**Original Investigation**

**Disparities by Race, Age, and Sex in the Improvement of Survival for Major Cancers**

Results From the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program in the United States, 1990 to 2010

Chenjie Zeng, MPH; Wanqing Wen, MD, MPH; Alicia K. Morgans, MD; William Pao, MD; Xiao-Ou Shu, MD, PhD; Wei Zheng, MD, PhD

**IMPORTANCE** Substantial progress has been made in cancer diagnosis and treatment, resulting in a steady improvement in cancer survival. The degree of improvement by age, race, and sex remains unclear.

**OBJECTIVE** To quantify the degree of survival improvement over time by age, race, and sex in the United States.

**DESIGN, SETTING, AND PARTICIPANTS** Longitudinal analyses of cancer follow-up data from 1990 to 2010, from 1.02 million patients who had been diagnosed as having cancer of the colon or rectum, breast, prostate, lung, liver, pancreas, or ovary from 1990 to 2009 and who were included in 1 of 9 population-based registries of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program.

**MAIN OUTCOMES AND MEASURES** Hazard ratios (HRs) and 95% CIs for cancer-specific death were estimated for patients diagnosed as having any of these cancers during 1995 to 1999, 2000 to 2004, and 2005 to 2009, compared with those diagnosed in 1990 to 1994.

**RESULTS** Significant improvements in survival were found for cancers of the colon or rectum, breast, prostate, lung, and liver. Improvements were more pronounced for younger patients. For patients aged 50 to 64 years and diagnosed from 2005 to 2009, adjusted HRs (95% CIs) were 0.57 (95% CI, 0.55-0.60), 0.48 (95% CI, 0.45-0.51), 0.61 (95% CI, 0.57-0.69), and 0.32 (95% CI, 0.30-0.36), for cancer of the colon or rectum, breast, liver, and prostate, respectively, compared with the same age groups of patients diagnosed during 1990 to 1994. However, the corresponding HRs (95% CIs) for elderly patients (those 75-85 years old) were only 0.88 (95% CI, 0.84-0.92), 0.88 (95% CI, 0.82-0.95), 0.76 (95% CI, 0.69-0.84), and 0.65 (95% CI, 0.61-0.70), for the same 4 cancer sites, respectively. A similar, although weaker, age-related period effect was observed for lung and pancreatic cancers. The adjusted HRs (95% CIs) for lung cancer were 0.75 (95% CI, 0.73-0.77) and 0.84 (95% CI, 0.81-0.86), respectively, for patients aged 50 to 64 years and 75 to 85 years diagnosed between 2005 and 2009, compared with the same age groups of patients diagnosed between 1990 and 1994 (0.73 [95% CI, 0.69-0.77] and 0.90 [95% CI, 0.85-0.95], respectively. Compared with whites or Asians, African Americans experienced greater improvement in prostate cancer survival. From 1990 to 2009, ovarian cancer survival declined among African Americans but improved among whites. No apparent sex difference in the degree of improvement for any non–sex-specific cancer was noted.

**CONCLUSIONS AND RELEVANCE** Younger patients experienced greater benefit from recent oncology advances than elderly patients. African Americans experienced poorer survival than whites for all cancers, and the racial difference decreased for prostate cancer but increased for ovarian cancer. Identifying factors associated with varied improvement in cancer survival can inform future improvements in cancer care for all.


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Cancer is a leading cause of death in the United States and many other countries.\textsuperscript{1,2} Substantial progress has been made in cancer diagnosis and treatment during the past few decades, with significant advances in surgery, radiotherapy, chemotherapy, and targeted therapies.\textsuperscript{3–5} These improvements in cancer treatments, along with advances in cancer screening and diagnosis, have led to steady improvements in survival of several common cancers over the past few decades.\textsuperscript{1}

The impact of advances in oncology may differ by race, sex, or age.\textsuperscript{6–8} It has been reported that African Americans, women, and elderly individuals may benefit less than their white, male, younger counterparts from recent therapeutic advances.\textsuperscript{6–8} In addition, the survival gap is widening for several common cancers, including breast and colorectal cancer, by race and age,\textsuperscript{9,10} and narrowing for some cancers, such as colorectal cancer, by sex.\textsuperscript{12,13} It has been suggested that patients who are African American, female, or elderly are less likely to receive novel therapies owing to their underrepresentation in clinical trials, causing clinicians uncertainty about the relative efficacy or toxicity of newer therapies in these populations.\textsuperscript{4,14–17} Patient preferences also may lead to avoidance of newer therapies they believe to be more aggressive or toxic.

Many studies have evaluated differences in cancer mortality by race, sex, and age.\textsuperscript{10,18–23} Because mortality is affected by both incidence and case fatality, it is not a direct measure of survival. Several cross-sectional studies have compared cancer survival rates by race, sex, and age.\textsuperscript{10,23} However, these studies did not address the secular trend of cancer survival, which measures the improvement of cancer survival (or the benefit from recent advances in oncology) over time. In this study, we sought to quantify the differences in the improvement of cancer survival by race, age, and sex in the past 2 decades. We evaluated data from 9 registries participating in the Surveillance, Epidemiology, and End Results (SEER) program (hereinafter, SEER 9) to determine whether improvements in cancer survival differ by race, sex, and age in the United States. For this analysis we selected 7 cancer sites, which are estimated to account for approximately 60% of US cancer deaths in 2014: colon or rectum, female breast, prostate, liver or intrahepatic bile duct, lung, pancreas, and ovary. Advances in cancer treatment differ among these cancer types. We assessed a spectrum of cancers to compare varying degrees of treatment improvement and to explore reasons for differences in survival over time across different cancer patient populations.

### Methods

The current study was conducted in compliance with the National Cancer Institute SEER limited-use data end user agreement. It was determined to be exempt from the institutional review board oversight at Vanderbilt University because the data used in this analysis had been deidentified. We analyzed data from 9 population-based cancer registries included in the SEER program of the National Cancer Institute: Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco-Oakland, California; Seattle–Puget Sound, Washington; and Utah.\textsuperscript{24} We selected patients with a single primary diagnosis (sequence number = 00) of cancer of the colon or rectum (\textit{International Classification of Diseases for Oncology}, 3rd edition\textsuperscript{25} site codes: C180 to C189; C199, C209), female breast (C500 to C509), liver or intrahepatic bile duct (C220 to C221), lung (C240 to 349), pancreas (C250 to C259), prostate (C619), or ovary (C569) from 1990 through 2009. Individuals were 20 to 85 years old at the time of diagnosis, and were followed through 2010. We excluded patients whose death was reported by autopsy only or death certification only (<1% of total patients for each cancer). Demographic variables (age at diagnosis, year of diagnosis, race, sex, and marital status) and tumor characteristics (stage and histologic types) were obtained from the registry databases. SEER collected race information from medical records, face sheet, and physician and nurse notes, and recoded the information into the following categories: white, black, American Indian/Alaskan Native, Asian/Pacific Islander, and unknown in the SEER 9 datasets.\textsuperscript{24} Owing to a small sample size of patients of American Indian/Alaskan Native origins,\textsuperscript{24} we did not analyze data specifically for this group of patients. SEER does not collect information on Hispanic ethnicity directly. SEER codes the Hispanic origin variable based on NAACCR (North American Association of Central Cancer Registries) Hispanic Identification Algorithm (NHIA), which searches the surname as well as maiden-name to determine the Hispanic ethnicity. Some data on the Hispanic origin at one of the SEER 9 registries (Connecticut) are considered unreliable and, thus, are often excluded from race/ethnicity-specific analyses.\textsuperscript{1,26} Therefore, we decided not to analyze data specifically for Hispanic ethnicity.

The primary outcome in this study was a measure of cancer-specific death, defined as a death with the specific cancer of interest listed as the primary cause of death in the SEER 9 registries.\textsuperscript{27} Patients still alive on December 31, 2010, or who had died of other causes were censored. Survival rates (at 1, 3, and 5 years) by cancer-specific death by age, sex, or race for patients diagnosed between 1990 and 1994 (the baseline period) were calculated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% CIs for cancer-specific death associated with age, sex, or race were calculated using Cox proportional hazards models, for patients diagnosed during the time.
Results

Analyses included 1,020,382 patients who were diagnosed as having cancers of the colon or rectum, breast, liver or intrahepatic bile duct, lung or bronchus, pancreas, prostate, or ovary from 1990 through 2009 (eTable 1 in the Supplement). During this period, the percentage of cancer cases diagnosed at a localized stage increased for all cancer sites except ovarian cancer (eTables 2-8 in the Supplement). For ovarian cancer, 27.7% of cases were diagnosed at a localized stage from 1990 through 1994; by the period 2005 through 2009, only 19.3% of cases were diagnosed at the localized stage (eTable 8 in the Supplement).

The distribution of other patient characteristics also changed over the 20-year study period (eTables 2-8 in the Supplement). In general, the percentage of white patients decreased and the percentage of African American patients increased for all cancer sites. The percentage of Asian patients also increased for all but liver cancer. The percentage of male patients increased for all non-sex-specific cancers except for lung cancer. For patients diagnosed from 1990 to 1994, survival rates for African Americans were the lowest for all cancers except for ovarian and pancreatic cancers (Table). For all cancer sites, survival rates were lowest in the oldest age group (75-85 years) and were lower among men than among women (Table).

With the exception of ovarian cancer among African American women, significant improvements in survival, shown by decreasing HRs over time, were observed for 6 other cancers from 1990 to 2009 in all 3 racial groups (Figure 1, eTable 9 in the Supplement). The largest improvement in survival was observed for prostate cancer patients, followed by those with breast, liver, colorectal, pancreatic, and lung cancers. However, white, African American, and Asian cancer patients experienced different degrees of improvement in survival from 1990 to 2009 for ovarian and prostate cancers. During the 20-year study period, there was a statistically significant decrease in ovarian cancer survival among African Americans, no improvement in survival in Asians, and a slight but significant improvement in survival among whites (P for interaction: 1.41×10^{-5}). Over the study period, African Americans experienced a greater improvement in survival of prostate cancer than whites or Asians (HR for 5-year increment of year of diagnosis: African Americans, 0.66 [95% CI, 0.64-0.68]; whites, 0.72 [95% CI, 0.71-0.73]; and Asians, 0.73 [95% CI, 0.69-0.77]).

No apparent racial differences in survival improvements were seen for the other cancers evaluated in this study.

From 1990 to 2009, all age groups demonstrated improved survival for all cancer sites with the exception of ovarian cancer (Figure 2, eTable 10 in the Supplement). Improvement in survival were greater for younger age groups, and tests for interaction were statistically significant for 5 of the 7 cancer sites (P < .001 for all interactions). For example, compared with those diagnosed from 1990 to 1994, the improvement in survival for colorectal cancer among patients younger than 75 years began among patients diagnosed from 1995 to 1999, whereas among patients 75 years or older, the improvement occurred later and was only evident in the cohort with cancer diagnoses after 2000. In addition, the degree of improvement in survival was greater among the younger age groups, with approximately a 45% reduction in colorectal cancer-specific deaths among patients younger than 65 years, compared with only a 12% reduction among those aged 75 to 85 years. A similar pattern of association was observed for breast, liver, lung, pancreatic, and prostate cancers. For ovarian cancer, a slight improvement in survival was observed only in the 50- to 64-year-old and 65- to 74-year-old age groups. However, the interaction between age and year of diagnosis was not statistically significant (P = .10).

There was a statistically significant improvement in cancer-specific survival for both men and women for all cancers studied (P < .001 for trend for all comparisons) (eTable 11 in the Supplement), and no statistically significant interactions between sex and year of diagnosis were found for any cancer.

Stratified analyses by cancer stage were performed to evaluate the possible influence of cancer stage at the time of diagnosis in the results related to age disparity for cancer survival (Figure 3, eTable 12 in the Supplement). Greater improvements in survival over time were observed for younger age groups for all stages of colorectal, breast, and lung cancers. For
breast and colorectal cancer, it seems that the age-related difference in survival improvement was somewhat more evident for localized and regional disease than for distant disease, although the test for heterogeneity across cancer stages was statistically significant for breast cancer only ($P = .02$). For lung cancer, the age-related difference in survival improvement was seen primarily for localized and regional disease ($P = .01$ for heterogeneity across cancer stages) (eTable 12 in the Supplement). For liver cancer, the difference for a greater survival improvement in the younger age group compared with the older age group over the study period was statistically significant only for localized stage cancer; and for pancreatic cancer, only for distant stage cancer; however, heterogeneity tests across cancer stages were not statistically significant were not statistically significant ($P = .16$ and $P = .23$ for pancreatic and liver cancer, respectively). For ovarian cancer, no significant improvement in survival over the study period was found, regardless of stage or age group. Similar stratified analyses evaluated possible influence of cancer stage at the time of diagnosis in the results related to sex and race disparity for cancer survival, and no statistically significant modifying effect by stages was observed (eTables 13 and 14 in the Supplement). Stratified analyses by SEER registry sites were performed to evaluate possible influence of geographic locations on our study results. Little evidence was identified for a possible modifying effect of geographic locations on the results found related to age at cancer diagnosis, race, or sex (eTable 15 in the Supplement).

**Discussion**

Using data from the SEER, we have showed a slower improvement in cancer survival over the past 20 years in the United States among older cancer patients, resulting in a widening gap in cancer survival for 6 of the 7 cancers evaluated in our study. We observed that the age-related gap was most pronounced for cancers with the largest diagnosis and treatment advances during the study period, including colorectal, breast, and prostate cancers. Furthermore, in the
stage-specific analyses of colorectal and breast cancer, there was a suggestion of greater differences in survival over time between younger and older age groups for localized and regional cancers than for advanced cancer. This is consistent with clinical trial data demonstrating improved survival with improved surgical techniques and novel adjuvant treatment for patients with localized and locally advanced colorectal and breast cancer. Among patients with liver, lung, pancreatic, or ovarian cancer, for which treatment improvements have been modest, the gap in improved survival between younger and older patients was also less evident. We observed an improvement in survival for liver can-

The HRs and 95% CIs were adjusted for marital status, common histologic types, SEER registry sites, SEER historic stage, age, and sex (if applicable), using the time period 1990-1994 as the reference. P values for interaction for year of diagnosis and race are presented. SEER indicates Surveillance, Epidemiology, and End Results.
According to Age at Diagnosis, in 9 SEER Registries, 1990-2009

<table>
<thead>
<tr>
<th>Age groups, y</th>
<th>HR (95% CI)</th>
<th>Age groups, y</th>
<th>HR (95% CI)</th>
<th>Age groups, y</th>
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<tr>
<td>20-49</td>
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<tr>
<td>1995-1999</td>
<td>0.84 (0.79-0.90)</td>
<td>1995-1999</td>
<td>0.82 (0.79-0.86)</td>
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<td>0.85 (0.80-0.90)</td>
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<td>2000-2004</td>
<td>0.70 (0.66-0.76)</td>
<td>2000-2004</td>
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<td>2005-2009</td>
<td>0.55 (0.51-0.60)</td>
<td>2005-2009</td>
<td>0.43 (0.40-0.46)</td>
<td>2005-2009</td>
<td>0.43 (0.40-0.46)</td>
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</table>

| 50-64        |             |              |             |              |             |
| 1995-1999    | 0.86 (0.83-0.90) | 1995-1999    | 0.75 (0.72-0.79) | 1995-1999    | 0.75 (0.72-0.79) |
| 2000-2004    | 0.72 (0.69-0.75) | 2000-2004    | 0.57 (0.54-0.59) | 2000-2004    | 0.57 (0.54-0.59) |
| 2005-2009    | 0.57 (0.53-0.61) | 2005-2009    | 0.48 (0.45-0.51) | 2005-2009    | 0.48 (0.45-0.51) |

| 65-74        |             |              |             |              |             |
| 1995-1999    | 0.95 (0.92-0.99) | 1995-1999    | 0.87 (0.83-0.92) | 1995-1999    | 0.87 (0.83-0.92) |
| 2000-2004    | 0.92 (0.89-0.96) | 2000-2004    | 0.69 (0.65-0.73) | 2000-2004    | 0.69 (0.65-0.73) |
| 2005-2009    | 0.92 (0.90-0.96) | 2005-2009    | 0.62 (0.58-0.68) | 2005-2009    | 0.62 (0.58-0.68) |

| 75-85        |             |              |             |              |             |
| 1995-1999    | 0.96 (0.91-1.02) | 1995-1999    | 0.96 (0.91-1.02) | 1995-1999    | 0.96 (0.91-1.02) |
| 2000-2004    | 0.91 (0.86-0.97) | 2000-2004    | 0.84 (0.79-0.89) | 2000-2004    | 0.84 (0.79-0.89) |
| 2005-2009    | 0.88 (0.83-0.95) | 2005-2009    | 0.73 (0.69-0.77) | 2005-2009    | 0.73 (0.69-0.77) |

| 80-89        |             |              |             |              |             |
| 1995-1999    | 0.94 (0.90-0.98) | 1995-1999    | 0.92 (0.89-0.98) | 1995-1999    | 0.92 (0.89-0.98) |
| 2000-2004    | 0.92 (0.88-0.96) | 2000-2004    | 0.89 (0.85-0.92) | 2000-2004    | 0.89 (0.85-0.92) |
| 2005-2009    | 0.88 (0.83-0.92) | 2005-2009    | 0.80 (0.76-0.84) | 2005-2009    | 0.80 (0.76-0.84) |

| 90+          |             |              |             |              |             |
| 1990-1994    | 0.84 (0.80-0.88) | 1990-1994    | 0.79 (0.74-0.85) | 1990-1994    | 0.79 (0.74-0.85) |
| 1995-1999    | 0.76 (0.71-0.81) | 1995-1999    | 0.72 (0.67-0.78) | 1995-1999    | 0.72 (0.67-0.78) |
| 2000-2004    | 0.70 (0.65-0.76) | 2000-2004    | 0.64 (0.60-0.70) | 2000-2004    | 0.64 (0.60-0.70) |
| 2005-2009    | 0.65 (0.60-0.71) | 2005-2009    | 0.59 (0.54-0.65) | 2005-2009    | 0.59 (0.54-0.65) |

The HRs and 95% CIs were adjusted for marital status, common histologic types, SEER registry sites, SEER historic stage, race, and sex (if applicable), using the time period 1990 to 1994 as the reference. P values for interaction for year of diagnosis and age groups are presented. SEER indicates Surveillance, Epidemiology, and End Results.

The widening gap in cancer survival between younger and older patients may be due to differential utilization of newer treatments for elderly patients.
There is ample evidence that elderly patients are less likely to receive potentially morbid treatments like surgery or chemotherapy regardless of disease stage. Older age has been associated with higher rates of toxic effects from treatment for both chemotherapy and radiotherapy. Functional impairment, malnutrition, and comorbidity among older patients may induce treating physicians to choose less aggressive therapy or abbreviated treatment courses in an effort to “do no harm” to a more frail patient population. In addition, because elderly patients have been underrepresented in clinical trials, there is insufficient evidence to determine how they will respond to novel targeted therapies or combinations of chemotherapeutic agents. There is concern that treatments that may be effective in younger patients in clinical trials may be more toxic and less effective in the elderly. Our findings demonstrate that age-associated disparities exist and underscore the importance of conducting clinical trials and postmarketing studies to identify optimal treatment regimens, necessary dose adjustments, and distinct toxic effects for elderly patients with cancer. This is particularly pressing because this population constitutes the fastest growing subpopulation of cancer patients in the United States.

We observed a widening gap in survival by race only in ovarian cancer. In several studies, racial disparities in ovarian cancer survival have been linked to stage at diagnosis and quality of care (adherence to National Comprehensive Cancer Network and other guidelines). Notably, we found that African American prostate cancer patients had larger improvements in survival over time than did whites. This result is supported by previous studies, which have shown narrower differences in prostate cancer mortality between African Americans and whites since the 1990s. One explanation for the greater improvement in prostate cancer survival among African Americans may be the targeted prostate cancer educational campaigns aimed at increasing prostate cancer awareness in the African American community during the past decade.}

<table>
<thead>
<tr>
<th>Stage and age group, y</th>
<th>HR (95% CI)</th>
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**Colon or rectum (P = .06)**

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<tr>
<td>50-64</td>
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<td>65-74</td>
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<td>75-85</td>
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**Breast (women only) (P = .02)**

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<tr>
<td>75-85</td>
<td>0.92</td>
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**Liver (P = .23)**

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<td>65-74</td>
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<tr>
<td>75-85</td>
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**Lung (P = .01)**

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<td>75-85</td>
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**Pancreas (P = .16)**

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<td>65-74</td>
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<td>75-85</td>
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**Ovary (P = .77)**

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<td>0.92</td>
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<tr>
<td>50-64</td>
<td>1.10</td>
<td>0.95</td>
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<td>65-74</td>
<td>1.05</td>
<td>0.87</td>
</tr>
<tr>
<td>75-85</td>
<td>1.11</td>
<td>0.91</td>
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HRs and 95% CIs were adjusted for marital status, common histologic types, SEER registry sites, race, and sex (if applicable), using the time period 1990-1994 as the reference. P values for heterogeneity across cancer stages are presented. SEER indicates Surveillance, Epidemiology, and End Results.
time were similar between men and women for all non–sex-specific cancers evaluated in this study except for localized liver cancer, for which women had smaller improvements than men. Previous studies have shown that women are equally likely to receive surgical interventions for localized liver cancers. However, it has been reported that women may be less likely to benefit from localized tumor destruction than are men. The underlying mechanisms driving this sex disparity remain to be investigated.

When considering the underlying reasons for the age- and race-related disparities reported in our study, it is important to discern whether improvements in screening may explain the change over time. We did not have data from the SEER registries for the evaluation of the impact of cancer screening and diagnosis on our results. In particular, lead-time bias could be a potential concern for this study, particularly where there are differences in the secular trend of cancer screening and early diagnosis among the comparison groups analyzed in this study. However, to our knowledge, no data are available to indicate that these differences exist. Our analyses by stages showed that the age-related disparities in degree of survival improvements over the past 20 years were present for virtually all stages, including late-stage cancer, suggesting that these disparities cannot be entirely explained by cancer screening practices during the study period, particularly since the late-stage diseases were less likely to be affected by screening. Although our data argue against changes in cancer screening and diagnosis patterns driving the age-related differences in cancer survival improvements, we could not exclude entirely the possibility for some influence of difference in screenings and diagnosis by age on our study findings.

The SEER 9 registries cover approximately 10% of the US population, and the population covered by the SEER program is, in general, similar to the general US population in terms of education and socioeconomic levels. However, SEER oversamples urban and foreign-born populations, which may affect the generalizability of our findings to the general US population. Other limitations include those inherent in retrospective database analyses. Data on individual socioeconomic status, lifestyle factors, and comorbidities were not available, and thus these variables cannot be adjusted in our study. Therefore, potential confounding effects by these variables on our results cannot be excluded.

Conclusions

Our data suggest that age- and race-related differences in survival improvements over time may be explained, at least in part, by differences in cancer care across these subpopulations. By demonstrating these disparities, we have taken an initial step toward acknowledging the possibility of differential care and/or responses to new therapies for different patients. We hypothesize that some differences in care, particularly those suggesting less improvement in survival among elderly and African American patients, may be related to the lack of evidence specific to these populations. Our findings are a call to action; future studies should strive to include diverse populations, particularly the elderly and African Americans, in order to establish an evidence base for treatment of all patients. Understanding differences in the rates of improvement in survival among these specific populations and addressing these differences in future studies is a crucial part of improving cancer care for all.

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human papillomavirus (HPV)-associated cancers and
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