Published in final edited form as:
Breast Cancer Res Treat. 2011 November ; 130(2): 587–597. doi:10.1007/s10549-011-1616-x.

Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger

Mia M. Gaudet,
Epidemiology Research Program, American Cancer Society, Atlanta, GA 30303, USA

Michael F. Press,
Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Robert W. Haile,
Department of Preventative Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Charles F. Lynch,
Department of Epidemiology, University of Iowa, Iowa City, IA, USA

Sally L. Glaser,
Cancer Prevention Institute of California (Formerly the Northern California Cancer Center), Fremont, CA, USA; Department of Health Research and Policy, Stanford University, Stanford, CA, USA

Joellen Schildkraut,
Division of Prevention Research, Department of Community and Family Medicine, The Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC, USA

Marilie D. Gammon,
Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

W. Douglas Thompson, and
Department of Applied Medical Sciences, University of Southern Maine, Portland, ME, USA

Jonine L. Bernstein
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Mia M. Gaudet: mia.gaudet@cancer.org

Abstract

Differences in incidence, prognosis, and treatment response suggest gene expression patterns may discern breast cancer subtypes with unique risk factor profiles; however, previous results were based predominantly on older women. In this study, we examined similar relationships in women ≤56 years, classified by immunohistochemical staining for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 for 890 breast cancer cases and 3,432 frequency-matched population-based controls. Odds ratios (OR) and 95% confidence intervals (CI) for tumor subtypes were calculated using multivariate polytomous regression models. A total

Correspondence to: Mia M. Gaudet, mia.gaudet@cancer.org.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-011-1616-x) contains supplementary material, which is available to authorized users.

Conflict of interest None.

of 455 (51.1%) tumors were considered luminal A, 72 (8.1%) luminal B, 117 (13.1%) non-luminal HER-2/neu+,and 246 (27.6%) triple negative. Triple negative tumors were associated with breast feeding duration (per 6 months: OR = 0.76, 95% CI 0.64–0.90). Among pre-menopausal women, increasing body size was more strongly associated with luminal B (OR = 1.73, 95% CI 1.07–2.77) and triple negative tumors (OR = 1.67, 95% CI 1.22–2.28). A history of benign breast disease was associated only with increased risk of luminal A tumors (OR = 1.89, 95% CI 1.43–2.50). A family history of breast cancer was a risk factor for luminal A tumors (OR = 1.93, 95% CI 1.38–2.70) regardless of age, and triple negative tumors with higher risks for women <45 (OR = 5.02, 95% CI 2.82–8.92; P for age interaction = 0.005). We found that little-to-no breastfeeding and high BMI were associated with increased risk of triple negative breast cancer. That some risk factors differ by molecular subtypes suggests etiologic heterogeneity in breast carcinogenesis among young women.

Keywords

Breast cancer; Estrogen receptor; Progesterone receptor; HER2; Risk factors

Introduction

Human breast tumors present with diverse clinical and histopathological features. Gene expression microarray profiles of breast cancer have demonstrated that tumors can be classified into molecular subtypes with distinct tumor characteristics, treatment responses, and prognosis [1-3]. Proxies of these molecular subtypes can be determined by immunohistochemical stains of estrogen receptor-α (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2/neu proteins. Together, the three markers are used to define four tumor subtypes: luminal A (ER+ or PR+ and HER-2/neu−), luminal B (ER+ or PR+, HER-2/neu+), non-luminal HER-2/neu+ (ER−, PR−, HER-2/neu+), and triple negative (ER−, PR−, and HER-2/ neu−). Data from clinical studies and tumor registries have demonstrated that 5-year recurrence-free and overall survival were lower for non-luminal HER-2/neu+ tumors and triple negative tumors, although most data were collected before the widespread use of the monoclonal antibody, trastuzumab, which interferes with the HER2/neu receptor and improves the survival of non-luminal HER-2/neu +. No such targeted therapies currently exist for triple negative tumors [4]. These tumors are also of concern because they have been associated with younger age, African ancestry, and *BRCA1* mutations [3, 5]; and worse prognosis [3]. Although triple negative tumors are heterogeneous with approximately 70% exhibiting basal-like characteristics, they are commonly referred to as a single group in the clinic and in previous studies. Previous studies conducted predominantly among postmenopausal women show that these subtypes may also vary with respect to risk factor profiles, such as reproductive history, use of exogenous hormones, and body size [6-10]. Given the bimodal age distribution of breast cancer overall and for ER/PR/HER-2/neu− defined subtypes [11], it is possible that breast cancer risk factors may vary by molecular characteristics and age/menopausal status [12]. To examine these relationships in younger women, we examined breast cancer risk factors by molecular tumor subtypes in 890 population-based breast cancer cases diagnosed ≤56 years and 3,432 matched controls [13].

Materials and methods

Study population

The Cancer and Steroid Hormone (CASH) Study was a multicenter, population-based, case–control study of breast, endometrial, and ovarian cancer, which was conducted to examine the association between oral contraceptive use and cancer risk [13]. Details have been

previously described. In brief, between December 1980 and December 1982, newly diagnosed breast cancer cases aged 20–56 years were ascertained through the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries in eight geographic locations [13]. For the current analyses, cases and controls were included from four of the eight SEER sites specifically, Connecticut, Detroit, Iowa, and the San Francisco–Oakland area of northern California. For all the cases, to ensure rapid case ascertainment (approximately 8–10 weeks after date of diagnosis), registry personnel reviewed pathology logbooks and other medical records of hospital and clinics at least monthly. The patients' personal physicians were then contacted for permission to approach the breast cancer case. Patients were first contacted by mail and then a phone call to set up an in-home interview with trained personnel. Controls were identified through random digit dialing in the same geographic areas as the cases and were frequency matched in five-year age groups. All CASH Study participants completed a standardized, 50-min questionnaire that included information on family history of female cancer, anthropometry, and reproductive, medical, and contraceptive histories using memory aids. Women who were still having regular menstrual cycles were considered pre-menopausal; women were considered post-menopausal if their periods had ceased for 1 year or longer; all other women were considered perimenopausal.

Tumor tissue

Out of the 3,517 breast cancer cases, 953 had available formalin-fixed paraffin-embedded tumor blocks. Tumor sections were cut from the tissue blocks, and a slide stained with hematoxylin-eosin (H + E) from each subject was reviewed by a single pathologist (M.F.P.) to confirm both that tumor was present and that the original pathological diagnosis and grade information were correct. Pathology/ surgical reports were reviewed for additional information, including location and size of tumor, and extent of nodal involvement. A total of 63 cases were excluded because the embedded tumor tissue was insufficient for staining of ER, PR, and HER-2/neu.

Slides were also stained for ER, PR, and HER-2/neu immediately after sectioning. The pathologist (M.F.P.) also scored all slides for extent and intensity. ER and PR statuses were determined based on previously published immunohistochemical methods [14, 15]. The results were scored semi-quantitatively based on the visual inspection of the estimated percent of positively stained tumor cell nuclei (minimum of 100 tumor cells) and the intensity of nuclear staining (−: no staining, +1: weak intensity, +2: intermediate intensity, +3: strong intensity). Tumor samples with ≥ 1% of immunostained tumor cell nuclei were considered as positive (ER+ or PR+). HER-2/neu was stained using an immunohistochemical staining method, as described previously [16, 17]. Results were assessed in a blinded fashion. Each of the cases was scored as positive or negative for each antibody and the percentage of positive tumor cells were assessed and recorded. Tumors were considered HER-2/neu− if there was no immunostaining or weak membrane immunostaining ($n = 701$) and HER-2/ neu+ if there was moderate or strong membrane immunostaining ($n = 189$).

A total of 890 breast cancer cases with evidence of invasive tumor tissue had available data on the status of ER, PR, and HER-2/neu staining. Based on the status data of these stains, breast tumors were classified into luminal A tumors (ER+ or PR+ and HER-2/neu−), luminal B (ER+ or PR+, HER-2/neu+), non-luminal HER-2/neu+ (ER−, PR−, HER-2/neu+), and triple negative (ER−, PR−, and HER-2/neu−) tumors.

Statistical analyses

The analytic set for the current study is 890 breast cancer cases and 3,432 matched controls, who were ascertained from the same four registries. In case–control analyses, odds ratios (OR) and 95% confidence intervals (CI) to estimate risk for molecular subtypes of breast cancer were calculated using a multivariate polytomous regression model, including age at reference (defined as the age at diagnosis for cases and the age at identification for controls), study site, menopausal status (premenopausal, perimenopausal, or postmenopausal), age at menarche (per 2 years), parity (nulliparous, or parous), age at first birth (per 5 years), duration of breastfeeding (per 6 months), body mass index (BMI; per World Health Organization (WHO) categories: <18.5, 18.5–24.9, 25.0–29.9, and 30.0+ kg/m^2), use of oral contraceptives (ever/never), history of benign breast disease (yes/no), and family history of first-degree relatives with breast cancer (yes/no). To test for differences in risk factor associations between molecular subtypes of breast tumors, we evaluated case-only logistic regression models, adjusted for all variables under study, with molecular subtype as the outcome variable and the risk factors as the explanatory variables. *P* values for tumor heterogeneity (p_{TH}) were reported using luminal A tumors as the 'control" tumor subgroup. We also examined case–control ORs by age at diagnosis (<45 years versus ≥45 years); *P* values for age interaction were calculated separately for tumor subtypes. Age 45 years was selected to capture the young age group of the bimodal distribution of breast cancer incidence [12], while maintaining sufficient numbers of the major subtypes in our data. We examined the alternate cut-point of age 40 years to compare results with a recent publication [18].

All statistical analyses were performed in STATA (version 10.0).

Results

Among the 890 breast cancer cases with available data, most cases were white and between 41 and 56 years. Most tumors were ER+ (53.3%), PR+ (50.1%), and HER-2/ neu− (78.8%). Considered together, 455 (51.1%) tumors were considered luminal A, 72 (8.1%) luminal B, 117 (13.1%) non-luminal HER-2/neu+, and 246 (27.6%) triple negative.

There were no substantial differences among the 890 breast cancer cases with tumor tissue retrieved, who were included in the current analyses than the 2,627 cases without tissue with respect to age and known breast cancer risk factors (Table 1). However, cases with tumor tissue were slightly less likely to have breastfed ($P = 0.037$).

Distribution patterns of established risk factors by subtypes of breast cancer and controls are presented in Table 2. Multivariable case–control analyses stratified by molecular subtype of the breast tumor (results reported as OR and 95% CI), as well as case-only analyses using luminal A as the baseline "control" group (results reported as p_{th}), were calculated to investigate possible heterogeneity in the breast cancer risk associations with known or suspected breast cancer risk factors (Table 3). Age at reference was significantly associated with risk of luminal A and non-luminal HER-2/neu+ tumors; however, compared to age of diagnosis of women with luminal A tumors, women diagnosed with luminal B ($p_{TH} = 0.003$) and triple negative tumors ($p_{TH} = <0.0001$) were younger. Age at menarche was inversely associated with breast cancer risk of luminal B and had suggestive associations for luminal A and non-luminal HER-2/neu+ tumors, but was not associated with risk of triple negative tumors, although the OR for triple negative tumors did not differ from that of luminal A tumors ($p_{TH} = 0.12$). Nulliparous women had a higher risk of luminal A and had suggestive associations with luminal B and non-luminal HER-2/neu+ tumor subtypes, but was not associated with risk of the triple negative subtype. Among parous women, older age at first birth was also associated with a weak increase in risk of luminal A, luminal B, and non-

luminal HER-2/neu+ tumors, although relative risk estimates were not statistically significant for luminal B and non-luminal HER-2/neu+ tumors. The estimated relative risk of triple negative tumors was inversely associated with duration of breast feeding (per 6 months: OR = 0.76, 95% CI 0.64–0.90), and significantly differed from the risk associated with luminal A tumors ($p_{TH} = 0.04$).

Larger body size among premenopausal women was associated with higher risk of luminal B tumors (per WHO category: OR = 1.73, 95% CI 1.07–2.77) and risk of triple negative tumors (per WHO category: OR = 1.67, 95% CI 1.22–2.28), although in the case-only analysis, only the risk associated with triple negative tumors was significantly different from that of luminal A tumors ($p_{TH} = 0.026$). For ever use of oral contraceptives, there was a suggestion of an inverse association with risk only among those with luminal A tumors (OR = 0.81, 95% CI 0.64–1.03), although results were not statistically significant. A history of benign breast disease was associated only with increased risk of luminal A tumors (OR = 1.89, 95% CI 1.43–2.50). Women with a positive family history of breast cancer were at a higher risk of luminal A tumors (OR = 1.93, 95% CI 1.38–2.70) and triple negative tumors (OR = 2.54, 95% CI 1.70–3.82).

Age-stratified results (<45 years of age (Supplemental Table 1) and ≥45 years of age (Supplemental Table 2)) were similar for known or suspected breast cancer with factors, with the exception of family history of breast cancer (*P*-values for age interaction are not shown in the tables). Women <45 years with a family history of first-degree relatives with breast cancer, compared to those that did not, had a fivefold higher risk of triple negative breast cancer (OR = 5.02, 95% CI 2.82–8.92), while the association for women ≥45 years was closer to the null (OR = 1.47, 95% CI 0.81–2.65; P for age interaction = 0.005). Since previous analyses have also considered using an age at diagnosis cut-off point of 40 years [18], we also performed an alternative set of stratified analyses by age 40 (data not shown) and found similar results as those stratified by age 45 (data not shown), albeit with wider confidence intervals due to smaller numbers, in the under-40 age groups.

Discussion

In our population-based case–control study of women 56 years or younger, we observed a higher risk of triple negative tumors associated with shorter duration of breastfeeding, and higher body size among premenopausal women with relative risks that differed from the risk of luminal A tumors. Overweight or obese women were also at higher risk of luminal B breast tumors. History of benign breast disease and family history of breast cancer were risk factors for luminal A tumors in both women <45 and ≥45 years at diagnosis. Women with a family history of breast cancer were also at higher risk of triple negative tumors with a five-fold increase in risk observed among women <45 years of age at reference.

Previous studies have examined known risk factors in relation to molecular subtypes of breast cancer using case– control study designs or cross-sectional studies of cases. Of the five case–control studies, the Polish Breast Cancer Study (PBCS; [19]) included 804 cases (18% triple negative; aged 20–74) and 2,502 population-based controls from a minimally screened population of women residing in the two major cities of Poland. In the Women's Contraceptive and Reproductive Experiences (CARE) Study [20, 21], 1,197 population-based cases (28% triple negative; aged 35–64) and 2,015 controls were enrolled from Los Angeles County or Detroit. Both case–control and case-only analyses were conducted in the Carolina Breast Cancer Study (CBCS; [6]) based on a racially diverse population of 1,424 premenopausal and postmenopausal cases of invasive and in situ breast cancer (26% triple negative of which 60% were the basal-like subtype) and 2,022 controls. Using the Seattle-Puget Sound SEER registry in two separate studies conducted between 1983–1990 and

1990–1992, 897 cases (20.8% triple negative) were recruited and age-matched to 1,569 controls aged 20–45, collectively referred to as the Seattle studies [18]. Two pooled case–control studies (referred to herein as the Washington studies [9, 10]) conducted in western Washington state recruited 1,224 ductal cases (6% triple negative) and 1,447 controls aged 55–79. The LACE/Pathway Studies [7], is a pooled case only study of 2,544 invasive breast cancer cases (11.3% triple negative), which were enrolled 11 and 39 months post-diagnosis. The long lag time in the LACE study likely introduced a survival bias, especially for the women diagnosed with triple negative breast cancer who have a high risk of death and recurrence in triple negative breast cancer in the first 2–3 years after diagnosis [22]. The long lag time may explain the lower prevalence of triple negative disease in that study.

The CASH Study, on the other hand, recruited and interviewed cases within 6 months of diagnosis, thus minimizing survival bias. We had a higher proportion of triple negative cases than some other studies presumably due to rapid ascertainment and the younger age distribution of the study population; however, our proportions are consistent with the Seattle studies [18] and with the SEER registry [23]. The study also benefited from well-characterized exposure information in a large, population-based series of breast cancer cases. However, our study only included a small portion of all eligible cases and may have biased observed findings for unmeasured risk factors. We had limited power to evaluate age interactions, and the small proportion of African-American cases precluded evaluating differences by race. ER, PR, and HER-2/neu was stained and scored by a single pathologist (M.F.P.), thus eliminating inter-observer variability, which is particularly problematic for scoring of HER-2/neu stains. More sensitive assays to detect the amplification of the *HER2* gene are now advocated in the clinical and research literature, although concordance between these methods and immunohistochemistry are strong and the proportion (21%) of HER-2/neu− cases in our study is consistent with the literature [24]. Although the tumor blocks used in this study were older, the slides were stained soon after they were cut, thus limiting antigen degradation and false negative staining results [25–27]. We were, however, limited by the lack of staining for the basal markers (e.g., CK5/6, EGFR) [28], and so we were unable to distinguish between basal-like tumors and unclassified (normal-like tumors), which some previous studies have suggested may have different etiologies [6, 8].

Overall, oral contraceptive use at the time of diagnosis and in the 10 years after ceasing use has been associated with a slight increase in risk of breast cancer [29]. In the current analysis, oral contraceptive use was not related to risk of any of the molecular subtypes of breast cancer, which is consistent with most previous studies [6, 7, 20] nor was the effect stronger when stratified by age. These findings are in contrast to the WISH study, which found women ≤40 years of age who used oral contraceptives for ≥1 year were at a fourfold higher risk of triple negative breast cancer (OR = 4.2, 95% CI 1.9–9.3), while oral contraceptive use was not associated with risk in women >40 years of age [18].

This study adds further evidence [6, 9, 20] of a seemingly paradoxical relationship for the risk of triple negative disease associated with parity and breastfeeding. Increased duration of breastfeeding, but not parity and late age at first birth, was associated with lower risk of triple negative tumors in our study and others [6, 9, 18–20]. Our findings further corroborate the collaborative reanalysis of 47 epidemiologic studies in 30 countries [30], which showed that the biological effects of long duration of breastfeeding are independent of the hormonal effects of parity and age at first birth. Taken together, the epidemiologic evidence supports biological mechanisms underlying the association with breastfeeding and triple negative breast cancer that relate to the beneficial differentiation of the breast terminal ductal lobular units [31, 32] or involution and re-absorption of initiated cells during breastfeeding cessation [33], rather than enduring changes in ovarian hormone production [34]. Large studies, including pooled analyses of existing studies, are necessary to confirm these observations

and mechanistic studies are warranted to further understand whether the protective aspects of lactation can be mimicked through lifestyle or pharmaceutical interventions.

Overall, overweight and obese women have been found to have a lower risk of premenopausal breast cancer and higher risk of postmenopausal breast cancer [35, 36]. The prevailing explanation of these disparate associations with greater body mass index are as follows: in premenopausal women, obesity is associated with a greater number of anovulatory cycles thus lower levels of estradiol [37]; while in postmenopausal women, obesity is associated with aromatization of steroid precursors to estrogens thus higher levels of estradiol [38, 39]. Other complimentary mechanisms, such as perturbations in the insulin/insulinlike growth-axis and release of pro-inflammatory molecules (e.g., interleukins, adipokines) [40–42], may also be at play. When cases were stratified into molecular subtypes of breast cancer, however, the findings were less straightforward. Among premenopausal women in this study and others [18, 19], the established inverse association with higher BMI values was limited to lower risk of non-triple negative breast cancer; whereas, risk of triple negative tumors is higher among obese premenopausal women. In the CBCS, waist-to-hip ratio, a measure of the biologically active visceral fat, was associated with higher risk of basal-like and luminal A tumors in premenopausal women [6]. Data on BMI and risk of breast cancer subtypes in pre-menopausal women is sparse; additional data are needed. If adiposity is confirmed to be associated with increased risk of triple negative breast cancer in premenopausal women, then targeted interventions and screening may improve risk profiles for women at high risk of this tumor subtype. Among postmenopausal women, the current data [6, 10, 19] as well as our own do not support modification of the BMI-breast cancer association by molecular subtypes.

A history of benign breast disease, a putative precursor of breast cancer, is associated with a two-fold increase in breast cancer risk overall and a five-fold increase when atypical hyperplasia is present [43]. We found that a history of benign breast disease increased risk of luminal A breast cancer in both younger and older women. In the PBCS, the prevalence of a history of benign breast disease was highest among luminal A breast cancer cases (11%) compared to controls (6%) [19].

In our study, risks of luminal A and triple negative breast tumors were associated with a family history of breast cancer. Particularly elevated risks of triple negative tumors were observed among women <45 with a family history of breast cancer. These observations are consistent with one previous study of postmenopausal women [10] and previous studies of women with inherited *BRCA1* mutations, who are more likely to be diagnosed with basal-like tumors [44]. However, other population-based studies reported that the proportion of cases with a family history of breast cancer was similar for all (or nearly all) breast cancer subtypes [6–8, 18, 21]. Most studies that found similar proportions of family history of breast cancer across molecular subtypes [6, 7, 18, 21] did not evaluate relative risk estimates in multivariate models, so the effect of confounding by known or suspected breast cancer risk factors is unknown. While the prevalence of *BRCA1/2* mutations is low [45] and unlikely to contribute to variability of findings across studies, it is possible that mutation prevalence of studies vary due to differences in age ranges and geographical locations. Unfortunately, neither this study nor the others have directly measured *BRCA1/2* mutations in their study populations. Furthermore, the confirmed common genetic variants identified to-date explain only 1.9 and 9.6% of familial risk of ER- and ER+ breast cancer [46]. Thus, the conflicting results across studies for family history of breast cancer could be due to uncontrolled confounding of non-genetic risk factors or by unaccounted genetic heterogeneity.

This study demonstrates the importance of considering molecular subtypes of breast cancer to identify etiological heterogeneity in this cancer diagnosed in young women. With the exception of family history of breast cancer, our results are consistent with previous studies of younger and older women; however, additional data are necessary to reject the hypothesis that etiological differences may exist by age and molecular characteristics of the tumor, as suggested by the age incidence patterns [11, 12]. Clarifying the risk factors for triple negative breast tumors are of particular interest because they account for 15–20% of breast cancers overall, have no targeted therapies, and are associated with poor 5-year survival [4]. We found that some risk factors had stronger associations with certain tumor subtypes than those published for breast cancer risk overall. In particular, little-to-no breastfeeding and high BMI were associated with increased risk of triple negative breast cancer. These results provide additional evidence that breastfeeding and an ideal body weight may reduce a woman's risk of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Xiaolin Liang for her data management assistance, as well as Dr. Karen Petrosyan, Armine Arakelyan, Armen Gasparyan, and Ivonne Villalobos for technical assistance and data management for the ER, PR, and HER-2/neu assays. This study was supported by the U.S. National Cancer Institute grant (NCI 5R01CA064245).

References

1. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein Lonning P, Borresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98(19):10869–10874. [PubMed: 11553815]
2. Sorlie T, Wang Y, Xiao C, Johnsen H, Naume B, Samaha RR, Borresen-Dale AL. Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: gene expression analyses across three different platforms. BMC Genomics. 2006; 7:127.10.1186/1471-2164-7-127 [PubMed: 16729877]
3. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295(21):2492–2502.10.1001/jama.295.21.2492 [PubMed: 16757721]
4. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, Perou CM. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007; 13(8):2329–2334.10.1158/1078-0432.CCR-06-1109 [PubMed: 17438091]
5. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, Flagg EW, O'Regan RM, Gabram SG, Eley JW. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat. 2009; 113(2):357–370.10.1007/s10549-008-9926-3 [PubMed: 18324472]
6. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, Livasy C, Carey L, Earp HS, Perou CM. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008; 109(1):123–139.10.1007/s10549-007-9632-6 [PubMed: 17578664]
7. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, Lee MM, Ambrosone CB, Caan BJ. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res. 2009; 11(3):R31.10.1186/bcr2261 [PubMed: 19463150]
8. Yang XR, Pfeiffer RM, Garcia-Closas M, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Cartun RW, Mandich D, Sasano H, Evans DB, Sutter TR, Sherman ME. Hormonal markers in

breast cancer: coexpression, relationship with pathologic characteristics, and risk factor associations in a population-based study. Cancer Res. 2007; 67(21):10608–10617.10.1158/0008-54 [PubMed: 17968031]

9. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer. Cancer. 2008; 113(7):1521–1526.10.1002/cncr.23786 [PubMed: 18726992]
10. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2008; 17(8):2078–2086.10.1158/1055-9965.EPI-08-0206 [PubMed: 18664548]
11. Anderson WF, Matsuno RK, Sherman ME, Lissowska J, Gail MH, Brinton LA, Yang XR, Peplonska B, Chen BE, Rosenberg PS, Chatterjee N, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Devesa SS, Garcia-Closas M. Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. Cancer Causes Control. 2007; 18(4):439–447.10.1007/s10552-006-0092-9 [PubMed: 17216325]
12. Anderson WF, Pfeiffer RM, Dores GM, Sherman ME. Comparison of age distribution patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev. 2006; 15(10):1899–1905.10.1158/1055-9965.EPI-06-0191 [PubMed: 17035397]
13. Wingo PA, Ory HW, Layde PM, Lee NC. The evaluation of the data collection process for a multicenter, population-based, case-control design. Am J Epidemiol. 1988; 128(1):206–217. [PubMed: 3381827]
14. Press M, Spaulding B, Groshen S, Kaminsky D, Hagerty M, Sherman L, Christensen K, Edwards DP. Comparison of different antibodies for detection of progesterone receptor in breast cancer. Steroids. 2002; 67(9):799–813. [PubMed: 12123792]
15. Press MF, Greene GL. An immunocytochemical method for demonstrating estrogen receptor in human uterus using monoclonal antibodies to human estrophilin. Lab Invest. 1984; 50(4):480–486. [PubMed: 6368973]
16. Press MF, Hung G, Godolphin W, Slamon DJ. Sensitivity of HER-2/neu antibodies in archival tissue samples: potential source of error in immunohistochemical studies of oncogene expression. Cancer Res. 1994; 54(10):2771–2777. [PubMed: 7909495]
17. Press MF, Slamon DJ, Flom KJ, Park J, Zhou JY, Bernstein L. Evaluation of HER-2/neu gene amplification and overexpression: comparison of frequently used assay methods in a molecularly characterized cohort of breast cancer specimens. J Clin Oncol. 2002; 20(14):3095–3105. [PubMed: 12118023]
18. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, Malone KE. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1157–1166.10.1158/1055-9965.EPI-08-1005 [PubMed: 19336554]
19. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Cartun R, Mandich D, Rymkiewicz G, Ligaj M, Lukaszek S, Kordek R, Garcia-Closas M. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007; 16(3):439–443.10.1158/1055-9965.EPI-06-0806 [PubMed: 17372238]
20. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, Press MF, Bernstein L. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer Res. 2010; 70(2):575–587.10.1158/0008-5472.CAN-09-3460 [PubMed: 20068186]
21. Ma H, Luo J, Press MF, Wang Y, Bernstein L, Ursin G. Is there a difference in the association between percent mammographic density and subtypes of breast cancer? Luminal A and triple-negative breast cancer. Cancer Epidemiol Biomarkers Prev. 2009; 18(2):479–485.10.1158/1055-9965.EPI-08-0805 [PubMed: 19190139]
22. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007; 109(9):1721–1728.10.1002/cncr.22618 [PubMed: 17387718]

23. Brinton LA, Sherman ME, Carreon JD, Anderson WF. Recent trends in breast cancer among younger women in the United States. J Natl Cancer Inst. 2008; 100(22):1643–1648.10.1093/jnci/djn344 [PubMed: 19001605]
24. Penault-Llorca F, Bilous M, Dowsett M, Hanna W, Osamura RY, Ruschoff J, van de Vijver M. Emerging technologies for assessing HER2 amplification. Am J Clin Pathol. 2009; 132(4):539–548.10.1309/AJCPV2I0HGPMGBSQ [PubMed: 19762531]
25. DiVito KA, Charette LA, Rimm DL, Camp RL. Long-term preservation of antigenicity on tissue microarrays. Lab Invest. 2004; 84(8):1071–1078.10.1038/labinvest.3700131 [PubMed: 15195116]
26. Fergenbaum JH, Garcia-Closas M, Hewitt SM, Lissowska J, Sakoda LC, Sherman ME. Loss of antigenicity in stored sections of breast cancer tissue microarrays. Cancer Epidemiol Biomarkers Prev. 2004; 13(4):667–672. [PubMed: 15066936]
27. Sherman ME, Howatt W, Blows FM, Pharoah P, Hewitt SM, Garcia-Closas M. Molecular pathology in epidemiologic studies: a primer on key considerations. Cancer Epidemiol Biomarkers Prev. 2011; 19(4):966–972.10.1158/1055-9965.EPI-10-0056 [PubMed: 20332257]
28. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. Nature. 2000; 406(6797):747–752. [PubMed: 10963602]
29. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1996; 347(9017):1713–1727. [PubMed: 8656904]
30. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002; 360(9328):187–195. [PubMed: 12133652]
31. McTiernan A, Thomas DB. Evidence for a protective effect of lactation on risk of breast cancer in young women. Results from a case-control study. Am J Epidemiol. 1986; 124(3):353–358. [PubMed: 3740036]
32. Petrakis NL, Wrensch MR, Ernster VL, Miike R, Murai J, Simberg N, Siiteri PK. Influence of pregnancy and lactation on serum and breast fluid estrogen levels: implications for breast cancer risk. Int J Cancer. 1987; 40(5):587–591. [PubMed: 3679587]
33. Lund LR, Romer J, Thomasset N, Solberg H, Pyke C, Bissell MJ, Dano K, Werb Z. Two distinct phases of apoptosis in mammary gland involution: proteinase-independent and -dependent pathways. Development. 1996; 122(1):181–193. [PubMed: 8565829]
34. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev. 1993; 15(1):17–35. [PubMed: 8405201]
35. Hulka BS, Stark AT. Breast cancer: cause and prevention. Lancet. 1995; 346(8979):883–887. [PubMed: 7564675]
36. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem. 2008; 114(1):71–83.10.1080/13813450801954303 [PubMed: 18465361]
37. Potischman N, Swanson CA, Siiteri P, Hoover RN. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. J Natl Cancer Inst. 1996; 88(11):756–758. [PubMed: 8637031]
38. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sieri S, Pala V, Venturelli E, Secreto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Kuller LH, Cummings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003; 95(16):1218–1226. [PubMed: 12928347]

39. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, Tehard B, Berrino F, Tjonneland A, Bigaard J, Olsen A, Overvad K, Clavel-Chapelon F, Nagel G, Boeing H, Trichopoulos D, Economou G, Bellos G, Palli D, Tumino R, Panico S, Sacerdote C, Krogh V, Peeters PH, Bueno-de-Mesquita HB, Lund E, Ardanaz E, Amiano P, Pera G, Quiros JR, Martinez C, Tormo MJ, Wirfalt E, Berglund G, Hallmans G, Key TJ, Reeves G, Bingham S, Norat T, Biessy C, Kaaks R, Riboli E. Body size and breast cancer risk: findings from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2004; 111(5):762–771. [PubMed: 15252848]
40. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr. 2007; 86(3):s858–s866. [PubMed: 18265479]
41. Cleary MP, Grossmann ME. Minireview: obesity and breast cancer: the estrogen connection. Endocrinology. 2009; 150(6):2537–2542.10.1210/en.2009-0070 [PubMed: 19372199]
42. Stoll BA. Upper abdominal obesity, insulin resistance and breast cancer risk. Int J Obes Relat Metab Disord. 2002; 26(6):747–753. [PubMed: 12037643]
43. Cook MG, Rohan TE. Benign breast disease: the relationship between its histological features and risk factors for breast cancer. Pathology. 1991; 23(4):286–290. [PubMed: 1784520]
44. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, Akslen LA. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst. 2003; 95(19):1482–1485. [PubMed: 14519755]
45. Offit K. BRCA mutation frequency and penetrance: new data, old debate. J Natl Cancer Inst. 2006; 98(23):1675–1677.10.1093/jnci/djj500 [PubMed: 17148764]
46. Mavaddat N, Pharoah PD, Blows F, Driver KE, Provenzano E, Thompson D, Macinnis RJ, Shah M, Search SO, Easton DF, Antoniou AC. Familial relative risks for breast cancer by pathological subtype: a population-based cohort study. Breast Cancer Res. 2010; 12(1):10.10.1186/bcr2476

Table 1

Distribution patterns of characteristics among cases with and without tissue and data for ER/PR/HER-2 status, CASH study

Factor	Cases excluded from analysis (*n* = 2,627)		Cases in analysis (*n* = 890)		*p*-Value
	N	%	*N*	%	
Age[a]					
<35	266	10.1	85	9.6	
35–39	342	13.0	110	12.4	
40–44	467	17.8	159	17.9	
45–49	676	25.7	204	22.9	
50–54	763	29.0	294	33.0	
55+	113	4.3	38	4.3	N/C
Missing	0		0		
Race[a]					
White	2,233	85.0	810	91.0	
Black	296	11.3	48	5.4	
Other	98	3.7	32	3.6	N/C
Missing	0		0		
Age at menarche					
<12	651	33.6	214	35.7	
12	664	36.9	241	34.6	
13	729	29.1	234	29.4	
14+	575	0.4	199	0.3	0.67
Missing	8		2		
Parity					
0	447	17.2	129	14.5	
1	334	12.8	95	10.7	
2	685	26.3	268	30.2	
3	563	21.6	191	21.5	
4+	577	22.1	204	23.0	0.059
Missing	21		3		
Age at first birth (among parous)					

Factor	Cases excluded from analysis (n = 2,627)		Cases in analysis (n = 890)		p-Value
	N	%	*N*	%	
<20	439	20.7	148	19.8	
20–22	626	29.6	219	29.2	
23–24	377	17.8	147	19.6	
25+	675	31.9	235	31.4	0.72
Missing	510		141		
Months of breastfeeding (among parous)					
0	1,158	54.1	410	54.4	
1–5	526	24.6	211	28.0	
6+	457	21.3	132	17.5	0.037
Missing	486		137		
Infertility problems					
No	2,018	81.3	690	81.2	
Yes	465	18.7	160	18.8	0.95
Missing	144		40		
Duration (months) of OC use[b]					
0	1,167	44.6	409	46.2	
1–5	131	5.0	36	4.1	
6–11	562	21.5	176	19.9	
12–60	544	20.8	193	21.8	
>60	212	8.1	72	8.1	0.61
Missing	11		4		
Menopausal status (abbreviated)					
Premenopausal	1,184	46.5	392	45.9	
Perimenopausal	494	19.4	153	17.9	
Postmenopausal	867	34.1	309	36.2	0.44
Missing	82		36		
Benign breast disease					
No	2,137	90.2	736	92.9	
Yes	442	9.8	143	7.1	0.55
Missing	48		11		

Factor	Cases excluded from analysis (*n* = 2,627)		Cases in analysis (*n* = 890)		*p*-Value
	N	%	*N*	%	
Family history of breast cancer					
No	2,168	87.6	720	87.7	
Yes	307	12.4	101	12.3	0.94
Missing	152		69		
BMI (kg/m^2) at reference (WHO categories)					
≤18.5	114	4.4	33	3.7	
18.6–25.0	1,863	71.3	615	69.4	
25.1–30.0	460	17.6	174	19.6	
>30.0	175	6.7	64	7.2	0.43
Missing	15		4		
Breast cancer tumor stage					
0			22	2.5	
I			396	44.5	
II			430	48.3	
III			0	0.0	
IV			31	3.5	
Missing			11	1.2	
Breast cancer tumor histology					
Ductal carcinoma in situ			32	3.6	
Invasive ductal carcinoma			642	72.1	
Lobular carcinoma in situ			51	5.7	
Invasive lobular carcinoma			1	0.1	
Medullary carcinoma			59	6.6	
Other			100	11.2	
Missing			5	0.6	

[a] Matching factors thus *p*-values were not calculated (N/C)

[b] Included women who are currently pregnant, recently pregnant, or currently breast feeding

Table 2

Distribution patterns of established breast cancer risk factors among young 890 breast cancer cases and 3,432 population-based controls

Factors	Control (n = 3,432)[a]	Luminal A (n = 455)[a]	Luminal B (n = 72)[a]	HER-2/neu (n = 117)[a]	Triple negative (n = 246)[a]
Age, mean (SD)	45.3 (0.14)	47.1 (0.30)	43.8 (1.0)	46.5 (0.7)	44.3 (0.5)
Race, no. (%)					
Caucasian	2,964	422 (52.1)	65 (8.0)	104 (12.8)	219 (27.0)
African-American	361	19 (39.6)	4 (8.3)	7 (14.6)	18 (37.5)
Other	107	14 (43.8)	3 (9.4)	6 (18.8)	9 (28.1)
Age at menarche, mean (SD)	12.7 (0.02)	12.6 (0.1)	12.1 (0.2)	12.5 (0.2)	12.5 (0.1)
No. of full-term births, no. (%)					
0	440	74 (57.4)	13 (10.1)	13 (10.1)	29 (22.5)
1	362	53 (55.8)	9 (9.5)	10 (10.5)	23 (24.2)
2	846	124 (46.3)	28 (10.5)	30 (11.2)	86 (32.1)
3	758	88 (46.1)	11 (5.8)	31 (16.2)	61 (31.9)
4–14	1,002	113 (55.4)	11 (5.4)	33 (16.2)	47 (23.0)
Age at first birth, mean (SD)	22.5 (0.1)	23.4 (0.2)	23.3 (0.4)	23.2 (0.4)	22.6 (0.3)
Months of breastfeeding (among parous), mean (SD)	5.0 (0.2)	3.8 (0.5)	2.0 (0.6)	3.4 (0.6)	2.4 (0.4)
Oral contraceptive use, no. (%)					
Never	1,362	215 (58.1)	25 (6.8)	46 (12.4)	84 (22.7)
Use for <3 months	209	31 (59.6)	3 (5.8)	5 (9.6)	13 (25.0)
Use for 3 or more months	1,851	207 (44.6)	44 (9.5)	64 (13.8)	149 (32.1)
Months of oral contraceptive use, mean (SD)	32.9 (0.9)	30.2 (2.4)	39.0 (6.1)	32.0 (4.6)	39.1 (3.3)
Menopausal status, no. (%)					
Premenopausal	1,282	198 (50.5)	38 (9.7)	47 (12.0)	109 (27.8)
Perimenopausal	659	93 (60.8)	13 (8.5)	12 (7.8)	35 (22.9)
Postmenopausal	1373	151 (48.9)	18 (5.8)	53 (17.2)	87 (28.2)
Age at menopause, mean (SD)	43.1 (0.2)	45.4 (0.5)	45.1 (1.3)	44.7 (0.8)	43.3 (0.7)
BMI among premenopausal women, no. (%)					
Underweight (<18.5 kg/m^2)	78 (6.1)	11 (5.6)	0 (0.0)	3 (6.4)	2 (1.8)
Normal (18.5 to <25.0 kg/m^2)	959 (75.5)	146 (73.7)	25 (65.8)	38 (80.9)	75 (68.8)
Overweight (25.0 to <30.0 kg/m^2)	161 (12.7)	28 (14.1)	9 (23.7)	4 (8.5)	20 (18.4)

Factors	Control (n = 3,432)[a]	Luminal A (n = 455)[a]	Luminal B (n = 72)[a]	HER-2/neu (n = 117)[a]	Triple negative (n = 246)[a]
Obese (30.0+ kg/m^2)	73 (5.7)	13 (6.6)	4 (10.5)	2 (4.3)	12 (11.0)
BMI among perimenopausal women, no. (%)					
Underweight (<18.5 kg/m^2)	20 (3.0)	4 (4.4)	1 (7.7)	1 (8.3)	0 (0.0)
Normal (18.5 to <25.0 kg/m^2)	443 (67.3)	63 (69.2)	7 (53.9)	8 (66.7)	23 (65.7)
Overweight (25.0 to <30.0 kg/m^2)	130 (19.8)	21 (23.1)	4 (30.8)	2 (16.7)	8 (22.9)
Obese (30.0? kg/m^2)	65 (9.9)	3 (3.3)	1 (7.7)	1 (8.3)	4 (11.4)
BMI among postmenopausal women, no. (%)					
Underweight (<18.5 kg/m^2)	57 (4.2)	6 (4.0)	1 (5.6)	2 (3.8)	2 (2.3)
Normal (18.5 to<25.0 kg/m^2)	924 (67.3)	98 (64.9)	10 (55.6)	37 (69.8)	60 (69.8)
Overweight (25.0 to<30.0 kg/m^2)	274 (20.0)	36 (23.8)	7 (38.9)	11 (20.8)	17 (19.8)
Obese (30.0+ kg/m^2)	118 (8.6)	11 (7.3)	0 (0.0)	7 (8.1)	7 (8.1)
Previous benign breast disease, no. (%)					
No	3,030	359 (48.8)	62 (8.4)	104 (14.1)	211 (28.7)
Yes	401	92 (64.3)	9 (6.3)	12 (8.4)	30 (21.0)
Breast cancer in first-degree relatives					
No	3,013	360 (50.0)	62 (8.6)	104 (14.4)	194 (26.9)
Yes	218	54 (53.5)	5 (5.0)	7 (6.9)	35 (34.7)

[a]Individual cell numbers may not sum to the total due to missing values

Table 3

Adjusted odds ratios (*OR*) and 95% confidence intervals (*CI*) for the association between known and suspected risk factors and risk of molecular subtypes of breast cancer

Factor	Luminal A (*n* = 455) controls vs.		Luminal B (*n* = 72) vs. controls			HER-2/neu+ (*n* = 117) vs. controls			Triple negative (*n* =246) vs. controls		
	OR	(95% CI)	OR	(95% CI)	p_{TH}[a]	OR	(95% CI)	p_{TH}[a]	OR	(95% CI)	p_{TH}[a]
Age at diagnosis	1.08	(1.06, 1.11)	1.01	(0.97, 1.06)	0.0030	1.04	(1.00, 1.08)	0.07	0.99	(0.97, 1.02)	<0.0001
Age at menarche per 2 years	0.87	(0.75, 1.01)	0.60	(0.42, 0.85)	0.13	0.82	(0.63, 1.07)	0.79	0.98	(0.81, 1.18)	0.12
Nulliparous	3.02	(1.47, 6.23)	4.11	(0.80, 21.07)	0.82	2.21	(0.60, 8.16)	0.68	1.08	(0.41, 2.81)	0.066
Age at first birth per 5 years (among parous)	1.16	(1.01, 1.33)	1.31	(0.95, 1.80)	0.64	1.19	(0.93, 1.53)	0.91	1.08	(0.90, 1.31)	0.48
Months of breastfeeding per 6 months (among parous)	0.94	(0.86, 1.02)	0.70	(0.48, 1.01)	0.15	0.85	(0.70, 1.04)	0.35	0.76	(0.64, 0.90)	0.039
BMI per WHO category[b] (by menopausal status)											
Premenopausal	1.11	(0.84, 1.48)	1.73	(1.07, 2.77)	0.088	0.67	(0.32, 1.41)	0.22	1.67	(1.22, 2.28)	0.026
Perimenopausal	0.81	(0.56, 1.17)	1.27	(0.63, 2.56)	0.19	0.55	(0.23, 1.33)	0.46	0.92	(0.56, 1.50)	0.41
Postmenopausal	1.16	(0.87, 1.54)	0.83	(0.36, 1.93)	0.58	0.93	(0.57, 1.52)	0.53	1.02	(0.70, 1.48)	0.72
Ever use of oral contraceptives	0.81	(0.64, 1.03)	1.09	(0.62, 1.94)	0.64	1.10	(0.71, 1.71)	0.46	1.21	(0.87, 1.67)	0.26
Benign breast disease	1.89	(1.43, 2.50)	1.25	(0.58, 2.67)	0.41	0.86	(0.45, 1.62)	0.028	1.01	(0.65, 1.58)	0.018
Positive family history of breast cancer	1.93	(1.38, 2.70)	1.17	(0.46, 2.97)	0.28	0.95	(0.43, 2.09)	0.095	2.54	(1.70, 3.82)	0.32

Adjusted for all variables in table as well as study site and menopausal status

[a] *pTH* p-values were calculated based on comparisons of each tumor subtypes compared to the luminal A group using a polytomous regression model adjusted for all variables in the table as well as study site and menopausal status

[b] World Health Organization (*WHO*) categories of BMI were treated as an ordinal variable and included underweight (BMI< 18.5 kg/m^2), normal weight (18.5 to <25.0 kg/m^2), overweight (25.0−<30.0 kg/m^2), and obese (30.0+ kg/m^2)