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Screening mammography mitigates breast cancer disparities through early detection of triple negative breast cancer

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Screening mammography mitigates breast cancer disparities through early detection of triple negative breast cancer

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ABSTRACT

Purpose: Screening mammography improves breast cancer survival through early detection, but Triple Negative Breast Cancer (TNBC) is more difficult to detect on mammography and has lower survival compared to non-TNBC, even when detected at early stages. TNBC is twice as common among African American (AA) compared to White American (WA) women, thereby contributing to the 40% higher breast cancer mortality rates observed in AA women. The role of screening mammography in addressing breast cancer disparities is therefore worthy of study.

Methods: Outcomes were evaluated for TNBC patients treated in the prospectively-maintained databases of academic cancer programs in two metropolitan cities of the Northeast and Midwest, 1998–2018.

Results: Of 756 TNBC cases, 301 (39.8%) were mammographically screen-detected. 46% of 189 AA and 38.5% of 460 WA patients had screen-detected TNBC ($p = 0.16$). 25.3% of 257 TNBC cases ≤50 years old had screen-detected disease compared to 47.3% of 499 TNBC cases >50 years old ($p < 0.0001$).

220/301 (73.1%) screen-detected TNBC cases were T1 lesions versus 118/359 (32.9%) non-screen-detected cases ($p < 0.0001$). Screen-detected TNBC was more likely to be node-negative (51.9% v. 40.4%; $p < 0.0001$). Five-year overall survival was better in screen-detected TNBC compared to nonscreen-detected TNBC (92.8% v. 81.5%; $p < 0.0001$) in the entire cohort. The magnitude of this effect was most significant among AA patients (Fig. 1). Screening-related survival patterns were similar among AA and WA patients in both cities.

Conclusion: Data from two different cities demonstrates the value of screening mammography to mitigate breast cancer disparities in AA women through the early detection of TNBC.

1. Introduction

1.1. Background/rationale

More than 40,000 women die from breast cancer in the United States annually.[1] Screening mammography improves breast cancer survival through early detection, and the largest-magnitude reduction in breast cancer specific mortality is achieved with annual screening starting at age forty.[2] Triple negative breast cancer (TNBC) is an inherently-aggressive phenotype that is more difficult to detect on mammography and has lower survival compared to non-TNBC, even when detected early.[3,4] TNBC is also twice as common among African American (AA) compared to White American (WA) women,[5,6] thereby contributing to the higher breast cancer mortality rates observed in AA women. The role of screening mammography in addressing breast cancer disparities is therefore worthy of study.

Robust data confirm that routine screening mammography significantly reduces breast cancer mortality,[2] but benefits of screening mammography through early detection of virulent breast cancer subtypes are less clear. Several studies have demonstrated that compared to non-TNBC, triple-negative tumors are less likely to have suspicious mammographic features such as microcalcifications or spiculated margins, are more likely to present as interval palpable cancers, and are more likely to be mammographically-occult.[7–11] Furthermore, population-based data demonstrate that breast cancer mortality rates are higher for TNBC compared to non-TNBC even after stratification by stage at diagnosis.[12]

Breast cancer mortality is 40% higher among AA compared to WA

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women.[13–16] This outcome disparity is explained by several factors, including a more advanced stage distribution at diagnosis and a two-fold higher incidence of TNBC in the AA population subset. Screening mammography is a potentially powerful strategy for reducing disparities by improving early detection of breast cancer in AA women, but the extent to which this benefit may be diminished by TNBC tumor biology and imaging challenges is unclear. One study previously demonstrated that screening mammography diminished breast cancer disparities through early detection of TNBC in AA patients, and in this study, we sought to further evaluate this finding in a larger and geographically diverse patient population.[17]

1.2. Objectives

Our primary objective was to determine if racial disparities in breast cancer outcome can be mitigated through early detection of TNBC via screening mammography.

2. Material and methods

This is a multi-center cohort study. We performed a retrospective review of all TNBC patients identified through prospectively maintained databases from academic cancer programs in two metropolitan cities of the Northeast and Midwest. These databases and analyses were approved by the institutional review boards of both healthcare systems, with approved waiver of informed consent.

TNBC was defined by American Society of Clinical Oncology guidelines as ER less than 1%; PR less than 1% and Her2/neu 0, 1+, or 2+ with confirmatory negative florescence in situ hybridization.[18] Analyzed cases were those diagnosed from January 1, 1998 to December 31, 2018. Follow up was continued until death, loss to follow up, or study termination. Median follow-up was 4.6 years in the northeast and 4.2 years in the Midwest.

Screen detected cancers were defined as lesions identified on scheduled screening mammography in the absence of clinical symptoms. Non-screen detected cancers were defined as lesions presenting with symptoms such as a new lump, skin changes or bloody nipple discharge. If mode of detection was unclear from retrospective chart review, it was classified as "unknown". Race was recorded as AA versus WA as per self-identification and documentation in the electronic medical record. Patients were categorized as "unknown" if race was not explicitly recorded.

Chi-square tests for categorical variables and two sample student's *t*-test for continuous variables were used to determine the significant differences in clinicopathological variables between status of mammography screen status and race groups. Follow up was continued

Table 1
Characteristics of TNBC patients stratified by site.

Variable	Level	Midwest	Northeast	p-Value
Race	African American	106 (54.9%)	83 (14.7%)	<0.001
	White American	87 (45.1%)	373 (66.3%)	
	NA	0 (0%)	107 (19.0%)	
Age 40	≤40	12 (6.22%)	79 (14.03%)	0.0059
	>40	181 (93.78%)	484 (85.97%)	
Age 50	≤50	46 (23.8%)	211 (37.5%)	<0.001
	>50	147 (76.2%)	352 (62.5%)	
Clinical T stage	T1a	11 (5.70%)	44 (7.82%)	0.248
	T1b	34 (17.62%)	72 (12.79%)	
	T1c	70 (36.27%)	131 (23.27%)	
	T2	56 (29.02%)	142 (25.22%)	
	T3	8 (4.15%)	28 (4.97%)	
	T4	14 (7.25%)	27 (4.80%)	
	NA	0 (0.00%)	119 (21.14%)	
N Stage	N0	148 (76.68%)	332 (58.97%)	0.488
	N1/2/3	42 (21.76%)	111 (19.72%)	
	NA	3 (1.55%)	120 (21.31%)	
Histology	Invasive ductal carcinoma	156 (80.83%)	485 (86.15%)	<0.001
	Invasive ductal carcinoma/invasive lobular carcinoma	23 (11.92%)	4 (0.71%)	
	Invasive lobular carcinoma	8 (4.15%)	10 (1.78%)	
	Metaplastic	2 (1.04%)	11 (1.95%)	
	Other	1 (0.52%)	26 (4.62%)	
	NA	3 (1.55%)	27 (4.80%)	
Any high grade disease	No	41 (21.24%)	60 (10.66%)	<0.001
	Yes	147 (76.17%)	467 (82.95%)	
	NA	5 (2.59%)	36 (6.39%)	
Any LVI	No	142 (73.6%)	290 (51.5%)	0.0278
	Yes	26 (13.5%)	93 (16.5%)	
	NA	25 (13.0%)	180 (32.0%)	
Contralateral prophylactic mastectomy	No	178 (92.23%)	407 (72.29%)	<0.001
	Yes	12 (6.22%)	111 (19.72%)	
Neoadjuvant chemotherapy	No	144 (74.61%)	391 (699.45%)	0.614
	Yes	41 (21.24%)	126 (22.38%)	
Adjuvant chemotherapy	No	55 (28.5%)	152 (27.0%)	0.724
	Yes	114 (59.1%)	289 (51.3%)	
Adjuvant radiation	Breast	91 (47.15%)	228 (40.50%)	0.301
	Breast/regional	16 (8.29%)	46 (8.17%)	
	Post mastectomy	19 (9.84%)	27 (4.80%)	
	None	57 (29.53%)	131 (23.27%)	
Local recurrence	No	171 (88.60%)	413 (73.36%)	0.0587
	Yes	15 (7.77%)	66 (11.72%)	
	NA	7 (3.63%)	84 (14.92%)	
Distant recurrence	No	158 (81.87%)	418 (74.25%)	0.391
	Yes	31 (16.06%)	65 (11.55%)	
	NA	4 (2.07%)	80 (14.21%)	

Table 2
Characteristics of all TNBC patients stratified mode of detection.

Variable	Level	Non-screen detected	Screen detected	NA	p-Value
Race	African American	83 (43.9%)	87 (46.0%)	19 (10.1%)	0.161
	White	222 (48.3%)	177 (38.5%)	61 (13.3%)	
	NA	54 (50.4%)	37 (34.6%)	16 (15.0%)	
Age 40	≤40	66 (72.53%)	8 (8.79%)	17 (18.68%)	<0.001
	>40	293 (44.06%)	293 (44.06%)	79 (11.88%)	
Age 50	≤50	155 (60.3%)	65 (25.3%)	37 (14.4%)	<0.001
	>50	204 (40.9%)	236 (47.3%)	59 (11.8%)	
Median size		2.1 cm	1.2 cm		<0.001
T stage	T1	118 (32.6%)	220 (60.77%)	24 (6.63%)	<0.001
	T2	136 (68.69%)	46 (23.23%)	16 (8.08%)	
	T3	29 (80.56%)	4 (11.11%)	3 (7.32%)	
	T4	33 (80.49%)	5 (12.20%)	3 (7.32%)	
	NA	48 (39.02%)	24 (19.51%)	50 (42.02%)	
N stage	N0	194 (40.42%)	249 (51.88%)	37 (7.71%)	<0.001
	N1/2/3	117 (76.47%)	28 (18.30%)	8 (5.23%)	
	NA	48 (39.02%)	24 (19.51%)	51 (41.46%)	
	No	211 (39.44%)	263 (49.16%)	61 (11.40%)	<0.001
Neoadjuvant CTX	Yes	131 (78.44%)	26 (15.57%)	10 (5.99%)	
	NA	17 (31.48%)	12 (22.22%)	25 (46.30%)	
	No	110 (53.14%)	87 (42.41%)	10 (4.83%)	0.147
Adjuvant CTX	Yes	176 (43.67%)	183 (45.41%)	44 (10.92%)	
	NA	73 (50.0%)	31 (21.23%)	42 (28.77%)	
	Breast	130 (40.75%)	159 (49.84%)	30 (9.40%)	<0.001
	Regional	49 (79.03%)	9 (14.52%)	4 (6.45%)	
Radiation Tx	PMRT	30 (65.22%)	13 (28.26%)	3 (6.52%)	
	No	89 (47.34%)	82 (43.62%)	17 (9.04%)	
	NA	61 (43.26%)	38 (26.95%)	42 (29.79%)	

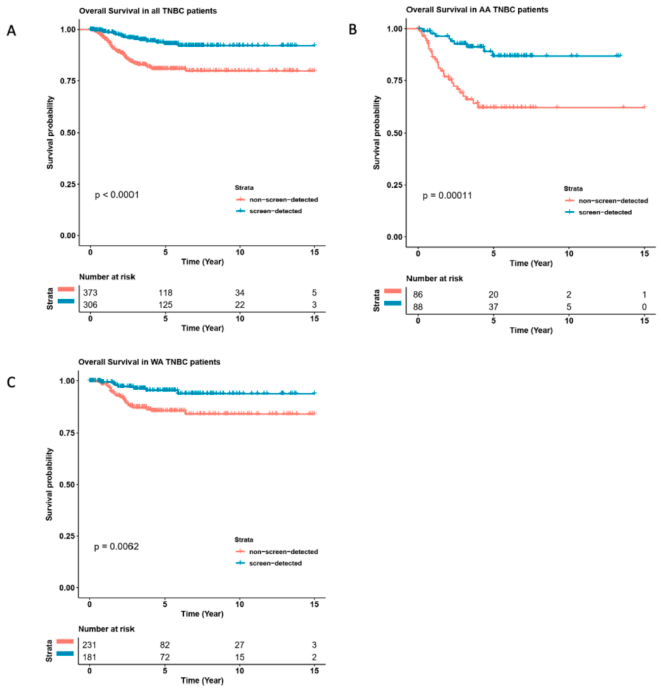

Fig. 1. Overall survival of TNBC patients; 1A. Overall survival of all TNBC patients, 1B. Overall survival of African American TNBC patients, 1C. Overall survival of White American TNBC patients.

until death, loss to follow up, or study termination. Kaplan-Meier plots were used for visualizing the overall survival of all patients after diagnosis, and log-rank test was used to assess the difference in survival among groups. Multivariable cox proportional hazard modeling was conducted for survival models, accounting for age, histologic grade, and race. Race specific models were conducted separately, using cox proportional hazard modeling to account for age, and histologic grade. All analyses were conducted using the R statistical programing version 4.0.2.

3. Results

3.1. Mammography specific outcomes

Combining data from both institutions participating in the study, 756 TNBC patients were identified. Analyzed by mode of detection, of these 756 TNBC patients, 301 (39.8%) were mammographically screen-detected, 359 were non-screen detected (47%), and 96 (12%) had unknown mode of detection. Of 257 TNBC patients under the age of 50, 25.3% had screen-detected disease compared to 47.3% of 499 TNBC patients over the age of 50 ($p < 0.001$) (Table 1).

Non-screen detected cancers were larger tumors at time of diagnosis; median size 2.1 cm vs 1.2 cm, $p < 0.0001$; 192 (72%) of non-screen detected cancers compared to 55 (20%) screen detected cancers were stage T2/T3/T4, ($p < 0.0001$). 118(32%) of non-screen detected cancers were T1 compared to 220 (60%) of screen detected($p < 0.0001$). Non-screen detected cancers also had higher rates of node positive status compared to screen-detected cancers (31.8% vs 9.9%; $p < 0.0001$) (Table 2).

Patients with non-screen detected cancers were more likely to receive neoadjuvant chemotherapy compared with screen detected cancers (131(78%) versus 26(15%); $p < 0.0001$). They were also more likely to receive breast/regional adjuvant radiation therapy; 49 (79%) non-screen detected patients received breast/regional adjuvant radiation therapy compared to 9 (14.5%) screen-detected ($p < 0.0001$) (Table 2).

5-year overall survival was better for screen-detected TNBC compared to non-screen-detected TNBC in the entire cohort (92.8% v. 81.5%; $p < 0.0001$) (Fig. 1). 5-year local recurrence free survival and distant recurrence free survival were better for screen detected TNBC compared to non-screen detected TNBC (74.5 vs 83.8%; $p = 0.003$ and 75.1% vs 87.3%; $p < 0.0001$ respectively) (Figs. 2–3).

3.2. Race specific outcomes

46% of 189 AA and 38.5% of 460 WA patients had screen-detected

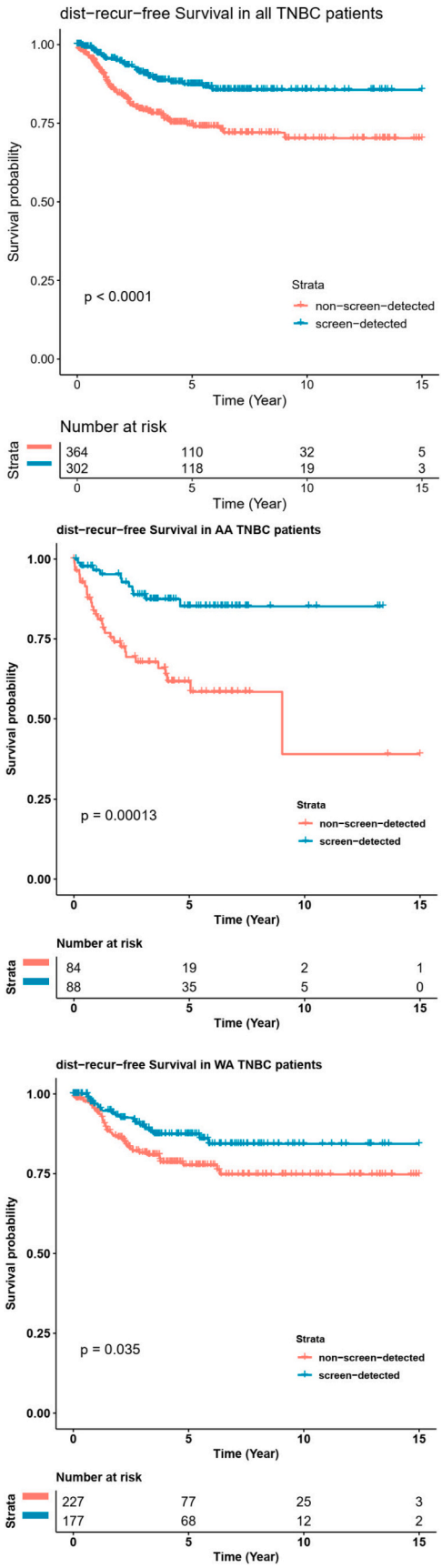

Fig. 2. Distant recurrence free survival of TNBC patients; 1A. Distant recurrence free survival of all TNBC patients, 1B. Distant recurrence free survival of African American TNBC patients, 1C. Distant recurrence free survival of White American TNBC patients.

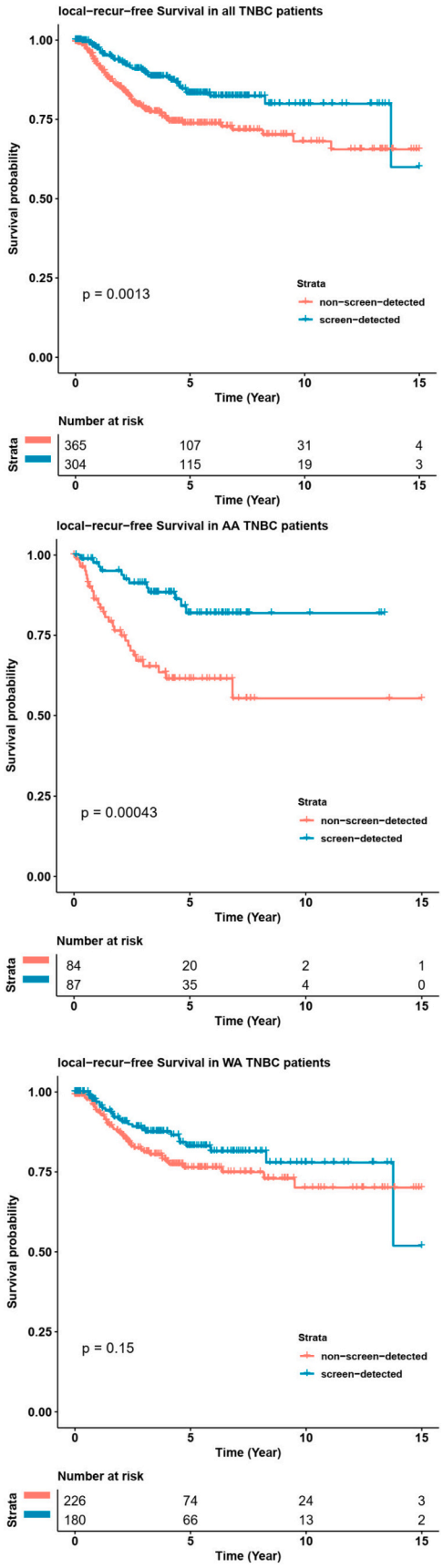

Fig. 3. Local recurrence free survival of TNBC patients; 1A. Local recurrence free survival of all TNBC patients, 1B. Local recurrence free survival of African American TNBC patients, 1C. Local recurrence free survival of White American TNBC patients.

Table 3
Characteristics of all TNBC patients stratified race.

Variable	Level	AA	WA	NA	p-Value
Mammo screen detected	No	83 (43.9%)	222 (48.3%)	54 (50.5%)	0.161
	Yes	87 (46.0%)	177 (38.5%)	37 (34.6%)	
	NA	19 (10.1%)	61 (13.3%)	16 (15%)	
Age 40	<40	21 (11.1%)	54 (11.7%)	16 (15%)	0.927
	>40	168 (88.9%)	406 (88.3%)	91 (85%)	
Age 50	≤50	58 (30.7%)	150 (32.6%)	49 (45.8%)	0.701
	>50	131 (69.3%)	310 (67.2%)	58 (54.2%)	
CPM	No	169 (89.42%)	333 (72.39%)	83 (77.57%)	<0.001
	Yes	9 (4.76%)	99 (21.52%)	15 (14.02%)	
	NA	11 (5.82%)	28 (6.09%)	9 (8.41%)	
T stage	T1	91 (48.1%)	228 (49.6%)	43 (40.2%)	0.276
	T2/T3/T4	79 (41.8%)	159 (34.6%)	37 (34.6%)	
	NA	19 (10.1%)	73 (15.9%)	27 (25.2%)	
N stage	N0	124 (65.6%)	301 (65.4%)	55 (51.4%)	0.261
	N1/N2/N3	45 (23.8%)	84 (18.3%)	24 (22.4%)	
	NA	20 (10.6%)	75 (16.3%)	28 (26.2%)	
Neoadjuvant chemotherapy	No	128 (67.72%)	336 (73.04%)	71 (66.36%)	0.0721
	Yes	51 (26.98%)	91 (19.78%)	25 (23.36%)	
	NA	10 (5.29%)	33 (7.17%)	11 (10.28%)	
Postop chemotherapy	No	55 (29.1%)	129 (28%)	23 (21.5%)	1
	Yes	104 (55%)	245 (53.3%)	54 (50.5%)	
	NA	30 (15.9%)	86 (18.7%)	30 (28%)	
Postop radiation	Breast	87 (46.03%)	189 (41.09%)	43 (40.19%)	0.568
	Breast/Reg	13 (6.88%)	36 (7.83%)	13 (12.15%)	
	PMRT	14 (7.41%)	20 (4.35%)	12 (11.21%)	
	None	55 (29.1%)	119 (25.87%)	14 (13.08%)	
	NA	20 (10.58%)	96 (20.87%)	25 (23.36%)	

TNBC (p = 0.16). AA pts had lower 5-year overall survival compared to WA (74% v. 90.9%; p < 0.0001), but age did not significantly impact survival (0.927) (Table 3).

Race-stratified analyses revealed that there were no differences in mean tumor size (median size AA 1.7 cm versus 1.6 cm WA; p = 0,25), with similar distribution of T2/T3/T4 vs T1 cancers (41.8% T2/T3/T4 vs 48.1% for AA and 34.6% vs 49.6% for WA; p = 0.27). There was also a similar age distribution, (30.7%) of AA women under the age of 50 compared to WA women (32.6%) (Table 3).

Five-year overall survival was better for screen-detected TNBC compared to non-screen-detected TNBC (for the entire cohort 92.8% v. 81.5%; p < 0.0001), and the magnitude of this effect was most significant among AA pts (Fig. 1B); 5-year overall survival for screen-detected versus non-screen-detected AA TNBC 86.6% v. 62.5%; p = 0.0002; and for WA TNBC 95.1% v. 86.5%; p = 0.015 (Fig. 1B–C). These screening-related survival benefits were consistent among AA and WA patients when stratified by city as well.

Five-year local recurrence free survival was better for screen detected patients and the magnitude of benefit was greater in AA populations (AA screen vs non-screen detected 81.7% vs 62%, p = 0.001; and WA screen versus non-screened 84.1% vs 77.6%; p = 0.19). This same trend was observed for distant recurrence free survival (AA screen vs non-screen detected 84.9% versus 62.0%; p < 0.001 and WA screen versus non-screen detected 87.5% vs 78.9%; p = 0.06) (Figs. 2–3).

3.3. Site specific outcomes

Proportion of AA patients in the Midwest was higher (54% AA and 45% WA in Midwest versus 15% AA and 66% WA in Northeast; p < 0.0001), and patients in the Midwest were older (76% of patients >50 years old in Midwest versus 63% patients >50 years old in Northeast; p < 0.0001). Patients were less likely to have contralateral prophylactic mastectomy in Midwest (6% in Midwest versus 20% in Northeast; p < 0.0001). There were no differences in administration of chemotherapy between sites (74.6% in Midwest versus 70% in Northeast; p = 0.614), or radiation (65% in Midwest versus 54% in Northeast; p = 0.301). There were no differences in T or N stage at presentation (60% T1 in Midwest and 44% T1 in Northeast; p = 0.401. 22% node negative in Midwest and 20% node negative in Northeast; p = 0.488). There were no differences in local recurrence (8% vs 12% local recurrence in Midwest and Northeast respectively; p = 0.0587) or distant recurrence (16% vs 12% distant recurrence in Midwest and Northeast respectively; p = 0.391) between sites.

Race-stratified clinicopathologic features were also compared by geographic region. For the Northeast health system, AA women had significantly larger lesions than WA women at time of diagnosis (median size 1.7 cm versus 1.55 cm, respectively, p = 0.197), and were more likely to have T2/T3/T4 vs T1 stage cancers (43.4% T2/T3/T4 vs 33.7% for AA and 33.2% vs 47.2% for WA; p = 0.041). AA women were also more likely to be under the age of 50 (41%) when diagnosed compared to WA women (34.2%), although this difference was not statistically significant (p = 0.3). Frequency of screen detected disease was similar for AA and WA women (30.1%AA and 37.0% WA; p = 0.575). For the Midwest health system, there were no differences in mean tumor size (2.2 [0.3–10.0]cm for AA patients vs 2.7 [0.1–27.0]cm for WA patients), nodal status (node negative: 80 AA [75.5%] and 68 WA patients [78.2%]), or mean age at diagnosis (61.3 [29–90] years for AA patients vs 61.0 [27–90] years for WA patients). Frequency of screen detected disease was similar for AA and WA women at the Midwest center (58.5% for AA vs 44.7% for WA).[19] Screen detected TNBC was associated with improved 4-year overall survival in AA patients (screen-detected cases: 93.2% [95% CI, 87.0%–99.9%]; non–screening detected cases, 59.1% [95% CI, 45.8%–76.2%]; p < 0.001). Screen detected TNBC was associated with a trend toward improved 4-year overall survival in WA patients, but the improvement was not significantly (screen-detected cases: 87.5% [95% CI, 76.5%–100%]; non–screen detected cases: 74.8% [95% CI, 62.3%–89.7%]).

4. Discussion

4.1. Screening mammography mitigates racial disparities

Overall, we found worse survival in AA compared to WA patients with TNBC, and the extent to which this outcome disparity is explained by differences in tumor biology and/or treatment response is beyond the scope of our analyses. Importantly however, our study also found that

mammography screen-detected TNBC was associated with an earlier stage distribution and improved overall survival. The survival advantage resulting from early detection and screening mammography was most prominent in AA patients. These patterns were consistent when stratified by city. Early detection of disease through screening mammography correlated with lower local as well as distant recurrence endpoints. The magnitude of recurrence-free survival benefit observed was larger in AA women, mirroring trends in overall survival by race. These findings reinforce the utility of screening mammography as a tool in mitigating racial disparities through earlier detection.

Overall, AA women were more likely to die from breast cancer when compared to WA women. The root cause of this disparity is multifactorial, including various socioeconomic factors and healthcare access barriers; however genetic factors and differences in tumor biology contribute as well.[20,21] We also found more advanced stage distribution for AA compared to WA patients in the northeast but not in the Midwest, suggesting that extent of disparities also varies by healthcare delivery system.

4.2. Screening mammography detects early stage TNBC

TNBC is more difficult to detect on mammography. This is because TNBCs often lack the typical mammographic distinctions of invasive cancers, including spiculated margins and suspicious calcifications.[22] These factors coupled with higher proportions of women diagnosed with TNBC at young ages, when breasts are composed of dense tissue, account for higher proportions of cancers that are mammographically occult and non-screen detected. Despite challenges in mammographic detection of TNBC, we found that screen-detected TNBCs were diagnosed at earlier stage. This finding underscores the utility of screening mammography specifically in diagnosing early stage TNBC, and reinforces the benefit of community efforts focused on improving screening mammography compliance in minority populations.

Though not statistically significant in our study, AA women tend to present with breast cancer at a younger age; having higher breast cancer incidence in women under the age of 50 compared to white women.[22] This brings into question optimal age of breast cancer screening initiation for AA women. 30.7% of AA patients in this study presented with TNBC before the age of 50. Currently, there is no consensus on screening initiation age among national societies, with recommendations for initiation age including 40 years old (the American College of Radiology/Society of Breast Imaging and the National Comprehensive Cancer Network); 45 years old (American Cancer Society); and 50 years old (the American Academy of Family Practice and the American College of Physicians, United States Preventive Services Task Force). Given these findings, it is evident further research is warranted to identify optimal age of screening initiation in AA populations in attempts to mitigate disparities through screening.[23]

4.3. Limitations

The study was limited by factors inherent to retrospective review. 96 (12.6%) of patients did not have mode of detection recorded, 10% of AA and 13.3% WA with this information missing. 107 (19%) patients did not have record of racial identification. Of note, patients with unknown mode of detection tended to be younger patients, with high grade disease. Though unlikely to change the findings in this study, more information on this subset of young patients with high grade disease could potentially contribute to our understanding of the nature of aggressive TNBCs. In addition, this study did not collect data on time of last mammogram. We were therefore unable to specifically evaluate outcomes for patients presenting with true interval breast cancers. Lastly, we were unable to evaluate the role of insurance and socioeconomic status on our outcomes data.

It is also important to address the possible effects of lead and length time bias in screen detected patients; however previous studies have shown stage at diagnosis is more strongly related to disease recurrence than mode of detection, and the largest effects of lead and length time bias are observed between patients of differing stage at diagnosis.[24] As survival analysis modeled for stage at diagnosis, it is less likely the observed survival benefit is solely attributable to lead and length time bias.

5. Conclusion

Data from this multi-center cohort study demonstrate the value of screening mammography in mitigating breast cancer disparities in AA compared to WA women through early detection of TNBC. Future research in race-related breast cancer outcomes is warranted.

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Declaration of competing interest

None.

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