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Differences in breast cancer outcomes amongst Black US-born and Caribbean-born immigrants

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Abstract

Background—There are few studies that directly investigate disparities in outcome within the African diaspora in the US. We investigated the association between nativity of Black women diagnosed with breast cancer (Caribbean or USA place of birth) and ethnicity, age at diagnosis, treatment, tumor characteristics and outcome.

Methods—The data were obtained from the University of Miami Health System, and Jackson Health System. Individual-level data from 1132 cases was used to estimate hazard rations (HRs) of women born in the Caribbean (Caribbean Blacks, CB) or in the USA (US Black, USB) using Cox proportional hazards regression analysis for overall survival.

Results—The cohort contains data from 624 (54.9%) USB women and 507 (45%) CB women diagnosed with breast cancer between 2006 and 2017. Compared to CB patients, USB patients had

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Conflict of interest There are no conflicts of interest.

Research involving human and animal participants This study did not involve animals.

Compliance with ethical standards

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Author contributions SHLG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SHLG, JH, PB-C. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: SHLG, PB-C, JH. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: MS, SHLG, DC. Obtained funding: SHLG, JH. Administrative, technical, or material support: SHLG, JH. Supervision: SHLG, JH.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This was a retrospective study; informed consent was not sought.

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more Estrogen Receptor negative (31.4% vs. 39.1%, P = 0.018) and triple negative breast cancers (19.6% vs. 27.9%, P = 0.003). CB women presented at more advanced stages III/IV (44.2% vs. 35.2%; P = 0.016). CB patients showed a better overall survival (hazard ratio, HR = 0.75; 95% CI 0.59–0.96; P = 0.024). Overall Black Hispanic patients had a better overall survival (HR = 0.51; 95% CI 0.28–0.93; P = 0.028) compared to non-Hispanic Black patients.

Conclusion—In conclusion the study found that CB immigrants diagnosed with breast cancer have an improved overall survival when compared with USB patients. This finding suggests that within the African diaspora in the USA, additional factors beyond race contribute to worse outcomes in African Americans.

Keywords

Breast cancer; Caribbean-born Black; US-born Black; Health disparities

Introduction

Breast cancer is a frequent cause of morbidity and mortality in women of African descent living in the US [1, 2]. Although African American women have a similar incidence of breast cancer compared to white women they experience worse outcomes [1–3]. Breast cancer is diagnosed at more advanced stages in Black women than in White women, and Black women are disproportionally diagnosed with the most aggressive forms of this disease [2–4].

The Black population living in the US is not monolithic. In the United States, the number of newly arrived immigrants from the Caribbean has grown, exceeding those from Europe [5]. One in ten Blacks living in the US is foreign born [6]. With the history of the Slave trade, then immigration of indentured laborers (East Indian and Chinese) the Caribbean is now very heterogeneous but the majority of the study participants self-identified as African descent with other 'mixes' indicating that individuals could not accurately report their precise ancestry. Caribbean nationals make up over 50% of the Non-Hispanic Black immigrant population in the US [7, 8]. The largest contributors to Caribbean Black (CB) immigration are Haiti, Jamaica, the Dominican Republic and Trinidad & Tobago [6].

In Florida, the CB population has a lower cancer mortality rate when compared to the USborn Black population [6, 9, 10]. New York and Florida, which have the two largest CB communities in the US, report the lowest mortality rate among the 17 states with black populations over 1 million [9]. Etiological studies of the cancer risks among Caribbean immigrant women have been sparse and limited [11–16] but Caribbean-born women living in the US and in their native country were shown to have differences in incidence and outcomes of breast cancer from that of African American women [9, 12]. Because a significant portion of Caribbean women self-classifies as African-American it is necessary to consider the unique characteristics of the Caribbean population when analyzing breast cancer in women of African descent living in the US. We performed a detailed review of 1132 self-identified Black patients, born in the United States or born in the Caribbean from 18 different countries to undertake a systematic analysis on the effect of nativity on breast

cancer outcome in Black women. We aimed to determine associations between nativity, breast cancer characteristics, treatment and overall survival.

Methodology

Study cohort

This is a retrospective cohort study conducted with Institutional Review Board approval from the University of Miami (protocol #2016-0291). Patients were identified through the University of Miami Health System (UMHS) and Jackson Health System (JHS) institutional tumor registry. We collected data, through medical chart abstraction, from 1368 individuals diagnosed with breast cancer between the years 2006 and 2017 from the UMHS. UMHS is an academic medical center with a Comprehensive Cancer Center, and JHS, a non-profit safety net hospital. Standard of care at both sites are similar. All data were de-identified prior to analysis. The safety net hospital in our system provides care for all patients, regardless of citizenship status, as long as the patient resides within the county. Abstracted data included sociodemographic factors, genetic testing results, and treatment histories. Male patients were excluded from the survival analyses. The inclusion criteria encompassed: (1) males and females aged 18 years or older, (2) pathologically diagnosed with breast cancer, (3) born in the Caribbean or the US, (4) self-identify as African descent. Exclusion criteria included patients with unknown or any non-Caribbean/non-USA birthplaces. Eight hundred and twenty-nine patients from JHS and 538 patients from UMHS were included in this study.

Data variables

Data extracted includes: (1) patient demographics: weight and height; medical and family health history; hormone exposures: menopausal status, age at: menarche and menopause; age at diagnosis; date of diagnosis; smoking and alcohol habit, (2) tumor characteristics: tumor node metastasis (TNM) status, stage, ER, PR, HER2, grade; germline genetic testing results; type and date of surgery, use of neoadjuvant or adjuvant therapy, (3) survival data: date of death, dates of relapse and last contact.

Statistical analysis

The data were captured into REDCap, a secure web application, HIPPA compliant server at the University of Miami. For analysis purposes, the women were divided in two groups: US born Black (USB) and Caribbean-born Black (CB). The USB group was composed of Blacks born in the USA, the CB were born in the Caribbean (the countries included were: Anguilla, Antigua, Aruba, Bahamas, Barbados, Belize, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, British Guyana, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, Trinidad Tobago, Turks and Caicos Islands, Suriname, US Virgin Islands and West Indies). We excluded patients where place of birth was listed as: unknown (211), other (6) and non-Caribbean, non-USA born (19). Statistical analyses were performed using SPSS (IBM SPSS Statistics Version 24) and STATA IC 14.2 (StataCorp, College Station, TX) (Supplement Table 1). All patients were included in the analyses, even when missing specific data points. Summary statistics were used to describe the patient cohort. Wilcoxon rank-sum was used for continuous variables in nonparametric distributions. Chi square

testing (or Fisher's Exact, when appropriate) was used to analyze associations between categorical variables. Univariable and multivariable Cox proportional hazards regression, the log-rank test, and the Kaplan–Meier method were utilized to assess survival outcomes. All patients were included in the survival analyses, and censored at date of last follow-up or date of death (all cause). Stepwise backwards multivariable regression analyses only included covariates with p values 0.05 from the univariable models (excluding triple negative breast cancer to remove redundancies with ER, PR and HER2). All tests were two-sided, with significance set at P < 0.05.

Results

Cohort characteristics

Table 1 shows the demographics of the cohort. The cohort was composed of 1131 Black individuals with breast cancer. There were 5 males, comprising 0.4% of the total sample, and 1126 women. There were 624 (55.1%) US-born Blacks (USB) patients and 507 (45%) Caribbean Black (CB) patient. The proportion of breast cancer patients born in the US or in the Caribbean are similar by treating institutions. The majority of the patients were seen at safety net hospital (USB = 69.5% and CB = 70.2%) while the private care health system had less than a third of the cohort (USB = 30.5% and CB = 29.8%; P = 0.78). The most frequent countries of birth for the Caribbean Black patient cohort were: Haiti (49.2%), Jamaica (17.5%), Bahamas (8.5%), Dominican Republic (7.5%), Cuba (7.5%) and Trinidad & Tobago (2.8%).

The mean age of diagnosis of the entire cohort was 56.7 years (sd. 13.1 years). The mean age at diagnosis in CB patients was 55.7 (sd. 12.1) years while it was 57.6 (sd. 13.9) for USB patients (P= 0.020). The mean age of Hispanic Black (HB) patients was 56.6 years (sd. 10.6) and that of non-Hispanic Blacks (NHB) patients was 56.7 years (sd. 13.4). USB patients had a Higher Body Mass Index (BMI), (30.9) when compared to CB patients (29.6; P= 0.015). The USB patients had a higher use of tobacco (7.2% vs. 1.6%, P< 0.001) and alcohol (19.9% vs. 11.9%; P< 0.001) as compared to CB patients.

CB patients had more ER-positive and PR-positive tumors, (ER = 68.7% vs. 61%; P= 0.019 and PR = 58.3% vs. 50.4%; P= 0.02) than the USB breast cancer patients. The USB breast cancer patients had more triple-negative breast cancer (TNBC) subtypes (27.8% compared to 19.7%; P= 0.004). The USB patients underwent surgery more often (72.9% vs. 68.5%; P = 0.011). More CB breast cancer patients received radiation treatment (35.2% vs. 28.1%; P = 0.05) and chemotherapy (48.5% vs. 42.7%; P= 0.016), compared to USB patients. The CB breast cancer patients had more stage III and IV disease at presentation (44.2% vs. 35.2%; P= 0.016), when compared with USB patients. Genetic germline testing was offered to 79 patients (7%). The proportions of tested CB (n = 39; 7.7%) compared to USB (n = 40; 6.4%) showed no significant difference (P= 0.414). Of those tested, there was no significant differences in inherited germline mutations between USB (21.9%) and CB patients (20.5%) (P= 0.83).

Survival analysis

As expected for the entire cohort, worse outcomes were observed when the breast cancer was triple-negative subtype (HR = 1.37, 95% CI 1.02–1.84; P= 0.039) or diagnosed at advanced stages: III and IV (HR=4.41; 95% CI 3.31–5.90; P< 0.001). Hormone receptor expression of ER (HR = 0.68, 95% CI 0.51–0.90; P= 0.007) and PR (HR=0.63, 95% CI 0.48–0.83; P=0.001), were protective factors in overall survival. Treatment by surgical intervention, (HR = 0.23, 95% CI 0.18–0.30; P< 0.001), hormone antagonism (HR = 0.59, 95% CI 0.44–0.77; P< 0.001) and radiotherapy (HR = 0.46, 95% CI 0.35–0.62; P< 0.001), were favorable factors consistent with the current literature [17]. There was no association between overall survival and BMI.

During a median follow-up of 144 months, there was a significant difference in outcomes by nativity. In a univariate model, Caribbean-born patients had a reduction of 25% in risk of death compared with the US-born cohort (HR = 0.75, 95% CI 0.59–0.96; P= 0.024) (Table 2; Fig. 1). Caribbean-born patients had significantly better median overall survival compared to US-born Black patients [1–47.9 months (95% CI 118.8–177.1) vs. 98.6 months (95% CI 82.1–115.2 months] (Log-Rank, Mantel-Cox P= 0.02). In the multivariate Cox proportional hazards regression model adjusting for ER, PR, surgery, hormonal treatment, radiation and stage, Caribbean-born Blacks continue to have a significantly better outcome (HR=0.68, 95% CI 0.49–0.94, P=0.018).

We then performed a comparison of overall survival stratified by treating institution by the Kaplan-Meier to rule out confounding variables such as socioeconomic status. Caribbeanborn patients continued to show a higher median overall survival of 115 months (95% CI 84.6–145.3) compared to 88.3 months (95% CI 75.08–101.5 months) (Log-Rank, Mantel-Cox P = 0.05) at the JMS treated group. CB patients had a median overall survival of 183.2 months (95% CI not available) compared to 149.3 months (95% CI 86–212.7) (Log-Rank, Mantel-Cox P = 0.07) when treated at UMHS.

Further analysis of matched ER, triple negative and stage were performed to determine if the difference in overall survival and better outcomes in the CB patient group was attributable to ER, TNBC and stage. CB patients maintained their overall survival outcome advantage with a median 58.8 months (95% CI 37.4-80.2 months) over USB, median 47.3 months (95% CI 35.9–58.9 months), Log-Rank P = 0.026 when controlled for ER, TNBC and stage (Supplement Table 3, Supplement Fig. 1A, B). We performed a second hazard regression model comparing ethnicity and clinical characteristics by nativity with the aim of identifying which factors had a significant effect on outcome for the two groups (Table 3). Variables that had a favorable effect on outcome for both CB and USB patients were PR expression (CB HR = 0.64, 95% CI 0.43–0.96; P = 0.032 and USB HR = 0.64, 95% CI 0.43–0.95; P =0.028), surgical intervention (HR = 0.19, 95% CI 0.13–0.27; P< 0.001 and USB HR = 0.26, 95% CI 0.19–0.36; P < 0.001) and radiotherapy (CB HR = 0.47, 95% CI 0.31–0.71; P <0.001 and USB HR=0.48, 95% CI 0.33–0.70; P = < 0.001). Advanced stage at diagnosis remained a factor related to worse outcomes in both CB (HR = 4.48, 95% CI 2.84-7.09; P <0.001) and USB groups (HR = 4.66, 95% CI 3.20-6.78; P < 0.001). In this analysis the effect of hormonal antagonism was only a significant variable in the USB patient population

(HR = 0.5, 95% CI 0.36–0.78; P= 0.001), indicating potential tumor characteristics amongst the groups.

In univariate analysis, all Black Hispanic patients independent of region of birth had a 49% reduced risk of death (HR = 0.51, 95% CI 0.28–0.93; P= 0.028) while Caribbean non-Hispanic Blacks had an increased risk of death compared to Caribbean Hispanic Black patients (HR = 1.98, 95% CI 1.00–3.94; P= 0.048). A multivariate analysis model adjusting for similar factors did not reach significance for the relationship between Hispanic ethnicity and place of birth (HR = 1.82, 95% CI 0.73–4.60; P= 0.20) (Supplement Table 2). Only 1.1% of the USB patient population self-identified as Hispanic and/or were indicated in their medical records, therefore, determining the positive effect on outcomes in the USB population is probably understated and restricted by sample size.

Discussion

This study is a comprehensive analysis of a large cohort of Black women diagnosed with breast cancer in the US with attention to Caribbean nativity. Our study included women diagnosed and treated within both a safety net hospital and an academic comprehensive cancer center. The proportion of US-born and Caribbean-born Black patients from each institution is similar, therefore, the outcome differences seen should be attributable to factors independent of treating institution. Prior studies looking at USB and CB breast cancer patients showed that US-born Blacks had favorable outcomes compared to Caribbean-born Blacks [12, 18]. However, these studies compared breast cancer patients across different health systems and in different countries which have substantial differences in gross domestic products (GDP) and access to healthcare.

In our study, Caribbean-born Blacks were more likely to have ER/PR-positive breast cancers, had more advanced stages of breast cancer at presentation and underwent chemotherapy treatment and radiation treatment more often than USB women with breast cancer. The USB patients presented with more early-stage breast cancer, underwent surgery more often, were more likely to be overweight and obese, and used alcohol and tobacco at higher rates than CB women with breast cancer. There was no difference in the percent of germline mutation carriers between USB and CB patients. In our previous work, we demonstrated that Caribbean natives diagnosed with breast and ovarian cancer, had higher than expected rates of hereditary breast cancer with a deleterious mutation seen in 25% of Bahamian women [19, 20] and 12% of women from Trinidad & Tobago [21, 22]. It is important to highlight that 5–10% of all women diagnosed with breast cancer in the USA are reported to have deleterious breast cancer gene mutation, 12% of Black women in general [23] and 20% of Black women with triple negative breast cancer [24]. Our current data show that Black women in South Florida are severely undertested. This undertesting should have a disproportionate effect on the CB women with breast cancer.

There is limited information on Hispanic Blacks, which constitute an important part of the Caribbean population. Recent data from Surveillance, Epidemiology and End Results Program (SEER) showed that the incidence of breast cancer in Hispanic women is increasing [25]. However, they have lower incidence compared to non-Hispanic White

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women (NHW) and non-Hispanic Black (NHB) [25]. There is conflicting data on Hispanic women's risk of breast cancer specific-mortality compared to NHW women. The scarce data available show worse outcomes to Hispanic Whites (HW) but lower or similar risk of breast cancer mortality to NHB, however, the reasons behind these findings have not yet been explored [26–29]. The majority of the Hispanic Black women in our cohort were born in Cuba and Dominican Republic. In our cohort, we observed that Hispanic Black women had better outcomes than non-Hispanic Black women and more so in the Caribbean-born Black patient cohort.

The present study has some limitations. First, this is a retrospective/database review and as such there is a possibility of misclassification or information bias. Two, our cohort represents a curated cohort of women diagnosed with breast cancer within a health system in South Florida. It is feasible that Caribbean-born immigrants in other parts of the United States have different overall outcomes due to specific local factors such as environment, health care access, stigma and discrimination. Nonetheless, our cohort has similar findings to improved cancer related outcomes in immigrant populations [9, 30]. Third, in this study, we grouped all breast cancer patients by region and not by individual country of origin. It is likely that there are subregional differences across the patient populations depending on country of origin as observed with Hispanic Black patients. Fourth, as a cofounder to nativity as a factor driving outcome, second generation Caribbean ancestry could not be taken into consideration. Finally, the study was unable to determine length of time in the US by the Caribbean immigrant population, and therefore, add time as a variable in hazard ratio calculations. This limitation provides an opportunity to conduct prospective studies to determine whether and how length of time in the US affects outcomes.

In conclusion, Black women diagnosed with breast cancer have worse outcomes compared to all other racial groups. Although US-born and Caribbean-born Black women are racially similar, there are significant differences in breast cancer presentation, type of breast cancer and overall outcomes. These differences may be due to differences in healthcare utilization, systemic barriers to accessing care, psychosocial factors such as chronic stress exposure, cultural norms, environmental exposures (native country and relocated environment) and differences in genomic ancestral diversity. These sub-racial disparities in breast cancer outcomes highlighted in this study, have identified opportunities to address immigrant and native specific risk factors to improve the health and quality of life of women diagnosed with breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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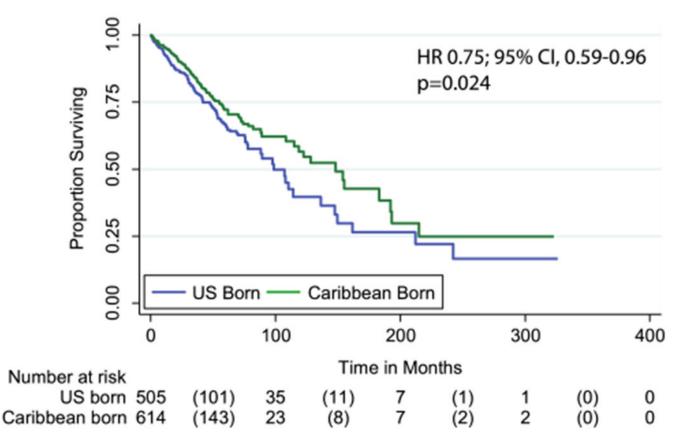


Fig. 1.

Kaplan–Meier graph of overall survival (months) stratified by Stage1/2 at diagnosis of Caribbean-born Blacks and US-born Blacks. USB (median 98.6 months) have worse overall survival than CB patients (median 1–47.9 months), Log-Rank Mantel Cox, P = 0.020

Table 1

Summary of the breast cancer in Black women cohort

Variable	Caribbean-born $(n = 507)$	USA-born $(n = 624)$	P value
Age at diagnosis, mean $(95\% \text{ CI})^a$	55.7 (54.7–56.8)	57.6 (56.4–58.7)	0.001
BMI, mean (95% CI) ^a	29.6 (28.9–30.3)	30.9 (30.1–31.7)	0.015
Genetic testing no. (%)			
Tested	39/507 (7.7)	40/624 (6.4)	0.414
Genetic mutation no. (%)			
Positive	8/39 (20.5)	9/40 (22.5)	0.83
HER-2 no. (%)			
Positive	93/406 (22.9)	78/441 (17.7)	0.061
Negative	313/406 (77.1)	363/441 (82.3)	
ER no. (%)			
Positive	276/402 (68.7)	288/472 (61.0)	0.019
Negative	126/402 (31.3)	184/472 (39.0)	
PR no. (%)			
Positive	238/408 (58.3)	231/458 (50.4)	0.020
Negative	170/408 (41.7)	227/458 (49.6)	
Triple-negative no. (%)	84/426 (19.7)	133/478 (27.8)	0.004
Ductal histology no. (%)			
Yes	342/459 (74.5)	404/566 (71.4)	0.254
No	117/459 (25.5)	162/566 (28.6)	
Stage at diagnosis no. (%)			
Ι	100/384 (26.0)	144/490 (29.4)	I
П	116/384 (30.2)	173/490 (35.3)	
Ш	90/384 (23.4)	94/490 (19.2)	
IV	78/384 (20.3)	79/490 (16.1)	
Stage at diagnosis no. (%)			
Early: I and II	218/385 (56.6)	317/490 (64.7)	0.016
Advanced: III and IV	167/385 (43.4)	173/490 (35.3)	
Current alcohol consumers no (%)	49/442 (11.9)	102/512 (19.9)	< 0.001

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Variable	Caribbean-born $(n = 507)$	USA-born $(n = 624)$	P value
Current smoker no. (%)	7/441 (1.6)	37/515 (7.2)	< 0.001
Surgery performed no. (%)			
Mastectomy/lumpectomy	345/504 (68.5)	454/623 (72.9)	0.011
No surgery	159/504 (31.5)	169/623 (27.1)	
Radiation treatment no. (%)			
Yes	182/507 (35.2)	175/624 (28)	0.010
No	326/507 (64.7)	449/624 (72)	
Chemotherapy treatment no. (%)			
Yes	235/507 (46.4)	248/624 (39.7)	0.027
No	272/507 (53.6)	376/624 (60.3)	
Hormone antagonist therapy no. (%)			
Administered	171/507 (33.8)	177/624 (28.4)	0.063
Not administered	336/507 (66.2)	337/624 (66.3)	
Treatment type (%)			

 a^{d} Comparison by independent *t* test. All other comparisons are by Chi squared correlation

< 0.001

608/615 (98.9) 7/615 (1.1)

431/507 (85) 76/507 (15)

0.041

193/299 (64.5)

205/283 (72.4)

Treatment type (%)

78/283 (27.6)

Ethnicity no. (%)

Neoadjuvant

Adjuvant

106/299 (35.5)

0.848

434/624 (69.6) 190/624 (30.4)

355/507 (70.0) 152/507 (29.9)

Comprehensive Cancer Center

Safety Net Hospital

Treating institution

Non-Hispanic

Hispanic

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Table 2

Univariate Cox proportional hazards model for overall survival

Variable	HR	95% CI	P value
Place of birth			
USA (referent)	0.75	0.59–0.96	0.024
Caribbean			
Ethnicity (all)			
Non-Hispanic (referent)	0.51	0.28-0.93	0.028
Hispanic			
Ethnicity among Caribbean			
Hispanic (referent)	1.98	1.00-3.94	0.048
Caribbean non-Hispanic			
BMI (continuous)-any increase in weight	0.99	0.98-1.01	0.55
Age at diagnosis (continuous)	1.01	1.00-1.02	0.015
Estrogen receptor (ER)			
Negative (referent)	0.68	0.51-0.90	0.007
Positive			
Progesterone receptor (PR)			
Negative (referent)	0.63	0.48-0.83	0.001
Positive			
HER2/neu			
Negative (referent)	1.01	0.72-1.42	0.95
Positive			
Triple negative			
No (referent)	1.37	1.02-1.84	0.039
Yes			
Genetic mutation			
No (referent)	2.04	0.57-7.25	0.27
Yes			
Surgery			
No (referent)	0.23	0.18-0.30	< 0.001
Yes			
Hormone antagonism			
No (referent)	0.59	0.44-0.77	< 0.001
Yes			
Chemotherapy			
No (referent)	1.07	0.84-1.36	0.57
Yes			
Radiation			
No (referent)	0.46	0.35-0.62	< 0.001
Yes			
Stage of disease			

Variable	HR	95% CI	P value
Stage I and II (referent)	4.41	3.31-5.90	< 0.001
Stage III and IV			
Histology			
Non-ductal (referent)	1.03	0.78-1.36	0.85
Ductal			

Table 3

Multivariate Cox proportional hazards model for overall survival in each group

Variable ^a	Caribbean born	USA born
Ethnicity (all)		
Non-Hispanic (referent)	I	I
Hispanic	0.46 (0.24 - 0.92), P = 0.028	2.75 (0.68–11.12), <i>P</i> = 0.16
BMI (continuous)	0.99 (0.96–1.03), <i>P</i> = 0.68	0.99 (0.97 - 1.02), P = 0.58
Age at diagnosis (continuous)	1.00 (0.99-1.02), P = 0.37	1.01 (1.00-1.03), P = 0.025
Estrogen receptor (ER)		
Negative (referent)	I	1
Positive	0.71 (0.47 - 1.08), P = 0.11	$0.70 \ (0.48 - 1.02), P = 0.06$
Progesterone receptor (PR)		
Negative (referent)	I	I
Positive	$0.64 \ (0.43 - 0.96), P = 0.032$	$0.64 \ (0.43-0.95), P = 0.028$
HER2/neu		
Negative (referent)	I	I
Positive	0.99 (0.61 - 1.62), P = 0.99	1.08 (0.67 - 1.74), P = 0.76
Triple negative		
No (referent)	I	I
Yes	1.17 (0.73–1.89), <i>P</i> = 0.51	$1.41 \ (0.96-2.07), P = 0.08$
Genetic mutation		
No (referent)	I	I
Yes	3.62 (0.51–25.9), <i>P</i> = 0.20	0.91 (0.16–5.23), <i>P</i> = 0.92
Surgery		
No (referent)	I	I
Yes	0.19 (0.13 - 0.27), P < 0.001	0.26 (0.19-0.36), P < 0.001
Hormone antagonism		
No (referent)	I	I
Yes	0.69 (0.46 - 1.04), P = 0.07	0.53 (0.36-0.78), P = 0.001
Chemotherapy		
No (referent)	1	I

variable		
Yes	0.99 (0.68-1.45), P = 0.98	1.19 (0.87–1.65), <i>P</i> = 0.27
Radiation		
No (referent)	I	I
Yes	0.47 (0.31 - 0.71), P < 0.001	0.48 (0.33–0.70), <i>P</i> < 0.001
Tobacco use		
Never/former (referent)	1	I
Current	0.62 (0.09 - 4.49), P = 0.64	1.23 (0.68-2.24), P = 0.48
Alcohol use		
Never/former (referent)	I	I
Current	0.17 (0.04-0.69), P = 0.013	0.79 (0.52 - 1.21), P = 0.29
Stage of disease		
Stage I and II (referent)	I	I
Stage III and IV	4.48(2.84-7.09), P < 0.001	4.66 (3.20–6.78), <i>P</i> < 0.001
Histology		
Non-ductal (referent)	I	I
Ductal	1.26(0.80-1.97), P = 0.32	0.88 (0.62 - 1.26), P = 0.50

⁴Referent variable listed first. Result expressed in the following order: HR (95% CI), *P*-value. The following variables were included in the model: stage, radiation, hormone antagonism, surgery, ER, PR, age at diagnosis and place of birth