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EPIDEMIOLOGY

Incidence and survival of inflammatory breast cancer between 1973 and 2015 in the SEER database

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Abstract

Purpose Inflammatory breast cancer (IBC) is an aggressive variant characterized by erythema, edema, and "peau d'orange" of the skin progressing within 6 months. We assessed the incidence and survival of IBC in the US over four decades.

Methods Using SEER*Stat, a case list of IBC patients diagnosed between 1973 and 2015 ($n=29{,}718$) was extracted from SEER 18 registries by using a combination of morphology, stage, and extent of disease criteria. M1 and M0 patients were included. Age-adjusted incidence rates, relative survival rates, and mean survival time were calculated. Significance was determined as non-overlapping 95% confidence intervals.

Results The overall incidence of IBC from 1973 to 2015 is 2.76 (2.73, 2.79) cases per 100,000 people, with white patients having an incidence rate of 2.63 (2.60, 2.67), black patients 4.52 (4.39, 4.65), and patients of other race 1.84 (1.76, 1.93). The overall IBC relative 5-year survival rate is 40.5% (39.0%, 42.0%), 42.5% (40.7%, 44.3%), and 29.9% (26.6%, 33.3%) for white patients and black patients, respectively. Patients diagnosed in 1978–1982 have a mean survival time of 62.3 (52.0, 72.6) months, while those diagnosed in 2008–2012 have mean survival time of 99.4 (96.4, 102.4) months. There is no significant difference in survival time between T4D patients and patients with other T staging and extent of disease coding consistent with clinical IBC presentation.

Conclusions IBC survival has increased over four decades. Despite the improvement in survival for all racial groups, a persistent survival disparity that has not narrowed over two decades remains between white and black patients.

Keywords Inflammatory breast cancer · Survival · Incidence · Disparities

Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive variant of stage IIID breast cancer, with increased likelihood of metastasis upon diagnosis relative to non-inflammatory breast cancer. Patients presenting with IBC experience diffuse or localized erythema and swelling of the breast, often with a "peau d'orange" appearance of the skin, that evolves and progresses within 6 months [1].

The literature on IBC examining survival using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program has assessed patients diagnosed before 2008 [2–5]. Studies with more recent patient data used pathological instead of clinical definitions of IBC, resulting in smaller patient cohorts as IBC is inconsistently noted on pathology reports [6], since the diagnosis relies on clinical presentation. There is therefore concern that the current literature on IBC survival is not capturing all patients who in fact have IBC. Nevertheless, a consistent observation across previous studies is that IBC incidence is higher in blacks than in whites, and that survival in IBC and other advanced breast cancers is worse in blacks than in whites [2–5], [7–9].

This study aimed to achieve a comprehensive view of the clinical and epidemiological evolution of IBC in the

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United States over the past four decades. Major global advocacy and education efforts [10] are hypothesized to have produced greater awareness and more timely diagnosis and implementation of multimodality treatments in IBC. We combine pathological and clinical definitions of IBC to capture most or all patients with a true clinical diagnosis of IBC, and we assess incidence and survival of IBC patients by race from 1973 to 2015 using SEER 18.

Methods

Data source and case definitions

We used SEER*Stat software version 8.3.5 to extract a case list of IBC patients from the November 2017 submission of SEER 18 registries for all cases diagnosed between 1973 and 2015. SEER 18 represents 27.8% of the US population, based on the 2010 census. In accordance with the consensus of the IBC International Consortium [10], we defined IBC patients as all female breast cancer patients coded with the ICD-O-3 code 8530 (IBC specifically noted on pathology report), the AJCC 6th edition code T4d (recommended coding for clinically presenting IBC—erythema and edema involving more than half the breast), or the extent of disease collaborative staging extension codes 510–750 (describe erythema, edema, and "peau d'orange" to varying extents—codes further expanded upon in ST1 and ST2). This results in a cohort of 29,718 IBC patients diagnosed between 1973 and 2015.

Incidence analyses

Different SEER registries began contributing data at different times, so our case list extraction represents a varying fraction of the US population sampled over time, as follows: 1973–1991, 9.4%; 1992–1999, 13.4%; and 2000–2015, 27.8%. In order to compare IBC case count to an appropriate healthy population, case count and healthy population count were extracted using SEER*Stat software package version 8.3.5 from the November 2017 submissions of SEER 9 for all patients diagnosed between 1973 and 1991, SEER 13 for 1992–1999, and SEER 18 for 2000–2015. Age-adjusted incidence rates were calculated for all races for women with IBC, with age-adjustment based on the 2000 U.S. standard population and 95% confidence intervals (CI) calculated using the Tiwari et al. modification [11], and p values were reported as significance tests for the difference between incidence rates.

Receptor status analyses

We sought to assess the proportion of IBC patients with hormone receptor (HR) + /HER2 − cancer, HR − / HER2 + cancer, and triple-negative breast cancer, given that prior studies focused mainly on single institution cohorts, with the exception of the recent study by Aurit et al. [12]. In our overall cohort of 29,718 IBC patients, 7799 patients (26.2%) had at least one HR and HER2 status known. Using this smaller cohort, we assessed the proportion of IBC patients with each receptor status, and investigated the contribution of race to mean age at diagnosis of IBC, by receptor status. Based on the 2010 collaborative stage coding guidelines, we include receptor status coded as "borderline" (formerly defined as 1–9% cells stained) as "positive" (currently defined as ≥ 1% of cells stained). Significance was determined as non-overlapping 95% CI of the mean ages for comparative groups, with 95% CI calculated as per Kaye et al. [13], and p values were reported as significance tests for the difference between mean age of diagnosis.

Survival analyses

Comparison of relative survival rates over calendar time

Relative survival rates are the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable healthy population, thus representing cancer survival apart from other causes of death. We calculated 5-, 10-, 15-, and 20-year relative survival rates using survival sessions on SEER*Stat software version 8.3.6 and the November 2015 submission of SEER 18 registries for cases diagnosed between 1973 and 2013, on a cohort of patients defined to have IBC using the coding from ST1. We used this database because it had the broadest range of years of diagnosis available in a SEER*Stat survival session, although it did not include patients from 2013 to 2015, as does our incidence analysis. Using this database yields a cohort of 23,130 IBC patients diagnosed between 1973 and 2013. We estimated relative survival rates stratified by race using the Ederer II method [14], and 95% CI were calculated using the Greenwood method [15]. p values were reported as significance tests for the difference between relative survival rates.

We use two methods of calculating relative survival rates: cohort analysis and period analysis. A schematic layout of patients included in these analyses is presented in SF1. Period survival analysis better predicts the survival of more recently diagnosed patients than does traditional

cohort analysis [16], so we compare period analysis rates to cohort analysis rates to assess difference in survival between recently diagnosed and historically diagnosed patients.

Comparison of mean survival over calendar time

Although period analysis assesses the survival of recently diagnosed patients, it does not compare survival of patients diagnosed in each calendar year. In order to calculate this, we use the recorded survival months of a cohort of 21,933 IBC patients with active follow-up who were diagnosed between 1973 and 2012 (see Supplementary Methods for cohort details) [17]. The average rate of loss-to-follow-up over 1973–2012 was 12.6% (see ST3).

To account for unobserved survival information for patients alive at the end of our selected time period, we impute their survival times by pseudo observations. We assume that patients born in similar years have similar survival dynamics and residual survival. Based on this assumption, we divided patients into cohorts based on birth year. Pseudo survival times for censored patients were imputed using survival models for each birth cohort (see Supplementary Methods).

Results

Incidence

As displayed in Fig. 1, the incidence of IBC as captured by the SEER program has changed over time. From 1973 to 1987, IBC incidence is relatively constant at 0.56 cases per 100,000 people, but from 1988 to 2003 the incidence of IBC rises to 2.03 cases per 100,000 people, followed by a sharp increase to 4.90 cases per 100,000 in 2004–2009, and then a near-return to previous levels of incidence with 2.80 cases per 100,000 in 2010–2015. The overall incidence of IBC from 1973 to 2015 is 2.76 cases per 100,000 people (ST4). Interestingly, the major changes in IBC incidence coincide with changes in SEER coding guidelines for IBC, i.e., the introduction of the "T4d" AJCC code in 1988 and the introduction of Extent of Disease Collaborative Staging codes in 2004. Notably, the larger increases in incidence that occur in 1988 and 2004 are followed by plateauing incidence rates in all races (Fig. 1b), suggesting that the increases are likely due to changes in SEER coding guidelines for IBC, rather than to underlying biological variations, an idea that has also been proposed in previous literature [7].

The overall age-adjusted incidence of IBC from 1973 to 2015 when stratified by race is 2.63 cases per 100,000 people for white patients, 4.52 for black patients, and 1.84 for patients of other races (Asian, Pacific Islander, Native American, etc.) (ST5). This pattern of black patients having significantly higher IBC incidence than white patients ($p < 0.00001$) and of patients of other races having lower IBC incidence than white patients ($p < 0.00001$) has been consistent throughout the history of SEER, becoming more pronounced as more registries contributed larger numbers of minority patients to the data in 1992 and 2000.

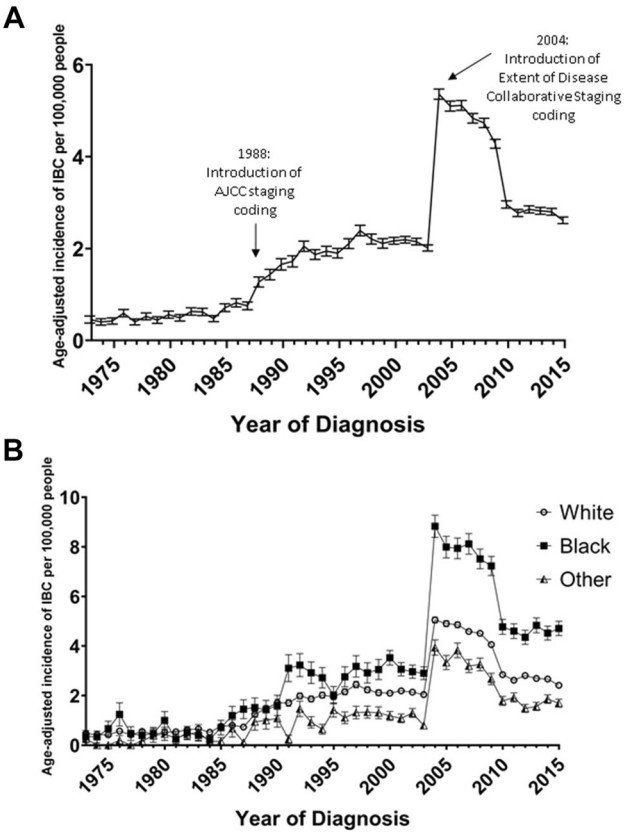

Fig. 1 **a** Age-adjusted incidence rates for inflammatory breast cancer per 100,000 people from 1973 to 2015, with bars representing standard error. IBC incidence increases in years when key coding changes were added to SEER (1988, 2004) and subsequently plateaus. **b** Age-adjusted incidence rates for IBC per 100,000 people from 1973 to 2015, by race, with bars representing standard error. Open circles: white patients; solid squares: black patients; open triangles: patients of other race. Black patients consistently have higher incidence of IBC than white patients, who consistently have higher incidence of IBC than patients of other race. IBC cases defined as all female breast cancer patients coded as ICD-O-3 8530, AJCC 6th edition T4d, or EoD CS-Extension 510–750

Receptor status

In our cohort of 7799 IBC patients with at least one HR and HER2 status known, 3464 (44.4%) were HR + /HER2 −, 1133 (14.5%) were HR −/HER2 +, and 1702 (21.8%) had triple-negative IBC (Table 1).

Table 1 IBC receptor status by race and mean age at diagnosis (in years)

Race	Total IBC with known receptors			at least one HR + and HER2 −			ER-, PR-, HER2 +			ER-, PR-, HER2 −		
	Count	Mean age	95% CI	Count (% total)	Mean age	95% CI	Count (% total)	Mean age	95% CI	Count (% total)	Mean age	95% CI
White	5736	61.8	(61.4, 62.2)	2600 (45.3)	63.4	(62.8, 63.9)	835 (14.6)	59.9	(59.0, 60.9)	1164 (20.3)	61.7	(60.8, 62.6)
Black	1453	57.8[a]	(57.1, 58.6)	585 (40.3)	59.2[a]	(58.1, 60.4)	195 (13.4)	55.5[a]	(53.6, 57.5)	435 (29.9)	57.7[a]	(56.4, 59.1)
Other	581	57.5[a]	(56.3, 58.6)	268 (46.1)	58.3[a]	(56.7, 60.1)	97 (16.7)	58.0	(55.4, 60.7)	97 (16.7)	57.3	(54.2, 60.3)
Unknown	29	56.1[a]	(51.9, 60.2)	11 (37.9)	57.9	(49.4, 66.4)	6 (20.7)	50.3[a]	(42.8, 57.9)	6 (20.7)	53.2[a]	(49.5, 56.9)

Significance relative to white patients, determined by non-overlapping 95% CI calculated as per Kaye et al. [13] and demonstrated by [a]

We find that across races, non-white patients are diagnosed with IBC at significantly younger ages than white patients (mean age at diagnosis for white patients = 61.8 years, for black patients = 57.8 years ($p < 0.00001$), and for patients of other race = 57.5 years ($p < 0.00001$)) (Table 1). Furthermore, for HR + /HER2 −, HR −/HER2 +, and triple-negative IBC, black patients are diagnosed significantly younger than white patients, by about 4 years ($p < 0.00001$, $p = 0.00004$, and $p < 0.00001$, respectively). Both white and black patients with IBC are diagnosed with HR −/HER2 + IBC at significantly younger ages than with HR + /HER2 − IBC ($p < 0.00001$ for white patients, $p = 0.00236$ for black patients), concordant with the age distribution for all breast cancers. For all races, mean age at diagnosis for triple-negative IBC is not significantly different from mean age at diagnosis for IBC overall ($p = 0.391$, $p = 0.396$, $p = 0.396$ for white, black, and other patients, respectively).

Relative survival rates

The comparison of relative survival rate estimates using cohort analysis and period analysis, stratified by race, is presented in Table 2. The 20-year relative survival rate calculated by period survival analysis for patients with IBC is 21.5% for all patients, 22.1% for white patients, 16.2% for black patients, and 26.9% for patients of other races, representing rates higher than those calculated by cohort-based analysis. Black patients have significantly lower relative survival rates for both cohort and period-based analysis compared with white patients: using period analysis, the 5-year relative survival rate of black patients is 29.9% and that of white patients is 42.5% ($p < 0.00001$), while the 10-year relative survival rate of black patients is 18.4% and that of white patients is 30.7% ($p < 0.00001$).

The comparison of 20-year period-based estimates and 5-, 10-, 15-, 20-year cohort-based estimates of relative survival rates is presented in Fig. 2. Relative 5-year survival rate of all patients using cohort-based analysis is 41.9%, 10-year is 28.0%, 15-year is 21.3%, and 20-year is 15.6%. In comparison, the period-based relative 20-year survival rate is 21.5%. The difference between cohort- and period-based survival is significant at $\alpha = 0.05$ for the 20-year survival rates of all patients ($p = 0.0158$).

Mean survival over calendar time

After multiple imputation using one Cox proportional hazard model with age of diagnosis as the only covariate, and another Cox proportional hazard model with age of diagnosis and race as covariates, the mean survival months of patients for each 5-year period of diagnosis from 1973 to 2012 are presented in Table 3. The mean survival months

Table 2 Relative Survival Rates for inflammatory breast cancer by race, % (95% CI)

		5-year	10-year	15-year	20-year
Black	Cohort	29.8 (26.7, 32.9)	14.8 (10.9, 19.4)	10.4 (5.0, 18.1)	3.7 (0.7, 11.2)
	Period	29.9 (26.6, 33.3)	18.4 (15.2, 21.8)	16.7 (12.9, 20.9)	16.2 (9.1, 25.1)
White	Cohort	44.0[a] (42.4, 45.7)	30.6[a] (28.2, 33.0)	22.1[a] (18.8, 25.6)	17.5[a] (13.4, 22.0)
	Period	42.5[b] (40.7, 44.3)	30.7[b] (28.9, 32.5)	25.1[b] (22.7, 27.5)	22.1 (19.2, 25.2)
Other	Cohort	46.8[a] (41.5, 51.8)	26.3 (18.5, 34.7)	19.1 (10.3, 29.9)	14.1 (3.8, 31.0)
	Period	43.6[b] (38.0, 49 .0)	32.6[b] (26.7, 38.7)	30.5 (22.8, 38.6)	26.9 (18.3, 36.3)
All	Cohort	41.9[a] (40.5, 43.3)	28.0[a] (25.9, 30.0)	21.3[a] (18.3, 24.4)	15.6[a] (12.1, 19.5)
	Period	40.5[b] (39.0, 42.0)	28.9[b] (27.4, 30.4)	24.0[b] (22.0, 26.1)	21.5 (18.9, 24.2)

Cohort cohort analysis, *Period* period analysis. Significance relative to black patients, determined by non-overlapping 95% CI calculated via the Greenwood method [15] and demonstrated by [a] for cohort and [b] for period analysis

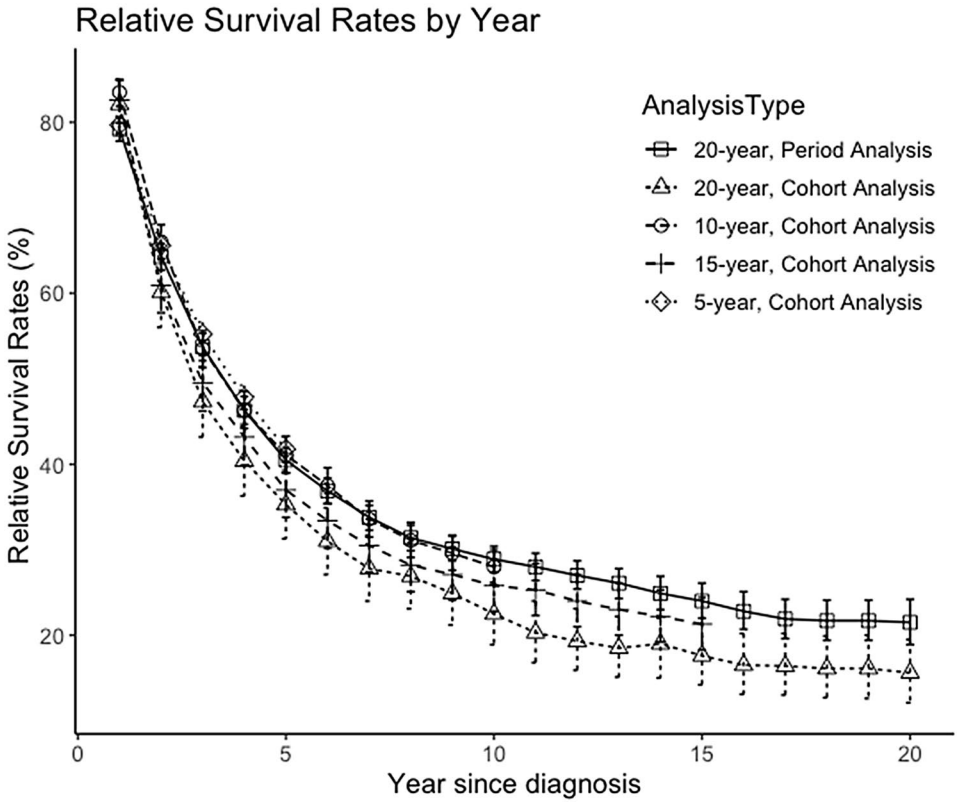

Fig. 2 20-year period-based and 5-year, 10-year, 15-year, and 20-year cohort-based relative survival curves for patients with IBC, with bars representing 95% CI. Open squares: 20-year period-based curve; open diamonds: 5-year cohort-based curve; open circles: 10-year cohort-based curve; dashed lines: 15-year cohort-based curve; open triangles: 20-year cohort-based curve. There is substantial separation between the 20-year period-based relative survival curve and the 20-year cohort-based relative survival curve, indicating an improvement in IBC survival in recent years compared to historical patients

calculated using both Cox models are similar, validating the obtained results—for patients diagnosed between 1973 and 1977, both models give mean survival of 48.0 months; mean survival steadily increases to 99.4 months in the double-covariate model for patients diagnosed between 2008 and 2012 ($p < 0.00001$) (see Fig. 3a).

Mean survival months for patients of different races are shown in Table 4 and Fig. 3b. The mean survival time for white patients is 81.9 months from diagnosis year 1988 to 1992, rising to 101.9 months from diagnosis year 2008 to 2012 ($p = 0.177$). The mean survival time for black patients is 48.5 months from diagnosis year 1988 to 1992, rising to 84.3 months from diagnosis year 2008 to 2012 ($p < 0.00001$). For both these time increments, white patients' mean survival time is significantly higher than black patients' ($p = 0.0157$ and $p = 0.00626$ for 1988–1992 and 2008–2012, respectively).

The comparison of mean survival months between patients coded with stage T4D, patients with stage "Any T with Mets," and patients with all other T stages is presented in Fig. 4a, and the breakdown of these data by race is presented in Fig. 4b. Patients with metastases have significantly lower survival than patients without metastases—in 2008–2012, the mean survival time for "Any T, Mets"

Table 3 Mean survival months before and after imputation of censored patients (95% CI)

Year	Mean survival time (Months)		
	Unadjusted	Cox model, adjusted for age	Cox model, adjusted for race and age
1973–1977	47.0 (37.4, 56.6)	48.0 (37.8, 58.2)	48.0 (37.9, 58.2)
1978–1982	61.9 (52.0, 71.9)	62.3 (51.9, 72.6)	62.3 (52.0, 72.6)
1983–1987	55.7 (48.3, 63.1)	58.9 (50.1, 67.7)	58.9 (50.1, 67.6)
1988–1992	68.5 (63.7, 73.3)	77.9 (71.5, 84.3)	77.9 (71.6, 84.3)
1993–1997	66.5 (63.4, 69.7)	84.5 (79.1, 90.2)	84.6 (79.1, 90.0)
1998–2002	62.2 (60.5, 63.8)	94.5 (90.2, 98.7)	94.3 (90.0, 98.5)
2003–2007	48.6 (47.9, 49.2)	95.1 (92.7, 97.6)	94.8 (92.3, 97.2)
2008–2012	28.2 (27.9, 28.6)	100.2 (97.2, 103.2)	99.4 (96.4, 102.4)

patients is 62.4 months, for T4D patients 108.2 months ($p < 0.00001$), and for other T patients 98.9 months ($p < 0.00001$). T4D patients and other T patients consistently have no significant differences in survival, with mean survival time in 2003–2007 101.6 months for T4D patients and 102.6 months for other T patients ($p = 0.374$), and in 1988–1992 75.5 months for T4D patients and 70.4 months for other T patients ($p = 0.301$). For patients with and without metastases, white patients' mean survival time is consistently higher than black patients' (see ST 6, 7).

The results of the linear model with number of survival months as the outcome (imputed using the Cox proportional hazard model with age of diagnosis and race as covariates) and race and year of diagnosis as the main effects are seen in ST 8: the effect of race on survival time is 26.05 (95% CI 21.8, 30.2), indicating that white patients have increased survival time compared to black patients, while the effect of year of diagnosis on survival time is 1.64 (95% CI 1.13, 2.15), indicating that patients diagnosed after the year 2000 have approximately 64% increased survival time compared to patients diagnosed prior to 2000. The interaction between race and year of diagnosis was not significant.

Discussion

Our calculated age-adjusted incidence rates of IBC are higher than those reported in recent literature, although our incidence rates by race are consistent with previously reported trends. We propose that this is due to our coding definition of IBC, which emphasizes the importance of clinical signs like diffuse erythema, edema, and "peau d'orange"—the defining characteristics of IBC—in the absence of a specifically stated pathologic or clinical diagnosis of IBC in the tumor registry record [18, 19]. We employed a specific definition that leverages the existing data on SEER that is pertinent to IBC and, importantly, that aligns with IBC diagnosis in the clinic—IBC is unique among solid tumor categories in that the diagnosis is primarily driven by clinical presentation and not by identification from the pathology report. This method of coding IBC cases might rarely capture cases of locally advanced non-IBC. However, as IBC incidence has historically been underreported due to lack of consensus about coding and diagnosis, our approach sought to assess all possible cases of IBC in the SEER databases, including cases that may have been misclassified under previous analyses. By using the SEER databases' coding variables relevant to the clinical diagnosis of IBC, this study is the most comprehensive assessment of incident cases and of survival reported to date. Our results demonstrate that patients coded as T4D and patients with other T staging who we identified as IBC patients based on Extent of Disease Collaborative Staging criteria have no significant difference in mean survival (Fig. 4a), validating that the Extent of Disease Collaborative Staging extension codes 510–750 are useful in capturing IBC patients who may not have been previously studied.

Recent studies have further suggested that IBC incidence is declining across the USA [12]. We propose that perception of a decline in IBC incidence may be due to the increase in IBC cases registered between 2004 and 2009 under newly implemented coding criteria in 2004, compared to cases coded in 2010–2015 (Fig. 1, ST 4), after the criteria had been in use and coding-related additional prevalent cases had already been captured. The apparent downward trend in incidence is possibly then an artifact of new coding method adoption, rather than a real biological phenomenon. Regarding the trends in IBC incidence from 1973 to 2015, our analysis suggests that true IBC incidence has remained relatively constant over the past 4 decades, based on the plateauing incidence rates observed following the major IBC coding changes of 1988 and 2004. Indeed, our calculated IBC incidence rates are concordant with IBC incidence reports spanning two decades in prior publications [3, 7, 8].

Investigating the relationship between mean age at diagnosis of IBC and receptor status revealed, unexpectedly,

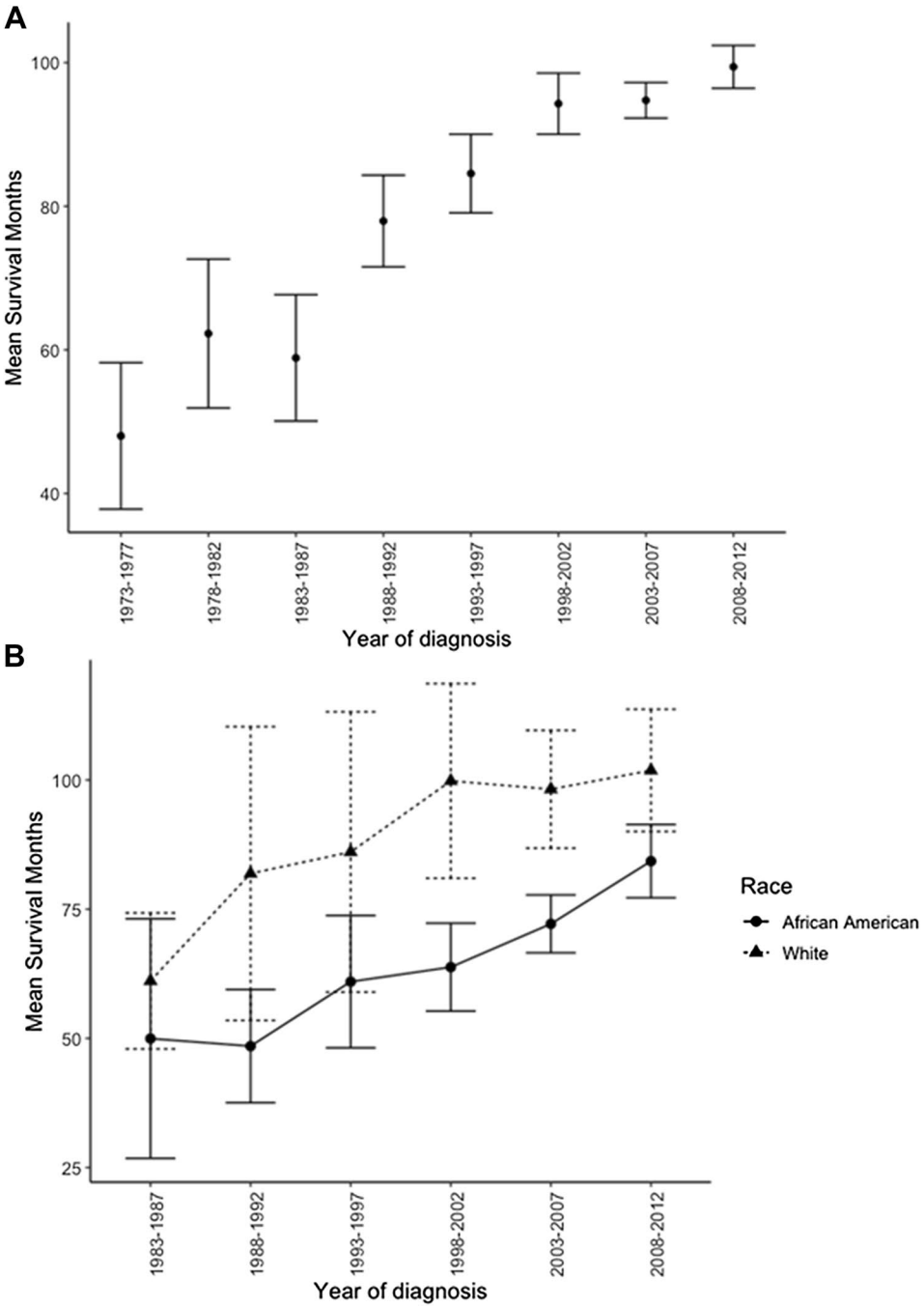

Fig. 3 **a** Adjusted mean survival time (in months) by year of diagnosis of IBC from 1973 to 2012, with bars representing 95% CI. Mean survival time increases significantly from 48 months for patients diagnosed between 1973 and 1977 to 99 months for patients diagnosed between 2008 and 2012. **b** Adjusted mean survival time (in months) by year of diagnosis stratified by race, using Cox proportional hazard model adjusting for age of diagnosis and race, with bars representing 95% CI. Solid circles: African American patients; solid triangles: white patients. While mean survival time increases for both races, white patients consistently have about 25 months more survival time in a given year of diagnosis than do African American patients

no significant difference between mean age at diagnosis of triple-negative IBC compared to IBC overall, unlike the trend seen in non-IBC cases, where triple-negative breast cancer is diagnosed at younger average age for all races. Furthermore, there was no significant difference between any receptor status and mean age at diagnosis that was robust across different races. However, these findings are limited by the relatively small sample size of our cohort with HR and HER2 status known (26.2% of our total cohort).

Our study demonstrates that black patients, regardless of receptor status, are diagnosed with IBC on average about 4 years younger than white patients. These results are concordant with the median age of diagnosis trends for breast cancer overall—we find that for IBC white patients' median age of diagnosis is 61.8 years compared to 57.8 for black IBC patients, whereas it has been shown that for all breast cancer white patients' median age of diagnosis is 63 and black patients' is 59 [20]. Moreover, while white patients have a higher incidence of breast cancer

Table 4 Mean survival months by race before and after imputation using Cox model adjusted for age and race (95% CI)

Year	Mean survival time (Months)			
	African American		White	
	Unadjusted	Adjusted	Unadjusted	Adjusted
1988–1992	46.4[a] (37.4, 55.4)	48.5 (37.5, 59.4)	71.3 (65.9, 76.7)	81.9 (53.5, 110.3)
1993–1996	49.1[a] (41.8, 56.4)	61.0 (48.2, 73.8)	68.1 (64.6, 71.6)	86.1 (59.0, 113.2)
1997–2002	47.4[a] (43.7, 51.2)	63.8[a] (55.3, 72.3)	64.8 (62.9, 66.7)	99.8 (81.0, 118.7)
2003–2007	41.0[a] (39.5, 42.5)	72.1[a] (66.6, 77.7)	49.9 (49.1, 50.6)	98.2 (86.8, 109.6)
2008–2012	25.7[a] (24.8, 26.4)	84.3 (77.2, 91.4)	28.7 (28.2, 29.1)	101.9 (90.0, 113.7)

Significance relative to white patients, determined by non-overlapping 95% CI and demonstrated by [a]

than black patients (2008–2012 incidence in white patients was 130.1 per 100,000 compared to 126.5 per 100,000 for black patients [21]), in 2006–2015 breast cancer incidence rates increased by 0.9% per year in black patients compared to 0.4% per year in white patients [22]. In IBC, on the other hand, we find that black patients consistently have higher incidence than patients of other races, and we also see a larger rate of increase in black IBC incidence compared to white IBC incidence over the past decade (see Fig. 1b).

Besides a higher incidence and younger median age at diagnosis of IBC, we also observe persistently lower survival for black patients with IBC compared to white patients. The period-based 5- and 10-year relative survival rates of black patients are about 12% lower than the rates of white patients, and although this gap narrows to about 6% lower for the 20-year relative survival rates, that is likely more reflective of the still-sobering survival rates of IBC as a disease rather than of a survival benefit to black patients. Furthermore, as depicted in ST 8, the relationship between race and year of diagnosis is insignificant, indicating that the survival gap between white patients and black patients as measured in mean survival months has not significantly narrowed over recent decades. To understand the etiology of the IBC survival gap between blacks and whites, it will be important to measure potential contributions to lower black IBC survival from differences in biology, access to prompt diagnostic studies at presentation, awareness of the signs and symptoms of IBC among black patients, timely initiation of appropriate multimodality treatments and follow-up, and survivorship care.

Importantly, this study finds that IBC survival overall has improved significantly over recent decades. As measured in mean survival months, IBC survival improved significantly between 1973–1977 and 1988–1992 and 1998–2002, approximately doubling over 30 years (1973–2003), and has continued to steadily increase since then. The difference in means between cohort-based and period-based relative rates of IBC survival also point to IBC survival having improved for all races over the years.

Our calculations of IBC mean survival months are possibly somewhat obscured by the wide confidence intervals that result from the multiple imputations we performed in order to conservatively estimate the survival of patients who had been diagnosed too recently to have more than 60 accrued months of post-diagnosis survival. Possibly a less conservative imputation method would still accurately estimate the survival of censored patients, and certainly a larger cohort of patients over a longer time period would provide a better picture of IBC survival differences between races. This would be especially helpful in comparing patients of non-white and non-black race (Asian, Pacific Islander, Native American, etc.), as the relatively low numbers of these patients compelled us to exclude them from the mean survival months analysis. However, our work here comprises the largest US cohort on which IBC survival has ever been reported.

Our results suggest that while actual IBC incidence has remained stable over time, IBC survival has moderately increased in recent years, for all races. However, despite the overall improvement in survival, there remains a persistent disparity in survival between white patients and black patients that has not narrowed over two decades. Further research is urgently needed to assess and address the root causes of this survival disparity.

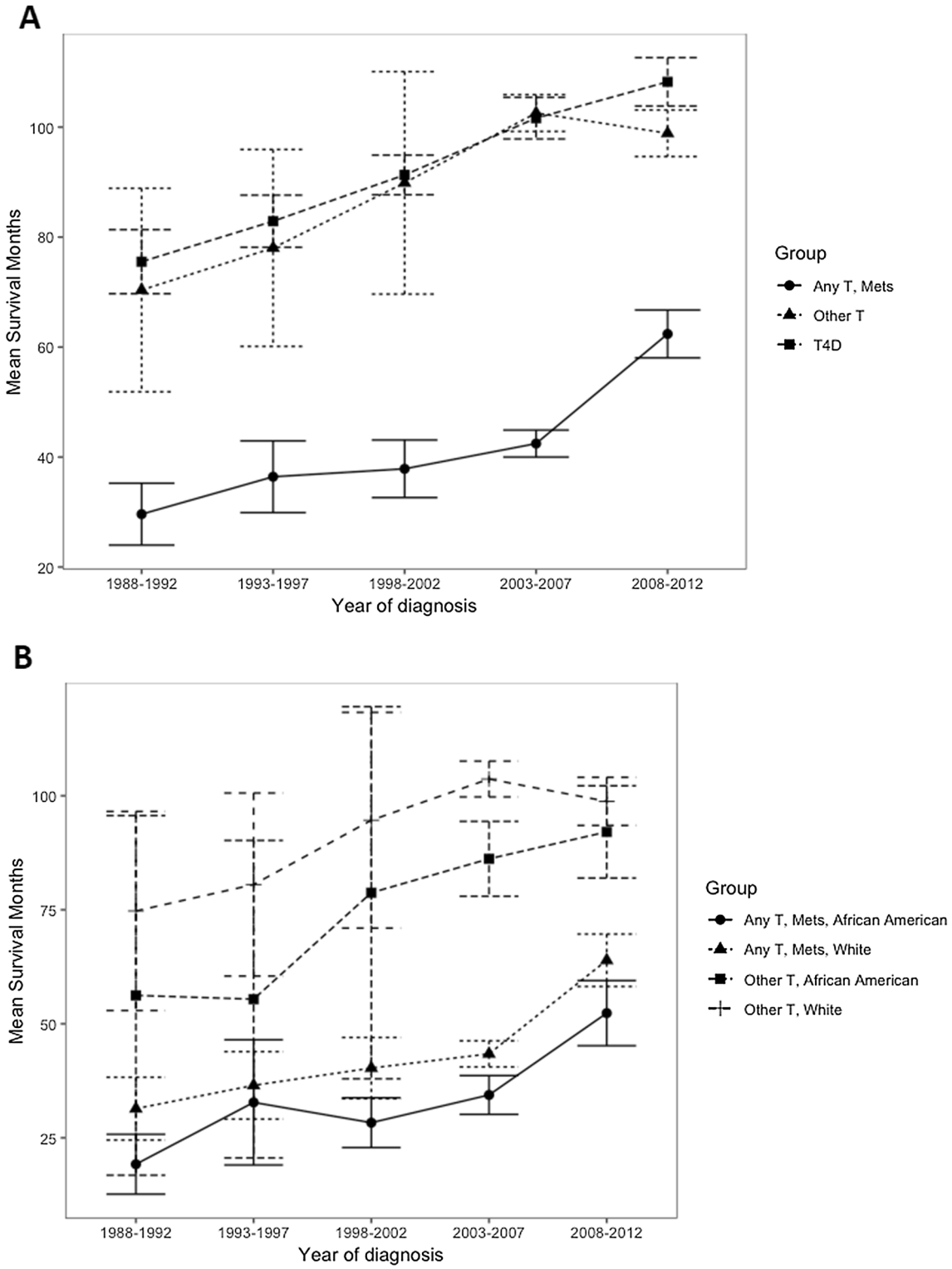

Fig. 4 **a** Adjusted mean survival time (in months) by stage T coding of IBC patients diagnosed between 1988 and 2012, with bars representing 95% CI. While survival increases for all groups over time, T4D (solid squares) and other T patients (solid triangles) without metastases have consistently similar survival, which is significantly higher than the survival time of Any T, Mets patients (solid circles). **b** Adjusted mean survival time (in months) by stage T coding stratified by race, using Cox proportional hazard model adjusting for age of diagnosis and race, with bars representing 95% CI. Solid circles: any T, Mets African American patients; solid triangles: any T, Mets white patients; solid squares: other T African American patients; dashed line: other T white patients. While mean survival time increases for both races, white patients consistently have higher survival in a given year of diagnosis than do African American patients

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Compliance with ethical standards

Conflict of interest Dr. Merajver is a founder and Chief Scientific Officer of InheRET, Inc. The work she performs for InheRET is unrelated to this manuscript. The authors have no other conflicts of interest to disclose.

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