Projected Reductions in Absolute Cancer–Related Deaths from Diagnosing Cancers Before Metastasis, 2006–2015

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ABSTRACT

Background: New technologies are being developed for early detection of multiple types of cancer simultaneously. To quantify the potential benefit, we estimated reductions in absolute cancer–related deaths that could occur if cancers diagnosed after metastasis (stage IV) were instead diagnosed at earlier stages.

Methods: We obtained stage-specific incidence and survival data from the Surveillance, Epidemiology, and End Results Program for 17 cancer types for all persons diagnosed ages 50 to 79 years in 18 geographic regions between 2006 and 2015. For a hypothetical cohort of 100,000 persons, we estimated cancer-related deaths under assumptions that cancers diagnosed at stage IV were diagnosed at earlier stages.

Results: Stage IV cancers represented 18% of all estimated diagnoses but 48% of all estimated cancer-related deaths within 5 years. Assuming all stage IV cancers were diagnosed at stage III, 51 fewer cancer-related deaths would be expected per 100,000, a reduction of 15% of all cancer-related deaths. Assuming one third of metastatic cancers were diagnosed at stage III, one third diagnosed at stage II, and one third diagnosed at stage I, 81 fewer cancer-related deaths would be expected per 100,000, a reduction of 24% of all cancer-related deaths, corresponding to a reduction in all-cause mortality comparable in magnitude to eliminating deaths due to cerebrovascular disease.

Conclusions: Detection of multiple cancer types earlier than stage IV could reduce at least 15% of cancer-related deaths within 5 years, affecting not only cancer-specific but all-cause mortality.

Impact: Detecting cancer before stage IV, including modest shifts to stage III, could offer substantial population benefit.

Introduction

Cancer is a major contributor to mortality in the United States, with 606,880 deaths estimated for 2019 (1). Among all causes of death, cancer ranks first in total person-years of life lost, with each death representing an average of 15.6 years of life lost (2). Risk of cancer-related death is lower when diagnosis occurs before metastasis of a primary tumor to distant organs (stage IV). For example, among patients with colorectal cancer, 5-year cancer-specific survival is 73% if diagnosed at stage III, but only 16% if diagnosed at stage IV (3). Earlier detection may improve patient outcomes by enabling more effective treatments or otherwise altering the course of cancer (4).

To date, screening asymptomatic persons for cancer involves isolating single anatomic regions for imaging, direct visualization, or retrieval of abnormal cells (5). At present, three single cancer types are recommended for population-wide screening by the U.S. Preventive Services Task Force (USPSTF): breast (6), cervical (7), and colorectal (8, 9). Lung cancer screening is also recommended, but only for a proportion of the population at risk (10). Altogether, these screening modalities have reduced cancer-related deaths due to those cancer types (11, 12), but have also been constrained by uneven population-level participation (13, 14), high proportions of false positive results (15), and diagnosis of indolent cancers that go on to be overtreated (16, 17).

Recently, innovations in genomic and molecular biology have set forth new possibilities for cancer detection that are not limited to a single anatomic site (5). For example, characterization of circulating tumor DNA has the potential to enable earlier detection of multiple cancer types simultaneously and noninvasively (18–20). To understand broadly the potential population-level impact of early detection across multiple and not just single cancer types, we estimated hypothetical reductions in absolute cancer mortality that could occur if invasive cancers currently diagnosed at metastatic stage were diagnosed at earlier stages.

Materials and Methods

Selection of cancer types for analysis

The American Cancer Society (ACS) reports annually for U.S. males and females the top 10 contributors to cancer incidence and mortality separately for men and women (1). As shown in Supplementary Table S1, for 2019, these cancers were prostate, breast, lung and bronchus, colorectal, urinary bladder, uterine corpus, melanoma of the skin, kidney and renal pelvis, non-Hodgkin lymphoma, pancreas, esophagus, liver and intrahepatic bile duct, oral cavity and pharynx, thyroid, ovary, leukemia, and brain/other nervous system (1), which together represent 76% of all U.S. cancer-related deaths (1). We selected these cancer types for our analysis, which precluded selection of cervical cancer despite its USPSTF recommendation for screening.

Incidence, survival, and mortality data

Surveillance, Epidemiology, and End Results Program (SEER) and National Centers for Health Statistics data were obtained from the

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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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SEER*Stat resource (3). Crude (i.e., not age-adjusted) incidence and cancer-specific survival rates (Supplementary Figs. S1 and S2) included persons diagnosed with primary invasive cancer in one of 18 regions (SEER18) from 2006 to 2015 and followed for vital status through December 31, 2016; restricted to those ages 50 to 79 years. We chose this age grouping to minimize competing risks of noncancer-related deaths among persons aged 80 and older and to overlap with existing cancer screening recommendations (e.g., USPSTF breast, colorectal, and lung) However, we repeated all analyses [Supplementary Tables S2 and S3 for an alternative age grouping that included persons ages 40–79 to better overlap with the recommendations that include persons 40–49 (e.g., USPSTF cervical, ACS breast and colorectal)]. Only the first eligible record for each person was included (e.g., excluding subsequent primary cancer diagnoses that occurred within the observation period). Survival statistics additionally excluded: cases diagnosed via autopsy or death certificate, and cases with zero survival time or with missing or unknown cause of death.

Within SEER, stage at diagnosis was classified according to the American Joint Committee on Cancer (AJCC) 6th edition (21) as stage I, II, III, IV, or unknown/unstaged. Cancer type was defined using SEER Site Recode, which is based on ICD-O-3 site and histology classifications. The 17 cancer types (described above) were analyzed individually, however, given that leukemia and brain/other nervous system cancers are not staged in the AJCC 6th edition scheme (e.g., AJCC stage at diagnosis is uniformly unknown), we grouped them together with other cancers not included in the ACS top 10 lists (1). Thus, the category "residual cancers" included leukemia, brain and other nervous system, and all other cancer types not included in the ACS top 10 lists (1). The category "All Cancers" comprised all invasive cancers reported to SEER, including the 15 selected for detailed individual analysis and the "residual cancers" category. NCHS crude mortality rates were calculated for all persons ages 50 to 84 years at time of death from 2006 to 2015 for specific causes of death categorized using the SEER cause of death recode (22).

Statistical analysis

The SEER incidence and survival rates were considered in a hypothetical cohort of 100,000 persons to estimate the potential reductions in mortality that could occur from detection of cancers before metastasis. Crude incidence rates per 100,000 were used to estimate numbers of stage-specific cancers that would arise within 1 year, whereas to estimate the absolute numbers of cancer-specific deaths that would accrue over 5 years of follow-up, the type- and stage-specific rates were multiplied by the corresponding type- and stage-specific 5-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). Estimation of the "all cancers" incident cases included those attributable to residual cancers. Estimations of the "all cancers" number of deaths were based on summing the stage-specific deaths for each cancer type category shown, including the residual category, for which deaths were estimated by multiplying the overall (e.g., not stage-specific) incidence and 5-year cumulative probabilities of death.

Using the hypothetical cohort, we considered baseline stage and death rates based on current SEER statistics (labeled as SEER) and two hypothetical scenarios by which all cancers in the cohort would be diagnosed before metastasis (labeled as "Stage Shift IV to III" and "Stage Shift IV to III, II, I"). In the first scenario, to mimic the effect of detecting stage IV cancer at stage III, all persons diagnosed with cancer at stage IV were assumed to have the same probability of cancer-related death as those diagnosed in stage III. In the second scenario, to more broadly understand the potential benefit of early cancer detection, we similarly assumed that all people diagnosed at stage IV cancer had the same probability of cancer-related deaths as those diagnosed in stage III, stage II, and stage I (one third each). Under each scenario, the proportion of deaths attributable to the cancer types with USPSTF-recommended screening paradigms (lung, colon, and breast) was also calculated. To compute the overall number of deaths expected under each scenario, stage-specific deaths were estimated for each cancer type (including residual) and summed. Calculations were additionally reviewed for the alternative age grouping 40 to 79 and are shown in Supplementary Tables S2 and S3.

Results

On average, 197 persons per 100,000 ages 50 to 79 years were diagnosed with metastatic (stage IV) cancer per year. This represented 18% of all invasive cancer diagnoses and 46% of all cancer-related deaths occurring within 5 years of diagnosis (**Table 1**). Lung cancer had the highest rate of diagnosis at metastatic stage (67 per 100,000), comprising one third of all cancers that were metastatic at diagnosis. Other cancers that were major contributors to the overall absolute occurrence of metastatic cancer were colorectal, non-Hodgkin lymphoma, pancreatic, and oral cavity/pharynx. Together, these five cancer types represented about two thirds (65%) of all metastatic cancer. Cancers for which at least one third were diagnosed at stage IV included pancreatic, lung, esophageal, oral cavity/pharynx, ovarian, and non-Hodgkin lymphoma (including cancers with unknown stage in the denominator). Five-year probability of cancer-specific death associated with diagnosis at stage IV was greater than 85% for lung, colorectal, pancreatic, liver, and esophageal cancers and greater than 60% for kidney, thyroid, and oral cavity/pharynx cancers. In contrast, 17% of liver cancers were diagnosed at stage IV, corresponding to 21% of all liver cancer–related deaths. The full stage-specific distributions of incidence and 5-year probability of cancer-related death are shown in Supplementary Figs. S1 and S2.

To estimate hypothetical reductions in absolute cancer–related deaths that could occur if cancers currently diagnosed at metastatic stage were diagnosed at earlier stages, we first considered a simple hypothetical "Stage Shift 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 this scenario were then compared for single cancer types, various groups of cancers, and all cancers combined (**Table 2**). Considering lung cancer, for example, all 67 individuals with stage IV that would have a 93% lung cancer–specific probability of death within 5-years (based on SEER statistics), were reassigned the outcome for stage III, 75% (Supplementary Fig. S2). Under this hypothetical scenario, the expected cancer-specific deaths for stage IV lung cancer decreased from 107 to 95 (or an absolute reduction of 12 deaths and a relative reduction of 11% of deaths). The largest absolute reductions were projected for lung and colorectal cancers (12 and 11 deaths, respectively); however, the relative reduction was much greater for colorectal (38%) than for lung (11%). Large relative reductions of individual cancer-specific deaths were also projected for cancers of the kidney/renal pelvis, prostate, and thyroid cancers (46%, 56%, and 79%, respectively), although for thyroid cancer, the expected deaths in 100,000 persons was only one. For both pancreatic and liver cancers, the 5-year cancer-specific death rates for stages III and IV were all greater than 90% (Supplementary Fig. S2). When considering only the four cancer types expected to contribute the most individual absolute deaths (lung, colorectal, prostate, and breast cancer), the expected

Table 1. Average annual incidence and 5-year cumulative probability of cancer-related deaths for cancers diagnosed at metastasis (stage IV) and overall, by cancer type, among persons ages 50–79 years, SEER18, 2006–2015.

Cancer type	Incidence rate[a]		Proportion stage IV	Probability of cancer-related death		Proportion of deaths due to stage IV[c]
	Stage IV	All[b]		Stage IV	All[b]	
All cancers	196.6	1,078	0.18	0.75	0.29	0.45
Selected cancers						
Lung	66.7	147.2	0.45	0.93	0.71	0.58
Colorectal	18.7	93.9	0.20	0.84	0.29	0.56
Pancreas	14.9	30.2	0.49	0.97	0.88	0.54
Liver	4.1	24.7	0.17	0.97	0.75	0.21
Breast	8.8	163.1	0.05	0.68	0.09	0.39
Non-Hodgkin lymphoma	15.2	43.5	0.35	0.31	0.22	0.48
Prostate	12.5	198.1	0.06	0.43	0.04	0.59
Kidney	6.4	37.8	0.17	0.83	0.21	0.64
Oral cavity and pharynx	12.8	28.9	0.44	0.40	0.28	0.62
Ovary	4.2	15.1	0.28	0.75	0.50	0.41
Esophagus	4	11.5	0.35	0.94	0.72	0.45
Bladder	3.4	20.9	0.16	0.79	0.30	0.41
Uterine	2.6	39.2	0.07	0.78	0.16	0.30
Melanoma	1.9	46.4	0.04	0.74	0.08	0.34
Thyroid	2.7	22.3	0.12	0.24	0.04	0.83

[a]Crude average annual rates per 100,000.
[b]Includes unknown/unstaged cancers.
[c]Estimated from multiplying stage-specific incidence and 5-year probabilities of death.

death reduction was 32. When considering all cancer types combined, the expected reduction in total cancer-specific deaths was 71 (from 336 to 285), reflecting a 15% reduction of expected cancer-related deaths overall.

The second hypothetical scenario was "Stage Shift IV to III, II, and I," whereby one third of stage IV cancers were shifted to stage III, one third shifted to stage II, and the last third shifted to stage I (**Table 3**). Considering lung cancer under this scenario, for example, one third of the 67 stage IV lung cancers were assigned the same outcome as stage III (24.9%), one third assigned the outcome of stage II (41.6%), and one third assigned the outcome of stage I (69.1%); this resulted in a 26% decrease in the expected number of cancer-specific deaths (from 107 to 80, or an absolute reduction of 27 deaths per 100,000). For pancreatic and liver cancers, the estimated reductions were small from

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

	Cancer diagnoses in first year	Deaths after 5 years	Deaths after hypothetical stage shift	Absolute deaths averted	Proportion deaths averted[a]
All cancers	1,078	336	285	51	0.15
Selected cancers					
Lung	147	107	95	12	0.11
Colorectal	94	28	18	11	0.38
Pancreas	30	26	26	0	0.01
Liver	25	19	19	0	0.02
Breast	163	15	11	4	0.27
Non-Hodgkin lymphoma	44	10	9	1	0.09
Prostate	198	9	4	5	0.56
Kidney	38	8	5	4	0.46
Oral cavity and pharynx	29	8	6	2	0.22
Ovary	15	8	7	1	0.11
Esophagus	12	8	8	1	0.10
Bladder	21	7	5	1	0.17
Uterine	39	7	6	1	0.18
Melanoma	46	4	3	1	0.17
Thyroid	22	1	0	1	0.79

[a]Estimated deaths shown rounded up to nearest integer, while proportion based on division of estimates with two decimal places.

Table 3. Absolute numbers of cancer cases and deaths expected in a hypothetical cohort of 100,000 persons after 5 years of follow-up, assuming a stage shift whereby one third of stage IV cancers had outcome similar to stage III, one third had outcome similar to stage II, and one third had outcome similar to stage I, based on incidence and cancer-specific mortality rates for persons ages 50–79 years from SEER18, 2006–2015.

	Cancer diagnoses in first year	Deaths after 5 years	Deaths after hypothetical stage shift	Absolute deaths averted	Proportion deaths averted[a]
All cancers	1,078	336	255	81	0.24
Selected cancers					
Lung	147	107	80	27	0.26
Colorectal	94	28	16	13	0.45
Pancreas	30	26	24	3	0.11
Liver	25	19	18	1	0.06
Breast	163	15	10	5	0.34
Non-Hodgkin lymphoma	44	10	8	2	0.18
Prostate	198	9	4	5	0.57
Kidney	38	8	4	4	0.53
Oral cavity and pharynx	29	8	5	3	0.36
Ovary	15	8	6	2	0.25
Esophagus	12	8	7	2	0.18
Bladder	21	7	5	2	0.25
Uterine	39	7	5	2	0.24
Melanoma	46	4	3	1	0.26
Thyroid	22	1	0	1	0.80

[a]Estimated deaths shown rounded up to the nearest integer, while proportion based on division of estimates with two decimal places.

both absolute and relative standpoints, however, shifting the four cancer types expected to contribute the most individual absolute deaths (lung, colorectal, prostate, and breast cancer) resulted in an expected reduction of 50 cancers, or about 45% of the total cancer-specific deaths. When considering all cancer types combined, the expected reduction in total cancer-specific deaths was 110 (from 325 to 255 per 100,000), just over one third (24%).

Figure 1 compares the potential change in total number of cancer-related deaths by cancer type for both of the hypothetical stage-shift scenarios to the current SEER statistics. Across all three summaries, the cancer types with USPSTF-recommended screening programs (lung, colorectal, and breast) contributed to approximately half of the expected cancer-related deaths within 5 years (**Fig. 1**). The cancer types for which a substantial reduction of overall expected

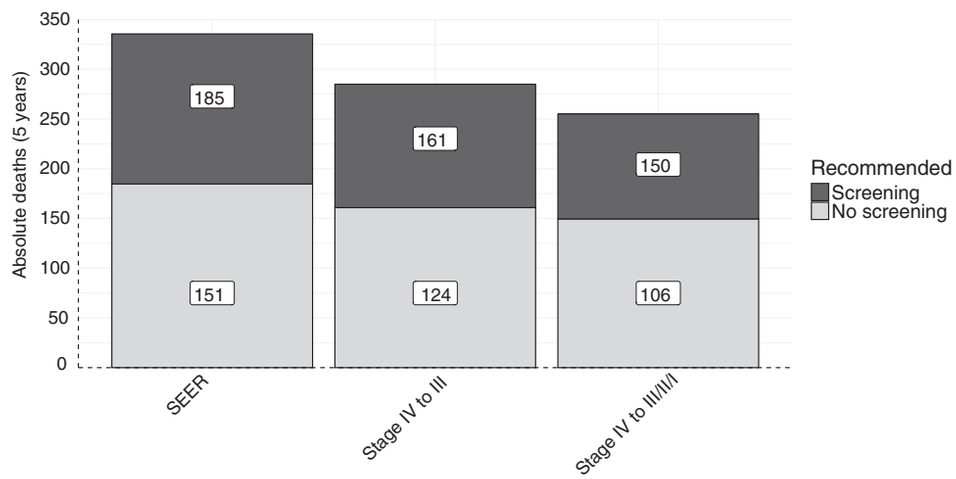

Figure 1.
Estimated 5-year cancer-related deaths under hypothetical stage shift scenarios among U.S. persons ages 50–79, with attention to recommended screening status of cancer types. Total cancer-related deaths expected in hypothetical cohort of 100,000 persons with characteristics similar to the SEER18 population ages 50–79 during the years 2006–2015. "SEER" refers to real SEER population. "Stage IV to III" refers to the scenario under which all stage IV cancer has outcome similar to stage III. "Stage IV to III/II/I" refers to scenario under which one third of stage IV cancers were diagnosed at stage III, one third diagnosed at stage II, and one third diagnosed at stage I. "Screening" refers to cancer types with USPSTF-recommended screening programs (lung, colorectal, and breast).

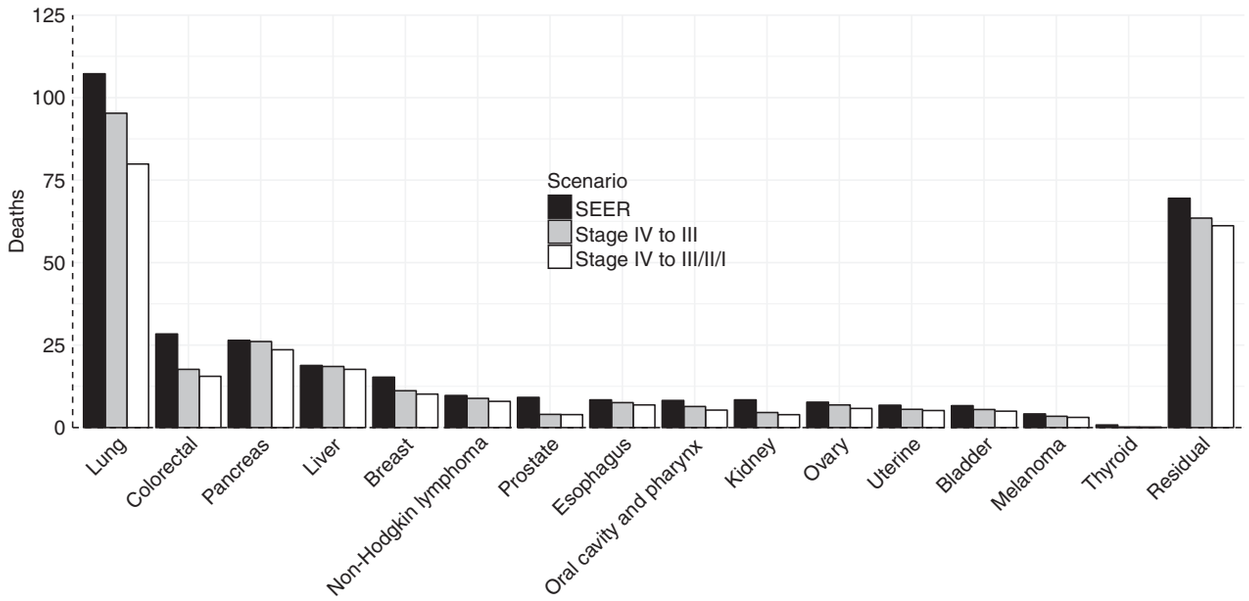

Figure 2.

Contributions of single cancer types to estimated 5-year cancer-related deaths under hypothetical stage shift scenarios among U.S. persons ages 50–79. Single cancer contributions to total cancer-related deaths expected in hypothetical cohort of 100,000 persons with characteristics similar to the SEER18 population ages 50–79 during the years 2006–2015. "SEER" refers to real SEER population. "Stage IV to III" refers to the scenario under which all stage IV cancer has outcome similar to stage III. "Stage IV to III/II/I" refers to scenario under which one third of stage IV cancers were diagnosed at stage III, one third diagnosed at stage II, and one third diagnosed at stage I. "Residual" cancers included cancer types not included in the ACS top 10 lists of contributors to cancer incidence and mortality for men and women (each), as well as leukemia and brain and other nervous system, which have unknown stage in the AJCC 6th edition scheme.

cancer-related deaths within 5 years was observed included lung, colorectal, prostate, and kidney cancers (**Fig. 2**). Although single cancers, especially lung and colorectal cancer, represent important contributors to overall cancer-related mortality, diagnosis of any cancer at stage IV represented a major contributor to the overall cancer burden. Among the hypothetical cohort of 100,000 persons, 336 cancer-related deaths were expected to occur within 5 years, the majority of which consisted of stage IV cancers. In contrast, under the stage-shift scenarios, deaths decreased and proportions of persons living after stage II and III cancer diagnosis increased.

Figure 3 puts the hypothetical reductions in context, comparing the expected number of deaths averted in these scenarios per year (51 and 81 per 100,000, respectively) to the expected deaths from accidents and unintentional injuries (51 persons per 100,000), or diabetes (55 persons per 100,000), or cerebrovascular diseases (75 per persons 100,000) per year among persons ages 50 to 84 over the same time period (2006–2015; ref. 22).

Discussion

This analysis, using contemporary SEER data, suggests that meaningful absolute and relative reductions in cancer-related deaths could occur if cancers currently diagnosed after metastasis were diagnosed earlier. Even for the more conservative scenario that assumed cancers diagnosed after metastasis could be detected at stage III, the relative reduction in overall cancer-related deaths could be as large as 15%. With the scenario that assumed more effective early detection (stage IV cancers diagnosed equally at stages I, II, and III), there could be a one-quarter reduction in overall cancer-related mortality, corresponding to a substantial reduction in all-cause mortality.

Our assessment focused on understanding the absolute contributions of downward stage shifts for individual and multiple cancers to overall cancer and all-cause mortality rates. We found that lung and colorectal cancers had the highest absolute rates of metastatic cancer and would be the largest contributors of deaths averted through earlier detection. We observed this in contemporary SEER data incorporating current patterns of utilization of screening for these cancers. Altogether, our data suggested that lung, breast, and colorectal cancers, currently targeted by USPSTF recommendations represent about half of cancer-related deaths, leaving the other half unrepresented. However, the proportion of deaths actually being addressed by recommended screening is likely much lower than one half, given that sizable proportions occur among unscreened persons (14). For example, in lung cancer, more than 70% of cases are diagnosed in persons not meeting USPSTF eligibility for lung screening (23) and utilization of screening among eligible persons remains below 5% (13, 24). With over half of all cancer-related deaths not being addressed by existing guideline-based screening, there remains large potential benefit of new approaches, especially those targeting multiple cancers.

We also observed that cancers with poor outcomes at all stages (pancreas and liver) might not avert many deaths despite earlier detection. It has been suggested that cancer screening approaches targeting single cancer types cannot be cost-effective due to their low-population prevalence, and that the number needed to screen effectively is much smaller for all cancers combined than for single cancers (5). Here, we show that potential benefits of death averted through early detection would accumulate across a spectrum of cancers, further supporting the notion that more deaths could be averted through screening multiple versus single cancers.

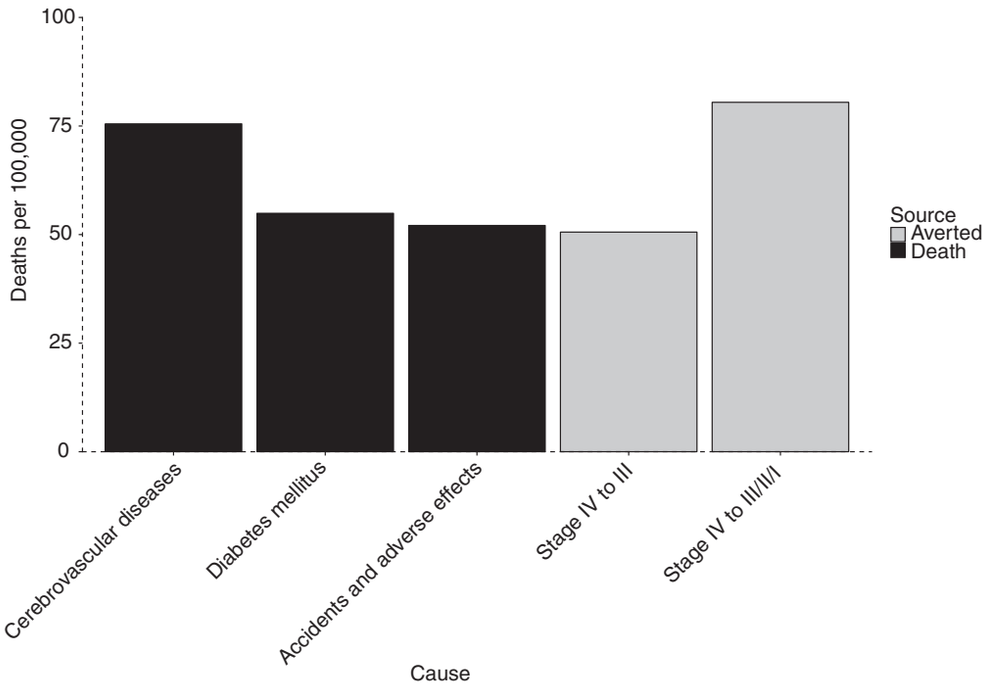

Figure 3.
Comparison of rates of deaths averted under hypothetical stage shift to other causes of death among U.S. persons ages 50–84, National Center for Health Statistics, 2006–2015 (22).

One strength of this analysis is the use of SEER data, which documents real-world cancer incidence and death in a large and representative U.S. population, reflecting contemporary patterns of utilization of cancer screening and treatment. Another strength involves the breadth of our assessment, which included 15 of the largest single-cancer contributors to the U.S. cancer burden. In addition, our estimates of deaths avertable accounted for the influence of uncommon, unstaged, and non-AJCC–staged cancers (e.g., brain or leukemia), which resulted in more conservative estimates.

This assessment cannot address the likelihood that cancers diagnosed at different stages may also have differences in tumor, clinical, and/or patient characteristics. Adjustment for such characteristics was beyond the scope of this assessment, as most are not collected by SEER (e.g., screen-detected status, detailed molecular characteristics, and gene expression profiles). Furthermore, our hypothetical, simplistic scenarios regarding shifts in stage at diagnosis did not attempt to address the possible influences of existing screening programs on the observed SEER stage and outcome distributions, including lead time and length biases (25) and overdiagnosis (26). For example, it has been suggested that imaging-based modalities for cancer screening (e.g., mammography, ref. 27, and low-dose CT for lung cancer, refs. 28, 29) may result in greater detection of indolent or slower growing cancers (e.g., "overdiagnosed cancers") with excellent outcomes that would presumably be more common in patients diagnosed at earlier stages. Therefore, it is possible that our second scenario, which assigned stage I outcomes to one third of cancers, could be affected by overdiagnosed cancers, especially indolent breast and prostate cancers. By designing simple scenarios involving only downward stage shift of cancers currently diagnosed at stage IV, as opposed to sophisticated shifts among earlier stages, our quantifications of potential benefit are grounded in the assumption that most cancers that go on to metastasize can be detected while locoregional (30). Indeed, the potential to reduce overall cancer-related mortality by 24% warrants both further detailed analyses to understand the single- and multi-cancer strategies for early detection that will maximize reduction of overall cancer-related mortality, as well as continued development of new technologies to diagnose cancers before metastasis.

Our assessment quantified possible reductions in cancer-related deaths from detection before metastasis, but does not speak to additional considerations others have articulated as necessary for earlier detection to reduce cancer-related deaths (31, 32), including understanding of a sufficiently long preclinical phase amenable to screening, and availability of treatment. Although prior lists of conditions did not specifically contemplate simultaneous detection of multiple cancers, additional requirements for such tests include ability to identify anatomic site of origin to direct efficient localization and treatment, very high specificity to reduce false positives, and preferential detection of aggressive as opposed to indolent cancers.

New and innovative approaches are urgently needed to reduce the societal burden of cancer. The absolute burden of cancer is expected to grow substantially in the United States and elsewhere with the aging of the "Baby Boomer" cohort into peak ages for cancer incidence (33). Recent projections suggest that the number of new cancer diagnoses in the United States increased over the last decade by 24% in men to more than 1 million cancers per year, and by 21% in women to more than 900,000 cases per year (34), attributable mostly to expansion of the populations at highest age-related risk of cancer. Increases in the cancer burden have also been projected from global increases in high body mass index (35). Innovation in cancer treatment, which has resulted in the development of new targeted and immune-based therapies, is yielding improvements in outcome at the population

level (36, 37). Synergistic with these therapies will be novel technologies for earlier cancer detection. To understand the overall potential of these innovations to reduce the burden of cancer at the population-scale, more sophisticated and dynamic estimations of their clinical, societal, and economic benefits are needed.

Disclosure of Potential Conflicts of Interest

C.A. Clarke is Principal Clinical Scientist at and has ownership interest in GRAIL, Inc. E. Hubbell is Distinguished Bioinformatics Scientist at and has ownership interest in GRAIL, Inc. A.-R. Hartman has ownership interest in GRAIL, Inc. G.A. Colditz is an advisor for GRAIL, Inc. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.A. Clarke, E. Hubbell
Study supervision: C.A. Clarke, A.-R. Hartman, S.L. Gomez

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