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RACIAL DIFFERENCES IN BREAST CANCER OUTCOMES BY HEPATOCYTE GROWTH FACTOR PATHWAY EXPRESSION

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Abstract

Purpose: Black women have a 40% increased risk of breast cancer-related mortality. These outcome disparities may reflect differences in tumor pathways and a lack of targetable therapies for specific subtypes that are more common in Black women. Hepatocyte Growth Factor (HGF) is a targetable pathway that promotes breast cancer tumorigenesis, is associated with basal-like breast cancer, and differentially expressed by race. This study assessed whether a 38-gene HGF expression signature is associated with recurrence and survival in Black and non-Black women.

Methods: Study participants included 1,957 invasive breast cancer cases from the Carolina Breast Cancer Study. The HGF signature was evaluated in association with recurrence (n=1,251,

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171 recurrences), overall, and breast-cancer specific mortality (n=706, 190/328 breast cancer/ overall deaths) using Cox proportional hazard models.

Results: Women with HGF positive tumors had higher recurrence rates [HR 1.88, 95%CI (1.19, 2.98)], breast cancer specific mortality [HR: 1.90, 95%CI (1.26, 2.85)], and overall mortality [HR: 1.69; 95%CI (1.17, 2.43)]. Among Black women, HGF positivity was significantly associated with higher 5-year rate of recurrence [HR: 1.73; 95%CI (1.01, 2.99)], but this association was not significant in non-Black women [HR 1.68; 95%CI (0.72, 3.90)]. Among Black women, HGF-positive tumors had elevated breast cancer-specific mortality [HR 1.80, 95%CI (1.05, 3.09)], which was not significant in non-Black women [HR:1.52; 95%CI (0.78, 2.99)].

Conclusion: This multi-gene HGF signature is a poor-prognosis feature for breast cancer and may identify patients who could benefit from HGF-targeted treatments, an unmet need for Black and triple negative patients.

Keywords

Breast cancer; Hepatocyte Growth Factor

Introduction

In the United states, Black women experience earlier breast cancer recurrence, higher breast cancer specific mortality rates, and poorer overall survival compared to white women[1–6]. It is unclear why these disparities in breast cancer outcomes persist. One explanation is more prevalent aggressive tumor subtypes; triple-negative/basal-like breast cancer has been shown to be more than twice as common among Black women than other racial groups[1,7]. However, this tumor subtype is challenging to target because it lacks hormone receptors and HER2. While these tumors are positive for epidermal growth factor receptor [8], clinical trials targeting EGFR in triple negative breast cancer patients have had limited success[9,10]. Thus the current standard of care is to treat basal-like cancers with chemotherapy, and while many basal-like tumors are sensitive to chemotherapy, these tumors are more likely to recur and have poorer short-term survival[11]. Identifying novel, targetable approaches is therefore of high importance for addressing outcome disparities.

The hepatocyte growth factor (HGF) pathway is an important pathway regulating the tumor microenvironment and has been found to be associated with breast tumorigenesis [12–16]. Clinical and laboratory based studies have found that the HGF/c-MET axis may be an important feature of triple negative/basal-like tumors [14,17–19]. Charafe-Jauffret et al. molecularly characterized 31 breast cell lines for breast cancer subtype classification (luminal vs basal-like) and found that the gene for HGF receptor c-MET was one of 10 genes associated with basal-like cell line classification[17]. Clinical trials have targeted the HGF pathway in breast cancer patients; however these studies have lacked methods for identifying patients who are most likely to benefit; there is an ongoing need for an effective predictive biomarker for HGF expression[20,21].

Here we present a 38-gene HGF gene expression signature as a candidate biomarker for HGF pathway function in invasive breast tumors. We examined the association of the

HGF signature with breast cancer recurrence and survival outcomes in the racially diverse Carolina Breast Cancer study.

Methods

Study population

The Carolina Breast Cancer Study (CBCS) is a North Carolina population-based study that has been described in detail previously[22,23]. Briefly, CBCS utilized rapid case ascertainment from the North Carolina Central Cancer Registry to identify new breast cancer cases. Inclusion criteria for all three study phases included North Carolina (NC) residency at diagnosis, English fluency, and age from 20–74 years old. Black women and women under the age of 50 were oversampled for participation, such that 50% of the population was Black and 50% is under age 50.

Phases 1 and 2 of CBCS were conducted in 24 central NC counties from 1993–2001. Overall and breast cancer specific survival were collected via linkage to the National Death Index through December 2018. Phase 3 of the Carolina Breast Cancer Study extended the original 24-county area to 44 counties. Phase 3 also collected recurrence information by medical record abstraction through December 2018 to calculate disease free survival. Phase 3 has not yet been linked to the National Death Index because patients are still being followed by medical-record; thus NDI-recorded deaths for Phase 3 participants are not yet available.

Formalin fixed paraffin embedded (FFPE) invasive breast cancer tumors were collected from all three phases of CBCS to assess RNA expression. Among the CBCS cases with gene expression data (n= 4,162), only women with invasive tumors and complete expression data for the 38-gene HGF expression signature were included in the current analysis (n=1,975). Among these, 706 women were from CBCS-1/2 and had breast cancer-specific and overall mortality data, and 1,251 women were from CBCS-3 and had recurrence data. Informed consent was obtained from each study participant under a protocol approved by the University of North Carolina at Chapel Hill- Office of Human Ethics and Institutional Review Board.

Clinical and patient demographics

All patient demographics (race, age at diagnosis, and family history of breast cancer) were self-reported and obtained from Carolina Breast Cancer Study questionnaires. Body mass index was recorded by the study nurse. Clinical factors including estrogen receptor (ER) status, tumor stage, and combined grade were obtained from medical records, and pathology reports. Stage 4 participants were removed from the survival analysis because treatment of metastatic patients follows very distinct clinical pathways [CBCS-1/2 (n=20) and in CBCS-3 (n= 47)]. Information on tumor grade was only available from CBCS Phase 1 & 3 and thus analyses regarding tumor grade excluded Phase 2 participants (n=454).

Gene expression data

RNA was isolated from Formalin fixed paraffin embedded (FFPE) invasive breast cancer tumor tissues using the Qiagen FFPE RNeasy isolation kit (Germantown, MD). RNA was quantified using Nanostring nCounter technology (Seattle, Washington), using a custom panel that included signatures for PAM50 (for classification of intrinsic breast cancer subtypes: luminal A, luminal B, HER2 overexpressing, basal-like- and normal-like) and the HGF 38-gene signature (classified as positive vs negative as described previously) [24,25]. Gene expression data were normalized using the RUVg function from the RUVSeq Bioconductor package as previously described by Bhattacharya et al.[26,27]. The HGF signature is a 38-gene weighted sum gene expression signature: *TMEM45B*, *AKR7L*, *AQP5*, *C1QTNF3*, *C2ORF27A*, *C4ORF31*, *C9ORF98*, *CAPN13*, *CASKIN1*, *CMYA5*, *DTX3*, *EFHD1*, *F7*, *FMNL2*, *FUT8*, *GCNT2*, *HRC*, *INPP4B*, *ISLR2*, *KCNMA1*, *KCNN4*, *KIF3A*, *MAGI2*, *MARVELD2*, *NME5*, *PKIB*, *PRRG2*, *PRRT2*, *PVRL2*, *REEP6*, *RIMS4*, *SCUBE2*, *SHROOM3*, *SKAP1*, *SYBU*, *TFF3*, and *TMSB15B* [25]. Tumors are characterized as HGF-positive if expression profiles match expression profiles of HGF protein treated breast cancer cells as described in Casbas-Hernandez et al[19].

Statistical methods

Descriptive analyses for demographic variables were calculated using frequency data for each clinical and patient characteristic. For survival analyses, proportional hazard assumptions were assessed using visual inspection of Kaplan Meier plots on the distribution of HGF gene expression signature and survival outcomes (disease-free, overall and breast cancer specific survival). Schoenfeld tests and residual plots were also used to test the proportional hazards assumption. HGF gene signature expression violated the proportional hazard assumption for overall/breast cancer-specific and disease-free survival. For this analysis 5-year risks/hazards are reported, as well as log-rank p-values over multiple time points (5-year & 10-year).

Overall survival is defined as time from study enrollment to death of any cause, and breast cancer specific survival is defined as time from breast cancer diagnosis to breast cancer-related death. In breast cancer specific survival analyses, death due to other causes is a censoring event. Disease free survival was defined as time from study enrollment to subsequent breast cancer recurrence. Hazard ratios and 95% confidence intervals for the association of HGF gene expression signature and survival outcomes were produced using Cox proportional hazard models. Effect measure modification in this study was assessed using likelihood ratio tests. Age (<50, 50+ years) and race (Black vs non-Black) were evaluated as effect measure modifiers for recurrence (p-values < 0.07) and mortality outcomes with statistical significance thresholds set at $p < 0.10$. To retain power in the study, race classifications of Black vs non-Black were used, although sensitivity analyses removed women who did not identify as Black or non-Hispanic white (n= 37 for recurrence, n= 8 for overall/breast cancer specific survival) and did not significantly change the study findings. Hazard ratios stratified by race are presented in the current analysis. To control for confounding, inverse probability of exposure weights were applied to both recurrence (CBCS-3) and mortality data (CBCS-1/2). For CBCS 3 stabilized weights included adjustment for grade, age and stage. Mortality data used stabilized weights to adjust for

age and stage only because grade information was missing for CBCS 2 participants. All standardized hazard ratios and risks used robust variance estimation for calculation of confidence intervals. All statistical analysis were completed in Stata 15 SE. This analysis is in accordance with the criteria described in the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[28–30].

Results

In Table 1 we present HGF status according to demographic characteristics and CBCS study phase. HGF positive tumors were more prevalent among Black women [CBCS 1/ 2: 64% vs 36%; CBCS3: 72% vs. 28%] than in non-Black women and in women under the age of 50 [CBCS 1/ 2: 65% vs 35%; CBCS 3: 60% vs 40%]. HGF positivity was strongly associated with PAM50 basal-like subtype. Women with HGF positivity tended to have higher tumor stage, grade, and BMI. Family history was not associated with HGF positivity. Figure 1 shows unadjusted survival curves for recurrence (1A), breast cancer specific mortality (1B) and all-cause mortality (1C) according to HGF-positivity. Median follow-up time for recurrence was 6.8 years (min: 0.4. years, max:10.7 years), 17.8 years for breast cancer -specific and overall survival (min: 0.17 years, max: 23.6 years). HGF-positivity was associated with early recurrence. HGF-positive and -negative curves were significantly different at 5 years of follow up (5- year log-rank p-value= 0.006), but this effect was attenuated over time and was no longer statistically significant at 10 years (10-year log-rank p-value= 0.07). Next, we assessed the association with HGF and breast cancer specific survival (Figure 1B). We found a pattern similar to that for recurrence, where HGF-positivity was related to early mortality (5-year log-rank p-value= 0.001), but the association attenuated with time (10- year log-rank p-value=0.45). Finally, the overall survival curves (Figure 1C) also showed HGF-positivity was a contributor to poorer survival compared to HGF negative tumors within the first 5 years of diagnosis (5-year log-rank p-value=0.006), but differences were not statistically significant at the 10- year mark (10-year log-rank p-value=0.37). HGF signature expression was not associated with overall mortality or breast cancer specific -mortality at longer periods of follow-up (? 10 years, p-value >0.05) (data not shown), however data were truncated at 10 years due to crossing hazards.

HGF-positivity is associated with basal-like subtype and with higher proliferation rates, both of which may mediate effects of this pathway on outcomes[25]. Therefore, we did not adjust for molecular subtype in assessing the effects of HGF-positivity on outcomes. However, we were interested to know whether HGF-positivity was associated with outcomes independent of standard clinical features (stage and grade). Table 2 shows estimates of the magnitude of association between HGF-positivity and breast cancer recurrence, overall and stratified on age and race. Women with HGF positive tumors had higher recurrence than women with HGF negative tumors [HR: 1.88; 95% CI (1.19, 2.98)]. Standardized 5-year risk of recurrence for HGF positive tumors was 18% compared to HGF negative tumors with a 10% standardized risk of recurrence. This pattern was apparent in analyses restricted to Black women [HR 1.73; 95%CI (1.01, 2.99)], but not significant among non-Black women [HR 1.68; 95%CI (0.72, 3.90)]. HGF-positivity was less common (17%) among non-Black women compared to Black women (37%). Black women with HGF positive

tumors had the highest 5-year risk of recurrence [20%; 95%CI (12%, 29%)]. Age did not modify the association between HGF-positivity and recurrence, with similar hazard ratio estimates for both age-defined strata [HR: 1.95; 95%CI (1.09, 3.50) for women <50 vs HR: 1.82; 95%CI (0.88, 3.75) for 50+]. Supplemental Table 1 shows 10-year risk of recurrence remains elevated for HGF-positive (vs. HGF-negative women) although differences were attenuated compared to at 5 years. Analyses stratified on basal-like subtype showed a slight, non-significant, increased risk of recurrence among Basal-like HGF positive tumors (HGF+ = 21.93% risk of recurrence, HGF- = 19.78%, data not shown).

Patterns for mortality were similar to those for recurrence and suggested an early impact of HGF status on outcomes (Table 3). HGF positive tumors had almost twice the rate of breast cancer specific mortality of HGF negative tumors [HR: 1.90; 95%CI (1.26, 2.85)], and again, the increase was statistically significant among Black [HR: 1.80; 95%CI (1.05, 3.09)] but not non-Black women [HR:1.52; 95%CI (0.78, 2.99)]. For 5-year breast cancer specific mortality, HGF-positivity was significantly associated with outcomes among women over the age of 50 [HR: 2.81; 95%CI (1.38, 5.70)], but not among women under 50 [HR: 1.53, 95%CI (0.94, 2.50)]. Similarly, 5-year overall mortality was associated with HGF positivity [HR: 1.69; 95%CI 1.17, 2.43)], but was only significant in women over 50 [HR: 2.08, 95%CI (1.19, 3.64) vs. HR:1.43, 95%CI (0.89, 2.29) for women <50]. HGF-positivity was not associated with 10-year breast cancer-specific and 10 year-overall mortality (Supplemental Table 1).

Discussion

We found that HGF positive tumors have poorer 5-year recurrence and mortality, especially among Black women where HGF positivity is more prevalent. Associations with HGF positivity were attenuated at the 10-year mark, supporting a potential role for HGF as an early prognostic factor in breast cancer-related outcomes. This early recurrence pattern also aligns with prior literature for basal-like breast cancer, showing that more aggressive subtypes like basal-like tend to recur early compared to less aggressive subtypes (i.e. luminal)[11,25], underscoring HGF gene expression as one hallmark of basal-like breast cancer.

Our results are concordant with other studies that have assessed the prognostic value of HGF expression with breast cancer recurrence and survival. Raghav et al. measured HGF pathway expression via c-MET and phosphorylated-MET protein levels in 257 breast cancers and found that HGF overexpression was correlated with increased recurrence and poorer overall survival within 5 years[31]. Also two separate meta-analyses examining the prognostic value of c-MET overexpression by a variety of RNA and protein based detection methods concluded that c-MET overexpression is associated with both breast cancer recurrence and overall survival[32,33]. In contrast, a large Dutch male breast cancer cohort (n= 841) found that HGF protein expression (as measured by immunohistochemistry) was protective against overall survival[34], however, this population is quite distinct and male breast cancer is predominantly of luminal subtype, which we found to have lower prevalence of HGF expression[34,35]. Our results add important new data based on a large, diverse study population. Racial diversity in the previous published literature on HGF is lacking.

The MET/HGF pathway has also been implicated in radioresistance, chemoresistance and targeted therapy resistance in several studies[36]. Also, some compounds in phase 3 clinical trials have not been able to sufficiently suppress HGF/MET signaling[36]. Identifying high risk populations that could benefit from HGF/MET targeted therapies in combination with traditional cancer treatment regimens and/or targeted therapies may improve breast cancer outcomes.

Our study has several strengths. One strength is that our HGF gene expression biomarker can be applied to formalin fixed paraffin embedded tumors. Furthermore, HGF is a soluble protein and c-MET is a receptor tyrosine kinase that can translocate to cell nuclei and both may be difficult to assay in a clinical setting [37]. Our multi-gene HGF expression signature captures that pathway as a whole and may be a candidate for clinical studies. Previous HGF-targeted trials have not identified predictive biomarkers for identifying participants that could benefit from HGF targeted therapies. Our study was also statistically powered to assess expression of this signature in relation to breast cancer outcomes in Black and young women, populations known to have the highest burden of adverse breast cancer outcomes, and who, in our study, had higher rates of HGF-positivity. Within our study we recognize race is a social construct. Race captures the interplay between social factors (e.g., discrimination or barriers to care) and biological factors (e.g., ancestry) that may contribute to breast cancer recurrence and mortality. Our findings support that there are racial differences in the prevalence of the HGF positive signature expression, and this could be the result of differences in genomic regulation of HGF as reported in clinical studies of HGF expression by race [38,39].

Our study also has some limitations. There was the potential for some selection bias in the tumors assayed, namely because some CBCS-1/2 tumor blocks had been depleted (13%). This would most likely bias the proportion of HGF-positive tumors upward, because tumors with residual blocks tended to have larger tumor size. However, we do not expect these missing data to distort the relationship between HGF positivity and survival outcomes. We also did not have the same outcomes on all participants (CBCS 1/ 2 had overall & breast-cancer specific mortality and CBCS 3 had recurrence data), however this allowed us to perform separate, independent time-to-event analyses in two similar populations. The concordance in direction of effect across these distinct datasets underscores the consistency of the associations we observed. Finally, we did not assess the effects of the HGF pathway independent of tumor subtype. This is because HGF is highly prevalent in basal-like breast cancers, verging on being a defining feature of this subtype, and we were interested in assessing whether it predicted outcomes, even if mediated by basal-like or proliferation-related gene expression.

Identification of pathways that can be targeted in triple negative/ basal-like tumors is important because of the poor prognosis and lack of available therapies for these subtypes. HGF is a stroma-derived targetable factor that may reflect a microenvironment-mediated pathway to aggressiveness in breast cancer[19,40–43]. Future studies should focus on evaluating the HGF gene expression signature to identify patients that may experience clinical benefit from HGF-targeted therapies. Predictive biomarkers that lead to targeted

treatment of basal-like breast cancers could play an important role in reducing disparities in breast cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The datasets generated during the current study are available from the corresponding author upon reasonable request. The code in this study is available from the corresponding author upon reasonable request.

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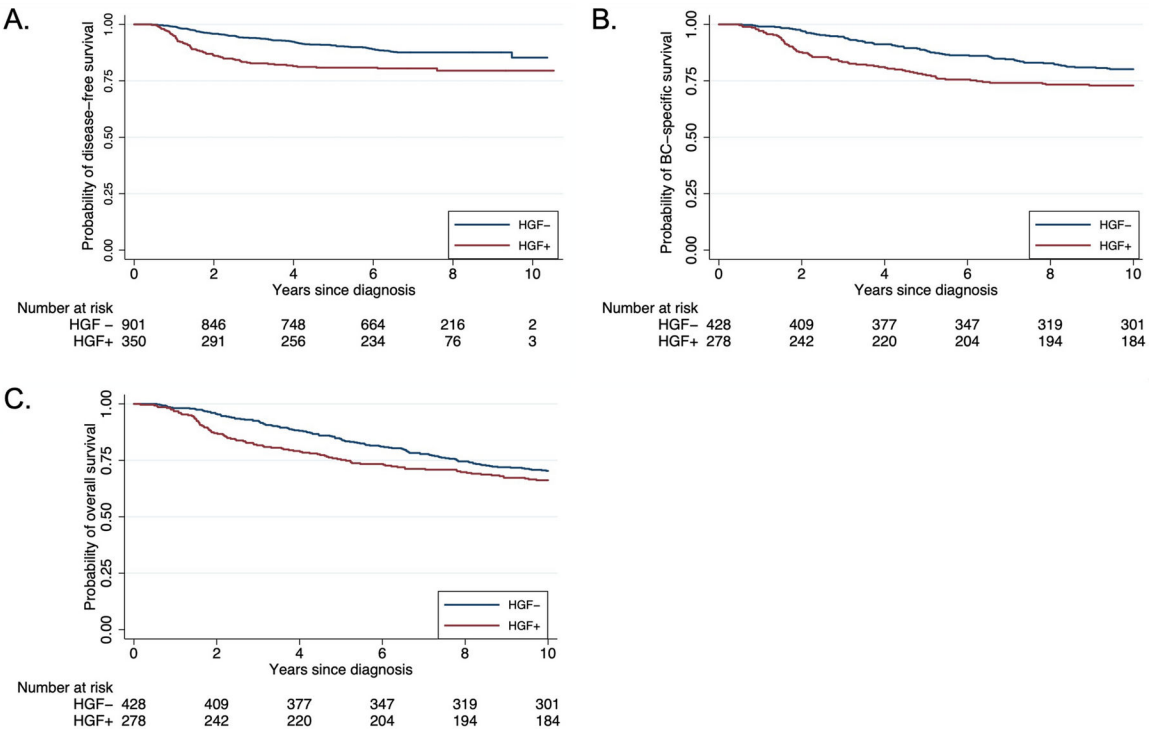

Fig 1. Kaplan Meier Plot of HGF association with survival outcomes in Carolina Breast Cancer Study.

Panel A- disease-free survival (CBCS-3), Panel B- breast cancer specific survival (CBCS-1/2), Panel C- overall survival (CBCS-1/2).

Table 1.

38-gene HGF status, patient, and clinical characteristics among Carolina Breast Cancer Study participants by study phase (CBCS-1/2, 1993–2001; CBCS-3, 2008–2013)

	CBCS 1 & 2 (N=706)		CBCS 3 (N=1251)	
	HGF Negative (N=428)	**HGF Positive (N= 278)**	**HGF Negative (N= 901)**	**HGF Positive (N=350)**
Race				
Black	171 (40%)	179 (64%)	432 (48%)	251 (72%)
Non-Black	257 (60%)	99 (36%)	469 (52%)	99 (28%)
Age at diagnosis				
< 50	208 (49%)	181 (65%)	442 (49%)	211 (60%)
50+	220 (51%)	97 (35%)	459 (51%)	139 (40%)
ER status				
Positive	315 (74%)	54 (20%)	798 (90%)	67 (21%)
Negative	108 (26%)	221 (80%)	89 (10%)	253 (79%)
PAM50				
Luminal A	283 (69%)	20 (8%)	535 (62%)	11 (3%)
Luminal B	74 (18%)	6 (2%)	214 (25%)	13 (4%)
HER2- Enriched	40 (10%)	23(9%)	82 (9%)	35 (10%)
Basal	13 (3%)	216 (81%)	32 (4%)	277 (83%)
Stage**				
Stage I	152 (38%)	74 (28%)	347 (40%)	84 (25%)
Stage II	208 (52%)	164 (62%)	397 (46%)	185 (55%)
Stage III	40 (10%)	25 (10%)	124 (14%)	67 (20%)
Grade*				
I/II	86 (62%)	28 (26%)	605 (68 %)	43 (12%)
III	52 (38%)	81 (74%)	285 (32%)	303 (88%)
BMI				
Median BMI (IQR)	27.10 (8.85)	28.99 (9.50)	29.66 (9.73)	30.52 (9.30)
Family history of breast cancer				
Yes	346 (83%)	217 (82%)	707 (81%)	280 (82%)
No	73 (17%)	49 (18%)	162 (19%)	61 (18%)

*Tumor grade was not collected in CBCS-2 and therefore was missing from 454 participants in CBCS-2. Tumor grade was missing from less than 2% of patients in CBCS-1 & CBCS-3.

**Stage 4 women were excluded (<3% for CBCS-1/2, <4% CBCS-3)

IQR: Interquartile range; ER: Estrogen receptor; BMI: Body Mass Index;

Table 2.

Risk or recurrence and hazard ratios by HGF signature status, race and age in Carolina Breast Cancer Study phase 3

	HGF	N (recurrences)	Crude 5-year risk of recurrence	*Standardized 5-year risk of recurrence	*Standardized 5-year Hazard ratio HR (95%CI)
	HGF-	901 (79)	8.76% (6.92, 10.61)	10.29% (8.01, 12,57)	Referent
	HGF+	350 (65)	18.57%(14.49, 22.65)	18.00% [11.62, 24.38)	**1.88 (1.19, 2.98)**
Non-Black	HGF-	469 (31)	6.61% (4.35,8.86)	7.90% (5.06, 10.74)	Referent
	HGF+	99 (18)	18.18% (10.55,25.81)	12.61% (3.54, 21.69)	1.68 (0.72, 3.90)
Black	HGF-	432 (48)	11.11% (0.81,14.08)	12.76% (9.18,16.32)	Referent
	HGF+	251 (47)	18.72% (13.89,23.56)	20.42% (12.21, 28.62)	**1.73 (1.01, 2.99)**
< 50	HGF-	442 (43)	9.72% (6.96,12.49)	11.42% (8.00,14.86)	Referent
	HGF+	211 (40)	18.96% (13.65,24.25)	20.22% (11.43, 29.01)	**1.95 (1.09, 3.50)**
50+	HGF-	459 (36)	7.84% (5.38,10.31)	9.06% (6.10, 12.03)	Referent
	HGF+	139(25)	17.99% (11.57,24.39)	15.65% (6.47,24.84)	1.82 (0.88, 3.75)

*Recurrence was standardized using inverse probability of exposure weights for tumor grade, age, and stage.

Table 3.

Risk of mortality and hazard ratios by HGF signature status, stratified by race and age in Carolina Breast Cancer study phase 1 and 2

	HGF	N (deaths)	Crude 5-year risk	*Standardized 5-year risk	*Standardized 5-year HR (95%CI)
Breast cancer specific mortality					
	HGF-	428 (48)	11.21% (8.22, 14.21)	11.37% (8.12, 14.62)	Referent
	HGF+	278 (62)	22.30% (17.40,27.20)	20.09% (15.18, 24.99)	**1.90 (1.26,2.85)**
Non-Black	HGF-	257 (24)	9.34% (5.78, 12.90)	9.84% (5.91, 13.77)	Referent
	HGF+	99 (17)	17.17% (9.70, 24.64)	14.45% (7.45, 21.46)	1.52 (0.78,2.99)
Black	HGF-	171(24)	14.03% (8.81, 19.26)	13.79% (8.14, 19.44)	Referent
	HGF+	179 (45)	25.13% (18.77,31.52)	23.16% (16.66, 29.66)	**1.80 (1.05, 3.09)**
<50	HGF-	208 (32)	15.38% (10.47,20.29)	15.00% (9.87, 20.12)	Referent
	HGF+	181 (43)	23.76% (17.53,29.97)	21.51% (15.40, 27.63)	1.53 (0.94,2.50)
50+	HGF-	220 (16)	7.27 (3.83, 10.71)	6.95% (3.43, 10.47)	Referent
	HGF+	97 (19)	19.59% (11.64,27.52)	18.34% (10.39, 26.29)	**2.81 (1.38,5.70)**
Overall mortality					
	HGF-	428 (66)	15.42% (11.99,18.85)	14.82% (11.24, 18.40)	Referent
	HGF+	278 (69)	24.82% (19.73,29.91)	23.29% (18.06, 28.52)	**1.69 (1.17, 2.43)**
Non-Black	HGF-	257 (34)	13.23% (9.07, 17.37)	12.48% (8.19, 16.76)	Referent
	HGF+	99 (18)	18.18% (10.54,25.81)	15.35% (8.18, 22.51)	1.28 (0.68,2.39)
Black	HGF-	171 (32)	18.71% (12.85,24.57)	18.53% (12.28, 24.78)	Referent
	HGF+	179 (51)	28.49% (21.86,35.12)	27.63% (20.66, 34.59)	1.60 (0.99,2.58)
<50	HGF-	208 (35)	16.83% (11.73,21.92)	16.54% (11.21, 21.86)	Referent
	HGF+	181 (44)	24.31% (18.04,30.58)	22.09% (15.91, 28.27)	1.43 (0.89,2.29)
50+	HGF-	220 (31)	14.09% (9.48, 18.70)	12.73% (8.15, 17.32)	Referent
	HGF+	97 (25)	25.77% (17.02,34.52)	24.75% (15.89, 33.61)	**2.08 (1.19,3.64)**

*Mortality outcomes were standardized using inverse probability of exposure weights for age, and stage.