Racial/Ethnic Differences in Cancer Diagnosed after Metastasis: Absolute Burden and Deaths Potentially Avoidable through Earlier Detection

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ABSTRACT

Background: Racial/ethnic disparities in cancer mortality are well described and are partly attributable to later stage of diagnosis. It is unclear to what extent reductions in the incidence of late-stage cancer could narrow these relative and absolute disparities.

Methods: We obtained stage- and cancer-specific incidence and survival data from the Surveillance, Epidemiology, and End Results Program for persons ages 50 to 79 years between 2006 and 2015. For eight hypothetical cohorts of 100,000 persons defined by race/ethnicity and sex, we estimated cancer-related deaths if cancers diagnosed at stage IV were detected earlier, by assigning them outcomes of earlier stages.

Results: We observed a 3-fold difference in the absolute burden of stage IV cancer between the group with the highest rate (non-Hispanic Black males, 337 per 100,000) and the lowest rate (non-Hispanic Asian/Pacific Islander females, 117 per 100,000). Assuming all stage IV cancers were diagnosed at stage III, 32–80 fewer cancer-related deaths would be expected across subgroups, a relative reduction of 13%–14%. Assuming one third of metastatic cancers were diagnosed at each earlier stage (I, II, and III), 52–126 fewer cancer-related deaths would be expected across subgroups, a relative reduction of 21%–23%.

Conclusions: Across population subgroups, non-Hispanic Black males have the highest burden of stage IV cancer and would have the most deaths averted from improved detection of cancer before metastasis.

Impact: Detecting cancer before metastasis could meaningfully reduce deaths in all populations, but especially in non-Hispanic Black populations.

See related commentary by Loomans-Kropp et al., p. 512

Introduction

Cancer is the second leading cause of death in the United States, with 1,898,160 new cancer cases and 608,570 cancer deaths projected to occur in 2021 (1). Cancer mortality rates in the United States are well understood to vary by race/ethnicity and sex (2). In particular, non-Hispanic Black males have had a disproportionately higher burden of cancer death than other groups, in part due to disparities in access to screening, diagnosis, and treatment (3, 4).

As risk of cancer death is lower when cancers are diagnosed and treated before they metastasize, early detection of cancer is central to reducing cancer mortality (5–7). Screening is recommended by the U.S. Preventive Services Task Force for only five cancer types: breast (8), cervical (9), and colorectal (10) in the general population; lung, in patients with a history of heavy smoking (11); and prostate, on an individualized basis (12). New multi-cancer early detection (MCED) blood tests, most based on next-generation sequencing of cell-free DNA, can screen asymptomatic persons for multiple forms of cancer simultaneously with a single blood draw (13–19). Although their implementation in clinical settings is recent, these tests may expand early detection of cancers beyond the few currently targeted by cancer screening guidelines. To avoid focus on any particular technology, we note that cancer mortality generally increases drastically with metastasis, which underscores the importance of developing novel means of detecting cancers before they metastasize.

To better understand the potential of enhanced cancer screening in the population at large, we previously assessed the population-level potential of earlier detection of common cancer types by examining current rates of diagnosis after metastasis and hypothesizing reductions in deaths that could occur if cancers were diagnosed at earlier stages (5). Here, that assessment is expanded by estimating these absolute and relative reductions separately for eight contemporary U.S. population subgroups defined by race/ethnicity and sex. The objective of this analysis is to quantify the potential benefits of improved detection before metastasis for population subgroups, which may inform the equitable implementation of new and existing approaches and technologies for addressing preventable cancer mortality.

Materials and Methods

Cancer incidence and mortality data

We obtained cancer incidence and survival data from the Surveillance, Epidemiology, and End Results Program (SEER) program (20). We calculated crude incidence and 5-year cancer-specific survival rates (https://github.com/grailbio-publications/Clarke_Metastasis_Disparities) for primary invasive cancer in 18 geographic regions (SEER18) from 2006 to 2015 and followed for vital status through December 31, 2017. Only the first eligible record for each person was included (i.e., excluding subsequent primary cancer diagnoses that occurred within the observation period). Survival statistics were limited to first primary cancers and excluded cases diagnosed via autopsy or death certificate, with zero survival time or with unknown cause of death.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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A total of 20 cancer types were considered separately in this assessment, including those ranking in the top 10 in burden across all races (based on American Cancer Society Facts and Figures 2021; ref. 1): prostate, breast, lung/bronchus, colorectal, urinary bladder, uterine corpus, melanoma of the skin, renal pelvis/kidney, non–Hodgkin lymphoma, pancreas, esophagus, liver/intrahepatic bile duct, oral cavity/pharynx, thyroid, ovary, leukemia, and brain/other nervous system (1). In addition, myeloma, stomach, and cervical cancer were also included, as they are among the leading cancer types diagnosed in African Americans (21) and Hispanics/Latinos (22). Except for leukemia and brain cancer, the 20 cancer types listed above were analyzed individually; however, because leukemia and brain/other nervous system cancers are not staged in the American Joint Committee on Cancer (AJCC) 6th edition (23) scheme (e.g., cancer stage at diagnosis is uniformly unknown), they are grouped with less-common cancers in the "other cancers" category; see Supplementary Data for full list. The category "all cancers" comprised all invasive cancers reported to SEER. Cancer type was defined using the SEER site recode (24) of ICD-O-3 site and histology codes and stage at diagnosis was classified according to the AJCC 6th edition (23) as stage I, II, III, IV, or unknown/unstaged.

Population subgroups

We focused on eight population subgroups defined jointly by race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, Hispanic) and sex (male, female). We limited inclusion to those 50–79 years of age at diagnosis to focus on the ages of highest risk across most cancer types in most population subgroups while minimizing competing risk of non–cancer-related deaths among persons older than 79 years.

Statistical analysis

For each of the eight population subgroups evaluated, we assumed a hypothetical cohort of 100,000 persons, and calculated the incidence and survival rates for each. We then used those rates to estimate the potential reductions in mortality that could occur from detection of cancers before metastasis (stage IV). Crude incidence rates were used to estimate numbers of type- and stage-specific cancers that would arise within 1 year, then type- and stage-specific rates were multiplied by the corresponding type- and stage-specific five-year cumulative probabilities of cancer-related death (i.e., one minus the cancer-specific survival rate). All such calculations included five categories of stage (I, II, III, IV, and unknown/unstaged). Estimates of the "all cancers" number of deaths were based on summing the stage-specific deaths for each cancer type category shown, including the other cancers category.

As in our previous assessment (5), we considered three scenarios: a baseline scenario, with stage at diagnosis and death rates based on contemporary data from the SEER database, and two hypothetical stage-shift scenarios by which cancers would be diagnosed before metastasis, as shown in **Fig. 1**. The "stage IV to III" scenario contemplates intercepting stage IV cancer at stage III; that is, all persons

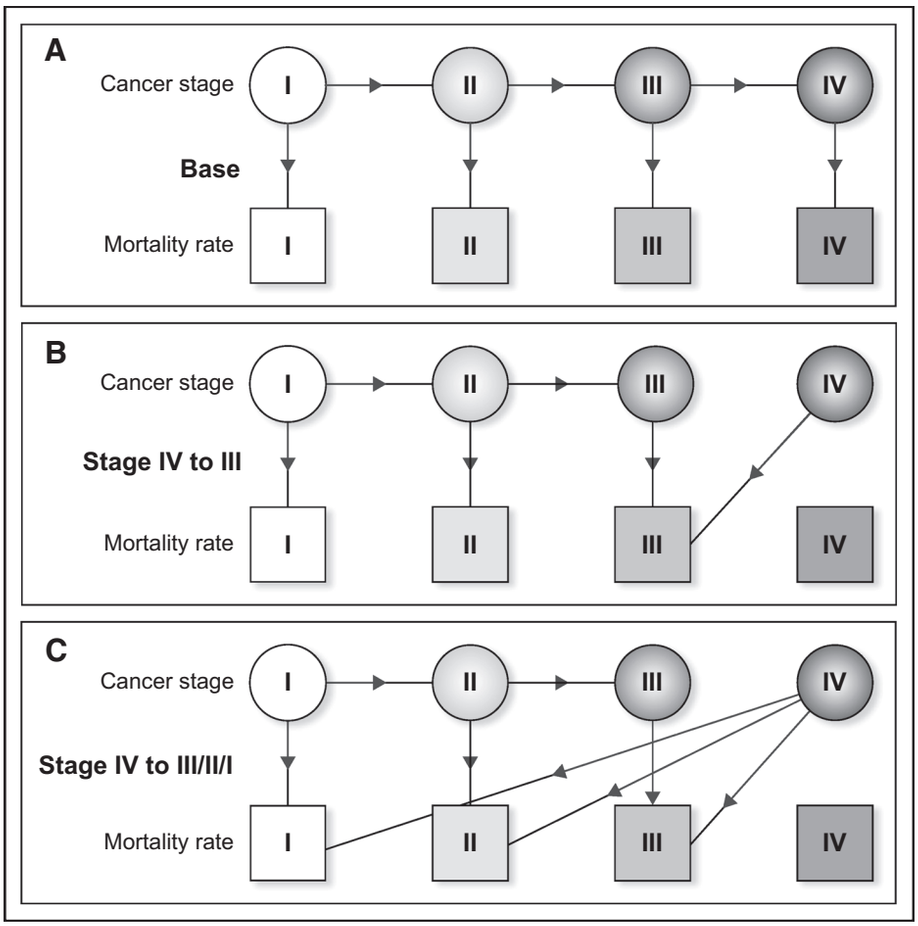

Figure 1.
Scenarios for improved mortality rates. **A,** Outcomes recorded in the SEER database with unadjusted mortality outcomes for cancers diagnosed at stage IV. **B,** Scenario where cancers currently diagnosed at stage IV are detected slightly earlier, shifting assigned mortality outcomes to those of cancers diagnosed at stage III. **C,** Scenario where cancers currently diagnosed at stage IV are detected even earlier, with one third of assigned outcomes evenly divided between those of stages III, II, and I.

diagnosed with cancer at stage IV were shifted to have the mortality outcomes associated with stage III cancer from the original date of diagnosis (25). This reflects both the modeling requirements that earlier detection should not on average shorten life, and the reduced hazard due to detection at an earlier stage. This abstraction avoids detailed modeling of lead time by starting changes from mortality after original diagnosis, so no lead time is added to survival. The "stage IV to III/II/I" scenario contemplates intercepting equivalent portions of stage IV cancers at each earlier stage; that is, one-third of people diagnosed with cancer at stage IV were assigned outcomes for stage III, one-third for stage II, and one-third for stage I cancer. To compute the overall number of deaths expected under each scenario, stage-specific deaths were estimated as above, but using the more favorable mortality for the earlier stage at detection for the stage IV cancers, for each cancer type and summed.

Extrapolation to U.S. population

To understand the absolute numbers of stage IV cancers and potential deaths averted for U.S. population subgroups ages 50–79, we multiplied incidence rates by U.S. bridged-race census counts of the resident population of the United States by sex and bridged race (White, Black, or African American, American Indian or Alaska Native, Asian or Pacific Islander), and Hispanic origin for April 1, 2010 obtained from the Centers for Disease Control (CDC; ref. 26).

Data availability statement

The R code and raw data used for this analysis are available at: https://github.com/grailbio-publications/Clarke_Metastasis_Disparities.

Results

Table 1 shows that across the eight population subgroups ages 50–79 years, incidence of stage IV cancer exhibited a 2.8-fold difference in incidence, being highest in non-Hispanic Black males and lowest in non-Hispanic Asian/Pacific Islander females. These differences corresponded to 220 more late-stage cancer diagnoses per 100,000 non-Hispanic Black males than the 117 reported per 100,000 non-Hispanic Asian-Pacific Islander females. Extrapolated to the larger U.S. population ages 50–79, this suggests that about 14,000 non-Hispanic Black males were diagnosed with stage IV cancer annually. Supplementary Table S1 shows the estimated numbers of stage IV cancer diagnoses for other population subgroups.

Non-Hispanic Black females had stage IV cancer rates that were higher than all other groups except non-Hispanic Black and non-Hispanic White males. Incidence of overall cancer followed the same pattern across population subgroups with a 2.2-fold spread across subgroups. Four-fifths of patients diagnosed with stage IV cancer died of cancer within 5 years, from 76% in Hispanic males to 86% in non-Hispanic Black females (**Table 1**). Stage IV cancer represented 19%–21% of all diagnoses (**Table 1**) but was responsible for a higher relative proportion of cancer deaths within 5 years, from 38% in Hispanic females to 45% in non-Hispanic Black males. Absolute numbers of cancer deaths in 5 years attributable to diagnosis at stage IV had a 3-fold difference across population subgroups: 276 per 100,000 non-Hispanic Black males, 206 per 100,000 non-Hispanic White males, 175 per 100,000 non-Hispanic Black females, and 91 per 100,000 non-Hispanic Asian/Pacific Islander females.

Figure 2 shows the proportion of stage IV diagnosis for each of 20 cancer types. The cancer types are rank ordered by the proportion of cancer deaths across all population subgroups. Together, lung and colorectal cancer represented a substantial proportion of all stage IV cancers (37% of stage IV in males and 34% in females) but did not demonstrate major variability by population subgroup. Non-Hispanic Black men had higher proportions of stage IV head and neck cancer diagnoses (**Fig. 2A**) and non-Hispanic Black women had higher proportions of stage IV head and neck and ovarian cancer diagnoses (**Fig. 2B**). Head and neck cancers diagnosed at stage IV varied by population subgroup more than other cancer types. Generally, across all cancer types, a higher percentage of cancers diagnosed at stage IV was associated with higher death and lower survival rates (Supplementary Fig. S1).

Figure 3 summarizes the results of our simple models of reductions in absolute cancer-related deaths that could occur if cancers currently diagnosed at metastatic stage were diagnosed earlier. First, we considered a simple hypothetical "stage IV to III" scenario wherein all cancers diagnosed at stage IV were assigned outcomes for stage III cancer; the expected changes in overall cancer-related mortality under

Table 1. Average annual incidence and expected cancer-related deaths per 100,000 for eight population subgroups with associated rate ratios among persons ages 50–79 years, SEER18, 2006–2015. Rank ordering by annual incidence rate of stage IV cancer.

	Annual incidence rate per 100,000[a]				Expected cancer deaths within 5 years				
					Stage IV		All stages		
	Stage IV	Rate ratio[b]	All stages[c]	Rate ratio[b]	Deaths (*N*)	Rate ratio[b]	Deaths (*N*)	Rate ratio[b]	Proportion due to stage IV[d]
Black, non-Hispanic males	337	2.8	1,636	2.2	276	3.0	610	2.7	45%
White, non-Hispanic males	269	2.3	1,435	2.0	206	2.3	483	2.2	43%
Black, non-Hispanic females	203	1.7	1,049	1.4	175	1.9	425	1.9	41%
White, non-Hispanic females	181	1.5	1,134	1.5	146	1.6	360	1.6	41%
Hispanic males	179	1.5	908	1.2	136	1.5	332	1.5	41%
Asian/Pacific Islander, non-Hispanic males	177	1.5	827	1.1	138	1.5	322	1.4	43%
Hispanic females	124	1.1	777	1.1	97	1.1	257	1.2	38%
Asian/Pacific Islander, non-Hispanic females	117	Reference	734	Reference	91	Reference	223	Reference	41%

[a]Crude average annual rates per 100,000 people for each subgroup.
[b]Rate ratio compares rate or count with the lowest subpopulation shown.
[c]AJCC 6th edition (18), includes unknown/unstaged cancers.
[d]Estimated by multiplying stage-specific incidence and 5-year probability of death.

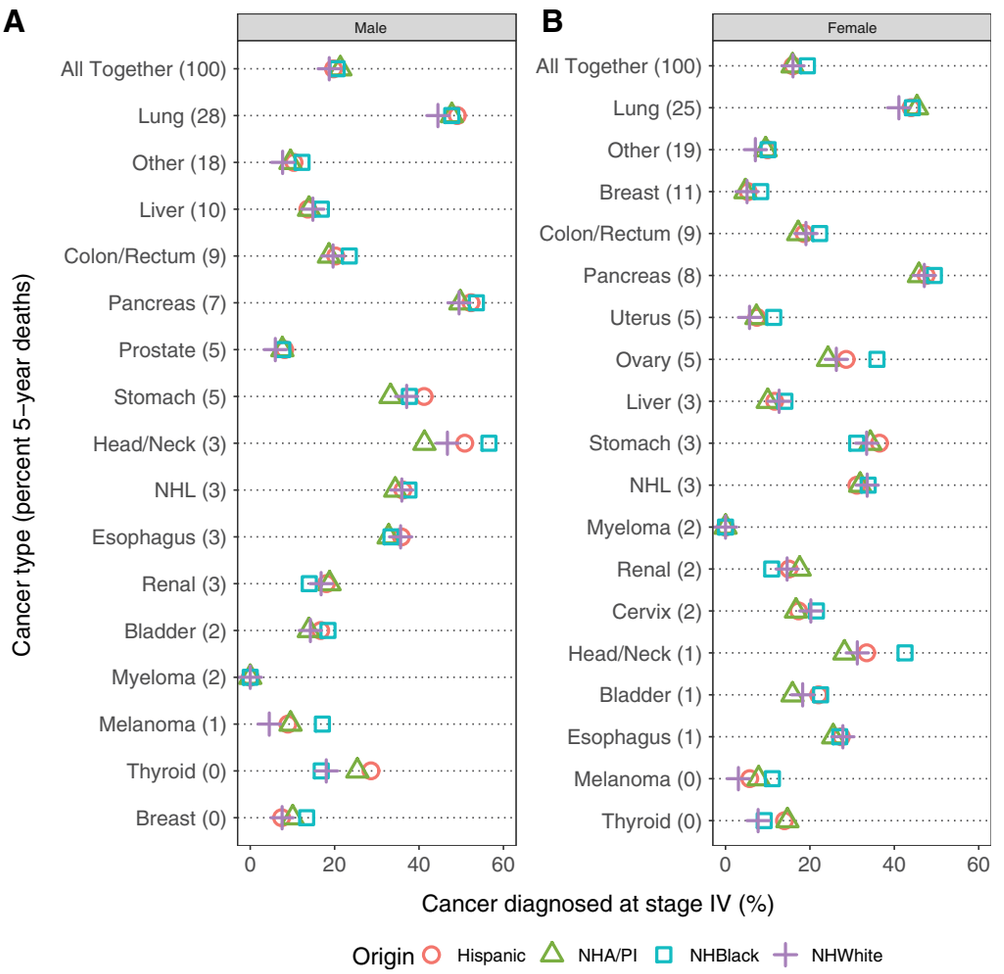

Figure 2.

Proportions of stage IV cancer for population subgroups defined by race/ethnicity and sex, SEER 2006–2015. The cancers that comprise stage IV diagnoses are listed in descending order of 5-year deaths contributed on average for males (**A**) and females (**B**) from the SEER database, with proportions of deaths given in parentheses next to the cancer type. "All Together" at the top of each panel is the total metastatic fraction, that is, all stage IV diagnoses across all invasive cancers combined. Broader spread on *x*-axis indicates greater difference between races in percentage of cancer diagnosed at stage IV. "Other" includes cancers detailed in Materials and Methods. A/PI, Asian/Pacific Islander; NH, non-Hispanic; NHL, non-Hodgkin lymphoma.

this scenario were then calculated. For this scenario, a relative reduction of 13%–14% in deaths over 5 years was estimated in each of the eight population subgroups, a surprisingly consistent relative effect. However, the absolute number of cancer deaths averted was not consistent among subgroups, with the largest potential benefit of 80 deaths per 100,000 observed in non-Hispanic Black males and the smallest absolute reduction in in non-Hispanic Asian/Pacific Islander females at 32 deaths per 100,000 (**Table 2**). The second hypothetical scenario was "stage IV to III/II/I," a more aggressive scenario wherein one-third of stage IV cancers were assigned outcomes of each earlier stage. For this scenario, a reduction of 21% in cancer deaths was expected in all eight population subgroups. As in the more conservative scenario reported above, the absolute reductions in cancer mortality were highest for non-Hispanic Blacks among males (126 deaths per 100,000) and females (68 deaths per 100,000). In all, the relative impact of earlier cancer detection was remarkably consistent in each subgroup, but the absolute impact varied by subgroup according to the baseline rate of stage IV cancer.

Supplementary Figures S2 and S3 detail for the two hypothetical scenarios the potential deaths averted by cancer type and population subgroups. As shown by the change in number of deaths in each scenario, earlier diagnosis has a larger impact on deaths for certain cancer types including breast, colorectal, prostate, head and neck, and renal cancers (Supplementary Figs. S2 and S3).

Discussion

This analysis, using recent SEER data, demonstrated major variation and disparities in cancer diagnosed after metastasis, and related death, across population subgroups defined jointly by race/ethnicity and sex. One of the most striking findings was the 3-fold difference in the racial/ethnic groups identified with the highest versus lowest rates of stage IV cancer diagnoses and associated deaths within 5 years, which were non-Hispanic Black males versus Asian/Pacific Islander females, respectively. These relative differences translated to major absolute differences in the burden of stage IV cancer and deaths.

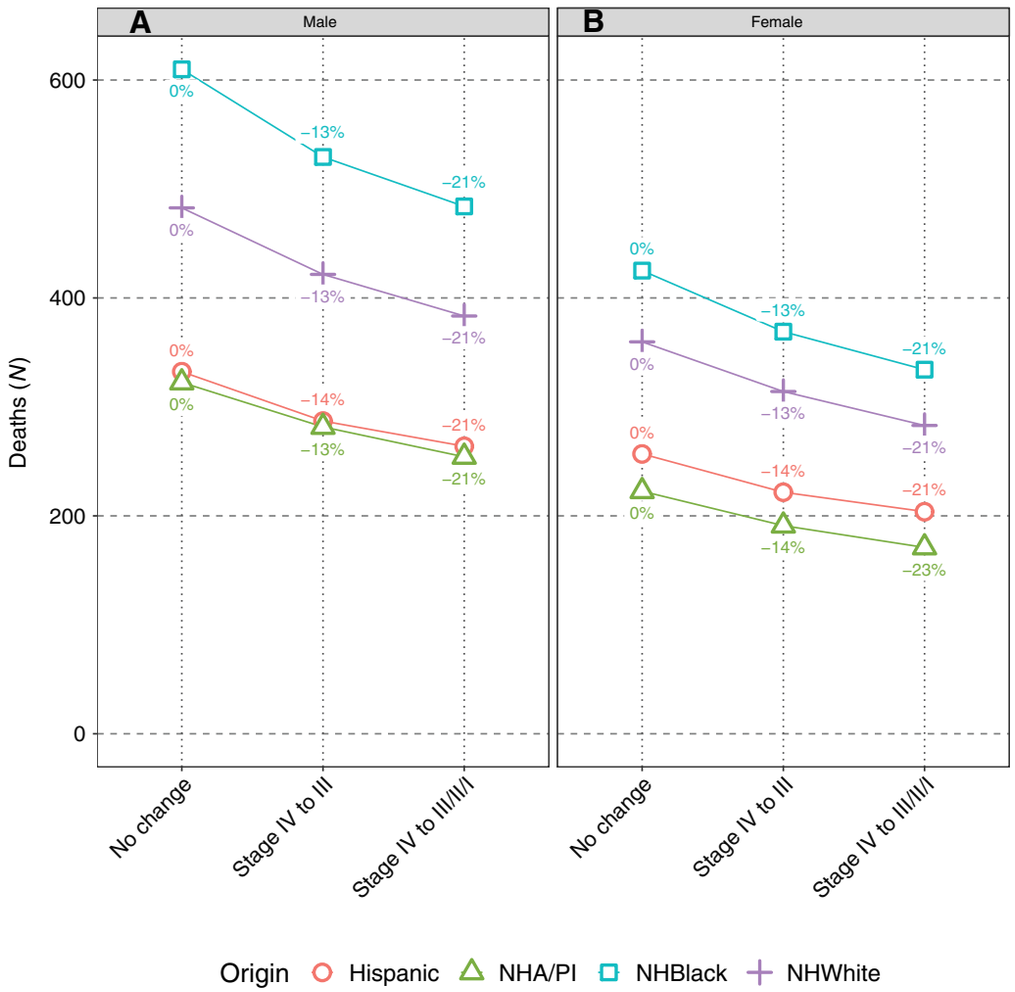

Figure 3.

Absolute and relative reductions in cancer-related deaths under assumptions of stage IV cancers diagnosed earlier, by population subgroups, among persons ages 50–79 years, SEER18, 2006–2015. **A,** Absolute 5-year death rates per 100,000 males of the four racial/ethnic subgroups, with relative percentage decrease in cancer-related deaths for each scenario examined, (**B**) same assessment for females. The percentage above each data point represents the relative reduction in cancer deaths from current treatment with each scenario in each ethnic/racial group by sex (e.g., no change to current screening protocol results in 0% reduction in cancer-related deaths). The *y*-axis indicates the absolute number of deaths corresponding to each percentage decrease. A/PI, Asian/Pacific Islander; NH, non-Hispanic.

Table 2. Absolute numbers of cancer deaths expected in hypothetical cohort of 100,000 persons after 5 years of follow-up, assuming two stage shift scenarios whereby all stage IV cancers had outcome similar to (i) stage III or (ii) a one-third stage III, II, and I, based on incidence and cancer-specific mortality rates for persons ages 50–79 years from SEER18, 2006–2015.

		Deaths averted per scenario[a]	
	Usual care deaths after 5 years	Stage IV to III	Stage IV to III/II/I
Black, non-Hispanic males	610	80	126
White, non-Hispanic males	483	61	99
Hispanic, all races males	332	45	68
Asian/Pacific Islander, non-Hispanic males	322	41	68
Black, non-Hispanic females	425	56	91
White, non-Hispanic females	360	46	77
Hispanic, all races females	257	35	53
Asian/Pacific Islander, non-Hispanic females	223	32	52

[a]Number of cancer deaths averted per 100,000 persons.

Efforts to detect cancer earlier in non-Hispanic Black males specifically could result in reductions in annual deaths (80 to 126 per 100,000) comparable with those reported for Alzheimer's (46 per 100,000), hypertension (55 per 100,000), and HIV (29 per 100,000) combined (27).

Our models suggest that major relative reductions in cancer mortality are possible in each racial/ethnic subgroup, ranging from 13%–21%, depending on how early cancers could be intercepted before metastasis. If cancers were merely detected at stage III instead of stage IV, that would result in 13%–14% reductions in mortality. The magnitude of this relative reduction is similar to the overall impact on cancer mortality attributable to the following risk factors: excess body weight, alcohol intake, poor diet, and physical inactivity, as estimated by the American Cancer Society (28). Together, these data underscore the substantial disparities in metastatic cancer burden across race/ethnicity subgroups, while also supporting that with equitable access to earlier cancer detection, all racial/ethnic groups could achieve a reduction in cancer-related mortality.

We found that non-Hispanic Black men and women have the highest overall burden of stage IV cancer diagnosis compared with other population subgroups, warranting enhanced cancer screening targeted to these groups. Recent CDC Behavioral Risk Factor Survey System data from 2018 suggest that non-Hispanic Black men are less likely to have received guideline-based colorectal cancer screening than non-Hispanic White men (ages 50–75, 66% vs. 71% in males; ref. 29). However, equal or higher proportions of non-Hispanic Black than non-Hispanic White women reported receiving guideline-based colorectal cancer screening (ages 50–75; 73% for both) or having had a mammogram in last 2 years (ages 50–74: 84% vs. 78%), or having had a pap test in the past 3 years (ages 21–65, 85% vs. 80%; ref. 29).

A strength of this analysis is the use of SEER data, a large and representative U.S. population covering diverse subpopulations that are receiving contemporary patterns of cancer screening and treatment. The SEER population experiences all of the causes of real-world disparities in cancer diagnosis and care, including but not limited to access to quality health care, contextual considerations of neighborhood and community, and competing health risks. An additional strength involves our simple, conservative model, which avoided complexity in stage-shift scenarios.

This simplistic approach also had some limitations. Even though the SEER data captures real-world disparities among population subgroups, our hypothesized earlier detections may overestimate achievable benefits given that access to health care is crucial to successful treatment. We focused on metastatic cancers only, which limited our ability to understand the effects of earlier detection on cancer types for which stage II or III are rapidly fatal. Although we did adjust our analyses for the different case-mix of cancer types in each population subgroup examined, we did not account separately for the contributions of the long tail of increasingly rare cancers, as well as the potential to prevent cancers of unknown primary origin. We included an age range where individuals are typically screened for cancers, although some racial/ethnic groups experience important disparities in cancer outcome among persons diagnosed under age 50 (e.g., non-Hispanic Black women with breast cancer). For this study, we omitted individuals with unknown or missing race/ethnicity in SEER, which may change the average stage and cancer incidence slightly from the whole population. Another key limitation involves our choice of 5-year cancer-specific survival as a proxy for long-term outcome. This endpoint, although practical, may not be long enough to capture racial/ethnic, stage-specific differences in longer-term outcomes.

Even though cancer death rates have been on a significant relative decline (1), two important demographic trends underscore the importance of early detection to narrowing disparities in the cancer burden. First, population aging portends an increase in the number of cancers diagnosed. Recent projections suggest that by 2030, total U.S. cancer incidence will increase to 2.3 million, driven disproportionately by cancers diagnosed in those patients ages 65 years and older (27). Second, non-White racial/ethnic populations are growing and aging at faster rates than non-Hispanic Whites, such that absolute numbers of cancer diagnoses will expand disproportionately among non-White racial/ethnic populations (30), especially among Hispanics and non-Hispanic Asian/Pacific Islanders. Mitigating the impact of these trends will require improved access to and utilization of established modes of single-cancer screening, continued investment and innovation in novel technologies and strategies for cancer screening and early detection, including MCED (6), and expansion of efforts in prevention (31).

Authors' Disclosures

C.A. Clarke reports other support from GRAIL during the conduct of the study. A.W. Kurian reports grants from Myriad Genetics outside the submitted work. E. Hubbell reports other support from GRAIL, LLC, a subsidiary of ILMN and ILMN outside the submitted work; in addition, E. Hubbell has multiple patents in the field of cancer detection pending to GRAIL, LLC. S.L. Gomez reports other support from NIH during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

C.A. Clarke: Conceptualization, formal analysis, methodology, writing–original draft, writing–review and editing. **A.V. Patel:** Writing–review and editing. **A.W. Kurian:** Writing–review and editing. **E. Hubbell:** Conceptualization, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **S.L. Gomez:** Conceptualization, data curation, writing–review and editing.

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