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Breast cancer survival in African-American women by hormone-receptor subtypes

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Abstract

Purpose—Breast cancer is the second leading cause of cancer-related deaths, accounting for over 200,000 annual cases among women. Few studies have investigated the association between breast cancer subtype and survival among African-American women. Here we investigate breast cancer survival among African-American women by breast cancer subtype.

Methods—We analyzed cancer-related deaths among African-American women using data obtained from the SEER database linked to the 2000 U.S. census data. We examined distribution of baseline socio-demographic and clinical characteristics by breast cancer subtypes and used Cox proportional hazard models to determine associations between breast cancer subtypes and cancer-related mortality, adjusting for age, socio-economic status, stage at diagnosis, and treatment.

Results—Among 19,836 female breast cancer cases, 54.4% were diagnosed with the HER2-/HR + subtype, with the majority of those cases occurring among women ages 55 and older. However, after adjusting for age, stage and treatment type (surgery, radiation, or no radiation and/or cancer directed surgery), TNBC (HR: 2.34; 95% CI: 1.95 – 2.81) and HER2+/HR- (HR: 1.39, 95% CI: 1.08 -1.79) cases had significantly higher hazards of cancer related deaths compared with HER2+/HR+ cases. Adjusting for socio-economic status did not significantly alter these associations.

Conclusions—African American women with TNBC were more likely to have a cancer-related death than African American women with other breast cancer subtypes. This association remained after adjustments for age, stage, treatment, and socio-economic status. Further studies are needed to identify subtype specific risk and prognostic factors aimed at better informing prevention efforts for all women.

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Keywords

Breast Cancer; Hormone-Receptor Subtype; Triple Negative; African-Americans; Survival

INTRODUCTION

Breast cancer accounts for over 200,000 cases annually and is the second leading cause of cancer-related deaths among women in the US[1]. Research suggests that there are racial differences in cancer outcomes as African-American women experience the highest mortality rate and lowest survival for breast cancer when compared to women of other races[1-7]. Multiple studies have indicated that socioeconomic status, comorbidities, prognoses, advanced stage at time of presentation, and healthcare disparities are underlying component causes for the observed racial disparities in breast cancer mortality [5-13].

Breast cancer can be classified according to hormone-receptor status into: HER2+/HR+, HER2-/HR+, HER2+/HR- and TNBC (triple-negative breast cancer, HER2-/HR-) subtypes, based on tumor estrogen receptor, progesterone receptor, and human epidermal receptor factor 2 status. Of these, triple-negative breast cancer (TNBC) has one of the poorest prognoses and highest risk of mortality compared with other subtypes [14,15]. Importantly, African-American women are more likely to be diagnosed with TNBC compared with Whites[16-18,14,6,19,15]. Few studies have investigated the association between breast cancer subtypes and survival among African-American women[15,17,20-24,16]. A recent study by Tao et al. using data from the California Cancer Registry (CCR) reported that compared to White women, African-American women experienced increased hazard for breast cancer related deaths among those diagnosed with stage II and III HR+/HER2- subtype, and stage III triple-negative breast cancer (TNBC) [20]. In addition, among patients with non-TNBC subtypes, African American women still experience lower survival compared to White women [25]. Since highly effective treatment exists for certain breast cancer subtypes, understanding survival differences by subtype may help identify groups of women in whom targeted efforts are needed to improve treatment and survival.

The purpose of this study was to examine whether there are differences in breast cancer survival among African-American women by breast cancer subtypes, using Surveillance, Epidemiology and End Results (SEER) data from 2010 through 2012. We hypothesized that breast cancer survival among African American women would be lower in women diagnosed with TNBC compared to other breast cancer subtypes.

METHODS

Data Source

Our analyses used data obtained from the National Cancer Institute SEER database linked to the 2000 U.S. census data. The study sample included all African-American women diagnosed with breast cancer between 2010 through 2012 in the SEER database. The SEER 18 population-based dataset includes all breast cancer cases diagnosed in the following SEER cancer registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San-

Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, rural Georgia, Greater California, Kentucky and New Jersey. SEER covers about 28% of the U.S. population, although the regions included tend to be more urban and suburban compared with the general U.S. population.

Study Variables

The primary outcome in this study was cancer-related death, defined as deaths within 12 months following breast cancer diagnosis. The primary exposure of interest in this study was the breast cancer subtype (i.e., HER2+/HR+, HER2-/HR+, HER2+/HR-, triple negative (TNBC), and unknown). The classification of cancer subtypes is based on SEER variables relating to the hormone receptor status of tumors recorded by the SEER program. TNBC is defined as tumors that are estrogen receptor negative, progesterone receptor negative, and human epidermal receptor factor 2 negative. Variable coding details of hormone receptor (HR) and HER2 have been published elsewhere [16] and are available through the SEER website (http://seer.cancer.gov/seerstat/databases/ssf/). Individual level variables assessed in this study included age at diagnosis, stage of diagnosis, number of positive lymph nodes, and first course treatment received. Stage of diagnosis was classified (I, II, III, IV) according to the American Joint Commission on Cancer's Cancer Staging Manual, 7th Edition[19]. As survival is partly influenced by socio-economic status (SES)[8], we included socio-economic status at the county level in our models based on percent below poverty line and percent with less than 9th grade high school education. We categorized county-level percent below poverty line and percent less than 12 9th grade education into quartiles based on the distribution of all cancer patients.

Ethics Statement

This study was considered exempt by the Institutional Review Board of the University of Alabama at Birmingham, as the SEER database is a publicly available and non-identifiable secondary data source.

Statistical Analysis

We examined differences in the distribution of breast cancer subtypes by individual characteristics using Chi-square tests and ANOVA. To estimate the relative mortality rates with 95% Confidence Intervals (CIs) by breast cancer subtype, we fit a series of Cox proportional hazards models with cancer-related death as the endpoint. We adjusted the estimates for age, stage at diagnoses, first course treatment received, county-level percent below poverty line and percent with less than 9th grade education. Women were censored for deaths other than breast cancer, or any deaths at the end of 2010. We used Statistical Analysis System version 9.4 (SAS Institute Inc, Cary, NC) and STATA/IC 13.1 (STATACorp LP, College Station, TX) for all analyses.

RESULTS

Baseline characteristics of the study population are described in Table 1. Among 19,836 African-American female breast cancer cases included in this analysis, the majority of cases were diagnosed between ages 55-64. More than half (54.4%) of the breast cancer cases were

diagnosed with the HER2-/HR+ subtype, and the majority of these cases occurred among women ages 55 and older. However, cases diagnosed with the HER2+/HR+ subtype were significantly younger (19.6% aged 15-44) compared with cases with other breast cancer subtypes ($p<0.001$). As shown in Figure 1, the proportion of HER2-/HR+ and cases of unknown subtype diagnosed increased with increasing age, while the proportion of other subtypes diagnosed declined with increasing age. Overall, 22.7% of all cases were diagnosed at advanced stages III and IV; however 33.2% of HER2+/HR- cases were diagnosed at advanced stages compared with 27.3% of HER2+/HR+, 25.3% of TNBC cases, and 19.9% of HER2-/HR+ cases.

The distribution of cases residing in low SES communities also varied significantly by subtype ($p<0.001$). Overall, 26.6% of all cases resided in the lowest quartile of communities with adults living below the poverty line; 27.5% of HER2-/HR+ cases, 26.3% each of TNBC and HER2+/HR- cases and 26.2% of HER2+/HR+ cases. Similarly, 24.9% of all cases resided in communities in the highest quartile of adults with less than 9th grade education; 24.5% of TNBC cases, 24.8% of HER2+/HR+ cases, 24.4% of HER2-/HR+ cases and 21.9% of HER2+/HR- cases. The majority (59.3%) of women received no radiation and/or cancer directed surgery as the first course of treatment for breast cancer.

The survival probabilities by subtype are presented in Figure 2, highlighting significant survival differences between the groups (Log-Rank: 314.6; p-value <0.001), and the lowest survival probability observed among cases with TNBC and unknown subtypes. In an unadjusted Cox regression model (Table 2), cases diagnosed with TNBC (HR: 1.97; 95% CI: 1.64 - 2.36) and HER2+/HR- (HR: 1.40; 95% CI: 1.08-1.80) subtypes had significantly higher hazards for cancer-related deaths compared with HER2+/HR+ subtype cases. After adjustment for age, stage and treatment type (surgery, radiation, or no radiation and/or cancer directed surgery) in model 2, the hazards of cancer-related deaths for TNBC (HR: 2.34; 95% CI: 1.95 – 2.81) and HER2+/HR-(HR: 1.39, 95% CI: 1.08 -1.79) cases was strengthened and remained statistically significant. In the fully adjusted model additionally adjusting for SES variables, the hazard for cancer-related mortality for TNBC and HER2+/HR- cases were attenuated slightly but remained statically significant.

DISCUSSION

To our knowledge, this is the largest study examining cancer-specific survival by hormone receptor subtype among African-American women diagnosed with breast cancer in the US. We observed that cancer related mortality among African-American women diagnosed with TNBC and HER2+/HR- subtypes were significantly higher compared with women diagnosed with other breast cancer subtypes. Even after adjustment for age, stage of disease, treatment and SES, TNBC and HER2+/HR- tumors were associated with a higher hazard for cancer-related death. The most common breast cancer subtype, yet least fatal, among African American women was HER2-/HR+, corresponding to more than half of all breast cancer cases and a case fatality of 6.5%.

To date, few studies have investigated the survival probability associated with breast cancer subtypes among African American women. A recent study reported that among women with

stage III TNBC, the hazard for cancer related-death was higher in African American women compared to White women [20]. Additionally, Bauer et al. found that African-American women with late-stage TNBC had the poorest survival, with a corresponding 5-year relative survival of 14% [21]. Both of these previous studies were conducted using the California cancer registry data, and our study adds to this growing body of literature by showing that among African-American women represented in the SEER registry, breast cancer subtype is an important predictor of survival.

Extensive studies have shown that SES plays a critical role in breast cancer survival among African American women [5,7-13], especially when compared with Whites [5,8,11]. This association is likely driven by differences in accessibility and affordability of high quality cancer care. As shown in our analysis, more than half of all cases did not receive radiation or surgery as the first course of treatment, even though almost 35% of cases were diagnosed at stages III and IV. This may be due to a combination of individual, provider and health system factors that influence the ability of African American women to obtain timely and guideline-adherent treatment. For instance, prior studies have shown that African American women are more likely to experience delays in treatment initiation for cancer, and when treated often receive lower quality treatment[9,26-33]. However, our findings suggests that hormone receptor subtype may play a more important role than SES in predicting survival among African American women. Adjusting for SES in our regression models did not appreciably alter the hazard ratio associated with subtype, signifying that improving survival rates among African-American breast cancer patients will require renewed focus on identifying subtype specific etiological factors, and ensuring adequate access to high quality, subtype specific treatment.

Although TNBC was associated with the lowest survival, HER2+/HR- cases also experienced significantly lower survival compared with HER2+/HR+ cases, although this subtype was less prevalent (<1%). On the other hand, TNBC accounted for close to 20% of the cases in our study, consistent with other studies reporting that the lifetime risk of TNBC was nearly doubled in African American women (1.98%, 95%CI: 1.80 – 2.17%) compared to all other races; Asian (0.77%; 95%CI: 0.67 - 0.88%), Hispanic (1.04%, 95%CI: 0.96 – 1.13%), and white women (1.25%; 95% CI: 1.20 – 1.30%)[22]. The risk differential in incidence of HR- subtypes, and the consistent association between hormone receptor negative subtypes and survival reported in several other studies [18,22,34-45], suggest that concerted efforts are needed to identify risk factors associated with HR- tumors, including biological and genetic contributors with a focus on primary prevention. For instance, a previous study showed that metabolic syndrome, a cluster of biochemical abnormalities more prevalent among African-American women compared with Whites, is associated with an almost 2.5-fold increase in the odds of TNBC [46]. In addition, further studies are needed to identify biomarkers of breast cancer risk by subtype, for instance, mammographic density, to further improve screening modalities and early detection. Furthermore, as has been discussed extensively, lack of access to timely and high-quality cancer care remains a significant issue for African-American women regardless of subtype. However few efficacious treatment strategies currently exist for HR- tumors relative to other subtypes[18,37,40,44,45,47-56], making this is a critical area of future research.

This analysis is strengthened by the use of the large, high-quality, standardized data available in the SEER dataset. However, these results should be viewed in light of certain limitations. First, there may be limited generalizability because SEER covers only about 26 percent of the total U.S. population. However, SEER covers geographically and demographically diverse US populations including residents from both rural and urban communities. Thus, in contrast to prior studies using single state registries or smaller study cohorts, this study has modest external validity. Secondly, minority racial/ethnic groups, foreign-born, and urban populations are groups of special interest to the SEER program and are therefore somewhat overrepresented in the database. Lastly, there is a possibility for misclassification bias because measures of SES (i.e., poverty and education) were obtained at times different than cancer diagnosis [8], and may underestimate individual level SES. However, these are the variables currently available in the SEER dataset, and the SES measures were obtained through standardized national surveys.

CONCLUSION

In conclusion, in the national SEER cohort, African American women with TNBC were more likely than African American women with other breast cancer subtypes to have a cancer- related death. This association remained after adjustment for age, stage, treatment, and SES. Further efforts should focus on illuminating underlying reasons outside of socio-economic factors that contribute to the higher prevalence and fatality of TNBC.

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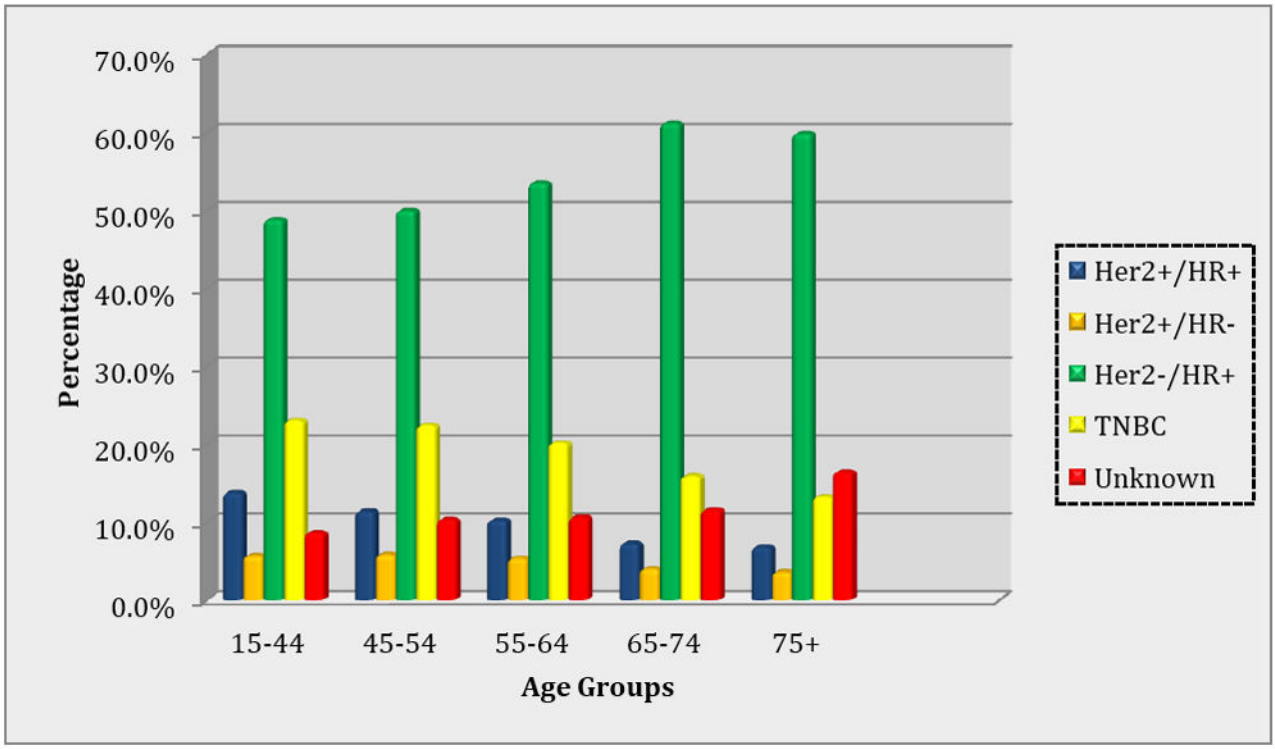

Figure 1.
Prevalence of breast cancer subtypes by age groups, SEER 2010 – 2012

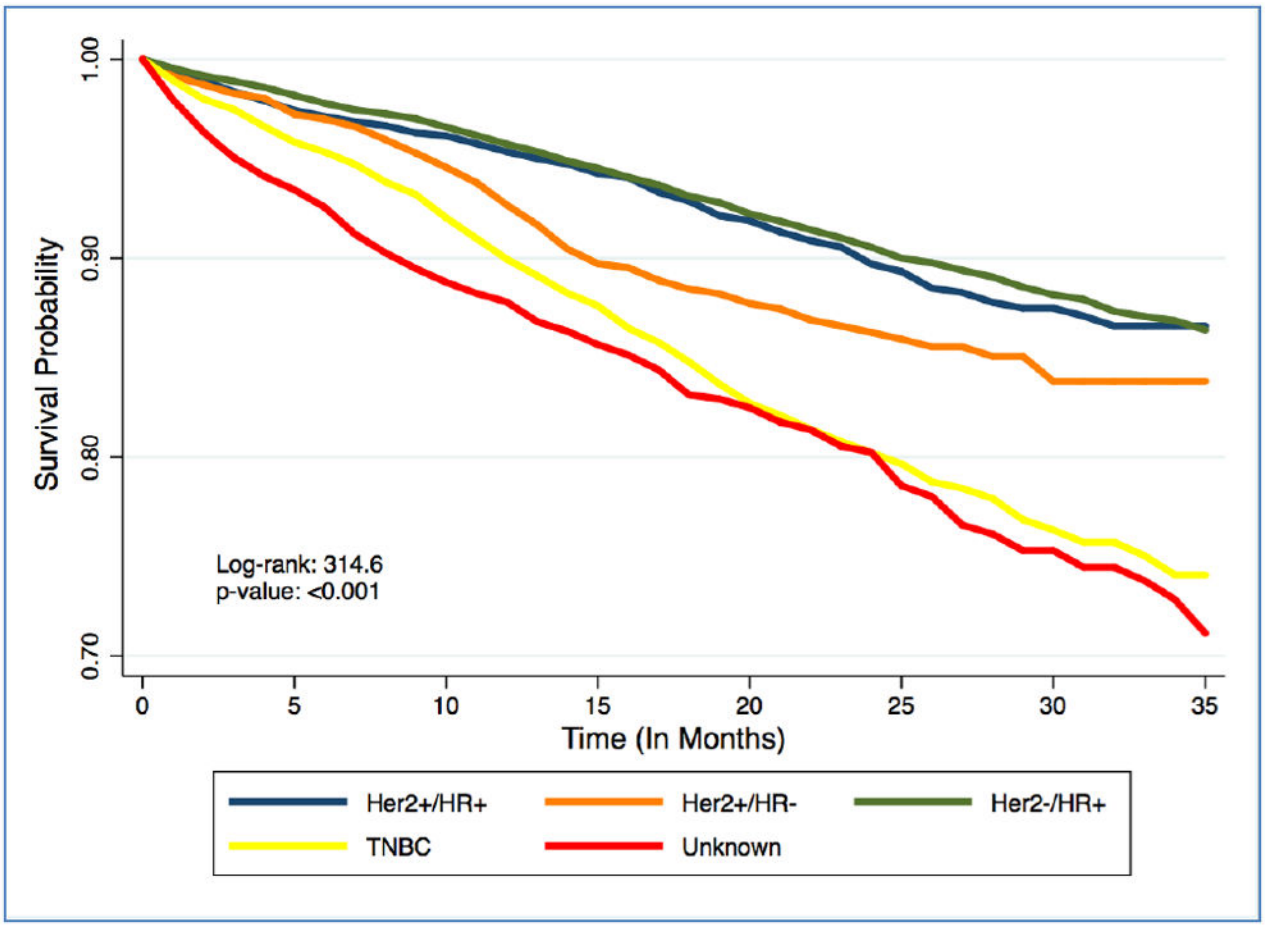

Figure 2.
Kaplan-Meier Plot for time until death among AA breast cancer cases stratified by breast cancer subtypes, SEER 2010 – 2012

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Table 1

Comparison of participants' characteristics by breast cancer subtype, SEER 2010 - 2012.

	Breast Cancer Subtype n (%)						
	Number of Cases (N= 19,836)	**TNBC N = 3,828 (19.3)**	**Her2+/HR+ N = 1,976 (10.0)**	**Her2+/HR- N = 993 (5.0)**	**Her2-/HR+ N = 10,799 (54.4)**	**Unknown N = 2,240 (11.3)**	**p-value**
Length of follow-up, months **	15.5 (10.2)	15.5 (10.1)	15.7 (10.3)	15.7 (10.2)	15.7 (10.2)	14.5 (10.6)	<0.001
Age at diagnosis (%)							
15-44	2,815 (14.2)	649 (17.0)	388 (19.6)	160 (16.1)	1,375 (12.7)	243 (10.9)	<0.001
45-54	4,831 (24.4)	1,083 (28.3)	551 (27.9)	282 (28.4)	2,416 (22.4)	499 (22.3)	
55-64	5,452 (27.5)	1,099 (28.7)	559 (28.3)	293 (29.5)	2,920 (27.0)	581 (25.9)	
65-74	3,896 (19.6)	620 (16.2)	284 (14.4)	156 (15.7)	2,386 (22.1)	450 (20.1)	
75+	2,842 (14.3)	377 (9.9)	194 (9.8)	102 (10.3)	1,702 (15.8)	467 (20.9)	
% Below poverty line * (%)							
1st Quartile (3.98 – 12.99)	5,267 (26.6)	1,005 (26.3)	517 (26.2)	261 (26.3)	2,971 (27.5)	513 (22.9)	<0.001
2nd Quartile (13.00 – 17.70)	4,654 (23.5)	848 (22.2)	446 (22.6)	226 (22.8)	2,530 (23.4)	604 (27.0)	
3rd Quartile (17.71 – 20.17)	4,956 (25.0)	933 (24.4)	501 (25.4)	247 (24.9)	2,706 (25.1)	569 (25.4)	
4th Quartile (20.18 – 47.98)	4,958 (25.0)	1,042 (27.2)	511 (25.9)	259 (26.1)	2,592 (24.0)	554 (24.7)	
% <9th High School Education * (%)							
1st Quartile (1.08 – 4.43)	5,002 (25.2)	991 (25.9)	500 (25.3)	278 (28.0)	2,736 (25.3)	497 (22.2)	<0.001
2nd Quartile (4.44 – 5.42)	5,146 (25.9)	1,036 (27.1)	530 (26.8)	279 (28.1)	2,806 (26.0)	495 (22.1)	
3rd Quartile (5.43 – 7.96)	4,749 (23.9)	865 (22.6)	456 (23.1)	219 (22.1)	2,623 (24.3)	586 (26.2)	
4th Quartile (7.97 – 20.88)	4,938 (24.9)	936 (24.5)	489 (24.8)	217 (21.9)	2,634 (24.4)	662 (29.6)	
AJCC Stage at Diagnosis (%)							
I	7,566 (38.1)	1,143 (29.9)	666 (33.7)	279 (28.1)	4,777 (44.2)	701 (31.3)	<0.001
II	6,815 (34.4)	1,615 (42.2)	710 (35.9)	361 (36.4)	3,608 (33.4)	521 (23.3)	
III	2,851 (14.4)	669 (17.5)	320 (16.2)	206 (20.8)	1,444 (13.4)	212 (9.5)	
IV	1,654 (8.3)	300 (7.8)	219 (11.1)	123 (12.4)	705 (6.5)	307 (13.7)	
Unknown	950 (4.8)	101 (2.6)	61 (3.1)	24 (2.4)	265 (2.5)	499 (22.3)	
First course treatment received (%)							

	Breast Cancer Subtype n (%)						
	Number of Cases (N= 19,836)	**TNBC N = 3,828 (19.3)**	**Her2+/HR+ N = 1,976 (10.0)**	**Her2+/HR- N = 993 (5.0)**	**Her2-/HR+ N = 10,799 (54.4)**	**Unknown N = 2,240 (11.3)**	**p-value**
Surgery	7,950 (40.1)	1,568 (41.0)	779 (39.5)	4,735 (43.9)	4,735 (43.9)	516 (23.0)	<0.001
Radiation	94 (0.5)	27 (0.7)	10 (0.5)	11 (1.1)	39 (0.4)	7 (0.3)	
No Radiation and/or Surgery	11,753 (59.3)	2,229 (58.2)	1,181 (59.8)	628 (63.2)	6,010 (55.7)	1,705 (76.1)	
Unknown	32 (0.2)	3 (0.1)	4 (0.2)	2 (0.2)	11 (0.1)	12 (0.5)	

*Estimated at the county-level

**Mean (Standard Deviation)

Table 2

Hazard ratio (HR, 95% CI) of cancer-specific mortality of AA breast cancer cases by subtype, SEER 2010 - 2012.

	No. Deaths (%) Case Fatality	Crude HR* (95% CI)	Model 1 [a] * (95% CI)	Model 2 [b] * (95% CI)	Model 3[c] * (95% CI)
Cancer Subtype					
Her2+/HR+ (Ref)	145 (7.3)	-	-	-	-
Her2+/HR-	102 (10.3)	1.40 (1.08 – 1.80)	1.38 (1.07 – 1.77)	1.39 (1.08 – 1.79)	1.37 (1.06 – 1.77)
Her2-/HR+	706 (6.5)	0.89 (0.74 – 1.06)	0.79 (0.66 – 0.95)	1.01 (0.85 – 1.21)	1.02 (0.85 – 1.21)
TNBC	546 (14.3)	1.97 (1.64 – 2.36)	1.96 (1.63 – 2.35)	2.34 (1.95 – 2.81)	2.33 (1.94 – 2.80)
Unknown	502 (22.4)	2.89 (2.40 – 3.49)	2.55 (2.11 – 3.08)	1.42 (1.18 – 1.73)	1.43 (1.18 – 1.73)
p-value for breast cancer subtype		<0.001	<0.001	<0.001	<0.001

[a] Adjusted for age only.

[b] Adjusted for age, stage and treatment.

[c] Adjusted for age, stage, treatment, % below poverty line, and % <9th grade education.

* Estimated from Cox proportional hazard model.