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Update on Triple Negative Breast Cancer Disparities for the United States – A Population Based Study from the United States Cancer Statistics database, 2010-2014

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Abstract

Background: Triple negative breast cancer (TNBC) has been associated with a more aggressive histology, poorer prognosis and nonresponsiveness to hormone therapy. It is imperative that cancer research identify factors that drive disparities and focus on prevention.

Methods: Using the United States Cancer Statistics database, we examined differences between triple-negative breast cancers compared to all other breast cancer in regard to age, race/ethnicity and stage at diagnosis.

Results: We identified 1,151,724 cases of breast cancer from 2010–2014, with the triple negative phenotype accounting for approximately 8.4% of all cases. In unadjusted analyses, non-Hispanic black women (OR = 2.27; 95%CI: 2.23, 2.31) and Hispanic women (OR = 1.22; 95%CI: 1.19, 1.25) had higher odds of diagnosis when compared to non-Hispanic white women. Women younger than 40 had the highest odds of diagnosis, compared to women age 50 – 64 (OR = 1.95; 95%CI: 1.90, 2.01). Diagnosis at AJCC stage III and beyond conferred higher odds of diagnosis of triple-negative breast cancer ($OR_{stageIII}$ = 1.69; 95%CI: 1.68, 1.72; $OR_{stageIV}$ = 1.47; 95%CI: 1.43, 1.51). Results varied slightly in adjusted analyses.

Conclusions: This study shows that there is significant burden of disease in triple negative breast cancer for women of color, specifically non-Hispanic black women, and younger women. Additional studies need to be conducted to determine drivers of disparities between race, age and stage.

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Triple negative breast cancer accounted for 8.4% of breast cancer cases from 2010–2014. There is significant burden of disease in triple negative breast cancer for women of color, specifically non-Hispanic black women, and younger women.

Keywords

Triple Negative Breast Neoplasms; Health Status Disparities; Continental Population Groups; Ethnic Groups; Epidemiology; Registries

Introduction

Triple negative breast cancer (TNBC) has been found to account for approximately 15% of all breast cancer cases, and is associated with aggressive histology, poorer prognosis, shorter survival, and unresponsiveness to usual hormone therapy.[1] A study conducted on a sample of 51,074 women using the California cancer registry found that the triple negative phenotype was statistically significantly associated with younger age, African American race/ethnicity, later stage diagnosis, lower SES and shortened survival.[2] This study is one of a few that include personal socioeconomic status(SES) data. Non-Hispanic black (NHB) women also had a significantly earlier age at diagnosis, high grade tumors, and a higher proportion of triple-negative breast cancers.[3,4] The focus on TNBC due to aggressive nature and poor prognosis; thus, it is imperative to continue identifying risk factors, albeit environmental or genetic, that exacerbate disparities in breast cancer diagnosis in order to develop and implement more efficacious population-based prevention strategies.

Although research has established multiple individual-level risk factors associated with general breast cancer diagnoses, racial disparities persist even after accounting for these risk factors, particularly between non-Hispanic white (NHW) and non-Hispanic black populations. While age-adjusted incidence rates for all types of breast cancer are higher in NHW women, mortality rates are higher in NHB women. According to SEER data, age-adjusted incidence rates from 2011– 2015 were 128.6 per 100,000 for NHW women and 126.9 per 100,000 for NHB women. The age-adjusted mortality rates from breast cancer in 2011–2015 for NHB women was 28.7 per 100,000 and 20.3 deaths per 100,000 for NHW women.[5] Research indicates that survival in NHB women may be worse due to a higher frequency of adverse histologic features.[1] The latest data published by the American Cancer Society show that age-adjusted rates of TNBC are two times greater among NHB women as compared to NHW women.[6] The SEER data from 2008 to 2014 show that even when disease stage was taken into account, Non-Hispanic black women had lower the 5-year relative survival rate compared to NHW women: 95.4% vs. 99.1% for localized, 76.6% vs. 86.4% for regional, and 19.7% vs. 28.1% for distant stages.[5]

Although older age has been linked to breast cancer overall, this relationship is reversed for TNBC.[7] It was demonstrated that TNBC occurs more frequently in younger women and in non-Hispanic black women.[1,8–12] What drives these disparities remains unknown.

To our knowledge, no studies have examined racial disparities in TNBC across the US with the United States Cancer Statistics (USCS) database, as few have looked beyond the scope

of one state. After unavoidable sample exclusions described below, the USCS database yielded 39 states with complete data for our study. Previous findings have been limited due to their small sample sizes from either local caner registries or SEER data, the smallest of which was 474 cases from a clinical trial to the largest of 452,215 cases over a 10-year period thus they are neither spatially representative nor generalizable.[11–13]

With the use of data from a more comprehensive population dataset this analysis aims to validate previous findings in the literature, confirming the proportion of breast cancer cases that are triple negative, and the effects of age, race and stage of diagnosis on the likelihood that the BC is the TNBC type. The research questions of interest are: Are the underlying distributions of age, race and stage at diagnosis different for women with TNBC compared to women with all other types of breast cancer? Do the odds of TNBC diagnosis among women with breast cancer differ by race, age or stage at diagnosis, at the individual level?

The research hypotheses are as follows: Non-Hispanic black women will have higher odds of TNBC diagnosis than their non-Hispanic white counterparts in nationally aggregated data analysis. Younger women will have higher odds of TNBC diagnosis and those diagnosed at late and distant stage will have higher odds of TNBC diagnosis.

Methods

We examined all breast cancer cases diagnosed during 2010–2014 from the restricted-use United States Cancer Statistics (USCS) database, which is a population-based surveillance system of cancer registries with data representing 99% of the U.S. population that combines both NCI/SEER and CDC/NPCR data.[14]All states participate in the USCS registry data system, but five did not provide county-level breast cancer data – Illinois, Kansas, Michigan, Minnesota and Missouri – and four did not code for triple negative data – Connecticut, Iowa, New Mexico, and Utah. Alaska and Hawaii were excluded from analysis due to missing contextual data. As this study population is a part of a larger geographically-focused study, these states were excluded to ensure comparability. The remaining 39 states were used for analysis. The study was limited to 2010– 2014 as USCS did not collect data on HER2 receptor status until 2010.

The dataset was analyzed using SAS Software (SAS 9.4, SAS Institute Inc., Cary, NC). Triple negative cases were identified using site specific factors 1, 2 and 15. Site-specific factors 1, 2 and 15 identify estrogen receptor, progesterone receptor and HER2 receptor, respectively. The classification variables are categorical for positive, negative, borderline, and other. Those coded as negative (‘020’) for each site-specific factor were considered triple-negative. Late stage was defined as diagnosis at AJCC (7^{th} edition)[15] Stage III and beyond, while distant stage is defined as diagnosis at AJCC Stage IV. Age groups were defined as less than 40, 40 – 49, 50 −64, 65 – 74, and 75 and older with age 50 −64 serving as the referent group. There were six race/ethnicity categories in the study: non-Hispanic white, Hispanic, non-Hispanic black, American Indian/Alaskan Native, Asian, and Other, with non-Hispanic white serving as the referent category. Descriptive statistics were calculated for age, race and stage variables in the dataset. Chi-Square tests and the student’s t-tests were employed to compare differences in the distribution of age, race, and stage in

triple negative cases versus all other breast cancer cases. Logistic regression was then used to determine the odds of diagnosis of triple negative breast cancer given breast cancer and its variation by race, age and stage. Unadjusted models included race, age, and stage as individual independent predictors of triple negative breast cancer given breast cancer. Adjusted models, that included age, race, and stage variables simultaneously, were run, and late stage and distant stage were included in separate models to avoid perfect collinearity, as 'distant' is a subset of 'late stage'. This approach is similar to the Bauer and colleagues (2007) who conducted the California registry study.[1]

Results

We identified 1,151,724 breast cancer cases from 2010–2014 in the 39 states in the dataset, with a mean age of diagnosis at 61.9. In this comprehensive collection of breast cancer cases, approximately 75% of the cases were NHW women; among all races/ethnicities, 27.7% were diagnosed at the late stage and approximately 5% were diagnosed at distant stage. In the examined time period, TNBC cases accounted for 8.4 % of all breast cancer cases (Table 1). NHB women accounted for a larger percentage of TNBC cases, 21.4%, compared to overall breast cancer cases, 10.9% (Table 2). The triple negative group had a lower mean age at diagnosis of 59.3 as compared to the non-TNBC breast cancer cases, 62.1 (p <.0001) (Table 2). As expected TNBC cases had higher percentage of late and distant stage diagnoses (Table 2).

The unadjusted logistic regression models confirmed the results presented in Table 3. NHB, Hispanic and American Indian/Alaskan Native women had higher odds of TNBC diagnosis, while Asian and Other women had lower odds, when using NHW women as the referent (Table 3). Compared to NHW women, NHB women had the highest odds of TNBC diagnosis (OR=2.27; 95% CI =2.23, 2.31), while women with race other than NHB had the lowest odds of being diagnosed with TNBC (OR=0.71; 95% CI=0.64, 0.77). Comparing age groups with the reference being women 50–64 years of age, women < 40 had the highest odds of TNBC diagnosis, (OR= 1.95; 95% CI=1.90, 2.01), while those age ≥75 had the lowest odds (OR= 0.75; 95%CI=0.73, 0.76). Women diagnosed at late stage were 69% more likely to be diagnosed with TNBC (OR= 1.69; 95%CI=1.68, 1.72), and women diagnosed at distant stage were 47% more likely to be diagnosed with TNBC (OR= 1.47; 95%CI=1.43, 1.51).

After controlling for the late stage diagnosis and age, NHB women had approximately twice the odds of diagnosis with TNBC compared to NHW women (Table 3), whereas Hispanic women had similar to NHW odds of TNBC diagnosis. The youngest age group had the highest odds of TNBC diagnosis, while the oldest had the lowest odds (Table 3). Women age 40–49 did not have different odds of diagnosis compared to women age 50–64. For those diagnosed at late stage, the odds of triple negative diagnosis were 1.58 times the odds for those diagnosed earlier than stage three. In the model adjusted for distant stage, the results were similar (Table 3). Women age 40–49 had a slightly higher odds of diagnosis with TNBC, 1.09, while the results remained the same for Hispanic women. Those diagnosed at distant stage had 1.39 times the odds of diagnosis of TNBC.

Discussion

The study conducted here is both the most geographically broad in terms of scope of states included, and also the most recent in terms of data examined. Using more current data ensures consistency of TNBC coding, providing an improved estimate of the overall burden of this highly problematic type of breast cancer. Having a broader sample brings greater heterogeneity in terms of local context into the realm of analysis, which can be fruitful when using variation across predictors to explain variations across geography in future studies.[16]

In the 39-state subset of the entire US breast cancer population, approximately 8.5% of cases were classified as triple negative using site-specific factors. Triple negative cases account for fewer breast cancer cases (8.5%) than found in previous studies, which used smaller samples and/or focused on a single state or city with estimates ranging between 10 and 15% [1,17–23] The localized studies used data from California[1,20], Atlanta, GA[19,22], and Detroit, MI[21]. The distribution of race was different for the triple-negative cases compared to all other breast cancer cases ($p<.0001$). NHB women accounted for 10.9% of the other breast cancer cases, but 21.4% of the triple negative cases. By contrast, NHW women accounted for 75.7% of the other breast cancer cases, but only accounted for 65.7% of triple negative cases. In Bauer and colleagues study[1], NHB women accounted 4.4% of other breast cancer cases and 10% of triple negative cases.

In the present study, age group distributions were different between other breast cancer and triple negative breast cancer cases ($p<.0001$). The youngest age group, less than 40, accounted for 3.8% of other breast cancer cases, and 7.7% of triple negative cases. In the most comparable registry study, which covered California data from 1999 −2003[1], this age group accounted for more breast (5.7%) and triple negative breast cancer cases (12.2%). The proportion of those diagnosed at late-stage and distant stage was higher in the triple negative group compared to the other breast cancer cases. Late stage diagnosis occurred in 37.9% of triple negative cases, and distant stage diagnosis occurred in 6.6% of triple negative cases. This finding is contrary to the Bauer study[1] that found that late stage cases of triple negative breast cancer account for approximately 15% of the cases and distant stage accounted for 4%. We found evidence of different distributions in age, race and stage at diagnosis compared to previous studies which used older data from more limited geographies. These stark differences demonstrate the importance of national population-based studies to learn generalizable findings to inform comprehensive cancer control efforts.

More generally, this descriptive analysis confirms disparities previously found in the literature and shows that there are significant burdens among women of color, specifically non-Hispanic black women, younger women, and women diagnosed at a later stage when it comes to triple-negative breast cancer diagnosis. This study found that those burdens are higher among these groups than previously estimated, as the disparities among groups are greater than previously found, even though the overall impact in breast cancer cases was lower, potentially due to the use of a more comprehensive population and more current data. These differences were confirmed in the logistic regression analyses. In both adjusted and unadjusted models, non-Hispanic black women had significantly higher odds of triple negative diagnosis compared to non-Hispanic white women. The youngest age group also

had significantly higher odds of triple negative diagnosis. Women diagnosed at late and distant stage had significantly higher odds of triple negative diagnosis.

The study is limited in the scope as it focuses solely on one subtype, triple-negative. Future studies can expand the scope to examine additional subtypes of breast cancer and elucidate differences between subtypes. Additionally, the study focused on stage III and beyond where morbidity and mortality is generally higher. Inclusion of additional stage information could provide insight in the distribution of disease in this particular population. Given the large sample size and geospatial coverage of the data, these results are somewhat different and also more generalizable than previous studies. The lower incidence of triple-negative cases could potentially be due to change in data collection from registries, as 2010 was the first year SEER began collecting data on HER2 receptor status for breast cancer cases. This analysis focused solely on individual characteristics to update the literature with more comprehensive and recent data on TNBC. It has been found that breast cancer subtype was a significant factor in prognosis, regarding survival, and that the triple negative subtype showed the worst prognosis irrespective and race, age or stage.[23] Considering these results, it is important to consider what additional external factors may influence individual level variations in diagnosis. Examining external factors such as physical and social environmental characteristics may further elucidate drivers of disparities, as the literature has consistently examined individual biological factors. Due to the aggressive nature of triple-negative breast cancer, and lack of therapeutic options, it is important to know which groups confer a higher risk to better provide intervention.

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Table 1.

Descriptive Statistics of Study Population, n=1151724

Variable	N	Percent	N_{TNBC}	$Percent_{TNBC}$ [+]
Race				
NHW	862205	74.86	63579	7.37
Hispanic	95507	8.29	8438	8.83
NHB	135389	11.76	20726	15.31
AI/AN	5504	0.48	502	9.12
Asian	44424	3.86	3042	6.85
Other	8695	0.75	462	5.31
Age				
Age Groups, mean	1151724	61.84	96749	8.40
<40	47329	4.11	7474	15.79
40–49	179715	15.6	17065	9.50
50–64	433798	37.67	37993	8.76
65–74	275982	23.96	19806	7.18
75+	214900	18.66	14411	6.71
Late Stage				
Yes	310588	27.68	36659	11.80
No	811633	72.32	59292	7.31
Distant Stage				
Yes	54073	4.82	6412	11.86
No	1068148	95.18	89539	8.38
Missing[≠]	29503	2.6	798	2.70
TNBC				
Yes	96749	8.4		
No	1054975	91.6		

[≠] This represents the number of cases that were missing stage data.

[+] This is the row percentage of TNBC cases.

Table 2.

Differences in Frequencies of Age, Race, and Stage for Other Breast Cancers and Triple Negative Breast Cancer

	Other BC n=1054975		TNBC n=96749		Test for Difference	
Variable	**N**	**Percent**	**N**	**Percent**	**statistic**	**p**
Race					χ^2=9851.15	<.0001
NHW	798626	75.70	63579	65.72		
Hispanic	87069	8.25	8438	8.72		
NHB	114663	10.87	20726	21.42		
AI/AN	5002	0.47	502	0.52		
Asian	41382	3.92	3042	3.14		
Other	8233	0.78	462	0.48		
Age Groups					χ^2=5051.62	<.0001
<40	39855	3.78	7474	7.73		
40–49	162650	15.42	17065	17.64		
50–64	395805	37.52	37993	39.27		
65–74	256176	24.28	19806	20.47		
75+	200489	19.00	14411	14.90		
Mean Age†		62.07		59.28	t=59.86	<.0001
Late Stage					χ^2=7182.29	<.0001
Yes	273929	25.97	36659	37.89		
No	752341	71.31	59292	61.28		
Distant Stage					χ^2=2311.43	<.0001
Yes	47661	4.52	6412	6.63		
No	978609	92.76	89539	92.55		
Missing‡	28705	2.72	798	0.82		

†Satterthwaite T-test used to compare mean age differences (F=1.08, p<.0001 test for equal variance). Percent is the mean age for each group.

‡This represents the number of cases that were missing stage data.

Table 3.

Association between TNBC diagnosis and Race/Ethnicity, Age and Stage at Diagnosis

	Unadjusted		Adjusted – Late Stage		Adjusted – Distant Stage	
Variable	**Odds Ratio**	**95% C.I.**	**Odds Ratio**	**95% C.I.**	**Odds Ratio**	**95% C.I.**
Race						
NHW	REF		REF		REF	
Hispanic	1.217	1.189, 1.247	1.106	1.08, 1.134	1.13	1.103, 1.158
NHB	2.271	2.233, 2.309	2.111	2.075, 2.148	2.159	2.122, 2.196
AI/AN	1.261	1.15, 1.382	1.188	1.083, 1.305	1.213	1.105, 1.332
Asian	0.923	0.889, 0.959	0.851	0.819, 0.885	0.847	0.816, 0.88
Other	0.705	0.642, 0.774	0.714	0.646, 0.788	0.7	0.634, 0.772
Age						
<40	1.954	1.902, 2.007	1.759	1.711, 1.808	1.886	1.835, 1.939
40–49	1.093	1.072, 1.114	1.066	1.046, 1.087	1.085	1.065, 1.106
50–64	REF		REF		REF	
65–74	0.805	0.791, 0.82	0.848	0.833, 0.864	0.832	0.817, 0.847
75+	0.749	0.734, 0.764	0.816	0.8, 0.833	0.808	0.792, 0.824
Late Stage						
Yes	1.698	1.675, 1.722	1.58	1.558, 1.602	-	
No	REF		REF			
Distant Stage						
Yes	1.47	1.431, 1.511	-		1.388	1.351, 1.426
No	REF				REF	