Lack of Reduction in Racial Disparities in Cancer-Specific Mortality Over a Twenty-Year Period

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Abstract:

Background: It remains unknown how race-based differences in cancer outcomes have changed with time. We sought to explore racial disparities in cancer-specific mortality.

Methods: Using the Surveillance, Epidemiology and End Results Program, we identified 2,713,474 patients diagnosed in 1988-2007 with lung, breast, prostate, or colorectal cancer. The impact of race on cancer-specific mortality was assessed using Fine and Gray’s regression; an interaction model evaluated trends over time.

Results: African Americans presented with more advanced stage (p<0.001) and underwent definitive therapy less often (p<0.001) than whites. After adjustment for demographics and diagnosis-year, African Americans had higher estimates of cancer-specific mortality than whites for all cancers combined (HR 1.27, 95% CI 1.25-1.29, p<.001) and within each individual cancer (each p<0.05). These differences did not change significantly between 1988-1997 and 1998-2007, except in breast cancer, wherein survival disparities increased. These findings remained significant after adjustment for stage at presentation and receipt of definitive therapy (HR for breast-mortality in African Americans versus whites: 1.37 from 1988-1997 and 1.53 from 1998-2007, p-interaction <0.001).

Conclusions: The survival gap for African Americans has not closed over time and persists independent of stage and treatment, suggesting that additional strategies beyond screening and improving access to care are needed.
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Glossary of Abbreviations:

AJCC – American Joint Committee on Cancer

EGFR – Epidermal growth factor receptor

ER – Estrogen receptor

ERG – Erythroblast transformation-specific (ETS)-related gene

HER2 – Human epidermal growth factor receptor 2

MBL – Mannose-binding lectin

NSCLC – Non-small cell lung cancer

PR – Progesterone receptor

SEER – Surveillance, Epidemiology, and End Results database

SOS1 – Son of sevenless homolog 1
Introduction:

As of 2010, 72% of the approximately 300 million residents of the United States identify their race exclusively as white.\(^1\) Although white patients compose the largest demographic that American doctors are likely to encounter, this category is also the slowest growing, indicating that the patient population of the United States is becoming increasingly diverse.\(^1\) In particular, Hispanic individuals accounted for more than half of the total growth in the United States from 2000 to 2010 and now comprise 16% of the total population. African American and Asian Americans within the United States have also shown growth and currently represent 13% and 5% of the total population, respectively.\(^1\)

Given the trend of increasing racial diversity in the United States, physicians ought to be increasingly more aware of health-based outcomes as they relate to race, as this may help physicians provide better clinical care. While race as a concept is an imperfect proxy for all of the features that make patients unique, it is useful in the sense that it may correlate not only with genetic inheritance but also with culture, albeit to varying, often unquantifiable degrees. One aspect of culture important to clinical medicine is that it often shapes patient values and preferences. Within oncology, specifically, these values and preferences are commonly taken into consideration when selecting from a range of possible treatments. For example, certain patients may be eager to undergo bilateral mastectomies for unilateral breast cancer, even if doing so results in significant morbidity without increasing odds of survival.

Alternatively, it is easy to envision a scenario in which a patient’s cultural background might serve as a barrier to receiving adequate cancer treatment. For example, if it were taboo within a patient’s culture to discuss a cancer diagnosis with his relatives, likely he would not
benefit from the same level of social support as a patient whose family accompanies him through treatment. Similarly, there are larger, societal issues that may also trend with race, such as access to care, which may also negatively influence clinical outcomes. Last, there exists the possibility that biologic differences between patients that trend with race are associated with oncologic phenotypes that exhibit varying levels of aggressiveness. Therefore, in order to understand which patients are more or less likely to experience favorable cancer-specific outcomes, it is imperative that oncologists are aware of race-based differences as they relate to cancer-specific outcomes.

Prior studies evaluating the impact of race on cancer-related mortality have been undertaken. For example, Ooi et al. published a retrospective study of disparities in breast cancer characteristics and outcomes by race and found that American Indian/Alaska Native, Asian Indian/Pakistani, African American, Filipino, Hawaiian, Mexican, Puerto Rican, and Samoan women were statistically more likely to present with metastatic disease as compared with white women. Similarly, all of these groups were also more likely than white patients to be diagnosed with hormone receptor negative (ER-/PR-) disease, with African American and Puerto Rican women showing the highest risk (2.4 and 1.9-fold increases, respectively), which implies that they are disproportionately afflicted with a more aggressive disease phenotype.

Robbins et al. showed similar results after completing a retrospective study of colorectal cancer patients treated from 1985 to 2008. They concluded that while overall, colorectal cancer mortality rates decreased for both African American patients and white patients, the magnitude of decrease was smaller for African American patients. Furthermore, this gap was observed for each stage, with the greatest difference accounted for by stage IV disease. Hence, Robbins concluded that the overall difference in mortality between African American patients and white patients was likely driven primarily by the disproportionate number of African American patients
whose disease had progressed to stage IV. However, this probable increased propensity for progression to stage IV disease observed in African Americans could have potentially been attributable to numerous causes.

Beyond colorectal and breast cancers, Pulte et al. aimed to determine whether racial disparities in cancer survival also apply to other disease sites and whether those disparities have changed over time. They completed a retrospective review of patients treated from 1992 to 1996 and compared those results with patients treated from 2002 to 2006. In doing so, they showed that survival disparities have decreased between white patients and those of other races in breast cancer, prostate cancer and non-Hodgkin’s lymphoma; however, there was no disparity reduction in the other cancers analyzed (e.g., lung and pancreatic).

As an aside, it may be illogical for the authors of this study to have used the word ‘disparity’ to describe the relative differences in survival that were observed. The very word ‘disparity’ implies that survival in this case would be expected to be equivalent across races, at least in a normative sense. This would imply that sociological factors, as opposed to underlying biology, are the primary drivers of the relative differences in survival observed between races. However, as alluded to above, this conclusion may be premature, especially in light of the fact that race tends to trend with disease phenotype, at least to some degree, in a way that is likely analogous to the way in which race trends with numerous other genetically inherited traits.

In spite of the aforementioned studies, there still exists a paucity of data on race-based differences as they relate specifically to mortality due to cancer. Few prior studies addressing this issue have combined the most relevant cancers into the same analysis and looked at mortality trends over time. Even fewer studies have constructed a multivariable model to assess for confounding. Furthermore, no study to date has incorporated all of these features and
reported cancer-specific mortality using a statistical model that includes a competing risks analysis.\(^5\)

The relevance of the final point is that when a retrospective study aims to analyze trends related to overall survival, this analysis captures patients who died of alternative causes in addition to the primary cause of interest. In actuality, these alternative causes of death serve as competing risks for mortality with the primary cause of interest. In the present analysis, for example, congestive heart failure and other causes of death unrelated to cancer, if not properly accounted for, would likely cause us to falsely overestimate mortality in the study population. Competing risks confound the results of any analysis of cancer-specific mortality if not properly taken into consideration, thereby limiting the generalizability of the conclusions.

Otherwise stated, analyses that report overall survival are less sensitive for detecting differences related specifically to mortality due to cancer, and as such, conclusions drawn from these studies are less informative for guiding assumptions about to cancer-specific issues such as levels of access to oncologic care and disproportionate affliction with more aggressive cancer phenotypes. To address this issue of competing risks, which is inherent to many types of clinical research, Fine and Gray created a proportional hazards model that enables the sub-distribution of competing risks, which thereby enables investigators to accurately report disease-specific mortality.\(^5\) This statistical model has particular utility in clinical oncology research, as cancer patients are often of advanced age and have numerous comorbidities; therefore, they are likely to harbor multiple competing risks for mortality.

In order to promote and facilitate clinical oncology research, the National Cancer Institute maintains a nationwide registry of cancer statistics. This registry is called the Surveillance, Epidemiology, and End Results (SEER) database, and it currently contains
information on roughly 26% of the United States population.\textsuperscript{6} It maintains data from as far back as 1973 and includes patient demographic information as well as pathologic and clinical data (e.g., stage at presentation and age at diagnosis).\textsuperscript{6} The purpose of our study was to use the SEER database to study a large cohort of approximately one million patients, use Fine and Gray’s proportional hazards model to draw generalizable conclusions regarding cancer-specific mortality as it relates to race, compare trends in cancer-specific mortality by race across the types of cancer that are the leading causes of death of men and women, and determine whether any differences in cancer-specific mortality observed between races have decreased over time.
Methods

Patient Population and Study Design

We used the SEER database to identify 2,713,474 patients diagnosed between 1988 and 2007 with one of the 3 leading causes of cancer-related death among males and females in the United States (i.e., lung, breast, prostate, and colorectal cancer).\(^7\) Sponsored by the National Cancer Institute, the SEER program collects and publishes cancer incidence, treatment, and survival data from population-based cancer registries. The program captures approximately 97% of incident cancers. As a result, the tumor registries cover approximately 26% of the US population.\(^6\)

The year 1988 was selected as the first year of our study given that certain covariates included in our multivariable analysis were introduced in SEER in 1988 and also because the SEER program switched to the 3rd edition of the American Joint Committee on Cancer (AJCC) staging system in 1988.\(^8\) Patients were excluded if clinical information was incomplete, they were found to have metastatic disease at the time of diagnosis or were diagnosed at autopsy, were diagnosed with more than one type of malignancy, had in situ disease, or if the cause of death was unknown. After these exclusion criteria were applied, there were 1,001,978 patients who remained in the final cohort. All patients in the final cohort had non-metastatic cancer.
Statistical Analysis

Baseline patient characteristics were compared with an analysis of variance for continuous variables and the chi-square test for categorical variables. For each malignancy, cumulative incidence curves displaying cancer-specific mortality, as stratified by race, were generated and compared using the Gray test. After adjustment for demographic factors (age, sex, marital status, residence type [urban vs. rural], education, and income), the Fine and Gray competing risks regression model (proportional sub-distribution hazards model) was used to assess the adjusted impact of race on cancer-specific mortality. These analyses were repeated after additional adjustment for cancer stage and use of definitive surgical or radiotherapeutic management.

Race was classified as white, African American, Hispanic, or Asian American, as determined by SEER. Patients listed as Hispanic may have been from any race; SEER contains a separate variable for Hispanic versus not. Patients of other races were excluded given the small numbers. Residence type was determined at the county level by linkage to the 2003 US Department of Agriculture rural-urban continuum codes. Educational status (quantified as the percentage of residents aged ≥25 years with a high school education) and income (quantified as median household income) were also determined at the county level through linkage to the 2000 US Census.

Stage of disease was determined using the 3rd edition of the AJCC staging manual for cases diagnosed between 1988 and 2004 and the 6th edition of the AJCC staging manual for cases diagnosed between 2004 and 2007. Appropriate definitive therapy was defined as surgery and/or radiotherapy for patients with prostate and lung cancer and only surgery for those with
breast and colorectal cancer. Age, education status, and income were treated as continuous variables in our regression model. Residence type, sex, year of diagnosis, and marital status were binary variables, and race and stage were nonbinary, categorical variables. A sensitivity analysis evaluating the impact of socioeconomic status was also performed.

The median follow-up among surviving patients was 5.6 years (range, 0.1 years-21.9 years). All $P$ values reported were 2-sided. Statistical analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC). Competing risks regression (proportional sub-distribution hazards model) was performed using R statistical software (version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the Institutional Review Board at the study institution; a waiver for informed consent was obtained.
Results

Patient Characteristics

Baseline patient characteristics are shown in Table 1. Although significant differences were noted with regard to age, sex, marital status, income, education, residence, year of diagnosis, stage of disease, and receipt of definitive therapy among patients of different races ($P < .001$ for each variable), the magnitude of such differences was generally small. It is interesting to note that African American patients were more likely to present with more advanced disease and not receive definitive therapy compared with patients of other races ($P < .001$ in both cases).

Cancer-specific Mortality

Cumulative incidence curves demonstrating cancer-specific mortality in each malignancy evaluated, as stratified by race, are shown in Figure 1. Estimates of 5-year cancer-specific mortality by race are shown in Table 2. Generally, African American patients demonstrated the highest estimates of cancer-specific mortality, followed by Hispanic patients, white patients, and Asian American patients ($P$ for comparison of cumulative incidence curves was $< .001$ in all cases). After adjustment for socio-demographic factors and year of diagnosis, African American patients demonstrated significantly greater cancer-specific mortality than white patients for all cancers combined (hazards ratio [HR], 1.28; 95% confidence interval [95% CI], 1.26-1.30 [$P < .001$]) and within each individual cancer examined ($P < .05$ in all cases).
Figure 2 shows cancer-specific mortality by race after further controlling for stage of disease at diagnosis and whether definitive therapy was received. In doing so, it indicates that African American patients continued to have significantly worse survival than white patients after these adjustments in the pooled analysis (adjusted HR, 1.16; 95% CI, 1.14-1.18) and for each individual cancer ($P < .05$ in all cases). Conversely, Asian American patients were found to have lower estimates of cancer-specific mortality compared with white patients for each cancer evaluated ($P < .05$) and in the pooled cohort as well (adjusted HR for Asian Americans versus whites, 0.87; 95% CI, 0.85-0.89 [$P < .001$]). Hispanic patients with breast and colorectal cancer demonstrated slightly greater adjusted cancer-specific mortality than whites, although such differences were not noted among patients with prostate cancer, and Hispanic patients with lung cancer displayed lower estimates of adjusted cancer-specific mortality than their white counterparts.

When analyzed on a year-by-year basis, cancer-specific mortality in all races improved over time (relative to the reference year of 1988), but Asian Americans demonstrated the greatest magnitude of improvement (Figure 3). When analyzed by era of diagnosis, differences in cancer-specific mortality in African American patients, Hispanic patients, and Asian American patients (relative to the reference group of white patients) did not change significantly between 1988 through 1997 and 1998 through 2007 ($P$ for interaction $> .05$ for every cancer evaluated), except for African American patients with breast cancer, who displayed poorer cancer-specific mortality in the modern era compared with the decade prior (adjusted HR for cancer-specific mortality, 1.37 from 1988-1997 vs 1.53 from 1998-2007; $P$ for interaction, $< .001$) (Table 3).
Discussion, Limitations, Conclusions, and Suggestions for Future Work:

The results of our study indicate that there are significant differences in cancer-specific mortality between African American, Hispanic, white, and Asian American patients. This difference persists even after adjusting for socio-demographic factors, cancer stage, and treatment received. Among all races evaluated, African American patients displayed the highest rate of cancer-specific mortality for prostate, breast, lung, and colorectal cancer. Asian Americans, meanwhile, displayed the lowest cancer-specific mortality rate for each malignancy evaluated. Examined over time (1988 to 2007), these racial discrepancies do not appear to be diminishing, and in the case of African Americans with breast cancer, the survival gap compared to white patients may even be increasing.

Our results, while novel, are similar to what has been observed in previous studies. For example, in 2008, researchers at Yale reviewed SEER data on patients aged 66 to 85 who were diagnosed with prostate, breast, lung, and colorectal cancer from 1992 through 2002. Over that entire study period, African American patients were found to be significantly less likely than white patients to have received therapy in several clinical situations. Specifically, they were less likely to have undergone surgical resection of early stage lung cancer, radiation after breast cancer lumpectomy, adjuvant therapy for stage III colorectal cancer, and definitive therapy for early stage prostate cancer. Additionally, patients of all races showed little to no improvement in the proportion of patients receiving appropriate treatment for most cancers evaluated over the duration of the study period.

While our study is similar to the Yale study, it is novel in that it examines cancer-specific mortality in addition to receipt of treatment. Therefore, it enables us to make more informed
conclusions than those drawn from prior studies about how cancer care has changed over time for patients within different racial categories. Based on our analysis, it appears that a gap in cancer-specific mortality for African Americans compared with other races has persisted from 1988 to 2007 and is not shrinking even after accounting for differences in stage and treatment. Because efforts to date at reducing this disparity have been unsuccessful, additional strategies over and above traditional efforts aimed at promoting increased screening and improving access to care likely will be required to close this gap.

There are multiple potential explanations for the results that we observed, some of which are related to underlying biology while others are sociological. While the ontological notion of race as a discrete categorization is false, there are heritable traits that are shared unevenly across the racial categories we customarily define, explaining why the concept of race has biological import despite the fact that it is essentially based on subjective appraisal (i.e., a social construct). Relevant to our data, there is increasing evidence that meaningful genetic, molecular, and immunologic differences exist between tumors from African American, white, Hispanic, and Asian American patients. These differences might have important oncologic consequences that contribute to the racial discrepancies in mortality we observed.

To place into context our finding that African American men experience higher rates of cancer-specific mortality for prostate cancer, there are several prior studies focused on the underlying biology of prostate cancer worthy of mention. Rosen et al. compared prostatectomy specimens from African American and white patients matched for age, pathologic grade, and stage. The study authors set out to determine whether these tumors differed in ETS-related gene (ERG) alterations. These genetic alterations were selected as a study endpoint because oncogenic activation of the ERG is a common early change in prostate cancer tumors. That
study compared 91 patients from both racial backgrounds and found that almost twice as many African American patients as white patients had ERG-positive tumors (41.9% vs. 23.9%, P < .0001), which is hypothesized to negatively affect prognosis.\textsuperscript{13}

Similarly, Magi-Galluzzi et al. studied the prevalence of TMPRSS2-ERG gene fusion, a specific ERG alteration, across prostate cancer tumors from patients of different racial backgrounds.\textsuperscript{14} Their study included prostatectomy samples from white, African American, and Japanese patients. They demonstrated quantitative and qualitative differences in TMPRSS2-ERG gene fusion in tumors from African American patients as compared with those from white and Japanese patients.\textsuperscript{14} The consequences of this difference may include downstream differences in molecular pathways that contribute to tumor progression, which may in effect afflict African American men disproportionately with more aggressive disease.\textsuperscript{14}

Furthermore, a study by Castro et al. found that prostate tumors from African American men that are clinically localized are genomically analogous to tumors from white men that are metastatic.\textsuperscript{15} The initial aim of that study was to determine whether there are areas of allelic loss or gain in prostate cancer tumors from African American men that differ significantly from those of white patients.\textsuperscript{15} To do this, they analyzed 20 tumor samples from African American men with single-nucleotide polymorphism arrays and identified 17 regions of interest showing significant loss and 4 showing significant gains. These regions of interest corresponded with results from prior genomic studies, and, surprisingly, when compared, the genomic profile of localized tumors from African American men most closely resembled metastatic tumors from white men.\textsuperscript{15}

It has also been observed that in primary prostate cancer epithelial cells, those from African American patients were more likely to overexpress son of sevenless homolog 1 (SOS1) gene.\textsuperscript{16} SOS1 was shown to correspond with a prostate cancer cell’s ability to proliferate,
migrate, and invade the basement membrane. It also correlated with Gleason score. Therefore, overexpression of SOS1 may also contribute to the disproportionately poorer cancer-specific survival of African American men with prostate cancer.\textsuperscript{16}

Still, others have identified differences in genes commonly related to immunobiology and inflammation that appear to differ in tumors from African American men.\textsuperscript{17} Wallace et al., by comparing gene expression profiles, showed that primary prostate tumors from African American men differ from those of white men in genes related to the immune response, stress response, cytokine signaling, and chemotaxis pathways.\textsuperscript{17} Additionally, tumors from African American men expressed increased levels of certain genes known to promote metastasis, such as autocrine mobility factor receptor, chemokine receptor 4, and matrix metalloproteinase 9.\textsuperscript{17} The upshot of these findings is that tumors from African American men likely have a unique tumor microenvironment that results in prominent differences in immunobiology from tumors of white men.

With regard to breast cancer, there also appear to be unique biologic features that distinguish tumors in African American patients. For example, breast cancers in African American women have been shown to be more likely than those from patients of other races to be triple-negative (i.e., lacking estrogen receptor [ER], progesterone receptor [PR], and human epidermal grown factor receptor 2 [HER2]).\textsuperscript{18} As these receptors serve as therapeutic targets, triple negative phenotype is an independent risk factor for poorer clinical outcomes, including increased risk of lung and brain metastases as well as reduced breast-cancer specific and overall survival.\textsuperscript{18}

Another study compared breast carcinoma specimens from Nigerian women with those from white women in the United Kingdom.\textsuperscript{19} It showed that Nigerian patients were more likely
to present with larger primary tumors, typically of higher grade, with more advanced nodal
spread and a higher level of vascular invasion. Furthermore, when matched for grade with
tumors from white women, tumors from Nigerian women were more likely to be triple-negative
and deficient in BRCA1, further evidence of underlying molecular differences.\textsuperscript{19}

In addition to showing a difference in cancer-specific mortality over the last two decades
between African American and white patients, our study also reveals that this difference is
increasing. One possible explanation for this phenomenon relates to the fact that trastuzumab
was approved by the United States Food and Drug Administration in 1998. Its availability is
likely to have preferentially improved the prognosis of white patients relative to African
Americans. This assumption is based on the fact that African American patients are less likely to
present with HER2 positive disease.\textsuperscript{20}

Furthermore, in addition to the unique molecular feature of breast malignancies from
African American women aforementioned, there have also been reports of breast carcinoma in
African American women showing greater microvessel density, increased pro-tumoral, M2
macrophage infiltration, higher levels of SOS1 gene (a marker of aggressive tumor biology), and
differential expression of insulin-like growth factor receptors.\textsuperscript{21,22,23} In light of all these
molecular differences, the biology underlying the more aggressive behavior of breast carcinoma
observed in African American women is likely complex and multifactorial. A better
understanding of these factors may be necessary in order to develop therapies with better
efficacy in this patient population.

With regard to lung cancer, African American patients with non-small cell lung cancer
(NSCLC) seem to express epidermal growth factor receptor (EGFR) mutations at the same rate
as white patients. As a result, these patients would be expected to respond to an equivalent
degree to receptor tyrosine kinase inhibitors. The upshot of this fact is that clinicians ought to prescribe tyrosine kinase inhibitors to African American patients as regularly as to patients of other races. However, despite an equivalent EGFR mutation rate there are still likely important biologic features disproportionately affecting African American lung cancer patients.

For example, significant differences in circulating cytokines have been observed in African American lung cancer patients. The study authors in that case showed that these differences in cytokines were associated with differences in survival. Nonetheless, given that that study was retrospective, it remains hypothesis generating only and its assertions require validation in a prospective trial. Alternatively, another study found that African American lung cancer patients have decreased levels of serum mannose-binding lectin (MBL) when compared with lung cancer patients of other races, a finding which may also influence prognosis. Overall, however, there is still a relative paucity of data on how the underlying molecular biology of lung cancer differs in African American patients.

The idea of differential biology disproportionately affecting African American patients also applies to colorectal cancer, for which the present study also shows a gap in cancer-specific survival. One hypothesis for this observation relates to circulating vitamin D levels. Vitamin D deficiency is a well-established risk factor for colorectal cancer. Furthermore, vitamin D deficiency has been found to be prevalent among African American individuals, in general, and African American colorectal cancer patients, in particular. One retrospective analysis has shown a direct association between vitamin D deficiency in African Americans and an increased susceptibility to colorectal cancer mortality, but again, because this association stems from retrospective data, it remains a hypothesis in need of prospective validation.
Beyond the issue of vitamin D exposure, colonic adenomas, the precursor lesion of colon cancer, obtained from African American patients appear to contain a higher proportion of cancer stem cells than those from white patients.\textsuperscript{30} This finding suggests that in African American patients, the mechanism by which adenomas change into cancer (the adenoma-carcinoma sequence) may progress more effectively, which may contribute to increased cancer incidence in this population. Another study showed that tumors from African American patients displayed unique gene expression profiles as compared with colorectal cancers from white patients, especially with regard to genes related to immunobiology and inflammation.\textsuperscript{31}

Also, unlike the aforementioned example of equivalent expected benefit in African American lung cancer patients treated with tyrosine kinase inhibitors, a large prospective cohort study in 2012 showed that African American colon cancer patients showed a lower response rate to bevacizumab.\textsuperscript{32} This observed difference was in contrast to the otherwise equivalent cancer mortality outcomes that were observed in the same study when African American and white patients were treated only with modern, standard chemotherapy. While there is a likely a scientific explanation for this difference in clinical response to bevacizumab (an anti-angiogenesis agent), it remains unclear at this time. However, this issue is deserving of further inquiry as it may help guide the management of African American colon cancer patients with advanced systemic disease. This last point is of special importance, as African American patients have been shown to be more likely than patients of other races to harbor occult colorectal metastases, which result in higher than expected levels of disease recurrence following surgical excision of node-negative tumors.\textsuperscript{33}

Compared with the number of studies devoted to examining differences between tumors from African American and white patients, there has been a relative paucity of inquiry devoted to
characterizing tumors from Hispanic patients. Our data revealed that Hispanic patients display similar estimates of cancer-specific mortality overall as white patients. Nonetheless, Hispanic patients showed significantly higher cancer-specific mortality rates than white patients for breast and colorectal cancers. Therefore, as appears to be the case for African American patients, there are likely important biologic mechanisms underlying the observed survival differences in Hispanic patients with breast and colorectal cancers that complicate the issue of survival parity. As such, understanding these differences may be necessary to close the observed survival gap, in addition to improving traditionally recognized social issues, such as screening and access to care.

Hines et al. aimed to determine whether Hispanic and white women presented with differing proportions of breast cancer phenotypic subtypes. Tumor specimens from white and Hispanic women were obtained and tumor markers were compared, along with clinical risk factors. Of note, Hispanic women showed a higher prevalence of tumors that were ER-negative as well as HER2-positive. In fact, the odds of HER2 positivity were 2.8 times higher in Hispanic patients, which actually suggests that, if treated adequately, they may be more likely overall to benefit from therapy with trastuzumab. Altogether, these findings suggest that breast carcinoma in Hispanic women likely has distinct underlying biology.

In support of that assertion, it is interesting to note that breast tumors from Hispanic women have been shown to display increased M2 macrophage tumor infiltration at levels that exceed even what was observed in tumors from African American women. M2 macrophages are associated with increased angiogenesis, stromal degradation, and suppression of innate immune responses, thereby facilitating disease progression. Unfortunately, while our study also highlighted a survival disparity in Hispanic patients with colon cancer relative to white patients, there is a paucity of basic science data on this topic. However, from a clinical perspective,
Hispanic patients have been shown to be less likely to receive timely follow-up colonoscopies after colorectal cancer resection.\textsuperscript{35} Therefore, this may be an area in which additional effort may improve the survival gap we identified.

For all malignancies evaluated, Asian Americans displayed the lowest rates of cancer-specific mortality in our study. Part of this phenomenon might be attributable to biology. In fact, numerous studies have identified distinct biological features among tumors in Asian Americans. For example, as previously mentioned, prostate cancers in Japanese patients have been found to differ both quantitatively and qualitatively in TMPRSS2-ERG gene fusion when compared with tumors from both white and African American patients. Again, these differences in TMPRSS2-ERG gene fusion may manifest as differences in downstream signaling pathways related to tumor progression, thereby leading to different levels of tumor aggressiveness.\textsuperscript{14} At the level of the chromosome, Misumi et al. showed that allelic imbalances at 13q14 are significantly more prevalent in prostate tumors from Japanese patients than those from white patients, which might also contribute to their less aggressive nature.\textsuperscript{36}

With regard to Asian patients with breast cancer, a large cohort of Chinese women, particularly those with a triple-negative phenotype, displayed better prognoses and clinical characteristics than those typically reported in corresponding white populations.\textsuperscript{37} Additionally, breast cancers in Japanese women have also been shown to be more favorable than those from women of other races with regard to both prognosis and proportion of favorable phenotypic subtypes.\textsuperscript{38} These data suggest that, similar to what has been demonstrated in prostate cancer, there are likely relevant differences in the underlying biology of breast cancer tumors from Asian American patients. However, basic science studies of this nature are lacking despite the fact they
may prove useful for identifying therapeutic targets relevant to Asian American patients if undertaken.

Lung tumors in Asian American patients deserve special mention, as they are widely known to express higher levels of EGFR. Therefore, Asian American patients on the whole are likely to respond more favorably than white patients to therapeutic regimens involving receptor tyrosine kinase inhibitors. However, there are also likely to be additional, as yet unidentified biological features of lung tumors in Asian Americans that also confer a survival advantage. In support of this assertion, Ahn et al. has identified Korean ethnicity status to be independently associated with a favorable prognosis in NSCLC. Taking this idea one step further, we suggest that for each race and cancer previously listed, there are likely to be numerous unidentified genetic and molecular differences of oncologic significance that may potentially be exploited for therapeutic gain.

In the same way that knowledge learned from basic science experimentation guides our understanding of clinical medicine, there is likely much to learn about the underlying biology of disease from patients who show exceptional responses to treatment. An example of this may be Asian Americans with colorectal cancer. Our data clearly show that Asian American patients with colorectal cancer had more favorable outcomes than patients of any other race. This trend held even after adjusting for all possible, known socio-demographic factors. Translational studies in this patient population may be warranted in order to identify the scientific mechanisms driving this clinical trend.

Moreover, the trend of favorable prognosis in Asian American patients, as previously stated, applied to all cancer types included in this analysis (i.e., prostate, breast, lung, and colorectal). Despite this fact, a review of the literature reveals that there has been relatively little
to no inquiry into this subject. Hence, there is still much to learn from Asian American patients. Perhaps were the underlying basic science better understood, it would inform the development of new therapies that might benefit all patients, regardless of racial background.

Apart from differences in the underlying biology, the mortality differences observed in our study could also be related to sociological factors. For example, while information on adherence to treatment is not available in SEER, there are numerous studies that document significant discrepancies in levels of treatment adherence by race. For example, Pitman et al. found that African American and Hispanic men were significantly more likely to wait a longer time after having positive prostate biopsy before undergoing radical prostatectomy than white men. However, it is possible that numerous factors were responsible for this delay, and the degree to which reduced adherence can be ascribed in this case remains unknown. Another study revealed that non-white patients who survive colorectal cancer are less likely to utilize colonoscopy for surveillance. Again, it is impossible to know whether patient adherence to provider recommendations was solely to blame. Overall, however, these studies highlight the need to improve treatment delivery to patients at risk for increased cancer-specific mortality, both before and after receipt of definitive therapy.

Furthermore, it can be difficult to disentangle a problem of patient non-adherence from one of provider mistrust. Importantly, these two issues are not mutually exclusive. Otherwise stated, while there are many reasons why minority patients may show lower levels of patient adherence, including language barriers, cultural preferences, and access to care, there are also legitimate reasons why certain populations may be less likely to trust health care providers. A famous example is the case of Henrietta Lacks.
Henrietta Lacks was an African American woman whose cervical cancer cells were cultured without her knowledge or informed consent in the 1950s. Their culture resulted in the aptly named, widely known HeLa cell line. In contrast, however, to the vast and lucrative scientific achievements that have been made possible by knowledge gathered from experimentation on HeLa cells, Lacks’ family to this day remains relatively impoverished, unable to even afford health insurance. This example shows why some minority communities might have legitimate reservations about trusting health care providers, as memories of past breaches of trust may linger.

Furthermore, even with an established, trusting provider relationship and access to medical care, some studies have suggested that African American individuals, in particular, may experience challenges in utilizing such care. For example, studies have shown that health literacy may be lower in African American patients as compared with white patients. The resulting implications of this concern not only the likelihood of patient adherence and timely receipt of appropriate treatment (as previously discussed), but also the likelihood of participation in preventative therapies and behaviors. Suboptimal relationships with health care providers and financial factors also seem to also play a role in the survival gap between African American and white patients even after care is established.

It is disappointing that over the last twenty years the survival gap between African American patients and white patients does not appear to be closing. To the extent that this persistent gap reflects differences in biology, there needs to be increased research specifically into African American patients with cancer. In addition, further emphasis ought to be placed on ensuring that African American patients are adequately represented in clinical trials. Currently,
African American patients may be as much as 30% less likely to participate in a trial than white patients.\textsuperscript{48}

Possible reasons for the limited participation of African American patients in clinical trials include a mistrust of the medical system given prior abuses, limited communication regarding trial availability to African American patients, and economic factors.\textsuperscript{49,50} Moreover, clinical trial enrollment, or lack thereof, may be an early indicator of change in terms of disparities in cancer care. Physicians ought to be cognizant of barriers to enrollment in clinical trials among African Americans. In addition, randomized trials may need to be stratified by race if there is a biological reason that the efficacy of a specific treatment may vary by race. To the extent that the persistent gap in cancer-specific survival reflects sociological issues, increased social supports and attention to the treatment adherence of at-risk populations may help alleviate this apparent disparity.

There are several potential limitations to the current study. First, we examined only the three leading causes of cancer-related death among males and females. Other less common cancers might also demonstrate important trends in cancer-specific mortality by race. Second, these results are not generalizable to patients with metastatic disease, as these patients were excluded from our analysis. Third, there are less prevalent races that were not included in sufficient numbers in SEER from which to draw meaningful conclusions regarding cancer-specific mortality rates. Fourth, our statistical adjustments for urban versus rural residence, education, and income are at the county level as opposed to the individual level, as more specific demographic information is not available in the SEER database for these variables. Fifth, it is impossible to make inferences regarding patient adherence to treatment based on the data contained in SEER, and this could be a meaningful confounder of the results of the current study.
Lastly, information regarding chemotherapy is not available in the SEER database. Some but not all studies have suggested that nonwhite patients may be less likely to receive chemotherapy than white patients.\textsuperscript{51,52,53} The impact of this potential confounder on the current study results cannot be determined with certainty. If rates of receipt of chemotherapy were similar among nonwhite and white patients, then the lack of inclusion of information relating to chemotherapy may be of minimal impact. If more white patients received chemotherapy than nonwhite patients, and if the receipt of such chemotherapy confers a survival benefit, then it is possible that the results of the current study overestimate the magnitude of the true relationship between race and outcome among patients with cancer.

In spite of these potential limitations, the current study highlights important racial discrepancies in cancer-specific mortality, particularly among African American patients, in whom survival is worse than for white patients, and in whom the racial gap in survival has not appeared to narrow over the last twenty years. This gap persists independent of stage of disease and treatment received, and therefore additional strategies beyond increased screening and improved access to care, such as research into tumor biology and molecular mechanisms that may disproportionately affect African American patients, and increased efforts to enroll African American patients on clinical trials, are needed to close the survival gap for African American patients with cancer.

Beyond the survival gap of African American patients, there is also much to learn from the survival of patients of the other racial backgrounds relative to that of white patients. For example, Hispanic patients, while showing survival trends similar to white patients in prostate and lung cancer, showed alarmingly higher rates of cancer-specific mortality for breast cancer and slightly higher rates for colorectal cancer. These findings should also be used to guide future
inquiry not only into basic science but also into social issues that may underlie differences in screening and preventive health utilization as they relate specifically to Hispanic patients.

One potential solution to improving the mortality trends we observed may be to create specialty clinics staffed by minority providers in order to ensure more optimal delivery of culturally competent care. For example, a Spanish language breast cancer clinic may help create a more comfortable atmosphere for certain Hispanic patients as they endure the stresses of diagnosis and treatment, even if they speak English fluently. A more comfortable clinical atmosphere may in turn improve adherence to treatment and ultimately improve the trend of cancer-specific survival. In an ideal world with unlimited resources, patients would have various language-specific clinics readily available and simply choose the clinical setting that seems most appealing.

Instead, we as a society are faced with making the most out of a limited pool of financial resources. With those, we must optimize the care that physicians are able to deliver to patients and ensure that patients, in turn, are making adequate use of resources available to them. The results of the current study show that there are important differences in cancer-specific mortality for the three leading causes of cancer-related death in men and women when compared across patients of different racial backgrounds. As previously stated, while there are notable biological differences of likely oncologic significance that appear to trend with race, there are also sociologic issues related to cancer care delivery that ought to be addressed. While the results of the current study are, in and of themselves, informative, their true value lies in what future actions they are able to inspire such that ultimately the survival gap may be reduced.
Summary:

To our knowledge, it remains unknown whether race-based differences in cancer outcomes have changed with time. In the current study, we assessed whether racial disparities in cancer-specific mortality have improved over the last twenty years. The Surveillance, Epidemiology, and End Results program was used to identify 2,713,474 patients diagnosed between 1988 and 2007 with either lung, breast, prostate, or colorectal cancer (the leading 3 causes of cancer-related mortality among each sex). After exclusions, 1,001,978 patients remained eligible for analysis. The impact of race on cancer-specific mortality was assessed using the regression model of Fine and Gray; an interaction model evaluated trends over time.

African Americans presented with a more advanced stage of disease (P < .001) and underwent definitive therapy less often (P < .001) than whites. After adjustment for demographics and year of diagnosis, African Americans were found to have higher estimates of cancer-specific mortality than whites for all cancers combined (hazards ratio, 1.28; 95% confidence interval, 1.26-1.30 [P < .001]) and within each individual cancer (each P < .05). These differences did not change significantly between 1988 through 1997 and 1998 through 2007, except among patients with breast cancer, in whom survival disparities increased. These findings remained significant after adjustment for stage of disease at presentation and receipt of definitive therapy (hazards ratio for breast cancer mortality in African Americans vs whites: 1.37 from 1988-1997 and 1.53 from 1998-2007; P for interaction, < .001).

The survival gap for African Americans has not closed over time. Race-based differences in outcome persist independent of stage of disease and treatment, suggesting that additional strategies beyond screening and improving access to care, such as further research into tumor
biologies disproportionately affecting African Americans, are needed to improve survival for African American patients with cancer.
References:


Tables and Figures

**TABLE 1. Baseline Demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>White N= 766,650</th>
<th>African American N= 103,882</th>
<th>Hispanic N= 75,216</th>
<th>Asian American N= 56,190</th>
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<td>61 (13)</td>
<td>61 (14)</td>
<td>62 (14)</td>
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</tr>
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<td>Mean income (SD)</td>
<td>48,000 (11,000)</td>
<td>44,000 (10,000)</td>
<td>47,000 (11,000)</td>
<td>52,000 (10,000)</td>
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<td>High school (%)</td>
<td>81 (7.4)</td>
<td>78 (6.8)</td>
<td>75 (7.2)</td>
<td>80 (6.9)</td>
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<tr>
<td>Male</td>
<td>314,552 (41)</td>
<td>48,507 (47)</td>
<td>30,241 (40)</td>
<td>21,360 (38)</td>
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<tr>
<td>Female</td>
<td>452,136 (59)</td>
<td>55,375 (53)</td>
<td>44,975 (60)</td>
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<td>Marital status, no. (%)</td>
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<td>Unmarried</td>
<td>274,326 (38)</td>
<td>55,221 (53)</td>
<td>27,433 (36)</td>
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<td>Married</td>
<td>492,370 (64)</td>
<td>48,881 (47)</td>
<td>47,763 (64)</td>
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<td>Residence, no. (%)</td>
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<td>Rural</td>
<td>103,777 (14)</td>
<td>7,955 (8)</td>
<td>3,584 (5)</td>
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<td>Urban</td>
<td>662,913 (86)</td>
<td>96,927 (92)</td>
<td>71,552 (95)</td>
<td>54,124 (96)</td>
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<td>Year of diagnosis, no. (%)</td>
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<tr>
<td>1989–1997</td>
<td>196,656 (25)</td>
<td>21,532 (20)</td>
<td>14,193 (19)</td>
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<td>1998–2007</td>
<td>571,032 (75)</td>
<td>62,344 (79)</td>
<td>61,023 (91)</td>
<td>40,113 (82)</td>
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<td>AJCC stage of disease, no. (%)</td>
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<tr>
<td>I</td>
<td>253,539 (33)</td>
<td>23,885 (23)</td>
<td>20,503 (27)</td>
<td>17,876 (32)</td>
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<td>II</td>
<td>315,896 (41)</td>
<td>49,715 (48)</td>
<td>36,164 (48)</td>
<td>22,522 (42)</td>
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<td>III</td>
<td>190,455 (25)</td>
<td>30,241 (29)</td>
<td>18,349 (25)</td>
<td>14,792 (26)</td>
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<td>Definitive treatment, no. (%)</td>
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<td>&lt;.001</td>
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<tr>
<td>No</td>
<td>74,874 (10)</td>
<td>14,580 (14)</td>
<td>7,485 (13)</td>
<td>5,180 (9)</td>
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<tr>
<td>Yes</td>
<td>691,776 (90)</td>
<td>89,302 (90)</td>
<td>67,731 (90)</td>
<td>51,010 (91)</td>
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<tr>
<td>Malignancy, no. (%)</td>
<td></td>
<td>&lt;.001</td>
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<tr>
<td>Prostate</td>
<td>161,446 (21)</td>
<td>28,523 (27)</td>
<td>17,880 (24)</td>
<td>9,231 (16)</td>
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<tr>
<td>Breast</td>
<td>309,161 (40)</td>
<td>36,895 (35)</td>
<td>34,357 (45)</td>
<td>24,827 (44)</td>
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<tr>
<td>Lung</td>
<td>131,658 (17)</td>
<td>16,229 (18)</td>
<td>7,366 (13)</td>
<td>8,252 (15)</td>
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<tr>
<td>Colorectal</td>
<td>164,422 (21)</td>
<td>20,435 (20)</td>
<td>16,113 (21)</td>
<td>18,889 (25)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: AJCC, American Joint Committee on Cancer; SD, standard deviation; USD, US dollars.
*Percentages may not add up to 100 due to rounding.
*County-level data.
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Prostate</th>
<th>Breast</th>
<th>Lung</th>
<th>Colorectum</th>
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<tr>
<td>White</td>
<td>2.1% (2.0%-2.2%)</td>
<td>8.2% (8.1%-8.3%)</td>
<td>65.5% (65.2%-65.7%)</td>
<td>20.7% (20.5%-20.9%)</td>
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<tr>
<td>African American</td>
<td>2.9% (2.7%-3.1%)</td>
<td>16.4% (16.0%-16.8%)</td>
<td>69.4% (68.7%-70.1%)</td>
<td>25.1% (24.5%-25.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.1% (1.9%-2.4%)</td>
<td>10.5% (10.2%-10.9%)</td>
<td>66.1% (64.9%-67.2%)</td>
<td>21.7% (21.0%-22.3%)</td>
</tr>
<tr>
<td>Asian American</td>
<td>1.5% (1.2%-1.8%)</td>
<td>7.0% (6.7%-7.3%)</td>
<td>63.0% (61.9%-64.1%)</td>
<td>18.6% (17.9%-19.2%)</td>
</tr>
</tbody>
</table>

*Percentages reflect 5-year cancer-specific mortality rate and associated 95% confidence intervals.*

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Era</th>
<th>HR(^a) for AA vs White (95% CI)</th>
<th>P</th>
<th>P-int(^b)</th>
<th>HR(^a) for Hispanic vs White (95% CI)</th>
<th>P</th>
<th>P-int(^b)</th>
<th>HR(^a) for Asian American vs White (95% CI)</th>
<th>P</th>
<th>P-int(^b)</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>1988-1997</td>
<td>1.34 (1.21-1.49)</td>
<td>&lt;.001</td>
<td>.69</td>
<td>0.99 (0.86-1.13)</td>
<td>.83</td>
<td>.74</td>
<td>0.73 (0.58-0.92)</td>
<td>.006</td>
<td>.85</td>
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<tr>
<td>Prostate</td>
<td>1998-2007</td>
<td>1.36 (1.26-1.51)</td>
<td>&lt;.001</td>
<td>.68</td>
<td>1.02 (0.90-1.15)</td>
<td>.79</td>
<td>.76</td>
<td>0.75 (0.52-0.91)</td>
<td>.003</td>
<td>.83</td>
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<tr>
<td>Breast</td>
<td>1988-1997</td>
<td>1.37 (1.31-1.44)</td>
<td>&lt;.001</td>
<td>.69</td>
<td>1.07 (1.01-1.13)</td>
<td>.01</td>
<td>.83</td>
<td>0.92 (0.86-0.99)</td>
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<td>1998-2007</td>
<td>1.53 (1.48-1.59)</td>
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<td>.69</td>
<td>1.10 (1.06-1.15)</td>
<td>.01</td>
<td>.84</td>
<td>0.86 (0.81-0.91)</td>
<td>&lt;.001</td>
<td>.06</td>
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<tr>
<td>Lung</td>
<td>1988-1997</td>
<td>1.01 (0.97-1.04)</td>
<td>.77</td>
<td>.31</td>
<td>0.97 (0.91-1.03)</td>
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<td>.39</td>
<td>0.89 (0.84-0.94)</td>
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<tr>
<td>Lung</td>
<td>1998-2007</td>
<td>1.03 (1.00-1.05)</td>
<td>.02</td>
<td>.31</td>
<td>0.96 (0.93-0.99)</td>
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<td>.86</td>
<td>0.86 (0.83-0.91)</td>
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<td>.09</td>
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<tr>
<td>Colorectal</td>
<td>1988-1997</td>
<td>1.18 (1.12-1.24)</td>
<td>&lt;.001</td>
<td>.57</td>
<td>1.10 (1.04-1.17)</td>
<td>.01</td>
<td>.45</td>
<td>0.94 (0.88-1.01)</td>
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<tr>
<td>Colorectal</td>
<td>1998-2007</td>
<td>1.20 (1.16-1.24)</td>
<td>&lt;.001</td>
<td>.57</td>
<td>1.07 (1.03-1.12)</td>
<td>.001</td>
<td>.45</td>
<td>0.98 (0.95-0.99)</td>
<td>&lt;.001</td>
<td>.06</td>
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<tr>
<td>Combined</td>
<td>1988-1997</td>
<td>1.14 (1.11-1.17)</td>
<td>&lt;.001</td>
<td>.15</td>
<td>1.08 (1.04-1.12)</td>
<td>&lt;.001</td>
<td>.01</td>
<td>0.90 (0.86-0.94)</td>
<td>&lt;.001</td>
<td>.08</td>
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<td>Combined</td>
<td>1998-2007</td>
<td>1.17 (1.14-1.19)</td>
<td>&lt;.001</td>
<td>.15</td>
<td>1.02 (1.00-1.05)</td>
<td>.08</td>
<td>.86</td>
<td>0.86 (0.84-0.88)</td>
<td>&lt;.001</td>
<td>.01</td>
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</table>

Abbreviations: 95% CI, 95% confidence interval; AA, African American; HR, hazards ratio; P-int, P value for interaction term.

\(^a\)HRs for the outcome measure of cancer-specific mortality were adjusted for the demographics of age, race, income, education, urban versus rural residence, cancer stage, and use of definitive therapy. Exceptions were lung and colorectal cancer, which were also adjusted for sex, and combined, which was also adjusted for primary tumor site.

\(^b\)P for interaction reflects whether HRs for 1988 through 1997 and 1998 through 2007 were significantly different (P <.05 indicates a statistically significant difference).
Figure Legends

**Figure 1:** Cumulative incidence curves depicting cancer-specific mortality in each malignancy evaluated are shown stratified by race. *P* values, as determined by the Gray test, were < .001 in all cases (pairwise testing not performed). Blue line indicates white patients; red line, African American patients; green line, Hispanic patients; purple line, Asian American patients.

**Figure 2:** Forest plots depicting odds ratios and 95% confidence intervals for the association between race and cancer-specific mortality are shown for each of the malignancies evaluated and among the entire cohort. Hazards ratios (HR) for the outcome measure of cancer-specific mortality were adjusted for the demographics of age, race, income, education, urban versus rural residence, cancer stage, and use of definitive therapy. Exceptions were lung and colorectal cancer, which were also adjusted for sex, and combined, which was also adjusted for primary tumor site. 95% CL, 95% confidence limit; LCL, lower confidence limit; UCL, upper confidence limit; AA, African American.

**Figure 3:** Bar graph displaying hazards ratios (HRs) for cancer-specific mortality by year of diagnosis is shown for patients of each race, relative to the reference year of 1988. HRs obtained from the competing risks regression model of Fine and Gray are shown after adjustment for the demographics of age, race, income, education, urban versus rural residence, primary malignancy, cancer stage, and use of definitive therapy. The height of the bars reflects the HR for cancer-specific mortality in a given race in the index year relative to the reference year of 1988.
Prostate Cancer
Breast Cancer
Colorectal Cancer
### Figure 2:

<table>
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<tr>
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<th>HR</th>
<th>LCL</th>
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- Favors Survival
- Favors Death

HR: Hazard Ratio, LCL: Lower Confidence Limit, UCL: Upper Confidence Limit
Figure 3:

[Bar graph showing relative hazard ratio over time for different racial groups (Whites, African Americans, Hispanics, Asian Americans). The x-axis represents the year of diagnosis, and the y-axis shows the increasing improvement in cancer-specific mortality over time. There are arrows indicating magnitude of improvement relative to 1988.]