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Examining the Potential for Lead-Time Bias by Estimating Stage-Specific Proportions of Deaths Due to Diagnosed Cancer

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INTRODUCTION

- Evaluating the potential impact of cancer screening on the population health burden of cancer can be complicated by lead-time bias, which occurs when cancer is detected earlier in time, but with no change in lifespan
- In contrast, analyses of mortality as an endpoint can overcome lead-time bias by incorporating long-term follow-up until death for all patients
- Identifying differences in causes of death by stage at cancer diagnosis can shed light on patient populations that would potentially benefit the most from earlier cancer detection
- Quantifying cause-specific mortality by stage at diagnosis also clarifies whether earlier detection of individual or multiple cancer types is likely to have a statistically observable public health impact on all-cause mortality, which is often identified as a primary or secondary outcome of interest in cancer screening trials
- Previous studies of causes of death among cancer patients have typically focused on one or a few cancer types or specific causes of death, and usually do not report results by stage at cancer diagnosis[1-3]

OBJECTIVE

- We undertook a novel analysis of causes of death by type and stage among US cancer patients using population-based cancer registry data to gain greater insight into mortality patterns by stage of cancer at diagnosis, while using long-term mortality data to measure the population-level impact of earlier-stage cancer diagnosis without the influence of lead-time bias
- We analyzed the following mortality outcomes by stage at diagnosis for all cancers combined and by index cancer type:
  - Overall causes of death, including index cancer (i.e., first incident cancer), non-index cancer (i.e., subsequent incident cancer other than the index cancer), and non-cancer
  - Specific non-index cancer and non-cancer causes of death

ACROSS CANCER TYPES, EARLY-STAGE CANCER USUALLY IS NOT FATAL, BUT LATE-STAGE CANCER USUALLY IS.

- Across all cancer types, a minority of cancer patients diagnosed at stages I–II (27%) went on to die from their index cancer, whereas most stage IV cancer patients (85%) did (**Figure 1**, All Types; **Table 1**)
  - Starting at stage III, the majority of deaths were due to the index cancer (63%). As expected, the highest proportion of deaths from the index cancer (85%) occurred at stage IV
  - From another perspective, of the 427 050 index cancer deaths with known stage at diagnosis, 40% were diagnosed at stage IV, 22% at stage III, 21% at stage II, and 17% at stage I
- These proportions were not appreciably affected after excluding index cancers with currently recommended screening protocols in the US (i.e., colorectal, female breast, lung, and uterine cervix)

Figure 1. Stage-specific distribution of causes of death (extrapolated if not observed) for cancer cases overall and by first primary incident cancer type, aged 50–84 years at diagnosis in 2006–2010, followed for mortality through 2019, Surveillance, Epidemiology, and End Results (SEER) 17 registries. Cancer types are ordered by numeric topography code according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). HR: hormone receptor; IH: intrahepatic; U: unknown/missing stage.

Table 1. Causes of death (extrapolated if not observed) by stage at diagnosis for first incident primary cancer cases aged 50–84 years at diagnosis in 2006–2010, followed for mortality through 2019, SEER 17 registries.

Stage at Diagnosis	Cause of Death*					
	Index Cancer		Other Cancer		Non-Cancer	
	n	%	n	%	n	%
I	70 717	26	33 221	12	164 466	61
II	88 757	27	42 535	13	194 428	60
III	95 374	63	10 015	7	46 880	31
IV	172 202	85	4351	2	25 793	13
Unknown/Missing	121 365	60	11 454	6	71 051	35

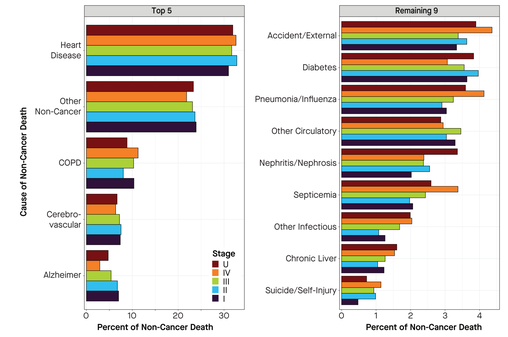
*Percentages may not sum to 100% due to rounding.

- The pattern of a lower proportion of index cancer deaths at earlier stages was observed across all index cancer types, but absolute percentages varied substantially by type (**Figure 1**, individual cancer types)
  - The lowest proportions of deaths from early-stage index cancers were seen for thyroid cancer, melanoma, uterine cancer, prostate cancer, and breast cancer
  - The highest proportions of deaths from early-stage index cancers were observed for cancers of the pancreas, liver/intrahepatic bile duct, esophagus, lung, and stomach
- In theory, if universal cancer screening were implemented in this population such that all of the stage IV index cancers were instead detected at stage III, 33 585 (6%) index cancer deaths would be prevented
  - If universal cancer screening instead led to detection of one third of the stage IV index cancers at each of stages I, II, and III, then, in theory, 61 244 (11%) index cancer deaths would be prevented
- Leading causes of non-index cancer death at each stage of index cancer diagnosis were similar to those in the general US population (**Figure 2**)[4]
  - For all index cancer types combined, the leading non-index cancer cause of death was lung cancer, with little variation in the percentage of attributed deaths across stages I–IV index cancers
  - The next most common non-index cancer causes of death were pancreatic cancer, colorectal cancer, liver/intrahepatic bile duct cancer, and leukemia
    - Breast and prostate cancers were precluded from being common causes of non-index-cancer death in part by their high frequency as index cancers

Figure 2. Stage-specific distribution of detailed non-index cancer causes of death (extrapolated if not observed) for cancer cases of all types combined, aged 50–84 years at diagnosis in 2006–2010, followed for mortality through 2019, SEER 17 registries. Leading causes of non-index cancer death are ordered by frequency for stage I index cancer, with different scales for left and right panels. U: unknown/missing stage.

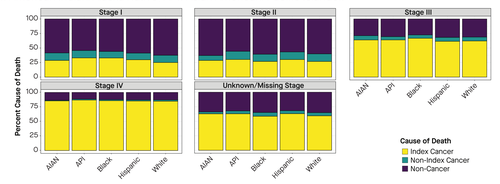
- The patterns of non-index cancer deaths were largely mirrored in analyses by type of index cancer (data not shown)
  - Lung cancer generally caused the plurality of non-index cancer deaths, especially for smoking-related index cancers (e.g., oral cavity/pharynx, esophagus, and bladder, respectively), followed by other leading causes of cancer death in the general population
  - Some concordance was also evident between index cancers and deaths from non-index cancers with shared risk factors (e.g., breast and ovary)
- Leading causes of non-cancer death at each stage of index cancer diagnosis were similar to those in the general US population (**Figure 3**)[5]
  - Across nearly all index cancer types at all stages, heart disease was the leading cause of non-cancer death, followed by COPD
  - Some causes of death, such as Alzheimer disease and diabetes, were somewhat more common after stages I–II cancer than stage IV, whereas others, such as septicemia, other infectious disease, and suicide/self-inflicted injury, were slightly more frequent after stage IV than stages I–II cancer

Figure 3. Stage-specific distribution of detailed non-cancer causes of death (extrapolated if not observed) for cancer cases of all types combined, aged 50–84 years at diagnosis in 2006–2010, followed for mortality through 2019, SEER 17 registries. Leading causes of non-cancer death are ordered by frequency for stage I index cancer, with different scales for left and right panels. COPD: chronic obstructive pulmonary disease; U: unknown/missing stage.



- Racial/ethnic differences in cause of death among cancer patients (1.3-fold difference in stage I index cancer death by race/ethnicity) were smaller than differences by stage at index cancer diagnosis (3.3-fold difference by stage) (**Figure 4**)
  - The frequency of death from stage I index cancer was modestly higher among all non-White groups, including Hispanic (30%) and non-Hispanic Black (33%), API (33%), and AIAN (29%) patients, than non-Hispanic White (25%) patients
  - The apparent racial/ethnic disparity in index cancer deaths diminished with advancing stage at diagnosis, especially at stage IV (85–87% for all racial/ethnic groups)

Figure 4. Stage-specific distribution of causes of death (extrapolated if not observed) by race/ethnicity for cancer cases overall, aged 50–84 years at diagnosis in 2006–2010, followed for mortality through 2019, SEER 17 registries. "Hispanic" includes all races and does not overlap with other racial/ethnic groups. AIAN: American Indian/Alaska Native; API: Asian American/Pacific Islander.



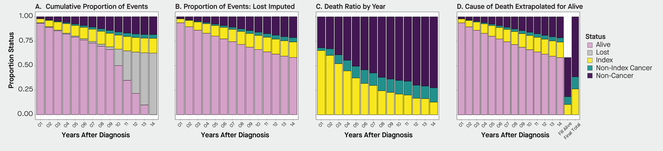
CONCLUSIONS

- Across all cancer types, the percentage of patients who went on to die from their cancer was three times greater at stage IV than at stages I–II
  - Stage III index cancer mortality was more than double that at stages I–II
  - These results reflect improved long-term outcomes by stage within cancer types, as well as differences in the types of cancer typically diagnosed at each stage
- As mortality patterns are not influenced by lead-time bias, our findings suggest that earlier stage at diagnosis generally translates to reduced risk of cause-specific death from cancer
  - Earlier cancer detection across the representative spectrum of cancer types that develop in a general population has potential to improve long-term mortality outcomes
- The modestly higher percentages of death from stage I index cancer among Black, Hispanic, API, and AIAN patients compared with non-Hispanic White patients indicate possible inequities in health care access and/or utilization for treatment and management of early-stage cancer
  - Differences in histopathologic subtype and tumor behavior for certain cancer types may also play a role
  - These findings indicate that delayed diagnosis and late-stage presentation are not the only explanations for well-known racial/ethnic disparities in cancer outcomes
- Given that each cancer type contributes modestly to overall mortality, single-cancer screening generally cannot be expected to reduce all-cause mortality[6,7]
  - Multi-cancer screening strategies, in contrast, can potentially reduce all-cause mortality at a population level by simultaneously reducing cause-specific mortality from dozens of cancers

METHODS

- This study uses cancer incidence and survival data from the US SEER population-based cancer registries for 17 geographic regions, including adults diagnosed with a first incident cancer at ages 50–84 years in 2006–2010, followed for mortality through December 31, 2019;[8] causes of death were classified by SEER based on death certificates
  - These diagnosis years were selected to enable uniform classification of cancer stage according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging manual,[9] and to allow for at least 9 years (up to 13 years and 11 months) of follow-up after cancer diagnosis
  - Cases were grouped by primary anatomic site using ICD-O-3 topography codes and by AJCC stage at diagnosis
    - We separately classified breast cancer as HR-positive, HR-negative, or HR-unknown based on estrogen receptor and progesterone receptor status using SEER Extent of Disease data, and we separately classified lung cancer as small-cell or non-small-cell carcinoma using ICD-O-3 morphology codes
- Subjects were followed until death, loss to follow-up, or the end of the study on December 31, 2019, whichever occurred first
- For subjects without an observed death, we extrapolated the likely cause of death in one of two ways, thereby generating an analytic cohort that was followed completely until death by observation or by extrapolation
  - For subjects lost to follow-up in any given year after their index cancer diagnosis, we imputed the cause of death based on the observed distribution of causes of death in that year (Figure S1)
  - For subjects who were alive at the end of study follow-up, we extrapolated the cause of death based on the observed distribution of causes of death in the most recent four years of observed data (Figure S1)
    - This extrapolation is supported by the plateauing in risk of index cancer death after approximately 10 years of follow-up, generally equating to statistical "cure"[10]
- To estimate the change in the distribution of causes of death that could arise from earlier stage at diagnosis due to universal cancer screening, we calculated proportions of cause-specific deaths under two hypothetical scenarios:
  - 1) if all stage IV cancers were shifted to stage III, and
  - 2) if all stage IV cancers were equally distributed among stages I, II, and III[11]
  - We calculated these values separately for each index cancer type, and then summed them across all cancer types
- This study is limited by the finite follow-up period, precluding observation of causes of death for a large proportion of patients
  - Although we compensated for changes in cause of death over time by using the last years of the follow-up period, simple extrapolation may overestimate deaths due to index cancers, since the risk of non-cancer death increases with each year of age, whereas index cancers may reach a residual constant risk of death[8]
- By restricting this analysis to cases diagnosed between 2006 and 2010, we enabled uniform classification of cancer stage according to a single staging system, and we also reduced the proportion of patients with unobserved causes of death; however, we thereby omitted years covering more recent advances in cancer management, such as effective treatments
- Analytic code was written in R using the tidyverse package[12,13] and is available upon request

Figure S1. Schematic of extrapolation of causes of death for subjects without observed death during study follow-up. A) Original data with observed vital status at the end of follow-up, including subjects lost to follow-up. B) Imputation of causes of death for subjects lost to follow-up, based on the appropriate distribution of causes of death in each year after diagnosis. C) Observed distribution of causes of death by follow-up year after diagnosis. D) Extrapolation of future causes of death for subjects alive at the end of follow-up, based on the distribution of causes of death in the last four years of follow-up.



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Disclosures

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