Original Article

Metastatic Breast Cancer Survival Improvement Restricted by Regional Disparity: Surveillance, Epidemiology, and End Results and Institutional Analysis: 1990 to 2011

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BACKGROUND: The extent of breast cancer outcome disparity can be measured by comparing Surveillance, Epidemiology, and End Results (SEER) breast cancer-specific survival (BCSS) by region and with institutional cohort (IC) rates. **METHODS:** Patients who were diagnosed with a first primary, de novo, stage IV breast cancer at ages 25 to 84 years from 1990 to 2011 were studied. The change in 5-year BCSS over time from 1990 to 2011 was compared using the SEER 9 registries (SEER 9) without the Seattle-Puget Sound (S-PS) region (n = 12,121), the S-PS region alone (n = 1931), and the S-PS region IC (n = 261). The IC BCSS endpoint was breast cancer death confirmed from chart and/or death certificate and cause-specific survival for SEER registries. BCSS was estimated using the Kaplan-Meier method. Hazard ratios (HzR) were calculated using Cox proportional-hazards models. **RESULTS:** For SEER 9 without the S-PS region, 5-year BCSS improved 7% (from 19% to 26%) over time, it improved 14% for the S-PS region (21% to 35%), and it improved 27% for the S-PS IC (29% to 56%). In the IC Cox proportional-hazards model, recent diagnosis year, chemotherapy, surgery, and age <70 years were associated with better survival. For SEER 9, additional significant factors were white race and positive hormone receptor status and S-PS region was associated with better survival (HzR, 0.87; 95% CI, 0.84-0.90). In an adjusted model, hazard of BC death decreased in the most recent time period (2005-2011) by 28% in SEER 9 without S-PS, 43% in the S-PS region and 45% in the IC (HzR, 0.72 [95% CI, 0.67-0.76], 0.57 [95% CI, 0.49-0.66], and 0.55 [95% CI, 0.39-0.78], respectively). **CONCLUSIONS:** Over 2 decades, the survival of patients with metastatic breast cancer improved nationally, but with regional survival disparity and differential improvement. To achieve equitable outcomes, access and treatment approaches will need to be identified and adopted. ***Cancer* 2020;126:390-399**.

KEYWORDS: differential survival, disease-specific survival (DSS), metastatic breast cancer, regional disparity.

INTRODUCTION

Variation in breast cancer recurrence and survival may be influenced by age, race, access to care, insurance coverage, socioeconomic status, geographic area of residence (urban/rural or metropolitan/nonmetropolitan), and timely diagnosis and treatment.[1-4] From national statistics, factors contributing to state variations in cancer incidence rates include risk factor prevalence, access to and utilization of early detection services, and completeness of reporting.[5] Despite survival improvements across poverty levels for all stages of disease, relative survival remains lower among women residing in poor areas compared with affluent women.[6] Some evidence links guideline compliance to improved and optimal outcomes, but a lack of ability to compare guideline adherence in national databases inhibits the ability to evaluate widespread adherence or efficacy.[7,8]

We previously observed significant improvement in 5-year disease-specific survival of patients with de novo stage IV metastatic breast cancer (MBC) over time from 1990 to 2010 without a concurrent improvement in the survival of patients with recurrent MBC from our study of an institutional cohort of breast cancer registry patients.[9] The 5-year breast cancer-specific survival (BCSS) rates in our institutional cohort of patients with stage IV breast cancer were significantly higher than the rates previously reported for stage IV breast cancer from Surveillance, Epidemiology, and End Results (SEER) registry data.[10]

Regional disparity in breast cancer outcomes can be measured by comparing BCSS rates from SEER across geographic regions and with the rates from a SEER-embedded institutional cohort. We compared SEER aggregate data to

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TABLE 1. Change in Systemic Therapy From 1990 to 2011: Stage IV Breast Cancer, IC Patients only, n = 261

Systemic Therapy	No. of Patients (%)			*P*
	1990-1998	1999-2004	2005-2011	
Initial chemotherapy, n = 175	51 (64)	40 (66)	84 (70)	.629
Taxane therapy, n = 99	11 (21)	24 (60)	64 (76)	<.001
Anthracycline therapy, n = 114	43 (83)	28 (70)	43 (51)	.001
Trastuzumab therapy: HER-2–positive patients, n = 45	0 (0)	8 (68)	25 (100)	<.001
Neoadjuvant therapy, n = 64	18 (23)	7 (12)	39 (33)	.007
Hormone therapy: HR-positive patients, n = 193	48 (86)	41 (89)	83 (91)	.583

Abbreviation: HR, hormone receptor.

the regional subset from the Seattle-Puget Sound (S-PS) area registry and to an institutional cohort (IC) located in the S-PS registry area whose cases are included in the S-PS Cancer Surveillance System (SEER 9 without S-PS, n = 12,121; S-PS, n = 1931; and Seattle IC, n = 261). Our objectives were to compare survival rates to evaluate regional disparity in de novo MBC survival, to compare survival rate improvement over time by region and institution, and to assess the impact of temporal advances in systemic therapies on trends in de novo stage IV MBC survival rates. In particular, our focus was on regional survival differences and the potential for survival rate improvement over time as patients with metastatic disease have a poor prognosis and are often treated with palliative rather than with stabilizing or curative intent.

MATERIALS AND METHODS

The analysis included patients aged 25 to 84 years with first primary breast cancer who were diagnosed with de novo stage IV breast cancer from 1990 to 2011 in the SEER 9 registries and an institutional cohort (IC) located in the SEER 9 S-PS region (vital status through 2016). We calculated 5 -year breast cancer-specific survival (BCSS) for 3 time periods (1990-1998, 1999-2004, and 2005-2011), during which adjuvant chemotherapy treatments changed significantly and was available for the IC patients (Table 1).[11] For the IC, the BCSS endpoint was breast cancer death confirmed from chart and/or death certificate. For SEER, SEER*Stat-documented cause-specific survival was used.[12] The SEER S-PS region was used separately for comparison with SEER 9 without S-PS and the IC. Five-year BCSS and 95% CIs and Cox proportional hazard models were calculated using SPSS 25.0 (IBM Corporation) for the institutional cohort and STATA (StataCorp LLC) for SEER 9.[13,14] BCSS was estimated as the net measure representing survival from death caused by the primary diagnosed breast cancer in the absence of other causes of death. Patients who died of causes other than those specified were considered to be censored.[15]

Cox proportional hazards modelling was used to estimate adjusted hazard ratios (HzR) with corresponding 95% CIs, with death from disease as the endpoint. The IC was used to build an a priori model informed by a chi-square analysis and tested by stepwise entry into the model with a subsequent forced-entry model to include all variables of interest in the SEER 9 population. The proportional hazards assumption was evaluated graphically using the log(-log[survival]) versus log of survival time. We found no evidence suggesting violation of the proportionality assumption. All *P* values were 2-sided using a .05 level of significance.

Data from the SEER 9 population-based cancer registries (Connecticut, Detroit, Atlanta, San Francisco-Oakland, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, and Utah) were included in our analysis.[16] The SEER program is funded by the National Institutes of Health and the National Cancer Institute and represents cancer incidence data for approximately 28% of the US population.

The institutional cohort (IC) breast cancer registry database, which was created in 1990, contains detailed information on diagnosis, pathology, staging, surgery, chemotherapy, radiation therapy, tumor markers, and vital status at follow-up, including cause-specific death. Incident breast cancer cases are entered at the time of diagnosis in a Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant and Institutional Review Board (IRB)-approved research registry. This project was HIPAA compliant and IRB approved. Patient vital and disease status, including date, site and type of recurrence, and date and cause of death, is collected prospectively through annual updates by a certified cancer registrar. Follow-up is obtained from: 1) electronic chart review; 2) an IRB-approved, physician-directed follow-up letter; 3) an institutional cancer registry; and 4) the SEER S-PS registry.[17]

TABLE 2. Baseline Demographic and Clinical Characteristics of Patients With Stage IV Breast Cancer by Location and Data Source

Characteristic	No. of Patients (%)			*P*
	SEER 9 Without S-PS, n = 12,121	SEER S-PS, n = 1931	Institutional Cohort, n = 271	
Age: Mean [range], y	61 [25-84]	61 [25-84]	55 [28-84]	<.001
Race				
White	9121 (75)	1723 (89)	211 (81)	<.001
Black	2019 (17)	79 (4)	16 (6)	
Other	898 (7)	129 (7)	34 (13)	
Diagnosis year				
1990-1998	4423 (36)	658 (34)	80 (31)	<.001
1999-2004	3255 (27)	516 (27)	61 (23)	
2005-2011	4443 (37)	757 (39)	120 (46)	
Proportion of invasive BC: de novo Stage IV	12,121 (5)	1931 (4)	261 (3)	<.001
Follow-up: Median [range], y	1.67 [0.08-25]	2.08 [0.08-25]	5.24 [0.05-22]	<.001
Hormone receptor status				
Positive	6798 (75)	1275 (77)	193 (77)	.013
Negative	2321 (25)	372 (23)	57 (23)	
Unknown: No. (% of total)	3002 (25)	284 (15)	11 (4)	
Surgery				
Yes	6768 (56)	1129 (58)	130 (50)	.029
No	5236 (43)	783 (41)	131 (50)	
Unknown	117 (1)	19 (1)	0 (0)	
Radiation				
Yes	7771 (64)	1135 (60)	121 (46)	.002
No/unknown	4350 (36)	762 (40)	140 (54)	
Chemotherapy				
Yes	6199 (51)	1033 (53)	175 (67)	.055
No/unknown	5922 (49)	898 (47)	86 (33)	
Location of residence				
Nonmetro urban	1615 (14)	187 (10)	8 (3)	<.001
Nonmetro rural	161 (1)	15 (1)	3 (1)	
Metro population <1 million	2818 (14)	603 (31)	26 (10)	
Metro population ≥1 million	7284 (61)	1126 (58)	224 (86)	

Abbreviations: BC, breast cancer; Metro, metropolitan; Nonmetro, nonmetropolitan; SEER 9, Surveillance, Epidemiology, and End Results 9 registries; S-PS, Seattle-Puget Sound.

RESULTS

The SEER 9 without S-PS population and the SEER S-PS region population were both older than the IC patients (mean age, 61 vs 55 years). More IC and S-PS patients identified as white race (IC, 81%; S-PS, 89%) than SEER 9 without S-PS patients (75%) (Table 2). Of all invasive breast cancers in the populations, 5% of those in SEER 9 without S-PS, 4% of those in the S-PS region, and 3% of those in the IC were de novo stage IV. Patients in the S-PS region and in the IC were more often hormone receptor (HR)-positive (66% and 74%, respectively, vs 56% in SEER 9 without S-PS). Stage IV surgical treatment was received by ≥50% of patients in all 3 groups (SEER 9 without S-PS, 58%; S-PS, 56%; IC, 50%). Patients in the IC were treated less often with surgery (50%) and radiation (46%) and more often with chemotherapy (67%) than the SEER population (range, 51%-53%). Patients in the IC more often resided in a metropolitan area with a population >1 million (86%) compared with patients in SEER 9 without S-PS (61%) and patients in the S-PS region (58%) (Table 2).

Data on the type of chemotherapy treatments used from 1990 to 2011 were available for the stage IV IC cohort. Chemotherapy treatment increased from 64% to 70% for patients who had stage IV disease, with taxane treatment increasing (from 21% to 76%) and anthracycline treatment decreasing (from 83% to 51%) (Table 1). The receipt of hormone therapy in HR-positive patients increased from 86% to 91% over time. Trastuzumab treatment became available in 1999, and treatment increased over time to 100% of patients with HER-2–positive, de novo, stage IV breast cancer in the most recent time period. Twelve percent of chemotherapy regimens received by patients in the IC who had de novo stage IV disease were considered nonstandard.

Over time, among patients in SEER 9 without S-PS who had stage IV breast cancer, 5-year BCSS improved 7%,

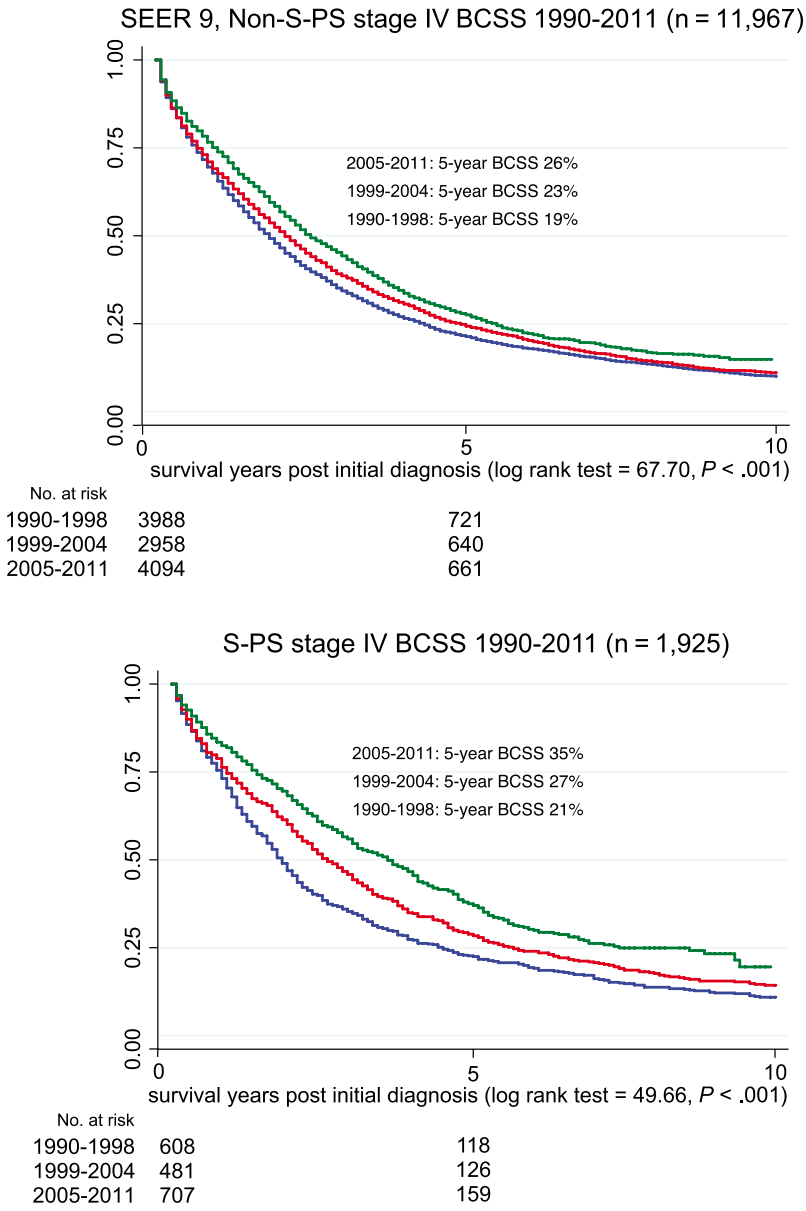

Figure 1. Stage IV breast cancer-specific survival (BCSS) is illustrated for the Surveillance, Epidemiology, and End Results (SEER) 9 registries without the Seattle-Puget Sound (S-PS) region and for the S-PS region alone from 1990 to 2011.

from 19% to 26% (1990-1998: 19%; 95% CI 18%, 21%; 1999-2004: 23%; 95% CI 21%, 24%; 2005-2011: 26%; 95% CI 24%, 27%; log-rank test 53.51, $P < .001$); and, among patients in the SEER S-PS region who had stage IV breast cancer, BCSS improved 14%, from 21% to 35% (1990-1998: 21%; 95% CI 18%, 24%; 1999-2004: 27%; 95% CI 23%, 31%; 2005-2011: 35%; 95% CI 32%, 39%; log-rank test 27.48, $P < .001$) (Fig. 1). Among patients in the IC who had stage IV breast cancer, 5-year BCSS improved 27% over the same period, from 29% to 56% (1990-1998: 29%; 95% CI 18%, 37%; 1999-2004: 47% 95% CI, 34%, 59%; 2005-2010: 56%; 95% CI 45%, 65%; log-rank test 10.97; $P = .004$) (Fig. 2, Table 3).

In the first period (1990-1998), the 5-year BCSS rate ranged from 19% to 29%, with overlapping 95% CIs for both populations and for the IC (Table 3). In the second period, 95% CIs in the 2 SEER populations overlapped, but the IC did not (5-year BCSS: 23%, 27%, and 47%, respectively). In the most recent period (2005-2011), the 5-year BCSS rate for SEER 9 without S-PS was 26%, for S-PS it was 35%, and for the IC it

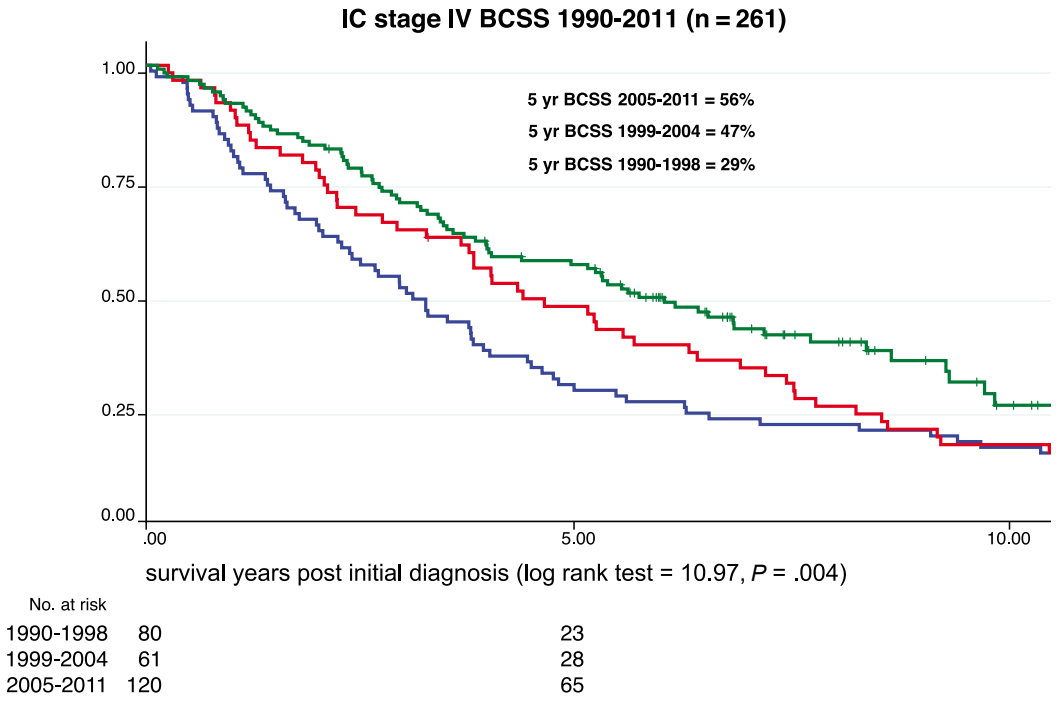

Figure 2. Stage IV breast cancer-specific survival (BCSS) is illustrated for the institutional cohort (IC) from 1990 to 2011.

TABLE 3. Changes in 5-Year Breast Cancer-Specific Survival and Overall Survival in Patients Aged 25 to 84 Years With Stage IV Breast Cancer From 1990 to 2011 by Surveillance, Epidemiology, and End Results Region and in the Institutional Cohort

	5-Year Survival Rates (95% CI)			
Population/Cohort	1990-1998	1999-2004	2005-2011	*P*
BCSS				
SEER 9 without SEER S-PS	19 (18-21)	23 (21-24)	26 (24-27)	<.001
SEER S-PS	21 (18-24)	27 (23-31)	35 (32-39)	<.001
institutional cohort	29 (18-37)	47 (34-59)	56 (45-65)	.004
OS				
SEER 9 without SEER S-PS	16 (15-18)	20 (19-21)	23 (22-24)	<.001
SEER S-PS	18 (15-21)	25 (21-28)	32 (28-35)	<.001
institutional cohort	29 (18-37)	47 (34-59)	56 (45-65)	.004

Abbreviations: BCSS, breast cancer-specific survival; OS, overall survival; SEER 9, Surveillance, Epidemiology, and End Results 9 registries; S-PS, Seattle-Puget Sound.

was 56% without 95% CI overlap, indicating a significant difference between all 3 ($P = .017$) (Table 3), The breast cancer-specific (BCSS) and overall survival (OS) rates were equivalent for patients in the IC. For the SEER cohort, the change over time was the same for OS and BCSS, and the 95% CIs overlapped, indicating no statistical difference between OS and BCSS (Table 3).

Among patients from the IC who had stage IV disease (n = 261), we ran a Cox proportional hazards forward conditional entry model with breast cancer-specific death as the outcome. Significant variables by order of entry were: 1) surgery (yes vs no: HzR 0.51; 95% CI 0.37, 0.71), 2) more recent diagnosis year (1990-1998 [reference]; 1999-2004: HzR 0.63; 95% CI 0.42, 0.94; 2005-2011: HzR 0.55; 95% CI 0.39, 0.78), 3) age (<70 vs ≥70 years: HzR 0.62; 95% CI 0.41, 0.92), and 4) initial chemotherapy (yes vs no: HzR 0.71; 95% CI 0.52, 0.98). Radiation therapy, HR status, and race (white/nonwhite) were not significant in the model. HER-2 status was run on the subset of patients after 1998 who had HER-2 test results, and the variable was not significant in the model (Table 4).

In the SEER 9 (n = 14,052), SEER 9 without S-PS region (n = 12,121), and SEER S-PS region (n = 1931) cohorts, we ran separate Cox proportional hazards models for breast cancer-specific death in each population. We used the model that was developed and tested in the IC study group but added race (white/black), HR status, and region (SEER 9 without S-PS and the SEER S-PS region) to the SEER 9 analysis (Table 5). Reduced hazard was associated with surgery, diagnosis year interval, and age <70 versus ≥70 years and was very similar, with overlapping 95% CIs, indicating no difference in HzR values

TABLE 4. Cox Proportional Hazards Model of Breast Cancer-Specific Death in an Institutional Cohort of Patients With Stage IV Breast Cancer, 1990 to 2011 (n = 261)

By Order of Entry into the Model:	HzR (95% CI)	*P*
Surgery		
No	Reference	<.001
Yes	0.51 (0.37, 0.71)	
Diagnosis year		
1990-1998	Reference	
1999-2004	0.63 (0.42, 0.94)	.001
2005-2011	0.55 (0.39, 0.78)	
Age, y		
≥70	Reference	.018
<70	0.62 (0.41, 0.92)	
Chemotherapy		
No	Reference	.036
Yes	0.71 (0.52, 0.98)	
Radiation therapy		
No	Reference	NS
Yes	0.75 (0.52, 1.07)	
Hormone receptor status		
Negative	Reference	NS
Positive	0.76 (0.51, 1.13)	
Race		
Nonwhite	Reference	NS
White	0.95 (0.64, 1.40)	

Abbreviations: HzR, hazard ratio; NS, nonsignificant.

between the SEER 9 groups. Initial chemotherapy was significant in SEER 9 and SEER 9 without S-PS, but not in the S-PS region alone. Radiation therapy was not significant in any of the SEER groups. HR status was significant in all 3 SEER groups, with the HzR ranging from 0.43 to 0.47 and overlapping 95% CIs. White race had a survival advantage in SEER 9 and SEER 9 without S-PS, but not in the S-PS region. In the adjusted model, the SEER S-PS region had a significant, independent 13% reduced hazard of mortality (HzR, 0.87; 95% CI, 0.79-0.88; reference: SEER 9 without S-PS).

In SEER 9, the survival of patients with stage IV disease improved significantly over time from 1990 to 2011, with the most improvement in the SEER S-PS region and less improvement in SEER 9 without S-PS (Table 5). In the adjusted model, compared with 1990 to 1998, SEER S-PS patients in 2005 to 2011 had a 43% reduced hazard of BC mortality (HzR, 0.57; 95% CI, 0.49-0.66), and a 28% reduction among SEER 9 without S-PS patients (HzR, 0.72; 95% CI, 0.67-0.76).

DISCUSSION

Five-year, stage IV, de novo metastatic BCSS improved significantly over time from 1990 to 2011 by 7% for SEER 9 without S-PS (from 20% to 27%), by 14% for the SEER S-PS region (from 21% to 35%) and by 20% in the IC located in the SEER S-PS region (from 29% to 56%). The relatively large, de novo, 5-year metastatic BCSS improvement observed over time, which was differential by region, is unexpected for metastatic disease, suggesting that a more aggressive approach, depending on the extent of disease, patient characteristics, and tumor characteristics, may extend survival.

The SEER S-PS region population and the IC included a higher percentage of white patients compared with SEER 9 without S-PS, and the patients more often were HR-positive, which may be interrelated because of the differential racial composition of the region's population.[18-20] Patients with stage IV disease in the SEER 9 without S-PS and S-PS region populations received more surgery and radiation but less initial chemotherapy than the IC patients. Adjusting for these factors and age, race, and HR status in a Cox proportional hazards model in the SEER 9 population, the S-PS region was independently associated with improved 5-year MBC survival.

In the IC Cox model, HR status and race were not associated with improved survival, but diagnosis time period coincident with temporal advances in systemic therapies was associated with an improvement. Improved survival over the same time periods was consistent in the SEER 9 population but to a lesser degree. The CIs for the SEER S-PS region and for SEER 9 without S-PS did not overlap, indicating a significant difference in survival improvement over time, with better survival in the SEER S-PS population. The IC had the highest chemotherapy treatment rate, the largest survival improvement over time, and the best 5-year survival in the most recent time period (56%). The finding of a differential IC survival improvement over time, confirming the results in the SEER S-PS region, indicates more aggressive chemotherapy for patients with stage IV breast cancer may be a factor in this stage IV survival divergence.

In a meta-analysis conducted by Caswell-Jin et al, among 8 studies of de novo MBC, the median survival increased significantly from 20 to 31 months between 1990 and 2010 coincident with significant advances in adjuvant treatment.[21] However, the study mixed TNM stage IV and "distant" SEER summary score, which is nonequivalent to TNM stage IV MBC.[22] In a SEER study by Dawood et al (1988-2003), a modest improvement in stage IV breast cancer survival was observed.[23] A Netherlands study found a relative median survival improvement from 1995 to 2008 related to age and extent of treatment.[24] In a Czech

TABLE 5. Cox Proportional Hazards Model of Breast Cancer-Specific Death in Patients With Stage IV Breast Cancer From the Surveillance, Epidemiology, and End Results 9 Registries, 1990 to 2011

Variable	HzR	95% CI	*P*
SEER 9 registries, n = 14,052			
Surgery			
No		Reference	
Yes	0.58	0.55, 0.61	<.001
Diagnosis year			
1990-1998		Reference	
1999-2004	0.83	0.78, 0.89	<.001
2005-2011	0.69	0.65, 0.73	<.001
Age, y			
≥70		Reference	
<70	0.76	0.72, 0.81	<.001
Chemotherapy			
No		Reference	
Yes	0.92	0.87, 0.96	.001
Radiation therapy			
No		Reference	
Yes	1.02	0.97, 1.07	.479
Hormone receptor status			
Negative		Reference	
Positive	0.47	0.44, 0.49	<.001
Race			
Nonwhite		Reference	
White	0.83	0.79, 0.88	<.001
SEER 9 without the S-PS region			
S-PS region	0.87	0.84, 0.90	<.001
SEER S-PS region, n = 1931			
Surgery			
No		Reference	
Yes	0.57	0.50, 0.66	<.001
Diagnosis year			
1990-1998		Reference	
1999-2004	0.74	0.63, 0.87	<.001
2005-2011	0.57	0.49, 0.66	<.001
Age, y			
≥70		Reference	
<70	0.72	0.62, 0.84	<.001
Chemotherapy			
No		Reference	
Yes	0.91	0.78, 1.05	.199
Radiation therapy			
No		Reference	
Yes	1.05	0.92, 1.19	.505
Hormone receptor status			
Negative		Reference	
Positive	0.43	0.37, 0.51	<.001
Race			
Nonwhite		Reference	
White	0.86	0.71, 1.05	.135
SEER 9 without the S-PS region			
Surgery			
No		Reference	
Yes	0.58	0.55, 0.61	<.001
Diagnosis year			
1990-1998		Reference	
1999-2004	0.85	0.80, 0.91	<.001
2005-2011	0.72	0.67, 0.76	<.001
Age, y			
≥70		Reference	
<70	0.77	0.73, 0.82	<.001
Chemotherapy			
No		Reference	
Yes	0.91	0.86, 0.97	.002
Radiation therapy			
No		Reference	
Yes	1.02	0.97, 1.07	.525
Hormone receptor status			
Negative		Reference	
Positive	0.47	0.44, 0.50	<.001
Race			
Nonwhite		Reference	
White	0.84	0.79, 0.89	<.001

Abbreviations: HzR, hazard ratio; SEER 9, Surveillance, Epidemiology, and End Results 9 registries; S-PS, Seattle-Puget Sound.

Republic study of survival trends from 2000 to 2008, no change was seen in stage IV survival.[25] Using SEER data, Di Meglio et al found a significant, modest improvement in de novo stage IV MBC survival over time for patients with ductal, but not lobular, stage IV disease (1990-2011).[26] Although the study by Jemal et al was not representative solely of patients with TNM stage IV MBC because of admixture with patients who had stage III disease, those authors reported substantial 5-year survival improvement in SEER 9 "distant" breast cancer, from 19% (1975-1977) to 34% (2006-2012); and the Cancer Statistics, 2019 report indicated a 27% 5-year relative survival rate for "distant" breast cancer (SEER 18 registries, 2008-2014).[27,28]

Younger patients with stage IV breast cancer have better survival than their older counterparts.[29,30] Race is a significant factor in MBC survival, with historic survival variation by black, white, Asian, and other racial categories. Recently, DeSantis et al and others have identified closing disparity in several US states between black and white survival rates.[31-33]

Over time from 1992 to 2006, patients who had HR-positive, stage IV breast cancer had significantly better and improving survival, nearly twice that of those with HR-negative breast cancer (2006: 40% vs 18%).[34] In a more recent study that added HER-2 status, HR-positive/HER-2–positive stage IV breast cancer had the best 4-year survival at 47%, followed HR-positive/HER-2–negative, HR-negative/HER-2–positive, and HR-negative/HER-2–negative, with very poor comparative survival at approximately 12%.[35] These findings indicate that, with current advances in systemic therapy, the extent to which patients with HR-positive and/or HER-2–positive stage

IV breast cancer receive molecular subtype-appropriate therapy, survival can be dramatically improved.[36] In a SEER analysis, stage IV breast cancer surgery was associated with increased survival, although stage IV breast cancer surgery declined in the United States over time (1988-2011).[37]

The IC data are from a registry database with dedicated medical record abstraction and follow-up for vital status, including cause of death. The SEER registry data endpoints are estimated using SEER*Stat cause-specific survival. The validity and accuracy of SEER registry data have been evaluated and graded for accuracy, with some data elements assessed as more accurate (age and stage) than others (such as treatment).[38] HER-2 status was not available from SEER data during study years 1990 through 2009 so was not included in the models. The degree to which HER-2–positive patients receive appropriate treatment could play a factor in the differential survival observed, but HER-2 testing and treatment have been widely available and well documented since 1999/2001. Because neither HER-2 status nor treatment was available, we cannot say whether they were a factor. Site of metastatic disease was not available for our analysis as the SEER registry did not record them until 2010.

The inability to directly compare treatment factors constituting optimal care between the SEER 9 population and the IC limited the direct identification of specific factors related to differential survival rates. We can postulate that the IC patients who were treated in the S-PS region urban area and followed in a carefully curated database may have received optimal care.

Primary, de novo, metastatic BCSS has improved over time toward prolonged disease control as treatments have advanced, especially in patients with favorable tumor characteristics, younger age (<70 years), and low-volume metastatic disease. Although only 3% to 5% of invasive breast cancers are currently diagnosed as stage IV disease, as fewer patients with early breast cancer suffer distant recurrences because of improved adjuvant treatment, those with de novo stage IV disease represent nearly one-half of the estimated 155,000 patients with MBC living in the United States today.[9,39,40] Our current results indicate that the stage IV population that is living longer may be benefiting from many of the same therapies used to treat early breast cancer, especially for patients who are able to handle adjuvant chemotherapy treatment and are HR-positive.

However, the lag in survival improvement across different population-based, geographic regions suggests that some groups and regions may benefit unequally from treatment advances as well as timely diagnosis.[41-44] Phelan et al hypothesize that such disparities persist because individuals with higher socioeconomic status and more resources also gain more immediate access to new medical treatments and technologies.[45] In a study of geographic distribution and survival among clinical trial participants, rural and urban patients with cancer who had uniform access to clinical trials had similar outcomes.[46] As precision medicine and targeted therapy oncology practice continue to progress, the potential for worsening disparities for MBC treatment and outcomes among under-resourced populations may grow if uniform access to care is not provided. It is not clear whether MBC survival improvement is achievable or aspirational in the current health care environment.

It appears from these results that we may be at a crossroads for MBC treatment and survival.[47] Access to appropriate, timely, and up-to-date diagnosis, care, treatment, and surveillance could turn this fatal disease into a chronic and treatable phenomenon, depending on patient factors, molecular subtype, and insurance capacity to pay for treatment. The potential for an improvement in MBC survival indicates progress in treatment and a possible statistical cure, in that patients may be able to live long enough with disease to die of other causes. Strategies to educate the broader population and improve access to early diagnosis and screening, new drugs and drug combinations, and clinical trials will be critical if we are to reduce the disparities seen here and allow all to benefit from the significant advances that continue to be made.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; had final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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