent medical evaluation for screening or for symptoms

* Value is not age adjusted

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Table 2

Laparoscopically confirmed endometriosis in relation to breast cancer risk, in the Nurses' Health Study II

Endometriosis	Cases/Person-years	Age and calendar time adjusted model	Multivariable adjusted model
Hazard Ratio (95% CI)**			
Breast Cancer Overall			
No	4479/ 2,329,489	1.0 (Referent)	1.0 (Referent)
Yes	500/ 215,434	1.07 (0.97–1.17)	0.96 (0.88–1.06)
Breast Cancer by Menopausal Status			
Premenopausal women			
No	2,258/ 1,356,591	1.0 (Referent)	1.0 (Referent)
Yes	167/ 82,517	1.16 (0.99–1.35)	1.05 (0.89–1.23)
Postmenopausal women			
No	1,419/ 501,465	1.0 (Referent)	1.0 (Referent)
Yes	235/ 97,068	0.98 (0.85–1.13)	0.93 (0.80–1.07)
Breast Cancer stratified by mode of menopause transition among postmenopausal women			
Natural Menopause			
No	1035/ 352,180	1.0 (Referent)	1.0 (Referent)
Yes	66/ 20,196	1.17 (0.91–1.50)	1.06 (0.82–1.36)
Any Surgery (Hysterectomy, oophorectomy)			
No	384/ 153,531	1.0 (Referent)	1.0 (Referent)
Yes	169/ 76,873	0.98 (0.82–1.18)	0.90 (0.75–1.09)

** Cox proportional hazard models used

Model 1: age and calendar time adjusted

Model 2: adjusted for Model 1 + family history of breast cancer in a mother or sister, age at menarche, BMI (kg/m^2), BMI at 18, smoking history, biopsy confirmed benign breast disease, alcohol intake, recent health seeking behavior, height, oral contraceptive use history, parity + age, total breast feeding, and birth weight

Table 3

Laparoscopically confirmed endometriosis in relation to breast cancer risk by tumor hormone receptor status, in the Nurses' Health Study II

Tumor hormone receptor status	Cases without endometriosis	Cases with endometriosis	Age and calendar time adjusted Model	Multivariable adjusted Model
			Hazard Ratio (95% CI) ^{***†}	
ER+/PR+	2,333	246	1.14 (1.00–1.30)	1.00 (0.87–1.14)
ER+/PR–	309	62	2.17 (1.65–2.85)	1.90 (1.44–2.50)
ER–/PR–	528	49	1.00 (0.75–1.34)	0.90 (0.67–1.21)

^{**} Cox proportional hazard models used

[†] Likelihood Ratio P-value for test of heterogeneity across hormone receptor status-defined tumor types=0.001

Model 1: age and calendar time adjusted

Model 2: model 1+family history of breast cancer, age at menarche, body mass index,[‡] body mass index at age 18 years,[‡] smoking, biopsy confirmed benign breast disease, alcohol intake, recent health seeking behavior, birth weight, parity + age at first birth,[‡] breastfeeding,[‡] oral contraceptive

^{*} Cox proportional hazard