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# The epidemiology of triple-negative breast cancer, including race

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## Abstract

**Objective—**Predictors of intrinsic breast cancer subtypes, including the triple-negative (TN) subtype, are largely unknown. We evaluated whether anthropometrics, demographics, and reproductive history were associated with distinct breast cancer subtypes.

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**Methods—**Invasive breast tumors from a population-based case–control study of 476 (116 black and 360 white) Atlanta women aged 20–54, diagnosed between 1990 and 1992, were centrally reviewed and immunohistochemically analyzed for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2); then grouped [TN (ER−PR−HER2−); ER−PR−HER2+; ER/PR+HER2+; ER/PR+HER2− (case-only reference group)]. Data were from interviews and anthropometric measurements; adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression, including both case-only and case-control comparisons.

**Results—**From the case-only analyses and compared with the ER/PR+HER2− subtype, women with TN tumors were more likely to be obese than normal/underweight [OR = 1.89 (95% CI = 1.22, 2.92)]. Regardless of HER2 status, ER−PR− tumors were associated with black race, young age at first birth, having a recent birth, and being overweight.

**Conclusions—**Distinct breast cancer subtypes have unique sociodemographic, anthropometric and reproductive characteristics and possibly different pathways for development.

### Keywords

Breast neoplasms; Molecular epidemiology; Tumor biology; Race

## Introduction

Genetic expression profiling analyses have identified intrinsic subtypes of female breast cancer, each of which has unique gene-expression patterns [1, 2]. These subgroups may represent distinct etiologies of breast cancer: they certainly have important implications for therapy administration and effectiveness and can influence recurrence and mortality risk [3–8]. In particular, the basal-like subtype of breast cancer is associated with a poor outcome [1, 3]. The RNA expression profile for the basal-like phenotype includes a lack of expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2), and the absence of protein expression of all three of these genes has been used to define a related clinical entity: the so-called triple-negative (TN) subtype of breast cancer, which has no viable targeted therapy [9]. The four basic subtypes as defined by ER, PR and HER2 status (TN; ER+ and/or PR+, HER2−; ER+ and/or PR+, HER2+; and ER−PR−HER2 +) are approximately equivalent to the subtypes developed through genetic hierarchal clustering, respectively: basal-like, Luminal A, Luminal B, and HER2 + (but distinct from Luminal B) [9, 10]. Although TN breast cancers do not have all the features of basal-like cancers [11], they have been shown to be associated with poorer survival relative to tumors expressing such receptors in several studies [4, 9, 12].

Black race, younger age, and later tumor stage are associated with the TN subtype [4, 7, 12–18]. What is less well known is whether anthropometrics, demographics, and reproductive history are independently associated with subtypes of breast cancer defined by ER, PR, and HER2 status, hereafter referred to triple subtype status [7, 13, 14, 19, 20]. Previous population-based work has observed that younger age at menarche or younger age at first pregnancy, higher parity, shorter duration of breast feeding, higher body mass index (BMI) or higher waist-to-hip ratio (WHR) were all associated with basal-like tumors versus luminal

A tumors (tumors characterized by positive ER and PR and negative HER2) [14]. An analysis of the Polish Breast Cancer Study found that early age at menarche and the highest BMI among premenopausal women were associated with basal-like disease, whereas elevated BMI decreased risk of luminal A tumors in premenopausal women [7]. An analysis among postmenopausal women observed that early age at menarche was associated with HER2+ disease and that breastfeeding was protective for luminal subtypes and triple-negative tumors [19]. Increased BMI was associated with luminal and TN tumors, but only among women not currently using hormone therapy [20]. Low socioeconomic status (SES) women were more likely to be diagnosed with TN tumors than other breast cancers in an analysis of California registry data [13]. Only one previous population-based study [14] was able to consider race and various exposures of interest, including anthropometrics and physical activity across life, therefore additional research is needed.

Our study is unique in its exclusive focus on younger women, a substantial proportion of who are black. Additionally, detailed information on demographics, reproductive history, anthropometrics and physical activity across the patient life-course were available, including measured anthropometrics around the time of diagnosis. We assessed whether demographic characteristics, anthropometrics, and reproductive history were associated with breast cancer subtype status in a population-based case–control study of younger (ages 20–54) women in Atlanta, GA, USA. A more complete understanding of the subtypes of breast cancer, in particular, the TN subtype, may help elucidate mechanisms influencing etiology and mortality associated with this aggressive, not-easily treated disease.

## Methods

### Source population

The source population for this study was the Atlanta arm of a multi-center population-based case–control study of breast cancer risk factors among younger women, which has previously been described [12, 21]. Briefly, the original study identified 950 black or white women, aged 20–54, residing in metropolitan Atlanta, Georgia (Cobb, Fulton, or DeKalb County), who were diagnosed with unilateral incident invasive breast cancer between 1 May 1990 and 31 December 1992. Rapid ascertainment of hospital admission, surgery, and pathology records identified the cases. Periodic checks against the metropolitan Atlanta Surveillance, Epidemiology and End Results (SEER) cancer registry assured completeness of ascertainment. Of the 835 cases originally interviewed, four were excluded (one later self-reported ‘other’ race and three were initially interviewed as controls, before becoming cases), resulting in 831 cases available for the current study (251 black and 580 white). Area controls were also interviewed [21] and for case–control analyses, 913 controls were ultimately analyzed. After Institutional Review Board approval at collaborating institutions, a more comprehensive medical record review was conducted and tumor specimens were obtained. Slides for centralized pathology review and archival tissue specimens suitable for further laboratory analysis were obtained for 476 (116 black and 360 white) of the 831 cases.

## Exposure data

Exposure data for this study came from several sources, including in-person interviews that were part of the original case–control study and the SEER registry. Follow-up interviews and extensive medical record abstraction from relevant medical institutions were also conducted among the cases. Most non-clinical information came from the case–control study in-person interviews [21], conducted shortly after diagnosis, which included questions on demographics, alcohol consumption, cigarette smoking status, reproductive and breastfeeding history, physical activity, and body composition throughout life. Anthropometrics (weight, height, waist and hip circumference) were measured during the interview. WHR was categorized based on the median level in the population (<0.8, ≥0.8). BMI was categorized based on National Health Lung Blood Institute guidelines (normal/underweight, <25 kg/$m^2$; overweight, 25–29 kg/$m^2$; obese, ≥30 kg/$m^2$) [22]. Demographic characteristics of interest, self-reported during the in-person interviews, included age at diagnosis (20–39, 40–49, or 50–54), race (white or black), education (<college graduate or ≥college graduate), and household income. The latter, along with the number of people supported by that household income, were used to calculate a poverty index (≤200%, low SES; 201–699%, middle SES; ≥700%, high SES) which was compared with the 1991 federal poverty line for a family of the corresponding size [23]. Insurance status (private or public/none) was based on data from case medical record abstraction and follow-up interviews, and was therefore unavailable for controls.

Stage at diagnosis was obtained from medical record abstraction and/or the SEER registry and was defined based on American Joint Committee on Cancer staging criteria [24]. Stage was ultimately categorized as I, IIA, IIB, or III/IV.

The centralized pathology review and associated laboratory methods have been described previously in detail [25] and were overseen by a single pathologist (PLP). All immunohistochemical (IHC) assays were conducted without the knowledge of patient characteristics. Standard IHC techniques were used to assay tumor marker proteins, including antigen retrieval when appropriate, on tumor tissue sections using the antibodies described below [26–30].

Levels of protein expression of estrogen receptor (ER; ERID5; Immunotech, Westbrook, ME) [31–33], progesterone receptor (PR; 1A6; Novocastra, Newcastle-Upon-Tyne, United Kingdom) [34], and c-ErbB-2 (HER-2/neu) oncogene protein (AO485/DAKO15; Dako, Capinteria, CA) [35] were assessed from representative tumor blocks. IHC positivity was determined according to staining intensity and percentage of tumor cells that were positive. Any nuclear staining for ER and PR was considered positive. HER2 antibody staining with the AO485 antibody was used before the HercepTest kit (Dako) became the currently approved technique for HER2 expression evaluation [36]. HER2 status was graded on a scale of 1–4 (no, low, moderate or high intensity membranous staining relative to normal breast epithelium) and those with low, moderate or high intensity staining were considered positive. Breast cancer cases were subsequently categorized into four IHC subtypes based on ER, PR, and HER2 expression positivity (+) or negativity (−): triple negative (ER−PR−HER2−); ER+ and/or PR+, HER2− (hereafter referred to as ER/PR+, HER2−); ER+ and/or PR+, HER2+ (hereafter referred to ER/PR+, HER2+); and ER−PR−HER2+.

### Statistical analyses

Since we were only able to obtain tumor specimens on a subset of eligible cases, we determined whether selection bias may have been introduced by comparing the cohort from whom we had specimens to the entire eligible population [25]. As previously described [25], black women were less likely to have a tumor specimen available for analysis, and black women with specimens were younger and more likely to die of breast cancer than black women in the eligible population. Among white women, no differences were observed between those with specimens and the eligible population. Therefore, to diminish the possibility of overestimating associations between tumor characteristics and race, all analyses were weighted based on the inverses of the probabilities that women in the eligible population were included in the pathology cohort, based on race, age at diagnosis (five groups), and vital status at the time of the follow-up interview [25].

We analyzed whether race, age, education, SES, insurance, smoking status, alcohol consumption, age at menarche, parity, age at first birth, recency of birth, breastfeeding, physical activity (at age 20 and the year before the original case–control study interview), BMI (age 20, the year before the original case-control study interview, and measured at the original case-control study interview), and WHR (measured at the original case–control study interview) were associated with breast cancer subtypes. Both case-only analyses (each triple subgroup compared to the referent group, ER/PR +, HER2− tumors) and case–control analyses (each triple subgroup compared to controls) were performed. ER/PR +, HER2− tumors were the referent group since they are the most common breast cancer subtype. All categorical variables were entered into models as indicator variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from logistic regression models adjusted for age and race (for case–control analyses) or age, race, and stage (for case-only analyses). The primary estimates of interest are the case-only analyses because our overarching goal was to understand the epidemiology of breast cancer subtypes. This may ultimately lead to a better understanding of why certain breast cancer patients present with more aggressive disease, and thus, are more likely to die. Case-only analyses can be useful for understanding heterogeneity among cases [37]. However, case–control estimates are presented for consistency with previous literature [7, 14] and to help clarify whether observed case-only differences were driven by effects among our referent group (ER/PR+, HER2− cases) only.

## Results

### Univariate analyses

Women with TN tumors were more likely to be younger (34% were 18–29 years of age) than were women with ER/PR+, HER2− tumors or among controls (18 and 23%, respectively) (Table 1). Women with TN tumors were also more often of lower SES, more likely to be obese, and to have experienced menarche at a younger age than were women with ER/PR+, HER2− tumors or controls.

### Case-only multivariate analyses

Among cases only with ER/PR+, HER2− tumors serving as the referent (Table 2), obesity was the only characteristic which had a statistically significant association with TN tumors

that did not appear to be associated with any other subtype [OR = 1.89 (1.22, 2.92)]. Similar patterns were observed for elevated BMIs at age 20 and in the year before interview (data not shown). Our estimates for BMI were similar in pre- and post-menopausal women and in women <50 years and ≥50 years of age (results not shown).

Regardless of HER2 status, several variables were associated with ER− and PR− tumors. With ER/PR+ HER2− tumors serving as the referent (Table 2), ER− and PR− tumors were more likely to be diagnosed among black women than white women, even after adjustment for age and stage [e.g., for TN tumors, OR = 2.98 (2.12, 4.20); for ER−PR−HER2+, OR = 1.90 (1.05, 3.46)]. ER− and PR− tumors also occurred at a higher proportion among women <18 years of age at first birth, among women who had recently given birth (within 5 years of diagnosis), and overweight women. Having public insurance or no insurance, having less education, and early menarche (<12 years), and high parity (≥4 births) appeared to be associated with both subtypes of ER− and PR− tumors, although estimates for some subgroups were not statistically significant.

Variables associated with some subtypes included age at diagnosis, SES, and smoking. TN and ER/PR+HER2+ tumors were more likely among women 20–39 years old than women 50–54 years old. ER−PR−HER2+ tumors were more common among low SES women than middle SES women [OR = 2.21 (1.06, 4.62)]. Current smoking was associated with ER−PR−HER2+ tumors [OR = 2.91 (1.43, 5.91)], but former smoking was associated with ER/PR+HER2+ tumors [OR = 1.87 (1.06, 3.32)]. The protective effect of longer durations of breast-feeding did not differ greatly among breast cancer subtypes, but the largest decrease was for ER/PR+HER2+ tumors. No association was observed between WHR and any subtype (results not shown).

### Case–control multivariate analyses

Compared with controls, most characteristics were associated with tumor subtypes defined by ER and PR status, regardless of HER2 status, although for some subgroups, results were not statistically significant. When compared with controls (Table 3), ER− and PR− tumors were more likely to be diagnosed among black women than white women [e.g., for TN tumors, OR = 2.41 (1.81, 3.21); for ER−PR−HER2+ tumors, OR = 1.69 (0.98, 2.92)]. ER− and PR− tumors were more frequent among those with low SES and those who experienced menarche at age 11 or younger. Having given birth (particularly at young ages) decreased risk for ER/PR+ tumors. ER/PR + tumors were less likely among the overweight or obese, but no effect of BMI was observed among ER− and PR− tumors.

Education and alcohol use were also associated with specific subtypes. Relative to controls, ER−PR−HER2 + tumors were positively associated with low education [2.11 (1.10, 4.05)], but was inversely associated with ER/PR + HER2− tumors [0.68 (0.54, 0.86)]. ER−PR−HER2 + and ER/PR + HER2− tumors were more common among alcohol drinkers than non-drinkers.

Former smoking tended to increase risk for all four tumor subtypes, but current smoking was associated with a decreased risk of all subtypes, except for ER−PR−HER2+ tumors. Longer durations of breast feeding were inversely associated with all four tumor subtypes. Greater

levels of physical activity were associated with decreased risk of all tumor types, except for ER/PR+HER2+. WHR was not associated with risk of any subtype (results not shown).

## Discussion

Among cases, being obese (across all time points) was associated with the TN subtype. Additional factors that were associated with the TN subtype and the other ER−PR− subtype (ER−PR−HER2+) included black race, being overweight, young age at first full-term pregnancy, and having a recent birth.

Relative to controls, predictors tended to cluster based on ER and PR status; HER2 status did not have as much discriminatory power. Low or high SES or young age at menarche predicted ER− and PR− tumors. Young age at first birth and having greater than or equal to four births were more likely among women with ER/PR+ tumors. While the reasons for this are unclear, it could be because our definition of TN only encompasses three markers, and as such, likely represents a mix of non-basal and basal subtypes (e.g., those defined by epidermal growth factor receptor and cytokeratin 5/6 positivity) of disease with different prognosis and potentially different etiologies [38]. The association between smoking status and breast cancer varied based on whether women were current or former smokers, but results were similar across all 4 tumor types. Also, longer durations of breastfeeding and physical activity tended to decrease the risk of most tumor types.

Our results among cases are largely consistent with those of Millikan et al., particularly for the reproductive factors [14]. In their population-based study, basal-like tumors were more likely among cases with a younger age at menarche, higher parity, and younger age at first full-term pregnancy. In case-only analyses, they found a stronger effect of breastfeeding for TN tumors than we did as well as a strong association with WHR [14], which we did not observe. Another study of postmenopausal Seattle-area women also observed a protective effect of breastfeeding on luminal and TN tumors [19]. Bauer et al. [13] observed a statistically significant association between low SES and TN tumors among cases (OR = 1.12 and 1.22 for the two lowest SES tertiles), that was similar in magnitude to our non-statistically significant point estimate (1.22) for low SES. Results from the Polish Breast Cancer Study indicated that increasing BMI was associated with less risk of luminal A tumors when compared with controls [7], similar to our results for ER/PR+HER2− tumors. Among postmenopausal women, increased BMI increased risk of luminal and TN tumors, but only among non-hormone therapy users [20]. In combination, results from our study and previous work [7, 14] suggest that elevated BMI does not increase risk of TN tumors relative to controls. However, because obesity decreased risk for ER/PR+HER2− (or luminal A) tumors versus controls, TN tumors were more likely among overweight or obese cases. Similar to our results, increased age at menarche was associated with decreased risk of basal-like tumors [7], but this was not observed in a study of postmenopausal women [19]. Discrepant results among studies could arise due to differences in sample sizes, study populations, laboratory methodologies, and different classifications for breast cancer subtypes (e.g., triple negative vs. basal-like).

The increasing evidence that specific subtypes of breast cancer have different etiologies is biologically plausible, based on the current understanding of the heterogeneity of breast cancer development due to hormone and growth factor status. For example, the contrasting results for elevated BMI and early age at menarche between TN and ER/PR+HER2− tumors are consistent with hormonally-associated factors affecting ER+PR+ tumors more strongly. Obesity, particularly in younger, premenopausal women, has been associated with lower estrogen levels [39], possibly due to anovulation, which would explain why elevated BMI reduced risk of ER/PR+HER2− tumors. In addition to analyses of tumor phenotypes based on an overall assessment of receptor and HER2 status, at least one study has observed that quantified receptor levels are associated with BMI; in premenopausal women BMI was inversely associated with receptor levels, but among postmenopausal women BMI and receptor levels were positively associated [40]. It has been speculated that the low serum hormone levels among overweight or obese premenopausal women may cause ER and PR level upregulation in normal breast epithelium, leading to an exaggerated hormone response after menopause [40].

Our results are consistent with previous findings that reproductive factors are typically more strongly associated with ER+ and/or PR+ tumors than with ER− and/or PR− tumors [41]. Traditional breast cancer risk factors, those exposures associated with higher hormone levels or decreased likelihood of terminal breast cell differentiation (e.g., early age at menarche, high parity, breast feeding), tend to be the same as those for ER/PR+HER2− or luminal A tumors, the most predominant type of breast cancer [7, 14]. Our study adds to the growing literature on more specific, clinically relevant molecular subtypes of breast cancer in an exclusively young population.

Additionally, results restricted to cases may help explain why certain characteristics have been observed to influence survival among breast cancer cases. For example, having a recent birth [7, 42, 43], high parity [42], and elevated BMI [44, 45] have been associated with increased mortality after breast cancer. Our results and those of others [7, 14], indicating that increases in BMI and various reproductive characteristics are associated with TN tumors, may partially explain why reproductive characteristics appear to influence survival.

There are some limitations to this study. We had tumor specimens on only a subset of eligible cases, thus limiting our sample size. However, the possibility of selection bias has been minimized by using weighted analyses. Estimates from unweighted analyses were not materially different from those of the weighted analyses. The small sample sizes for some subgroups may have led to false-positive findings [46], but our findings are largely consistent with previous literature suggesting that our results are replicable. Estimates from models adjusted for multiple factors simultaneously were similar to those from the minimally adjusted (age, race, and/or stage) models. In particular, race was still strongly associated with the triple negative subtype, even after adjusting for multiple socioeconomic factors (education, poverty and insurance status), reproductive and anthropometric characteristics (e.g., comparing TN vs. ER/PR+HER2− tumors = 2.17 (95% CI = 1.44–3.27). Given the small sample sizes for certain subgroups, and to be consistent with other literature [14, 19, 20], we have decided to report only the estimates from the minimally adjusted models. Also, women in this study are only from one geographic location; however,

there is no reason to suspect that these results would not apply to other, similar women. Our study population included both pre- and post-menopausal women, but our results were largely unchanged when restricted only to premenopausal women. The exception was for black race where the estimate for TN versus ER/PR+, HER2− tumors increased from 2.98 among pre- and postmenopausal women to 4.60 (2.96, 7.15) among premenopausal women only. TN tumors are similar to basal-like tumors, but not completely concordant [11]. Additionally, our IHC results were not confirmed by fluorescence in situ hybridization, and HER2 results of 2+ were considered positive; therefore many HER2+ tumors could actually be HER2− and our results for TN tumors may be underestimates of the true association.

Despite the limitations, this study has several strengths. It was population-based and focused on younger breast cancer cases, who are less well-studied and who have higher mortality than older cases [47]. A large number of black women were included; ~30% of the case population was black. The data were of high-quality, detailed, and included anthropometric measurements. Centralized pathology review and standardized IHC assay methods were used. Lastly, to our knowledge, this is only the second paper to report on a number of anthropometric, demographic, and reproductive history characteristics as predictors of triple subtype status and to additionally account for race.

In conclusion, this study confirms the previously observed associations of black race and younger age with TN status [4, 7, 12–18], and adds to our understanding of demographic, reproductive, and anthropometric factors that are associated with breast cancer subtypes, independent of race and age. This suggests that, in addition to biological and tumor factors, reproductive history, socio-demographics, and anthropometrics influence the presentation and development of triple negative tumors. Our understanding of TN tumors is in its infancy and further research is needed to elucidate why certain populations are more likely to present with this intractable disease.

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## Abbreviations

| | |
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| **TN** | Triple negative |
| **ER** | Estrogen receptor |
| **PR** | Progesterone receptor |
| **HER2** | Human epidermal growth factor receptor 2 |
| **WHR** | Waist to hip ratio |
| **BMI** | Body mass index |
| **SES** | Socioeconomic status |
| **SEER** | Surveillance, Epidemiology and End Results |

**IHC** Immunohistochemical

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**Table 1**

Frequencies (percentages[a]) of breast cancer triple subtypes and patient demographics, Atlanta, GA, 1990–1992

| | TN (*n* = 135) | ER−PR−HER2+ (*n* = 33) | ER/PR+HER2+ (*n* = 36) | ER/PR+HER2− (*n* = 272) | Controls (*n* = 913) |
|---|---|---|---|---|---|
| Race | | | | | |
| Black | 56 (49.1) | 12 (39.5) | 7 (25.7) | 41 (21.3) | 251 (27.5) |
| White | 79 (50.9) | 21 (60.5) | 29 (74.3) | 231(78.7) | 662 (72.5) |
| Age at diagnosis *, *y* | | | | | |
| 20–39 | 51 (34.1) | 9 (23.3) | 11 (27.7) | 53 (17.8) | 205 (22.5) |
| 40–49 | 57 (46.3) | 17 (55.4) | 20 (59.8) | 146 (55.2) | 469 (51.4) |
| 50–54 | 27 (19.6) | 7 (21.3) | 5 (12.6) | 73 (27.0) | 239 (26.2) |
| Stage | | | | | |
| I | 38 (28.2) | 9 (27.4) | 13 (37.4) | 131 (46.2) | N/A |
| IIA | 46 (36.3) | 5 (14.8) | 13 (36.4) | 69 (25.6) | N/A |
| IIB | 27 (18.9) | 10 (29.0) | 8 (20.4) | 37 (14.2) | N/A |
| III/IV | 22 (16.6) | 9 (28.7) | 2 (5.7) | 35 (14.0) | N/A |
| Education * | | | | | |
| <College grad | 86 (64.5) | 26 (79.1) | 22 (63.5) | 145 (54.1) | 581 (63.6) |
| College grad+ | 49 (35.5) | 7 (20.9) | 14 (36.5) | 127 (45.9) | 332 (36.4) |
| Poverty index * (SES) | | | | | |
| ≤200 (low) | 32 (26.6) | 11 (33.0) | 3 (9.0) | 31 (13.4) | 132 (15.0) |
| 201–700 (middle) | 66 (49.5) | 14 (43.6) | 18 (53.6) | 154 (57.3) | 537 (60.9) |
| >700 (high) | 34 (24.0) | 8 (23.5) | 13 (37.4) | 79 (29.3) | 213 (24.2) |
| Insurance status *, *b* | | | | | |
| Private | 110 (79.9) | 25 (75.3) | 32 (88.7) | 254 (92.4) | – |
| Public/none | 25 (20.1) | 8 (24.7) | 4 (11.3) | 18 (7.6) | – |
| Smoking status | | | | | |
| Never | 67 (49.9) | 12 (37.6) | 13 (40.5) | 127 (47.2) | 450 (49.3) |
| Former | 53 (38.6) | 11 (31.3) | 21 (53.9) | 110 (40.0) | 266 (29.1) |
| Current | 15 (11.5) | 10 (31.1) | 2 (5.6) | 35 (12.8) | 197 (21.6) |
| Alcohol *, drinks/week | | | | | |

*Cancer Causes Control*. Author manuscript; available in PMC 2016 May 02.

| | TN (*n* = 135) | ER−PR−HER2+ (*n* = 33) | ER/PR+HER2+ (*n* = 36) | ER/PR+HER2− (*n* = 272) | Controls (*n* = 913) |
|---|---|---|---|---|---|
| Never | 55 (43.5) | 9 (26.2) | 12 (37.8) | 73 (28.8) | 381 (41.8) |
| <7 | 58 (41.8) | 17 (49.5) | 17 (45.1) | 145 (51.9) | 397 (43.5) |
| 7+ | 22 (14.8) | 7 (24.2) | 7 (17.2) | 52 (19.3) | 134 (14.7) |
| Age at menarche *, *y* | | | | | |
| <12 | 43 (32.9) | 10 (32.5) | 8 (21.2) | 66 (23.7) | 201 (22.1) |
| 12+ | 91 (67.1) | 23 (67.5) | 28 (78.8) | 206 (76.3) | 708 (77.9) |
| Age at first birth, *y* | | | | | |
| Nulliparous | 30 (21.5) | 3 (9.6) | 12 (31.4) | 60 (22.1) | 155 (17.0) |
| <18 | 13 (11.4) | 5 (16.3) | 2 (5.0) | 7 (2.9) | 89 (9.8) |
| 18+ | 92 (67.1) | 25 (74.1) | 22 (63.5) | 205 (75.1) | 668 (73.3) |
| No. full-term births * | | | | | |
| 0 | 30 (21.5) | 3 (9.6) | 12 (31.4) | 60 (22.1) | 155 (17.0) |
| 1–3 | 89 (66.5) | 27 (82.2) | 20 (58.3) | 197 (72.5) | 630 (69.0) |
| ≥4 | 16 (12.0) | 3 (8.1) | 4 (10.3) | 15 (5.5) | 128 (14.0) |
| Recency of birth, *y* | | | | | |
| Nulliparous | 30 (21.5) | 3 (9.6) | 12 (32.3) | 60 (22.1) | 155 (17.1) |
| ≤5 | 20 (14.7) | 5 (12.9) | 4 (10.2) | 14 (4.6) | 78 (8.6) |
| >5 | 85 (63.8) | 25 (77.4) | 19 (57.5) | 198 (73.4) | 674 (74.3) |
| Breastfeeding | | | | | |
| Never (nvr pg/≤2 weeks) | 85 (65.1) | 21 (63.1) | 25 (71.2) | 162 (60.4) | 534 (58.5) |
| Ever (>2 weeks) | 50 (35.0) | 12 (36.9) | 11 (28.8) | 110 (39.6) | 379 (41.5) |
| BMI (kg/m$^2$) at interview * | | | | | |
| Underweight/normal (<25) | 54 (38.2) | 15 (44.7) | 23 (65.9) | 171 (60.0) | 408 (46.2) |
| Overweight (25.0–29.9) | 39 (28.5) | 11 (33.5) | 7 (17.6) | 57 (21.2) | 248 (28.1) |
| Obese (30+) | 41 (33.3) | 7 (21.8) | 6 (16.5) | 43 (18.9) | 227 (25.7) |
| Physical activity- year before interview (RU) | | | | | |
| <13.54 (below median) | 68 (51.5) | 19 (57.4) | 14 (42.7) | 139 (52.8) | 363 (40.4) |
| ≥13.54 (median+) | 67 (48.5) | 14 (42.7) | 22 (57.3) | 133 (47.2) | 536 (59.6) |

*Mantel–Haenszel Chi-square *p*-value <0.05

[a]All percentages are weighted column percentages

[b] Insurance status was obtained from case medical records and follow-up interviews and is unavailable for controls

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TN, triple negative

## Table 2

Associations (ORs) between breast cancer triple subtypes (vs. ER/PR+, HER2−) according to patient and tumor characteristics among cases only, Atlanta, GA

| | TN OR[a] (95% CI) | ER−PR−HER2+ OR[a] (95% CI) | ER/PR+HER2+ OR[a] (95% CI) |
|---|---|---|---|
| Race | | | |
| Black | 2.98 (2.12, 4.20) | 1.90 (1.05, 3.46) | 1.16 (0.62, 2.17) |
| White | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Age at diagnosis, *y* | | | |
| 20–39 | 2.13 (1.34, 3.39) | 1.61 (0.70, 3.71) | 3.03(1.25, 7.34) |
| 40–49 | 1.09 (0.72, 1.64) | 1.31 (0.65, 2.64) | 2.26 (1.02, 5.02) |
| 50–54 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Stage | | | |
| I | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| IIA | 1.73 (1.16, 2.58) | 0.84 (0.35, 1.99) | 1.67 (0.90, 3.10) |
| IIB | 1.65 (1.02, 2.67) | 2.93 (1.38, 6.22) | 1.72 (0.82, 3.61) |
| III/IV | 1.48 (0.90, 2.43) | 3.00 (1.41, 6.38) | 0.52 (0.17, 1.66) |
| Education | | | |
| <College grad | 1.35 (0.97, 1.89) | 2.79 (1.42, 5.49) | 1.62 (0.92, 2.84) |
| College grad+ | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Poverty index (SES) | | | |
| ≤200 (low) | 1.22 (0.77, 1.93) | 2.21 (1.06, 4.62) | 0.62 (0.23, 1.71) |
| 201–700 (middle) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| >700 (high) | 1.06 (0.71, 1.57) | 1.07 (0.53, 2.16) | 1.30 (0.72, 2.35) |
| Insurance status | | | |
| Private | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Public/none | 1.51 (0.91, 2.53) | 2.49 (1.17, 5.30) | 1.41 (0.55, 3.61) |
| Smoking status | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Former | 1.14 (0.80, 1.62) | 1.03 (0.53, 2.00) | 1.87 (1.06, 3.32) |
| Current | 0.86 (0.51, 1.46) | 2.91 (1.43, 5.91) | 0.50 (0.16, 1.59) |
| Alcohol, drinks/week | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <7 | 0.72 (0.50, 1.04) | 1.19 (0.60, 2.34) | 0.62 (0.33, 1.14) |
| 7+ | 0.72 (0.44, 1.17) | 1.78 (0.80, 3.97) | 0.67 (0.30, 1.47) |
| Age at menarche, *y* | | | |
| <12 | 1.55 (1.08, 2.23) | 1.68 (0.92, 3.08) | 0.80 (0.42, 1.52) |
| 12+ | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Age at first birth, *y* | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <18 | 2.83 (1.30, 6.14) | 9.49 (2.64, 34.11) | 1.30 (0.32, 5.29) |
| 18+ | 0.99 (0.67, 1.48) | 2.05 (0.82, 5.12) | 0.57 (0.31, 1.05) |

| | TN OR[a] (95% CI) | ER−PR−HER2+ OR[a] (95% CI) | ER/PR+HER2+ OR[a] (95% CI) |
|---|---|---|---|
| No. full-term births | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 1–3 | 0.98 (0.65, 1.45) | 2.28 (0.92, 5.68) | 0.55 (0.30, 1.01) |
| ≥4 | 2.40 (1.24, 4.64) | 2.89 (0.76, 11.03) | 1.25 (0.45, 3.48) |
| Recency of birth, *y* | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| ≤5 | 2.25 (1.16, 4.36) | 5.05 (1.43, 17.86) | 1.09 (0.38, 3.11) |
| >5 | 0.95 (0.64, 1.42) | 2.14 (0.86, 5.34) | 0.52 (0.28, 0.97) |
| Breastfeeding | | | |
| Never (never pg/≤2 weeks) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Ever (>2 weeks) | 0.97 (0.69, 1.36) | 0.95 (0.53, 1.71) | 0.59 (0.33, 1.06) |
| Breastfeeding, months | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <12 | 1.02 (0.70, 1.48) | 1.02 (0.54, 1.93) | 0.79 (0.43, 1.46) |
| 12+ | 0.83 (0.48, 1.43) | 0.50 (0.17, 1.51) | 0.19 (0.04, 0.85) |
| BMI ($kg/m^2$) at interview | | | |
| Under/normal (<25) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Overweight (25.0–29.9) | 1.90 (1.27, 2.85) | 1.94 (1.01, 3.73) | 0.67 (0.33, 1.37) |
| Obese (30+) | 1.89 (1.22, 2.92) | 0.93 (0.42, 2.08) | 0.90 (0.40, 2.02) |
| Physical activity- year before interview | | | |
| <13.54 (<median) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| ≥13.54 (median+) | 1.38 (0.99, 1.92) | 1.08 (0.60, 1.92) | 1.73 (1.00, 3.00) |

[a]OR are weighted, compared to the ER/PR+, HER2− subtype and are adjusted for race, age and stage (race models are adjusted for age and stage; age models are adjusted for race and stage; stage models are adjusted for age and race)

BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; TN, triple negative

**Table 3**

Associations (ORs) between breast cancer triple subtypes (vs. controls) according to patient and tumor characteristics among cases and controls, Atlanta, GA

| | TN OR[a] (95% CI) | ER−PR−HER2+ OR[a] (95% CI) | ER/PR+HER2+ OR[a] (95% CI) | ER/PR+HER2− OR[a] (95% CI) |
|---|---|---|---|---|
| Race | | | | |
| Black | 2.41 (1.81, 3.21) | 1.69 (0.98, 2.92) | 0.85 (0.47, 1.53) | 0.73 (0.56, 0.95) |
| White | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Age at diagnosis, *y* | | | | |
| 20–39 | 1.77 (1.18, 2.64) | 1.17 (0.53, 2.59) | 2.64 (1.11, 6.24) | 0.80 (0.58, 1.12) |
| 40–49 | 1.14 (0.78, 1.65) | 1.27 (0.65, 2.48) | 2.45 (1.12, 5.34) | 1.05 (0.81, 1.37) |
| 50–54 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Education | | | | |
| <College grad | 0.93 (0.69, 1.26) | 2.11 (1.10, 4.05) | 1.13 (0.66, 1.93) | 0.68 (0.54, 0.86) |
| College grad+ | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Poverty index (SES) | | | | |
| ≤200 (low) | 1.57 (1.07, 2.30) | 2.83 (1.46, 5.45) | 0.70 (0.27, 1.83) | 1.06 (0.75, 1.50) |
| 201–700 (middle) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| >700 (high) | 1.62 (1.12, 2.34) | 1.44 (0.72, 2.87) | 1.78 (0.99, 3.18) | 1.22 (0.94, 1.59) |
| Smoking status | | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Former | 1.56 (1.14, 2.14) | 1.51 (0.79, 2.86) | 2.40 (1.39, 4.14) | 1.37 (1.07, 1.75) |
| Current | 0.53 (0.34, 0.82) | 1.89 (0.99, 3.58) | 0.31 (0.10, 0.96) | 0.61 (0.44, 0.85) |
| Alcohol, drinks/week | | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <7 | 1.16 (0.84, 1.59) | 2.09 (1.10, 4.00) | 1.08 (0.61, 1.93) | 1.68 (1.30, 2.17) |
| 7+ | 1.22 (0.79, 1.89) | 2.98 (1.40, 6.35) | 1.29 (0.61, 2.75) | 1.86 (1.34, 2.60) |
| Age at menarche, *y* | | | | |
| <12 | 1.60 (1.17, 2.19) | 1.63 (0.92, 2.88) | 0.93 (0.50, 1.73) | 1.09 (0.84, 1.42) |
| 12+ | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Age at first birth, *y* | | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <18 years | 0.67 (0.39, 1.17) | 2.53 (0.84, 7.68) | 0.32 (0.09, 1.13) | 0.23 (0.12, 0.44) |
| 18+ years | 0.79 (0.55, 1.14) | 1.85 (0.75, 4.55) | 0.53 (0.30, 0.95) | 0.75 (0.57, 1.00) |
| No. full-term births | | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 1–3 | 0.80 (0.55, 1.15) | 2.08 (0.85, 5.10) | 0.50 (0.28, 0.91) | 0.77 (0.58, 1.02) |
| ≥4 | 0.62 (0.36, 1.07) | 0.90 (0.25, 3.23) | 0.53 (0.20, 1.41) | 0.28 (0.17, 0.46) |
| Recency of birth, *y* | | | | |
| Nulliparous | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| ≤5 years | 1.04 (0.62, 1.74) | 2.53 (0.81, 7.94) | 0.62 (0.24, 1.61) | 0.46 (0.27, 0.79) |
| >5 years | 0.72 (0.49, 1.05) | 1.82 (0.73, 4.52) | 0.46 (0.25, 0.85) | 0.74 (0.56, 0.99) |

| | TN OR[a] (95% CI) | ER−PR−HER2+ OR[a] (95% CI) | ER/PR+HER2+ OR[a] (95% CI) | ER/PR+HER2− OR[a] (95% CI) |
|---|---|---|---|---|
| Breastfeeding | | | | |
| Never (never pg/≤2 weeks) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Ever (>2 weeks) | 0.84 (0.62, 1.13) | 0.88 (0.51, 1.52) | 0.57 (0.33, 1.00) | 0.90 (0.72, 1.13) |
| Breastfeeding, months | | | | |
| Never | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| <12 | 0.77 (0.55, 1.08) | 0.77 (0.42, 1.41) | 0.62 (0.34, 1.12) | 0.78 (0.60, 1.01) |
| 12+ | 0.53 (0.32, 0.85) | 0.37 (0.13, 1.08) | 0.12 (0.03, 0.56) | 0.68 (0.48, 0.96) |
| BMI (kg/m$^2$) at interview | | | | |
| Under/normal (<25) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Overweight (25.0–29.9) | 1.11 (0.78, 1.59) | 1.12 (0.60, 2.07) | 0.45 (0.23, 0.90) | 0.58 (0.44, 0.77) |
| Obese (30+) | 1.25 (0.87, 1.79) | 0.72 (0.35, 1.47) | 0.45 (0.22, 0.94) | 0.58 (0.43, 0.78) |
| Physical activity- year before interview | | | | |
| <13.54 (<median) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| ≥13.54 (median+) | 0.73 (0.55, 0.98) | 0.53 (0.31, 0.92) | 0.89 (0.53, 1.50) | 0.57 (0.45, 0.71) |

[a]OR are weighted, compared to controls and are adjusted for race and age (race models are adjusted for age; age models are adjusted for race)

BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; TN, triple negative