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Intrinsic Breast Tumor Subtypes, Race, and Long-Term Survival in the Carolina Breast Cancer Study

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Abstract

Purpose: Previous research identified differences in breast cancer–specific mortality across 4 intrinsic tumor subtypes: luminal A, luminal B, basal-like, and human epidermal growth factor receptor 2 positive/estrogen receptor negative ($HER2^+/ER^-$).

Experimental Design: We used immunohistochemical markers to subtype 1,149 invasive breast cancer patients (518 African American, 631 white) in the Carolina Breast Cancer Study, a population-based study of women diagnosed with breast cancer. Vital status was determined through 2006 using the National Death Index, with median follow-up of 9 years.

Results: Cancer subtypes luminal A, luminal B, basal-like, and $HER2^+/ER^-$ were distributed as 64%, 11%, 11%, and 5% for whites, and 48%, 8%, 22%, and 7% for African Americans, respectively. Breast cancer mortality was higher for participants with $HER2^+/ER^-$ and basal-like breast cancer compared with luminal A and B. African Americans had higher breast cancer–specific mortality than whites, but the effect of race was statistically significant only among women with luminal A breast cancer. However, when compared with the luminal A subtype within racial categories, mortality for participants with basal-like breast cancer was higher among whites (HR = 2.0, 95% CI: 1.2–3.4) than African Americans (HR = 1.5, 95% CI: 1.0–2.4), with the strongest effect seen in postmenopausal white women (HR = 3.9, 95% CI: 1.5–10.0).

Conclusions: Our results confirm the association of basal-like breast cancer with poor prognosis and suggest that basal-like breast cancer is not an inherently more aggressive disease in African American women compared with whites. Additional analyses are needed in populations with known treatment profiles to understand the role of tumor subtypes and race in breast cancer mortality, and in particular our finding that among women with luminal A breast cancer, African Americans have higher mortality than whites. *Clin Cancer Res; 16(24); 6100–10. ©2010 AACR.*

Introduction

Although breast cancer survival has increased substantially over the last 30 years, a large racial disparity remains, with African Americans experiencing higher mortality and shorter survival time than whites (1). The difference is particularly pronounced among women diagnosed before 50 years of age. Prognostic differences among breast tumor subtypes could contribute to the survival disparity, as the subtypes are not equally distributed between race and age groups (2, 3). Breast tumors may be classified using 5 immunohistochemical (IHC) tumor markers: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), HER1, and cytokeratin 5/6 (CK 5/6; refs. 2, 4–8).

As shown in a previous analysis of participants from the Carolina Breast Cancer Study (CBCS), although luminal A (ER^+ or PR^+ and $HER2^-$) is the most common IHC subtype overall, premenopausal African American women have a high prevalence of basal-like breast cancer (ER^-, PR^-, $HER2^-$, and either $HER1^+$ or CK $5/6^+$; ref. 2). There are currently no targeted therapies for the basal-like subtype, which has higher mortality than the most common subtype, luminal A. Patients with luminal A tumors can be treated with estrogen receptor inhibitors such as tamoxifen or aromatase inhibitors. Tumors expressing HER2 but not ER or PR ($HER2^+/ER^-$ subtype) were associated with the worst survival in the CBCS (2), although the development

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Translational Relevance

Previous research identified differences in breast cancer–specific mortality across 4 intrinsic tumor subtypes: luminal A, luminal B, basal-like, and human epidermal growth factor receptor 2 positive/estrogen receptor negative ($HER2^+/ER^-$). Using data from a population-based study, we observed that African American women had higher breast cancer mortality than whites, but the effect of race was statistically significant only for women with luminal A breast cancer, a subtype with defined therapeutic targets. Race-stratified estimates for the effect of intrinsic subtype on mortality indicated that basal-like breast cancer was not inherently more aggressive in African American women. For smaller tumors, participants with basal-like breast cancer showed greater lymph node involvement than luminal A, whereas the reverse was true for larger tumors. Heterogeneity was observed in the relationship between tumor subtypes and long-term survival, with crossover effects after 5 years of follow-up.

of trastuzamab and other HER2-targeted agents to treat $HER2^+$ tumors has since improved prognosis. Carey et al. (2) found that the $HER2^+/ER^-$ subtype was fairly rare in all age and race groups, comprising less than 10% of cancers in each subpopulation.

Other studies have replicated the finding that basal-like breast cancer is more common in young African Americans (3, 9, 10) and younger women in Africa (11, 12) compared with European American, European, and Asian women (3–8, 13–21). In addition, nearly all studies agree that basal-like and $HER2^+/ER^-$ tumors have poorer prognoses than luminal A, regardless of the source population (3, 4, 6, 7, 10, 15–24). However, many of these studies used only 3 IHC markers (ER, PR, and HER2) to classify subtypes, thus combining all basal-like and unclassified cancers into a single "triple-negative" subtype. As several studies have corroborated that these 2 subtypes are biologically and prognostically distinct (4, 7, 13, 15, 22, 23), subtype misclassification could substantially bias effect estimates.

Despite the abundance of studies on this topic, only the original CBCS study (2), an Atlanta-based case–control study (3), and a California-based cancer registry study (20) have compared IHC subtype frequency distributions in multiracial, population-based samples. Of those, only 1 study presented racial differences in survival by IHC subtype (3), albeit with ER, PR, and HER2 markers only, and none have examined survival differences by race and menopausal status. For this reason, an updated analysis of the CBCS data, which includes an additional 4 years of follow-up and nearly 1,000 more participants enrolled during phase II of the study, was conducted to help elucidate the relationship between race, menopausal status, breast cancer IHC subtype, and survival. Recognizing that the effect of tumor markers may vary over time (25, 26), we conducted these analyses using flexible models in addition to standard statistical techniques.

Materials and Methods

Study population

The CBCS is a population-based, case–control study conducted in 24 counties of North Carolina (NC). Invasive breast cancer patients diagnosed from 1993 to 1996 (phase I) and 1996 to 2001 (phase II) were identified using rapid case ascertainment in cooperation with the NC Central Cancer Registry. Survival results were previously published for phase I (2). For both phases of the CBCS, participants were selected using weighted sampling probabilities for each race and age subgroup to ensure approximately equal numbers of pre- and postmenopausal African Americans, and pre- and postmenopausal whites (27). Overall, 1,808 women with breast cancer were enrolled, 1,149 of which had tumor tissue available for subtype analysis. This included 238 premenopausal African Americans, 280 postmenopausal African Americans, 323 premenopausal whites, and 308 postmenopausal whites.

Race was determined by self-report, with all individuals categorized as either African American or white. Less than 2% of participants self-identified as multiracial, Hispanic or other race/ethnicities and were classified as white for statistical analyses. Information on menopausal status and other potential covariates were collected during in-home interviews (9). Women younger than 50 years were considered postmenopausal if they had undergone natural menopause, bilateral oophorectomy, or irradiation to the ovaries, whereas women older than 50 years were assigned a menopausal status on the basis of menstrual cessation (2). Tumor size, axillary lymph node status, and stage at diagnosis were abstracted from medical records. ER and PR status were also abstracted from the medical record for approximately 80% of the participants (2).

IHC subtypes

The collected tumor tissue was sectioned and stained for a panel of IHC markers at the Immunohistochemistry Core Laboratory at the University of North Carolina. Using medical records and markers modeling gene expression profiles of HER2, HER1, CK 5/6, and, if necessary, ER and PR, IHC subtypes were assigned as follows: luminal A (ER^+ and/or PR^+, $HER2^-$), luminal B (ER^+ and/or PR^+, $HER2^+$), $HER2^+/ER^-$ (ER^-, PR^-, $HER2^+$), basal-like (ER^-, PR^-, $HER2^-$, $HER1^+$ and/or CK $5/6^+$), or unclassified (negative for all 5 markers). A more detailed description of the development of these IHC markers as proxies for gene expression analysis can be found elsewhere (2, 28, 29).

Outcome assessment

Participants were matched to National Death Index (NDI)-recorded deaths occurring before January 1, 2007. True matches were determined using weighted probabilistic scores and *a priori* matching cutoffs to establish a maximum of 1 match per individual. The NDI also provided date of

death and cause of death for each expired individual. The sensitivity of NDI search is estimated to be 98% and specificity approximately 100% (30). Using International Classification of Disease (ICD) codes, we categorized cause of death as either breast cancer–specific (ICD-9 174.9 or ICD-10 50.9) or other cause of death based on the first listed primary cause of death.

Statistical analysis

We first did descriptive analyses of age, menopausal status, stage, IHC subtype, hormone receptor status, vital status, and cause of death for each racial group. Frequency distributions were adjusted for the sampling probabilities used to identify the appropriate proportion of eligible participants in each race and age group (phase I: 100% of African Americans < 50, 75% of African Americans $\geq$ 50, 67% of whites < 50, and 20% of whites $\geq$ 50; phase II: 100% of African Americans, 50% of whites < 50, and 20% of whites $\geq$ 50).

After censoring living individuals at December 31, 2006, we modeled breast cancer–specific and overall survival curves by race, menopausal status, IHC subtypes, and ER, PR, and HER2 status using the Kaplan–Meier method. For the breast cancer–specific analysis, we censored individuals who died of causes other than breast cancer at time of death. We conducted additional analyses combining the luminal A and B subtypes and excluding unclassified individuals. Survival curves were compared using a log-rank test, and log cumulative hazards plots were examined for possible deviation from proportional hazards assumptions.

We then conducted survival comparisons for race, menopausal status, IHC subtype, and hormone receptor status using Cox proportional hazards models, regardless of whether proportional hazards assumptions were met. We selected age, race, and date of diagnosis as covariates with the aid of a directed acyclic graph (31, 32), a technique that uses *a priori* knowledge of the relationship between the main exposure, possible covariates, and survival to determine the set of necessary adjustment variables. HRs were adjusted for age and race because of their known associations with both IHC subtype (2, 9) and survival. Date of diagnosis was included in the models as a continuous variable to adjust for secular changes in breast cancer diagnosis, assessment, and treatment over the enrollment period.

As there is evidence that IHC subtype can be assessed in precancerous *in situ* lesions (9), stage at diagnosis could represent an intervening variable between IHC subtype and breast cancer mortality. Therefore, adjusting for stage at diagnosis could potentially bias HR estimates (33). However, stage at diagnosis also serves as a proxy for treatment, and analyses of breast cancer survival commonly adjust for stage. Thus, we present models adjusted and not adjusted for stage at diagnosis in addition to age, race, and date of diagnosis. We excluded a number of potential confounding variables, such as socioeconomic status (income, education) and body size (body mass index, waist–hip ratio), because we only had information on baseline measures and we felt that adjusting for non–time-varying estimates would be insufficient and potentially biasing if they were affected by a woman's breast cancer diagnosis. No treatment information was available for participants in the CBCS.

After conducting these survival analyses in the entire study population using both adjustment sets (i.e., race, age, and date of diagnosis or race, age, date of diagnosis and stage of disease), we then completed the same analyses within racial strata using both adjustment sets (excluding race) and within strata defined by race and menopausal status, adjusting for age and enrollment year only. We also estimated HRs for the effect of stage, tumor size (diameter), lymph node status, or presence of metastatic disease on mortality within each subtype strata to better evaluate the interaction between stage and IHC subtype. These models were adjusted for race, age, and date of diagnosis. In addition, the relationship of axillary lymph node status (percent of participants exhibiting lymph nodes positive for malignancy, average number of positive nodes, and percent of positive nodes for each participant) and tumor size ($\leq$2 cm, 2–5 cm, >5 cm) was examined using chi-square and Wilcoxon rank-sum tests.

To assess departure from proportional hazards assumptions, we examined 1-, 2-, or 3-degree polynomial time by exposure interaction terms. We also modeled the change in the HR over time using restricted cubic splines (34), with knots at the 5th, 35th, 65th, and 95th percentiles. We examined the polynomial and spline models for patterns in how the HRs changed over time to identify meaningful cutoffs for appropriate time-stratified proportional hazards models. All analyses were conducted using SAS version 9.2 (SAS Institute) and all figures were created using R 2.9.0 (The R Foundation for Statistical Computing, http://www.r-project.org/foundation).

Results

Population characteristics

Characteristics of study participants are presented in Supplementary Table 1. African American participants were younger than white participants, more likely to be premenopausal (41% vs. 32%), diagnosed at later stage (65% vs. 48% at stage II or higher), and have ER^- (51% vs. 32%) or PR^- (55% vs. 36%) disease. The proportion of participants with HER2-positive disease was similar in African Americans and whites (15% and 18%, respectively). The distribution of "intrinsic" IHC subtypes according to race and menopausal status indicated that although luminal A was the most common subtype of breast cancer overall (57%, 67%, 40%, and 55% of premenopausal white, postmenopausal white, premenopausal African American and postmenopausal African American women, respectively), premenopausal African American women exhibited a higher percentage of basal-like tumors (29%) compared with premenopausal whites (15%), postmenopausal whites (10%), and postmenopausal African Americans (17%).

Survival statistics

Median follow-up time was 9.0 years (range 0.2–13.7 years). There were 347 total deaths, with 239 due to breast cancer. Time plots for a 5% random sample of participants can be seen in the supplement (Supplementary Figs. 1 and 2). We estimated the 5-year risk of death due to any cause as 17% and the 5-year risk of death due to breast cancer as 14% (Kaplan–Meier curve and table found in Supplementary Fig. 3). African American women were more likely to die of breast cancer than whites, with 17% 5-year breast cancer–specific mortality, versus 11% for whites (Supplementary Table 2). Participants with luminal A tumors had the lowest 5-year breast cancer–specific mortality (9%), followed by luminal B (12%). Women with $HER2^+/ER^-$ tumors exhibited the highest breast cancer–specific mortality, with 26% deaths within 5 years of diagnosis, followed by basal-like and unclassified, with 24% and 18% deaths, respectively.

Survival statistics and HRs for breast cancer–specific mortality for all study participants combined are presented in Supplementary Table 3. Statistically significant differences in breast cancer–specific mortality were observed according to race, menopausal status, IHC subtype, ER, PR, and HER2 status (P value for log-rank test <0.05). African Americans had higher breast cancer–specific mortality than whites (HR = 1.7, 95% CI: 1.3–2.2), even after adjustment for stage at diagnosis (HR = 1.7, 95% CI: 1.3–2.2), or stage and IHC subtype (HR = 1.6, 95% CI: 1.2–2.0). Analyzed as single markers, participants with $HER2^+$ tumors did not have a worse prognosis than participants with ER^- or PR^- tumors (HR = 1.5, 95% CI: 1.1–2.0; HR = 1.6, 95% CI: 1.2–2.1; and HR = 1.7, 95% CI: 1.3–2.2 for the effect of HER2, ER, and PR, respectively), particularly after adjusting for stage at diagnosis (HR = 1.2, 95% CI: 0.9–1.7; HR = 1.4, 95% CI: 1.1–1.8; and HR = 1.5, 95% CI: 1.1–1.9). However, when these tumor markers were considered jointly and incorporated into the 5-marker scheme defining "intrinsic" IHC subtypes, a different pattern emerged. Among all participants, women with $HER2^+/ER^-$ disease had the highest risk of death (HR = 2.3, 95% CI: 1.5–3.6), followed by basal-like (HR = 1.7, 95% CI: 1.2–2.4). Survival statistics and HRs were also estimated for overall (all-cause) mortality (data not shown). HRs were more precise but slightly attenuated using overall (all-cause) mortality as the outcome (data not shown).

Subtype and race

Race-stratified Kaplan–Meier plots and HRs for the effect of race (African American vs. white) for each IHC subtype are presented in Figure 1. Although African American participants showed higher breast cancer–specific mortality than whites for each IHC subtype, the effect of race was statistically significant only among women with luminal A breast cancer. Adjustment for stage at diagnosis did not substantially change the magnitude of the HRs, with the exception of the $HER2^+/ER^-$ subtype, which showed a stronger association with race after adjustment for stage.

Race-stratified survival results are presented in Table 1. HRs for menopausal status, ER, PR, and HER2 were fairly similar for African Americans and whites, as were most of the race-stratified IHC subtype effect estimates. HRs for basal-like breast cancer compared with luminal A were slightly higher among whites than African Americans. Adjustment for stage at diagnosis resulted in HRs of similar direction and magnitude for race and menopausal status but resulted in attenuated effect estimates for IHC subtype and hormone receptor status. The most extreme example was among whites, where the HR for $HER2^+/ER^-$ versus luminal A breast cancer was 2.4 when adjusted for age and date of diagnosis, but only 1.4 when adjusted for age, date of diagnosis, and stage.

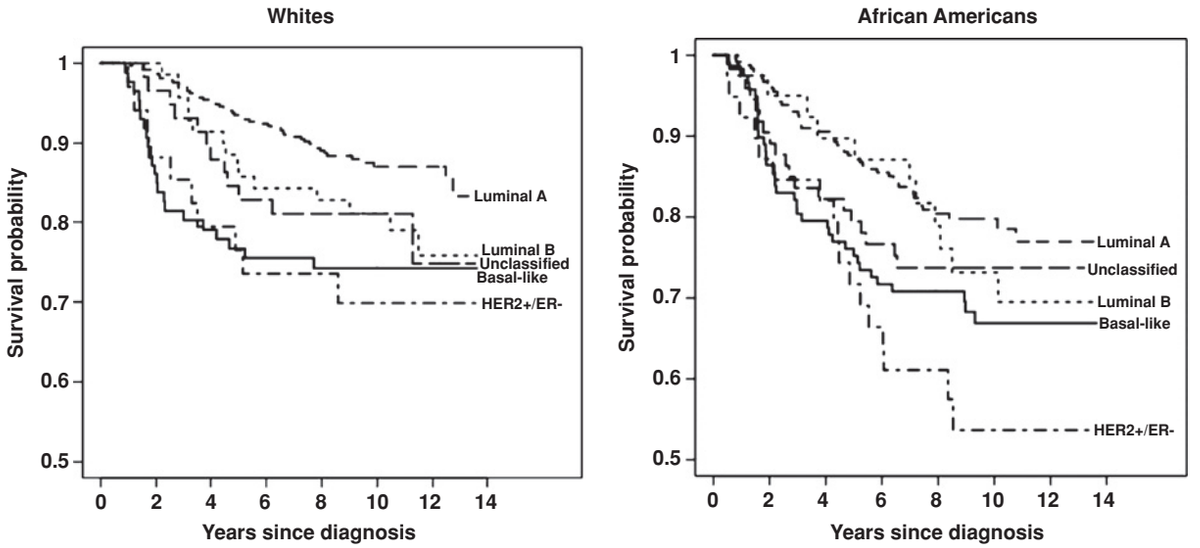
Subtype, race, and menopausal status

HRs stratified according to race and menopausal status are presented in Table 2. HRs were imprecise owing to small sample size within strata. For the IHC subtype analysis, HRs were highest among postmenopausal whites with either $HER2^+/ER^-$ or basal-like breast cancer, compared with luminal A. The $HER2^+/ER^-$ subtype consistently had the highest HR for each participant subgroup. Importantly, HRs for basal-like breast cancer were slightly higher among premenopausal white compared with premenopausal African American participants and higher among postmenopausal white compared with postmenopausal African American participants. HRs for PR^- versus PR^+, and $HER2^+$ versus $HER2^-$ were highest for postmenopausal whites, whereas the HR for ER^- versus ER^+ was highest among postmenopausal African American participants. When these models were additionally adjusted for stage at diagnosis, effect estimates were similar but attenuated.

Flexible modeling techniques

Results from polynomial time interaction models indicated that the proportional hazards assumption was valid when comparing breast cancer–specific mortality by menopausal status ($P = 0.8$) or HER status ($P = 0.4$), but the assumption was violated when comparing race, ER status, PR status, IHC subtype, and combined IHC subtype ($P \leq 0.01$ for each test; data not shown). For ER status, PR status, and IHC subtype, a 1-degree polynomial time interaction provided the best model fit, but race and combined subtype required cubic time interaction terms.

After determining the best fit model for each exposure, we plotted the data to investigate how the HR changed over time for each analysis. For example, the best polynomial model for the subtype analysis was a 1-degree time interaction model, so this appears as 4 diagonal lines, 1 for each subtype comparison (vs. luminal A). Spline models were also plotted for each exposure. Plots showing the best fitting polynomial and spline models for breast cancer–specific mortality and subtype are presented in Supplementary Figure 4. On the basis of these plots, we concluded that stratifying HR estimates into 2 time periods, 0 to 5 years and greater than 5 years, would be an appropriate way to capture heterogeneity in the HRs over time without



Hazard ratios for the effect of race on breast cancer–specific mortality		
	HR for race (AA vs. white) adjusted for age at diagnosis and date of diagnosis (95% CI)	HR for race (AA vs. white) adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)
Luminal A	1.9 (1.3–2.8)	1.9 (1.3–2.9)
Luminal B	1.4 (0.6–3.1)	1.3 (0.6–3.0)
Basal-like	1.2 (0.7–2.1)	1.3 (0.8–2.3)
HER2+/ER-	1.7 (0.8–3.8)	2.2 (1.0–5.1)
Unclassified	1.4 (0.7–2.9)	1.2 (0.6–2.6)

Fig. 1. Race-stratified Kaplan–Meier plots and race effect estimates for breast cancer–specific mortality by immunohistochemical subtype in the Carolina Breast Cancer Study, 1993–2006. AA, African Americans.

sacrificing interpretability of the effect estimates. Five years of follow-up was the point where most HRs approached the null or changed directions for both the polynomial and spline models.

Time-stratified estimates for breast cancer–specific mortality are provided in Table 3. Single estimates are provided for models that did not violate the proportional hazards assumptions (menopausal status, HER2 status). Effect estimates for basal-like and unclassified breast cancer were greater than 1 in the first 5 years and less than 1 after 5 years of follow-up. The HR for $HER2^+/ER^-$ was higher in the first 5 years but remained greater than 1, whereas the HR for luminal B increased slightly with time. HRs for ER and PR were greater than 1 during the first 5 years, but dropped to 1.0 or less than 1.0 for the second time period. HRs for African American race were greater than 1 and statistically significant for both time periods. HRs adjusted for stage showed similar patterns but were closer to the null (data not shown).

Subtypes and stage

HRs for stage at diagnosis, tumor size, number of positive axillary lymph nodes, and presence of metastatic disease, overall and stratified by IHC subtype, are presented in Table 4. For all subtypes, later stage at diagnosis, larger tumor size, increasing number of axillary lymph nodes, and presence of metastatic disease resulted in higher mortality. Trends were increasing and monotonic, but differed slightly between subtypes. For basal-like tumors, the HRs for a tumor measuring 2 to 5 cm versus less than 2 cm was 1.5 (95% CI: 0.8–2.9), whereas for luminal A, luminal B, and $HER2^+/ER^-$, the HRs were greater than 2.0. For larger tumors (>5 cm), basal-like and luminal B tumors exhibited lower HRs than luminal A and $HER2^+/ER^-$. It should be noted that CIs were wide and overlapped across IHC subtypes.

Subtypes and lymph node status

To further explore the relationship between IHC subtypes, tumor size, and variables related to axillary lymph node status, additional analyses were conducted. As presented in Table 5, a stronger association was observed for each lymph node variable and increasing tumor size for luminal A, luminal B, $HER2^+/ER^-$, and unclassified, but not basal-like tumors. Additional analyses were conducted comparing the distribution of lymph node variables in

Table 1. Hazard ratios for breast cancer–specific mortality, stratified by race

	White ($n = 631$)		African American ($n = 518$)	
	HR adjusted for age at diagnosis and date of diagnosis (95% CI)	HR adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)	HR adjusted for age at diagnosis and date of diagnosis (95% CI)	HR adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)
Menopausal status				
Premenopausal	1.00	1.00	1.00	1.00
Postmenopausal	0.6 (0.3–1.0)	0.6 (0.3–1.0)	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Subtype				
Luminal A	1.00	1.00	1.00	1.00
Luminal B	1.6 (0.9–2.9)	1.5 (0.8–2.7)	1.3 (0.6–2.4)	1.2 (0.6–2.2)
Basal-like	2.0 (1.2–3.4)	1.7 (1.0–2.9)	1.5 (1.0–2.4)	1.4 (0.9–2.1)
$HER2^+/ER^-$	2.4 (1.2–4.7)	1.4 (0.7–2.9)	2.3 (1.3–4.0)	1.8 (1.0–3.1)
Unclassified	1.6 (0.9–3.1)	1.6 (0.9–3.1)	1.3 (0.8–2.3)	1.2 (0.7–2.0)
Subtype combined				
Luminal A or B	1.00	1.00	1.00	1.00
Basal-like	1.8 (1.1–3.0)	1.6 (0.9–2.6)	1.5 (1.0–2.2)	1.3 (0.9–2.0)
$HER2^+/ER^-$	2.1 (1.1–4.2)	1.3 (0.6–2.6)	2.2 (1.3–3.7)	1.7 (1.0–2.9)
ER status				
ER^+	1.00	1.00	1.00	1.00
ER^-	1.5 (1.0–2.2)	1.3 (0.9–1.9)	1.7 (1.2–2.5)	1.5 (1.0–2.2)
PR status				
PR^+	1.00	1.00	1.00	1.00
PR^-	1.8 (1.2–2.7)	1.6 (1.1–2.4)	1.6 (1.1–2.3)	1.4 (0.9–2.0)
HER2 status				
$HER2^-$	1.00	1.00	1.00	1.00
$HER2^+$	1.5 (0.9–2.3)	1.2 (0.7–1.9)	1.4 (0.9–2.2)	1.3 (0.8–1.9)

basal-like versus luminal A participants. For tumors 2 cm or less, participants with basal-like breast cancer had a higher percentage of lymph node–positive tumors ($P = 0.04$), more positive lymph nodes per participant ($P = 0.03$), and a higher percentage of positive lymph nodes per participant ($P = 0.01$) than women with luminal A breast cancer. However, in larger tumors, the reverse was true. For tumors 2 to 5 cm or greater, each of the lymph node variables was higher among luminal A compared with basal-like participants ($P = 0.02$ for all 3 tests of association).

Discussion

The prognostic significance of "intrinsic" IHC breast cancer subtypes was determined using data from the Carolina Breast Cancer Study, a population-based epidemiologic study of African American and white women in North Carolina with a median follow-up time of 9 years. We evaluated how hazard ratios for IHC subtypes were modified by race, menopausal status, and duration of follow-up and also examined the contributions of tumor size, lymph node status, and presence of metastatic disease. HRs for race, IHC subtypes, ER, PR, HER2 status, and stage at diagnosis were consistent with previously reported data from other recent studies (3, 4, 6, 7, 10, 13, 15–26). Participants with $HER2^+/ER^-$ breast cancer had the worst prognosis, followed by basal-like. The CBCS was conducted prior to the introduction of trastuzumab and other HER2-targeted agents to treat $HER2^+$ tumors.

Race-stratified analyses in the CBCS indicated that breast cancer mortality was higher for African American women compared with white women, even after adjustment for stage at diagnosis and "intrinsic" IHC subtype. However, the effect of race was statistically significant only among women with luminal A breast cancer. HRs for basal-like breast cancer compared with luminal A were slightly higher in white participants compared with African Americans, and this was true among pre- as well as postmenopausal women. Thus, basal-like breast cancer does not appear to be inherently more aggressive in African American women compared with whites in the CBCS. Racial differences in breast cancer mortality are likely to be driven by differences in treatment and access to care (as represented by income or education) for luminal A and other subtypes of breast cancer (35), in addition to the higher prevalence of basal-like breast cancer among younger African American women.

Although CBCS results generally agree with those reported by Lund et al. (3), our analyses provide more precise estimates with additional information about the

Table 2. Hazard ratios for breast cancer–specific mortality, stratified by race and menopausal status and adjusted for age at diagnosis and date of diagnosis

	White		African American	
	Premenopausal ($n = 323$)	Postmenopausal ($n = 308$)	Premenopausal ($n = 238$)	Postmenopausal ($n = 280$)
Subtype				
Luminal A	1.00	1.00	1.00	1.00
Luminal B	1.2 (0.6–2.5)	2.9 (1.0–8.4)	1.2 (0.5–2.9)	1.3 (0.5–3.6)
Basal-like	1.8 (1.0–3.4)	3.9 (1.5–10.0)	1.3 (0.8–2.3)	1.9 (0.9–3.8)
$HER2^+/ER^-$	2.1 (0.9–5.0)	4.3 (1.4–13.6)	1.9 (0.9–4.2)	3.1 (1.3–7.2)
Unclassified	1.4 (0.7–3.0)	2.1 (0.6–7.4)	1.0 (0.5–2.0)	1.9 (0.8–4.3)
Subtype combined				
Luminal A or B	1.00	1.00	1.00	1.00
Basal-like	1.8 (1.0–3.2)	3.0 (1.2–7.4)	1.3 (0.8–2.2)	1.8 (0.9–3.6)
$HER2^+/ER^-$	2.0 (0.9–4.8)	3.4 (1.1–10.3)	1.9 (0.9–4.0)	3.0 (1.3–6.9)
ER status				
ER^+	1.00	1.00	1.00	1.00
ER^-	1.4 (0.9–2.2)	2.1 (1.0–4.2)	1.3 (0.8–2.2)	2.3 (1.3–3.9)
PR status				
PR^+	1.00	1.00	1.00	1.00
PR^-	1.9 (1.2–3.0)	2.1 (1.0–4.2)	1.4 (0.9–2.3)	1.9 (1.1–3.4)
HER2 status				
$HER2^-$	1.00	1.00	1.00	1.00
$HER2^+$	1.2 (0.7–2.1)	2.3 (1.1–5.1)	1.4 (0.8–2.5)	1.5 (0.8–2.9)

relative prognostic importance of each IHC subtype within racial strata, and we were able to provide separate estimates for basal-like and unclassified tumors. Classical prognostic factors, such as stage at diagnosis, tumor size, number of affected lymph nodes, and presence of metastases, were predictive of mortality across all IHC subtypes. As reported in previous studies (14, 36), we observed a somewhat attenuated relationship between tumor size and survival for basal-like breast cancer, particularly when comparing HRs across IHC subtypes for tumors 2 to 5 cm or greater in size. For tumors of 2 to 5 cm or greater, only 41% of basal-like breast tumors exhibited positive axillary lymph nodes, a lower percentage than for other IHC subtypes (range 47%–61%). Lower levels of lymph node metastasis could possibly contribute to the superior survival seen for patients with larger basal-like breast tumors compared with patients diagnosed with other subtypes of similar size. Conversely, higher levels of lymph node metastasis in smaller basal-like tumors could contribute to poor prognosis in this group of patients. Because stage at diagnosis was predictive of mortality for each IHC subtype, and subtype was predictive of mortality with and without adjustment for stage, we deduce that both IHC subtype and stage affect prognosis and need to be evaluated together in the clinical setting.

One debatable issue is whether breast cancer–specific or all-cause mortality should be the main outcome of interest. We chose to focus on breast cancer–specific mortality as the main outcome because we were interested in evaluating the effects of specific breast tumor–related markers on survival time. However, as misclassification could have occurred if a death was breast cancer–related, but not primarily due to breast cancer (e.g., heart disease related to chemotherapy), or if the physician filling out the death certificate misattributed cause of death (e.g., stating that death was due to lung cancer instead of breast cancer metastasized to the lung), we conducted analyses using both outcomes. If most of the causes of death were correctly attributed, we would expect to observe weaker but more precise estimates for all-cause mortality than for breast cancer–specific mortality. Because this pattern was observed in our data, we conclude that valid inferences can be drawn on the basis of breast cancer–specific mortality.

Statistical analyses using flexible modeling techniques for time-to-event data showed that HRs for IHC subtypes varied over time. Interestingly, for basal-like and unclassified tumors, the time-stratified effect estimates were on the opposite sides of the null. This suggests that individuals who were triple negative for ER, PR, and HER2 (which includes basal-like, claudin-low, and unclassified tumors) had higher mortality initially, when compared with participants with luminal A breast cancer, but lower mortality once they survived the first 5 years. Similar findings were reported by Dent et al. (36, 37) and Tischkowitz et al. (38). With respect to breast cancer recurrence, several studies have shown high risk of early relapse among hormone receptor–negative and triple-negative breast cancer patients, and a more constant rate of relapse for hormone receptor–positive disease (39).

Table 3. Time-stratified hazard ratios, breast cancer–specific mortality adjusted for race, age at diagnosis, and date of diagnosis

	Breast cancer–specific, time-stratified HR (95% CI)	
	Years 0–5	**Years > 5**
Race		
White	1.00	1.00
African American	1.6 (1.2–2.3)	1.9 (1.2–3.0)
Menopause		
Premenopausal	1.00	
Postmenopausal	0.8 (0.6–1.1)[a]	
Subtypes		
Luminal A	1.00	1.00
Luminal B	1.3 (0.7–2.5)	1.5 (0.8–2.8)
Basal	2.7 (1.8–4.0)	0.6 (0.3–1.3)
$HER2^+/ER^-$	2.9 (1.7–5.0)	1.6 (0.8–3.5)
Unclassified	1.9 (1.2–3.2)	0.8 (0.3–1.8)
Combined subtypes		
Luminal A and B	1.00	1.00
Basal	2.5 (1.7–3.7)	0.6 (0.3–1.1)
$HER2^+/ER^-$	2.8 (1.6–4.6)	1.5 (0.7–3.2)
ER status		
ER^+	1.00	1.00
ER^-	2.5 (1.8–3.5)	0.7 (0.4–1.1)
PR status		
PR^+	1.00	1.00
PR^-	2.2 (1.6–3.1)	1.0 (0.6–1.6)
HER2 status		
$HER2^-$	1.00	
$HER2^+$	1.4 (1.0–1.8)[a]	

[a]Single estimate given because proportional hazards assumption was not violated.

Some of the crossover effect may be due to the fact that only surviving women in each stratum are included when estimating effects for later time periods (40).

Over 20 years ago, Gore et al. (41) reported nonproportional hazards for breast in relation to menopausal status, nodal status, tumor size, and other clinical variables, and recommended a stepwise analysis of breast cancer survival in 5-year increments. Although the 5-year cutoffs is somewhat arbitrary, statistical tests of proportional hazards assumptions using CBCS data indicated deviations from a constant HR. We used graphs of the survival functions, polynomial models, and spline models to select 5 years of follow-up as the optimal cutoffs for time stratification. Choosing defined cutoff for time stratification allows for a much simpler interpretation of hazard functions than would be possible with a polynomial or spline model, but still allows for heterogeneity in HRs over time (25, 26, 34). Regardless of the exact stratification point, we feel strongly that time-to-event analyses should carefully evaluate proportional hazards assumptions and be open to exploring more flexible models, because such methods may reveal information about the nature of exposure–outcome relationship that cannot be captured using standard techniques. The fact that HRs for IHC subtypes vary over time could have important policy implications in terms of monitoring breast cancer survivors.

Our study has several limitations. The differences we observe by subtype and race may be due to unobserved treatment differences by race. In addition, there is the potential for misclassification of 1 or more covariates. As the IHC tumor markers are proxies for gene expression profiling, there may have been some misclassification of intrinsic breast cancer subtype. Further misclassification may have occurred if medical record reports of ER and PR status or disease stage were inaccurate, although previous exploration of this issue among CBCS participants revealed that IHC cutoffs for receptor positivity were reasonably standardized across all included laboratories (42, 43). Although some causes of death may have been misattributed, validation studies showed the NDI to be highly accurate (44, 45), indicating that misclassification should not have substantially biased our findings.

Although all participants had complete data for race, age, and date of diagnosis, several had missing data for stage at

Table 4. Hazard ratios for clinical characteristics according to tumor subtype, breast cancer–specific mortality, adjusted for race, age at diagnosis, and date of diagnosis

	All (n = 1,149)	Basal-like (n = 205)	Luminal A (n = 625)	Luminal B (n = 112)	HER2$^+$/ER$^-$ (n = 73)	Unclassified (n = 134)
Stage						
Stage I	1.00	1.00	1.00	1.00	1.00	1.00
Stage II or III	2.9 (2.0–4.1)	3.6 (1.4–9.1)	3.0 (1.8–5.0)	2.6 (0.9–7.6)	3.6 (0.8–15.8)	1.3 (0.6–2.9)
Stage IV	12.7 (7.4–21.7)	6.4 (1.5–27.0)	18.9 (7.8–46.0)	11.0 (1.8–68.6)	14.0 (2.5–77.5)	13.1 (3.8–45.8)
Tumor size						
≤2 cm	1.00	1.00	1.00	1.00	1.00	1.00
>2–5 cm	2.2 (1.7–3.1)	1.5 (0.8–2.9)	2.5 (1.6–4.0)	2.0 (0.8–4.9)	2.7 (0.8–9.6)	1.8 (0.8–4.1)
>5 cm	3.9 (2.7–5.9)	3.2 (1.5–7.1)	5.3 (2.9–9.8)	3.3 (1.0–11.5)	9.4 (2.2–40.1)	1.0 (0.3–3.7)
Number of lymph nodes positive for malignancy						
None	1.00	1.00	1.00	1.00	1.00	1.00
1—2	2.0 (1.4–3.8)	2.7 (1.4–5.4)	2.2 (1.2–3.9)	1.6 (0.5–5.6)	2.0 (0.5–7.3)	1.0 (0.3–3.6)
3—5	3.7 (2.5–5.4)	6.4 (2.6–15.5)	4.9 (2.7–8.7)	2.4 (0.7–8.3)	2.5 (0.9–7.3)	1.8 (0.6–5.7)
≥6	5.4 (3.9–7.5)	7.2 (3.7–14.2)	7.7 (4.5–13.0)	5.4 (1.9–14.7)	4.7 (1.6–14.4)	1.9 (0.7–4.9)
Metastasis						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	5.8 (3.7–9.2)	2.2 (0.7–7.2)	8.9 (4.0–19.4)	5.2 (1.1–25.3)	4.5 (1.6–12.7)	11.3 (3.7–34.9)

diagnosis, and 659 otherwise eligible individuals were excluded entirely because of missing IHC subtype information. Analyses comparing participants with and without IHC subtype information showed that the 2 groups were very similar in terms of age, menopausal status, ER and PR status, and vital status, but those with missing subtype information were more likely to have HER2$^-$ disease, lower stage at diagnosis, smaller tumors, fewer positive lymph nodes, and were less likely to have died from their breast cancer. Because stage at diagnosis and HER status, in particular, have strong effects on mortality, excluding these individuals may have biased our results. However, this bias

Table 5. Axillary lymph node variables stratified by tumor size, according to breast tumor subtype

	Basal-like (n = 199)	Luminal A (n = 608)	Luminal B (n = 111)	HER2$^+$/ER$^-$ (n = 69)	Unclassified (n = 132)
Lymph node status, % positive tumors (n)					
≤2 cm	30 (70)	19 (329)	35 (57)	23 (22)	21 (63)
>2–5 cm	41 (106)	54 (228)	61 (44)	59 (37)	47 (51)
>5 cm	57 (21)	79 (48)	86 (7)	100 (10)	56 (18)
P value[a]	0.07	<0.0001	0.004	0.0002	0.002
Number of positive lymph nodes, mean (median)					
≤2 cm	1.4 (0)	0.7 (0)	1.4 (0)	0.5 (0)	1.3 (0)
>2–5 cm	1.8 (0)	2.2 (1.0)	3.1 (1.0)	3.2 (1.0)	2.5 (0)
>5 cm	4.0 (1.0)	5.4 (2.0)	7.6 (4.0)	6.3 (6.0)	4.1 (1.0)
P value[b]	0.04	<0.0001	0.001	<0.0001	0.002
% positive lymph nodes, mean (median)					
≤2 cm	13% (0)	5% (0)	13% (0)	5% (0)	10% (0)
>2–5 cm	14% (0)	19% (7%)	19% (10%)	19% (11%)	22% (4%)
>5 cm	24% (8%)	34% (18%)	46% (54%)	47% (42%)	29% (7%)
P value[b]	0.17	<0.0001	0.005	<0.0001	0.007

[a]Chi-square test (%) comparing categories of tumor size.
[b]Wilcoxon rank-sum test (medians) comparing categories of tumor size.

is likely toward the null because patients with $HER2^-$ and/or lower stage disease are more likely to have luminal A disease, thus removing patients with longer survival times from the referent group for HR estimation. Thus, differences in survival between patients with luminal A compared with the other IHC subtypes may be even greater than observed in our study.

Limited follow-up information in the CBCS makes it impossible to examine racial disparities in access to care and associated mortality differences or to do analyses using the shorter endpoint of breast cancer recurrence. Although this was by far the largest multiracial study of breast cancer IHC subtypes and survival time, the sample size was still not large enough to produce precise effect estimates in subgroups defined by menopausal status and race. Therefore, we believe that additional analyses are needed in other equally diverse populations with known treatment profiles to more fully understand the role of intrinsic subtypes and race in breast cancer mortality.

Our study had several strengths. The study population was a large, population-based sample, with sampling probabilities used to obtain unique diversity by race and age at diagnosis. The population-based design facilitated ascertainment of a full spectrum of disease stages, which is often not available in clinical trial–based samples. Another strength was that each participant was given an extensive home interview and asked to provide medical records and tumor samples. This provided us with detailed information on relevant covariates and allowed us to conduct IHC analyses to assess cancer subtypes. Finally, because participant follow-up began just after diagnosis and continued for an extended period of time using a reliable data resource, there was minimal loss to follow-up.

In conclusion, long-term survival analysis of CBCS participants confirms the association of basal-like breast cancer with poor prognosis. Although our data show a higher prevalence of basal-like breast cancer in younger African American patients, basal-like breast cancer does not appear to be an inherently more aggressive disease in African American women compared with whites. Disparities in access to care, including established treatments for ER^+ (luminal A or B) breast cancer, could also contribute to higher breast cancer mortality in African American women. Additional analyses are needed in populations with known treatment profiles and recurrence data to more fully understand the role of tumor subtypes and race in breast cancer mortality. Flexible statistical models that address heterogeneity for 0 to 5 years versus greater than 5 years of follow-up will be needed, as recently shown for ER^+ and ER^- breast cancer patients in the National Surgical Adjuvant Breast and Bowel Project (46). We also found that participants with larger basal-like tumors have on an average fewer positive lymph nodes and a better prognosis relative to patients with other intrinsic subtypes. The complex interplay of tumor size, lymph node status and prognosis is an important area of investigation (47), and it will be interesting to determine whether our findings are replicated in other patient populations.

Disclosure of Potential Conflicts of Interest

The authors have no conflicts of interest to declare.

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References

1. Seer.cancer.gov [Internet]. Bethesda, MD: National Cancer Institute. Available from: http://seer.cancer.gov. Accessed January 12, 2010.
2. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492–2502.
3. Lund MJ, Trivers KF, Porter PL, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat 2009;113:357–70.
4. Cheang MC, Voduc D, Bajdik C, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008;14:1368–76.
5. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev 2007;16:439–43.
6. Kim MJ, Ro JY, Ahn SH, Kim HH, Kim SB, Gong G. Clinicopathologic significance of the basal-like subtype of breast cancer: a comparison with hormone receptor and Her2/neu-overexpressing phenotypes. Human Pathol 2006;37:1217–26.
7. Kurebayashi J, Moriya T, Ishida T, et al. The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races. Breast 2007;16:S72–77.
8. Lin CH, Liau JY, Lu YS, et al. Molecular subtypes of breast cancer emerging in young women in Taiwan: evidence for more than just westernization as a reason for the disease in Asia. Cancer Epidemiol Biomarkers Prev 2009;18:1807–14.
9. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 2007;109:123–9.

10. Ihemelandu CU, Naab TJ, Mezghebe HM, et al. Treatment and survival outcome for molecular breast cancer subtypes in black women. Ann Surg 2008;247:463–9.
11. Nalwoga H, Arnes JB, Wabinga H, Akslen LA. Frequency of the basal-like phenotype in African breast cancer. APMIS 2007; 115:1391–9.
12. Huo D, Ikpatt F, Khramtsov A, et al. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. J Clin Oncol 2009;27:4515–21.
13. Sihto H, Lundin J, Lehtimäki T, et al. Molecular subtypes of breast cancers detected in mammography screening and outside of screening. Clin Cancer Res 2008;14:4103–10.
14. Foulkes WD, Grainge MJ, Rakha EA, Green AR, Ellis IO. Tumor size is an unreliable predictor of prognosis in basal-like breast cancers and does not correlate closely with lymph node status. Breast Cancer Res Treat 2009;117:199–204.
15. Shin BK, Lee Y, Lee JB, et al. Breast carcinomas expressing basal markers have poor clinical outcome regardless of estrogen receptor status. Oncol Rep 2008;19:617–25.
16. Nakajima H, Fujiwara I, Mizuta N, et al. Prognosis of Japanese breast cancer based on hormone receptor and HER2 expression determined by immunohistochemical staining. World J Surg 2008;32:2477–82.
17. Spitale A, Mazzola P, Soldini D, Mazzucchelli L, Bordoni A. Breast cancer classification according to immunohistochemical markers: clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. Ann Oncol 2009;20:628–35.
18. Zhao J, Liu H, Wang M, et al. Characteristics and prognosis for molecular breast cancer subtypes in Chinese women. J Surg Oncol 2009;100:89–94.
19. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009;7:4–13.
20. Parise CA, Bauer KR, Brown MM, Caggiano V. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999–2004. Breast J 2009;15:593–602.
21. Muñoz M, Fernández-Aceñero MJ, Martín S, Schneider J. Prognostic significance of molecular classification of breast invasive ductal carcinoma. Arch of Gynecol and Obstet 2009;280:43–8.
22. Liu H, Fan Q, Zhang Z, Li X, Yu H, Meng F. Basal-HER2 phenotype shows poorer survival than basal-like phenotype in hormone receptor-negative invasive breast cancers. Hum Pathol 2008;39:167–74.
23. Yamamoto Y, Ibusuki M, Nakano M, Kawasoe T, Hiki R, Iwase H. Clinical significance of basal-like subtype in triple-negative breast cancer. Breast Cancer 2009;16:260–7.
24. Ibrahim E, Al-Gahmi AM, Zeenelin AA, et al. Basal vs. luminal A breast cancer subtypes: a matched case-control study using estrogen receptor, progesterone receptor and HER-2 as surrogate markers. Med Oncol 2009;26:372–8.
25. Gray RJ. Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. J Am Stat Assoc 1992;87:942–51.
26. Natarajan L, Pu M, Parker BA, et al. Time-varying effects of prognostic factors associated with disease-free survival in breast cancer. Am J Epidemiol 2009;169:1463–70.
27. Newman B, Moorman PG, Millikan RC, et al. The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology. Breast Cancer Res Treat 1995;35:51–60.
28. Perou CM, Srlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.
29. Srlie T, Perou C, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98:10869–74.
30. Rich-Edwards JW, Carsano KA, Stampfer MJ. Test of the National Death Index and Equifax nationwide death search. Am J Epidemiol 1994;140:1016–9.
31. Pearl J. Causal diagrams for empirical research. Biometrika 1995;82:669–710.
32. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37–48.
33. Cole SR, Hernán MA. Fallibility in estimating direct effects. Int J Epidemiol 2002;31:163–5.
34. Harrell F. Regression Modeling Strategies, with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.
35. Komenaka IK, Martinez ME, Pennington RE Jr, et al. Race and ethnicity and breast cancer outcomes in an underinsured population. J Natl Cancer Inst 2010;102:1178–87.
36. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Time to disease recurrence in basal-type breast cancers: effects of tumor size and lymph node status. Cancer 2009;115;4917–23.
37. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–34.
38. Tischkowitz M, Brunet JS, Bégin LR, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134.
39. Anderson WF, Jatoi I, Devesa SS. Assessing the impact of screening mammography: breast cancer incidence and mortality rates in Connecticut (1943–2002). Breast Cancer Res Treat 2006;99:333–40.
40. Hernán M. The hazards of hazard ratios. Epidemiology 2010;21:13–15.
41. Gore SM, Pocock SJ, Kerr GR. Regression models and non-proportional hazards in the analysis of breast cancer survival. App Stat 1984;33:176–95.
42. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. Am J Epidemiol 2000;151:703–14.
43. Ma H, Wang Y, Sullivan-Halley J, Weiss L, et al. Breast cancer receptor status: do results from a centralized pathology laboratory agree with SEER registry reports? Cancer Epidemiol Biomarkers Prev 2009;18:2214–20.
44. Fillenbaum GG, Burchett BM, Blazer DG. Identifying a national death index match. Am J Epidemiol 2009;170:515–8.
45. Sathiakumar N, Delzell E, Abdalla O. Using the National Death Index to obtain underlying cause of death codes. J Occup and Environ Med 1998;40:808–13.
46. Huang L, Johnson KA, Mariotto AB, Dignam JJ, Feuer E. Population-based survival-curve analysis of ER-negative breast cancer. Breast Cancer Res Treat 2010 Feb 4. [Epub ahead of print].
47. Foulkes WD, Reis-Filho JS, Narod SA. Tumor size and survival in breast cancer – a reappraisal. Nat Rev Clin Oncol 2010 Mar 23. [Epub ahead of print].

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