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HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Cancer Causes Control. 2016 October ; 27(10): 1229–1237. doi:10.1007/s10552-016-0801-y.

Endometriosis and Mammographic Density Measurements in the Nurses' Health Study II

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Abstract

Purpose—Endometriosis and mammographic density have been hypothesized to be influenced by sex-steroid hormonal exposures in adolescence and early adulthood. We investigated the association between endometriosis and mammographic density, a consistent and independent risk factor for breast cancer.

Methods—We conducted a cross-sectional analysis among 1,581 pre- and post-menopausal women not previously diagnosed with breast cancer in the Nurses' Health Study II cohort. We measured average percent mammographic density and absolute dense and non-dense breast area using a validated computer-assisted method. Multivariable linear regression was used to estimate the association between endometriosis and mammographic density among pre- and postmenopausal women separately.

Results—Among premenopausal women, average percent mammographic density was 43.1% among women with endometriosis (n=91) and 40.5% among women without endometriosis (n=1,150). Endometriosis was not associated significantly with mammographic density among pre-menopausal (% difference=2.00 percentage points 95% CI:(−1.33,5.33)) or among post-menopausal women (% difference = −0.89 percentage points 95% CI:(−5.10,3.33)). Among premenopausal women, there was heterogeneity by BMI at age 18 (P-value= 0.003), with a suggested association among those who were lean at age 18 (BMI< 20.6 kg/m^2) (% difference=3.74 percentage points 95% CI:(−0.29,7.78)).

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Conflict of Interest: The authors declare that they have no conflict of interest.

Conclusion—Endometriosis was not found to be associated with overall measurements of mammographic density.

Keywords

endometriosis; mammographic density; breast density; breast cancer

Introduction

Women with endometriosis, a chronic gynecologic disorder that affects approximately 10% of women (1-3), may have an altered hormonal and inflammatory milieu (2, 4-6). It is well established that sex steroid hormones play an important role in endometriosis (4) with endometriosis lesions depending on circulating estrogen for growth and maintenance (1, 2, 7). Recent research has indicated that women with endometriosis may be at increased risk for several chronic diseases including cardiovascular disease and certain types of cancer, including ovarian and possibly breast (8). Epidemiologic evidence for a relationship between endometriosis and breast cancer risk has been mixed (8-11) with eleven studies suggesting modest positive associations between endometriosis and the risk of breast cancer (8, 12-21, 77), four studies showing no clear association (22-25), and five studies reporting an inverse relationship (26-30).

One of the strongest and most consistent risk factors for breast cancer is mammographic density, a measure of the amount of fibroglandular tissue in the breast comprised of epithelial and stromal cells. Mammographic density can be assessed on a mammogram--dense breast tissue appears light on a mammogram, whereas non-dense tissue appears dark. Women with ≥ 75% mammographic density have a four- to six-fold increased risk of developing breast cancer compared to women with almost entirely fatty breasts, i.e. mammographic density <5% (31-33).

Mammographic density is established in early adulthood, with highest density occurring before menopause and has been hypothesized to be associated with sex-steroid hormone exposure (34-37). This is supported by reported relationships with risk factors, including exogenous hormone therapy use which increases mammographic density (4, 38-44) and with menopausal status which decreases mammographic density (39-41, 43-47). Despite the fact that endometriosis is associated with highly estrogenic environment and that endometriosis may be associated with breast cancer, no prior study has investigated the relationship between endometriosis and mammographic density.

We investigated the relationship between endometriosis and mammographic density within the Nurses' Health Study II (NHSII) cohort. We hypothesized that women with endometriosis would have higher mammographic density compared to women without the disease.

Methods

The NHSII 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 patterns.

Follow-up questionnaires were sent biennially to collect information on environmental, dietary, and lifestyle risk factors with cumulative response rates over 90%. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Study Population

Within the NHSII, original mammogram collection was conducted within a breast cancer case-control study, which was nested within the sub-cohort of women who provided a blood sample. Controls were randomly selected from the sub-cohort of women who returned a blood sample and had never reported a diagnosis of cancer. One or two controls were matched to breast cancer cases on year of birth, menopausal status, hormonal therapy use, race/ethnicity, and time of day, month, and fasting status at time of blood draw. Mammograms were received from approximately 80% of eligible women in the nested case-control study and were collected for years close to blood collection (1996-1999). We additionally collected mammograms (conducted from around 1997) from eligible women (breast cancer cases and non-cases) who provided cheek cell samples or completed an adolescent diet questionnaire in NHSII. Women for whom mammograms could not be obtained did not differ from those with available mammograms with regard to breast cancer risk factors, including BMI, parity and family history of breast cancer (35, 48).

Given that high mammographic density is associated positively with increased risk of breast cancer, to prevent a spurious association between endometriosis and mammographic density, we restricted the study population to controls for this analysis (n=1,581, after exclusions). If women reported hormone therapy use, they were removed from the analysis if they were a smoker and between the ages of 46-54 or a non-smoker or current smoker and between the ages of 48-56 due to inability to determine menopausal status. Women missing information on endometriosis were excluded from the analysis.

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 biennial subsequent questionnaire. Self-reported endometriosis diagnosis was previously validated using the medical records of 200 randomly selected participants (3). Among women who reported laparoscopic confirmation, a laparoscopic (surgical) diagnosis of endometriosis was confirmed in 96% of women. Conversely, among women without laparoscopic confirmation, evidence of clinical diagnosis was found in only 54% of medical records. Thus, to reduce the magnitude of misclassification, we restricted our definition of endometriosis to those women with a laparoscopic confirmation. Women who only reported clinical, not surgical, diagnosis were excluded from both the endometriosis and non-endometriosis groups. Women were classified as having endometriosis if they ever reported a laparoscopic diagnosis prior to the time of mammogram.

Outcome Definition

From the mammograms collected, the cranio-caudal views of both breasts were digitized 261μm/pixel with a Lumysis 85 laser film scanner (Lumysis, Sunnyvale, CA) or a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) (using comparable resolution of 150 dots per inch and 12 bit depth inch and 12 bit depth). Average percent mammographic density has been the primary measure of breast density given its consistent relationship to breast cancer risk (48, 49) and thus was our primary outcome of interest, however recent literature has suggested that both absolute dense and non-dense area are independent predictors of breast cancer risk (49-52) therefore we also examined these outcomes separately in secondary analyses. To estimate absolute dense area, absolute non-dense area (total breast area minus dense area), and percent mammographic density (dense area divided by total breast area), we used Cumulus software (University of Toronto, Toronto, Canada) for computer-assisted thresholding (53, 54). The reader selects two thresholds according to the intensity of the pixels: one to delineate the breast edge and the other to distinguish dense tissue from non-dense tissue. The software then calculates the number of pixels of the entire breast and those of the area identified as dense.

Mammograms were read by a single reader in two batches approximately 3 years apart. Our trained reader is blinded to case and control status and consistently achieves a within-person intraclass correlation coefficient of 0.91 and an intraclass correlation coefficient of 0.90 for comparison with an external expert (48). We found evidence of batch-to-batch variability in the two batches of mammogram density measurements read approximately 3 years apart. Mammographic density measurements measured in the second batch were corrected to produce the measurement that would have been obtained had the mammogram been included in the first batch, using a statistical technique described in detail previously (35, 55).

Statistical Methods

Given the consistent relationship between menopausal status and breast density (31), with breast density being lower among postmenopausal women, all analyses were stratified by menopausal status *a priori*. Women were considered postmenopausal if they reported 1) no menstrual periods for 12 months, 2) having had a bilateral oophorectomy, or 3) being 54 years old or older if a current smoker or 56 years or older if a non-smoker or former smoker at time of mammogram.

We fit multivariable linear regression models to quantify the cross-sectional association between endometriosis (independent variable) and measures of mammographic density (dependent variable). Generalized estimating equations were used to account for correlation among matched controls using an unstructured correlation matrix. Robust (sandwich) standard errors were used to minimize potential violations in the assumptions of normality of residuals and homoscedasticity for linear regression. Model 1 adjusted for current age and BMI, known important predictors of both endometriosis and mammographic density. Model 2 additionally adjusted for potential confounding by other *a priori* risk factors for mammographic density: alcohol intake (<4 gms/day vs. ≥ 4 gms/day), family history of breast cancer, smoking history (current, never, smoker), history of benign breast disease,

BMI at age 18 (<18.5, 18.5-22.4, 22.5-24.9, 25-29.9, ≥ 30), parity (1, 2, 3, ≥ 4) , age at menarche (<12, 12, 13, 14, >14), oral contraceptive use history (never, past, current), and breastfeeding history (never, 1-5 months, 6-11 months, ≥ 12 months). Since some treatments for endometriosis may alter mammographic density, model 3 additionally adjusted for those covariates that may be potential mediators of the relationship between endometriosis and mammographic density: hysterectomy, hormone therapy use (never, past, current), and oophorectomy (none, unilateral, bilateral) (postmenopausal women only). Endometriosis diagnosis history and covariate status were defined at the closest questionnaire cycle to the time of the mammogram. Due to the known relationship between body size and endometriosis (56, 57) and body size and mammographic density (58, 59), effect modification was investigated for BMI at age 18, and current BMI among premenopausal women, and likelihood ratio tests were used to test for significance of interaction terms. The small number of postmenopausal women with endometriosis in our study (n=77) precluded meaningful analysis of interactions in this subgroup. To account for possible diagnostic delay of endometriosis and to investigate potential selection bias, we conducted sensitivity analyses that used endometriosis diagnostic status of 2, 4, and 6 years before the nurses' reported date of surgical diagnosis and restricted our endometriosis diagnosis definition to those women diagnosed after cohort inception.

Results

Around the time of mammogram, pre- and post-menopausal women with endometriosis reported lower current BMI and lower BMI at age 18, were more likely to be nulliparous or to have low parity, to have undergone oophorectomy (unilateral or bilateral) or hysterectomy, and to be past or current users of hormone therapy, compared to women without endometriosis (**Table 1**). Premenopausal women with endometriosis were more likely to have had earlier age at menarche compared to premenopausal women without endometriosis, whereas postmenopausal women with endometriosis were more likely to report later age at menarche compared to women without endometriosis.

Among premenopausal women, women with endometriosis appeared to have modestly higher average percent mammographic density of 43.1% (SD:17.5) compared to healthy women (40.5% (17.9)) (**Table 2**). However, in models adjusting for potential confounding and mediating factors, endometriosis was not associated with percent mammographic density (% density: 2.00 percentage points difference, 95% CI: −1.33, 5.33), nor was endometriosis associated with average dense (0.10 cm^2 difference, 95% CI: −9.74, 9.94) or non-dense area (−8.45 cm^2 difference, 95% CI: −22.34, 5.44) (Table 2; Model 3). Among postmenopausal women, there was also no significant difference in average percent mammographic density (% density:−0.89 percentage points difference, 95% CI: −5.10, 3.33), average dense area (−2.71 cm^2 difference, 95% CI: −15.34, 9.93), or average non-dense area (3.38 cm^2 difference, 95% CI: −15.82, 22.57) for women with and without endometriosis (Table 2; Model 3). Given the opposing directions of percent mammographic density in pre- and post-menopausal women, the effect of endometriosis on percent mammographic density varied by menopausal status (P-value test for interaction: 0.02). Sensitivity analyses predating onset of endometriosis diagnosis or defining endometriosis diagnosis as after 1989 did not substantially alter the results (results not shown).

We found significant heterogeneity in associations of endometriosis and average percent mammographic density by BMI at age 18 (P-value test for interaction: 0.03), but not by current BMI (i.e., near time of mammogram) (P-value test for interaction: 0.31) (**Table 3**). Among women who were lean at age 18 (BMI < 20.6, the median value in the population), those with endometriosis had significantly higher percent mammographic density in models adjusted for age and current BMI (4.44 percentage points difference, 95% CI: 0.12, 8.76) compared to those without endometriosis, which was attenuated slightly in fully adjusted models (3.74 percentage points difference, 95% CI: −0.29, 7.78). We saw no difference in the association between endometriosis and non-dense area for BMI at time of mammogram (P-value test for interaction= 0.83) nor for BMI at age 18 (P-value test for interaction = 0.09). The association between endometriosis and total dense area did not vary by BMI at time of mammogram (P-value test for interaction= 0.12). However, there was a suggestion of a difference in the association between endometriosis and total dense area between lean and non-lean BMI at age 18 (P-value test for interaction= 0.05); among those who were lean at age 18, those diagnosed with endometriosis had a trend towards greater total dense area (7.14 cm^2 difference, 95% CI: −6.62, 20.90).

Discussion

In this study nested within the NHSII, endometriosis was not found to be associated with average percent mammographic density, dense area, or non-dense area in premenopausal or postmenopausal women overall. However, the relationship between endometriosis and percent mammographic density in premenopausal women was modified by BMI at age 18. Among women who were lean at age 18, those with endometriosis had moderately higher percent mammographic density later in life, compared to those without endometriosis.

To our knowledge, this study is the first investigation of endometriosis and mammographic density to date. Women with endometriosis were found not to have altered mammographic density overall compared to women without endometriosis. Thus, if endometriosis is associated with increased risk of breast cancer, our data suggest that the relationship may not be mediated through mammographic density. In this cohort, we previously found that while women with endometriosis were not at increased risk for overall breast cancer, they were at an increased risk for estrogen receptor positive, progesterone receptor negative (ER+/PR-) tumors (77). A recent pooled analysis has found that the effect of mammographic density on breast cancer risk did not vary by tumor PR status, but did appear stronger among ER− compared to ER+ tumors in women <55 years old (0.04) (60).

Early life body size has been inversely associated with endometriosis (56, 61, 62, 77), mammographic density (58, 59, 63-66), and breast cancer (59, 65, 67). In *a priori* sensitivity analyses, we found that among premenopausal women who were lean at age 18, those with endometriosis had a trend towards higher average percent mammographic density (3.7% difference) which was driven by higher average dense area (7 cm^2 difference). This finding is striking given the large magnitude of effect compared to other reproductive risk factors. For example, it is estimated that each pregnancy decreases average percent mammographic density by 2%(36), exogenous hormone therapy usage increases mammographic density by 3.1-4.8% (36, 38),and tamoxifen decreases mammographic density by 5-8% which has been

associated with decreased breast cancer recurrence (68, 69). For every additional percentage point increase of mammographic density, breast cancer risk has been estimated to increase by 2% (70). Additionally, women who are lean at age 18 already have higher mammographic density than overweight women, putting them at higher risk of breast cancer. Samimi et al. reported that higher mammographic density in those with lean body size at age 18, independent of adult body fatness, was estimated to correspond to a 5-15% increased risk of breast cancer (64).

While the prospective cohort design of our study allowed for detailed, updated information on exposure and covariate status, the mammographic density measurements are from one cross-sectional point in time and thus may not accurately capture density across the life course. As breast density is known to change as women age, all analyses were adjusted for age and stratified by menopausal status. Due to a potential delay between symptom onset and endometriosis diagnosis, some members of our cohort may have asymptomatic endometriosis or endometriosis that has not yet been diagnosed at time of mammogram. However, since the prevalence of endometriosis is ~10%, the inclusion of undiagnosed endometriosis cases in the unexposed group would have a small effect(71), given the number of truly unexposed women (72) and while this misclassification still may bias our estimates, the bias would most likely be non-differential in relation to mammographic density and thus attenuate our findings toward the null. In sensitivity analyses, we investigated this potential diagnostic delay by predating endometriosis exposure, which did not substantially alter our results. As discussed previously, hormonal treatments for endometriosis may influence mammographic density, and thus were conceptualized not as traditional confounders, but rather as potential mediators. While NHS II participants contributed information on hormone therapy and oral contraceptives, which did not significantly alter reported associations, we did not have sufficiently detailed information on other hormonal treatments which are sometimes used for endometriosis such as danazol and leuprolide. Leuprolide has been shown to reduce mammographic density and has also been used as a breast cancer treatment (73, 74). Thus, there may be unmeasured confounding or mediation by these hormonal treatments, which may lead to an underestimation of the association between endometriosis and mammographic density, if a true relationship exists. However, these treatments were more commonly used early in cohort follow-up (7, 75) and sensitivity analyses restricting incident endometriosis after 1989 showed similar results. Future research should investigate this potential limitation. Furthermore, due to the limited number of endometriosis cases, we may not have been adequately powered to detect modest differences in mammographic density.

This investigation into endometriosis and mammographic density is the first study to investigate this relationship. It has many strengths including its validated exposure definition of laparoscopically confirmed endometriosis and validated quantitative outcome assessment of percent and absolute mammographic density from screening mammograms with high intra-reader reliability. We were also able to adjust for potentially important confounding and mediating factors of the endometriosis and mammographic density relationship.

Mammographic density is an important risk factor for breast cancer and public awareness is growing as more patients are informed of their mammographic density after receiving a

mammogram. In this study, endometriosis was not significantly associated with mammographic density. Future research could focus on replicating our finding among women lean women at age 18, among whom a consistent association with high mammographic density, endometriosis, and risk of breast cancer has been found (62, 65, 76). However, overall women with endometriosis do not appear to have greater mammographic density.

Acknowledgements

This work was supported by National Institutes of Health, National Cancer Institute [UM1 CA176726, 3R25CA057711 to LVF], National Institute of Child Health and Human Development [HD57210, T32HD060454 to LVF], the Dana Farber and Harvard Cancer Center Mazzone Award, and the Breast Cancer Research Foundation

References

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004; 364:1789–99. [PubMed: 15541453]
2. Missmer SA, Cramer DW. The epidemiology of endometriosis. Obstet Gynecol Clin North Am. 2003; 30:1–19. vii. [PubMed: 12699255]
3. Missmer SA, Hankinson SE, Spiegelman D, et al. Reproductive history and endometriosis among premenopausal women. Obstet Gynecol. 2004; 104:965–74. [PubMed: 15516386]
4. Parente Barbosa C, Bentes De Souza AM, Bianco B, Christofolini DM. The effect of hormones on endometriosis development. Minerva Ginecol. 2011; 63:375–86. [PubMed: 21747346]
5. Jones RK, Bulmer JN, Searle RF. Phenotypic and functional studies of leukocytes in human endometrium and endometriosis. Hum Reprod Update. 1998; 4:702–9. [PubMed: 10027623]
6. Osteen KG, Rodgers WH, Gaire M, Hargrove JT, Gorstein F, Matrisian LM. Stromalepithelial interaction mediates steroidal regulation of metalloproteinase expression in human endometrium. Proc Natl Acad Sci U S A. 1994; 91:10129–33. [PubMed: 7937850]
7. Giudice LC. Clinical practice. Endometriosis. The New England journal of medicine. 2010; 362:2389–98. [PubMed: 20573927]
8. Kvaskoff M, Mu F, Terry KL, et al. Endometriosis: a high-risk population for major chronic diseases? Hum Reprod Update. 2015
9. Anifantaki F, Boutas I, Kalampokas T, Kalampokas E, Sofoudis C, Salakos N. Association of endometriosis and breast cancer: mini review of the literature. Arch Gynecol Obstet. 2016; 293:5–10. [PubMed: 26138306]
10. Munksgaard PS, Blaakaer J. The association between endometriosis and gynecological cancers and breast cancer: a review of epidemiological data. Gynecol Oncol. 2011; 123:157–63. [PubMed: 21742370]
11. Pontikaki A, Sifakis S, Spandidos DA. Endometriosis and breast cancer: A survey of the epidemiological studies. Oncol Lett. 2016; 11:23–30. [PubMed: 26870162]
12. Mogensen JB, Kjaer SK, Mellemkjaer L, Jensen A. Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study. Gynecol Oncol. 2016
13. Weiss HA, Brinton LA, Potischman NA, et al. Breast cancer risk in young women and history of selected medical conditions. International journal of epidemiology. 1999; 28:816–23. [PubMed: 10597976]
14. Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. Acta obstetricia et gynecologica Scandinavica. 2004; 83:395–400. [PubMed: 15005789]
15. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol. 1997; 176:572–9. [PubMed: 9077609]
16. Melin A, Sparen P, Bergqvist A. The risk of cancer and the role of parity among women with endometriosis. Hum Reprod. 2007; 22:3021–6. [PubMed: 17855408]

17. Moseson M, Koenig KL, Shore RE, Pasternack BS. The influence of medical conditions associated with hormones on the risk of breast cancer. International journal of epidemiology. 1993; 22:1000–9. [PubMed: 8144280]
18. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA. Breast cancer risk associated with gynecologic surgery and indications for such surgery. International journal of cancer. Journal international du cancer. 1997; 70:150–4. [PubMed: 9009152]
19. Kok VC, Tsai HJ, Su CF, Lee CK. The Risks for Ovarian, Endometrial, Breast, Colorectal, and Other Cancers in Women With Newly Diagnosed Endometriosis or Adenomyosis: A Population-Based Study. Int J Gynecol Cancer. 2015; 25:968–76. [PubMed: 25893280]
20. Nichols HB, Visvanathan K, Newcomb PA, et al. Bilateral oophorectomy in relation to risk of postmenopausal breast cancer: confounding by nonmalignant indications for surgery? Am J Epidemiol. 2011; 173:1111–20. [PubMed: 21430192]
21. Chuang SC, Wu GJ, Lu YS, Lin CH, Hsiung CA. Associations between Medical Conditions and Breast Cancer Risk in Asians: A Nationwide Population-Based Study in Taiwan. PLoS One. 2015; 10:e0143410. [PubMed: 26605792]
22. Bertelsen L, Mellemkjaer L, Frederiksen K, et al. Risk for breast cancer among women with endometriosis. International journal of cancer. Journal international du cancer. 2007; 120:1372–5. [PubMed: 17187365]
23. Melin A, Sparen P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod. 2006; 21:1237–42. [PubMed: 16431901]
24. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer. 2002; 94:1612–8. [PubMed: 11920519]
25. Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet. 1999; 354:1586–90. [PubMed: 10560672]
26. Matta JL, Flores I, Morales LM, Monteiro J, Alvarez-Garriga C, Bayona M. Women with endometriosis have a higher DNA repair capacity and diminished breast cancer risk. Mol Cancer Biol. 2013; 1
27. Baron JA, Weiderpass E, Newcomb PA, et al. Metabolic disorders and breast cancer risk (United States). Cancer causes & control : CCC. 2001; 12:875–80. [PubMed: 11808705]
28. Brinton LA, Westhoff CL, Scoccia B, et al. Causes of infertility as predictors of subsequent cancer risk. Epidemiology. 2005; 16:500–7. [PubMed: 15951668]
29. Gemmill JA, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Cancers, infections, and endocrine diseases in women with endometriosis. Fertil Steril. 2010; 94:1627–31. [PubMed: 19945097]
30. Morales L, Alvarez-Garriga C, Matta J, et al. Factors associated with breast cancer in Puerto Rican women. J Epidemiol Glob Health. 2013; 3:205–15. [PubMed: 24206792]
31. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst. 1995; 87:1622–9. [PubMed: 7563205]
32. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst. 2010; 102:1224–37. [PubMed: 20616353]
33. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006; 15:1159–69. [PubMed: 16775176]
34. Gierach GL, Patel DA, Falk RT, et al. Relationship of serum estrogens and metabolites with area and volume mammographic densities. Horm Cancer. 2015; 6:107–19. [PubMed: 25757805]
35. Bertrand KA, Eliassen AH, Hankinson SE, et al. Urinary estrogens and estrogen metabolites and mammographic density in premenopausal women. Breast Cancer Res Treat. 2012; 136:277–87. [PubMed: 23053640]
36. Martin LJ, Boyd NF. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res. 2008; 10:201. [PubMed: 18226174]
37. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density: a hormonally responsive risk factor for breast cancer. J Br Menopause Soc. 2006; 12:186–93. [PubMed: 17178021]

38. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst. 2003; 95:30–7. [PubMed: 12509398]
39. Harvey JA, Pinkerton JV, Herman CR. Short-term cessation of hormone replacement therapy and improvement of mammographic specificity. J Natl Cancer Inst. 1997; 89:1623–5. [PubMed: 9362162]
40. Leung W, Goldberg F, Zee B, Sterns E. Mammographic density in women on postmenopausal hormone replacement therapy. Surgery. 1997; 122:669–73. discussion 73-4. [PubMed: 9347841]
41. Lundstrom E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: differences according to treatment. Am J Obstet Gynecol. 1999; 181:348–52. [PubMed: 10454681]
42. McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. J Natl Cancer Inst. 2005; 97:1366–76. [PubMed: 16174858]
43. Persson I, Thurfjell E, Holmberg L. Effect of estrogen and estrogen-progestin replacement regimens on mammographic breast parenchymal density. J Clin Oncol. 1997; 15:3201–7. [PubMed: 9336356]
44. Stomper PC, Van Voorhis BJ, Ravnikar VA, Meyer JE. Mammographic changes associated with postmenopausal hormone replacement therapy: a longitudinal study. Radiology. 1990; 174:487–90. [PubMed: 2136958]
45. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control. 2000; 11:653–62. [PubMed: 10977110]
46. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Taplin S. Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. JAMA : the journal of the American Medical Association. 2001; 285:171–6. [PubMed: 11176809]
47. Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk: interactions of percent density, absolute dense, and non-dense areas with breast cancer risk factors. Breast Cancer Res Treat. 2015; 150:181–9. [PubMed: 25677739]
48. Tamimi RM, Hankinson SE, Colditz GA, Byrne C. Endogenous sex hormone levels and mammographic density among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2005; 14:2641–7. [PubMed: 16284390]
49. Pettersson A, Graff RE, Ursin G, et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst. 2014:106.
50. Pettersson A, Hankinson SE, Willett WC, Lagiou P, Trichopoulos D, Tamimi RM. Nondense mammographic area and risk of breast cancer. Breast Cancer Res. 2011; 13:R100. [PubMed: 22017857]
51. Lokate M, Peeters PH, Peelen LM, Haars G, Veldhuis WB, van Gils CH. Mammographic density and breast cancer risk: the role of the fat surrounding the fibroglandular tissue. Breast Cancer Res. 2011; 13:R103. [PubMed: 22030015]
52. Stone J, Ding J, Warren RM, Duffy SW, Hopper JL. Using mammographic density to predict breast cancer risk: dense area or percentage dense area. Breast Cancer Res. 2010; 12:R97. [PubMed: 21087468]
53. Byng JW, Boyd NF, Little L, et al. Symmetry of projection in the quantitative analysis of mammographic images. Eur J Cancer Prev. 1996; 5:319–27. [PubMed: 8972250]
54. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2007; 99:1178–87. [PubMed: 17652278]
55. Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: some methodological issues. Am J Epidemiol. 2008; 167:653–66. [PubMed: 18230679]
56. Hediger ML, Hartnett HJ, Louis GM. Association of endometriosis with body size and figure. Fertil Steril. 2005; 84:1366–74. [PubMed: 16275231]

57. Lafay Pillet MC, Schneider A, Borghese B, et al. Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case-control study. Hum Reprod. 2012; 27:265–72. [PubMed: 22025227]
58. Bertrand KA, Baer HJ, Orav EJ, et al. Body fatness during childhood and adolescence and breast density in young women: a prospective analysis. Breast Cancer Res. 2015; 17:95. [PubMed: 26174168]
59. Andersen ZJ, Baker JL, Bihrmann K, Vejborg I, Sorensen TI, Lynge E. Birth weight, childhood body mass index, and height in relation to mammographic density and breast cancer: a register-based cohort study. Breast Cancer Res. 2014; 16:R4. [PubMed: 24443815]
60. Bertrand KA, Tamimi RM, Scott CG, et al. Mammographic density and risk of breast cancer by age and tumor characteristics. Breast Cancer Res. 2013; 15:R104. [PubMed: 24188089]
61. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. Hum Reprod. 2010; 25:1325–34. [PubMed: 20172865]
62. Shah DK, Correia KF, Vitonis AF, Missmer SA. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. Hum Reprod. 2013; 28:1783–92. [PubMed: 23674552]
63. Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 2003; 63:6096–101. [PubMed: 14522941]
64. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. Breast Cancer Res Treat. 2008; 109:113–22. [PubMed: 17592770]
65. Harris HR, Tamimi RM, Willett WC, Hankinson SE, Michels KB. Body size across the life course, mammographic density, and risk of breast cancer. Am J Epidemiol. 2011; 174:909–18. [PubMed: 21911827]
66. Dorgan JF, Klifa C, Shepherd JA, et al. Height, adiposity and body fat distribution and breast density in young women. Breast Cancer Res. 2012; 14:R107. [PubMed: 22800711]
67. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. Am J Epidemiol. 2010; 171:1183–94. [PubMed: 20460303]
68. Nyante SJ, Sherman ME, Pfeiffer RM, et al. Prognostic significance of mammographic density change after initiation of tamoxifen for ER-positive breast cancer. J Natl Cancer Inst. 2015:107.
69. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst. 2011; 103:744–52. [PubMed: 21483019]
70. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995; 87:670–5. [PubMed: 7752271]
71. Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. Hum Reprod. 2002; 17:1415–23. [PubMed: 12042253]
72. Kenneth, J.; Rothman, SG.; Timothy, L.; Lash. Modern Epidemiology. 3 ed.. Lippincott Williams & Wilkins; Philidelphia: 2008.
73. Jones KL, Buzdar AU. A review of adjuvant hormonal therapy in breast cancer. Endocr Relat Cancer. 2004; 11:391–406. [PubMed: 15369444]
74. Spicer DV, Ursin G, Parisky YR, et al. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. J Natl Cancer Inst. 1994; 86:431–6. [PubMed: 8120917]
75. Saltiel E, Garabedian-Ruffalo SM. Pharmacologic management of endometriosis. Clin Pharm. 1991; 10:518–31. [PubMed: 1830521]
76. Rosner B, Glynn RJ, Tamimi RM, et al. Breast cancer risk prediction with heterogeneous risk profiles according to breast cancer tumor markers. Am J Epidemiol. 2013; 178:296–308. [PubMed: 23645624]

77. Farland LV, Tamimi RM, Eliassen AH, Spiegelman D, Hankinson SE, Chen WY, Missmer SA. "The Relationship between Laparoscopically Confirmed Endometriosis and Breast Cancer in the Nurses' Health Study II.". Obstetrics and Gynecology.

Table 1

Characteristics of women in the Nurses' Health Study II at time of mammogram by endometriosis status (n=1,581)

	Premenopausal		Postmenopausal	
	Endometriosis			
	No (n=1,150)	**Yes (n=91)**	**No (n=263)**	**Yes (n=77)**
	Mean(SD)			
Age*	44.4(4.1)	44.4(3.1)	50.5(4.0)	48.2(4.8)
Body Mass Index (BMI) (kg/m2)	26.0(5.6)	25.3(4.5)	26.3(5.6)	25.2(5.5)
BMI at age 18	21.1(2.9)	20.9(2.4)	21.3(3.1)	20.4(2.5)
Alcohol (gms/day)	4.3(7.4)	5.0(8.5)	2.9(5.9)	2.7(4.0)
Percent Mammographic Density	40.5(17.9)	43.1(17.5)	32.2(17.5)	32.3(16.3)
	%			
Family history of breast cancer, %	9.3	5.3	10.4	14.5
Biopsy confirmed BBD, %	18.1	16.4	17.9	22.7
Parity				
- Nulliparous, %	16.4	31.8	22.7	19.8
- 1 pregnancy, %	12.9	16.6	14.7	36.5
- 2 pregnancies, %	39.6	31.2	35.5	34.3
- 3+ pregnancies, %	31.0	20.4	27.2	9.4
Age at menarche				
- <12 years, %	23.4	34.7	25.1	19.6
- 12-13 years, %	29.5	27.7	31.2	18.3
- >=14 years, %	47.1	37.5	43.8	62.1
Oral contraceptive use				
- Never, %	14.6	8.0	9.0	12.4
- Past, %	78.6	86.7	90.7	87.6
- Current, %	6.7	5.3	0.3	0.0
Smoking status				
- Never, %	69.8	59.6	69.9	60.1
- Past, %	23.9	36.2	17.4	26.5
- current, %	6.3	4.2	12.7	13.3
Oophorectomy				
- No procedure, %	96.3	83.1	46.8	4.0
- Unilateral, %	3.7	16.9	0.6	1.0
- Bilateral, %	0.0	0.0	52.6	95.0
Hysterectomy, %	4.5	17.6	51.9	95.4
Hormone Therapy use				
- Never, %	79.3	66.5	5.1	0.0
- Past, %	17.5	29.6	14.5	7.8

	Premenopausal		Postmenopausal	
	Endometriosis			
	No (n=1,150)	Yes (n=91)	No (n=263)	Yes (n=77)
- Current, %	3.2	3.9	80.3	92.2

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

*Value is not age adjusted

Table 2

The association between endometriosis and average mammographic density measurements (linear regression estimates) in the Nurses' Health Study II

		Model 1	Model 2	Model 3[a]
	Mean +/− SD	Difference (95% CI)		
Premenopausal Women (n=1,241) (No endometriosis n=1,150, Endometriosis n=91)				
Average Percent Mammographic Density				
No Endometriosis	40.54 +/− 17.87	0 (ref)	0 (ref)	0 (ref)
Endometriosis	43.07 +/− 17.54	1.77 (−1.71, 5.24)	2.03 (−1.28, 5.34)	2.00 (−1.33, 5.33)
Average Dense Area (cm^2)				
No Endometriosis	94.86 +/− 52.52	0 (ref)	0 (ref)	0 (ref)
Endometriosis	96.61 +/−49.58	1.17 (−9.49, 11.83)	1.32 (−8.82, 11.47)	0.10 (−9.74, 9.94)
Average Non-Dense Area (cm^2)				
No Endometriosis	147.52 +/−76.15	0 (ref)	0 (ref)	0 (ref)
Endometriosis	137.75 +/− 75.95	−5.70 (−19.00, 7.61)	−8.80 (−22.39, 4.80)	−8.45 (−22.34, 5.44)
Postmenopausal Women(n=340) (No endometriosis n=263, Endometriosis n=77)				
Average Percent Mammographic Density				
No Endometriosis	32.24 +/− 17.47	0 (ref)	0 (ref)	0 (ref)
Endometriosis	32.33 +/− 16.26	−1.38 (−5.02,2.26)	−2.04 (−5.74,1.67)	−0.89 (−5.10,3.33)
Average Dense Area (cm^2)				
No Endometriosis	75.12 +/− 48.91	0 (ref)	0 (ref)	0 (ref)
Endometriosis	73.86 +/−39.77	−4.02 (−14.84,6.80)	−3.60 (−14.27,7.07)	−2.71(−15.34,9.93)
Average Non-Dense Area (cm^2)				
No Endometriosis	167.97+/−84.81	0 (ref)	0 (ref)	0 (ref)
Endometriosis	167.34 +/− 79.31	4.28 (−12.93, 21.50)	4.41 (−13.88, 22.70)	3.38 (−15.82, 22.57)

Model 1 Adjusted for age and BMI at mammogram

Model 2 Additionally adjusted for alcohol consumption, family history of breast cancer, smoking history, history of benign breast disease, bmi at age 18, parity, age at menarche, oral contraceptive use history, and breastfeeding history

Model 3 a:Pre-menopausal additionally adjusted for hysterectomy, hormone theraphy

[a]Post-menopausal additionally adjusted for hysterectomy, oophorectomy, and hormone therapy

Table 3

The association between endometriosis and average percent mammographic density among pre-menopausal women at time of mammogram in the Nurses' Health Study II stratified by covariates of interest

	N (%)	Model 1	Model 2	Model 3	P-value, test for effect modification
		Difference (95% CI)			
BMI 18 < 20.6[a]	614	4.44 (0.12, 8.76)	3.68 (−0.35, 7.71)	3.74 (−0.29, 7.78)	0.03
BMI 18 ≥ 20.6	616	−0.87 (−5.50, 3.77)	−0.07 (−4.85,4.71)	−0.21 (−5.09, 4.67)	
BMI < 25	670	2.04 (−1.82, 5.91)	1.69 (−2.07, 5.46)	1.79 (−1.98, 5.57)	0.31
BMI ≥ 25	523	2.89 (−2.66, 8.44)	3.46 (−1.86, 8.77)	2.59 (−3.05, 8.23)	

Model 1 Adjusted for age and BMI at mammogram

Model 2 Additionally adjusted for alcohol consumption, family history of breast cancer, smoking history, history of benign breast disease, bmi at age 18, parity, age at menarche, oral contraceptive use history, breast feeding history,

Model 3 Additionally adjusted for hysterectomy, hormone therapy

[a]Median value