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Original Article

Changing trends and disparities in 5-year overall survival of women with invasive breast cancer in the United States, 1975-2015

Mu Yang[1,2], Xin Hu[3], Wei Bao[4], Xinmin Zhang[5], Yong Lin[6,7], Sasha Stanton[8], Bruce Haffty[6], Wenwei Hu[6], Yibin Kang[9], Shi Wei[10], Lanjing Zhang[1,6,11,12]

[1]Department of Pathology, Princeton Medical Center, Plainsboro, NJ, USA; [2]Department of Pathology, Shanghai General Hospital, Shanghai Jiaotong University, Shanghai 200080, China; [3]Yale Center for Analytical Sciences, School of Public Health, Yale University, New Haven, CT, USA; [4]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA; [5]Department of Pathology, Cooper University Hospital, Cooper Medical School of Rowan University, Camden, NJ, USA; [6]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [7]Department of Biostatistics and Epidemiology, School of Public Health, Rutgers University, Piscataway, NJ, USA; [8]Cancer Vaccine Institute, University of Washington, Seattle, WA, USA; [9]Department of Molecular Biology, Princeton University, Princeton, NJ, USA; [10]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA; [11]Department of Biological Sciences, Rutgers University, Newark, NJ, USA; [12]Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA

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Abstract: Relative survival is the ratio of overall survival (OS) over survival of the general population, and widely used in epidemiological studies. But it is artificially higher than OS and thus inferior to OS for cancer prognostication of individual patients. Moreover, trend-changes and disparities in OS of breast cancer are unclear while the relative survival of breast cancer has been reported on a regular basis. Therefore, we estimated trends in age-standardized 5-year OS of invasive breast cancer, using data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry program and piecewise-linear regression models. Among 188,052 women with breast cancer diagnosed during 2007-2010 (SEER-18, 155,515 [79.3%] survived by year 5), the 5-year OS significantly differed by age, histology, tumor grade, tumor stage, hormone receptors, race/ethnicity, insurance status, region, rural-urban continuum and selected county-attributes. Among 469,498 women with breast cancer diagnosed during 1975-2010 (SEER-9) in the U.S., we observed an upward trend in the age-standardized 5-year OS (stage- and race/ethnicity-adjusted annual percentage change = 0.97 [95% CI, 0.76-1.18]). The 36-year trends/slopes in age-standardized 5-year OS of breast cancer differed by histology, tumor grade, stage, race/ethnicity, region and socioeconomic attributes of the patient's residence-county, but not by those of rural-urban continuum. The 3-joinpoint model on the 36-year trend identified significant slope changes in 1983, 1987 and 2000, with the largest slope (2.5%/year) during 1983-1987. In conclusion, we here show trends in the age-standardized 5-year OS among U.S. women with breast cancer changed in diagnosis-years of 1983, 1987 and 2000, and differed by tumor characteristics and race/ethnicity. More efforts are needed to understand the trend changes and to address the OS disparities of breast cancers.

Keywords: Breast cancer, histology, survival rate, trends, disparity

Introduction

Breast cancer is the most common cancer (excluding non-melanoma skin cancer) and the second leading-cause of cancer deaths among women in the U.S. [1]. In clinical practice, 5-year overall survival (OS) is the most commonly used indicator to evaluate disease prognosis and treatment effectiveness [2]. Several studies showed an increasing trend in OS of invasive breast cancer, but were limited by their short timeframe (1990-2008) and young patient-age [3], coverage of only 4 registries (Detroit, Hawaii, Utah and Seattle-Puget Sound) [4], or a single histologic type of cancer (inflammatory breast cancer) [5]. Therefore, there is a need for reporting the current rate and long-term trends of 5-year OS of invasive breast cancer, the former of which is the gold standard for assessing cancer outcomes and the major subject of out-

come research [2]. These trend analyses are particularly valuable for assessing cancer outcomes in recent years because breast cancer treatments are becoming much less aggressive [6, 7].

Here, in this population-based study, we examined the current rates (cancers diagnosed 2007-2010) and 36-year trends of age-standardized 5-year OS of U.S. women with invasive breast cancer diagnosed during 1975-2010 (follow-up through 2015). We also reported the rates and trends of age-standardized 5-year OS stratified by sociodemographic and clinicopathologic characteristics so that clinicians and patients could know the age-standardized 5-year OS in selected populations, such as that of a specific stage or pathologic type of breast cancer.

Methods

We extracted the age-standardized 5-year OS data by year and the factors of interest from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database [8]: SEER-9 includes 9 of the eldest, yet high-quality, cancer registries of SEER with data since 1975 that now covers 29,022,086 (9.4%) residents of the U.S. population, while SEER-18 is the largest SEER database including cases from 18 states and covering near 30% of the U.S. population [9, 10]. The datasets have been widely used and validated for research on breast, thyroid and colorectal cancers [9, 11-13]. Since the SEER database is an existing, de-identified, publicly available dataset, this study is exempt from Institutional Review Board (IRB) review under exempt category 4.

We included all qualified women with invasive breast cancers (site and morphology. Primary site-labeled: C50, and C50.0 to C50.9.) in SEER-9 diagnosed during 1975-2010 or SEER-18 during 2007-2010 with follow-up to December 2015 (2018 data-release). The 2007-2010 study period was chosen for calculating the latest OS because insurance statuses were reported in SEER only for the cases diagnosed after 2006 (i.e. 2007+ year). The age-standardized 5-year OS were computed using SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version <8.3.5>). The age-standardization was conducted using a 4-bracket age variable (<50, 50-64, 65-74, and 75+ years) and the International cancer standard 1- ages 15+ years in the "Age Standardize" option of the statistic tab through SEER*Stat software. The following boxes were also checked in the Standard Case Selection tab, Selection only: Microscopically examined and malignant behavior; First Primary Only (Sequence Number 0 or 1); Exclusion criteria: All death certificate only and autopsy only, and Alive with no survival time; Exclusion to match the expected survival table: age value not found in table, invalid year and values not found for other variables. The parameters for OS data extraction were pre-calculated duration, with duration- survival months (from complete dates) chosen, December 2015 as Cutoff date, and Censor when attained age exceeds expected table max.

The age-standardized OS was stratified by race, stages, grade, statuses of ER and PR, Census regions, and rural-urban continuum, as well as insurance status and socioeconomic attributes of county where patents resided (for SEER18 data only). The race and race/ethnicity were recoded according to the SEER coding manual (starting 2005). The tumors were classified into local, regional, distant, and unstaged/unknown using the historic A staging theme, which was applicable to the cases diagnosed in 1975 and onward. The tumors diagnosed between 2007-2010 were also staged using the 6th edition of American Joint Commission on Cancer (AJCC-6) staging manual. The tumors' histology was classified and categorized using the International-Classification of Disease for Oncology (ICD-O)-3 [14], according to the pathology diagnosis in medical charts. We grouped the tumors into invasive ductal carcinoma (IDC, ICD-O-3 8500/3), invasive lobular carcinoma (ILC, ICD-O-3 8520/3), mixed invasive ductal and lobular carcinoma (IDLC, ICD-O-3 8522/3) and non-ductal non-lobular carcinomas (all other ICD-O-3 codes) for the primary analyses. The ER and PR statuses of breast cancer in SEER appeared to be reasonably reliable in validation studies [15]. The registries were grouped intro 4 geographic regions according to the U.S. Census Bureau's definitions. The rural-urban continuum of the patient's location (county-level) was defined using the 1993 or 2003 version to mitigate the

potential changes across the years [16] since major changes of rural-urban continuum rarely occurred. The county-level data of the socio-economic factors were extracted from the 2007-2011 Census American Community Survey (ACS) 5-year file [17]. Only few missing data were observed, and were included in the others group for the analyses.

We assessed the temporal trends of age-standardized 5-year OS using Stata (version 15, StataCorp LLC, College Station, TX) and Joinpoint program (Version 4.6.0.0., Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD) [18]. The model of no joinpoints was used to analyze the overall trends, and that of 3 joinpoints used to analyzed additional joinpoints. The following default parameters were used for trend analyses: Log transformation option was chosen; standard errors (provided) option for Heteroscedastic Errors Option (Weighted Least Squares); grid search method was chosen with 2 as the minimal number of observations from a joinpoint to either end of the data (excluding the first or last joinpoint if it falls on an observation) and the minimal number of observations between two joinpoints (excluding any joinpoint if it falls on an observation). The model selection method was permutation test with overall significance level of .05, and 4499 permutations. We also chose Fit an uncorrelated errors mode for the Autocorrelated Errors Option, and the Parametric model option for the annual percentage change (APC)/Tau Confidence Intervals [19]. On very rare occasions, age-standardized overall-survival rates were unavailable due to an insufficient number of cases, and observed overall-survival rates were used to compute the trends. We also used the nonlinear least-squares estimation and 4-segment piecewise linear spline models of the Stata to estimate joinpoints and slopes with univariate and multivariable regression models [20, 21], the latter of which were not available in the Joinpoint program. All *P* values were two-tailed. A $P<0.05$ was considered statistically significant.

Results

Age-standardized 5-year overall survival of breast cancer diagnosed between 2007-2010 and followed up through 2015

Among the 188 052 women with invasive breast cancer diagnosed during 2007-2010 (83743 [44.5%] AJCC-6 stage I, 62728 [33.4%] stage II, 22531 [12.0%] stage III, 9879 [5.3%] stage IV, and 9171 [4.9%] other/unknown), 155 515 survived by follow-up year 5. The age-standardized 5-year OS differed significantly by age, histology, tumor grade, tumor stage, hormone receptors, race/ethnicity, insurance status, region and rural-urban continuum, as well as several county attributes including percentage of less than high school education, percentage of persons <200% of poverty, percentage of unemployed and median household income (**Table 1**). Importantly, the age-standardized 5-year OS was 90.0% (95% CI, 89.7-90.2%) for American Joint Commission on Cancer 6th edition (AJCC-6) stage I, 81.4% (95% CI, 81.0-81.8%) stage II, 63.4% (95% CI, 62.7-64.1%) stage III, 22.8% (95% CI, 21.9-23.6%) stage IV, and 64.7% (95% CI, 63.7-65.7%) other/unknown stage. We also detected no significant trends of the age-standardized 5-year OS among the cases diagnosed during 2007-2010 by the strata of examined factors, except the race of Asian Pacific Islander, being uninsured and the county with 36-40% % persons <200% of poverty (ACS 2007-2011) (Table S1).

Trends in age-standardized 5-year overall survivals of breast cancer diagnosed during 1975-2010 and followed up through 2015

Among the 469 498 women with invasive breast cancer diagnosed during 1975-2010, 277545 [59.1%] were diagnosed with Historic A localized stage, 152587 [32.5%] with regional stage, 28347 [6%] with distant stage, and 11019 [2.3%] with other/unknown stage. The age-standardized 5-year OS was 84.3% (95% CI, 84.1%-84.4%) for localized stage, 67.8% (95% CI, 67.5%-68.0%) for regional stage, 21.5% (95% CI, 21.1%-22.0%) for distant stage, and 58.3% (95% CI, 57.3%-59.2%) for other/unknown stage. It increased from age-standardized 5-year OS of invasive breast cancer (Figure S1) and in all analyzed subgroups (**Table 2**). The slopes of the trends (APC) were similar within the subgroups of age, and rural-urban continuum (1993 version), but different within those of histology, tumor grade, tumor historic-stage, AJCC-6 stage (diagnosed 1988-2010), Estrogen Receptor (ER)/Progesterone Receptor (PR) (diagnosed 1990-2010), race/ethnicity and U.S. Census region (**Table 2** and **Figure 1**). Adjusted for stage (historic-A staging theme) and race/ethnicity, the APC of overall trend in

Table 1. Age-standardized 5-year overall survivals of invasive breast cancer diagnosed between 2007-2010, with linkage to death registry through 2015

Characteristics	All Patient, n (%)	Alive Patient, n (%)	Age-standardized 5-year OS (95% CI)	*P*[a]
All	188052	155515	79.3 (79.5-82.5)	
Age[b]				
<50 years	45510 (24.2)	40296 (26.0)	88.8 (88.5-89.1)	<.001
50-64 years	72275 (38.4)	63073 (40.7)	87.5 (87.3-87.8)	
65-74 years	37698 (20.0)	31445 (20.3)	83.8 (83.4-84.2)	
75+ years	32571 (17.3)	20152 (13.0)	62.4 (61.9-62.9)	
Histology				
IDC	137904 (73.3)	115071 (74.0)	79.8 (79.5-80.0)	<.001
ILC	15671 (8.3)	12865 (8.3)	80.0 (79.3-80.6)	
IDLC	10956 (5.8)	9439 (6.1)	83.2 (82.4-84.0)	
NDLC	23521 (12.5)	18138 (11.7)	75.0 (74.4-75.6)	
Tumor grade				
Grade 1-2	112043 (59.6)	98263 (63.2)	85.0 (84.8-85.2)	<.001
Grade 3	62432 (33.2)	47984 (30.9)	71.1 (70.7-71.5)	
Other/unknown	13577 (7.2)	9243 (5.9)	64.8 (63.9-65.6)	
American Joint Commission on Cancer staging, 6th edition				
I	83743 (44.5)	77393 (49.8)	90.0 (89.7-90.2)	<.001
II	62728 (33.4)	53869 (34.6)	81.4 (81.0-81.8)	
III	22531 (12.0)	15679 (10.1)	63.4 (62.7-64.1)	
IV	9879 (5.3)	2479 (1.6)	22.8 (21.9-23.6)	
Other/unknown	9171 (4.9)	6060 (3.9)	64.7 (63.7-65.7)	
Hormone receptor				
ER-PR-	33502 (17.8)	24690 (15.9)	68.5 (67.9-69.1)	<.001
ER+PR-	21573 (11.5)	17066 (11.0)	76.5 (75.9-77.1)	
ER-PR+	1898 (1.0)	1415 (0.9)	68.3 (65.6-70.8)	
ER+PR+	119087 (63.3)	103653 (66.7)	83.8 (83.5-84.0)	
Other/unknown	11992 (6.4)	8673 (5.6)	69.7 (68.9-70.6)	
Race/Ethnicity				
Hispanic	19093 (10.2)	15964 (10.3)	78.5 (77.7-79.3)	<.001
NH-White	132169 (70.3)	109844 (70.6)	80.2 (80.0-80.5)	
NH-Black	20211 (10.7)	15055 (9.7)	69.9 (69.2-70.7)	
NH-API	14708 (7.8)	13032 (8.4)	84.8 (84.1-85.6)	
Other/unknown	1871 (1.0)	1638 (1.1)	84.6 (82.1-86.7)	
CHSDA Region				
Alaska	197 (0.1)	155 (0.1)	69.8 (59.9-77.6)	<.001
East	72207 (38.4)	58573 (37.7)	77.5 (77.1-77.8)	
Northern Plains	16596 (8.8)	13518 (8.7)	78.7 (78.1-79.4)	
Pacific Coast	90747 (48.3)	76396 (49.1)	80.9 (80.6-81.2)	
Southwest	8305 (4.4)	6871 (4.4)	79.1 (78.1-80.1)	
Insurance status[c]				
Uninsured	3472 (1.8)	2557 (1.6)	70.4 (66.9-73.7)	<.001
Any Medicaid	20690 (11.0)	15028 (9.7)	68.2 (67.4-69.0)	
Insured	131961 (70.2)	112553 (72.4)	81.9 (81.6-82.1)	
Insured/No specifics	27014 (14.4)	21603 (13.9)	77.6 (77.1-78.2)	
Insurance status unknown	4915 (2.6)	3702 (2.4)	72.3 (70.9-73.6)	
Rural-urban continuum (2003)				
Metropolitan Counties	167117 (88.9)	138893 (89.3)	79.7 (79.5-79.9)	<.001
Nonmetropolitan Counties	20661 (11.0)	16409 (10.6)	76.6 (76.0-77.2)	
Unknown	274 (0.1)	217 (0.1)	72.8 (65.1-79.1)	

Note: Data from the 18 registries of the Surveillance, Epidemiology, and End Results (SEER)-18; OS, age-standardized overall survival; CI, confidence intervals; AJCC, American Joint Commission on Cancer; TNM, tumor, node and metastasis; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal and lobular carcinoma; NDLC, non-ductal non-lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; NH, non-Hispanic; API, Asian Pacific Islanders; CHSDA, Contract Health Service Delivery Areas. [a]*P* values for overall differences among subgroups. [b]Observed 5-year survivals shown in the age subgroups because age-standardization was not possible in age subgroups. [c]Some of the patients older than 65 years of age may be misclassified as uninsured or status unknown, but were eligible for or enrolled in the Medicare.

Table 2. Trends in age-standardized 5-year overall survivals of invasive breast cancer diagnosed during 1975-2010, with linkage to death registry within 5 years of diagnosis

Characteristics	Age-standardized 5-year overall survival, % (95% CI)							AAPC	P^a	$P^b_{parallelism}$
	1975-1980	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010			
All Patient, n	50894	50767	62548	68284	77530	78426	81049			
Alive Patient, n	34455	35283	46848	52784	62257	64309	67838			
All	64.3 (63.9-64.8)	66.7 (66.3-67.2)	72.9 (72.5-73.2)	75.1 (74.7-75.4)	77.7 (77.4-78)	79.0 (78.7-79.3)	80.2 (79.9-80.5)	0.7 (0.6-0.8)	<.001	
Age[c]										
<50 years	75.1 (74.3-75.8)	76.6 (75.9-77.4)	80.2 (79.5-80.8)	83.2 (82.6-83.8)	86.5 (86.0-86.9)	88.3 (87.8-88.7)	90.2 (89.8-90.6)	0.6 (0.6-0.7)	<.001	Reference
50-64 years	71.2 (70.6-71.9)	73.7 (73.1-74.4)	80.1 (79.5-80.7)	83.3 (82.8-83.8)	86.6 (86.2-87.1)	87.7 (87.3-88.0)	88.6 (88.2-88.9)	0.7 (0.6-0.7)	<.001	.23
65-74 years	67.6 (66.7-68.4)	70.5 (69.6-71.3)	76.7 (76.0-77.3)	79.0 (78.4-79.6)	80.6 (80.0-81.2)	82.5 (81.9-83.1)	84.5 (83.9-85.1)	0.6 (0.6-0.7)	<.001	.27
75+ years	49.6 (48.5-50.6)	51.7 (50.7-52.7)	58.5 (57.7-59.4)	59.2 (58.4-60.0)	61.9 (61.1-62.6)	62.7 (61.9-63.4)	63.2 (62.4-64.0)	0.7 (0.6-0.8)	<.001	.054
Histology										
IDC	64.7 (64.2-65.3)	66.9 (66.4-67.5)	73.5 (73.0-73.9)	75.6 (75.2-76.0)	78.3 (77.9-78.6)	79.2 (78.8-79.6)	80.7 (80.3-81.1)	0.7 (0.6-0.8)	<.001	Reference
ILC	70.4 (68.5-72.2)	72.6 (71.0-74.2)	75.7 (74.3-77.0)	79.4 (78.2-80.4)	80.2 (79.2-81.1)	80.2 (79.2-81.2)	80.6 (79.6-81.6)	0.4 (0.3-0.5)	<.001	<.001
IDLC	72.9 (66.5-78.3)	71.7 (68.6-74.5)	79.3 (77.2-81.2)	78.2 (76.5-79.8)	83.2 (82.0-84.3)	83.5 (82.5-84.5)	84.1 (82.9-85.2)	0.3 (0.1-0.5)	0.002	<.001
NDLC	62.0 (61.1-62.8)	63.8 (62.8-64.7)	68.2 (67.3-69.1)	70.3 (69.4-71.2)	70.7 (69.8-71.6)	75.0 (74.2-75.8)	75.9 (75.0-76.7)	0.7 (0.6-0.8)	<.001	<.001
Tumor grade										
Grade 1-2	71.1 (69.4-72.7)	72.8 (71.6-74.0)	79.2 (78.5-79.9)	81.8 (81.3-82.3)	84.1 (83.7-84.4)	85.1 (84.7-85.4)	85.6 (85.3-86.0)	0.5 (0.4-0.5)	<.001	Reference
Grade 3	54.5 (53.1-55.8)	56.7 (55.4-57.9)	63.9 (63.0-64.8)	66.2 (65.4-66.9)	69.0 (68.4-69.7)	70.4 (69.7-71.0)	71.7 (71.1-72.4)	0.8 (0.7-0.9)	<.001	<.001
Other/unknown	65.2 (64.7-65.7)	67.7 (67.2-68.1)	73.7 (73.2-74.2)	74.8 (74.2-75.4)	71.5 (70.6-72.4)	67.9 (66.7-69.0)	64.7 (63.3-66.1)	0.4 (0.2-0.6)	0.001	.97
Historic Stage A										
Localized	77.5 (77.0-78.1)	79.0 (78.5-79.5)	83.4 (83.0-83.8)	84.1 (83.8-84.5)	85.4 (85.1-85.7)	86.5 (86.1-86.8)	87.6 (87.3-87.9)	0.4 (0.3-0.4)	<.001	Reference
Regional	58.0 (57.3-58.8)	60.8 (60.1-61.5)	65.2 (64.5-65.9)	66.9 (66.2-67.7)	71.5 (70.8-72.1)	74.3 (73.7-75.0)	75.9 (75.3-76.6)	0.9 (0.9-1.0)	<.001	<.001
Distant	16.3 (15.0-17.5)	16.7 (15.4-18.0)	18.7 (17.4-20.0)	18.4 (17.2-19.7)	22.8 (21.5-24.1)	24.7 (23.5-26.0)	28.8 (27.5-30.0)	1.9 (1.6-2.3)	<.001	<.001
Unstaged/unknown	60.1 (57.6-62.4)	57.8 (55.4-60.2)	55.4 (53.1-57.7)	58.5 (56.2-60.7)	59.6 (57.1-62.0)	58.7 (55.7-61.6)	60.0 (57.0-62.9)	0.0 (-0.2-0.3)	0.761	.02
Race/Ethnicity[d]										
Hispanic	67.5 (64.0-70.8)	68.2 (65.0-71.1)	72.3 (70.0-74.5)	76.6 (74.5-78.5)	75.3 (73.5-77.0)	78.2 (76.5-79.7)	78.5 (77.0-80.0)	0.5 (0.3-0.6)	<.001	Reference
NH-White	64.9 (64.5-65.4)	67.6 (67.2-68.1)	73.8 (73.4-74.2)	76.0 (75.6-76.4)	78.6 (78.2-78.9)	80.1 (79.8-80.4)	81.1 (80.8-81.5)	0.7 (0.6-0.8)	<.001	.25
NH-Black	52.4 (50.2-54.4)	53.8 (51.9-55.6)	60.4 (58.8-62.0)	61.7 (60.2-63.2)	66.6 (65.2-67.9)	67.1 (65.7-68.4)	70.7 (69.5-71.9)	1.0 (0.9-1.1)	<.001	<.001
NH-API	70.2 (66.4-73.6)	70.5 (67.5-73.3)	77.2 (75.1-79.1)	80.6 (78.9-82.2)	83.5 (82.2-84.8)	82.4 (81.2-83.6)	84.4 (83.4-85.5)	0.5 (0.4-0.6)	<.001	.57
Other/unknown	66.7 (57.6-74.3)	58.2 (48.4-66.8)	68.1 (60.3-74.7)	74.8 (68.5-79.9)	75.2 (69.8-79.8)	78.0 (73.4-81.9)	83.8 (80.3-86.7)	0.7 (0.4-1.0)	<.001	.045
CHSDA Region										
East	63.4 (62.5-64.3)	66.2 (65.3-67.1)	72.4 (71.7-73.2)	74.2 (73.5-74.9)	76.7 (76.1-77.4)	78.4 (77.7-79.0)	79.7 (79.0-80.3)	0.7 (0.6-0.8)	<.001	Reference
Northern Plains	62.3 (61.5-63.1)	65.2 (64.4-65.9)	70.8 (70.1-71.4)	73.3 (72.7-73.9)	76.0 (75.4-76.6)	77.3 (76.7-77.9)	78.4 (77.8-79.0)	0.7 (0.7-0.8)	<.001	.17
Pacific Coast	66.9 (66.1-67.7)	68.8 (68.0-69.5)	75.0 (74.4-75.6)	77.5 (76.9-78.1)	80.0 (79.4-80.5)	81.1 (80.6-81.6)	82.5 (82.0-83.0)	0.7 (0.6-0.8)	<.001	.16
Southwest	65.1 (63.5-66.6)	66.4 (64.9-67.9)	73.2 (72.0-74.4)	74.3 (73.2-75.4)	77.1 (76.1-78.0)	77.5 (76.5-78.4)	78.7 (77.8-79.6)	0.6 (0.5-0.7)	<.001	.02
Rural-urban continuum (1993 version)										
Metropolitan Counties	64.2 (63.7-64.7)	66.5 (66.0-67.0)	72.7 (72.3-73.1)	74.8 (74.5-75.2)	77.7 (77.3-78.0)	79.0 (78.6-79.3)	80.4 (80.1-80.7)	0.7 (0.6-0.8)	<.001	Reference
Nonmetropolitan Counties	64.1 (63.0-65.2)	67.0 (65.9-68.1)	72.4 (71.4-73.3)	75.0 (74.1-75.8)	77.0 (76.1-77.8)	79.0 (78.2-79.7)	79.3 (78.5-80.0)	0.7 (0.6-0.8)	<.001	.18
Unknown	70.4 (67.1-73.3)	71.6 (68.9-74.0)	79.4 (77.4-81.3)	80.2 (78.4-81.9)	81.7 (80.1-83.2)	75.3 (62.0-84.5)	76.8 (63.3-85.9)	0.7 (0.5-0.9)[e]	<.001	NA[e]

Note: Data from the 18 registries of the Surveillance, Epidemiology, and End Results (SEER)-9; AAPC, Average annual percentage changes; OS, age-standardized overall survival; CI, confidence intervals; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal and lobular carcinoma; NDLC, non-ductal non-lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; NH, non-Hispanic; API, Asian Pacific Islanders; CHSDA, Contract Health Service Delivery Areas; NA, not available. [a]*P* values for linearity of overall trends among subgroups. [b]$P_{parallelism}$ were calculated using test for parallelism of the Joinpoint program. A $P<0.05$ indicates different trends in the examined 2 subgroups. [c]Observed 5-year overall survivals shown in the age subgroups because age-standardization was not possible in age subgroups. [d]The observed 5-year overall survival in 1978 of the Other group was used in place of age-standardized 5-year survival which was not possible to compute due to lack of data in some age subgroups. [e]The age-standardized 5-year overall survivals in 2000-2010 were not possible to compute due to the lack of data in some age groups. Hence, only the data of 1975-1999 were used for calculating AAPC. [f]Several factors shown in **Table 1** were only available for later years in SEER-9, including tumor stage (the 6th American Joint Commission on Cancer staging manual, 1988+, see **Figure 2**), status of hormone receptors (1990+, see **Figure 2**) and insurance status (2007+).

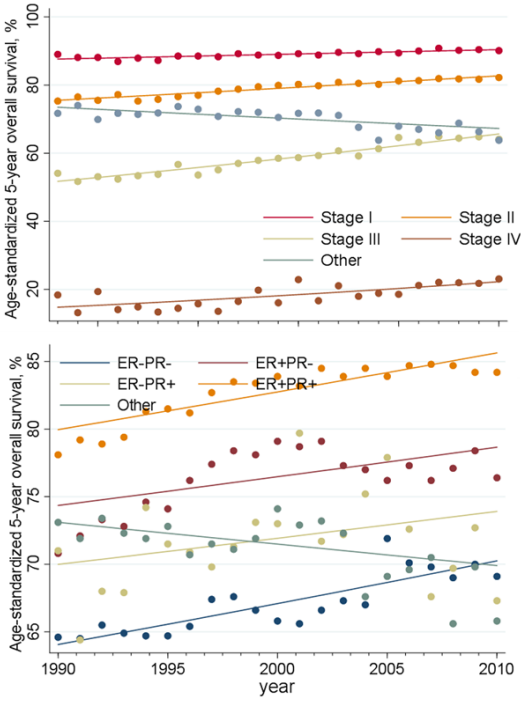

Figure 1. Trends in the age-standardized 5-year overall survivals among women with invasive breast cancer in the U.S. by AJCC-6 staging and hormone receptor status. The lines represent fitted models with slopes showing the annual percent changes (APC). Top. Among the U.S. women with breast cancer diagnosed during 1988-2010, there were significant increasing trends in the stage I (APC=0.1 [95% CI, 0.1-0.2]), stage II (APC=0.4 [95% CI, 0.4-0.5]), stage III (APC=1.1 [95% CI, 1.0-1.2]), and stage IV (APC=1.9 [95% CI, 1.1-2.7]) groups, but a decreasing trend in the unstaged/unknown group (APC=-0.4 [95% CI, -0.6–0.2]), P_{trend}<.001 for all. Bottom. Among the U.S. women with breast cancer diagnosed during 1990-2010, there were significant increasing trends in the ER-PR- (APC=0.5 (95% CI, 0.3-0.6), *P*<0.001), ER+PR- (APC=0.3 [95% CI, 0.1-0.5], *P*=0.006) and ER+PR+(APC=0.3 [95% CI, 0.3-0.4], *P*<0.001) groups, and a decreasing trend in the other/unknown group (APC=-0.2 [95% CI, -0.4-0.0], *P*=0.017), but no detectable trends in the ER-PR+ group (APC=0.3 [95% CI, -0.1-0.7], *P*=0.153). AJCC-6, American Joint Commission on Cancer staging manual 6th edition, ER, Estrogen Receptor; PR, Progesterone Receptor.

age-standardized 5-year OS was 0.97 (95% CI, 0.76-1.18, *P*<0.001).

The Joinpoint program's modelling of 3-joinpoint trends identified the joinpoints of 1983, 1987 and 2000, at which trend slopes intercepted (**Figure 2** and Table S2), which were similar to those identified by the piecewise linear regression model (Table S3). The largest

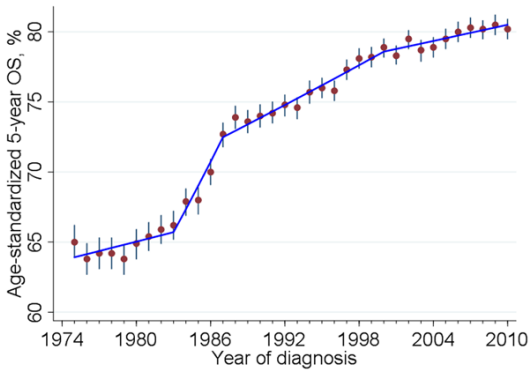

Figure 2. The model of three joinpoints for the trends of 5-year overall survival of breast cancer diagnosed 1975-2010, with linkage to death registry through 2015. Three joinpoints (4 trend slopes) were identified in age-standardized 5-year overall survivals among women with invasive breast cancer in the U.S., including the slopes of 1975-1983 (APC[annual percent change]=0.3 [95% CI, 0.0-0.7], *P*=0.036), 1983-1987 (APC=2.5 [95% CI, 1.3-3.7], *P*<0.001), 1987-2000 (APC=0.6 [95% CI, 0.5-0.7], *P*<0.001), and 2000-2010 (APC=0.2 [95% CI, 0.1-0.3], *P*<0.001). APC, annual percentage change; CI, confidence intervals; Error bars show the 95% CI.

APC/slope was 2.5 during 1983-1987, followed by 0.6 during 1987-2000. However, adjusted for stage (historic-A staging theme) and race/ethnicity, the nonlinear least-squares estimation only identified one joinpiont in 1985 (APC for 1975-1985=-0.34 [95% CI, -3.37 to 2.69], *P*=0.826; APC for 1985-2010=1.08 (95% CI 0.31 to 1.85), *P*=0.006) in a 4-segment model. Interestingly, IDC had an increasing trend in 5-year OS during the last 12 years (**Figure 3**, P<0.001), but ILC, IDLC and NDNLC had no significant changes of the trend in 5-year OS during the last 8-16 years, respectively.

Discussion

Among the 469 498 U.S. women with invasive breast cancer diagnosed during 1975-2010 (follow-up through 2015), the age-standardized 5-year overall survival increased from 64.3% for the cancers diagnosed in 1975-1980 to 80.2% for those diagnosed in 2006-2010, with an adjusted APC of 0.97 (95% CI, 0.76-1.18). The trends in age-standardized 5-year OS differed by histology, tumor grade, stage, race/ethnicity and region, but not rural-urban continuum. The recent age-standardized 5-year OS of U.S. women with breast cancer also differed by cancer characteristics, patient race/ethnici-

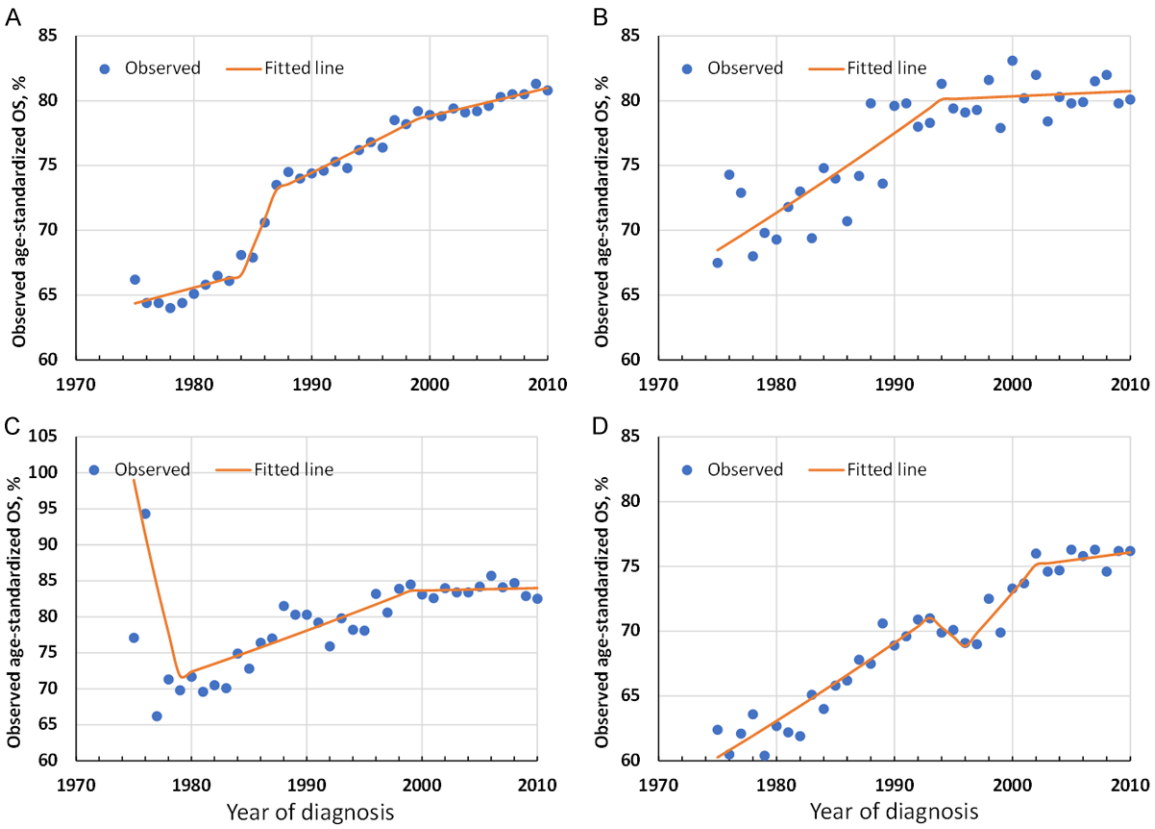

Figure 3. Trends in the age-standardized 5-year overall survivals (OS) among women with invasive breast cancer in the U.S. by histology. The lines represent fitted models with slopes showing the annual percent changes (APC). A. Invasive duct carcinoma had 4 trend slopes, including 1975-1984 (APC=0.372*), 1984-1987 (APC=3.181*), 1987-1999 (APC=0.605*) and 1999-2010 (APC=0.272*). B. Invasive lobular carcinoma had 2 trend slopes, including 1975-1994 (APC=0.829*) and 1994-2010 (APC=0.05). C. Mixed invasive ductal and lobular carcinoma 3 trend slopes, including 1975-1979 (APC=-7.71), 1979-1999 (APC=0.763*) and 1999-2010 (APC=0.042). D. Non-ductal non-lobular carcinoma had 4 trend slopes, including 1975-1993 (APC=0.915*), 1993-1996 (APC=-1.022), 1996-2002 (APC=1.46*) and 2002-2010 (APC=0.16). * Indicates APC was significantly different from 0 at the alpha level of 0.05.

ty and socioeconomic attributes of the county where the patients resided. There were significant APC/slope changes in 1983, 1987 and 2000 with the largest APC/slope of 2.5 during 1983-1987, which coincided with the joinpoint of 1985 identified in multivariable piecewise linear-regression model.

We here reported the changes and disparities of trends in age-standardized 5-year OS of invasive breast cancer. First, there were differently increasing trends in age-standardized 5-year OS within racial/ethnic groups of U.S. women with invasive breast cancer. These findings are somewhat contradictory to the racial disparity in all-cause and breast-cancer specific mortality [22], cause-specific survival [23, 24], and relative survival [23, 25], but consistent with the other report on cancer-specific survival [26]. For example, all Blacks or Non-Hispanic Blacks, if Hispanic ethnicity was considered, had higher increasing trends of relative survival than other/unknown races, despite still having lower relative survival [24, 27]. Our findings suggest that the racial disparity in breast cancer OS is narrowing as compared to the past decades. Second, this comprehensive long-term study showed significant histologic differences in OS trends of women with breast cancer, while earlier works covered mostly the period of 1990-2011 and only 3 common types or a rare type of breast cancer [28, 29]. The uncommon histologic types (non-ductal non-lobular cancers) of breast cancer, despite their increasing trend similar to that of ductal carcinoma, have had the worst age-standardized

5-year OS among the 4 histologic groups in the past 36 years. Given the persistent gap in the 5-year OS between the common and uncommon types of breast cancer among U.S. women, our findings highlight a critical need to determine the risk factors for long-term outcomes of uncommon histologic types of breast cancer (e.g., medullary carcinoma, inflammatory carcinoma and adenocarcinoma not-otherwise-specified). Third, we observed steeper increasing OS trends in late-stage invasive breast cancers and high grade (grade 3) cancers than early-stage and low-grade cancers, respectively (**Figure 1**, Top). These data suggest that the current and past standards of care have improved the outcomes of these breast cancers. However, the standardized 5-year OS trended downward in the other/unknown groups of AJCC-6 staging and ER/PR status (**Figure 1**, bottom), which needs further study. Finally, we found no rural-urban disparity in trends of age-standardized 5-year in women with invasive breast cancer during 1975-2010, supporting a recent report of no rural-urban disparity in the mortality trend of breast cancer (2004-2013) [28]. In contrast, there was significant rural-urban disparity in breast cancer survival trends in Australia [30], as well as regional differences in the trends and rates of 5-year OS of breast cancer shown here and by others [25]. It may be interesting to better understand the reasons for the lack of rural-urban disparity in breast cancer OS trends in the U.S.

We also identified the difference of ER/PR status in the OS trends, which was reported by a prior study on cancer-specific survivals (1990-2006) [31], except that ER+PR- female breast cancer had an overall increasing OS trend in our cohort but a decreasing trend in cancer-specific survival in theirs [31]. The difference in our view may be attributable to the OS (vs cancer-specific survival), age-standardization and the longer timeframe in our study. Moreover, the geographic disparity reported here is similar to that reported in earlier studies on breast cancer mortality and relative survivals [25, 32]. Finally, we also explored and showed the disparity in the trends of 5-year OS by histology in the last decade. The patients with IDC benefited increasing 5-year OS in the past decade, but all other histology types of invasive breast cancer did not, which should be addressed in future works and clinical practice.

Several strengths of our study are noteworthy. The major strength of this study is the long study-period (36 years), identification of APC/slope changes, reporting of age-standardized 5-year OS, and the large sample size. The only joinpoint of 1985 identified in multivariable model and the largest APC/Slope of 2.5 during 1983-1987 reported here coincided with the implementation of breast cancer screening for U.S. women aged 40-49 in 1983 [33]. The two previous studies using data of >34 years were focused on relative survivals, only modeled the data in selected time periods and did not report APC/slope [27, 32]. The relative survival (ratio) is widely used in epidemiological studies for its adjustment for the survivals of the general population. However, it is the ratio of overall survival over the survival of general population (approximately 85-90%). It is therefore approximately 11% larger than overall survival and may be misleading if used for patient prognostication. The other two interesting studies of long-period data (1975-2010) did not quantify the survival trends (i.e. no coefficient or APC reported) [24, 34, 35]. Many other prior studies only covered the past 10-20 years [3, 29, 31, 36]. Moreover, we comprehensively examined both clinicopathologic and socioeconomic factors in a single population, while past works only assessed either clinicopathologic [3, 31, 34, 36] or socioeconomic factors alone [4, 27, 32, 37, 38]. Associations of these factors with the OS trends of invasive breast cancer were also largely unknown, but investigated in this study. Furthermore, OS is critical for assessing cancer outcomes, conducting outcome research and individual-level prognostication [2], but was only examined in few studies [3]. This population-based study hence may provide a benchmark on the breast cancer 5-year OS among U.S. women by clinicopathologic and socioeconomic factors. Finally, age-standardization in trend analysis reduces the bias associated with the changes of age-distribution in past decades, as used before [32, 39] and in this study.

This study has several limitations. First, there were several changes in histology diagnostic criteria, and staging schemes, including the publication of several versions of World Health Organization classification on breast tumors [14, 40], and AJCC staging manuals [13, 40]. However, these changes only impact a small

portion of the cases since many of the changes seemed incremental. Second, the diagnostic criteria and pathologic terms of invasive breast cancer have gradually evolved in the past decades and may be conflicting among resources [14, 41]. For example, intraductal papillary carcinoma and comedocarcinoma were considered as malignancy by ICD-O-3 [14], but not invasive carcinoma by the latest WHO classification [41]. Caution should be used when applying the findings related to these tumors. Third, cancer registry data may inherently have some coding errors, misclassifications and misdiagnoses, although SEER dataset has a rigorous data-quality control process and has been validated by many studies [15, 40, 42]. Nonetheless, a central pathologic review of the cases may be needed to ensure minimal interobserver variances in the diagnoses. Fourth, breast cancer incidence by age, race/ethnicity and histology has changed substantially over the time period studied, and may influence the aggregated OS. We therefore reported the OS by the strata of these parameters and others, while the potential interaction of these factors may still exist and are not the focus of this descriptive study. Future works may be needed to address this limitation. Finally, ER, PR and HER2 statuses were not available for many years in the dataset. However, SEER-9 is the earliest and the longest-running cancer registry dataset covering a considerable portion of the U.S. population. For the interest of study-period length, we chose to use SEER-9, instead of other SEER datasets with more coverage but shorter timeframes. We too estimated the age-standardized 5-year OS by hormone receptor status using SEER-9, which covered the same study period as other SEER datasets. Despite its important predictive and prognostic values [43], HER2-status data were not collected in the SEER program until 2010. Thus, we had only one data-year for calculating 5-year OS at the time of our study, which was insufficient for trend analysis.

Conclusions

We show trends in the age-standardized 5-year OS among U.S. women with breast cancer changed in diagnosis-years of 1983, 1987 and 2000, and differed by histology, tumor grade, stage, race/ethnicity and region, but not rural-urban continuum. More efforts are needed to understand the trend changes and to address the OS disparities of breast cancers.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lanjing Zhang, Department of Pathology, Princeton Medical Center, 1 Plainsboro Rd, Plainsboro, NJ 08536, USA. E-mail: lanjing.zhang@rutgers.edu; ljzhang@hotmail.com

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Table S1. Trends in age-standardized 5-year overall survivals of U.S. women with invasive breast cancer diagnosed during 2007-2010, with linkage to death registry through 2015

Variables	APC (95% CI) of OS[a]	P_{trend}
Age[b]		
<45 years	0.05 (-0.74-0.84)	0.82
45-54 years	0.01 (-0.70-0.73)	0.96
55-64 years	-0.26 (-0.94-0.41)	0.24
65-74 years	0.28 (-0.12-0.69)	0.09
75-84 years	0.15 (-1.54-1.88)	0.74
American Joint Commission on Cancer staging, 6th edition		
I	0.00 (-0.81-0.82)	>0.99
II	0.05 (-0.13-0.23)	0.37
III	0.58 (-0.67-1.84)	0.18
IV	0.82 (-3.24-5.05)	0.48
Other/unknown	-1.65 (-7.04-4.04)	0.33
Histology		
IDC	0.19 (-0.72-1.10)	0.48
ILC	-0.73 (-1.51-0.04)	0.06
IDLC	0.28 (-1.22-1.79)	0.51
[OTHER]	0.35 (-0.80-1.51)	0.32
Tumor grade		
Grade 1-2	0.05 (-0.13-0.22)	0.37
Grade 3	0.05 (-1.83-1.95)	0.93
Other/unknown	-2.28 (-4.84-0.35)	0.07
Hormone receptor		
ER-PR-	-0.16 (-1.39-1.09)	0.64
ER+PR-	-0.43 (-1.99-1.17)	0.37
ER-PR+	-0.27 (-7.36-7.37)	0.89
ER+PR+	-0.12 (-0.28-0.04)	0.09
[OTHER]	-1.06 (-3.38-1.32)	0.19
Race/Ethnicity		
NH White	0.01 (-0.54-0.57)	0.93
Hispanic	-0.31 (-2.21-1.63)	0.56
NH Black	0.59 (-0.69-1.88)	0.19
API	0.56 (0.32-0.80)	0.01
[OTHER]	1.42 (-3.13-6.18)	0.32
U.S. Census Region		
Northeast	0.44 (-0.36-1.24)	0.14
South	0.36 (-1.15-1.89)	0.42
Midwest	-0.31 (-1.54-0.94)	0.40
West	-0.07 (-1.25-1.12)	0.82
Rural-urban continuum (2003)		
Metropolitan Counties	0.05 (-0.44-0.54)	0.70
Nonmetropolitan Counties	-0.07 (-0.28-0.15)	0.33
Unknown	3.52 (-12.24-22.11)	0.46
Insurance status[c]		
Uninsured	5.63 (0.46-11.06)	0.04
Any Medicaid	0.16 (-1.56-1.92)	0.72
Insured	0.17 (-0.01-0.35)	0.06

Insured/No specifics	-0.40 (-1.45-0.67)	0.25
Insurance status unknown	-0.64 (-4.18-3.04)	0.53
% less than high school education in the county (ACS 2007-2011)		
<10	0.27 (-0.76-1.32)	0.38
10-13.3	0.64 (-0.73-2.02)	0.18
13.4-16.6	-0.24 (-0.80-0.32)	0.21
16.7-23.3	-0.12 (-1.64-1.42)	0.77
>23.4	-0.29 (-1.73-1.17)	0.48
Median household income in the county (ACS 2007-2011)		
<$50 k	-0.24 (-1.32-0.86)	0.45
$50 k-$59 k	0.00 (-0.39-0.39)	>0.99
$60 k-$69 k	0.39 (-0.52-1.30)	0.21
>$70 k	0.17 (-1.49-1.86)	0.70
% persons <200% of poverty in the county (ACS 2007-2011)		
<25	0.44 (-0.51-1.41)	0.18
26-30	0.22 (-0.47-0.92)	0.30
31-35	0.27 (-0.51-1.05)	0.28
36-40	-0.66 (-1.12--0.20)	0.03
>41	-0.05 (-1.23-1.14)	0.87
% unemployed in the county (ACS 2007-2011)		
<8	0.09 (-0.01-0.18)	0.06
8.0-8.9	0.14 (-1.13-1.42)	0.69
9.0-9.9	0.14 (-0.01-0.28)	0.05
>10	-0.14 (-1.21-0.93)	0.62

Note: No comparison of the trend slopes was performed due to the lack of significant trend in almost all strata. The data were extracted from the 18 registries of the Surveillance, Epidemiology, and End Results (SEER)-18; OS, age-standardized overall survival; CI, confidence intervals; AJCC, American Joint Commission on Cancer; TNM, tumor, node and metastasis; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal and lobular carcinoma; NDLC, non-ductal non-lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; NH, non-Hispanic; API, Asian Pacific Islanders; ACS, the Census American Community Survey (ACS) 5-year file. [a]Annual percentage change of age-standardized 5-year overall survival unless otherwise indicated. [b]Observed 5-year survivals shown in the age subgroups because age-standardization was not possible in age subgroups. [c]Some of the patients older than 65 years of age may be misclassified as uninsured or status unknown, but were eligible for or enrolled in the Medicare.

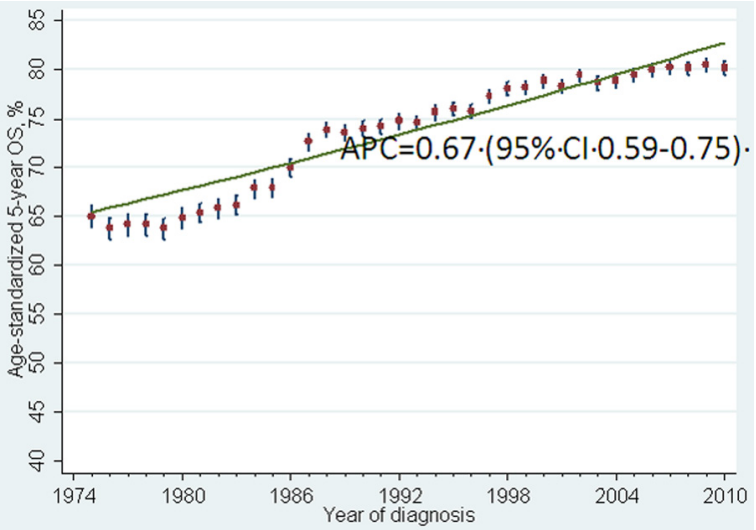

Figure S1. Trends in age-standardized 5-year overall survivals among women with invasive breast cancer in the U.S., 1975-2015. APC, annual percentage change, 95% confidence intervals (CI) shown in the parentheses; Error bars show the 95% CI. *P*<.001 for the trend.

Table S2. Models of 3 joinpoints for the trends in age-standardized 5-year overall survivals of women with invasive breast cancer diagnosed during 1975-2010, with linkage to death registry through 2015*

Characteristics	Number of Joinpoints in the best-fit model	Sequential number of the Segment	Segment Start	Segment End	APC	APC 95% LCL	APC 95% UCL	*P*-Value[a]
All	3	0	1975	1983	0.346	0.025	0.668	0.036
All	3	1	1983	1987	2.486	1.331	3.654	<0.001
All	3	2	1987	2000	0.624	0.522	0.725	<0.001
All	*3*	*3*	*2000*	*2010*	*0.241*	*0.134*	*0.348*	*<0.001*
Age recode (<45, 64, 74, 84, 85+)[b]								
<45 years	3	0	1975	1985	0.159	-0.113	0.431	0.24
<45 years	3	1	1985	1988	1.861	-0.959	4.761	0.188
<45 years	3	2	1988	2006	0.635	0.563	0.707	<0.001
<45 years	*3*	*3*	*2006*	*2010*	*0.012*	*-0.524*	*0.55*	*0.965*
45-54 years	3	0	1975	1979	-0.793	-1.807	0.232	0.123
45-54 years	3	1	1979	1988	1.214	0.871	1.559	<0.001
45-54 years	3	2	1988	2000	0.636	0.506	0.766	<0.001
45-54 years	*3*	*3*	*2000*	*2010*	*0.242*	*0.13*	*0.354*	*<0.001*
55-64 years	3	0	1975	1983	0.479	-0.117	1.077	0.111
55-64 years	3	1	1983	1987	2.402	0.109	4.748	0.041
55-64 years	3	2	1987	2000	0.762	0.567	0.959	<0.001
55-64 years	*3*	*3*	*2000*	*2010*	*0.063*	*-0.125*	*0.252*	*0.496*
65-74 years	2	0	1975	1983	0.562	0.006	1.122	0.048
65-74 years	2	1	1983	1988	2.089	0.86	3.334	0.002
65-74 years	*2*	*2*	*1988*	*2010*	*0.438*	*0.374*	*0.503*	*<0.001*
75-84 years	2	0	1975	1982	0.044	-0.86	0.955	0.922
75-84 years	2	1	1982	1987	3.051	1.296	4.837	0.001
75-84 years	*2*	*2*	*1987*	*2010*	*0.471*	*0.385*	*0.558*	*<0.001*
Histology								
IDC	3	0	1975	1984	0.372	0.066	0.679	0.019
IDC	3	1	1984	1987	3.181	0.697	5.726	0.014
IDC	3	2	1987	1999	0.605	0.469	0.74	<0.001
IDC	*3*	*3*	*1999*	*2010*	*0.272*	*0.158*	*0.387*	*<0.001*
ILC	1	0	1975	1994	0.829	0.534	1.125	<0.001
ILC	*1*	*1*	*1994*	*2010*	*0.05*	*-0.166*	*0.266*	*0.64*
IDLC	2	0	1975	1979	-7.71	-18.188	4.11	0.183
IDLC	2	1	1979	1999	0.763	0.45	1.076	<0.001
IDLC	*2*	*2*	*1999*	*2010*	*0.042*	*-0.301*	*0.386*	*0.805*
[OTHER]	3	0	1975	1993	0.915	0.74	1.091	<0.001

[OTHER]	3	1	1993	1996	-1.022	-5.794	3.992	0.672
[OTHER]	3	2	1996	2002	1.46	0.377	2.554	0.01
[OTHER]	*3*	*3*	*2002*	*2010*	*0.16*	*-0.332*	*0.654*	*0.51*
Historic stage A								
Localized	2	0	1975	1982	-0.049	-0.46	0.363	0.808
Localized	2	1	1982	1988	1.238	0.68	1.798	<0.001
Localized	*2*	*2*	*1988*	*2010*	*0.235*	*0.195*	*0.275*	*<0.001*
Regional	3	0	1975	1989	1.137	0.964	1.31	<0.001
Regional	3	1	1989	1995	0.468	-0.214	1.153	0.17
Regional	3	2	1995	2000	1.701	0.784	2.626	0.001
Regional	*3*	*3*	*2000*	*2010*	*0.418*	*0.232*	*0.605*	*<0.001*
Distant	1	0	1975	1978	-8.622	-21.574	6.468	0.238
Distant	*1*	*1*	*1978*	*2010*	*2.249*	*1.935*	*2.563*	*<0.001*
Unstaged/unknown	0	0	1975	2010	0.037	-0.194	0.268	0.749
Race/Ethnicity[c]								
Hispanic	*0*	*0*	*1975*	*2010*	*0.433*	*0.287*	*0.579*	*<0.001*
NH-White	3	0	1975	1982	0.308	-0.097	0.714	0.13
NH-White	3	1	1982	1988	1.973	1.453	2.495	<0.001
NH-White	3	2	1988	2002	0.554	0.458	0.65	<0.001
NH-White	*3*	*3*	*2002*	*2010*	*0.191*	*0*	*0.382*	*0.049*
NH-Black	0	0	1975	2010	0.953	0.831	1.076	<0.001
NH-API	1	0	1975	1997	0.89	0.616	1.166	<0.001
NH-API	*1*	*1*	*1997*	*2010*	*0.132*	*-0.099*	*0.363*	*0.253*
[OTHER]	*0*	*0*	*1975*	*2010*	*0.851*	*0.563*	*1.139*	*<0.001*
Census Region								
West	3	0	1975	1984	0.302	-0.052	0.658	0.092
West	3	1	1984	1987	3.021	-0.07	6.208	0.055
West	3	2	1987	2000	0.567	0.436	0.698	<0.001
West	*3*	*3*	*2000*	*2010*	*0.191*	*0.043*	*0.339*	*0.014*
Northeast	2	0	1975	1981	0.252	-0.711	1.225	0.597
Northeast	2	1	1981	1988	1.921	1.156	2.692	<0.001
Northeast	*2*	*2*	*1988*	*2010*	*0.535*	*0.455*	*0.614*	*<0.001*
Midwest	3	0	1975	1983	0.457	0.02	0.897	0.041
Midwest	3	1	1983	1987	2.405	0.783	4.052	0.005
Midwest	3	2	1987	2000	0.68	0.53	0.83	<0.001
Midwest	*3*	*3*	*2000*	*2010*	*0.235*	*0.048*	*0.422*	*0.016*
South	1	0	1975	1998	0.924	0.712	1.136	<0.001
South	*1*	*1*	*1998*	*2010*	*0.041*	*-0.307*	*0.391*	*0.81*

Rural-urban continuum (1993 version)								
Metropolitan Counties	3	0	1975	1983	0.286	-0.047	0.62	0.089
Metropolitan Counties	3	1	1983	1987	2.502	1.277	3.741	<0.001
Metropolitan Counties	3	2	1987	2000	0.642	0.528	0.756	<0.001
Metropolitan Counties	*3*	*3*	*2000*	*2010*	*0.299*	*0.17*	*0.429*	*<0.001*
Nonmetropolitan Counties	1	0	1975	1997	0.993	0.844	1.142	<0.001
Nonmetropolitan Counties	*1*	*1*	*1997*	*2010*	*0.151*	*-0.064*	*0.366*	*0.162*
Unknown/missing/no match[d]	*0*	*0*	*1975*	*1999*	*0.718*	*0.491*	*0.945*	*<0.001*

Note: Data from the 9 registries of the Surveillance, Epidemiology, and End Results (SEER)-9; the last segments are highlighted in Italics. APC, Annual percentage changes; UCI, upper confidence interval; LCI, lower confidence interval; OS, age-standardized overall survival; CI, confidence intervals; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IDLC, invasive ductal and lobular carcinoma; NDLC, non-ductal non-lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; NH, non-Hispanic; API, Asian Pacific Islanders. The last trend-segment is highlighted in Italics. *Several factors shown in **Table 1** were only available for later years in SEER-9, including tumor stage (the 6th American Joint Commission on Cancer staging manual, 1988+, see **Figure 2**), status of hormone receptors (1990+, see **Figure 2**) and insurance status (2007+). [a]*P* values for linearity of overall trends among segments. [b]Observed 5-year overall survivals shown in the age subgroups because age-standardization was not possible in age subgroups. [c]The observed 5-year overall survival in 1978 of the Other group was used in place of age-standardized 5-year survival which was not possible to compute due to lack of data in some age subgroups. [d]The age-standardized 5-year overall survivals in 2000-2010 were not possible to compute due to the lack of data in some age groups. Hence, only the data of 1975-1999 were used for calculating AAPC.

Table S3. Piecewise linear regression model for the trends in age-standardized 5-year overall survivals of women with invasive breast cancer diagnosed during 1975-2010, with linkage to death registry through 2015

Segment number	Starting year	Ending year	APC (95% CI)	*P*
1	1975	1983	0.29 (0.05 to 0.53)	0.019
2	1983	1988	2.18 (1.68 to 2.67)	<0.001
3	1988	2000	0.59 (0.47 to 0.71)	<0.001
4	2000	2010	0.27 (0.10 to 0.44)	0.003

APC, Annual percentage changes; UCI, upper confidence interval.