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A Prospective study of Endometriosis and Risk of Benign Breast Disease

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Abstract

Purpose—Given the altered hormonal and inflammatory environment of women with endometriosis, several studies have suggested a positive association between endometriosis and breast cancer, although findings have been mixed. This study investigates the relationship between endometriosis and benign breast disease (BBD), benign lesions that are associated with an increased risk of breast cancer.

Methods—Among women in the Nurses' Health Study II followed from 1991–2003 (n=76,393), we investigated the association between laparoscopically confirmed endometriosis and biopsy confirmed BBD. Cox proportional hazard models, adjusted for *a priori* potential confounding factors, were used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Across follow-up, 2,011 BBD biopsies were collected and centrally reviewed by study pathologists (non-proliferative = 675, proliferative = 1,336). Effect modification by infertility history and use of screening mammography was investigated.

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Compliance with Ethical Standards:

Conflict of Interest:

The authors have no conflicts of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Results—Endometriosis was associated with a modest increased risk of biopsy confirmed BBD in crude and multivariable adjusted models (HR:1.20, 95% CI:1.00–1.43). When evaluating subtypes of BBD, we did not see different associations for nonproliferative or proliferative BBD lesions, as endometriosis was associated with a modest increased risk for both (HR nonproliferative:1.15, 95% CI:0.84–1.57; HR proliferative:1.22, 95% CI:0.98–1.52). The association between endometriosis and proliferative BBD appeared strongest among women who had ever experienced infertility (HR: 1.50, 95% CI:1.12–2.03; P-value, test for heterogeneity=0.05). Sensitivity analyses investigating screening behaviors between those with and without endometriosis did not significantly alter results.

Conclusion—Endometriosis was associated with a modest increased risk of both proliferative and non-proliferative BBD, although future work should replicate this novel finding.

Keywords

Benign Breast Disease; Epidemiology; Endometriosis; Breast Cancer

Introduction

Breast cancer is the most common cancer for women, with approximately 300,000 women in the United States diagnosed with the disease in 2013 alone [1]. Benign breast disease (BBD) confers an increased risk of breast cancer and may represent an earlier stage of breast carcinogenesis. BBD is a heterogeneous condition with several histologic subtypes; research has consistently found that proliferative BBD without atypia moderately increases risk of breast cancer later in life (1.3–1.9 fold), while proliferative BBD with atypical hyperplasia confers between 4 and 13-fold increased risk of breast cancer [8, 11, 12, 22, 35].

Women with endometriosis, a chronic gynecologic disorder that affects approximately 10% of women [16, 27, 28], may have an altered hormonal and inflammatory milieu [7, 27, 36]. This has led to research investigating whether women with endometriosis have an altered risk for breast cancer [21], however the literature is mixed. Eleven studies suggested modest positive associations between endometriosis and the risk of breast cancer [4, 5, 10, 13, 20, 21, 25, 29, 31, 32, 39, 43], four studies showed no clear association [3, 26, 34, 40], and five studies reported an inverse relationship [2, 6, 14, 24, 30]. To our knowledge, no previous study has prospectively investigated endometriosis in relation to risk of BBD, a breast cancer risk factor and possible preliminary marker of carcinogenesis.

In this manuscript, we prospectively investigated the relationship between endometriosis and BBD within the Nurses' Health Study II (NHSII), a longitudinal cohort study of over 100,000 women. Given the altered hormonal and inflammatory environment of women with endometriosis, we hypothesized that women with endometriosis would be at increased risk of proliferative BBD compared to women without endometriosis.

Methods

The NHSII is a prospective cohort study that began in 1989 when 116,430 female 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 on each questionnaire cycles is over 90%. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Exposure definition

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 throughout cohort follow-up.

Self-reported endometriosis was validated previously among 200 participants using medical records [28]. Among women who reported laparoscopic confirmation, a laparoscopic diagnosis of endometriosis was confirmed in 96% of medical records. Conversely, among those women without laparoscopic confirmation, evidence of clinical diagnosis was found in only 54% of medical records. Thus, to reduce the magnitude of misclassification, endometriosis exposure was restricted to those women with laparoscopic confirmation. Women who reported endometriosis diagnosis without laparoscopic confirmation who later had a confirmation by laparoscopy were assigned to the endometriosis exposed group at the time of the initial clinical diagnosis. Those who reported endometriosis diagnosis but never laparoscopic confirmation were censored at the report of clinical diagnosis.

Outcome definition

In 1989, women were first asked whether or not they had received a diagnosis of fibrocystic or other benign breast disease. On each subsequent questionnaire, women reported whether they received a physician diagnosis of benign breast disease and whether the diagnosis was confirmed by biopsy and/or aspiration. If women reported a biopsy confirmed benign breast disease between 1993 and 2003, they were contacted to ask permission to obtain biopsy specimens and seek confirmation of their diagnosis. Collection of these samples has been described previously [18]. A total of 3,588 women reported a first diagnosis of biopsy-confirmed BBD, among whom 2,643 gave permission to review their biopsy records and pathology slides. Pathology material was obtained and reviewed for 2,313 women (87.5% of those who had given their permission); and 2,208 women had valid biopsy information. The main reasons for exclusion included that the pathology specimen did not contain breast tissue or that the biopsy date was before 1989.

Benign breast biopsy slides were obtained and reviewed by one of three pathologists who were blinded to the participants' endometriosis status (L.C. Collins, S. J. Schnitt, J. L. Connolly). Dupont and Page criteria were used to classify benign breast disease into three categories: nonproliferative, proliferative without atypia, and atypical hyperplasia [12]. Biopsy samples that showed atypia or questionable atypia were jointly reviewed by two pathologists to reach consensus. Samples with intraductal papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of atypical hyperplasia were classified as proliferative without atypia. Our

primary outcome was biopsy confirmed BBD, subcategorized into proliferative and non-proliferative diseases.

Statistical Methods

Women who reported a diagnosis of prior BBD or cancer (other than non-melanoma skin cancer) prior to June 1991 were excluded from our analysis. Women contributed person-time from 1991 until return of the 2003 questionnaire. Women were followed from entry into the cohort sample until confirmed i) death, ii) BBD, or iii) cancer (other than non-melanoma skin cancer).

Cox proportional hazard models stratified by calendar time with age (months) as the time scale were used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of BBD (Model 1). The proportional hazard assumption was assessed using a likelihood ratio test for the interaction between exposure and age (months); the assumption was not violated ($p>0.05$). Known *a priori* risk factors for endometriosis and BBD were adjusted for and time-varying covariates were updated biennially at every questionnaire cycle. Some treatments for endometriosis, such as hysterectomy, oophorectomy, hormone therapy use (HT), and analgesic use, may be on the causal pathway between endometriosis and BBD. We therefore updated them during each questionnaire cycle and they were included in the final model. To compare subtypes of BBD (proliferative vs. non-proliferative), we accounted for competing risks in Cox regression by using the Lunn and McNeil approach [23, 42].

Sensitivity Analyses

We conducted sensitivity analyses for our outcome definition of proliferative BBD lesions --- proliferative disease was further divided into lesions with and without atypia, since historically these lesion types have different magnitudes of association with breast cancer. The small number of women with proliferative BBD with atypia ($n=108$) precluded meaningful multivariable adjusted analyses; however models were adjusted for age and calendar time.

History of infertility may influence the relationship between endometriosis and BBD, therefore we examined whether the effect of endometriosis on BBD differed by whether or not women ever experienced infertility (12 months of trying to conceive without success), and tested the significance of interactions by likelihood ratio tests. Additionally, given the complexity of diagnosis of both endometriosis and benign breast disease, we investigated effect modification by creating a proxy for the participants' connection with the medical system. We assessed whether the effect of endometriosis on BBD differed by history of mammography or breast exam for screening purposes.

Several additional *a priori* sensitivity analyses were conducted to investigate the presence and quantify the magnitude of potential biases related to our endometriosis exposure definition. 1) We excluded prevalent endometriosis cases diagnosed before cohort enrollment (1989). 2) In studies of endometriosis, there is concern about a lengthy diagnostic delay between symptoms onset and surgical diagnosis. In the NHSII, the average diagnostic delay from symptom onset to disease diagnosis was approximately 4 years [28], while international multicenter studies have observed an average delay of 7 years [33]. To

investigate the effect of this temporal misclassification of exposure, the diagnostic date of endometriosis was set earlier by 4, 6, and 8 years. 3) We expanded our endometriosis definition to include diagnoses with and without laparoscopic confirmation.

Results

Compared to women without endometriosis in 1991 (n=72,995), women with the disease (n=3,398) were leaner at age 18 and in 1991, were more likely to be nulliparous, to report screening mammograms, to report clinical breast exams, to have had a hysterectomy or oophorectomy, and to report use of HT and oral contraceptives. Between 1991 and 2003, there were 2,011 women with biopsied BBD information (1,336 with proliferative and 675 with nonproliferative BBD) (Table 1).

Women with endometriosis had a modest increased risk of proliferative BBD in crude (HR: 1.33, 95% CI: 1.09–1.63) and multivariable adjusted models (HR: 1.22, 95% CI: 0.98–1.52) (Table 2). Attenuation after model adjustment was driven by a combination of age at first birth, family history of breast cancer, BMI, and health seeking behavior (recent mammogram or other screening test). There was no difference in associations between endometriosis and proliferative and nonproliferative BBD lesions (heterogeneity P-value: 0.99). Endometriosis was also associated with increased risk of nonproliferative BBD in multivariable adjusted models (HR: 1.15, 95% CI: 0.84–1.57). When proliferative and nonproliferative BBD cases were combined, endometriosis increased risk for overall BBD diagnosis (HR: 1.20, 95% CI: 1.00–1.43) (Table 2).

In age and calendar time adjusted sensitivity analyses, endometriosis was significantly associated with an increased risk of proliferative BBD without atypia (n=1,228) (HR Proliferative BBD without atypia: 1.35, 95% CI: 1.10–1.67) and the effect estimate was similar although not statistically significant for proliferative BBD with atypia (n=108) (HR Proliferative BBD with atypia: 1.12, 95% CI: 0.52–2.41).

When analyses were stratified by infertility history, we observed a suggestion of heterogeneity in the association of endometriosis with proliferative BBD between women with and without infertility (test for heterogeneity of proliferative BBD p-value: 0.05) (Table 3). Endometriosis was associated with increased risk of proliferative BBD among women who had ever experienced infertility (HR: 1.50, 95% CI: 1.12–2.03), but not among women who had never experienced infertility (HR: 0.93, 95% CI: 0.65–1.33). We did not observe significant heterogeneity by infertility history for nonproliferative BBD (P-value: 0.70).

In sensitivity analyses to investigate differences by participants' connection with the medical system, we stratified results by report of mammogram or breast exam for screening purposes, we found no significant difference in the relationship between endometriosis and proliferative BBD (P-value: 0.98) or nonproliferative BBD (P-value: 0.66) between those who did and who did not report screening behaviors. Additional sensitivity analyses which 1) excluded prevalent endometriosis cases, 2) predated endometriosis diagnosis, and 3) expanded endometriosis cases to include those diagnosed without laparoscopic confirmation

were not materially different than those results reported in the main analysis (data not shown).

Discussion

Benign breast disease is an important risk factor for breast cancer. In our analysis, we observed a modest risk of biopsy confirmed BBD, both proliferative and nonproliferative lesions, among women with endometriosis. The strongest increased risk of proliferative BBD in women with endometriosis was observed among women with a history of infertility.

Contrary to our *a priori* hypothesis, we found that endometriosis was associated with an increased risk of both proliferative and nonproliferative lesions. This finding is difficult to interpret given the lack of uniformity for classifying nonproliferative benign lesions across studies. In their seminal study, Dupont and Page found no increased breast cancer risk among women with nonproliferative BBD [12]. However, more recent research has found modest increased risk of breast cancer among nonproliferative lesions [9, 17, 41]. Wang et al. in a companion study to the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial found that women in the “lower category” of BBD had 1.6 times the risk of breast cancer compared to healthy women [41]. Hartman et. al. found that women with nonproliferative BBD had a 1.27 (95% CI: 1.15–1.41) fold risk of breast cancer among a cohort of women from the Mayo Clinic [17]. And most recently, Castells et. al. found nonproliferative lesions conferred a 2.23 fold (95% CI: 1.86–2.68) increased risk of breast cancer in a population based screening cohort [9]. Few studies have investigated risk factors for both proliferative and nonproliferative lesions given the mixed findings among nonproliferative lesions related to breast cancer risk.

The relationship between endometriosis and proliferative BBD, the histologic type of BBD which confers the highest risk of breast cancer, was strongest among women who had reported previous history of infertility. While endometriosis is often thought to be highly correlated with infertility, these women may have varying levels of disease severity [15, 16]. Women with endometriosis and infertility may represent endometriosis lesions that were severe enough to have caused impaired fecundity or these women may represent asymptomatic endometriosis cases that were diagnosed during a routine fertility evaluation because of pre-existing infertility caused by another condition [37]. Unfortunately information on reason for endometriosis diagnosis (pain or infertility presentation) was not collected in this study. Future research in this area should investigate if mechanism of endometriosis diagnosis modifies the relationship with BBD.

Women who received a diagnosis of endometriosis may be more connected with the medical system than women who are not diagnosed. Since BBD is often discovered through screening procedures such as a mammogram or breast exam, it is possible that any relationship found between endometriosis and BBD may represent a spurious association being driven by connection to medical system. While the effect of this bias is likely minimal given that this is a cohort of medical professionals, all analyses were adjusted for recent health seeking behavior which could be a proxy for connection with the medical system (including mammography, clinical breast exam, and other screening behaviors including Pap

smear, colonoscopy and hypertension screening). Additionally, sensitivity analyses were conducted stratifying by use of mammography or clinical breast exam for screening and no significant differences in the relationship between endometriosis and BBD were observed between women who did and did not undergo breast cancer screening behavior. However, we cannot fully rule out the possibility of residual confounding by connection with the medical system, which our self-reported proxy measures may not fully capture.

Women with endometriosis may have an altered hormonal and inflammatory milieu [7, 27, 36]. It is well established that estrogen plays an important role in endometriosis [36], with endometrial lesions depending on circulating estrogen for growth and maintenance [27]. Recent research has found increased levels of steroid hormones, particularly endogenous estrogens among women with BBD compared to healthy controls [38]. Thus, the pathogenesis of both diseases may be regulated through a shared hormonal etiology.

This study has several limitations. Due to the delay in endometriosis diagnosis, some members of our cohort may have asymptomatic disease or disease that has not yet been diagnosed. Since the prevalence of endometriosis is ~10%, the inclusion of undiagnosed endometriosis cases in the unexposed group would likely have a limited effect among the large number of truly unexposed women in this cohort [19, 44], and while this misclassification still may bias our estimates, the bias would most likely attenuate our findings. A bias by diagnostic delay was investigated more thoroughly through the sensitivity analyses which predated endometriosis diagnoses. We found that predated endometriosis cases did not materially alter results. While the participants in our study were 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 and reduces confounding by education and socio-economic status.

This study has many strengths. To reduce the likelihood of misclassification of our outcomes, our BBD case definition was centrally reviewed by experienced breast pathologists. Additionally, our validated exposure definition was restricted to endometriosis cases confirmed by laparoscopy to decrease misclassification. In the first study to investigate the association between endometriosis and risk of BBD, we were able to adjust for time-varying covariates and assess possible mediating factors.

Women with endometriosis may be at a modest increased risk of benign breast disease, which may put them at a heightened risk for breast cancer later in life. Future research should focus on replicating this novel finding.

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Table 1

Characteristics of women in the Nurses' Health Study II at baseline in 1991 by endometriosis status

	Laparoscopically Confirmed Endometriosis	
	No (n=72,995)	Yes (n=3,398)
	Mean (SD)	
Age (years)*	35.5 (4.7)	36.4 (4.3)
Height (meters)	1.6 (0.1)	1.7 (0.1)
Body Mass Index (kg/m ²)	24.9 (5.5)	24.5 (5.0)
Body Mass Index at age 18 (kg/m ²)	21.4 (3.4)	20.9 (3.2)
Parity (among parous)	2.2 (0.9)	1.9 (0.8)
	%	
Never reported a successful pregnancy, %	25.3	38.3
Family history of breast cancer, %	4.8	5.3
Current oral contraceptive use		
- Never, %	16.2	10.0
- Past, %	71.9	80.6
- Current, %	11.8	9.4
Age at first menstrual period		
- <12 years, %	24.0	27.9
- 12 years, %	30.0	30.3
- 13 years, %	27.7	26.3
- 14 years, %	10.5	9.2
- >14 years, %	7.8	6.4
Mammogram in 1991		
- No, %	64.4	60.9
- Yes Screening, %	33.5	36.4
- Yes Symptoms, %	2.1	2.7
Breast Exam		
- No, %	16.8	12.5
- Yes Screening, %	81.4	85.0
- Yes Symptoms, %	1.8	2.5
Hysterectomy, %	4.1	21.0
Oophorectomy		
- No procedure, %	98.3	82.8
- Unilateral, %	0.6	3.1
- Bilateral, %	1.2	14.1
Hormone Therapy Use		
- Never User, %	87.5	61.7
- Past User, %	9.6	21.4
- Current User, %	2.9	16.8

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

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

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Table 2

Laparoscopically confirmed endometriosis in relation to BBD risk in the Nurses' Health Study II (1991–2003)

Endometriosis	Cases/Person-years	Age and calendar time adjusted model	Multivariable adjusted model
Relative Risk(95% CI)			
Nonproliferative BBD ^I			
No	627/812,417	1.0 (Referent)	1.0 (Referent)
Yes	48/53,492	1.29 (0.96–1.73)	1.15 (0.84–1.57)
Proliferative BBD ^I			
No	1,234/811,806	1.0 (Referent)	1.0 (Referent)
Yes	102/53,438	1.33 (1.09–1.63)	1.22 (0.98–1.52)
BBD ^I (Combined Nonproliferative + Proliferative)			
No	1,861/811,242	1.0 (Referent)	1.0 (Referent)
Yes	150/53,395	1.32 (1.12–1.56)	1.20 (1.00–1.43)

Cox proportional hazard Model 1: age (months) and calendar time (years) adjusted

Model 2: adjusted for Model 1 + potential confounders: family history of breast cancer in a mother or sister, age at menarche(<12, 12, 13, 14, >14), BMI (kg/m²) (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, ≥30), BMI at 18 (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, ≥30), smoking history (never, past, current), alcohol intake (no alcohol, <5 gms/day, 5–10 gms/day, >10 gms/day), recent health seeking behavior(yes, no), height, oral contraceptive use history (never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years at first birth, 1–2 children and ≥25 at first birth, ≥3 children and <25 years at first birth, ≥3 children and ≥25 at first birth), total breast feeding (<1 month, 1–3 months, 3–12 months, >12 months), adolescent alcohol intake (no alcohol, <5gms alcohol per day, 5–10 gms/day, >10 gms/day) hormone therapy use (never, past, current), hysterectomy, oophorectomy, any analgesic greater than 2+ times per week, menopause status

^IBased on centralized pathology review of H&E slides

Table 3

Laparoscopically confirmed endometriosis in relation to BBD risk in the Nurses' Health Study II (1991–2003) stratified by infertility history

Endometriosis	Cases/Person-years	Age and calendar time adjusted model	Multivariable adjusted model	Test for heterogeneity P-value
Relative Risk (95% CI)				
Nonproliferative BBD Never Infertility				
No	508/650,305	1.0 (Referent)	1.0 (Referent)	0.70
Yes	21/23,295	1.32 (0.85–2.04)	1.07 (0.67–1.71)	
Ever Infertility				
No	119/162,113	1.0 (Referent)	1.0 (Referent)	
Yes	27/30,197	1.29 (0.84–1.96)	1.32 (0.84–2.07)	
Proliferative BBD Never Infertility				
No	992/64,9820	1.0 (Referent)	1.0 (Referent)	0.05
Yes	36/23,279	1.07 (0.77–1.50)	0.93 (0.65–1.33)	
Ever Infertility				
No	242/161,986	1.0 (Referent)	1.0 (Referent)	
Yes	66/30,159	1.55 (1.18–2.05)	1.50 (1.12–2.03)	
BBD (Combined Nonproliferative + Proliferative) Never Infertility				
No	1500/649,358	1.0 (Referent)	1.0 (Referent)	0.07
Yes	57/23,260	1.15 (0.88–1.50)	0.98 (0.74–1.30)	
Ever Infertility				
No	361/161,884	1.0 (Referent)	1.0 (Referent)	
Yes	93/30,136	1.46 (1.16–1.84)	1.42 (1.10–1.81)	

Cox proportional hazard Model 1: age and calendar time adjusted

Model 2: adjusted for Model 1 + potential confounders: family history of breast cancer in a mother or sister, age at menarche(<12, 12, 13, 14, >14), BMI (kg/m²) (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, ≥30), BMI at 18 (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, ≥30), smoking history (never, past, current), alcohol intake (no alcohol, <5 gms/day, 5–10 gms/day, >10 gms/day), recent health seeking behavior (yes, no), height, oral contraceptive use history (never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years at first birth, 1–2 children and ≥25 at first birth, ≥3 children and <25 years at first birth, ≥3 children and ≥25 at first birth), total breast feeding (<1 month, 1–3 months, 3–12 months, >12 months), adolescent alcohol intake (no alcohol, <5gms alcohol per day, 5–10 gms/day, >10 gms/day), hormone therapy use (never, past, current), hysterectomy, oophorectomy, any analgesic greater than 2+ times per week, menopause status