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Racial differences in outcomes of triple-negative breast cancer

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Abstract

African American (AA) women have a higher incidence of triple-negative breast cancer (TNBC: negative for the expression of estrogen receptor, progesterone receptor, and HER2 gene amplification) than Caucasian (CA) women, explaining in part their higher breast cancer mortality. However, there have been inconsistent data in the literature regarding survival outcomes of TNBC in AA versus CA women. We performed a retrospective chart review on 493 patients with TNBC first seen at the Washington University Breast Oncology Clinic (WUBOC) between January 2006 and December 2010. Analysis was done on 490 women (30 % AA) for whom follow-up data was available. The median age at diagnosis was 53 (23–98) years and follow-up time was 27.2 months. There was no significant difference between AA and CA women in the age of diagnosis, median time from abnormal imaging to breast biopsy and from biopsy diagnosis to surgery, duration of follow-up, tumor stage, grade, and frequency of receiving neoadjuvant or adjuvant chemotherapy and pathologic complete response rate to neoadjuvant chemotherapy.

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Conflict of interest All authors disclose no conflict of interest.

There was no difference in disease free survival (DFS) and overall survival (OS) between AA and CA groups by either univariate or multivariate analysis that included age, race, and stage. The hazard ratio for AA women was 1.19 (CI 0.80–1.78, $p = 0.39$) and 0.91 (CI 0.62–1.35, $p = 0.64$) for OS and DFS, respectively. Among the 158 patients who developed recurrence or presented with stage IV disease (AA: $n = 36$, CA: $n = 122$), no racial differences in OS were observed. We conclude that race did not significantly affect the clinical presentation and outcome of TNBC in this single center study where patients received similar therapy and follow-up.

Keywords

Race; Triple-negative breast cancer; Outcome; Retrospective study

Introduction

African American women have a lower incidence of breast cancer, but a higher mortality rate when compared to other racial groups [1–4]. Factors potentially contributing to the racial disparity in breast cancer outcome include socioeconomic status, cultural beliefs, insurance variables that could lead to delays in diagnosis and treatment, decreased compliance with recommended screening, increased comorbidities, decreased adherence to therapy, and potential biological factors [1, 5–21]. However, the higher incidence of triple-negative breast cancer (TNBC) observed in AA women is suggested as one of the most important factors [21–24]. TNBC is a subgroup of breast cancers characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 gene amplification. TNBC is often associated with a higher tumor grade and an aggressive clinical course, manifested as early relapse, a tendency for visceral metastasis and shorter survival [25–27]. Compared to Caucasian women, African American women are twice as likely to develop TNBC [21–23].

An outstanding question is whether the biology of TNBC differs between African American and Caucasian women. Only a few studies have focused on the TNBC population in particular and compared the outcomes between African American and Caucasian women. Some reported a worse survival for African American women with TNBC [21–24]. However, others concluded no survival difference between the two races [28–30]. To investigate this issue further, we reviewed the clinical presentation and outcome of patients with TNBC who sought care in the Washington University Breast Oncology Clinic in St. Louis and compared the outcomes between African American and Caucasian women.

Patients and methods

Patient population

We constructed a database of 493 patients, including only African Americans and non-Hispanic Caucasians, with a diagnosis of TNBC. These are consecutive patients who presented for their first visit to the Breast Oncology Clinic at Washington University in Saint Louis, MO between January 1st 2006 and December 16th 2010. Four hundred and ninety patients were included in the analysis, two were not included because of unknown

date of diagnosis and 1 because of lack of follow-up data. For all patients, including those diagnosed elsewhere and having received medical oncology care before treatment at our institution, data collection, follow-up time, and analysis were from the time of initial diagnosis. Exclusion criteria included ER or PR or HER2 positivity, unknown date of diagnosis, an additional malignancy, male sex, race other than African American or Caucasian, Hispanic ethnicity, and unknown race or ethnicity. This study was approved by Washington University Institutional Review Board.

Tumor staging and pathology

Initial pathological stage was determined based on American Joint Committee on Cancer Criteria at the time of diagnosis. Biopsy specimens from other institutions, when available, were reviewed by pathologists at Barnes Jewish Hospital. Histological grade and ER, PR, and Her-2/neu status were recorded from pathology reports. ER and PR were considered negative if immunohistochemistry indicated an Allred score below 3 or less than 1 % tumor cells staining positive. HER2 was considered to be negative by FISH or 0 or 1+ on immunohistochemistry. Pathologic complete response (pCR) was defined as absence of residual invasive disease in the breast and axillary lymph nodes.

Clinical parameters

We recorded clinical parameters including race, ethnicity, age, time from imaging to biopsy diagnosis, tumor characteristics, time from biopsy diagnosis to surgery, surgical intervention, pathological stage, whether patients received neoadjuvant and/or adjuvant treatment, pathologic response to neoadjuvant therapy, menopausal status, follow-up information, recurrence information and date of death (obtained from the Social Security Death Index).

Outcome measures

The primary outcomes included overall survival (OS) and disease free survival (DFS). OS was defined as the time from diagnosis to death due to any cause, and survivors were censored at the date of last contact. DFS was defined as time from surgery to any invasive breast recurrence (local or distant) or death, whichever occurred first. Those patients alive and recurrence-free were censored at date of last contact. Patients who presented with stage IV disease at diagnosis or who had not undergone surgery were excluded from DFS analysis. Time from recurrence to death was defined as time from recurrence or diagnosis (if stage IV disease at initial presentation) to death due to any cause, and survivors were censored at date of last contact.

Statistical analysis

The distribution of demographic and clinical characteristics between racial groups (African American and Caucasian) was compared using Chi square test, Wilcoxon rank sum test, or two-sample *t* test as appropriate. Survival curves by racial groups were estimated using the Kaplan–Meier product-limit method and compared by log-rank test. Univariate Cox proportional hazard models were fit to identify factors significantly related to OS or DFS. To assess whether the racial status was an independent predictor of survival, a multivariate

Cox model was constructed to adjust for other demographic and clinical characteristics that were significant in the univariate analyses. Two-way interaction terms between racial status and other factors in the multivariate Cox model were also assessed. All analyses were two-sided and significance was set at a p value of 0.05. Statistical analyses were performed using SAS (SAS Institutes, Cary, NC).

Results

Comparison of patient characteristics between races

Among the 490 patients with TNBC who initially presented to the Washington University Breast Oncology Clinic between January 2006 and December 2010, 146 patients were African American (30 %) and 344 patients were Caucasian (70 %). Table 1 shows the comparison of patient characteristics between races. Median age at diagnosis was 53 years for both races. Most patients had high grade tumors and early stage breast cancer at initial presentation. There was no statistical difference between races in age, menopausal status, tumor grade, and stage at diagnosis.

Sixty-five patients (26 African American and 39 Caucasian) who presented with early stage disease (stage I: $n = 37$, stage II: $n = 18$, stage III: $n = 10$) did not receive neoadjuvant or adjuvant chemotherapy. The most common reasons for not receiving chemotherapy included stage I disease for which chemotherapy was not recommended by the treating physician ($n = 22$), age/co-morbidities ($n = 11$), and patient refusal ($n = 11$). The percentage of patients who received neoadjuvant or adjuvant chemotherapy was not different between races (Table 1). In addition, there was no racial difference in the rate of pCR to neoadjuvant chemotherapy (Table 1).

To investigate potential diagnostic and treatment delays, we reviewed time from the date of abnormal imaging study to biopsy diagnosis and the date from biopsy diagnosis to surgery. The median time from the date of abnormal imaging study to biopsy was similar in both ethnic groups. The median time from biopsy diagnosis to surgery without neoadjuvant chemotherapy was longer in African American than Caucasian women (African American: 26 days vs Caucasian: 21 days, $p = 0.01$), although the clinical significance is uncertain. The median time from biopsy diagnosis to surgery with neoadjuvant chemotherapy was similar in both groups (Table 1).

Comparison of survival outcomes between races

The median follow-up time was 27.2 months (with an inter-quartile range (IQR) of 13.5–46.1 months). Duration of follow-up was not significantly different between races, median for African Americans was 24.4 months (IQR: 13.5–40.5 months) and for Caucasians was 28.9 months (IQR: 13.2–47.3 months). There were 120 deaths due to any cause (25.3 % in African Americans and 24.1 % in Caucasians) and 134 recurrences (24.7 % in African Americans and 35.4 % in Caucasians) during the follow-up period. There was no significant difference in DFS between groups (HR 0.78, $p = 0.21$). There was also no difference in OS between races (HR 1.19, $p = 0.38$). In addition, there was no significant difference between races in OS for those who presented with recurrence or stage IV disease, with a median time

to death of 17.5 months for African Americans and 22.6 months for Caucasians. The estimated 3-year OS was 71.0 % for African Americans and 80.0 % for Caucasians, while the 3-year DFS was 66.8 % for African Americans and 62.8 % for Caucasians (Fig. 1).

Univariate and multivariate analysis of other variables on survival outcomes

In univariate analysis, menopausal status and grade were not predictive of DFS or OS. Older age was associated with a trend toward worse OS ($p = 0.07$), but not DFS ($p = 0.64$). Pathological stage was significantly predictive of DFS and OS. Stage IIB or III disease predicted significantly worse DFS, while stage III or IV at presentation predicted significantly worse OS (Table 2). The status of response to neoadjuvant chemotherapy was also significantly related to DFS and OS. Those who did not achieve a pCR with neoadjuvant chemotherapy experienced significantly worse DFS and OS compared to those who achieved a pCR with neoadjuvant chemotherapy (Table 2; Fig. 2).

In multivariate analysis, pathological stage was the only significant independent predictor of DFS and OS. The survival differences between races remained insignificant for DFS (HR 0.91, $p = 0.64$) and OS (HR 1.19, $p = 0.39$) after adjusting for pathological stage (Table 3).

Discussion

The purpose of this study was to examine differences in clinical presentation, treatment, and survival between African American and Caucasian women diagnosed with TNBC who presented for medical oncology therapy in a single academic center. The survival outcomes assessed included DFS, OS, and OS after recurrence. Our study indicated no racial differences in survival outcomes between African American and Caucasian women with TNBC and suggested that TNBC in African American women is not intrinsically different from that in Caucasians.

Previous studies that focused on racial disparities in outcomes of TNBC yielded inconsistent data, some suggested a worse outcome in the African American population [21, 22, 24], others did not [28–30] (Table 4). Our data support the conclusion that TNBC does not have worse survival outcomes for African American women when compared to Caucasians. Several factors were different between some of the prior studies and ours. One, we had a self-selected patient population who sought medical oncology treatment at a single medical center. As shown in Table 1, the median time from an abnormal imaging study to diagnostic biopsy, stage at presentation, and treatment with chemotherapy were similar between races. Therefore, diagnostic delays and treatment differences reported in other studies were not apparent in our patient population. In two recent studies, by Dawood et al. and Sparano et al. [28, 30], patients received the same treatments and there was no racial difference in TNBC survival outcomes. These results, coupled with ours, suggest that when treatment is similar between races, that there is no racial difference in TNBC survival. This argues against the idea that a biological reason explains racial differences in survival seen in earlier studies and suggests that disparities in management may have affected outcomes.

Second, this study has a large sample size compared to many of the previous studies, which allowed an adequate power for the intended comparison. Many of the prior studies, with the

exception of the studies by Dawood et al. [28], Sparano et al. [30], and the California Cancer Registry [22], only had approximately 100–200 TNBC patients [21, 24, 29]. Thus, some of these earlier, smaller studies, may not be as representative of the TNBC population.

Third, the vast majority of patients in our study (85.1 %) were diagnosed from 2006 onwards. This is in contrast to some of the prior studies, in which patients were diagnosed during the 1990s. Diagnostic and treatment differences in these time periods could have contributed to differences in outcomes. This is supported by a French study that showed improved disease-specific and event-free survival for breast cancer patients when comparing later to earlier treatment time periods (1990–1993, 1994–1997, and 1998–2001) [31]. In addition, some of the studies assessing patients diagnosed in the early 1990s may have selected patient populations before the full effect of mammographic screening had a chance to take place [32]. Also, environmental (e.g., diet, exercise, radiation or chemical exposure) and cultural differences (e.g., beliefs of cancer risk, beliefs surrounding the utility of mammography, perceived levels of discomfort of mammography, fear of cancer discovery, and fatalistic views of cancer diagnosis) during earlier and later diagnostic time periods could have contributed to different outcomes [33, 34].

One potential limitation of our study is the relatively short follow-up. Although comparable or longer in duration than those reported by Dawood et al. [28] and Sachdev et al. [24], the median follow-up of our study was shorter than several previous studies that included breast cancers of various receptor subtypes [21, 22, 29, 30] (Table 4). However, since TNBC has an early relapse pattern, with the highest risk of relapse within the first 2–3 years of diagnosis [26, 33], the median follow-up of 27.2 months in our study is likely to have captured most recurrence outcomes. In addition, we took a time-to-event analysis approach in the assessment of OS and DFS, which automatically accounts for the length of follow-up time. In such a time-to-event setting, the statistical power was determined primarily by the number of events, and a considerable proportion of events were detected in our study (120 deaths due to any cause and 134 recurrences).

In our study, achieving pCR to neoadjuvant chemotherapy was associated with a significantly improved DFS and OS. There was no difference in the rate of pCR between African American and Caucasian women. These results are in agreement with those reported by Dawood et al. [28] and are consistent with the well accepted observation that achieving pCR is predictive of improved survival outcomes for patients with TNBC. Another finding is that patients who did not achieve pCR experienced worse survival outcomes compared to those who received only adjuvant chemotherapy. Similar results have been observed in other population studies [34]. This is likely due to the higher tumor stage of those who went on neoadjuvant versus adjuvant chemotherapy. In our study, 39.1 % of patients who received neoadjuvant chemotherapy without a pCR had pathologic stage III disease, which is significantly higher than the 15.5 % of stage III disease in those who received only adjuvant chemotherapy ($p < 0.0001$).

In summary, our study suggests that African American women with TNBC have similar outcomes as Caucasian women in a single center study where access to care and treatment are similar. These results are in agreement with three other studies [28–30]. Our data

suggests there is likely no biological difference between races for TNBC tumors. Future studies comparing the molecular characteristics of TNBC from different races are needed.

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Fig. 1.

Comparison of survival outcomes between African American and Caucasian Women. K-M survival curves of OS for all patients (a), DFS for patients with early stage breast cancer (b), OS for patients with recurrent or stage IV at presentation (c), by race are shown

Fig. 2.

Comparison of survival outcomes among patients with early stage disease who received neoadjuvant or adjuvant chemotherapy. K-M survival curves of OS (**a**) and DFS (**b**) comparing patients who achieved pCR to neoadjuvant chemotherapy, non-pCR to neoadjuvant chemotherapy and those who received adjuvant chemotherapy alone are shown

Table 1

Comparison of characteristics between african american and Caucasian women

Race	AA (<i>n</i> = 146)	CA (<i>n</i> = 344)	<i>p</i>
Menopausal status			0.39
Premenopausal	49 (33.6 %)	120 (34.9 %)	
Postmenopausal	88 (60.3 %)	191 (55.5 %)	
Unknown	9 (6.10 %)	33 (9.60 %)	
Age (median in years, range)	53, 27–84	53, 23–98	0.43
Median days from imaging to biopsy diagnosis (range)	7 (0–80)	8 (0–137)	0.82
Median days from biopsy diagnosis to surgery in those without	26 (0–326)	21 (0–453)	0.01
Neoadjuvant chemotherapy (range)	(<i>n</i> = 88)	(<i>n</i> = 216)	
Median days from biopsy diagnosis to surgery in those with	174 (89–271)	165 (8–574)	0.23
Neoadjuvant chemotherapy (range)	(<i>n</i> = 41)	(<i>n</i> = 98)	
Chemotherapy for stage I–III disease			0.21
Neoadjuvant and adjuvant chemotherapy	9 (6.6 %)	21 (6.4 %)	
Neoadjuvant chemotherapy alone	35 (25.5 %)	82 (25.0 %)	
Adjuvant chemotherapy alone	67 (48.9 %)	186 (56.7 %)	
No chemotherapy	26 (19.0 %)	39 (11.9 %)	
	(<i>n</i> = 137)	(<i>n</i> = 328)	
Response to neoadjuvant chemotherapy			0.89
pCR	11/44 (25.0 %)	22/103 (21.4 %)	
Pathological stage			0.42
pCR	11 (7.53 %)	23 (6.69 %)	
I	39 (26.7 %)	113 (32.8 %)	
IIA	40 (27.4 %)	86 (25.0 %)	
IIB	22 (15.1 %)	34 (9.88 %)	
III	24 (16.4 %)	67 (19.5 %)	
IV	9 (6.16 %)	16 (4.65 %)	
Unknown	1 (0.68 %)	5 (1.45 %)	
Histology grade			0.98
I/II	20 (13.7 %)	46 (13.4 %)	
III	125 (85.6 %)	290 (84.3 %)	
Unknown	1 (0.68 %)	8 (2.33 %)	

Table 2

Univariate analysis of variables with respect to survival outcomes

Variable	DFS		OS	
	HR (95 % CI)		HR (95 % CI) <i>p</i>	
Race		0.21		0.38
African American	0.78 (0.53–1.15)		1.19 (0.81–1.76)	
Caucasian	Reference group		Reference group	
Age (per 1 yr increase)	1.00 (0.99–1.01)	0.64	1.01 (1.00–1.03)	0.07
Chemotherapy for stage I–III disease		<0.001		<0.001
pCR, neoadjuvant chemotherapy	Reference group		Reference group	
Non-pCR, neoadjuvant chemotherapy	4.01 (1.45–11.12)	0.008	5.61 (1.35–23.26)	0.02
Adjuvant chemotherapy alone	1.68 (0.61–4.63)	0.31	1.87 (0.45–7.80)	0.39
Menopausal status ^a		0.32		0.90
Premenopausal	1.20 (0.84–1.70)		1.03 (0.69–1.54)	
Postmenopausal	Reference group		Reference group	
Pathological stage		<0.001		<0.001
pCR	Reference group		Reference group	
I	1.56 (0.55–4.39)	0.40	2.64 (0.63–11.2)	0.19
IIA	1.65 (0.58–4.66)	0.34	1.52 (0.35–6.69)	0.58
IIB	3.30 (1.14–9.54)	0.03	3.95 (0.91–17.2)	0.07
III	4.89 (1.76–13.6)	0.002	6.91 (1.66–28.7)	0.01
IV	Not included		44.1 (10.3–190.0)	<0.001
Grade		0.13		0.75
3	1.50 (0.89–2.55)		1.09 (0.63–1.88)	
1 and 2	Reference group		Reference group	

^aNot considered in the multivariate analysis due to its high correlation with age

Table 3

Multivariate analysis of variables with respect to survival outcomes

Variable	DFS		OS	
	HR (95 % CI)	<i>p</i>	HR (95 % CI)	<i>p</i>
Race		0.64		0.39
African American	0.91 (0.62–1.35)		1.19 (0.80–1.78)	
Caucasian	Reference group		Reference group	
Age (per 1 yr increase)	Not included		1.01 (1.00–1.03)	0.08
Pathological stage		<0.001		<0.001
pCR	Reference group		Reference group	
I	1.55 (0.55–4.39)	0.41	2.50 (0.59–10.64)	0.22
IIA	1.66 (0.59–4.71)	0.34	1.46 (0.33–6.45)	0.61
IIB	3.16 (1.09–9.17)	0.03	3.93 (0.91–17.09)	0.07
III	4.88 (1.75–13.60)	0.003	7.17 (1.72–29.9)	0.01
IV	Not included		39.9 (9.04–169.0)	<0.001

Table 4

Studies comparing survival outcomes between races for women with TNBC

Study	Study population	Period diagnosed	Median age in years (range) ^a	Patient (n) ^a	TNBC or Basal-like (n)	Median F/u in years (range) ^a	Outcome
Lund et al. [21]	3 counties in metropolitan Atlanta, GA (multi-center population-based, case control study)	May 1990–Dec 1992	20–54	476	135 AA: 56 CA: 79	11.4	HR for OS 2.0 (95 % CI 1.0–3.7) for AA (adjusted for age, stage, grade, poverty index, treatment and treatment delay)
O'Brien et al. [29]	24 counties of eastern and central North Carolina (multi-center, population-based, case control study), enriched for AA and age < 50 years	1993–2001	20–74	1,149	197 AA: 117 CA: 80	9 (0.2–13.7)	HR for breast cancer specific survival 1.3 (95 % CI 0.8–2.3) for AA (adjusted for age, date and stage of diagnosis)
Sparano et al. [30]	Participants in a randomized adjuvant chemotherapy trial E1199	Oct 1999–Jan 2002 ^b	51 (19–84)	4,817	886 AA: 129 Non-AA: 757	7.9 (0–9.9) ^c	HR for breast cancer specific survival 0.81 (95 % CI 0.51–1.28, $p = 0.37$) for AA
Bauer et al. [22]	A population-based registry covering the state of California	Jan 1999–Dec 2003	TNBC median 54, other breast cancer types median 60	51,074	6,370 AA: 636 CA: 3959	N/A	5 yr survival: AA 14 % stage III/IV, CA 36 % stage III/IV, Hispanic 37 % stage III/IV
Dawood et al. [28]	Prospective cohort study of database patients at MD Anderson Cancer Center	1996–2005	AA: 47 (22–75) Other: 48 (25–78)	471	471 AA: 100 Other: 371	2 (0.02–9.75)	HR for DFS 1.08 (95 % CI 0.69–1.68) for CA, HR for OS 1.08 (95 % CI 0.69–1.68, $p = 0.735$) for CA
Sachdev [24]	Retrospective cohort study of patients presenting to the University of Tennessee Cancer Institute	Sep 2003–Dec 2008	51 (26–82)	124	124 AA: 88 CA: 36	1.91 (0.08–10.3)	HR for DFS 0.62, $p = 0.29$ for CA, HR for breast cancer specific survival 0.36, $p = 0.18$ for CA
Pacheco et al. (current study)	Retrospective cohort study of patients presenting to the Washington University Saint Louis Breast Oncology Clinic	Jan 1st 2006–Dec 16th 2010	53 (23–98)	490	490 AA: 146 CA: 344	2.26 (0.01–16.2)	HR for DFS 0.91 (CI 0.62–1.35) $p = 0.64$ for AA, HR for OS 1.19 (CI 0.80–1.78) $p = 0.39$ for AA (adjusted for age and stage)

^aValues represent those for all breast cancer subtypes combined^bEnrolled during this time period for adjuvant therapy, not diagnosed during this time period^cMedian follow-up for surviving patients