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Epidemiological Risk Factors Associated with Inflammatory Breast Cancer Subtypes

Rachel L. Atkinson[1,2], **Randa El-Zein**[2,3], **Vicente Valero**[2,4], **Anthony Lucci**[2,5], **Therese B. Bevers**[1], **Tamer Fouad**[2,4], **Weiqin Liao**[1], **Naoto T. Ueno**[2,4], **Wendy A. Woodward**[2,5], and **Abenaa M. Brewster**[1]

[1]Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, Texas

[2]MD Anderson Morgan Welch Inflammatory Breast Cancer Research Program and Clinic

[3]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas

[4]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

[5]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

[6]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Background—In this single-institution case-control study, we identified risk factors associated with inflammatory breast cancer (IBC) subtypes based on staining of (estrogen receptor [ER], progesterone receptor [PR]) and expression of human epidermal growth factor 2 (HER2neu) to determine distinct etiologic pathways.

Methods—We identified 224 women with IBC and 396 cancer-free women seen at the MD Anderson Cancer Center. Multinomial logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between breast cancer risk factors and the IBC tumor subtypes: luminal (ER+ and/or PR+/Her2neu−), Her2neu+ (any ER and PR, Her2neu+), and triple-negative (ER−/PR−/Her2neu−).

Results—In multivariable analysis, compared with women age ≥26 at first pregnancy, women age <26 had a higher risk of triple-negative IBC (OR 3.32, 95% CI 1.37–8.05). Women with a history of breastfeeding had a lower risk of triple-negative (OR 0.30; 95% CI: 0.15–0.62) and luminal IBC (OR 0.35, 95% CI 0.18–0.68). A history of smoking was associated with an increased risk of luminal IBC (OR 2.37; 95% CI 1.24–4.52). Compared with normal-weight women, those

Corresponding author: Abenaa Brewster MD, MHS, Clinical Cancer Prevention, 1155 Pressler St., Unit 1360, P.O. Box 301439, Houston, TX 77230, (713) 745-4929.

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who were overweight or obese (body mass index ≥25 kg/m^2) had a higher risk of all three tumor subtypes (P<0.01 for all subtypes).

Conclusion—Overweight or obese status are important modifiable risk factors for IBC of any subtype. Modifiable risk factors, age at first pregnancy (≥26), breastfeeding and smoking may be associated with specific IBC subtypes. These results highlight the importance of evaluating epidemiologic risk factors for IBC for the identification of subtype-specific prevention strategies.

Introduction

Inflammatory breast cancer (IBC) is rare, accounting for roughly 2.5% of all invasive breast cancers; however, this percentage may be higher because of variability in the definitions of IBC (1). According to data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence rate of IBC increased from 2.0 (per 100,000 woman-years) between 1988 and1990 to 2.5 between 1997 and 1999 (1, 2). IBC is the most lethal form of breast cancer, and the median survival time from 1988 through 2000 was 2.9 years (1). Improvements in survival have been noted recently with the introduction of trastuzumab-based systemic therapy and the use of multidisciplinary treatment (3, 4). However, despite these advances in adjuvant treatment, many women every year die from IBC, highlighting the importance of identifying risk factors associated with IBC that may be targeted for disease prevention.

Breast cancer is a heterogeneous disease, defined by gene expression profiling into four distinct molecular subtypes that can be approximated by estrogen receptor (ER), progesterone receptor (PR) and Her2neu (5,6): luminal/ ER+, basal-like/ER−/PR−/Her2neu −, Her2-enriched/Her2neu+ and unclassified. Van Laere et al. showed using three distinct gene expression datasets obtained through the World IBC Consortium, that the molecular subtypes described in non-IBC are detectable in IBC, albeit with a different frequency (7). To date, risk factors for IBC that have been identified from a small number of case-control and case-case studies include long duration of breastfeeding, young age at first birth, and high body mass index (BMI) ≥25 kg/m^2 (8–10). Whether risk factors for IBC differ according to molecular or clinically defined tumor subtypes has not been well studied. Schairer et al. used the Breast Cancer Surveillance Consortium database to evaluate the risk factors for ER+ compared to ER− IBC and found that older age at first birth was associated with a reduced risk of ER− IBC (10). Higher BMI was associated with an increased risk of both ER+ and ER− IBC and the association between BMI and IBC risk did not vary by menopausal status (10). Some of the limitations of the study were the lack of information on additional risk factors such as breast feeding and the triple negative and Her2neu+ subtypes were not accounted for in the analysis.

Prior epidemiologic studies have demonstrated varying risk factor associations for the ER+ and triple-negative subtypes of non-IBC that may have significant implications for prevention (11–15). For example, absent or short duration of breastfeeding has been consistently associated with a higher risk of triple-negative non-IBC compared with the luminal A or ER+ defined subtypes of non-IBC (12,13, 16). Since the triple-negative subtype is overrepresented among IBC compared to non-IBC (7), identifying the risk factors

for this aggressive tumor subtype and others is relevant for investigating biological mechanisms underlying the etiology of IBC and for developing strategies for subtype-specific breast cancer prevention (1,17).

We conducted a large hospital-based case-control study of women seen at the University of Texas MD Anderson Cancer Center to comprehensively examine risk factors associated with IBC and according to the following tumor subtypes: luminal (ER+ and/or PR+, Her2neu−), Her2neu+ (any ER/PR, Her2neu+), and triple-negative (ER−, PR−, Her2neu−). We hypothesized that, like non-IBC, distinct epidemiological risk factors would be associated with each of the clinical subtypes, supporting the concept that IBC subtypes have heterogeneous etiology.

Materials and Methods

Patient population

Cases and controls were patients seen at the MD Anderson Cancer Center. This analysis included 224 patients with confirmed IBC according to the World IBC consortium consensus case definition (18) or the American Joint Committee on Cancer (AJCC) criteria (19). The minimal criteria for the diagnosis of IBC that was recommended at the World IBC consortium consensus meeting held December, 2008 included the rapid onset of breast erythema (occupying at least one-third of the breast), edema and/or peau d'orange and/or warm breast, with or without an underlying palpable mass with duration of symptoms of no more than 6 months. Prior to December, 2008, IBC cases were defined using the AJCC criteria as `a clinicopathological entity characterized by diffuse erythema and edema of the breast, often without an underlying palpable mass'. Since 2004, all newly diagnosed women with IBC receiving treatment at the MD Anderson Morgan Welch IBC clinic are invited to participate in a multi-centered IBC registry. Patients are asked to complete an in-person interviewer administered questionnaire containing detailed information on lifestyle and breast cancer risk factors at the time of recruitment. The median time from diagnosis to completion of the interviewer administered questionnaire for the IBC cases was 19 days. For this study, we included a subset of 224 IBC cases from the registry who were age ≥18 years at diagnosis, resided in the US (62% were Texan residents), diagnosed between 2004 to 2012 and had no prior history of cancer except for non-melanoma skin cancer or cervical cancer in situ.

Controls were 396 healthy women undergoing routine screening mammography at the MD Anderson Cancer, Center Cancer Prevention Center who were recruited between June 2005 and January 2006 for a non-IBC case-control study that was conducted to identify genetic changes in candidate genes associated with the development of invasive breast cancer. The controls were consecutively screened for eligibility at the time of their clinic appointment in the Cancer Prevention Center and approached for participation. The inclusion criteria for the controls enrolled on the parent study were Caucasian, age ≥18 years, resident in the state of Texas and no prior history of cancer except for non-melanoma skin cancer or cervical cancer in situ. All controls completed an in-person interviewer-administered questionnaire containing information on lifestyle and breast cancer risk factors. For this study, we included all 396 controls who were recruited for the parent non-IBC case-control study. Missing or

incomplete information in the questionnaires administered to the IBC cases and controls could be obtained from the medical record.

The variables selected for inclusion in the study were similarly worded between the different questionnaires that were administered to the IBC cases and controls. Body weight and height at the time of the interview were collected from the medical record, and body mass index (BMI) was calculated as body weight (kg) / height $(m)^2$. Categories for BMI were based on National Heart, Lung, and Blood Institute cut-points (<25 kg/m^2 normal or underweight, ≥25 kg/m^2 overweight and obese). Women who had smoked at least 100 cigarettes in their lifetime, who had children, or who had breastfed children were classified as "ever" in terms of smoking history, parity, and breastfeeding history, respectively. The breastfeeding and age at first pregnancy comparisons were restricted to parous women. Participants provided written informed consent to participate using documents approved by the MD Anderson Cancer Center institutional review board.

Statistical analysis

Pearson Chi-square tests were used to test for distribution differences between risk factors for IBC cases and controls. Multinomial logistic regression was used to estimate odds ratios (ORs) as a measure of the association between potential risk factors and tumor subtypes, with 95% confidence intervals (CIs). Tumor subtypes were classified as luminal (ER+ and/or PR+, HER2neu−), HER2neu+ (any ER or PR, Her2neu+) or triple negative (ER−, PR −, HER2neu−) and the control subjects were used as the comparison group. Variables with a *P* value threshold of 0.25 in the univariate analysis were included in the multivariable model, and a stepwise selection procedure was used to determine the most parsimonious multivariable model with a *P* value threshold of 0.05. The risk factors collected in the questionnaires and included in the multivariable model were age, age at menarche, menopausal status, number of children, number of abortions or miscarriages, age at first pregnancy, breast feeding history, BMI, smoking history, breast cancer family history. *P* values to test for heterogeneity of the ORs between risk factors and IBC subtypes were obtained using logistic regression for the comparison of triple-negative and HER2neu+ IBC subtypes to the luminal IBC subtype. To evaluate for interaction between BMI, menopausal status and risk of IBC subtype, likelihood ratio tests were used to calculate *P* values comparing models with main effects to models with main effects plus relevant interaction terms. All P values were reported at two-sided test with an alpha level of 0.05. Statistical analyses were performed with Stata 12.0 (StataCorp LP, College Station, TX).

Results

Distribution of descriptive statistics

The distribution of characteristics of reproduction history and lifestyle risk factors for IBC cases and controls are presented in Table 1. Among the 224 IBC cases, 64 (29%) had triple-negative disease, 85 (38%) had HER2neu+ disease, and 75 (33%) had luminal disease. The mean ages were similar between the IBC cases and controls. Reproductive factors found to be associated with IBC included parity (*P*<.01), increasing number of children (*P*<.01), age <26 at first pregnancy (*P*<.01) and lack of breastfeeding (*P*<.01). Lifestyle factors

associated with IBC included overweight or obese status (P<.01) and a history of smoking (P=.02). IBC cases were less likely to have had a family history of breast cancer compared with controls (P<.01) although it should be noted that 9.8% of cases were missing family history information compared to 0% of controls.

Univariable analysis by IBC tumor subtypes

The age-adjusted associations between reproductive and lifestyle risk factors and the three IBC subtypes (triple-negative, Her2neu+, luminal) compared with controls are presented in Table 2. Parity was positively associated with an increased risk of Her2neu+ IBC (OR=3.17; 95% CI 1.48 –6.80). Women who were age <26 at first pregnancy compared to age ≥26, were at increased risk of all IBC subtypes, with the strongest association observed for triple-negative (OR 3.90; 95% CI 1.93–7.99). A history of breastfeeding was associated with a lower risk of both triple-negative IBC (OR=0.35; 95% CI 0.19–0.64) and luminal IBC (OR=0.36; 95% CI 0.20–0.66). Having a BMI ≥25 kg/m^2 was positively associated with all subtypes of IBC, with the strongest association for Her2neu+ IBC (OR=4.95; 95% CI 2.72–8.98). Having a family history of breast cancer among first degree relatives was associated with a decreased risk of all three IBC subtypes (P<0.01) and a history of smoking was associated with an increased risk of Her2neu+ IBC (OR=1.84; 95% CI 1.14–2.96).

Multivariable analysis by IBC tumor subtypes

The multivariate associations between reproductive and lifestyle risk factors and the three IBC subtypes (triple-negative, Her2neu+, luminal) compared with controls are presented in Table 3. In addition, P values are shown for the comparisons between risk factors and triple negative and Her2neu+ IBC subtypes with luminal IBC as the referent group. Women age < 26 at first pregnancy were at higher risk of triple-negative (OR=3.32; 95% CI 1.37–8.05, $P_{heterogeneity}$=0.13) compared to women ≥age 26. A history of breastfeeding was associated with a lower risk of triple-negative IBC (OR=0.30; 95% CI 0.15–0.62, $P_{heterogeneity}$ =0.73) and luminal IBC (OR=0.35; 95% CI 0.18–0.68). A history of smoking was associated with an increased risk of luminal IBC (OR 2.37; 95% CI 1.24–4.52). Women with a BMI ≥25 kg/m^2 were at significantly increased risk of all IBC subtypes (P<.001 for all subtypes) compared with women with a normal BMI. There was no significant interaction between BMI and menopausal status and risk of IBC subtype (P for interaction =0.29).

Discussion

To our knowledge, this is the largest hospital-based case-control study of IBC from a single institution conducted to date. We identified distinct epidemiologic risk factors that were associated with specific subtypes of IBC, specifically age at first pregnancy, a history of smoking, and breastfeeding. Being overweight or obese was positively associated with risk of the three IBC tumor subtypes. Our results suggest that similar to non-IBC, established modifiable breast cancer risk factors may be differentially associated with IBC subtypes and could be essential for subtype specific risk assessment and disease prevention.

Risk factors for IBC have generally been found to be similar to those for triple-negative non-IBC tumors (8, 10). Specifically, younger age at diagnosis, younger age at the birth of the

first child, and high BMI have been linked with increased risk in both populations (8, 10, 12). Similarly, we found that women with triple-negative IBC were younger at first pregnancy than controls. In a previous study at MD Anderson, 68 patients with IBC were compared with 134 patients with cancer at other anatomic sites, and the BMI was found to be significantly higher in the patients with the IBC (8). Similar results were also reported in a larger study of the Breast Cancer Surveillance Consortium database, with higher BMI found to be associated with increased IBC risk regardless of menopausal status or ER expression (10). One possible hypothesis for the relationship between IBC and higher BMI, regardless of menopausal status is that obese women may have chronically inflamed breast tissue, and increased numbers of macrophages, that could increase susceptibility to the development of IBC (20,21). In support of this hypothesis, gene expression profiles from IBC tumors compared with those of non-IBC tumors have identified an expression signature characterized by activated inflammation and immune-related genes that is seen more often in IBC tumors than in non-IBC tumors (22).

A finding unique to our study was the association between ever breastfeeding and decreased risk of both the triple-negative and ER+ IBC subtypes. Le et al. investigated the relationship between breastfeeding and IBC among IBC cases and non-IBC breast cancer controls and reported that longer duration of breastfeeding was associated with an increased risk of IBC (9). However, that study had significant bias in that both the non-IBC cancer controls and the IBC cases were from different countries of origin and therefore the association may have reflected differences in the prevalence of breastfeeding between regions. Our finding that breastfeeding influences IBC risk regardless of ER expression may be related to inherent differences in the biology and natural history of IBC vs non-IBC tumors. Iwamoto et al. reported that the ER+ IBC subtype may not demonstrate the favorable prognosis typically associated with ER+ non-IBC (23,24).

Biological mechanisms through which absent or short duration of breastfeeding influences risk of IBC may be related to the effects of the microenvironment surrounding the tumor during development. Lack of breastfeeding may lead to the failure of progenitor cells in breast tissue to undergo terminal differentiation and apoptosis making the breast susceptible to carcinogenic insult (25) especially if it occurs earlier in life. Our results that lack of breast feeding and early age at first pregnancy increase the risk of triple-negative IBC are consistent with those of Milikan et al (12) and Trivers et al. (26) but no association between the reproductive risk factors and triple-negative breast cancer has been observed in other studies (27).

Our study had several limitations, some of which are inherent in a hospital-based case-control study design. For example, referral bias played a role in the high proportion of controls in our study who reported a family history of breast cancer, because healthy women seen at the Cancer Prevention Center for breast cancer screening are at higher risk of breast cancer compared to women in the general population (28). The cases and controls included in the study analysis may also not be reflective of the IBC and cancer-free patients seen at MD Anderson or the general population since they were not sampled at random. A proportion of IBC cases in our study were referred from outside the state of Texas and

ascertainment bias is unavoidable if the distribution of risk factors for IBC differs among women residing in different regions of the U.S.

There is sparse data on risk factors for IBC subtypes defined using ER, PR and Her2neu and a strength of our hospital based case-control study was the availability of these biomarkers for clinical care among a relatively large number of patients with IBC. We were unable to further classify the luminal tumors into surrogate categories for luminal A and luminal B due to incomplete data on proliferation markers (29). Given the small sample size, we classified Her2neu+ tumors regardless of ER and PR status. However, data shows that incomplete hormone resistance occurs with co-expression of Her2 and ER suggesting that there may be a shared etiological pathway (30). It is possible that the lack of heterogeneity of the associations between risk factors and IBC subtypes could have been due to the limited power of the study and should be further assessed in larger studies.

The finding that smoking was associated with the luminal IBC subtype is intriguing as the epidemiological evidence that smoking is associated with specific breast cancer subtypes is limited. The Women's Health Initiative Cohort study approximated tumor subtype by ER and PR and Her2neu status and found that duration and intensity of smoking were positively associated with an increased risk of ER+ but not an increased risk of triple-negative breast cancer (31). Whether smoking promotes the development of certain IBC subtypes due to its association with other breast cancer risk factors e.g. lower BMI, higher alcohol consumption and lower physical activity (32) is an important area of investigation. Although we were not able to include information on other important breast cancer risk factors due to incomplete and/or missing data, e.g., oral contraceptives and hormone replacement therapy, the epidemiologic factors that were investigated represent the most comprehensive set published to date in the IBC literature with subtype information. The majority of cases and controls were white women and therefore we were unable to explore ethnic differences in the prevalence of risk factors.

In conclusion, high BMI was found to be strongly and significantly associated with an increased risk of IBC of any subtype. Given the rate of obesity in the United States (33) and corresponding increases in incidence of IBC over time (1), research efforts should be focused on determining the biological mechanisms through which BMI may increase susceptibility to IBC. Other modifiable risk factors, e.g. age at first pregnancy, breast feeding and smoking history appear to have similar associations with IBC subtypes as reported in the literature for non-IBC subtypes. Therefore the opportunity may exist for the development of comprehensive subtype-type specific prevention strategies to reduce the risk of both inflammatory and non-IBCs.

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References

1. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst. 2005; 97:966–75. [PubMed: 15998949]
2. Low JA, Berman AW, Steinberg SM, Danforth DN, Lippman ME, Swain SM. Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. J Clin Oncol. 2004; 22:4067–74. [PubMed: 15483018]
3. Natori A, Hayashi N, Soejima K, Deshpande GA, Takahashi O, Cristofanilli M, et al. A comparison of epidemiology, biology, and prognosis of inflammatory breast cancer in Japanese and US populations. Clinical breast cancer. 2013; 13:460–4. [PubMed: 24084032]
4. Tsai CJ, Li J, Gonzalez-Angulo AM, Allen PK, Woodward WA, Ueno NT, et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed therapy. American journal of clinical oncology. 2013
5. Sorlie T, Perou R, Tibshirani R, ASA T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98:10869–10874. [PubMed: 11553815]
6. Perou CM, Sorlie R, Eisen MB, Van De Rijn M, Jeffrey SS, Ress CA, et al. Moleculare portraits of human breast tumors. 2000; 406:747–752.
7. Van Laere SJ, Ueno NT, Finetti P, Vermeulen P, Lucci A, Robertson FM, et al. Intergrated analysis of three distinct affymetrix gene expression datasets. Clinical Cancer Research. 2013; 19:4685–96. [PubMed: 23396049]
8. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. J Clin Oncol. 1998; 16:3731–5. [PubMed: 9850015]
9. Le MG, Arriagada R, Bahi J, Pfeiffer F, Cammoun M, Tabbane F, et al. Are risk factors for breast cancer similar in women with inflammatory breast cancer and in those with non-inflammatory breast cancer? Breast. 2006; 15:355–62. [PubMed: 16198566]
10. Schairer C, Li Y, Frawley P, Graubard BI, Wellman RD, Buist DS, et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. J Natl Cancer Inst. 2013; 105:1373–84. [PubMed: 24046390]
11. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res. 2009; 11:R31. [PubMed: 19463150]
12. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008; 109:123–39. [PubMed: 17578664]
13. Shinde SS, Forman MR, Kuerer HM, Yan K, Peintinger F, Hunt KK, et al. Higher parity and shorter breastfeeding duration: association with triple-negative phenotype of breast cancer. Cancer. 2010; 116:4933–43. [PubMed: 20665494]
14. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, et al. Association between common risk factors and molecular subtypes in breast cancer patients. Breast. 2013; 22:344–50. [PubMed: 22981738]
15. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007; 16:439–43. [PubMed: 17372238]
16. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, et al. Breastfeeding and breast cancer risk by receptor status-a systematic review and meta-analysis. 2015; 26:2398–407.
17. Kohler BA, Shermann RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual report to the nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst. 2015; 107(6) djv048.
18. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011; 22:515–23. [PubMed: 20603440]
19. Green, F.; Page, D.; Flemming, I., et al., editors. AJCC Cancer Staging Manual. 6th edition. Springer-Verlag; New York: 2002. p. 225-281.Breast

20. Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Zhou XK, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res (Phila). 2011; 4:1021–9. [PubMed: 21622727]
21. Sun X, Casbas-Hernandez P, Bigelow C, Makowski L, Joseph Jerry D, Smith Schneider S, et al. Normal breast tissue of obese women is enriched for macrophage markers and macrophage-associated gene expression. Breast Cancer Res Treat. 2012; 131:1003–12. [PubMed: 22002519]
22. Van Laere SJ, Ueno NT, Finetti P, Vermeulen P, Lucci A, Robertson FM, et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct affymetrix gene expression datasets. Clin Cancer Res. 2013; 19:4685–96. [PubMed: 23396049]
23. Iwamoto T, Bianchini G, Booser D, Qi Y, Coutant C, Shiang CY, et al. Gene pathways associated with prognosis and chemotherapy sensitivity in molecular subtypes of breast cancer. J Natl Cancer Inst. 2011; 103:264–72. [PubMed: 21191116]
24. Iwamoto T, Bianchini G, Qi Y, Cristofanilli M, Lucci A, Woodward WA, et al. Different gene expressions are associated with the different molecular subtypes of inflammatory breast cancer. Breast Cancer Res Treat. 2011; 125:785–95. [PubMed: 21153052]
25. Atkinson RL, Yang WT, Rosen DG, Landis MD, Wong H, Lewis MT, et al. Cancer stem cell markers are enriched in normal tissue adjacent to triple negative breast cancer and inversely correlated with DNA repair deficiency. Breast Cancer Res. 2013; 15:R77. [PubMed: 24008095]
26. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg WE, Coates, et al. The epidemiology of triple negative breast cancer, including race. Cancer Causes Control. 2009; 20:1071–1082. [PubMed: 19343511]
27. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat. 2014; 144:1–10. [PubMed: 24477977]
28. Bailes AA, Kuerer HM, Lari SA, Jones LA, Brewster AM. Impact of race and ethnicity on features and outcome of ductal carcinoma in situ of the breast. Cancer. 2013; 119:150–7. [PubMed: 22736444]
29. Ades F, Zardvas D, Bozovic-Spasojevic I, Pugliano L, Fumagalli D, de Azambuja E, Viale G, et al. Luminal B Breast Cancer: Molecular Characterization, Clinical Management and Future Perspectives. J Clin Oncol. 2014; 32:2794–2803. [PubMed: 25049332]
30. Dowsett M. Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer. Endocr Relat Cancer. 2001; 8:191–5. [PubMed: 11566610]
31. Kabat GC, Kim M, Phipps AI, Li Ci, Messina CR, Wactawski-Wende J, et al. Smoking and alcohol consumption in relation to risk of triple negative breast cancer in a cohort of postmenopausal women. Cancer Causes Control. 2011; 22:775–783. [PubMed: 21360045]
32. Travier N, Agudo AM, May C, Gonzalez J, Luan H, Besson, et al. Smoking and body fatness measurements: a cross-sectional analysis in the EPIC-PANACEA study. Prev Med. 2009; 49:365–373. [PubMed: 19716380]
33. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. Jama. 2012; 307:491–7. [PubMed: 22253363]

TABLE 1

Descriptive characteristics of IBC cases and controls

	IBC Cases (n=224)		Controls (n=396)		
	Range	Mean	Range	Mean	P value
Age, year	23–80	51.2	24–68	50.8	0.69

	Number	Percentage	Number	Percentage	P value[¥]
Age, year					
> 50	120	53.6	205	51.8	
≤50	104	46.4	191	48.2	0.67
Race					
White	173	77.2	396	100.0	
Hispanic	22	9.8	0	0.0	
Asian	6	2.7	0	0.0	
Black	23	10.3	0	0.0	<0.01
Age at Menarche					
≥13	113	50.4	229	57.8	
< 13	105	46.9	166	41.9	
Unknown	6	2.7	1	0.3	0.14
Parity					
Nulliparous	30	13.4	99	25.0	
Parous	192	85.7	297	75.0	
Unknown	2	0.9	0	0.0	<0.01
Number of Children					
Nulliparous	30	13.4	99	25.0	
1 child	37	16.5	55	13.9	
≥2 children	155	69.2	242	61.1	
Unknown	2	0.9	0	0.0	<0.01
Number of Abortions/Miscarriage					
0	154	68.8	270	68.2	
≥l	68	30.4	126	31.8	
Unknown	2	0.8	0	0.0	0.76

	IBC Cases (n=224)		Controls (n=396)		
	Number	Percentage	Number	Percentage	P value[¥]
Age at First Pregnancy[*]					
≥26	58	30.1	147	49.5	
< 26	133	67.9	150	50.5	
Unknown	2	2.0	0	0.0	<0.01
Breastfeeding History[*]					
Never	87	44.9	91	30.6	
Ever	97	50.0	205	69.0	

	IBC Cases (n=224)		Controls (n=396)		
	Number	**Percentage**	**Number**	**Percentage**	**P value¥**
Unknown	10	5.1	1	0.3	<0.01
BMI, (kg/m^2)					
< 25	46	20.5	201	50.8	
≥25	177	79.0	194	49.1	
Unknown	1	0.5	1	0.2	<0.01
Smoking History					
Never	129	57.6	267	67.4	
Ever	94	42.0	129	32.6	
Unknown	1	0.4	0	0.0	0.02
Menopausal Status					
Premenopausal	72	32.1	151	38.1	
Postmenopausal	149	66.5	245	61.9	
Unknown	3	1.4	0	0.0	0.11
Breast Cancer Family History					
No	187	83.5	295	74.5	
Yes	15	6.7	101	25.5	
Unknown	22	9.8	0	0.0	<0.01

*Percentages for the categories are among parous women.

¥P-values derived from chi square test

TABLE 2

Case-control univariate analysis of risk factors and inflammatory breast cancer subtypes

	Subtypes of Inflammatory Breast Cancer					
	Triple-negative (n=64)		Her2neu + (n=85)		Luminal (n=75)	
	No. cases	OR* (95% CI)	No. cases	OR* (95% CI)	No. cases	OR* (95% CI)
Age, year						
> 50	34	Referent	45	Referent	41	Referent
≤50	30	0.95 (0.56–1.61)	40	0.95 (0.60–1.53)	34	0.89 (0.54–1.46)
Age at Menarche						
≥13	29	Referent	49	Referent	35	Referent
< 13	32	1.52 (0.89–2.61)	36	1.01 (0.63–1.63)	37	1.46 (0.88–2.41)
Parity						
Nulliparous	9	Referent	8	Referent	15	Referent
Parous	55	2.03 (0.97–4.27)	76	3.17 (1.48–6.80)	67	1.55 (0.82–2.95)
Number of Children						
Nulliparous	9	Referent	8	Referent	13	Referent
1 child	11	2.20 (0.86–5.66)	13	2.92 (1.14–7.46)	13	1.82 (0.79–4.19)
≥2 children	44	1.99 (0.94–4.24)	63	3.23 (1.49–6.99)	48	1.49 (0.77–2.88)
Number of Abortions / Miscarriages						
0	45	Referent	53	Referent	56	Referent
≥1	19	0.91 (0.56–1.72)	31	1.26 (0.77–2.01)	18	0.69 (0.39–1.23)
Age at First Pregnancy						
≥26	11	Referent	26	Referent	21	Referent
< 26	44	3.90 (1.93–7.88)	49	1.88 (1.10–3.20)	40	1.88 (1.05–3.36)
Breastfeeding History						
Never	29	Referent	27	Referent	31	Referent
Ever	23	0.35 (0.19–0.64)	48	0.83 (0.45–1.34)	26	0.36 (0.20–0.66)
Body Mass Index (kg/m^2)						
< 25	14	Referent	15	Referent	17	Referent
≥25	50	3.77 (2.00–7.08)	70	4.95 (2.72–8.98)	57	3.51 (1.96–6.29)
Smoking History						
Never	43	Referent	45	Referent	41	Referent
Ever	20	0.96 (0.54–1.69)	40	1.84 (1.14–2.96)	34	1.71 (1.03–2.82)
Menopausal Status						
Premenopausal	20	Referent	30	Referent	22	Referent
Postmenopausal	42	1.44 (0.74–2.81)	54	1.09 (0.61–1.96)	53	1.58 (0.85–2.96)
Breast Cancer Family History						
No	54	Referent	70	Referent	63	Referent
Yes	4	0.22 (0.08–0.61)	8	0.33 (0.16–0.72)	3	0.14 (0.04–0.45)

Abbreviations: IBC (inflammatory breast cancer), BMI (body mass index), CI (confidence interval).

*Odds ratio and 95% CI were obtained from case-control comparison using multinomial logistic regression analysis adjusted for age.

TABLE 3

Case-control multivariable analysis of risk factors and inflammatory breast cancer subtypes

	Triple-negative (n=64)			Her2neu+ (n=85)			Luminal (n=75)	
	Odds Ratio*	95% CI	p†	Odds Ratio*	95% CI	p†	Odds Ratio*	95% CI
Age, year								
>50	1.00	Referent		1.00	Referent		1.00	Referent
≤50	1.96	0.90–4.29	0.79	1.29	0.66–2.52	0.52	1.72	0.82–3.65
Menopausal Status								
Premenopausal	1.00	Referent		1.00	Referent		1.00	Referent
Postmenopausal	1.66	0.69–4.02	0.74	1.04	0.53–2.04	0.46	1.37	0.60–3.10
Age at first Pregnancy								
≥26	1.00	Referent		1.00	Referent		1.00	Referent
<26	3.32	1.37–8.05	0.13	1.57	0.86–2.88	0.89	1.49	0.73–3.02
Breastfeeding History								
Never	1.00	Referent		1.00	Referent		1.00	Referent
Ever	0.30	0.15–0.62	0.73	1.01	0.55–1.87	0.008	0.35	0.18–0.68
Smoking History								
Never	1.00	Referent		1.00	Referent		1.00	Referent
Ever	1.14	0.57–2.29	0.08	1.79	1.01–3.16	0.46	2.37	1.24–4.52
Breast Cancer Family History								
No	1.00	Referent		1.00	Referent		1.00	Referent
Yes	0.21	0.06–0.74	0.85	0.38	0.16–0.91	0.30	0.18	0.05–0.62
BMI (kg/m^2)								
<25	1.00	Referent		1.00	Referent		1.00	Referent
≥25	5.13	2.04–12.10	0.52	4.33	2.18–8.62	0.68	3.54	1.65–7.64

*Odds ratio and 95% CI were obtained from case-control comparison using stepwise multinomial logistic regression analysis adjusted for age at menarche, menopausal status, number of children, age at first pregnancy, breast feeding history, BMI, smoking history, breast cancer family history.

†P values for comparisons of the subtypes Her2neu+ and triple-negative compared to luminal IBC using logistic regression adjusted forage at menarche, menopausal status, number of children, age at first pregnancy, breastfeeding history, BMI, smoking history, breast cancer family history.
Abbreviations: IBC (inflammatory breast cancer), BMI (body mass index), CI (confidence interval)