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Racial/ethnic disparities in inflammatory breast cancer survival in the Michigan Cancer Surveillance Program

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Abstract

Purpose While racial disparities in inflammatory breast cancer (IBC) incidence are fairly well documented, with black women having significantly higher rates compared to white women; less is known about whether IBC prognosis differs by race/ethnicity. Therefore, the objective of this study was to assess racial/ethnic disparities in survival among women diagnosed with IBC in the Michigan Cancer Surveillance Program (MCSP) from 1998 to 2014.

Methods We examined the frequency and percentage of breast cancer cases coded to the various IBC codes in the MCSP registry over the study period. We used age-adjusted and multivariable Cox Proportional hazard regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations of race/ethnicity with all-cause mortality.

Results Using a comprehensive case definition of IBC, 1324 IBC patients were identified from women diagnosed with invasive breast cancer in the MCSP [Non-Hispanic Black (NHB) = 227; Non-Hispanic White (NHW) = 984; Hispanic = 86; other = 27]. The percentage of all breast cancer cases defined as IBC in the MCSP registry differs considerably across registry codes from 0.02 to 1.1%. We observed significantly higher risk of death among NHB compared with NHW [HR (95% CI), 1.21 (1.01–1.45)], while no significant survival differences were observed between NHW and Hispanics or other racial/ethnic minorities.

Conclusions A comprehensive case definition should be utilized to avoid underestimation of IBC and to better understand this aggressive disease. Further research is needed to identify underlying causes and develop effective interventions to reduce IBC survival disparities between NHB and NHW women.

Keywords Inflammatory breast cancer · Survival · Disparities

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Introduction

Inflammatory breast cancer (IBC) is an aggressive form of breast cancer, largely due to its strong metastatic potential [1, 2], with 30% of IBC patients presenting with metastasis at diagnosis, compared to 10% of women with non-IBC [3]. With the introduction of multimodality treatment options (i.e., radiation, surgery, and chemotherapy), IBC survival has markedly improved [4]; although prognosis remains worse as compared to non-IBC patients [5, 6]. Thus, while IBC accounts for roughly 2% of breast cancer incidence, it represents 7% of breast cancer deaths [7].

Various classification systems have been used to define IBC over time, including both clinical and pathological definitions [6, 8]; and the lack of a standard case definition for IBC has severely limited our understanding of the disease [7, 9]. The pathological definition of IBC is the most conservative [9, 10], requiring invasion of dermal lymphatics of

the breast with tumor emboli (DLI) [10]. Alternatively, the clinical definition of IBC is based on the presence of clinical symptoms (i.e., edema, erythema, peau d'orange) [11], and does not require pathological evidence of DLI. The most widely referenced case definition at present time is from the American Joint Committee on Cancer (AJCC; code T4d), which describes IBC as 'a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass [12]. A comprehensive definition of IBC including breast cancer cases coded to any of the aforementioned clinical or pathological codes has been recommended to identify IBC cases from cancer registries [13, 14].

Data on risk factors for IBC are limited, and the contributions of hereditary versus environmental/lifestyle factors remain a subject of controversy [15]. However, findings from several studies suggest that longer duration of breast feeding, younger age at first birth, and higher body mass index (BMI) are associated with an increased risk of IBC [16, 17]. Moreover, higher IBC incidence [7, 9, 10, 18, 19] and poorer survival [7, 9, 20, 21] among black compared to white women have been observed in prior population-based prior studies in the US. For example, the median survival time in black women with IBC was only 2 years compared with 3 years among white women in the US [7]. However, previous studies have utilized inconsistent definitions of IBC, relied largely on older data before the widespread use of trimodal therapies, and did not consider survival differences among other racial/ethnic groups (e.g., Hispanic women).

Thus, the purpose of this analysis was to assess racial disparities in IBC survival utilizing a comprehensive definition of IBC and including Non-Hispanic Black (NHB), Non-Hispanic White (NHW), Hispanic women and other racial/ethnic minorities in the Michigan Cancer Surveillance Program from 1998 to 2014. We also examined the potential impact of cancer registry coding changes on the ascertainment of IBC in the registry.

Methods

Data source and study population

The data for this study were obtained from Michigan Cancer Surveillance Program (MCSP), a statewide population-based registry in operation since 1981, with legally mandated cancer reporting and statewide population coverage since 1985 [22]. The sample in this dataset includes all women diagnosed with invasive breast cancer in the State of Michigan between 1998 and 2014 ($n = 155{,}509$). Of these, cases not coded to any of the IBC-designated registry codes ($n = 154{,}136$), and those without survival time information ($n = 49$) were excluded from analyses of racial disparities in

IBC survival, leaving a final analytical sample size of 1324 women with IBC.

IBC assessment

The clinical presentation and pathologic characteristics of IBC are heterogeneous and, therefore, the identification of IBC can be challenging. These complications are reflected in the varied and evolving coding rules for documenting IBC in cancer registries over time. The International Classification of Diseases for Oncology (ICD-O 8530) registry code is reserved for breast cancers with pathologic evidence of IBC (i.e. plugging of the dermal lymphatics with tumor emboli) [10]. The extent of disease (EOD-E 70) registry code corresponds to inflammatory breast carcinoma, including diffuse (beyond that directly overlying the tumor) dermal lymphatic permeation or infiltration [20]. The most commonly used registry codes for IBC are from the AJCC (code T4d), which defines IBC as a composite clinicopathologic entity [12]. The comprehensive case definition is meant to capture all the clinical or pathological elements of the disease (AJCC T4d or ICD-O 8530, or EOD-E 70). For this study, we examined how the changing criteria for defining IBC impacts the ascertainment of IBC in the MCSP from 1998 to 2014. We also evaluated whether the ascertainment of IBC using the various codes differed according to race/ethnicity. We used the comprehensive definition of IBC to examine racial disparities in IBC survival in multivariable models.

Outcome and exposure of interest

The outcome of interest in this study was survival time (in years) since diagnosis, defined as the time from date of diagnosis to the date of death, or last date of contact. The primary exposure of interest was race/ethnicity [Non-Hispanic Black (NHB; $n = 227$), Non-Hispanic White (NHW; $n = 984$), Hispanic ($n = 86$) and other ($n = 27$), which included American Indian, Filipino, Asian Indian or Pakistani, Other Asian, and unknown race/ethnicity].

Potential confounders

Based on our prior knowledge of factors associated with race/ethnicity and mortality, we evaluated the following factors as potential confounders in the multivariable model; age at diagnosis, tumor stage, marital status, estrogen receptor (ER) status, place of residence (rural vs. urban) and neighborhood poverty level. Women's place of residence was based on the Rural Urban Continuum codes, which separates counties into metropolitan (urban; codes 01-03) and non-metropolitan (rural; codes 04-09) counties based on the census tract of residence at the time of diagnosis. Neighborhood poverty level was assigned based on the 2000 US Census

(for cases diagnosed from 1998 to 2004) and the American Community Survey (for cases diagnosed since 2005) using the census tract of residence at the time of diagnosis. We examined the percent change in estimates with the addition of each covariate to the model, and also used the stepwise regression selection method to obtain a parsimonious multivariable model, given our relatively small sample size. The final multivariable model included age at diagnosis (continuous), tumor stage (local/region, distant, unstaged), marital status (married, unmarried, unknown), and estrogen receptor (ER) (positive, negative, missing). We created dummy variables for each category of categorical variables in the model to estimate Hazard Ratios for each racial/ethnic group.

Statistical analysis

Mean and standard deviation (for continuous variables) as well as frequency and percentage (for categorical variables) were used to describe the study population by race/ethnicity category. We also examined the frequency and percentage of breast cancer cases coded to the various IBC codes in the MCSP registry over the study period. We used Cox Proportional hazard regression model with age as the underlying time metric to estimate hazard ratios (HR) and 95% confidence interval (CI) for associations of race/ethnicity with all-cause mortality. We examined age-adjusted and multivariable models with NHW women as a reference group. Data analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC); p values are two-sided, with an α level of 0.05 considered statistically significant.

Results

Demographic and clinical characteristics of IBC patients

Overall, IBC patients were diagnosed at an average age of 59 years, and had a mean survival time of 1.8 years (Table 1). IBC tumors were slightly more likely to be ER+ versus ER− tumors (43.6 vs. 42.8%) and were diagnosed most often at a localized/regional tumor stage (58.6%). On average, NHB women (57.8 years) and other racial/ethnic groups (53.6 years) were diagnosed at younger ages than Hispanic women (60.5 years) and NHW women (59.3 years). The average survival time was the longest among Hispanic women (2 years) and was shortest among other racial/ethnic groups (1.5 years). While IBC tumors among NHW women were more likely to be ER+ versus ER− (45.6 vs. 41.8%), tumors diagnosed among NHB (36.6 vs. 47.6%), Hispanic (38.4 vs. 40.7%), and other racial/ethnic (44.4 vs. 48.2%) groups were more likely to be ER−. Moreover, NHB women (40.5%) and Hispanic women (40.7%) were more likely to be diagnosed at an advanced stage of disease (i.e., distant), compared to NHW (31.5%) women and women reporting other race/ethnicities (25.9%). The majority of NHB (72.9%) women were unmarried followed by Hispanic (62.2%) women, with the lowest % unmarried observed among women of other race/ethnicities (37.5%).

Table 1 Demographic and clinical characteristics of IBC cases by race/ethnicity

Characteristics	Race/ethnicity				
	Overall ($n=1324$)	Non-Hispanic White ($n=984$)	Non-Hispanic Black ($n=227$)	Hispanic ($n=86$)	Others ($n=27$)
Age at diagnosis, mean (SD)	59.0 (14.1)	59.3 (14.0)	57.8 (14.1)	60.5 (15.1)	53.6 (12.9)
Survival time, mean (SD)	1.8 (2.0)	1.8 (2.0)	1.7 (1.9)	2.0 (1.9)	1.5 (1.9)
Estrogen receptor (ER)					
Positive	577 (43.6)	449 (45.6)	83 (36.6)	33 (38.4)	12 (44.4)
Negative	567 (42.8)	441 (41.8)	108 (47.6)	35 (40.7)	13 (48.2)
Missing	180 (13.6)	124 (12.6)	36 (15.9)	18 (20.9)	2 (7.4)
Tumor stage, n (%)					
Localized/regional	776 (58.6)	597 (60.7)	120 (52.9)	39 (45.4)	20 (74.1)
Distant	444 (33.5)	310 (31.5)	92 (40.5)	35 (40.7)	7 (25.9)
Unstaged/missing	104 (7.9)	77 (7.8)	15 (6.6)	12 (14.0)	0 (0)
Marital status, n (%)					
Married	599 (45.3)	496 (50.4)	57 (25.1)	31 (36.1)	15 (55.6)
Unmarried	633 (47.8)	420 (42.7)	153 (67.4)	51 (59.3)	9 (33.3)
Unknown	92 (7.0)	68 (6.9)	17 (7.5)	4 (4.7)	3 (11.1)

Unmarried: it includes never married, separated, divorced, and widowed

Identifying IBC cases using different criteria

The frequencies and percentages of IBC cases (out of all breast cancers) using the different registry codes in the MCSP from 1998 to 2014 are summarized in Table 2. The pathologic ICD-O 8530 code has been utilized throughout the study period, although it identified only 452 IBC cases (i.e., 32.9% of IBC cases using the comprehensive definition). The extent of disease EOD-E:70 codes has been used in the MCSP from 2008 to 2014, and identifies the lowest number of IBC cases (i.e., $n = 16$, 0.02%). Of the 1324 IBC cases identified by the comprehensive technique during 1998–2014, majority of them were identified by *AJCC v6* codes [used from 2004 to 2014 ($n = 1142$, 83.2%)] followed by AJCC v7 [used from 2010 to 2014 ($n = 476$, 34.7%)]. The percentage of all breast cancer cases defined as IBC in the MCSP registry differs drastically across codes. Using the pathologic code ICD-O 8530 results in 0.3% of breast cancer cases considered as IBC, while the comprehensive definition identifies 0.9% of the breast cancer cases as IBC. In the same manner, EOD-E:70 code identifies only 0.02% as IBC whereas AJCC v6 and AJCC v7 identify 1.1% and 1.0%, respectively. Results were similar in analysis stratified by race/ethnicity.

IBC survival by race/ethnicity

During a median follow-up period of 1.13 years (range = 0.12 months to 16.5 years), 876 deaths occurred among the 1324 women with IBC in the MCSP registry. Table 3 shows the relative risk of death among IBC patients by race/ethnicity from age-adjusted and multivariable models. Compared to NHW women, NHB women were 32% more likely to die (HR 1.32; CI 1.11–1.56) in the age-adjusted model. Hispanic women had a 23% higher risk of death compared to NHW women although, likely due to the small sample size, these results were not statistically significant (HR 1.23; CI 0.97–1.57). In multivariable models, NHB women had mortality risks that were 21% (95% CI 1.01–1.45) higher than NHW women, and survival differences among Hispanic women and women of other race/ethnicities were not statistically significant.

Discussion

In this study of 1324 women with IBC, we observed significantly higher risk of death among NHB compared to NHW women, and no significant survival differences between

Table 2 Identifying IBC cases from other breast cancers using different criteria (1998–2014)

Year at diagnosis	All breast cancer cases	Inflammatory breast cancer (IBC)				
		ICD-O 8530	EOD-E:70	AJCC v6	AJCC v7	Comprehensive
	n	n (%)	n (%)	n (%)	n (%)	n (%)
1998	8769	33 (0.4)				33 (0.4)
1999	8913	43 (0.5)				43 (0.5)
2000	9094	43 (0.5)				43 (0.5)
2001	9215	39 (0.4)				39 (0.4)
2002	9276	44 (0.5)				44 (0.5)
2003	8885	24 (0.3)				24 (0.3)
2004	8769	41 (0.5)		115 (1.3)		115 (1.3)
2005	8797	30 (0.3)		108 (1.2)		108 (1.2)
2006	9002	38 (0.4)		98 (1.1)		98 (1.1)
2007	9073	19 (0.2)		96 (1.1)		96 (1.3)
2008	8947	21 (0.2)	1 (0.01)	91 (1.0)		92 (1.0)
2009	9411	12 (0.1)	2 (0.02)	90 (1.0)		90 (1.0)
2010	8964	16 (0.2)	5 (0.06)	118 (1.3)	100 (1.1)	119 (1.3)
2011	9447	11 (0.1)	1 (0.01)	123 (1.3)	112 (1.2)	123 (1.3)
2012	9627	15 (0.2)	4 (0.04)	111 (1.2)	101 (1.0)	112 (1.2)
2013	9905	13 (0.1)	2 (0.02)	94 (0.9)	83 (0.8)	95 (1.0)
2014	9415	10 (0.1)	1 (0.01)	98 (1.0)	80 (0.8)	99 (1.1)
1998–2014	155,509	452 (0.3)	16 (0.02)	1142 (1.1)	476 (1.0)	1373 (0.9)

ICD-O 8530: International Classification of Diseases for Oncology 8530 (ICD-O 8530)

EOD-E: 70: Extent of Disease Code (EOD-E:70)

AJCC: American Joint Committee on Cancer (AJCC) sixth edition (coded as T4d),

Comprehensive: Includes any of the following; ICD-O 8530, EOD-E:70, AJCC v6, AJCC v7

Table 3 Hazard ratios and 95% confidence intervals for overall survival in relation to race/ethnicity for IBC cases

Race/ethnicity	No of deaths	Age-adjusted model, hazard ratio	95% CI	Multivariable[a] model, hazard ratio	95% CI
Non-Hispanic White	614	1.00	Referent	1.00	Referent
Non-Hispanic Black	174	1.32	1.11–1.56	1.21	1.01–1.45
Hispanic	78	1.23	0.97–1.57	1.40	0.89–1.46
Others	10	0.69	0.37–1.31	0.81	0.43–1.53

[a]Adjusted for tumor stage (localized/regional, distant, unstaged/missing), marital status (married, unmarried, unknown), estrogen hormone receptor (EHR) (positive, negative, missing), and Age at diagnosis (continuous)

NHW women and Hispanics or other racial/ethnic minorities. However, given the smaller number of Hispanic and other racial/ethnic minorities in this study, we had limited statistical power to detect differences in these groups. After controlling for demographic and tumor characteristics, including tumor stage and hormone receptor status, NHB women had a 21% higher risk of death compared to NHW women with IBC. Moreover, we observed marked variation in the percentage of breast cancers identified as IBC in the MCSP registry from 1998 to 2014 depending on the registry codes used. Thus, a comprehensive definition of IBC should be utilized in future cancer registry studies to avoid dramatic underestimates of IBC.

Racial disparities in breast cancer survival are well documented [23]; and these disparities may vary depending on breast cancer subtype [24–26]. For example, the greatest black and white survival disparity has largely been observed among women with less aggressive breast tumors (e.g., luminal subtypes), where multiple effective treatment regiments are available. However, in IBC, perhaps the most aggressive subtype of breast cancer, racial disparities in survival have been consistently reported in the literature [7, 9, 20, 21]. For example, African American women with IBC had hazard ratios ~ 30% higher than their NHW counterparts even after adjusting for county-level socioeconomic position, age at diagnosis, tumor and treatment characteristics in a large population-based registry in the US [20]. In a similar analysis using the Florida cancer registry, disparities were even more stark, with African American women with IBC (diagnosed from 1998 to 2002) being twice as likely to die relative to Caucasian women in multivariable analysis [21]. Our study adds to the bulk of evidence suggesting racial disparities in IBC survival between NHB and NHW women and suggests that even among breast tumors with generally poor prognosis, race independently predicts worse outcomes.

The observed survival difference between NHB and NHW women in our study may be partially explained by differences in tumor characteristics and/or stage at diagnosis. In fact, black women are more likely to be diagnosed with aggressive breast cancer subtypes, including triple-negative or basal-like tumors, compared to other racial/ethnic groups [27, 28]. Being diagnosed with negative estrogen receptor (ER) and late-stage tumors is associated with poorer survival, which is often more apparent among black women compared with their white counterparts. Although in our study, the survival differences were still apparent after adjustment for tumor characteristics, including ER status and stage at diagnosis in the multivariable model. However, residual confounding is always possible, and there may be other underlying factors affecting survival (e.g., body mass index, human epidermal growth factor receptor 2) that were unaccounted for in our analyses of cancer registry data.

Strengths of this study include the use of the comprehensive case definition to identify IBC cases from MCSP over (a relatively) extended period of time. We were also able to overcome limitations of other studies by examining survival differences among women from other racial/ethnic groups (e.g., Hispanic women). The study also has several limitations. For example, the registry data did not consistently include important prognostic factors such as treatment modalities (chemotherapy, hormonal therapy, surgery, radiation therapy), comorbidities, and socioeconomic status variables; thus, we were unable to adjust for these potentially important prognostic factors. However, tumor characteristics and stage at diagnosis, which were accounted for in our study, were the largest mediators of racial disparities in breast cancer survival in a prior study of over 17,000 women in the National Comprehensive Cancer Network centers; treatment and other demographic factors were not as important [29]. Additionally, we were limited by a short follow-up period, and further studies are warranted to examine how survival disparities persist over longer follow-up time. However, the early period after diagnosis has been suggested as a susceptibility where racial disparities in non-inflammatory breast cancer survival may promulgate [29]. Finally, we had limited power to detect survival differences among Hispanic women and those reporting other race/ethnicities. Additional studies to examine IBC survival disparities among these racial/ethnic groups are warranted.

In summary, we observed poorer overall survival among NHB relative to NHW women with IBC, with an over 20% higher risk of death among NHB over follow-up. Future

research should focus on identifying the underlying factors contributing to the observed racial disparities in IBC survival and developing effective targeted interventions to eliminate this disparity. Moreover, utilizing a comprehensive definition to identify IBC cases from cancer registries can improve the detection of IBC cases and advance our understanding of this aggressive disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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