HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Cancer. 2015 May 1; 121(9): 1469–1476. doi:10.1002/cncr.29178.

United States Breast Cancer Mortality Trends in Young Women According to Race

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Abstract

Purpose—There is a negative prognostic impact of young age at diagnosis on outcome in breast cancer (BC). We sought to determine if there is a differential effect of race and examined mortality trends according to race and age.

Methods—SEER was used to identify women <50 with invasive BC diagnosed between 1990 and 2009. Multivariate regression analyses were performed to determine the risk-adjusted likelihood of survival for whites and blacks. Annual hazards of BC death according to race and calendar period, and adjusted relative hazards of death for whites and blacks stratified by age were computed.

Results—162,976 women were identified; 126,573 whites, 20,405 blacks, and 15,998 other races. At a median follow-up of 85 months, five-year disease specific survival rates were 90.1% for whites, 79.3% for blacks. Annual hazards for death in whites decreased by 26% at 5 years after diagnosis, in contrast to the hazards in blacks decreasing by only 19%. With 1990 as referent, the adjusted relative hazards for death in women <40 in year 2005 were 0.55 (95% CI 0.46-0.66) and 0.68 (95% CI 0.49-0.93) for whites and blacks, respectively. In women 40-49, adjusted hazards for death were 0.53 (95% CI 0.47-0.60) and 0.78 (95% CI 0.61-0.99) for whites and blacks.

Conclusion—Among young women diagnosed with BC, blacks have a worse outcome than whites. Mortality declines have been observed over time in both groups, although more rapid gains have occurred in whites. Emphasis should be placed on improving outcomes for young BC patients.

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Conflicts of Interest: None

Keywords

breast cancer; young age; survival; trends

Introduction

Among adolescent and young women, breast cancer (BC) ranks as the most frequently diagnosed invasive cancer, and represents one quarter of BC seen in all women diagnosed in the United States.[1, 2] The biology of BC in young women remains poorly understood and appears to be different from BC seen in older women. It is associated with more aggressive histopathologic characteristics, such as, higher grade tumors, more advanced stage, and lower hormone receptor positivity.[1, 3] Additionally BC in young women has a worse clinical course than in older women.[4-7] The incidence of BC in young women also varies by race with young black women having a much higher incidence compared to white women in the same age group.[8-11]

BC mortality trends suggest that rates have decreased by approximately 2% per year over the last two decades.[12] For women under the age of 50 years, death rates have decreased by 3% per year as opposed to a yearly decrease of 1.9% in women ≥ 50 years, presumably as a result of more aggressive systemic treatment in younger women and less comorbidity. Since a larger proportion of black women present with earlier onset and more aggressive BC than whites, it is unclear whether the mortality gains seen in young women overall are due to improvements in whites alone. It is also unknown whether the disadvantages in clinical outcome in young BC patients and the negative effect black race exerts on survival are cumulative for young black patients. Consequently, we sought to examine the impact of race on BC outcomes as well as time trends in survival according to race, in a United States population-based cohort of young women diagnosed with BC.

Patients and methods

Study population

Data for this study were obtained from the Surveillance, Epidemiology and End Results (SEER) database which represents the largest population-based cancer registry in the United States. It covers 28% of the population and captures 97% of incident cancer cases in regions participating in SEER.[12] The SEER registries collect information on demographics, primary tumor site and characteristics, first course of treatment, and survival from medical records, but do not have central pathologic review. The program started in 1973 and thus provides the greatest longevity for cancer statistics. The analyses included records for females aged 18-49 years who had been diagnosed with invasive BC between 1990 and 2009. Individuals who were diagnosed at death or autopsy only, had other first primary cancers, or did not have a record of race were excluded from this analysis (Figure 1). After exclusions were applied, data on 162,976 women were available for analysis.

Statistical analysis

The distribution of patient and clinical characteristics between race groups was compared using the Chi-square test or two-sample t-test, as appropriate. Overall survival (OS) was defined as the time from the date of diagnosis to death due to any cause. Survivors were censored at the date of last contact. Disease-specific survival (DSS) was defined as the time from diagnosis to death due to BC. Survival curves by race groups were estimated using the Kaplan-Meier product-limit method and compared by log-rank test. Univariate Cox proportional hazard models were fit to identify other demographic and clinical characteristics significantly related to OS. Multivariate Cox models were constructed to assess whether race was an independent predictor of survival, while adjusting other patient/clinical characteristics that were significant in the univariate analyses. Two-way interaction terms between race and other factors in the multivariate Cox model were assessed. To better understand the change of mortality risk over time, smoothed hazard functions were also estimated in each race group at different periods of diagnosis using non-parametric kernel-based methods.[13] All analyses were two-sided and significance was set at a *P*-value of 0.05. The estimation of smoothed hazard was implemented using “muhaz” library in the statistical package R, while all the other analyses were performed using SAS 9.2 (SAS Institutes, Cary, NC).

Results

Patient characteristics

Among the study patients, 126,573 (77.7%) were white, 20,405 (12.5%) were black, and 15,998 (9.8%) were categorized as other races. Characteristics for the entire cohort are summarized in Table 1. Differences between patient characteristics by race were observed with respect to age at diagnosis, American Joint Committee on Cancer (AJCC) stage, grade, estrogen receptor (ER), and nodal status. A progressively higher number of patients overall were diagnosed from 1990-1994 to 2005-2009 (12.9%, 16.3%, 34.9% and 35.7%, respectively). This was evident in all racial categories. Patients who were categorized as other races, had clinicopathologic features similar to white patients. For example, approximately 76%, 16%, and 3% of both whites and others had AJCC stage I/II, III, and IV disease respectively.

Impact of race on outcomes

At a median follow up of 85 months, a total of 32,506 (20%) women had died. The 5 year OS rates were 87.9% for whites, 74.9% for women blacks, and 88.5% for others. The 10 year OS rates were 79.5% for whites, 64.3% for blacks, and 80.7% for others. Median OS was not reached in any race category. Unadjusted Kaplan-Meier estimates indicated differences in OS by race (Figure 2). Cox regression analysis for OS demonstrated the association of black race, ER and progesterone receptor (PR) negativity, inflammatory BC, higher grade disease, more advanced stage, and nodal involvement as independent prognostic factors for survival (Table 2). Similar results were seen with DSS.

Time trends in mortality

Smoothed annual hazards for mortality according to race and period of diagnosis are shown in Figure 3. Both whites and blacks showed improvements over calendar period of diagnosis. During all periods of diagnosis, there was a sharp rise in the annual hazard of death for the first 2-3 years after diagnosis for whites and blacks; however, for each time period from initial diagnosis, blacks had a correspondingly higher hazard of death than whites. For instance, at 5 years after initial diagnosis, the annual risk in whites decreased from 2.7% per year for patients diagnosed in 1990-1994 to 1.9% per year for 2005-2009, representing a decline of 26%. Conversely, in blacks there was a more modest decline of only 19% (4.7% per year for 1990-1994 versus 3.8% per year in 2005-2009). Specific annual risk for years 1, 3, and 5 post diagnoses are shown in Table 3.

Figure 4 shows the hazard ratio (HR) of death over time, stratified by race and age at diagnosis (<40 and ≥40 years), and adjusting for stage, grade, histology, node status, tumor size, ER and PR (Table 2). Adjusted HR declined over time for both races, although there was much more variability in blacks than whites. Compared with 1990, the HR for mortality in whites < 40 years diagnosed in 2009 was 0.53 (0.41-0.69), and 0.80 (0.54-1.19) in blacks, representing a 47% and 20% decrease from 1990 respectively (Table 4). Similar findings were seen in the ≥ 40 age group as well. Although mortality improvements were observed in blacks over time, those improvements were largely not statistically significant unlike those seen in whites.

Discussion

In this study, we aimed to determine the relationship between race and survival in a population-based cohort of patients with early-onset BC. To achieve this aim, we analyzed 162,976 patients under age 50 years from the SEER database. Several findings emerged. First, it is evident that young black women with BC continue to have a worse outcome than young white women. Although this dilemma has been observed in patients with BC in general, only one other study has looked at this relationship specifically in young women.[14] That study by Newman et al. also found race-related differences in survival favoring whites in a cohort of 500 blacks and 1400 whites with BC under age 40. The survival disadvantage conferred by race in young women is likely multifactorial. Black women are more likely to be diagnosed with basal-like BC, which has a poorer outcome, partly due to lack of therapeutic targeted drugs. However, even when biology is held constant, outcome differences are still seen as observed in this present study. Numerous studies have also shown racial discrepancies in treatment adherence,[15-17] receipt of appropriate local therapies, and barriers in accessing care due to socioeconomic factors,[18-20] which impact survival outcomes in BC. In clinical trials, it appears that black women derive similar benefits from adjuvant chemotherapy,[21] although efficacy does not always translate to effectiveness in the general non-trial population.[22] Another possible mechanism for poorer outcomes is the differences in immune-related genes between blacks and whites with BC. Although this has been shown to influence breast carcinogenesis,[23, 24] it also appears that there may be a link between BC progression and racial differences in immune-related genes.[25] This concept becomes more important to consider in view of the fact that trends in

racial differences in mortality have been consistent over time, perhaps suggesting a genetic rather than environmental etiology.[26] In addition, similarities in biology and clinical outcome in indigenous blacks in Africa and blacks from the United States or other developed countries suggest a common molecular factor contributing to poorer outcomes.[27, 28]

Consistent with other studies,[22] we also observed that mortality trends have improved over time for all patients, although racial gaps previously seen in survival have not closed. In addition for all young women the highest risk of recurrence and mortality appears to be in the first 2-3 years followed by a progressive gradual decline. This is similar to patterns of recurrences seen with ER negative cancers. ER status undoubtedly influences recurrences and survival in young patients over time,[29] however, the degree to which the traditional prognostic factors such as ER influence outcome in young BC patients is unclear, considering that over 60% of patients in our study had ER positive disease (whites 64%, blacks 48%, others 67%). Earlier relapses and mortality in young women suggest that there may be other unknown biologic differences that may account for the more aggressive behavior.

Thirdly, consistent with observations we and other have made, the incidence of invasive BC in younger women of all races appear to be increasing.[30-32] This might be explained by stage migration, the change in reproductive risks profile over time such as women having first pregnancies at later ages and breast feeding for shorter durations, or increased awareness and consequently higher uptake of screening in those 40 years and older.

Our data must be interpreted in the light of its limitations. It is possible that the inability to include data on HER2 status may confound the interpretation of these results. However, there is no scientific evidence to suggest that trends in HER2 positivity have changed over time in young women. Similarly, this analytic cohort has missing data on ER in 11-15% of patients. Consistent with other studies, black patients appeared to have a slightly higher proportion of missing ER than whites.[33] It is unclear what directional changes to the results these biases may have introduced. Although others have used statistical approaches to impute missing data, we have not done so in this particular analysis due to our hesitation in employing such techniques to reassign unknown ER status, a crucial classifier of BC. Information on systemic treatment is also not collected in SEER; however, most young women are generally treated more aggressively with chemotherapy. The cutoff age of 49 selected for the purposes of these analyses is somewhat arbitrary as there is no unanimously established definition of ‘early-onset’ BC. Finally, it is now quite clear that the molecular classification of BC[34] is probably more pertinent in clinical outcome than ER, PR, and HER2, however, this information is not yet used in routine clinical practice.

In conclusion, young black women have higher mortality rates than other young women with BC irrespective of stage or hormone receptors. Further studies investigating the unique tumor biology that leads to black women having the greatest risk of death are warranted.

Acknowledgments

This publication was made possible by Grant Number 1K12CA167540 through the National Cancer Institute (NCI) at the National Institutes for Health (NIH) and Grant Number UL1 TR000448 through the Clinical and Translational Science Award (CTSA) program of the National Cancer for Advancing Translational Sciences (NCATS) at the NIH. The authors also wish to acknowledge the support of the Siteman Cancer Center Biostatistics Core and the NCI Cancer Center Support Grant P30 CA091842. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the NCI, NCATS, or NIH.

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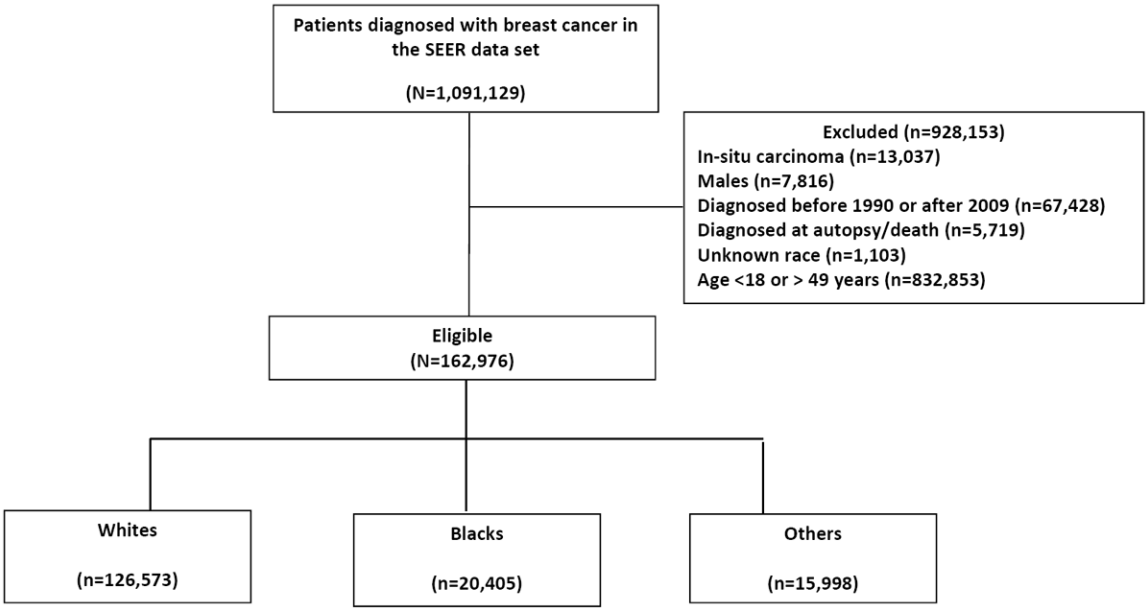

Figure 1.

Patients with breast cancer included in the analytical cohort.

Consort diagram showing number of patients with breast cancer diagnosed between 1990 and 2009 that were included or excluded from the analytical cohort

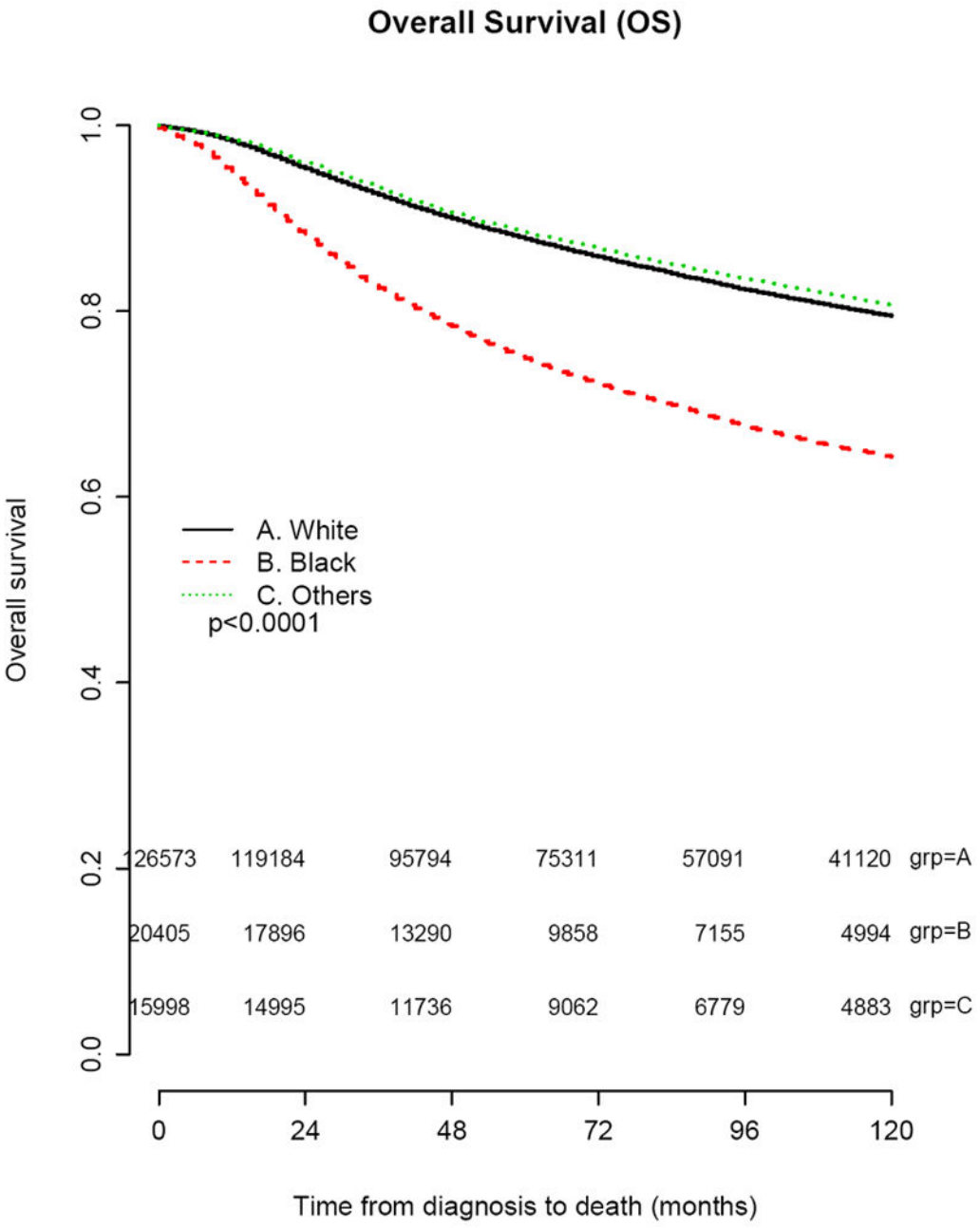

Figure 2.

Kaplan-Meier survival curves showing estimates of overall survival by race for all patients included in the analytical cohort

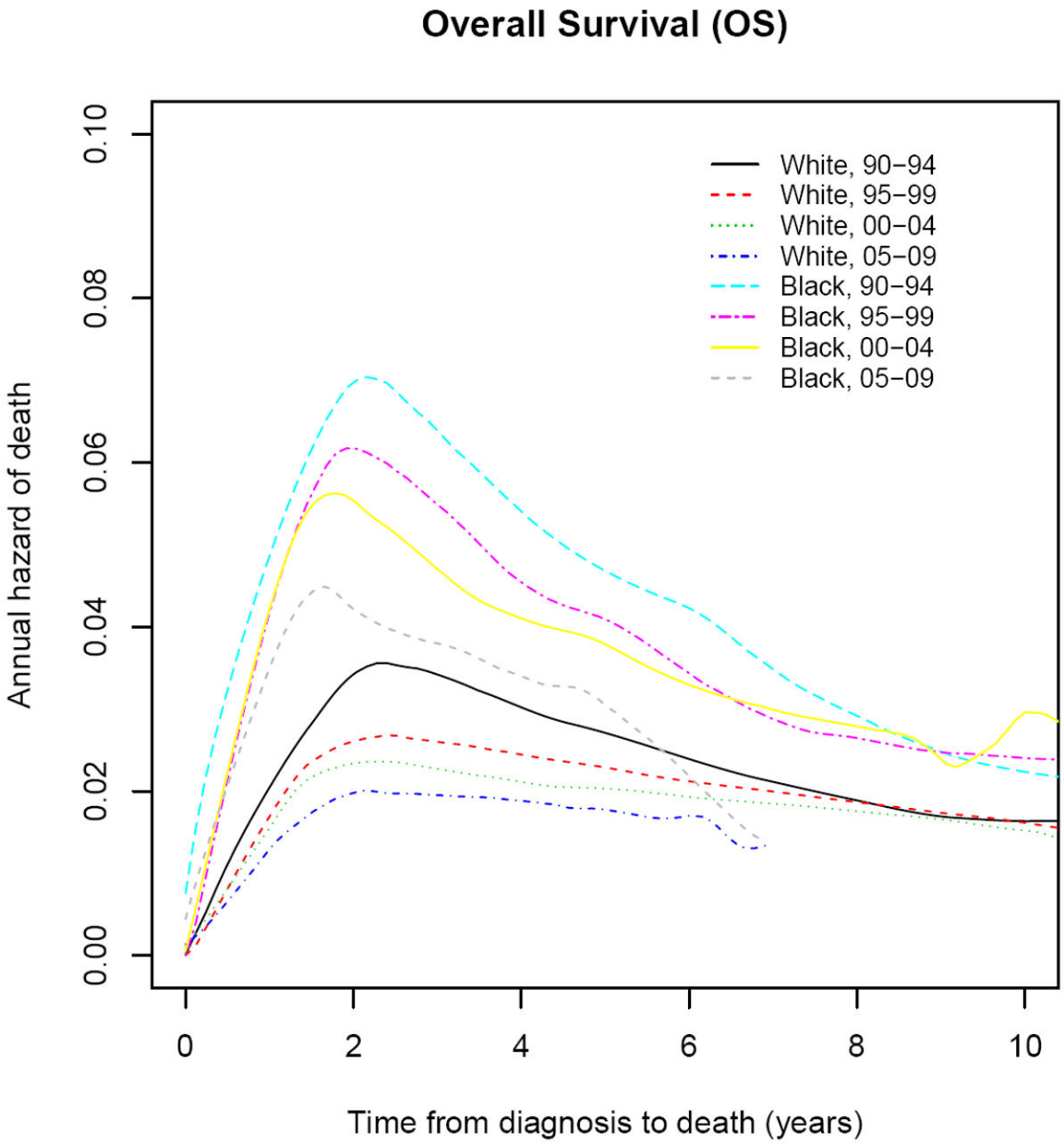

Figure 3.

Smoothed Annual Hazard Rates of Breast Cancer Death according to Race and Calendar Period. Curves show absolute death rates at a stated time period after diagnosis.

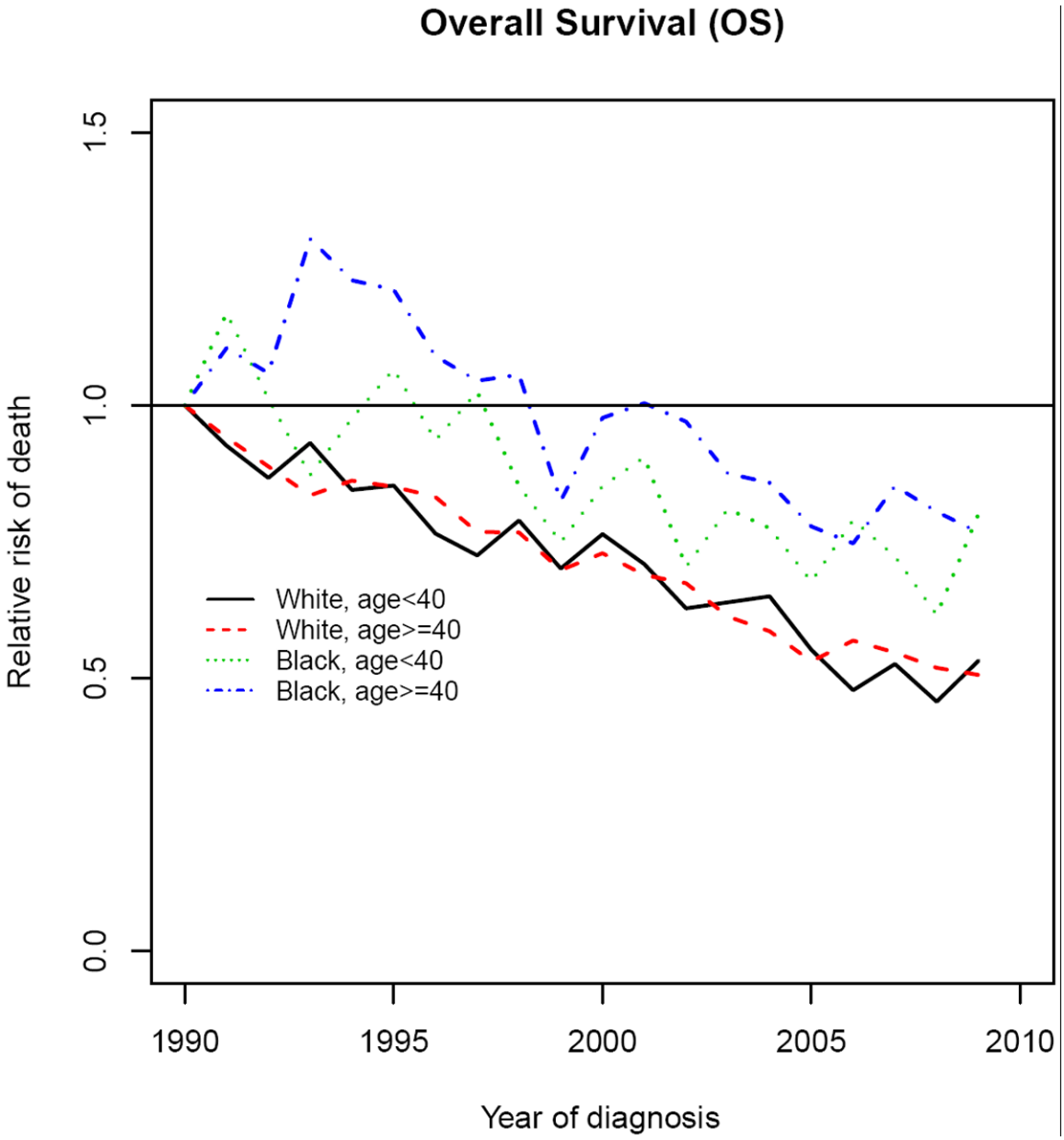

Figure 4.

Relative Risk of Breast Cancer Death according to Race and Age at Diagnosis. RR are adjusted for stage, ER, PR, histology, age, diagnosis year, tumor size, nodal status, and grade.

Table 1

Patients' characteristics by race

Variable		White		Black		Others		P value
		N	%	N	%	N	%	
		126573	77.7	20405	12.5	15998	9.8	
Age	<30	2422	1.9	676	3.3	352	2.2	<.0001
	30-39	26184	20.7	5095	25.0	3728	23.3	
	40-49	97967	77.4	14634	71.7	11918	74.5	
ER status	Positive	80992	64.0	9755	47.8	10738	67.1	<.0001
	Negative	30851	24.4	7626	37.4	3526	22.1	
	Unknown	14730	11.6	3024	14.8	1734	10.8	
PR status	Positive	73575	58.1	8535	41.8	9894	61.9	<.0001
	Negative	36604	29.0	8609	42.2	4134	25.8	
	Unknown	16394	12.9	3261	16.0	1970	12.3	
AJCC[1] stage	I	48334	38.2	5500	26.9	6098	38.1	<.0001
	II	46869	37.0	8254	40.4	6126	38.3	
	III	20555	16.2	4193	20.6	2480	15.5	
	IV	3762	3.0	1093	5.4	460	2.9	
	Unknown	7053	5.6	1365	6.7	834	5.2	
Grade	1	16258	12.8	1422	6.9	1984	12.4	<.0001
	2	43866	34.7	5215	25.6	5834	36.5	
	3	50846	40.2	10861	53.2	6370	39.8	
	4	2825	2.2	503	2.5	337	2.1	
	Unknown	12778	10.1	2404	11.8	1473	9.2	
Tumor size (cm)	<2	59912	47.3	7039	34.5	7247	45.3	<.0001
	2-5	48887	38.6	9096	44.6	6502	40.6	
	>5	8770	6.9	2321	11.4	1223	7.6	
	Unknown	9004	7.1	1949	9.5	1026	6.4	

Variable		White		Black		Others		P value
		N	%	N	%	N	%	
Nodes involved	Negative	67228	53.1	9045	44.3	8797	55.0	<.0001
	Positive	48194	38.1	8414	41.2	5871	36.7	
	Unknown	11151	8.8	2946	14.4	1330	8.3	
Histology	Ductal	98011	77.4	16402	80.4	12880	80.5	<.0001
	Lobular	7693	6.1	839	4.1	601	3.8	
	Mixed	12478	9.9	1434	7.0	1336	8.4	
	Inflammatory	1461	1.1	347	1.7	102	0.6	
	others	6930	5.5	1383	6.8	1079	6.7	
Diagnosis year	1990-94	16690	13.2	2478	12.1	1908	11.9	<.0001
	1995-99	20682	16.3	3078	15.1	2875	18.0	
	2000-04	44621	35.3	7211	35.3	5188	32.4	
	2005-09	44580	35.2	7638	37.4	6027	37.7	

[1] American Joint Committee on Cancer

Table 2

Multivariate model results for overall (OS) and disease specific survival (DSS)

Variable	OS	DSS
	Hazard ratio (95% CI) *P*	**Hazard ratio (95% CI) *P***
Race ([1]ref: white)		
• Black	1.59 (1.55-1.64) <.0001	1.56 (1.52-1.62) <.0001
• Others	0.98 (0.94-1.02) .2966	0.99 (0.94-1.03) 0.5468
Age group (ref:<30)		
• 30-39	0.86 (0.81-0.92) <.0001	0.84 (0.78-0.90) <.0001
• 40-49	0.79 (0.74-0.84) <.0001	0.71 (0.66-0.76) <.0001
Histology (ref:ductal)		
• Lobular	0.96 (0.91-1.01) 0.1467	0.90 (0.85-0.96) <.0001
• Mixed	0.98 (0.94-1.02) 0.4066	0.97 (0.92-1.02) 0.1940
• Inflammatory	1.56 (1.47-1.67) <.0001	1.57 (1.46-1.68) <.0001
• Others	0.66 (0.63-0.70) <.0001	0.62 (0.58-0.66) <.0001
ER (ref:negative)		
• Positive	0.74 (0.72-0.77) <.0001	0.73 (0.71-0.76) <.0001
PR (ref:negative)		
• Positive	0.81 (0.78-0.83) <.0001	0.80 (0.77-0.83) <.0001
Grade (ref:1)		
• 2	1.60 (1.51-1.71) <.0001	2.06 (1.89-2.24) <.0001
• 3	2.12 (2.03-2.29) <.0001	2.87 (2.64-3.11) <.0001
• 4	2.19 (2.02-2.39) <.0001	2.94 (2.64-3.26) <.0001
Stage (ref:I)		
• II	1.15 (1.09- 1.21) <.0001	1.37 (1.29-1.45) <.0001
• III	2.39 (2.26-2.52) <.0001	2.99 (2.81-3.20) <.0001
• IV	7.83 (7.38-8.31) <.0001	10.23 (9.53-10.98) <.0001
Node (ref:negative)		
• Positive	1.74 (1.68-1.80) <.0001	1.87 (1.79-1.95) <.0001
Tumor size (ref:<2cm)		
• 2-5	1.46 (1.42-1.51) <0.001	1.58 (1.52-1.64) <.0001
• >5	1.73 (1.65-1.81) <.0001	1.89 (1.81-1.99) <.0001
Diagnosis year (ref:1990-94)		
• 1995-1999	0.89 (0.86-0.92) <.0001	0.86 (0.82-0.89) <.0001
• 2000-2004	0.80 (0.78-0.83) <.0001	0.77 (0.74-0.79) <.0001
• 2005-2009	0.66 (0.64-0.69) <.0001	0.62 (0.59-0.65) <.0001

[1]Reference

Table 3

Annual Hazard Rates for Mortality at 1, 3, and 5 Years after Diagnosis

Period of Diagnosis	Year 1		Year 3		Year 5	
	White	Black	White	Black	White	Black
1990-1994	2.2[1]	5.1	3.4	6.4	2.7	4.7
1995-1999	1.8	4.4	2.6	5.5	2.3	4.1
2000-2004	1.7	4.4	2.3	4.7	2.0	3.8
2005-2009	0.8	2.4	1.9	4.5	1.9	3.8

[1] Annual hazard rates are % per year hazard of death

Table 4

Adjusted relative risks of death over time according to race and age group

Variable		Whites RR[1] (95% CI)	Blacks RR (95% CI)
< 40 years	1995[2]	0.85 (0.72-1.02)	1.07 (0.77-1.47)
	2000	0.76 (0.65-0.89)	0.85 (0.65-1.12)
	2005	0.55 (0.46-0.66)	0.68 (0.49-0.93)
	2009	0.53 (0.41-0.69)	0.80 (0.54-1.19)
40-49 years	1995	0.85 (0.76-0.96)	1.21 (0.93-1.57)
	2000	0.73 (0.66-0.81)	0.98 (0.78-1.22)
	2005	0.53 (0.47-0.60)	0.78 (0.61-0.99)
	2009	0.51 (0.43-0.60)	0.77 (0.56-1.05)

[1] Relative risk

[2] All years have 1990 as referent

Analysis adjusted for tumor size, grade, histology, lymph node status, ER, PR, and stage.