Trends in Survival Over the Past Two Decades Among White and Black Patients With Newly Diagnosed Stage IV Breast Cancer

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ABSTRACT

Purpose

Overall, breast cancer mortality has been declining in the United States, but survival studies of patients with stage IV disease are limited. The aim of this study was to evaluate trends in and factors affecting survival in a large population-based cohort of patients with newly diagnosed stage IV breast cancer.

Patients and Methods

We searched the Surveillance, Epidemiology, and End Results registry to identify female patients with stage IV breast cancer diagnosed between 1988 and 2003. Patients were divided into three groups according to year of diagnosis (1988 to 1993, 1994 to 1998, and 1999 to 2003). Survival outcomes were estimated by the Kaplan-Meier method, and Cox models were fit to determine the characteristics independently associated with survival.

Results

We identified 15,438 patients. Median age was 62 years. Median follow-up was 16 months, 18 months, and 11 months in periods 1988 to 1993, 1994 to 1998, and 1999 to 2003, respectively. Median breast cancer-specific survival was 23 months. In the multivariate model, earlier year of diagnosis, grade 3 disease, increasing age, being unmarried, hormone receptor-negative disease, and no surgery were all independently associated with worse overall and breast cancer-specific survival. With each successive year of diagnosis, black patients had an increasingly greater risk of death compared with white patients (hazard ratio, 1.03; 95% CI, 1.00 to 1.06; $P = .031$).

Conclusion

The survival of patients with newly diagnosed stage IV breast cancer has modestly improved over time, but these data suggest that the disparity in survival between black and white patients has increased.

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INTRODUCTION

In 2007, an estimated 180,510 new cases of breast cancer was diagnosed, with approximately 40,910 women expected to die of metastatic disease.¹ Of the new cases diagnosed annually, 10% are metastatic at the time of presentation, and an additional 30% of patients with early-stage disease will develop a recurrence.² The 5-year survival rate for patients with metastatic disease is estimated to be 20%, with a median survival duration of 18 to 24 months.³ In patients with predominantly visceral sites of disease, median survival is approximately 6 to 13 months.⁴

Overall, survival has improved for women with breast cancer; mortality rates are decreasing by approximately 2.3% annually.¹ In part, this decline in

mortality can be attributed to more widespread participation in screening programs, with a greater proportion of patients being diagnosed with in situ and early-stage breast cancer. Furthermore, the decline in mortality rates is also a result of the increasing use of adjuvant anthracycline-based polychemotherapy regimens⁵ and the monoclonal antibody trastuzumab,^{6,7} both of which have been associated with improved survival in clinical trials.

Modest improvements in survival also have been observed over the decades in patients with recurrent⁸ and newly diagnosed⁹ metastatic disease. These improvements are the result of several factors, which may include better supportive measures using agents, such as bisphosphonates,¹⁰ and a trend toward more aggressive disease management.¹¹ The use of

more effective therapeutic agents, such as taxanes, aromatase inhibitors, or trastuzumab,¹² may have also had an impact on survival in this cohort.

Previous studies reporting temporal changes in the survival of patients with stage IV breast cancer have been limited to small institutional retrospective reviews.^{8,9} In addition, these studies have not evaluated whether improvements in survival differ by patient race/ethnicity. The purpose of this study was to evaluate trends in survival over time in a large population-based cohort of patients with newly diagnosed stage IV breast cancer and determine factors that affect survival.

PATIENTS AND METHODS

Patient Selection

This retrospective study was conducted using data obtained from population registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry, the only comprehensive source of population-based data in the United States.¹³ In the SEER registry, cancers are coded according to the International Classification of Diseases for Oncology, third edition.¹⁴ We searched the SEER 17 registry database for female patients with stage IV newly diagnosed breast cancer diagnosed between 1988 and 2003. Stage IV was defined according to SEER's American Joint Cancer Committee third edition criteria. Patients who were male, did not have microscopic confirmation of invasive breast cancer, had more than one primary tumor, or had a prior malignancy were excluded.

Outcome Measures

All registries participating in the SEER registry regularly update patient follow-up information and vital status. In our analysis, the follow-up cutoff was December 31, 2003. Overall survival was calculated from the date of diagnosis to the date of death from any cause or the follow-up cutoff. Breast cancer-specific survival was calculated from the date of diagnosis to the date of death from breast cancer or the follow-up cutoff. Patients who died from causes other than breast cancer were considered censored at their date of death in the analysis of breast cancer-specific survival.

Statistical Analysis

Patients were divided into three groups according to their year of diagnosis: group 1 was 1988 to 1993, group 2 was 1994 to 1998, and group 3 was 1999 to 2003. Survival outcomes were estimated using the Kaplan-Meier product limit method and compared between groups using the log-rank statistic. Cox proportional hazards models were fit to determine the association between year of diagnosis and survival outcomes after adjustment for patient characteristics. The proportional hazards assumption was assessed visually with plots of the model residuals.

To control for the association between potential follow-up time and year of diagnosis, follow-up time was censored at 3 years in the Cox models. Models were adjusted for year of diagnosis, SEER registry, race/ethnicity, grade, surgery, age at diagnosis, marital status, and hormone receptor status (estrogen receptor and progesterone receptor status combined). Tumor size and number of lymph nodes variable were not included due to large amounts of missing data. We included interaction terms between year of diagnosis and race/ethnicity and between year of diagnosis and hormone receptor status because we wished to evaluate whether survival trends differed by race or hormone receptor status. As our patient cohort was derived from multiple SEER registries (including 9, 13, and 17), we repeated the analyses limiting the data set obtained only from the SEER 9 registry (covers approximately 10% of the US population). The results obtained did not differ substantially from our primary analysis. We thus present the results of our larger primary data set. *P* values less than .05 were considered statistically significant. All computed *P* values were two sided. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and R 2.4.0 (<http://www.R-project.org>).

RESULTS

In this study 15,438 patients fit the eligibility criteria. Table 1 summarizes patient characteristics by year of diagnosis and ethnicity. In the cohort 3,796 patients (24.6%) were diagnosed between 1988 and 1993 (group 1), 3,954 patients (25.6%) were diagnosed between 1994 and 1998 (group 2), and 7,688 patients (49.8%) were diagnosed between 1999 and 2003 (group 3). The median patient age at diagnosis in these three groups was 64 years (range, 23 to 100 years), 62 years (range, 19 to 99 years), and 62 years (range, 16 to 103 years), respectively. In total 2,219 patients (14.4%) were classified as black, 11,049 women (71.6%) were classified as non-Hispanic white, 2,075 (13.4%) were classified as other race, and the race of 75 patients (0.6%) was unknown. The SEER registry began collecting estrogen and progesterone receptor information in 1990. Among patients about whom this information was known, 69% had estrogen receptor-positive disease and 56% had progesterone receptor-positive disease. Please note that the data in Table 1 reflect the characteristics of the cohort of patients in this study, and no conclusions can be drawn about changes in cancer incidence over time between the groups.

Survival Outcomes

Median follow-up among all patients was 16 months (range, 0 to 191 months), 18 months (range, 0 to 119), and 11 months (range, 0 to 59 months) for groups 1, 2, and 3, respectively. At the time of this analysis, 11,207 patients (76%) have died from all causes and 9,465 (61%) died from breast cancer. Median overall survival was 18 months overall and 16, 18, and 20 months for groups 1, 2, and 3, respectively (Table 2). Median breast cancer-specific survival was 23 months overall and 20, 21, and 25 months for groups 1, 2, and 3, respectively. Overall and breast cancer-specific survival, unadjusted for patient characteristics, increased across the three time periods (Fig 1). When compared with non-Hispanic whites, black women had poorer survival. One-year overall survival rates for black, non-Hispanic white and other race/ethnic patients were 54.1% (95% CI, 51.9% to 56.2%), 60.2% (95% CI, 59.3% to 61.1%), and 62.4% (95% CI, 60.2% to 64.5%), respectively (*P* < .001). One-year breast cancer-specific survival rates for black, non-Hispanic white and other race/ethnic patients were 59% (95% CI, 56.8% to 61.1%), 65.7% (95% CI, 64.7% to 66.6%), 67.5% (65.3% to 69.6%), respectively (*P* < .0001).

Overall and breast cancer-specific survival rates, stratified by race/ethnicity and year of diagnosis, are presented in Table 3. Among non-Hispanic white patients, overall survival and breast cancer-specific survival significantly increased (*P* < .0001) over the three time periods. The absolute increases in overall survival and breast cancer-specific survival at 1 year from time periods 1 to 3 were 4.3% and 4.4%, respectively. However, no significant changes over time in overall and breast cancer-specific survival rates were observed among black women. Figure 2 illustrates survival curves by period of diagnosis and ethnicity.

Table 4 illustrates the results of the multivariable models for overall and breast cancer-specific survival. The final model included 6,111 patients. In the multivariable model, earlier year of diagnosis, grade 3 disease, older age, being unmarried, hormone receptor-negative disease, and no surgery were all independently associated with worse overall and breast cancer-specific survival. The

Survival Among White and Black Patients With De Novo Stage IV Breast Cancer

Table 1. Distribution of Patient Characteristics by Period of Diagnosis and Ethnicity

Characteristic	%					
	Period of Diagnosis			Ethnicity		
	1988-1993	1994-1998	1999-2003	Black	Non-Hispanic White	Other
No. of patients	3,796	3,954	7,688	2,219	11,049	2,075
Median age at diagnosis, years	64	62	62	58	64	56
Race/ethnicity						
Black	13.5	14	15	100	0	0
Non-Hispanic White	75.6	70.9	69.9	0	100	0
Other	10.4	14.6	14.3	0	0	100
Unknown	0.4	0.5	0.8	—	—	—
Married						
No	53.3	52.5	52.5	66.8	51.2	46.3
Yes	43	44.6	42.9	28.6	45.2	50.1
Unknown	3.7	2.9	4	4.6	3.7	3.6
Tumor size, mm						
≤ 20	15.5	11.4	11.4	10.4	13.3	10.1
> 20	28.6	28.3	27.5	25.7	28.4	28.6
≤ 50						
> 50	19.9	21.4	20.6	25.8	19.1	23.3
Unknown	36	38.8	40.5	38.1	39.3	38
Grade						
I	1.5	3.2	3.7	2.3	3.2	2.9
II	14.4	19.7	23.7	16.4	21.3	19.8
III/IV	37.5	44.4	43.6	46.7	40.4	48.3
Unknown	46.5	32.7	29	34.7	32.7	29
ER						
Negative	13.2	20.9	22.2	24.7	18	23
Positive	30.7	43.6	50.5	34.1	45.8	42.5
Unknown	56.2	35.5	27.8	41.2	36.2	34.5
PR						
Negative	18.6	26.9	31.4	32	25.7	29.3
Positive	23.9	35.7	37.9	25	35.9	32.9
Unknown	57.5	37.5	30.6	43	38.4	37.7
HR						
Negative	10.5	17.2	20	22.1	15.5	19.4
Positive	32.8	47	51.8	36.2	48.1	45.2
Unknown	56.7	35.9	28.1	41.7	36.4	35.4
Surgery						
Breast conserving	23.9	19.5	13.3	14.8	18.6	15.1
Mastectomy	31.7	27.8	20.3	22.5	25.1	27.6
None	44.2	52.4	44.5	50.2	45.7	46.1
Unknown	0.2	0.3	21.9	12.4	10.6	11.2
No. of positive nodes						
0	3.7	2.8	4.3	3.7	3.9	3.1
1-3	7.7	7.7	9	8.2	8.3	8.6
4-9	6.6	6.6	7.5	6.5	7	7.7
10+	7.8	6.3	7.2	6.6	6.9	9.2
Unknown	74.2	76.6	72.1	75.1	73.9	71.4

Abbreviations: PR, progesterone receptor; ER, estrogen receptor; HR, hormone receptor.

interaction term between hormone receptor status and year of diagnosis was statistically significant for both breast cancer–specific survival and overall survival (hazard ratio [HR], 0.98; 95% CI, 0.96 to 1.00), indicating that over time patients with hormone receptor–positive disease had a decreasing risk of death relative to patients with hormone receptor–negative disease. An interaction term between race/ethnicity (black v white) and year of diagnosis was statistically significant breast cancer–specific survival (HR, 1.03; 95% CI, 1.00 to

1.06; $P = .031$), indicating that over time the risk of death for black patients relative to non-Hispanic white patients increased (Fig 2). A similar nonsignificant trend for overall survival was observed for the interaction term between race/ethnicity (black v white) and year of diagnosis. The interaction term between race/ethnicity of other patients versus white patients and year of diagnosis was not statistically significant for both overall ($P = .88$) and breast cancer–specific ($P = .582$) survival. We also looked at the interaction term

Table 2. Overall and Breast Cancer–Specific Survival

Characteristic	Overall Survival			Breast Cancer–Specific Survival		
	Median (months)	1 Year (%)	95% CI	Median (months)	1 Year (%)	95% CI
All	18	59.7	58.9 to 60.5	23	65.0	64.2 to 65.8
Diagnosis period						
1988-1993	16	57.4	55.8 to 59.0	20	62.9	61.3 to 64.5
1994-1998	18	59.1	57.5 to 60.6	21	64.4	62.8 to 65.9
1999-2003	20	61.3	60.1 to 62.4	25	66.6	65.4 to 67.7
Race/ethnicity						
Black	14	54.1	51.9 to 56.2	17	59.0	56.8 to 61.1
Non-Hispanic white	19	60.2	59.3 to 61.1	23	65.7	64.7 to 66.6
Other	21	62.4	60.2 to 64.5	26	67.5	65.3 to 69.6
Married						
No	15	54.5	53.4 to 55.6	19	60.6	59.4 to 61.7
Yes	23	66.2	65.0 to 67.4	27	70.3	69.1 to 71.4
Tumor size, mm						
≤ 20	24	63.5	61.2 to 65.7	31	69.3	67.0 to 71.4
> 20-≤ 50	23	65.7	64.2 to 67.1	27	70.1	68.6 to 71.5
> 50	17	59.5	57.7 to 61.3	20	63.3	61.5 to 65.0
Grade						
I	30	67.9	63.3 to 72.1	38	74.0	69.5 to 77.9
II	27	69.9	68.2 to 71.5	32	74.6	72.9 to 76.1
III/IV	17	58.2	57.0 to 59.5	19	62.3	61.1 to 63.5
ER						
Negative	13	50.1	48.3 to 52.0	14	54.6	52.7 to 56.5
Positive	28	71.6	70.5 to 72.7	32	75.5	74.4 to 76.5
PR						
Negative	16	56.4	54.8 to 57.9	18	60.6	59.0 to 62.1
Positive	28	72.1	70.8 to 73.3	34	76.0	74.8 to 77.2
HR						
Negative	12	49.3	47.3 to 51.3	14	53.9	51.8 to 55.9
Positive	27	70.9	69.8 to 72.0	31	74.7	73.6 to 75.7
Surgery						
Breast conserving	23	64.7	62.8 to 66.4	27	69.7	67.9 to 71.5
Mastectomy	27	74.6	73.2 to 75.9	30	77.1	75.8 to 78.4
None	12	49.4	48.3 to 50.6	16	56.1	54.9 to 57.2

Abbreviations: PR, progesterone receptor; ER, estrogen receptor; HR, hormone receptor.

between race/ethnicity and hormone receptor status. The test for this interaction term was not significant for both overall survival ($P = .41$) and breast cancer–specific survival ($P = .45$).

DISCUSSION

As expected, our results show moderate improvements in both overall and breast cancer–specific survival over the three consecutive time periods explored. Furthermore, breast cancer–specific and overall survival were significantly better among patients with hormone receptor–positive disease compared with those with hormone receptor–negative disease. Over time it was observed that patients with hormone receptor–positive disease had decreasing risk of death compared with patients with hormone receptor–negative disease. Consistent with previous studies,¹⁵⁻¹⁸ our analysis demonstrates higher mortality rates among black versus non-Hispanic white women, with absolute differences of approximately 6% observed for both 1-year overall and breast cancer–specific survival. In the unadjusted analyses, we have also shown that the survival of non-Hispanic white women has significantly increased over time, while that of black women has

remained unchanged. Of concern, in the multivariable analyses, the disparity in survival between black women and non-Hispanic white women is worsening over time. Across the three time periods studied, the 1-year breast cancer–specific survival rates were 2.8%, 6.8%, and 8.8% higher, respectively, in non-Hispanic white women than in black women.

Several factors have been implicated in the differential survival observed between non-Hispanic white and black women with breast cancer. Biologic factors known to be associated with poor prognosis, such as aggressive histopathology, larger tumor size at presentation, greater nodal involvement, and negative estrogen receptor status, have been noted to occur with higher frequency in black women.¹⁹⁻²¹ Also, black women tend to have lower baseline WBC counts, which could result in a lower dose of chemotherapy being prescribed²² and, consequently, shorter survival. Although these biologic factors would not be expected to change over time the introduction of new more effective therapeutic agents may be causing a relative change in frequency distribution of these factors. Using SEER registry data, Ravdin et al²³ recently showed that the age adjusted incidence rates for breast cancer were decreasing

Fig 1. Trends in (A) overall survival and (B) breast cancer-specific survival over time.

especially for estrogen receptor–positive breast cancer. Using clinical information and tissue samples from the Carolina Breast Cancer Study, Carey et al²⁴ showed a higher prevalence of basal-like tumors among premenopausal black women. Thus, the increasing disparity in survival over time among black and white women maybe a direct consequence of the relative increase in estrogen receptor–negative disease among black women as well as the fact that the prognosis of black women with triple negative disease has

been unaffected by the introduction of agents, such as aromatase inhibitors and trastuzumab, which are improving prognosis among women with estrogen receptor–positive disease and HER-2–positive disease respectively.

Poor access to health care,²⁵ less utilization of screening programs, comorbid conditions,²⁶ and treatment differences^{27,28} have also been cited as causal factors for shorter survival in black women. If these factors have changed over time, they could potentially explain

Table 3. Overall and Breast Cancer-Specific Survival, Stratified by Race and Year of Diagnosis

Survival by Diagnosis Period	Median	1 Year		5 Year		P
		Estimate (%)	95% CI	Estimate (%)	95% CI	
Overall						
Non-Hispanic white						
1988-1993	16	57.7	55.9 to 59.5	15.0	13.7 to 16.4	< .0001
1994-1998	19	59.9	58.0 to 61.6	18.6	17.2 to 20.1	
1999-2003	21	62.0	60.6 to 63.3	—	—	
Black						
1988-1993	15	55.1	50.7 to 59.3	12.7	10.0 to 15.7	.08
1994-1998	13	52.0	47.7 to 56.1	7.4	5.4 to 9.8	
1999-2003	15	54.8	51.7 to 57.8	—	—	
Other						
1988-1993	18	58.0	52.9 to 62.7	16.2	12.7 to 20.0	.06
1994-1998	20	62.3	58.2 to 66.2	17.8	14.8 to 21.1	
1999-2003	22	64.1	61.0 to 67.1	—	—	
Breast cancer specific						
Non-Hispanic white						
1988-1993	20	63.2	61.4 to 65.0	20.1	18.6 to 21.8	< .0001
1994-1998	22	64.9	63.1 to 66.7	23.4	21.7 to 25.1	
1999-2003	27	67.6	66.3 to 68.9	—	—	
Black						
1988-1993	17	60.4	55.9 to 64.6	16.8	13.4 to 20.5	.18
1994-1998	16	58.1	53.7 to 62.2	10.8	8.1 to 14.0	
1999-2003	17	58.8	55.6 to 61.8	—	—	
Other						
1988-1993	22	63.2	58.1 to 67.8	20.8	16.6 to 25.3	.10
1994-1998	26	67.9	63.8 to 71.6	23.7	19.9 to 27.7	
1999-2003	28	69.0	65.9 to 71.8	—	—	

NOTE. P values are two sided.

Fig 2. Differences in breast cancer-specific survival between non-Hispanic white women and black women over time.

the widening disparity in survival between black and non-Hispanic white women. Obesity, known to be associated with more advanced disease at diagnosis²⁹ and an increased risk of cancer-related death among postmenopausal breast cancer patients,^{30,31} has been shown to be more prevalent among black women with breast cancer.³² The increasing prevalence of obesity and its related comorbid conditions, namely diabetes mellitus, hypertension, coronary heart disease, and cerebrovascular disease, may be contributing to the reduced survival of black women with breast cancer and to the widening survival disparity.³³

In a cohort of 834 women with recurrent breast cancer treated at The University of Texas M. D. Anderson Cancer Center between 1974 and 2000, Giordano et al⁸ recently reported a 1% reduction in risk of death for each successive year. Andre et al⁹ evaluated the survival of 724 patients with newly diagnosed metastatic breast cancer treated in three French cancer centers. Median survival significantly increased from 23 months in patients diagnosed from 1987 to 1993 to 29 months in patients diagnosed from 1994 to 2000, with associated significant increases of 27% to 44% in 3-year and 11% to 28% in 5-year survival rates, respectively. Our study concurs with these data, revealing modest improvements in both

overall and breast cancer-specific survival over the three time periods studied. One hypothesis to explain the improvements observed is use of new and more effective therapeutic agents and supportive measures.

Studying temporal changes in survival using large databases can be complicated by a number of factors that may bias the results, including changes in disease classification, stage migration, improvements in diagnostic tests over time, variations in the completeness of reporting, degree of representation of the population group, and fluctuations in the accessibility and popularity of screening programs. We chose to study patients with newly diagnosed stage IV breast cancer whose data were recorded within the SEER program because it comprises registries that cover approximately 26% of the US population, making it an ideal database in which to examine trends in survival across diverse population groups and explore the dissemination of advances in treatment. In addition, the SEER program provides high-quality, near-complete data sets, with at least 98% of all malignant and in situ cancers reported within 22 months of diagnosis.¹⁴

One technique available at present to evaluate trends in survival between different malignancies and population groups is the evaluation of cancer-specific mortality data. The source of such information

Table 4. Multivariable Models (N = 6,111): Follow-Up Censored at 3 Years (adjusted for Surveillance, Epidemiology, and End Results registry)

Characteristic	Survival					
	Overall			Breast Cancer Specific		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Year of diagnosis, continuous	0.98	0.96 to 1.00	.011	0.98	0.96 to 1.00	.027
Black v non-Hispanic white	0.96	0.73 to 1.25	.742	0.92	0.69 to 1.23	.588
Other v non-Hispanic white	1.10	0.82 to 1.46	.527	1.15	0.84 to 1.55	.385
Grade 2 v 1	1.14	0.95 to 1.36	.168	1.10	0.91 to 1.34	.329
Grade 3 v 1	1.45	1.22 to 1.73	< .0001	1.48	1.22 to 1.79	< .0001
BCS v mastectomy	1.18	1.08 to 1.29	.0002	1.11	1.02 to 1.22	.023
No surgery v mastectomy	1.84	1.71 to 1.99	< .0001	1.79	1.65 to 1.94	< .0001
Age at diagnosis, continuous	1.02	1.02 to 1.02	< .0001	1.02	1.01 to 1.02	< .0001
Married (yes v no)	0.80	0.74 to 0.85	< .0001	0.82	0.76 to 0.88	< .0001
HR (positive v negative)	0.62	0.51 to 0.75	< .0001	0.62	0.5 to 0.76	< .0001
Interaction HR, year of diagnosis	0.98	0.96 to 1.00	.028	0.98	0.96 to 1.00	.030
Interaction black, year of diagnosis	1.03	1.00 to 1.05	.056	1.03	1.00 to 1.06	.031
Interaction other, year of diagnosis	1.00	0.97 to 1.03	.880	0.99	0.96 to 1.02	.582

NOTE. P values are two sided.

Abbreviations: BCS, breast-conserving surgery; HR, hormone receptor.

in SEER is death certificates, the accuracy of which has been somewhat controversial. Percy et al³⁴ explored the accuracy of death records in patients with single primary tumors and found that among patients with breast cancer, the cancer-related cause of death was documented accurately in 95% of cases. Another study demonstrated that undercounting of breast cancer deaths occurred in fewer than 4% of cases.³⁵ In the United States, standardized death certification procedures (issued by the National Center for Health Statistics) are used, with cause of death recorded by trained nosologists, and death certificates are routinely evaluated for quality of data by the National Center for Health Statistics. Thus, in the absence of a more reliable method of evaluating mortality trends and in the presence of studies that suggest that documentation of cause of death among patients with breast cancer is accurate, we chose to evaluate survival using cancer-specific mortality data as well as overall mortality data. We assumed that any potential discrepancies in the recording of cause of death were homogeneous over different time periods, regions, and population groups in the United States. In addition, we saw the same trends in overall survival that were seen in cancer-specific survival.

When studying differences in survival among black women using data derived from the SEER registry, certain flaws need to be acknowledged. The SEER registry was originally designed to monitor cancer within geographically defined population groups rather than racially defined cohorts. The geographical regions initially covered by the SEER program included large urban areas and, therefore, represented a group of black women with potentially higher educational and socioeconomic status.³⁶ One of the goals of the SEER program expansion initiative is to include more rural and southern black women. Nonetheless, inclusion of a larger cohort of rural black women in the most recent time period of our study likely would have increased the difference in survival observed between black and non-Hispanic white women.

In conclusion, our data support the results of other studies showing that over the past two decades, overall and breast cancer-specific

survival of patients with stage IV breast cancer has improved. Although site of metastases may have had an impact on survival, we could not assess for this because SEER registry does not record this vital piece of information. In addition, our results indicate an increasing disparity in overall and breast cancer-specific survival over time between non-Hispanic white and black women with stage IV breast cancer. We acknowledge that our study has the inherent limitations that normally accompany any retrospective study that involves a large population database; however, the observed differences in survival outcomes between the two racial groups provide the grounds for further research. Health policymakers need to be aware of this increasing gap in survival and study the possible causes of such evolving discrepancies and implement appropriate steps to halt and reverse this phenomenon.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

- Jemal A, Siegel R, Ward E, et al: Cancer statistics 2007. *CA Cancer J Clin* 57:43-66, 2007
- Harris JR, Morrow M, Bonnadonna G: Cancer of the breast, in De Vitta VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology* (ed 4). Philadelphia, PA, JB Lippincott, 1993, pp 1264-1332
- Cardoso F, Di LA, Lohrisch C, et al: Second and subsequent lines of chemotherapy for metastatic breast cancer: What did we learn in the last two decades? *Ann Oncol* 13:197-207, 2002
- O'Shaughnessy J: Clinical experience of capecitabine in metastatic breast cancer. *Eur J Cancer* 38:10-14, 2002
- Early Breast Cancer Trialists' Collaborative Group: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomized trials. *Lancet* 365:1687-1717, 2005
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1659-1684, 2005
- Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1673-1684, 2005
- Giordano SH, Buzdar AU, Smith TL, et al: Is breast cancer survival improving? *Cancer* 100:44-52, 2004
- Andre F, Slimane K, Bachelot T, et al: Breast cancer with synchronous metastases: Trend in survival during a 14-year period. *J Clin Oncol* 22:3302-3308, 2004
- Mundy GR: Metastasis to bone: Causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2:584-593, 2002
- Babiera GV, Roshni R, Feng L, et al: Effect of primary tumor extirpation in breast cancer patients with stage IV disease and an intact primary tumor. *Ann Surg Oncol* 13:776-782, 2006
- Slamon DJ, Leyland-Jones B, Shak S, et al: Human breast cancer: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001
- Hankey BF, Ries LA, Edwards BK: The Surveillance, Epidemiology, and End Results program: A national resource. *Cancer Epidemiol Biomarkers Prev* 8:1117-1121, 1999
- Fritz A, Percy C, Jack A, et al: *International Classification of Diseases for Oncology* (ed 3). Geneva, Switzerland, World Health Organization, 2000
- Hayat MJ, Howler N, Reichman ME, et al: Cancer statistics, trends, multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) program. *Oncologist* 12:20-37, 2007
- Newman LA, Griffith KA, Jatoi I, et al: Meta-analysis of survival in African American and White American patients with breast cancer: Ethnicity compared with socioeconomic status. *J Clin Oncol* 24:1342-1349, 2005
- Chlebowski RT, Chen Z, Anderson GL, et al: Ethnicity and breast cancer: Factors influencing differences in incidence and outcome. *J Natl Cancer Inst* 97:439-448, 2005
- Sarker M, Jatoi I, Becher H: Racial differences in breast cancer survival in women under age 60. *Breast Cancer Res Treat* 106:135-141, 2007
- Henson DE, Chu KC, Levine PH: Histologic grade, stage, and survival in breast carcinoma: Comparison of African American and Caucasian women. *Cancer* 98:908-917, 2003
- Chen VW, Correa P, Kurman RJ, et al: Histological characteristics of breast carcinoma in blacks and whites. *Cancer Epidemiol Biomarkers Prev* 3:127-135, 1994
- Elledge RM, Clark GM, Chamness GC, et al: Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. *J Natl Cancer Inst* 86:705-712, 1994

22. Hershman D, Wienberg M, Rosner Z, et al: Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. *J Natl Cancer Inst* 95:1545-1548, 2003
23. Ravdin PM, Cronin KA, Howlader N, et al: The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 356:1670-1674, 2007
24. Carey LA, Perou CM, Livasy CA, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer study. *JAMA* 295:2492-2502, 2006
25. Coates RJ, Bransfield DD, Wesley M, et al: Differences between black and white women with breast cancer in time from symptom recognition to medical consultation: Black/White Cancer Survival Study group. *J Natl Cancer Inst* 84:938-950, 1992
26. Tammemagi CM, Nerenz D, Neslund-Dudas C, et al: Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA* 294:1765-1772, 2005
27. Mandelblatt JS, Kerner JF, Hadley J, et al: Variations in breast carcinoma treatment in older Medicare beneficiaries: Is it black or white? *Cancer* 95:1401-1414, 2002
28. Griggs JJ, Sorbero ME, Stark AT, et al: Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. *Breast Cancer Res Treat* 81:21-31, 2003
29. Jones BA, Kasi SV, Curnen MG, et al: Severe obesity as an explanatory factor for the black/white difference in stage at diagnosis of breast cancer. *Am J Epidemiol* 146:394-404, 1997
30. Huang Z, Hankinson Se, Colditz GA, et al: Dual effects of weight and weight gain on breast cancer risk. *JAMA* 278:1407-1411, 1997
31. Petrelli JM, Calle EE, Rodriguez C, et al: Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. *Cancer Causes Control* 13:325-332, 2002
32. Flegal KM, Carroll MD, Ogden CL, et al: Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 288:1723-1727, 2002
33. Polednak AP: Racial differences in mortality from obesity-related chronic diseases in US women diagnosed with breast cancer. *Ethn Dis* 14:463-468, 2004
34. Percy C, Stanek E, Gloeckler L: Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 71:242-250, 1981
35. Brinkley D, Haybittle JL, Alderson MR: Death certification in cancer of breast. *BMJ (Clin Res Ed)* 289:465-467, 1984
36. Nattinger AB, McAuliffe TL, Schaphira MM: Generalizability of the Surveillance, Epidemiology, and End Results registry population: Factors relevant to epidemiologic and health care research. *J Clin Epidemiology* 50:939-945, 1997