HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Cancer Causes Control. 2015 December ; 26(12): 1737–1750. doi:10.1007/s10552-015-0667-4.

Associations between sociodemographic and clinicopathological factors, and breast cancer subtypes in a population-based study

Adana A.M. Llanos[1], **Sheenu Chandwani**[1], **Elisa V. Bandera**[1], **Kim M. Hirshfield**[2], **Yong Lin**[3], **Christine B. Ambrosone**[4], and **Kitaw Demissie**[1]

[1]Department of Epidemiology, Rutgers School of Public Health and Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[2]Division of Medical Oncology, Rutgers Robert Wood Johnson Medical School and Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[3]Department of Biostatistics, Rutgers School of Public Health and Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[4]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY

Abstract

Purpose—This study examines the factors distinguishing breast cancer (BC) subtypes.

Methods—We examined subtypes in 629 women with invasive BC, diagnosed from 2006–2012 and enrolled in an epidemiological study in New Jersey. Using molecular characteristics from pathology reports, BCs were categorized as luminal A, luminal B, non-luminal HER2-expressing, or triple-negative breast cancer [TNBC] subtypes. Multinomial logistic models (luminal A as referent) were used to describe BC subtype associations.

Results—Women with luminal B tumors were more likely to be younger at diagnosis (Odds ratio [OR] 1.8, 95% confidence interval [CI] 1.0–3.4) and to have higher grade (OR 2.6, 95% CI 1.5–4.7), larger (OR 1.9, 95% CI 1.0–3.6), and Ki67 positive tumors (OR 2.1, 95% CI 1.1–4.0). Women with non-luminal HER2-expressing BCs were more likely to have higher grade tumors (OR 14.5, 95% CI 5.3–39.7). Women with TNBCs were more likely to be African American (OR 1.9, 95% CI 1.0–3.4) and to have higher grade (Or 9.7, 95% CI 5.1–18.4), larger (OR 2.2, 95% CI 1.0–4.8), and Ki67 positive (OR 2.9, 95% CI 1.6–5.2) tumors. Notably, compared to the luminal A subtype, luminal B, non-luminal HER2-expressing and triple-negative subtypes were more frequently self-detected; however, these associations were attenuated in multivariable models.

Address correspondence and requests for reprints to: Adana A.M. Llanos, PhD, MPH, Department of Epidemiology, Rutgers School of Public Health, 683 Hoes Lane West, Room 211, Piscataway, NJ 08854, Telephone: (732) 235-4017, Fax: (732) 235-5418, Adana.Llanos@Rutgers.edu.

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

Authors' contributions: All authors made substantive intellectual contributions to this study. AL, SC, EB, KH, YL, CA, and KD 1) made substantial contributions to conception and design, or acquisition of data, and/or analysis and interpretation of data; 2) were involved in drafting the manuscript and revising it critically for intellectual content; 3) gave final approval of the final version; and 4) agree to be accountable for all aspects of the work.

Conclusions—These findings suggest that some BC subtypes were associated with features denoting more aggressive phenotypes, namely higher grade, larger size, and Ki67 positivity, and possibly patient self-detection among some women. These findings highlight a need for enhanced screening, particularly among younger women, racial/ethnic minorities and lower socioeconomic subgroups.

Keywords

breast cancer; clinicopathological factors; aggressive features; subtypes; African American women

Introduction

Breast cancer (BC) exists as several heterogeneous subtypes, based on global gene expression patterns [1–5] and/or clinical approximation using molecular expression patterns (immunohistochemistry [IHC]) [6–8], with differing distributions, risk factors, tumor behaviors and clinical outcomes [9,5,10–14]. Based on gene expression profiles, at least four intrinsic subtypes of BC have been identified, including luminal A, luminal B, HER2-enriched and basal-like, as well as a normal breast-like type [1,2]. Although gene expression profiling is the gold standard for BC subtyping, data have indicated that IHC expression patterns of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are fairly concordant with gene expression profiles and have substantial clinical utility [9,3]. BCs that are clinically defined as $ER^+/PR^+/HER2^-$ approximate the luminal A subtype. The luminal B subtype include BCs that are categorized as having lower expression of ER and/or PR compared to the luminal A, increased growth factor receptor expression, increased Ki67 expression, and tend to be HER2 positive (with positive HER2 amplification and IHC expression levels in approximately 20% of tumors) [15–18]. HER2-positive cancers are similarly complex in that they may be of the luminal (i.e., ER^+/PR^+) or non-luminal (ER^-/PR^-) type; there is evidence to suggest these are clinically and biologically distinct [19]. While some studies have used the terms basal-like subtype (characterized as $ER^-/PR^-/HER2^-$, cytokeratin [CK] 5/6 positivity, and/or epidermal growth factor receptor [EGFR] positivity) and “triple-negative breast cancer” (TNBC) interchangeably, evidence has shown that although most TNBCs are basal-like, up to 20–30% of them are not; additionally, not all basal-like BCs are TNBCs [20–22]. For simplicity, herein, we define TNBCs as $ER^-/PR^-/HER2^-$, based only on IHC expression of these receptors.

Recent Surveillance, Epidemiology, and End Results (SEER) data has shown that, among incident BC cases in the U.S., the luminal A subtype is predominant (72%), followed by TNBC (12.2%), $ER^+/PR^+/HER2^+$ (10.3%), and $ER^-/PR^-/HER2^+$ (4.6%) [11]. The aforementioned study [11] and others [9,12,10,5] support marked differences in BC subtype distributions by age, race, socioeconomic status (SES), and BC stage and grade. These studies have demonstrated that BC subtypes exhibiting more aggressive phenotypes are more frequently diagnosed among African American than white women, and that this is particularly true among women diagnosed at younger ages (<50 years). For example, African American women have twice the odds of being diagnosed with TNBCs than whites and TNBCs have about 20 times the odds of being high grade (compared to luminal A BCs)

[9,5,11,12,10]. The HER2-expressing subtypes are also associated with presenting more aggressive phenotypes. Compared to the luminal A subtype, the HER2-expressing subtypes are associated with substantially increased odds of advanced stage and higher grade [11,9,23]. Relatedly, it is clear that compared to whites, African Americans and other racial/ethnic minorities have increased risk of BC mortality, which may be related to differences in subtype incidence as well as differences in tumor biology by subtype in these groups [2,24].

The purpose of this study was to examine the associations between sociodemographic characteristics, clinical and reproductive factors, and clinicopathological tumor features, and BC subtypes approximated using molecular patterns defined by ER, PR, and HER2. We focused on factors associated with the HER2-expressing subtypes, luminal B ($ER^+/PR^+/HER2^+$) and non-luminal HER2-expressing ($ER^-/PR^-/HER2^+$), and TNBC ($ER^-/PR^-/HER2^-$) in comparison to the luminal A subtype. These data would provide insight into etiological pathways as well as help explain some of the prognostic differences observed between BC subtypes, likely contributing to our understanding of the causes of disparities in BC outcomes.

Materials and Methods

Study sample

We conducted case-case analysis of 629 incident, early stage, invasive BC cases diagnosed in New Jersey, utilizing data collected through interview-administered questionnaires and abstraction of detailed medical and pathology records. BC cases were participants in the Breast Cancer Treatment Disparity Study (BCTDS) [25], which was an extension of the New Jersey site of the Women's Circle of Health Study (WCHS) [26]. BC cases enrolled in WCHS included incident BC cases diagnosed in NJ, and: 1) self-identified as African American or white; 2) 20–75 years of age; 3) able to read and understand English; 4) were newly diagnosed (within 9 months of study enrollment) with histologically confirmed stage, I, II, or T3N1M0 BC between 2006–2012; and 3) had no history of cancer except non-melanoma skin cancer. BC cases were identified through rapid case ascertainment, by New Jersey State Cancer Registry (NJSCR) staff, from all major hospitals in nine counties: Bergen, Burlington, Essex, Hudson, Mercer, Middlesex, Monmouth, Passaic, and Union. All eligible African American cases were identified by the NJSCR and frequency-matched with white cases by age (±5 years) and county of residence. BC cases who agreed to the release of their medical records were included in BCTDS (approximately 84% of WCHS cases); all clinicopathological data required for the analysis described herein were available for these cases.

Verbal consent was obtained by NJSCR staff from identified cases prior to research staff contact. Written informed consent was obtained from all participants before data collection and this study was approved by the Institutional Review Board of all participating institutions.

Data collection

The data collection methods utilized in this study have been detailed elsewhere [26,27,25]. Briefly, in-depth, in-person interviews were conducted at participants' homes or a mutually agreed upon location. The survey instrument queried on known and suspected BC risk factors, including: family history, medical and reproductive history, occupational history, and other lifestyle factors. Anthropometric measurements were also taken, using standardized protocols and instruments [27].

For collection of detailed BC diagnosis information, medical records and pathology reports were obtained for each participant upon consenting to having their medical records released [25]. Records were obtained from all providers (e.g., primary care physician, and surgical, medical, and radiation oncologists) and relevant institutions (e.g., hospitals where surgical procedures were performed) identified by the patient. Diagnostic information and pathology reports were obtained from one year prior to one year following the initial BC diagnosis. Trained abstractors reviewed each record, recorded data on a standardized medical records abstraction form, and entered data into an electronic database. For quality assurance, values were checked for errors during data entry, and if errors were detected the original abstractor was contacted with instructions to re-check the medical records/pathology report, allowing for confirmation of the recorded data.

Classification of breast cancer subtypes

Surrogate classifications, based on IHC expression of estrogen receptor (ER), progesterone receptor (PR), and overexpression of human epidermal growth factor receptor 2 (HER2; by IHC and/or FISH), recorded in pathology reports, were used to approximate BCs into four mutually exclusive subtypes. These subtypes were the following: luminal A (ER^+ and/or $PR^+/HER2^-$), luminal B (ER^+ and/or $PR^+/HER2^+$), non-luminal HER2-expressing ($ER^-/PR^-/HER2^+$), and TNBC ($ER^-/PR^-/HER2^-$).

Statistical analysis

Baseline participant characteristics overall and by BC subtype were described using frequencies and proportions. Chi-square tests were used to compare sociodemographic, clinical, reproductive, and tumor characteristics by BC subtype. Multinomial logistic regression models (with the luminal A subtype as the referent group) were used to estimate unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) of the associations between characteristics of interest and BC subtype. Variables that were statistically significant in univariate models were included in the multivariable models, to keep a parsimonious approach for adjustment. All reported *P*-values are two-sided and $P < 0.05$ was considered statistically significant. Analyses were performed using SAS (v9.3 SAS Institute, Cary, NC).

Results

In this study of 629 women with early stage, invasive BC (49% African American), luminal A cancers were the most frequently diagnosed (68.4%), followed by the TNBC (14.5%), luminal B (11.1%), and non-luminal HER2-expressing (6.0%) subtypes. Sociodemographic

characteristics of the study sample, overall and by BC subtype, are shown in Table 1. Higher proportions of luminal A BCs were diagnosed among women age ≥45 years (84.2%), while higher proportions of TNBCs were diagnosed among African American women (67.0%) and among women whose educational attainment was below a college degree (57.1%). Several striking differences in breast tumor clinicopathological features by subtype were observed (Table 2). A higher proportion of TNBCs were initially identified through patient self-detection (60.4%), whereas a higher proportion of luminal A tumors were not patient self-detected (63.5%; P <0.0001). Luminal A cancers more frequently exhibited clinicopathological features consistent with a less aggressive phenotype (namely, lower grade [74.9%], earlier stage [59.8%], smaller size [40.5%], and both p53 [96.5%] and Ki67 [82.3%] negativity) than non-luminal HER2-expressing and TNBC subtypes.

In univariate multinomial logistic regression models where the luminal A subtype was the referent group (Table 3), women with the luminal B subtype were more likely to be younger at diagnosis (<45 years; OR 2.1, 95% CI 1.2–3.8), African American (OR 1.9, 95% CI 1.1–3.1), and premenopausal (OR 1.9, 95% CI 1.1–3.1) and less likely to have non-private health insurance (OR 0.4, 95% CI 0.2–0.08) and ≥1 comorbid condition (OR 0.6, 95% CI 0.3–1.0) relative to women with luminal A tumors. Women with luminal B BC were also more likely to have tumors that were self-detected (OR 1.8, 95% CI 1.1–3.1), poorly differentiated (OR 3.3, 95% CI 1.9–5.6), higher stage (OR 1.9, 95% CI 1.1–3.2), larger (OR 2.0, 95% CI 1.1–3.5), Ki67 positive (OR 2.6, 95% CI 1.5–4.5), and had lymphovascular invasion (OR 1.9, 1.1–3.4) compared to luminal A tumors. No sociodemographic, clinical or reproductive factors were associated with the non-luminal HER2-expressing BC subtype. Women with the non-luminal HER2-expressing subtype were also more likely to have tumors that were self-detected (OR 2.4, 95% CI 1.2–4.7), poorly differentiated (OR 16.7, 95% CI 6.7–41.5), higher stage (OR 2.6, 95% CI 1.3–5.2), larger (OR 2.5, 95% CI 1.1–5.7), p53 positive (OR 3.3, 95% CI 1.0–10.4), and Ki67 positive (OR 2.7, 95% CI 1.33–5.5) compared to the luminal A subtype. Compared to the luminal A subtype, women with TNBCs were more likely to be younger at diagnosis (OR 1.7, 95% CI 1.0–2.9), African American (OR 2.7, 95% CI 1.7–4.3), and of lower SES (less than college educated: OR 1.6, 95% CI 1.0–2.7 and income below the state median of $70,000: OR 1.8, 95% CI 1.1–3.2). Additionally, women with TNBCs were more likely to have tumors that were self-detected (OR 2.7, 95% CI 1.7–4.2), poorly differentiated (OR 13.8, 95% CI 7.9–24.4), higher stage (OR 1.8, 95% CI 1.2–2.9), larger (OR 3.4, 95% CI 1.9–6.2), p53 positive (OR 5.0, 95% CI 2.3–10.8), and Ki67 positive (OR 2.7, 95% CI 1.3–5.5); and were less likely to have a history of benign breast disease (OR 0.6, 95% CI 0.4–1.0).

In multivariable multinomial logistic regression models (adjusted for all covariates in the model) where the luminal A subtype was the referent group (Table 4), women with luminal B cancers were less likely to have less than a college education (OR 0.5, 95% CI 0.3–1.0) and were more likely to be younger at diagnosis (OR 1.8, 95% CI 1.0–3.4), to have tumors that were poorly differentiated (OR 2.6, 95% CI 1.4–4.7), larger (OR 1.9, 95% CI 1.0–3.6), and Ki67 positive (OR 2.3, 95% CI 1.2–4.4). Compared to women with luminal A cancers, those with the non-luminal HER2-expressing subtype were more likely to have poorly differentiated tumors (OR 14.5, 95% CI 5.3–39.7), while those with TNBCs were more

likely to be African American (OR 1.9, 95% CI 1.0–3.4), and to have tumors that were poorly differentiated (OR 9.7, 95% CI 5.1–18.4), larger (OR 2.2, 95% CI 1.0–4.8), and Ki67 positive (OR 2.9, 95% CI 1.6–5.2).

Discussion

Findings from this study support associations between sociodemographic characteristics and clinicopathological breast tumor features indicative of more aggressive phenotypes among luminal B, non-luminal HER2-expressing, and TNBC subtypes as compared to luminal A tumors, which may increase the odds of patient self-detection. In particular, we observed that women with luminal B tumors were more likely to be younger age at diagnosis and to have tumors with higher grade, were larger, and Ki67 positive. Women with the non-luminal HER2-expressing subtype were more likely to have higher grade tumors. Women with TNBCs were more likely to be African American and to have tumors that were higher grade, larger, and Ki67 positive. This study highlights some similarities between non-luminal HER2-expressing tumors and TNBCs, in terms of prevalence of more aggressive clinicopathological features and the possibility that these tumors are more frequently self-detected (i.e., before screening). Furthermore, these data suggest that, as observed among TNBCs, younger age, African American race, and lower SES may also be predictors of the non-luminal HER2-expressing subtype.

These findings suggest differences in tumor biology by BC subtype and lend support to studies demonstrating that BC outcomes may vary markedly by clinicopathological features [2,24], warranting further exploration of etiological differences, risk factors and prognostic indicators among subtypes so as to address some of the observed disparities in BC outcomes. While many epidemiologic studies have focused primarily on the TNBC subtype as a result of its more (and maybe even most) aggressive nature and limited treatment options, our study demonstrates that $HER2^+$ tumors overall (i.e., both luminal B and non-luminal HER2-expressing subtypes) may similarly be diagnosed more frequently among younger women belonging to racial/ethnic minority groups, and exhibit significantly more aggressive phenotypes than the luminal A subtype. Non-luminal HER2-expressing tumors particularly, while representing a very small proportion (approximately 6%) of breast tumors in this and other studies [12,11,9,14,10,5], were significantly associated with poor differentiation. This finding is consistent with previous studies [10,9,5,11]. The non-luminal HER2-expressing subtype was also associated with Ki67 positivity, a factor shown to be associated with higher grade [28]. Evidence also shows that Ki67 expression is highest among TNBCs, followed by non-luminal HER2-expressing and luminal B subtypes, as well as with poorer prognosis among early stage BC cases, specifically increased risk of relapse and mortality [29,30]. Although we observed no significant association between Ki67 positivity and the non-luminal HER2-expressing subtype in multivariable models, a statistically significant positive association was evident for the luminal B and TNBC subtypes in the present study. Studies [31–34] have suggested that Ki67 positivity may reliably predict prognosis in ER-positive tumors, whereas there are little data to support this association among HER2-positive and ER-negative tumors. Non-luminal HER2-expressing and TNBC subtypes were also associated with p53 positivity in this study. Although these associations were attenuated in the multivariable models, these data would be consistent

with recent studies showing that p53 IHC expression was associated with more aggressive tumor characteristics, namely higher grade, ER- and PR-negativity, and poorer prognosis among African American women and those of lower SES [35,36]. It may be that Ki67 and p53 both contribute to the negative prognostic effect among HER2-expressing and TNBC subtypes; additional studies examining the clinical utility of these markers as well as the most clinically relevant cut-off values for these markers are needed to clarify these relationships.

Notably, findings from this study suggested that patient self-detection was highest among women with TNBCs, non-luminal HER2-expressing tumors, and luminal B tumors. We hypothesize that there are differences in tumor biology when comparing BC subtypes, which potentially translate into differences in the likelihood of patient self-detection. Specifically, larger tumor size and more noticeable symptoms associated with the more aggressive subtypes may inherently lead to more frequently self-detected interval tumors (i.e., those arising within the 12 months following a normal screening mammogram) [37,38] among TNBCs and HER2-expressing subtypes, which further exacerbate BC outcomes disparities. Patient self-detection was no longer significantly associated with BC subtype in multivariate analysis (which included adjustment for SES factors, race and education), suggesting that the associations with mode of breast tumor detection may have been confounded by SES [39]. Recent data has shown that a large proportion (approximately 60%) of BC cases in the U.S. is discovered through self-detection, particularly among low-SES women [40,39]. In our study, 42.9% of BC patients reported self-detection and HER2-expressing and TNBC subtypes were 2–3 times more likely to be self-detected than the luminal A subtype. Previous evidence supports the association between mode of detection and prognosis, indicating that BC self-detection is associated with significant disadvantage in survival outcomes [41–48]. It is plausible that tumors exhibiting aggressive features would be more symptomatic than those with less aggressive features, and therefore would have a tendency to be perceived by the patient before she seeks care from a medical professional. Additional research, particularly examining these associations among diverse samples of women in the U.S., is needed to confirm these associations.

There were some limitations of this study that should be considered in the interpretation of our findings. First, our use of hormone receptor expression by IHC rather than gene expression data for classification of BC subtypes was an obvious limitation, although one could argue that gene expression has its limitations as well. Several studies have demonstrated overall imperfect but fairly good concordance between IHC and gene expression classification schemes for the major intrinsic subtypes, supporting clinical utility of these biomarkers [3,9]. Furthermore, the distributions of the BC subtypes reported herein were similar as those observed in other studies [3,4,11,8,1,2,5]. An additional consideration was that given the sample size, there were relatively small samples of luminal B, non-luminal HER2-expressing, and TNBC subtypes (n = 70, 38, and 91, respectively), potentially resulting in limited statistical power to examine subtype-stratified associations. Nonetheless, we observed several statistically significant findings, which would likely prove stronger in larger studies. Despite these considerations, the population-based study design and our use of detailed data, collected through medical record and pathology report abstraction, from all major medical facilities in the target area, as well as data collected

through interviewer-administered questionnaires, were important strengths. Additionally, our inclusion of SES, clinical, and clinicopathological tumor characteristics in the examination of predictors of BC subtypes also strengthened this study.

The findings of this study support associations between sociodemographic and clinicopathological features of tumors, and BC subtypes based on biomarker status, specifically showing that the more aggressive tumor phenotypes were more likely to occur among women who were younger at diagnosis, African American, and/or of lower SES. This study also suggests that these BC subtypes commonly exhibit Ki67 and p53 positivity, which may be important clinical markers for understanding differences in prognosis. Additionally, in light of the observation that larger tumors and those exhibiting more aggressive clinicopathological features are associated with BC self-detection, it may be necessary to enhance efforts to extend screening and minimize excess mortality, particularly among younger, racial/ethnic minority, and lower SES populations who would substantially benefit from earlier clinical diagnosis.

Acknowledgments

This work was supported by grants from the National Cancer Institute (R01CA133264, R01 CA100598, P01 CA151135, and Cancer Center Support Grants P30 CA072720 [Rutgers Cancer Institute of New Jersey] and P30 CA016056 [Roswell Park Cancer Institute]), the American Cancer Society (RSGT-07-291-01-CPHPS), the Susan G. Komen Breast Cancer Foundation (POP131006), the US Army Medical Research and Material Command (DAMD-17-01-1-0334), the Breast Cancer Research Foundation, a gift from the Philip L. Hubbell family, and a gift from the Buckingham Foundation. We sincerely thank our research personnel at the Rutgers Cancer Institute of New Jersey, Roswell Park Cancer Institute, Rutgers School of Public Health, and the New Jersey State Cancer Registry, as well as our African American breast cancer advocates and community partners, and all the women who generously donated their time and participation to the study.

List of abbreviations

BC	breast cancer
BCTDS	Breast Cancer Treatment Disparity Study
EGFR	epidermal growth factor receptor
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
NJ	New Jersey
NJSCR	New Jersey State Cancer Registry
PR	progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
SES	socioeconomic status
TNBC	triple-negative breast cancer
WCHS	Women’s Circle of Health Study

References

1. 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): 747–752.10.1038/35021093 [PubMed: 10963602]
2. 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, Lonning PE, Borresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98 (19):10869–10874.10.1073/pnas.191367098 [PubMed: 11553815]
3. Bastien RR, Rodriguez-Lescure A, Ebbert MT, Prat A, Munarriz B, Rowe L, Miller P, Ruiz-Borrego M, Anderson D, Lyons B, Alvarez I, Dowell T, Wall D, Segui MA, Barley L, Boucher KM, Alba E, Pappas L, Davis CA, Aranda I, Fauron C, Stijleman IJ, Palacios J, Anton A, Carrasco E, Caballero R, Ellis MJ, Nielsen TO, Perou CM, Astill M, Bernard PS, Martin M. PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers. BMC medical genomics. 2012; 5:44.10.1186/1755-8794-5-44 [PubMed: 23035882]
4. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. Nature. 2012; 490 (7418):61–70.10.1038/nature11412 [PubMed: 23000897]
5. Sweeney C, Bernard PS, Factor RE, Kwan ML, Habel LA, Quesenberry CP Jr, Shakespear K, Weltzien EK, Stijleman IJ, Davis CA, Ebbert MT, Castillo A, Kushi LH, Caan BJ. Intrinsic subtypes from PAM50 gene expression assay in a population-based breast cancer cohort: differences by age, race, and tumor characteristics. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014; 23 (5):714–724.10.1158/1055-9965.EPI-13-1023
6. Bhargava R, Striebel J, Beriwal S, Flickinger JC, Onisko A, Ahrendt G, Dabbs DJ. Prevalence, morphologic features and proliferation indices of breast carcinoma molecular classes using immunohistochemical surrogate markers. International journal of clinical and experimental pathology. 2009; 2 (5):444–455. [PubMed: 19294003]
7. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, Deitz AC, Connolly JL, Schnitt SJ, Colditz GA, Collins LC. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast cancer research : BCR. 2008; 10 (4):R67.10.1186/bcr2128 [PubMed: 18681955]
8. Morrison DH, Rahardja D, King E, Peng Y, Sarode VR. Tumour biomarker expression relative to age and molecular subtypes of invasive breast cancer. British journal of cancer. 2012; 107 (2):382–387.10.1038/bjc.2012.219 [PubMed: 22713661]
9. 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 : the journal of the American Medical Association. 2006; 295 (21):2492–2502.10.1001/jama.295.21.2492 [PubMed: 16757721]
10. Sineshaw HM, Gaudet M, Ward EM, Flanders WD, Desantis C, Lin CC, Jemal A. Association of race/ethnicity, socioeconomic status, and breast cancer subtypes in the National Cancer Data Base (2010–2011). Breast cancer research and treatment. 2014; 145 (3):753–763.10.1007/s10549-014-2976-9 [PubMed: 24794028]
11. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, Cronin KA. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. Journal of the National Cancer Institute. 2014; 106(5)10.1093/jnci/dju055
12. Clarke CA, Keegan TH, Yang J, Press DJ, Kurian AW, Patel AH, Lacey JV Jr. Age-specific incidence of breast cancer subtypes: understanding the black-white crossover. Journal of the National Cancer Institute. 2012; 104 (14):1094–1101.10.1093/jnci/djs264 [PubMed: 22773826]
13. Kroenke CH, Sweeney C, Kwan ML, Quesenberry CP, Weltzien EK, Habel LA, Castillo A, Bernard PS, Factor RE, Kushi LH, Caan BJ. Race and breast cancer survival by intrinsic subtype based on PAM50 gene expression. Breast cancer research and treatment. 2014; 144 (3):689–699.10.1007/s10549-014-2899-5 [PubMed: 24604094]

14. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, Gaudet M, Schmidt MK, Broeks A, Cox A, Fasching PA, Hein R, Spurdle AB, Blows F, Driver K, Flesch-Janys D, Heinz J, Sinn P, Vrieling A, Heikkinen T, Aittomaki K, Heikkila P, Blomqvist C, Lissowska J, Peplonska B, Chanock S, Figueroa J, Brinton L, Hall P, Czene K, Humphreys K, Darabi H, Liu J, Van't Veer LJ, van Leeuwen FE, Andrulis IL, Glendon G, Knight JA, Mulligan AM, O'Malley FP, Weerasooriya N, John EM, Beckmann MW, Hartmann A, Weihbrecht SB, Wachter DL, Jud SM, Loehberg CR, Baglietto L, English DR, Giles GG, McLean CA, Severi G, Lambrechts D, Vandorpe T, Weltens C, Paridaens R, Smeets A, Neven P, Wildiers H, Wang X, Olson JE, Cafourek V, Fredericksen Z, Kosel M, Vachon C, Cramp HE, Connley D, Cross SS, Balasubramanian SP, Reed MW, Dork T, Bremer M, Meyer A, Karstens JH, Ay A, Park-Simon TW, Hillemanns P, Arias Perez JI, Menendez Rodriguez P, Zamora P, Benitez J, Ko YD, Fischer HP, Hamann U, Pesch B, Bruning T, Justenhoven C, Brauch H, Eccles DM, Tapper WJ, Gerty SM, Sawyer EJ, Tomlinson IP, Jones A, Kerin M, Miller N, McInerney N, Anton-Culver H, Ziogas A, Shen CY, Hsiung CN, Wu PE, Yang SL, Yu JC, Chen ST, Hsu GC, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Lindblom A, Margolin S, Jakubowska A, Lubinski J, Huzarski T, Byrski T, Gorski B, Gronwald J, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Kriege M, Tilanus-Linthorst MM, Collee M, Wang-Gohrke S, Pylkas K, Jukkola-Vuorinen A, Mononen K, Grip M, Hirvikoski P, Winqvist R, Mannermaa A, Kosma VM, Kauppinen J, Kataja V, Auvinen P, Soini Y, Sironen R, Bojesen SE, Orsted DD, Kaur-Knudsen D, Flyger H, Nordestgaard BG, Holland H, Chenevix-Trench G, Manoukian S, Barile M, Radice P, Hankinson SE, Hunter DJ, Tamimi R, Sangrajrang S, Brennan P, McKay J, Odefrey F, Gaborieau V, Devilee P, Huijts PE, Tollenaar RA, Seynaeve C, Dite GS, Apicella C, Hopper JL, Hammet F, Tsimiklis H, Smith LD, Southey MC, Humphreys MK, Easton D, Pharoah P, Sherman ME, Garcia-Closas M. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. Journal of the National Cancer Institute. 2011; 103 (3):250–263.10.1093/jnci/djq526 [PubMed: 21191117]

15. Ades F, Zardavas D, Bozovic-Spasojevic I, Pugliano L, Fumagalli D, de Azambuja E, Viale G, Sotiriou C, Piccart M. Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014; 32 (25):2794–2803.10.1200/JCO.2013.54.1870 [PubMed: 25049332]

16. Prat A, Cheang MC, Martin M, Parker JS, Carrasco E, Caballero R, Tyldesley S, Gelmon K, Bernard PS, Nielsen TO, Perou CM. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013; 31 (2):203–209.10.1200/JCO.2012.43.4134 [PubMed: 23233704]

17. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS, Perou CM, Ellis MJ, Nielsen TO. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. Journal of the National Cancer Institute. 2009; 101 (10):736–750.10.1093/jnci/djp082 [PubMed: 19436038]

18. Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. Breast care. 2013; 8 (2):102–109.10.1159/000351193 [PubMed: 24000280]

19. Prat A, Carey LA, Adamo B, Vidal M, Tabernero J, Cortes J, Parker JS, Perou CM, Baselga J. Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. Journal of the National Cancer Institute. 2014; 106 (8)10.1093/jnci/dju152

20. Bertucci F, Finetti P, Cervera N, Esterni B, Hermitte F, Viens P, Birnbaum D. How basal are triple-negative breast cancers? International journal of cancer Journal international du cancer. 2008; 123 (1):236–240.10.1002/ijc.23518 [PubMed: 18398844]

21. Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, Nielsen TO. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clinical cancer research : an official journal of the American Association for Cancer Research. 2008; 14 (5):1368–1376.10.1158/1078-0432.CCR-07-1658 [PubMed: 18316557]

22. Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, Davies S, Fauron C, He X, Hu Z, Quackenbush JF, Stijleman IJ, Palazzo J, Marron JS, Nobel AB, Mardis E, Nielsen TO, Ellis MJ, Perou CM, Bernard PS. Supervised risk predictor of breast cancer based on intrinsic subtypes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27 (8):1160–1167.10.1200/JCO.2008.18.1370 [PubMed: 19204204]

23. Haque R, Ahmed SA, Inzhakova G, Shi J, Avila C, Polikoff J, Bernstein L, Enger SM, Press MF. Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012; 21 (10): 1848–1855.10.1158/1055-9965.EPI-12-0474
24. Iwamoto T, Bianchini G, Booser D, Qi Y, Coutant C, Shiang CY, Santarpia L, Matsuoka J, Hortobagyi GN, Symmans WF, Holmes FA, O'Shaughnessy J, Hellerstedt B, Pippen J, Andre F, Simon R, Pusztai L. Gene pathways associated with prognosis and chemotherapy sensitivity in molecular subtypes of breast cancer. Journal of the National Cancer Institute. 2011; 103 (3):264–272.10.1093/jnci/djq524 [PubMed: 21191116]
25. George P, Chandwani S, Gabel M, Ambrosone CB, Rhoads G, Bandera EV, Demissie K. Diagnosis and Surgical Delays in African American and White Women with Early-Stage Breast Cancer. J Womens Health (Larchmt). 201510.1089/jwh.2014.4773
26. Ambrosone CB, Ciupak GL, Bandera EV, Jandorf L, Bovbjerg DH, Zirpoli G, Pawlish K, Godbold J, Furberg H, Fatone A, Valdimarsdottir H, Yao S, Li Y, Hwang H, Davis W, Roberts M, Sucheston L, Demissie K, Amend KL, Tartter P, Reilly J, Pace BW, Rohan T, Sparano J, Raptis G, Castaldi M, Estabrook A, Feldman S, Weltz C, Kemeny M. Conducting Molecular Epidemiological Research in the Age of HIPAA: A Multi-Institutional Case-Control Study of Breast Cancer in African-American and European-American Women. Journal of oncology. 2009; 2009:871250.10.1155/2009/871250 [PubMed: 19865486]
27. Bandera EV, Chandran U, Zirpoli G, Gong Z, McCann SE, Hong CC, Ciupak G, Pawlish K, Ambrosone CB. Body fatness and breast cancer risk in women of African ancestry. BMC cancer. 2013; 13:475.10.1186/1471-2407-13-475 [PubMed: 24118876]
28. Sarode VR, Han JS, Morris DH, Peng Y, Rao R. A Comparative Analysis of Biomarker Expression and Molecular Subtypes of Pure Ductal Carcinoma In Situ and Invasive Breast Carcinoma by Image Analysis: Relationship of the Subtypes with Histologic Grade, Ki67, p53 Overexpression, and DNA Ploidy. International journal of breast cancer. 2011; 2011:217060.10.4061/2011/217060 [PubMed: 22295212]
29. de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, Durbecq V, Sotiriou C, Larsimont D, Piccart-Gebhart MJ, Paesmans M. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. British journal of cancer. 2007; 96 (10):1504–1513.10.1038/sj.bjc.6603756 [PubMed: 17453008]
30. Stuart-Harris R, Caldas C, Pinder SE, Pharoah P. Proliferation markers and survival in early breast cancer: a systematic review and meta-analysis of 85 studies in 32,825 patients. Breast. 2008; 17 (4):323–334.10.1016/j.breast.2008.02.002 [PubMed: 18455396]
31. Zhang GC, Qian XK, Guo ZB, Ren CY, Yao M, Li XR, Wang K, Zu J, Liao N. Pre-treatment hormonal receptor status and Ki67 index predict pathologic complete response to neoadjuvant trastuzumab/taxanes but not disease-free survival in HER2-positive breast cancer patients. Med Oncol. 2012; 29 (5):3222–3231.10.1007/s12032-012-0242-8 [PubMed: 22547076]
32. Kashiwagi S, Yashiro M, Takashima T, Aomatsu N, Ikeda K, Ogawa Y, Ishikawa T, Hirakawa K. Advantages of adjuvant chemotherapy for patients with triple-negative breast cancer at Stage II: usefulness of prognostic markers E-cadherin and Ki67. Breast cancer research : BCR. 2011; 13 (6):R122.10.1186/bcr3068 [PubMed: 22126395]
33. Niikura N, Masuda S, Kumaki N, Xiaoyan T, Terada M, Terao M, Iwamoto T, Oshitanai R, Morioka T, Tuda B, Okamura T, Saito Y, Suzuki Y, Tokuda Y. Prognostic significance of the Ki67 scoring categories in breast cancer subgroups. Clinical breast cancer. 2014; 14 (5):323–329. e323.10.1016/j.clbc.2013.12.013 [PubMed: 24492237]
34. Sueta A, Yamamoto Y, Hayashi M, Yamamoto S, Inao T, Ibusuki M, Murakami K, Iwase H. Clinical significance of pretherapeutic Ki67 as a predictive parameter for response to neoadjuvant chemotherapy in breast cancer: is it equally useful across tumor subtypes? Surgery. 2014; 155 (5): 927–935.10.1016/j.surg.2014.01.009 [PubMed: 24582496]
35. Dookeran KA, Dignam JJ, Holloway N, Ferrer K, Sekosan M, McCaskill-Stevens W, Gehlert S. Race and the prognostic influence of p53 in women with breast cancer. Annals of surgical oncology. 2012; 19 (7):2334–2344.10.1245/s10434-011-1934-6 [PubMed: 22434242]

36. Dookeran KA, Dignam JJ, Ferrer K, Sekosan M, McCaskill-Stevens W, Gehlert S. p53 as a marker of prognosis in African-American women with breast cancer. Annals of surgical oncology. 2010; 17 (5):1398–1405.10.1245/s10434-009-0889-3 [PubMed: 20049641]
37. Eriksson L, Czene K, Rosenberg LU, Tornberg S, Humphreys K, Hall P. Mammographic density and survival in interval breast cancers. Breast cancer research : BCR. 2013; 15 (3):R48.10.1186/bcr3440 [PubMed: 23786804]
38. Domingo L, Blanch J, Servitja S, Corominas JM, Murta-Nascimento C, Rueda A, Redondo M, Castells X, Sala M. Aggressiveness features and outcomes of true interval cancers: comparison between screen-detected and symptom-detected cancers. Eur J Cancer Prev. 2013; 22 (1):21–28.10.1097/CEJ.0b013e328354d324 [PubMed: 22584215]
39. Thind A, Diamant A, Hoq L, Maly R. Method of detection of breast cancer in low-income women. J Womens Health (Larchmt). 2009; 18 (11):1807–1811.10.1089/jwh.2008.1224 [PubMed: 19951215]
40. Roth MY, Elmore JG, Yi-Frazier JP, Reisch LM, Oster NV, Miglioretti DL. Self-detection remains a key method of breast cancer detection for U.S. women. J Womens Health (Larchmt). 2011; 20 (8):1135–1139.10.1089/jwh.2010.2493 [PubMed: 21675875]
41. Crispo A, Barba M, D'Aiuto G, De Laurentiis M, Grimaldi M, Rinaldo M, Caolo G, D'Aiuto M, Capasso I, Esposito E, Amore A, Di Bonito M, Botti G, Montella M. Molecular profiles of screen detected vs. symptomatic breast cancer and their impact on survival: results from a clinical series. BMC cancer. 2013; 13:15.10.1186/1471-2407-13-15 [PubMed: 23305429]
42. Dawood S, Hu R, Homes MD, Collins LC, Schnitt SJ, Connolly J, Colditz GA, Tamimi RM. Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study. Breast cancer research and treatment. 2011; 126 (1):185–192.10.1007/s10549-010-1113-7 [PubMed: 20711652]
43. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28 (10):1684–1691.10.1200/JCO.2009.24.9284 [PubMed: 20194857]
44. Wang Y, Yin Q, Yu Q, Zhang J, Liu Z, Wang S, Lv S, Niu Y. A retrospective study of breast cancer subtypes: the risk of relapse and the relations with treatments. Breast cancer research and treatment. 2011; 130 (2):489–498.10.1007/s10549-011-1709-6 [PubMed: 21837481]
45. Dawson SJ, Duffy SW, Blows FM, Driver KE, Provenzano E, LeQuesne J, Greenberg DC, Pharoah P, Caldas C, Wishart GC. Molecular characteristics of screen-detected vs symptomatic breast cancers and their impact on survival. British journal of cancer. 2009; 101 (8):1338–1344.10.1038/sj.bjc.6605317 [PubMed: 19773756]
46. Kim J, Lee S, Bae S, Choi MY, Lee J, Jung SP, Kim S, Choe JH, Kim JH, Kim JS, Lee JE, Nam SJ, Yang JH. Comparison between screen-detected and symptomatic breast cancers according to molecular subtypes. Breast cancer research and treatment. 2012; 131 (2):527–540.10.1007/s10549-011-1836-0 [PubMed: 22042364]
47. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. Journal of the National Cancer Institute. 2005; 97 (16):1195–1203.10.1093/jnci/dji239 [PubMed: 16106024]
48. Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, Anttila A, Lundin M, Isola J, Lundin J. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. JAMA : the journal of the American Medical Association. 2004; 292 (9):1064–1073.10.1001/jama.292.9.1064 [PubMed: 15339900]

Table 1

Sociodemographic characteristics of breast cancer patients, overall and by breast cancer subtype, N=629

	Overall (N = 629)	Luminal A (n = 430)	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)	
Characteristic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	***P*-value[a]**
Age at diagnosis (years)						**0.0197**
<45	120 (19.1)	68 (15.8)	20 (28.6)	10 (26.3)	22 (24.2)	
≥45	509 (80.9)	362 (84.2)	50 (71.4)	28 (73.7)	69 (75.8)	
Race						**0.0002**
White	322 (51.2)	244 (56.7)	29 (41.4)	19 (50.0)	30 (33.0)	
African American	307 (48.8)	186 (43.3)	41 (58.6)	19 (50.0)	61 (67.0)	
Marital status[b]						0.5370
Married or living as married	273 (43.4)	188 (43.7)	32 (45.7)	14 (36.8)	39 (42.9)	
Unmarried	220 (35.0)	144 (33.5)	25 (35.7)	19 (50.0)	32 (35.2)	
Unknown	136 (21.6)	98 (22.8)	13 (18.6)	5 (13.2)	20 (22.0)	
Education						**0.0425**
Below college	312 (49.6)	209 (48.6)	30 (42.9)	21 (55.3)	52 (57.1)	
College graduate and above	240 (38.2)	164 (38.1)	36 (51.4)	15 (39.5)	25 (27.5)	
Unknown	77 (12.2)	57 (13.3)	4 (5.7)	2 (5.3)	14 (15.4)	
Annual household income[c]						0.3840
<$70,000	220 (35.0)	138 (32.1)	26 (37.1)	16 (42.1)	40 (44.0)	
≥$70,000	229 (36.4)	165 (38.4)	25 (35.7)	13 (34.2)	26 (28.6)	
Unknown	180 (28.6)	127 (29.5)	19 (27.1)	9 (23.7)	25 (27.5)	
Primary health insurance						0.2236
Non-private	158 (25.1)	118 (27.4)	9 (12.9)	8 (21.1)	23 (25.3)	
Private	433 (68.8)	286 (66.5)	56 (80.0)	29 (76.3)	62 (68.1)	
Unknown	38 (6.0)	26 (6.0)	5 (7.1)	1 (2.6)	6 (6.6)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

[a] *P*-values generated from chi-square or Fisher's exact tests.

[b] The unmarried group was composed of those who are single/never been married, separated, divorced, or widowed.

[c] $70,000 is the median income among households in New Jersey and thus was used as the cut-point to dichotomize the income variable.

Table 2

Reproductive, clinical, and tumor characteristics of breast cancer patients, overall and by breast cancer subtype

Characteristic	Overall (N = 629) n (%)	Luminal A (n = 430) n (%)	Luminal B (n = 70) n (%)	Non-luminal HER2-expressing (n = 38) n (%)	Triple-negative breast cancer (n = 91) n (%)	*P*-value[a]
Reproductive and clinical characteristics						
Menopausal status						0.0831
Premenopausal	220 (35.0)	138 (32.1)	33 (47.1)	14 (36.8)	35 (38.5)	
Postmenopausal	409 (65.0)	292 (67.9)	37 (52.9)	24 (63.2)	56 (61.5)	
Age at menarche (years)						0.7042
<12	144 (22.9)	99 (23.0)	12 (17.1)	10 (26.3)	23 (25.3)	
12 – 13	246 (39.1)	160 (37.2)	32 (45.7)	17 (44.7)	37 (40.7)	
>13	97 (15.4)	69 (16.0)	13 (18.6)	5 (13.2)	10 (11.0)	
Unknown	142 (22.6)	102 (23.7)	13 (18.6)	6 (15.8)	21 (23.1)	
Parity						0.8557
Nulliparous	104 (16.5)	71 (16.5)	11 (15.7)	7 (18.4)	15 (16.5)	
Parous	385 (61.2)	258 (60.0)	47 (67.1)	25 (65.8)	55 (60.4)	
Unknown	140 (22.3)	101 (23.5)	12 (17.1)	6 (15.8)	21 (23.1)	
Number of children[b]						0.9681
1 – 2 children	242 (62.9)	161 (62.4)	31 (66.0)	16 (64.0)	34 (61.8)	
≥3 children	143 (37.1)	97 (37.6)	16 (34.0)	9 (36.0)	21 (38.2)	
History of breastfeeding[b]						0.6232
No	201 (52.2)	133 (51.6)	23 (48.9)	12 (48.0)	33 (60.0)	
Yes	184 (47.8)	125 (48.5)	24 (51.1)	13 (52.0)	22 (40.0)	
History of oral contraceptive use						0.7489
Never	165 (26.2)	115 (26.7)	19 (27.1)	11 (28.9)	20 (22.0)	
Ever	324 (51.5)	214 (49.8)	39 (55.7)	21 (55.3)	50 (54.9)	
Unknown	140 (22.3)	101 (23.5)	12 (17.1)	6 (15.8)	21 (23.1)	
History of HRT use						0.6899
Never	387 (61.5)	259 (60.2)	49 (70.0)	25 (65.8)	54 (59.3)	
Ever	100 (15.9)	68 (15.8)	9 (12.9)	7 (18.4)	16 (17.6)	

Cancer Causes Control. Author manuscript; available in PMC 2016 December 01.

Characteristic	Overall (N = 629) n (%)	Luminal A (n = 430) n (%)	Luminal B (n = 70) n (%)	Non-luminal HER2-expressing (n = 38) n (%)	Triple-negative breast cancer (n = 91) n (%)	*P*-value[a]
Unknown	142 (22.6)	103 (24.0)	12 (17.1)	6 (15.8)	21 (23.1)	
Family history of breast cancer						0.4919
Yes	255 (40.5)	181 (42.1)	29 (41.4)	12 (31.6)	33 (36.3)	
No	374 (59.5)	249 (57.9)	41 (58.6)	26 (68.4)	58 (63.7)	
BMI (kg/m^2)						0.1746
<25.0	205 (32.6)	143 (33.3)	25 (35.7)	15 (39.5)	22 (24.2)	
25.0 – 29.99	181 (28.8)	119 (27.7)	18 (25.7)	13 (34.2)	31 (34.1)	
≥30.0	237 (37.7)	166 (38.6)	26 (37.1)	10 (26.3)	35 (38.5)	
Unknown	6 (1.0)	2 (0.5)	1 (1.4)	0 (0.0)	3 (3.3)	
Comorbid conditions						0.1661
0	144 (22.9)	93 (21.6)	23 (32.9)	10 (26.3)	18 (19.8)	
≥1	485 (77.1)	337 (78.4)	47 (67.1)	28 (73.7)	73 (80.2)	
Diabetes						0.4086
Yes	83 (13.2)	52 (12.1)	11 (15.7)	8 (21.1)	12 (13.2)	
No	546 (86.8)	378 (87.9)	59 (84.3)	30 (78.9)	79 (86.8)	
Hypertension						0.4599
Yes	287 (45.6)	193 (44.9)	31 (44.3)	15 (39.5)	48 (52.7)	
No	342 (54.4)	237 (55.1)	39 (55.7)	23 (60.5)	43 (47.3)	
Osteoporosis/osteopenia						0.0925
Yes	174 (27.7)	132 (30.7)	15 (21.4)	7 (18.4)	20 (22.0)	
No	455 (72.3)	298 (69.3)	55 (78.6)	31 (81.6)	71 (78.0)	
Arthritis						0.3919
Yes	145 (23.1)	105 (24.4)	15 (21.4)	10 (26.3)	15 (16.5)	
No	484 (76.9)	325 (75.6)	55 (78.6)	28 (73.7)	76 (83.5)	
Tumor characteristics						
Mode of detection						**<.0001**
Patient self-detecting	270 (42.9)	157 (36.5)	36 (51.4)	22 (57.9)	55 (60.4)	
Patient not self-detecting	359 (57.1)	273 (63.5)	34 (48.6)	16 (42.1)	36 (39.6)	
History of benign breast disease						0.2025

Cancer Causes Control. Author manuscript; available in PMC 2016 December 01.

Characteristic	Overall (N = 629) n (%)	Luminal A (n = 430) n (%)	Luminal B (n = 70) n (%)	Non-luminal HER2-expressing (n = 38) n (%)	Triple-negative breast cancer (n = 91) n (%)	*P*-value[a]
No	408 (64.9)	270 (62.8)	48 (68.6)	23 (60.5)	67 (73.6)	
Yes	221 (35.1)	160 (37.2)	22 (31.4)	15 (39.5)	24 (26.4)	
Tumor grade						**<.0001**
Well/moderately differentiated	380 (60.4)	322 (74.9)	34 (48.6)	6 (15.8)	18 (19.8)	
Poorly differentiated	226 (35.9)	93 (21.6)	32 (45.7)	29 (76.3)	72 (79.1)	
Unknown	23 (3.7)	15 (3.5)	4 (5.7)	3 (7.9)	1 (1.1)	
AJCC stage						**0.0087**
Stage I	343 (54.5)	257 (59.8)	31 (44.3)	14 (36.8)	41 (45.1)	
Stage II and above	278 (44.2)	167 (38.8)	38 (54.3)	24 (63.2)	49 (53.8)	
Unknown	8 (1.3)	6 (1.4)	1 (1.4)	0 (0.0)	1 (1.1)	
Tumor size (cm)						**<0.0001**
≤1.0	215 (34.2)	174 (40.5)	18 (25.7)	8 (21.1)	15 (16.5)	
>1.0	414 (65.8)	256 (59.5)	52 (74.3)	30 (78.9)	76 (83.5)	
Lymph node status						0.9316
Negative	458 (72.8)	318 (74.0)	48 (68.6)	28 (73.7)	64 (70.3)	
Positive	163 (25.9)	106 (24.7)	21 (30.0)	10 (26.3)	26 (28.6)	
Unknown	8 (1.3)	6 (1.4)	1 (1.4)	0 (0.0)	1 (1.1)	
Histology						**0.0006**
Invasive ductal	519 (82.5)	345 (80.2)	60 (85.7)	31 (81.6)	83 (91.2)	
Invasive lobular	66 (10.5)	59 (13.7)	5 (7.1)	0 (0.0)	2 (2.2)	
Other invasive	44 (7.0)	26 (6.0)	5 (7.1)	7 (18.4)	6 (6.6)	
Lymphovascular invasion present						0.0741
No	408 (64.9)	291 (67.7)	41 (58.6)	21 (55.3)	55 (60.4)	
Yes	123 (19.6)	78 (18.1)	21 (30.0)	6 (15.8)	18 (19.8)	
Indeterminate	23 (3.7)	12 (2.8)	2 (2.9)	4 (10.5)	5 (5.5)	
Unknown	75 (11.9)	49 (11.4)	6 (8.6)	7 (18.4)	13 (14.3)	
p53 status positive						**0.0001**
No	591 (94.0)	415 (96.5)	65 (92.9)	34 (89.5)	77 (84.6)	
Yes	38 (6.0)	15 (3.5)	5 (7.1)	4 (10.5)	14 (15.4)	

Characteristic	Overall (N = 629) n (%)	Luminal A (n = 430) n (%)	Luminal B (n = 70) n (%)	Non-luminal HER2-expressing (n = 38) n (%)	Triple-negative breast cancer (n = 91) n (%)	*P*-value[a]
Ki67 status positive						**<.0001**
No	471 (74.9)	354 (82.3)	45 (64.3)	24 (63.2)	48 (52.7)	
Yes	158 (25.1)	76 (17.7)	25 (35.7)	14 (36.8)	43 (47.3)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index; HRT, hormone replacement therapy; AJCC, American Joint Committee on Cancer.

[a] *P*-values generated from chi-square or Fisher's exact tests.

[b] Number of children and history of breastfeeding were among parous women only (N = 385).

Table 3

Univariate multinomial logistic regression analyses of the associations between sociodemographic, reproductive, clinical, and tumor characteristics, and breast cancer subtype

	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)
Characteristic	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**
Sociodemographic characteristics			
Age at diagnosis (years)			
<45	**2.1 (1.2, 3.8)**	1.9 (0.9, 4.1)	**1.7 (1.0, 2.9)**
≥45	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Race			
White	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
African American	**1.9 (1.1, 3.1)**	1.3 (0.7, 2.5)	**2.7 (1.7, 4.3)**
Marital status[b]			
Married or living as married	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Unmarried	1.0 (0.6, 1.8)	1.8 (0.9, 3.7)	1.1 (0.6, 1.8)
Unknown	0.8 (0.4, 1.6)	0.7 (0.2, 2.0)	1.0 (0.5, 1.8)
Education			
Below college	0.7 (0.4, 1.1)	1.1 (0.5, 2.2)	**1.6 (1.0, 2.7)**
College graduate and above	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Unknown	**0.3 (0.1, 0.9)**	0.4 (0.1, 1.7)	1.6 (0.8, 3.3)
Annual household income[c]			
<$70,000	1.2 (0.7, 2.3)	1.5 (0.7, 3.2)	**1.8 (1.1, 3.2)**
≥$70,000	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Unknown	1.0 (0.5, 1.9)	0.9 (0.4, 2.2)	1.2 (0.7, 2.3)
Primary health insurance			
Non-private	**0.4 (0.2, 0.8)**	0.7 (0.3, 1.5)	0.9 (0.5, 1.5)
Private	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Unknown	1.0 (0.4, 2.7)	0.4 (0.1, 2.9)	1.1 (0.4, 2.7)
Reproductive and clinical characteristics			
Menopausal status			

	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)
Characteristic	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**
Pre	**1.9 (1.1, 3.1)**	1.2 (0.6, 2.5)	1.3 (0.8, 2.1)
Post	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Age at menarche (years)			
<12	0.6 (0.3, 1.5)	1.4 (0.5, 4.3)	1.6 (0.7, 3.6)
12 – 13	1.1 (0.5, 2.1)	1.5 (0.5, 4.1)	1.6 (0.8, 3.4)
>13	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Unknown	0.7 (0.3, 1.5)	0.8 (0.2, 2.8)	1.4 (0.6, 3.2)
Parity			
Nulliparous	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Parous	1.2 (0.6, 2.4)	1.0 (0.4, 2.4)	1.0 (0.5, 1.9)
Unknown	0.8 (0.3, 1.8)	0.6 (0.2, 1.9)	1.0 (0.5, 2.0)
Parity[d]			
1 – 2 children	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
≥3 children	0.9 (0.4, 1.6)	0.9 (0.4, 2.2)	1.0 (0.6, 1.9)
History of breastfeeding[d]			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	1.1 (0.6, 2.1)	1.2 (0.5, 2.6)	0.7 (0.4, 1.3)
History of oral contraceptive use			
Never	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Ever	1.1 (0.6, 2.0)	1.0 (0.5, 2.2)	1.3 (0.8, 2.4)
Unknown	0.7 (0.3, 1.6)	0.6 (0.2, 1.7)	1.2 (0.6, 2.3)
History of HRT use			
Never	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Ever	0.7 (0.3, 1.5)	1.1 (0.4, 2.6)	1.1 (0.6, 2.1)
Unknown	0.6 (0.3, 1.2)	0.6 (0.2, 1.5)	1.0 (0.6, 1.7)
Family history of breast cancer			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	1.0 (0.6, 1.6)	0.6 (0.3, 1.3)	0.8 (0.5, 1.3)
BMI (kg/m^2)			

	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)
Characteristic	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**
<25.0	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
25.0 – 29.99	0.9 (0.5, 1.7)	1.0 (0.5, 2.3)	1.7 (0.9, 3.1)
≥30.0	0.9 (0.5, 1.6)	0.6 (0.3, 1.3)	1.4 (0.8, 2.4)
Unknown			
Comorbid conditions			
0	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
≥1	**0.6 (0.3, 1.0)**	0.8 (0.4, 1.6)	1.1 (0.6, 2.0)
Diabetes			
Yes	1.4 (0.7, 2.7)	1.9 (0.8, 4.5)	1.1 (0.6, 2.2)
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Hypertension			
Yes	1.0 (0.6, 1.6)	0.8 (0.4, 1.6)	1.4 (0.9, 2.2)
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Osteoporosis/osteopenia			
Yes	0.6 (0.3, 1.1)	0.5 (0.2, 1.2)	0.6 (0.4, 1.1)
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Arthritis			
Yes	0.8 (0.5, 1.6)	1.1 (0.5, 2.4)	0.6 (0.3, 1.1)
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Tumor characteristics			
Mode of detection			
Patient self-detecting	**1.8 (1.1, 3.1)**	**2.4 (1.2, 4.7)**	**2.7 (1.7, 4.2)**
Patient not self-detecting	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
History of benign breast disease			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	0.8 (0.5, 1.3)	1.1 (0.6, 2.2)	**0.6 (0.4, 1.0)**
Tumor grade			
Well/moderately differentiated	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Poorly differentiated	**3.3 (1.9, 5.6)**	**16.7 (6.7, 41.5)**	**13.8 (7.9, 24.4)**
Unknown	--	--	--

Cancer Causes Control. Author manuscript; available in PMC 2016 December 01.

	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)
Characteristic	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**
AJCC stage			
Stage I	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Stage II and above	**1.9 (1.1, 3.2)**	**2.6 (1.3, 5.2)**	**1.8 (1.2, 2.9)**
Unknown	--	--	--
Tumor size (cm)			
≤1.0	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
>1.0	**2.0 (1.1, 3.5)**	**2.5 (1.1, 5.7)**	**3.4 (1.9, 6.2)**
Lymph node status			
Negative	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Positive	1.3 (0.8, 2.3)	1.1 (0.5, 2.3)	1.2 (0.7, 2.0)
Unknown	--	--	--
Lymphovascular invasion present			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	**1.9 (1.1, 3.4)**	0.9 (0.4, 2.4)	1.2 (0.7, 2.1)
Unknown	0.9 (0.3, 2.1)	1.7 (0.7, 4.2)	1.3 (0.7, 2.6)
p53 status positive			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	2.1 (0.7, 6.1)	**3.3 (1.0, 10.4)**	**5.0 (2.3, 10.8)**
Ki67 status positive			
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Yes	**2.6 (1.5, 4.5)**	**2.7 (1.3, 5.5)**	**4.2 (2.6, 6.7)**

Abbreviations: HER2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval; BMI, body mass index; HRT, Hormone Replacement Therapy; AJCC, American Joint Committee on Cancer.

[a] ORs and 95% CIs were generated from univariate multinomial logistic regression models with the luminal A subtype as the referent group.

[b] The unmarried group was composed of those who were single/never been married, separated, divorced, or widowed.

[c] $70,000 is the median income among households in New Jersey and thus was used as the cut-point to dichotomize the income variable.

[d] Number of children and history of breastfeeding were among parous women only (N = 385).

Table 4

Multivariable multinomial logistic regression analyses of the associations between sociodemographic and clinicopathological characteristics, and breast cancer subtype

	Luminal B (n = 70)	Non-luminal HER2-expressing (n = 38)	Triple-negative breast cancer (n = 91)	
Characteristic	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**OR (95% CI)[a]**	**P-value for heterogeneity of ORs**
Age at diagnosis (years)				0.9351
<45	**1.8 (1.0, 3.4)**	1.6 (0.6, 3.7)	1.7 (0.9, 3.2)	
≥45	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
Race				0.6209
White	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
African American	1.6 (0.9, 2.8)	1.2 (0.6, 2.7)	**1.9 (1.0, 3.4)**	
Education				**0.0401**
Below college	**0.5 (0.3, 1.0)**	1.1 (0.5, 2.4)	1.3 (0.7, 2.5)	
College graduate and above	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
Tumor grade				**0.0005**
Well/moderately differentiated	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
Poorly differentiated	**2.6 (1.5, 4.7)**	**14.5 (5.3, 39.7)**	**9.7 (5.1, 18.4)**	
Tumor size (cm)				0.8663
≤1.0	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
>1.0	**1.9 (1.0, 3.6)**	2.5 (0.8, 7.9)	**2.2 (1.0, 4.8)**	
Ki67 status positive				0.6065
No	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	
Yes	**2.1 (1.1, 4.0)**	2.0 (0.9, 4.5)	**2.9 (1.6, 5.2)**	

Abbreviations: HER2, Human Epidermal Growth Factor Receptor 2; OR, Odds Ratio; CI, Confidence Interval.

[a]ORs and 95% CIs were generated from multivariable multinomial logistic regression models (mutually adjusting for all covariates in the model) with the luminal A subtype as the referent group.