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Competing Risk Analyses for African American and White Breast Cancer Patients

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ABSTRACT

Background: Overall survivability in breast cancer has improved in the past decade yet African American Black (AA/B) patients still experience disproportionately higher mortality compared to whites, with some studies showing a widening disparity. Emerging evidence suggests that comorbidities might play an important role in explaining this disparity. Few studies to date, however, have examined if co-mordbidities tend to be linked more with other causes of death versus breast cancer pointing towards the need of better controlling of existing co-morbidities. Traditional methods of assessing cause-specific deaths, however, are prone to error in cause-specific outcomes due to censoring all other causes of deaths. **Methods**: We analyzed data from the Connecticut SEER tumor registry (n=2558) with equivalent proportions of AA/B and white patients, and a random subset (n=416) of these patients for whom a medical record review was conducted, seventeen prognostic clinical conditions (e.g., heart disease, diabetes) listed in the Charlson Co-Morbidity Index (CCI) were identified. We compared estimates of breast cancer specific mortality using Cox Proportional Hazard Survival Analysis to calculate hazard ratios (HR) with the Subdistributional Hazard method (SD-HR), which calculates hazard ratios taking into account other causes of death. **Results**: AA/B patients were less likely to have no co-morbidities compared to whites (58.9% vs. 82.8 %, respectively, p=<.0001). Among patients with local stage disease, the traditional Cox Method showed comparable breast cancer specific mortality risk for AA/B compared to whites in the full sample (HR=0.97 95% CI 0.87-1.08) whereas the subdistributional method showed an increase breast cancer mortality risk for African Americans (SD-HR=1.43 95% CI 0.97-2.12). For regional

stage, both estimates were statistically significant but a greater effect was observed using the subdistributional method (SD-HR=1.31 95% CI 1.13-1.52 and SD-HR=1.84 95% CI 0.1.34-2.53). When the CCI score was added to analyses in the sub-sample, a substantially reduced risk of breast cancer-specific death was observed for AA/B patients compared to whites (SD-HR=0.17 95% CI 0.03-0.92) but no difference in risk was observed when using the Cox Method (HR=0.97 95% CI 0.70-1.17). For patients with Regional stage in the sub-sample, adding the CCI score to the Cox model revealed no difference in breast cancer specific mortality (HR=0.98 95% CI 0.67-1.43) but was suggestive of a higher risk when using the sub-distributional analysis (SD-HR=1.99 95% CI 0.90-4.345). **Conclusion**: In the larger sample, a higher risk of breast cancer specific mortality for AA/B patients was observed when using the sub-distribution analytical method compared to the traditional survival analysis. Adding the Charlson Co-morbidity Index into models, however, revealed a reduced risk of breast cancer specific death for those with local disease suggesting that existing medical conditions might drive mortality when the cancer burden is lower.

Introduction:

Breast cancer survival disparities are puzzling given that African American Black (AA/B) women are less likely to develop breast cancer compared to white women. The Centers for Disease Control (CDC) reports that breast cancer is the second leading cause of cancer deaths in African Americans (Black) women.[3] Although mortality rates from breast cancer have declined over the past decade for all ethnic groups, AA/B continue to suffer a higher burden of death.[3] For decades, African-American/Black (AA/B) breast cancer patients between the ages of 45-60 have had a 60% greater death rate than their white counterparts[1]. Eliminating this racial survival disparity in breast cancer is a public health priority. By establishing sufficient evidence, targeted interventions can be created at the health care level to improve survival rates.

Numerous studies have implicated the three-fold greater prevalence of the aggressive Triple-Negative Breast Cancer (TNBC) subtype (i.e., HER2-ER-PR-) in African American/Black (AA/B), compared to non-Hispanic Whites, in the differential poor survival prognosis[2]. One TNBC study, however, found that the presence of co-morbidities at diagnosis was comparably predictive of mortality as TNBC.[1] Those findings are consistent with emerging data that AA/B breast cancer patients with specific types of co-morbidities might be at disproportionate risk of mortality.[7,26] Though the impact of co-morbidities in survival in breast cancer patients has been studied, analyses of competing risk of death in the presence of existing co-morbidities has not been assessed to date. That is, given relatively higher rates of co-morbidities among African-Americans [3,7], it is of interest to determine if African-American breast cancer patients are more likely to die from other causes of death (e.g., heart disease) versus breast cancer, and if differences in cause of death suggest the need for better control of co-morbidities. Traditional methods of assessing cause-specific death, however, are prone to underestimate the cause of interest (e.g., death from breast cancer) because all other causes of death are censored.[46-47]In our study, therefore, we will compare breast-cancer specific mortality using the traditional statistical method (i.e., Cox Proportional Hazards Survival Analysis) versus the subdistributional hazard ratio (SHR) model in which mortality for breast cancer as well as other causes of death are estimated. Additionally, use of the SHR model is appropriate in study samples consisting of older

patients where competing causes of death may be relatively high such is the case in cancer patients, a disease of aging.[46-47]Therefore, it is important to consider models that take in account competing events when estimating cause-specific mortality from breast cancer.

Research Aims:

The primary aim of this research project is to conduct a survival analysis using the subdistributional competing risks approach versus the traditional technique in a large sample of breast cancer patients (n=2558) from the Connecticut Tumor Registry. We will determine whether mortality is due to any cause of death or breast cancer as the cause of deathSecond, in a sub-set of this sample (n=416) for whom we conducted a chart review, we will perform a competing risks analysis accounting for existing co-morbidities ascertained using the Charlson Co-Morbidity Index (CCI) measurement tool.

Background and Significance:

African-American status continues to be an independent predictor of poor breast cancer outcome, even after accounting for socioeconomic factors (SES), inadequate health care access[9] and controlling for common treatment. While there is evidence that reduced accessibility to healthcare and delays in treatment can explain survival disparities,[10-12] findings from a large cooperative national clinical trial with nearly identical treatment and conditions, African American/black ethnicity still remained an independent predictor of breast cancer outcomes[13] suggesting that underlying biological disease or other clinical factors, such as co-morbidities at diagnosis might play a role.

Competing Risks of Death. By analyzing both subdistributional and traditional cause-specific models, we can compare their ability to estimate specific causes of mortality. Some studies have indicated that since elder population (age>65) have a higher risk of dying from any cause, rates of death from breast cancer might be erroneously estimated in traditional analyses that do not account for other causes of death in analyses.[46-47] That is, AA/B breast cancer patients actually ***less*** prone to death from breast cancer than are white patients because AA/B patients are dying disproportionally more from other causes?

Traditional analyses tend to show that AA/B patients are more likely to die from breast cancer than whites, but that finding might be questioned when non-breast cancer deaths are censored in traditional survival analyses. Examining this question is further complicated if the age at diagnosis differs meaningfully between groups. Given the effects of age on breast cancer incidents, death often occurs in the presence of competing risk factors such as heart disease or diabetes.[5] Because AA/B breast cancer patients tend to be diagnosed at earlier ages, then the likelihood of a comorbid condition could also differ. Generally in older breast cancer patients, death occurs in the presence of competing risk factors such as, for example, heart disease or diabetes.[5]

The likelihood of erroneous estimation of breast cancer specific mortality using the traditional methods of analysis, such as the Kaplan-Meier method and Cox Proportional Hazards Survival Analysis, is due to the stipulation of a binary outcome variable: those who experience the event of interest (e.g., breast cancer), and those who do not. Those who do not experience the event are labeled censored, which includes those who are presumed alive and those who died from a different cause. [6,48] Understanding the reasons behind the greater mortality in African-American breast cancer patients requires analyzing the death from other causes as well.[5]

Co-Morbidities and Mortality. In breast cancer patients older than 50 years, non-cancer mortality exceeds breast cancer mortality. Severe co-morbidities in early stage breast cancer has been associated with all-cause mortality and breast cancer-specific mortality.[8] Prior research shows that patients with serious comorbidities have outcomes that are comparable to those observed in the later stages of tumor.[14] A Danish nationwide study concluded that successful treatment of existing co-morbidities in breast cancer patients can improve survival rates of the patients.[7] Non-cancer mortality is higher in black patients than whites at ages younger than 70.[15] Another study showed that carefully accounting for comorbid illnesses, particularly diabetes and hypertension, explained much of the racial disparity in non-cancer mortality.[16]

Specific Co-Morbidities. [14] African American women are considered at higher risk of chronic conditions such as diabetes, hypertension and cardiovascular disease.[7]

Measures of specific comorbidities may reflect the survival outcome more clearly than do summarized measures that often give the same weight to all morbidities despite their different impact. Age-adjusted death rates for coronary heart disease and stroke has been shown to be higher in African Americans.[22] These factors can very well raise the risk of overall mortality and breast cancer specific mortality.

In recent years, more and more researchers have started looking at co-morbidities at diagnosis of breast cancer that may explain survival outcomes in black patients. These conditions as previously mentioned can be preexisting diabetes, hypertension, obesity and number of other common chronic diseases. Preexisting conditions, though unrelated to breast cancer, can pose a great threat to overall survival. A Black/White Cancer study has shown that uncontrolled co-morbidities have an adverse effect on cancer treatment and cancer survival outcomes.[25]

African American women have suboptimal blood pressure control based on Healthy People of 2010 standards. As many as 64% of African American women may have uncontrolled hypertension.[27] In Blacks, severe hypertension and targeted organ complicated hypertension are more common than in whites. Both are associated with cardiovascular disease. Black Americans have a much higher risk of experiencing hypertension related complications such as nephropathy, stroke, heart failure and type 2 diabetes.[28] A study conducted in 2007 across 12 southeastern states found that the pattern of treatment of diabetes in Black patients results from "suboptimal implementation of evidence-based hypertension treatment guidelines".[31] Randomized controlled studies have shown adequate blood pressure control in African Americans who receive and adhere to optimal evidence-based hypertensive treatment with dietary changes, ruling out biological differences as the root cause. Similarly, diabetes in combination with hypertension is also a major public health problem in African Americans. African Americans with diabetes are three times more likely to have uncontrolled hypertension than those without diabetes.[29] The CDC estimates that black women have a 90% higher prevalence of diabetes than white women. The burden of diabetes disproportionally affects blacks with more black women ending up with end-stage-renal diseases than white women. Black women have also had 22% highest

hospitalization rate related to diabetes in the 1990s compared to black men and a striking 215% higher than white women.[30]

A recent study showed that breast cancer patients with a history of diabetes have an increased risk of breast cancer specific mortality.[26] Results from this study estimated a 2-fold increase in breast cancer-specific mortality if diabetes was not treated in breast cancer patients. Similarly, history of myocardial infarction was found to increase the risk of breast cancer specific mortality. This pattern was observed in African Americas, Asian Americans and Latinas.[26] Additionally, those with a history of diabetes had a significantly elevated risk of breast cancer specific mortality without chemotherapy or radiotherapy compared to those without a history of diabetes and without chemotherapy. More so, breast cancer specific mortality was significantly elevated among cases with diabetes that didn't receive chemotherapy versus those without diabetes and chemotherapy.[26] Diabetes and hypertension have been strongly and widely associated with obesity.[33,34] More than 75% African American women are overweight or obese.[34]

Tumor Burden and Biology. Advanced stage at diagnosis also has been examined as an explanatory factor in survival disparity. African American women are typically diagnosed at an advanced stage and at younger ages even though the mammography utilization and screening rate is comparable in whites and blacks.[18] Advanced disease, however, does not explain the survival gaps because the survival disparities are found within each stage and not just at the advanced stage level [3.]

In the past decade, adverse tumor biology has emerged as a focus in breast cancer disparities emerged.[17] In particular, African American/black women have three-fold greater prevalence of triple negative breast cancer (TNBC) compared to white women [1,19] TNBC tumor lacks the expression of estrogen, progesterone and HER2 receptors in breast cancer cells. Receptors are found on cancer cells and attach to certain substances such as hormones that circulate in the blood. Some breast cancer cells have receptors that bind to estrogen or progesterone hormones. Estrogen and progesterone hormones are both known to fuel the growth of breast cancer cells. Breast cancer cells that either express receptors for estrogen or progesterone are known as

hormone-receptor positive breast cancer. Almost 20% of breast cancer patients have a breast cancer cell growth protein called HER2/neu that promotes the growth of cancer cells. Breast cancer cells that express increased levels of HER2/neu proteins are classified as HER2 positive and tend to grow more aggressively compared to other cancers. The hormone receptor positive and HER2/neu positive breast cancer have targeted hormonal therapy, and therefore have better prognosis.[3] Because TNBC tumors lack hormone receptors, no hormonal therapy is useful. When compared to other subtypes of cancer tumors, TNBC tumors have been shown to result in significantly worse prognosis outcomes[9.] However, a recent study shows that African American women with breast cancer continue to experience survival disadvantages in advanced disease whether or not the tumor expresses the TNBC subtype.[20] This evident suggests that other clinical and psychosocial factors must be studied to fully understand the survival gap. Recently, presence of co-morbidities has emerged as a potential risk factor for the African American women with breast cancer [21.]

Hypotheses. Based on our prior research that showed evidence of co-morbidities being the independent prognosis factor for African American with breast cancer[1], we hypothesize that there is an association between co-morbidities and specific cause of death in African American breast cancer patients. We anticipate that African Americans are more likely to die of non-breast cancer related causes such as heart disease or diabetes compared to white breast cancer patients. Hence, in our total sample (n=2558), we predict that competing risk factor analyses will reveal differences in cause-specific death mortality between blacks and whites. Second, given that it is likely that the survival disparities in African Americans breast cancer patients might be due to the higher chances of dying from the existing co-morbidities at breast cancer diagnoses, we expect to see a positive relationship between the co-morbidity score and mortality hazard ratio resulting from one or the combination of those co-morbidities as analyzed in the sub-sample (n=416) of the chart review. We predict that these patterns will be independent of TNBC status and breast cancer stage.

METHODS: Study population: Our overall sample consists of all AA/B breast cancer cases (ICD-O-3 C50.0-C50.9) diagnosed between January 1, 2000 and December 31,2007 and an age-matched random sample of an equivalent number of white patients during the study period (n=2558). From this sample and a random sample (n=416) medical record review on African American (AA/B) and White female breast cancer patients. The random sample of 416 female breast cancer patients is derived from our parent study (full sample) of 2558 patients diagnosed with primary breast cancer (ICD-O-3 C50.0-C50.9) between January 1, 2000 and December 31, 2007 in the State of Connecticut. Data were obtained from the Connecticut Tumor Registry (CTR), a participant site in the NCI-SEER program. In statistical analyses for n=416, we excluded patients who had missing data on age, race, TNBC status, comorbidity score, vital status, Seer Summary stage advance/distant and those who were lost to follow up. Access to medical records was approved by the Institutional Review Boards at University of Connecticut Health Center, Yale Cancer Center, Hartford Hospital, and the Human Investigation Committee at the Connecticut Department of Public Health.

Causes of Death: Case records were followed untill December 2015 for vital statuses including causes-of-death. Causes of deaths were grouped into five categories including breast cancer, cardiovascular diseases, non-cardiovascular diseases, other cancers and unknown causes.

Descriptive Analyses: Clinicopathological characteristics between white and AA/B patients are compared for full sample (n=2558) and random sample (n=416) using χ^2 test for the following categorical variables: age, histological subtype, SEER summary stage, tumor grade and TNBC. SEER summary stage distant will be excluded from parent population for survival analyses.

Clinicopathological Data. Information in the CTR database includes: ER, PR, age at diagnosis, SEER Summary Stage (local, regional) and ICD-O-3 histologic subtypes. Local stage is defined in SEER as invasive cancer confined to the breast; and, regional stage is defined, as cancer detected to have spread to the axillary lymph nodes or contiguous tissue. Information about first-course of chemotherapy is available in the

CTR database, although in recent years SEER no longer makes this information available in the public dataset due to substantial missing data and unreliability of the information.[37] TNBC status was derived from both the CTR database (i.e., ER, PR) and abstraction of summary pathology reports (i.e., HER2) at the registry as described in our previous investigations using this study sample.[28]

Co-Morbidity Information. Medical conditions were abstracted using the validated Charlson Co-Morbidity Index (CCI), a weighted list of 17 items developed in 1987[40] and a prominent tool in cancer research.[41] The CCI includes measurement of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic lung disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, hemiplegia, neoplasia, moderate/severe liver disease, metastatic disease, human immunodeficiency virus, and renal disease. A cumulative score is calculated based on a no (0) or yes (1) for each condition, and weighted according to a specific protocol.[40] Briefly, the weight applied to a particular condition reflects the associated hazard ratio of death within one-year of cancer diagnosis.

Due to emerging evidence of the prognostic importance of hypertension in distinguishing mortality risk in cancer survival disparities[38], we adopted the CCI following an approach in Braithwaite and Tammemagi[39] to assign an additional point by including high blood pressure (CCI+HBP) as comorbidity. Scores for the CCI (0-17) and CCI+HBP indices were employed in statistical analyses as either a continuous or categorical variable (0, 1-2, ≥ 3). We will look at the weight distribution of AA/B and whites for CCI score with hypertension and compare the differences between the two.

Competing Risks Survival Analyses: Survival time is measured for all patients as the duration of date of diagnoses to date of death or last follow up. When conducting a competing risk analyses, patients still alive at the date of last follow up are considered 'censored' and those who died of a disease under study are considered an 'event'. Patients who die of an unrelated cause are considered competing risk events.[6]

Kaplan-Meier or cause-specific method estimates the distribution of time to event of interest such as death from breast cancer and ignores all the other events This method censors all competing events and may yields biased results. While a cause-specific model is better suited for examining the etiology of diseases, the subdistributional hazard ratio model is more useful in predicting an individual's competing-risks.[35] In this model, those subjects that experience a competing risk event are retained even after the competing event but with gradually decreasing weight.[35-36] We used The Fine and Gray subdistributional hazard ratio (described elsewhere)[35] to compare the absolute mortality risk for breast cancer and all-cause deaths for the full sample (n=2558) and to asses AA/B versus White breast cancer patients' mortality in the presence of competing risks by age and tumor size for local and regional stages. Briefly, in this model the hazard ratio is based on a modified risk set where those subjects that experience a competing event remain in the risk set even after experiencing that event. The weight of the subjects that are retained in the risk set artificially reduces gradually. SAS edition 9.0 was used for Phreg functions analyzing subdistributional hazard ratio and standard cox/cause specific hazard model**.**[42] We also applied the subdistributional hazard model for breast cancer and all cause deaths in AA/B verses White breast cancer patients by age, tumor size for the subset analyses (n=416) with and without co-morbidity index score in the model. We used the standard cox regression/cause-specific hazard model for all-cause mortality and by breast cancer-specific death in AA/B and white breast cancer patients by multivariate age and tumor size for the full sample. Cause-specific hazard model was used for the sub-sample (n=416) by multivariate age and tumor size with and without Co-morbidity score (+/-). In order to infer the added benefits of co-morbidity in analyzing competing risk hazard ratio for breast cancer, we compared the differences in hazard ratio using cause-specific model and subdistributional model for breast cancer specific mortality in AA/B and Whites between full sample and sub-sample with co-morbidity index score at the local stage.

Next, we explored all-cause and breast cancer specific Co-morbidity index hazard ratio using cause-specific model for AA/B and whites by multivariate age, co-morbidity index score, and tumor size at local and regional stages in the presence of competing event.

Risks to human subjects: Data collected for this project is from Connecticut tumor registry located in the department of public health. By legislation law, all licensed Connecticut hospitals are required to provide information on cancer incidence, treatment and follow up. The Connecticut General Statue 19a-25 protects the identities of all the human subjects/patients. Confidentiality and privacy of subjects is approved by the Investigations Committee of the Connecticut once reviewing the study's protocol, methods and procedures for protecting the patient's privacy and confidentiality. Completely anonymous data is used with unique study ID numbers for all individuals to safeguard subject's privacy. No such data is used that might lead to a particular individual's bio-data.

RESULTS

In the total sample n=2558 (Table1), the most common histology subtype in both whites and AA/B was ductal (67.1% and 68.6%, respectively) yet the overall histological patterns were statistically significant (P <.0001 omnibus) due to variations in prevalence of lobular and medullary sub-types. Compared to black patients, white patients were almost twice as likely to have lobular histology, which is comparatively more favorable histology (10.3% vs. 5.6%, respectively, p<0.0001) and less likely to be diagnosed with the more aggressive medullary breast cancer (0.4% vs. 8.1%, p<.0001). Similar trends were observed in the n=416 subsample (Table 1). As expected, white patients were more likely than blacks to have early stage disease in both the full (65.8% vs. 57.1%, respectively, p<0.0001) and sub-sample (68.7% vs. 62.0%, respectively p=.0.209) but the difference reached statistical significance in the full sample (Table 1). AA/B breast cancer patients had a higher prevalence of TNBC in the total sample as well as subsample n=416 (30.3% vs. 12.8% p<0.0001 and 26.0% vs. 16.4% p<.001)

Charlson Co-Morbidity Index (n=416 sub-sample):

AA/B breast cancer patients were more likely to have higher CCI scores (Table 2, omnibus p<.0001) as determined by the weighted sum of conditions present within one-year (before and after) the breast cancer diagnosis. Specifically, substantially more white breast cancer patients had no existing co-morbidity compared to black patients

(82.7 % vs. 58.9%, respectively, p,.0001); 25.7% of AA/B had a CCI score of 1-2 compared to only 11.2% of whites (p<0.0001); and, proportionally more AA/B Americans had CCI scores of 3 or more compared to their white counterparts (15.3% vs. 6.1% p<0.0001). When hypertension was added to the index, the proportion of AA/B patients without any co-morbidity decreased by one-third (58.9% to 39.1%), and, for white patients, the drop was about one-fourth (82.7% to 60.7%).

Causes of Death:

The median survival time after diagnosis was comparable (10.4 vs. 10.2 yrs) for both AA/B and whites in the full and sub-samples (Table 3). While breast cancer was the leading cause of death in both AA/B patients and white patients in the sub-sample (Table 3), somewhat more AA/B patients died of breast cancer compared to whites (50.7% vs 43.8%, omnibus P=.810)

All-Cause Hazard Ratio:

Among patients diagnosed with local stage of breast cancer (i.e., tumor has not spread to regional lymph nodes), AA/B did not appear to be at increased risk of mortality compared to whites in the full (Crude HR=0.973, 95% CI 0.872-1.087) or sub-sample (Crude HR=0.955, 95% CI =0.741-1.231) (Table 4). When adding the standard CCI score to the analysis, the HR estimate did not appreciably change. At the regional stage, AA/B patients were found to be at increased risk for overall death in full sample (HR=1.310, 95% CI= 1.128-1.522). Regarding patients diagnosed with regionally advanced breast cancer, adding CCI did not change the all cause mortality ratio for AA/B women (HR=1.006, 95% CI= 0.691-1.466).

Breast Cancer Specific Hazard Ratios

For the full sample, as seen in Table 5, blacks were more likely to die from breast cancer when analyzed with the sub-distribution analysis methodology (SD-HR=1.434 95% CI 0.969-2.122) yet no effect was revealed using the traditional Cox Proportional Hazards Survival analysis (HR= 0.966, 95% CI=0.865-1.079). This difference in findings, however, was not observed when analyzing the sub-sample in which no black-

white difference in survival was observed by either method. When adding the CCI score to the model, the traditional method revealed no black-white difference in dying from breast cancer yet the risk of death from breast cancer among blacks compared to whites was significantly reduced when using the subdistributional model (HR=0.168, 95% CI 0.0310-0.902).

For patients diagnosed with regional disease in the full sample, AA/B show an increased risk of death from breast cancer compared to whites (HR=1.307, 95% CI=1.125-1.519). Subdistributional model also shows a heightened increased risk of breast cancer specific mortality for AA/B at regional stages (HR=1.841, 95% CI 1.339-2.530). Adding CCI in the multivariate model suggests an increased risk of breast cancer specific mortality for AA/B compared to whites when using the sub-distribution model only (HR=1.999, 95% CI 0.902-4.346). Findings in Table 5 are illustrated graphically in Fig 1.a (full sample) and Fig 1.b (sub-sample).

Risk of breast cancer specific death in relation to Charlson Comorbidity: As an independent factor, the CCI was associated with statistically significant increases in the hazard ratio per one unit score using both statistical methods for patients with local disease (HR=1.363 95% CI 1.223-1.518 and SD-HR=2.088 95% CI 1.633-2.67) and for regional disease (HR=1.132 95% 1.034-1.240 and SD-HR 1.167 95% CI 1.063-1.280).

DISCUSSION:

In order to diminish inequities in survival among breast cancer patients, it is important to understand the role that existing co-morbidities play in mortality given higher rates of various conditions among AA/B patients. We addressed this issue in two ways: 1) Incorporating a co-morbidity score (CCI) into multivariate analyses; and, 2) Assessing if African-Americans tend to die at a higher proportion from breast cancer versus co-morbidities (e.g, heart disease). Additionally, when evaluating cause-specific deaths, we compared the use of traditional cox-regression model, which censors non-breast cancer deaths with the subdistributional hazard model, which takes into account all causes of deaths.

Descriptive Analyses. Using the Charlson Co-Morbidity Index, our descriptive analyses showed that African Americans breast cancer patients were far more likely to have an existing co-morbidity at the diagnosis compared to whites. Specifically, about

41% of AA/B patients had at least one co-morbidity at diagnosis compared to 17% of whites. This prevalence appears somewhat consistent with a Medicare claim data analyses that had shown that almost 42% of patients diagnosed with breast cancer has one or more co-morbidities.[46] This difference in comorbidities at the diagnoses of breast cancer is not due to the differences in age between AA/B and whites. Whites are diagnosed at an older age and should have higher number of existing comorbidities yet AA/B still experience higher rates of existing comorbidities despite being diagnosed with breast cancer at a younger age. The Charlson co-morbidity index does not include hypertension in its 17-listed comorbidities, and based on a prior study by Braithwaite et al[39] we added hypertension for comparative analyses. As expected, the score for AA/B breast cancer patients increased disproportionally compared to the increase in white patients.

Causes of death between African American and whites showed marked differences as well. In the larger study group (n=2558), AA/B experienced higher rates of death from breast cancer compared to whites. However, in the smaller group of n=416 with comorbidity index included, the difference between blacks and whites was reduced. A possible reason could be that rate of co-morbidities differed between the two study samples, although we employed a randomization scheme to create the smaller sample for the chart review. We base this hypothesis on prior studies that have shown, paradoxically, that delays or under treatment for conditions such as diabetes and myocardial infarction can actually result in increased breast cancer specific mortality[26.] More so, it is well-established that AA/B have a higher prevalence of undertreated and uncontrolled diabetes. [31]

Survival Analyses. We employed the traditional Cox Proportional Hazards regression model and, for comparison, the subdistributional hazard model, which has been found to provide a more accurate estimate of risk when there is a high degree of deaths from other causes in the study population (i.e., competing risks).[46-48] Among patients diagnosed with Local Stage disease, when the traditional Cox method with breast cancer specific mortality as the end-point (all other endpoints censored) was employed in the larger sample (n=2558), we observed comparable mortality risks for African American and whites (HR=0.966 95% CI 0.865-1.079), yet the subdistributional method

showed an increase in breast cancer mortality risk for African Americans (SD-HR=1.434 95% CI 0.969-2.122). The corresponding estimates for Regional Stage were (HR=1.307 95% CI 1.125-1.519 and SD-HR=1.841 95% CI 0.1.339-2.530). It appears, therefore, that the traditional model appears to have indeed overestimated hazard mortality for whites. On the other hand, the analyses for the small sample (n=416), did not show these patterns, and showed a reduced risk of breast cancer specific mortality among blacks compared to whites (SD-HR=0.17 95% CI 0.03-0.92) at the local level. The Cox method however revealed no differences (HR=0.97 95% CI 0.70-1.17).

Regarding the addition of co-morbidity scores into the multivariate models, we observed that at the local stage breast cancer-specific mortality for AA/B was significantly reduced suggesting that existing comorbidities might drive mortality when the cancer burden is low. Racial disparities in breast cancer-specific mortality were also noted when using the subdistribution analysis in Regional Stage with higher breast cancer-specific mortality, pointing towards a greater burden of death at the advancing stage. The impact of comorbidities is prevalent in local stage versus the regional stage possibly due to the increased mortality risk resulting from the added anatomical burden of regional disease. This is consistent with our previous findings from 2015 that emphasized the role of existing conditions as playing a role for AA/B in worsening their survival outcomes particularly at the local stage level. Prior studies also have shown that the presence of a co-morbidity at the time of diagnosis of breast cancer have significantly worse survival outcomes.[14] The combined effects of advanced stage and existing comorbidities for AA/B compared to whites suggests a possible additive or multiplicative effect.

Our findings are not consistent, however, with Schairer and colleagues who have shown a lower breast cancer specific mortality at regional stage with advanced age. Other studies have shown a larger effect of all cause mortality with advancing age.[50-51]. While Schairer et al did not account for comorbidities, they speculated that higher probability of death from breast cancer and other causes in blacks compared to whites might also be attributed to obesity related morbidities.[49] Breast cancer-specific mortality showed results that were independent of age, breast cancer subtype and race. AA/B race was not a prognostic factor for worsening breast cancer-specific mortality hazard

ratio but rather the advancing stage and comorbidities seem to play a role. Adding the Charlson Co-morbidity Index in the model showed significant differences for AA/B risks for breast cancer mortality at the local stage. Other studies have also shown an increase in mortality rate from other causes with advancing age.[49-50] There are also reports that look at 5 to 8 year relative survival showing no decline in breast cancer mortality with advancing age.[51-52]

Further exploration can point towards treatment differences, poorly controlled conditions and possibly genetic differences such as higher prevalence of sickle cell anemia. African Americans have a high prevalence of sickle cell trait. Results from National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that stage and pathological differences did not fully account for differences in outcome between African Americans and white women with breast cancer. In addition when stage and treatment was comparable, blacks and white breast cancer patients had similar outcomes. Despite the fact that clinical differences are important for breast cancer survival prognosis, appropriate and timely treatment may yield better outcomes for African American women with breast cancer.[43] Previous literature review and case reports have shown adverse events in breast cancer patients with sickle cell trait possibly due to higher chances of hypoxia and sickling resulting from cancer therapy. Literature indicates that in the presence of sickle cell trait, enhanced patient monitoring and treatment adjustment is needed. Furthermore, genotyping might be another necessary step for African Americans with breast cancer prior to treatment.[44-45]

African women also experience high CCI hazard ratio breast-cancer specific mortality rate due to existing comorbidities at the local stage. White Americans with the same comorbidity index score, not showing the same detrimental increase in CCI hazard compared to African American women, may indicate that presence of poorly controlled conditions like hypertension, cardiovascular disease and diabetes can be responsible for worse breast cancer specific outcomes for African Americans. It may also be due to certain genetic predispositions such as sickle cell trait that has been overlooked. In addition, it reinforces the need to further investigate the clinical and pathophysiological differences in existing conditions between different racial groups.

Public health implications:

Complex and interwoven factors contribute to observed disparities in breast cancer deaths among racial and ethnic minorities. The probability of death from causes other than breast cancer in the presence of competing risks appears to be a more accurate measure of mortality across different ethnicity/racial group. While socioeconomic factors have been under extensive study, existing conditions such as cardiovascular disease and diabetes are the emerging competing risks that play a role in cancer survival and treatment. One of the main goals of public health is to eliminate health disparities using improved prognostic information by assessing the burden of mortality from breast cancer and other causes by race and comorbidities. Studying breast cancer survival differences among the racial minority help us draw a map of the contributing factors and their possible solution. This study will help to elucidate if AA/B and white differ in competing risks for breast cancer mortality and all-cause mortality. By understanding the risks, we can focus on reducing these risk factors in both African American and white breast cancer patients.

Strengths and Limitations:

We had multiple strengths in our study. Our population was derived from reputable NCI-SEER Tumor registry of Connecticut. One of the strength of our analyses was establishing a comorbidity index score for our breast cancer patients with the addition of hypertension, which confirmed higher rates of co-morbidities scores for AA/B vs. Whites at the time of breast cancer diagnoses. Our n=416 sample was comparable to our larger study population and showed similar histopathological findings. More so, our histopathological findings such as TNBC subtype and tumor subtypes were concurrent with other cancer survival studies. There are two main limitations to this study. One limitation of this study was sample size due to which we were not able to look at specific co-morbidities such as diabetes and myocardial infarction separately. Another limitation that came with the small sample was not having large enough numbers of cardiovascular or diabetes deaths. Therefore, the causes of death had to be studied as breast cancer versus non-breast cancer. Lack of treatment data is another potential limitation given that a number of studies have shown that different treatment patterns may explain some survival disparities in breast cancer.

Table 1a: **Clinicopathological Characteristics of Breast Cancer Patients (According to Race, Age, NCI SEER Tumor Registry, and TNBC)**

	N=2558			N=416		
	White n=1405	**AA/B n=1152**	**P-Value**	**White n=214**	**AA/B n=202**	**P-Value**
Age						
<=40	80	123		11	30	
	5.8%	10.8%		5.1%	14.8%	
>40	1285	1011	<.0001	203	172	0.005
	94.1%	89.1%		94.8%	85.1%	
Mean Age	62	57		58	55	
(SD)	54.9%	45.1%	.721	51.4%	48.6%	<.0001
Histological Subtype *						
Ductal	907	777		124	127	
	67.1%	68.6%		57.9%	62.9%	
Lobular	139	63		24	12	
	10.3%	5.6%	<.0001	11.2%	5.9%	0.043
Mixed (Ductal, Lobular)	191	143		52	37	
	14.1%	12.6%		24.3%	18.3%	
Medullary	6	33		2	4	
	0.4%	2.9%		0.9%	2.0%	
Other	109	116		12	20	
	8.1%	10.2%		5.6%	10.9%	
SEER Summary Stage						
Local	885	637		145	119	
	65.8%	57.1%	<.0001	68.7%	62.0%	0.209
Regional	393	411		66	73	
	29.2%	36.9%		31.3%	38.0%	
TNBC subtype						
ER- PR- HER2-	117	243		35	52	
	12.8%	30.3%	<.0001	16.4%	25.7%	<0.0001
ER- PR- HER2+	39	80		6	20	
	4.3%	10.0%		2.8%	9.9%	
ER / PR+ HER2-	637	397		143	117	
	69.7%	49.6%		66.8%	57.9%	
ER / PR+ HER2+	121	81		30	13	
	13.2%	10.1%		14.0%	6.4%	

Table 2 CCI score with and without HBP (n=416)

	White	Black	P Value
CCI score			
0	177 82.7%	119 58.9%	
1-2	24 11.2%	52 25.7%	<.0001
3+	13 6.1%	31 15.3%	
CCI score with HBP			
0	130 60.7%	79 39.1%	
1-2	64 29.9%	84 41.6%	<.0001
3+	20 9.3%	39 19.3%	

Table 3 Vital Status, Survival and Cause of Death in relation to Whites and AA/B

	N=2558		P-Value	N=416		P-Value
	White	**Black**		**White**	**Black**	
Alive	913 65.4%	687 60.5%	**.011**	166 77.6%	31 65.8%	**.008**
Median Survival (years)	10.2	10.4		9.7	10.3	
Cause of Death						
Breast Ca	182 37.7%	225 50.1%		21 43.8%	35 50.7%	
Other Ca	63 13.0%	55 12.2%	**.001**	8 16.7%	8 11.6%	**.810**
CVD	86 17.8%	64 14.3%		6 12.5%	7 10.1%	
Non-CVD and Other/Unk	152 31.5%	105 23.3%		13 27.1%	19 27.5%	

Table 4 Multivariate* All-Cause Hazard Ratios and 95% CIs with and without Charlson Co-Morbidity Index (CCI)

	n=2558	n=416	n=416
Local Stage			
	Black vs. White HR	**Black vs. White HR**	**Black vs. White CCI HR**
No CCI	.973 0.872-1.087	0.955 0.741-1.231	
With CCI	-	0.906 0.700-1.173	**1.363** **1.223-1.518**
Regional Stage			
No CCI	**1.310** **1.128-1.522**	1.088 0.753-1.572	
With CCI	-	1.006 0.691-1.466	**1.129** **1.032-1.236**

Table 5 Multivariate* Breast Cancer Specific Hazard Ratios and 95% CIs with and without Charlson Co-Morbidity Index

	n=2558		n=416	
	HR	**SD-HR**	**HR**	**SD-HR**
Black vs White				
Local Stage				
No CCI	0.966 0.865-1.079	1.434 0.969-2.122	0.955 0.739-1.233	0.870 0.290-2.613
With CCI			0.906 0.700-1.173	**0.168** **0.031-0.902**
Regional Stage				
No CCI	**1.307** **1.125-1.519**	**1.841** **1.339-2.530**	1.061 0.733-1.535	**2.378** 1.106-5.113
With CCI			0.980 0.671-1.429	1.999 0.902-4.346
			CCI HR	
	Local Stage		**1.363** **1.223-1.518**	**2.088** **1.633-2.670**
	Regional Stage		**1.132** **1.034-1.240**	**1.167** **1.063-1.280**

Fig 1a.

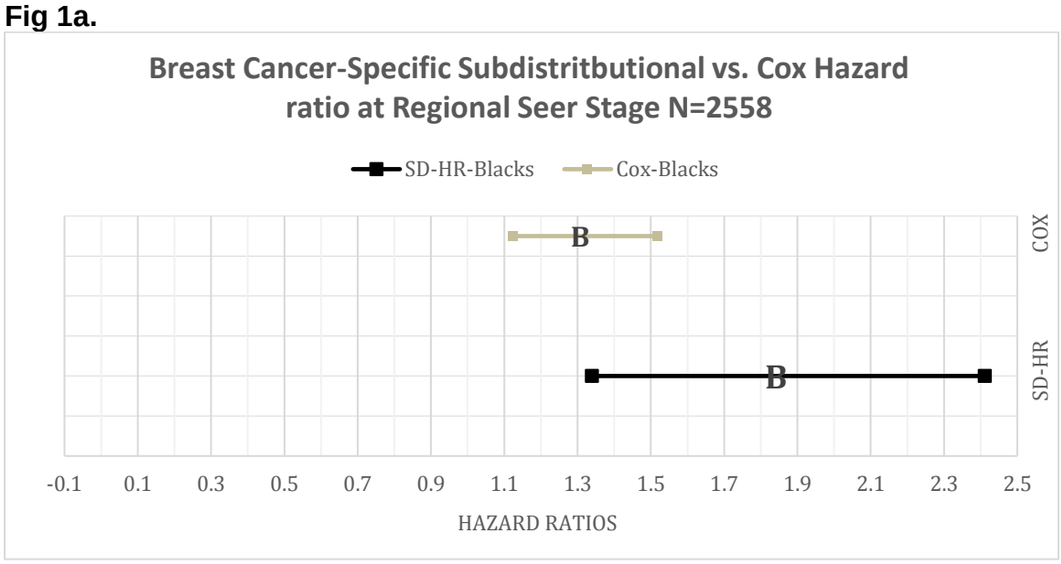
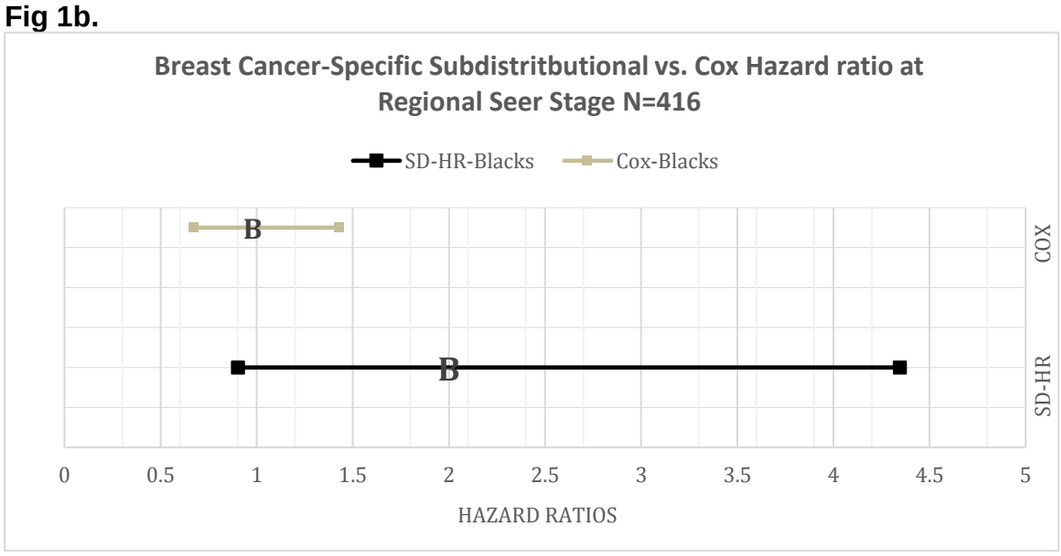

Breast Cancer-Specific Subdistritbutional vs. Cox Hazard ratio at Regional Seer Stage N=2558
SD-HR-Blacks
Cox-Blacks
B
B
COX
SD-HR
-0.1
0.1
0.3
0.5
0.7
0.9
1.1
1.3
1.5
1.7
1.9
2.1
2.3
2.5
HAZARD RATIOS

Fig 1b.


Breast Cancer-Specific Subdistritbutional vs. Cox Hazard ratio at Regional Seer Stage N=416
SD-HR-Blacks
Cox-Blacks
B
B
COX
SD-HR
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
HAZARD RATIOS

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