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MODELING REDUCTIONS IN ABSOLUTE CANCER MORTALITY FROM DIAGNOSING CANCERS BEFORE METASTASIS, 2006-2015

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INTRODUCTION

- Cancer is a major contributor to morbidity and mortality in the United States (US), with 1,762,450 new cancer cases diagnosed and 606,880 cancer deaths estimated for 2019.[1]
- Earlier detection may alter the course of cancer, enable more effective treatments, and improve patient outcomes.[2]
- New technologies are being developed to screen populations for multiple cancer types simultaneously.

OBJECTIVE

- Understand broadly the potential benefit of early cancer detection using the latest data from the Surveillance, Epidemiology, and End Results (SEER) Program[3] to estimate hypothetical reductions in absolute cancer deaths if cancers diagnosed after metastasis (stage IV) were diagnosed earlier, when the likelihood for survival is higher.

METHODS

- Data were obtained for persons aged 50–79 years when diagnosed with primary invasive cancer in 18 SEER regions between 2006–2015.[3]
- We focused on 15 cancer types identified in 2019 by the American Cancer Society as among the top ten contributors to cancer incidence or mortality in US males and females,[1] including lung, colorectal, pancreas, liver, breast, non-Hodgkin lymphoma, prostate, kidney, oral cavity and pharynx, ovary, esophagus, bladder, uterine, melanoma, and thyroid; we did not include cancers not staged by traditional systems (e.g., leukemia, brain), grouping those and other less common cancers into the "other cancers" category for analysis (see Figure 1). The "all cancers" category for analysis includes all invasive cancers reportable to SEER, including those that are not staged by traditional systems.
- Assuming earlier detection (downward stage shift), numbers of deaths were estimated by assigning associated stage-specific incidence and 5-year probability of cancer death. Estimated numbers and percentages of deaths averted within 5 years of diagnosis were calculated by multiplying incidence and 5-year probability of cancer deaths across five stages (I, II, III, IV, and unknown).
- We estimated these deaths under two stage-shift scenarios:
  - All persons who would be diagnosed with metastatic (stage IV) cancers would instead be diagnosed with stage III cancers and the corresponding probability of death;
  - One-third of persons who would be diagnosed with stage IV cancers would be diagnosed with stage III cancers and the corresponding probability of death, one-third with stage II cancers and the corresponding probability of death, and one-third with stage I cancers and the corresponding probability of death.
- Hypothetical 5-year mortality rates were calculated for individual cancers, all cancers combined, and for cancers grouped based on those with or without a current recommendation for screening (in at-risk individuals) by the United States Preventive Services Task Force (USPSTF) (breast: mammography; colorectal: colonoscopy or stool tests; lung: low dose CT scan; cervical: cytology and viral testing).[4]
  - Cervical cancer was excluded from the screen-recommended versus not-screen recommended cancer type analysis because its occurrence was not high enough to meet the criteria for the 15 selected cancers.

RESULTS

Overall Cancer Burden

- In a hypothetical cohort of 100,000 persons aged 50–79, 1,078 were estimated to be diagnosed with any cancer the first year, of whom 310 were expected to die within 5 years (Table 1).
  - Although the overall proportion of individuals diagnosed with stage IV cancer was 18% (197/1,078), the 147 individuals diagnosed with stage IV cancer expected to die within 5 years contributed to 45% (147/310) of the total expected deaths due to metastatic cancer.
  - Lung cancer represented the greatest single cancer contributor to stage IV diagnoses and deaths.

Table 1. Burden of Stage IV Disease

	Incidence rate*			5-year Probability of Cancer Death		
	Stage IV	All**	Proportion stage IV	Stage IV	All**	Proportion of deaths due to stage IV***
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	0.2	0.84	0.29	0.56
Pancreatic	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	0.4	0.28	0.62
Ovary	4.2	15.1	0.28	0.75	0.5	0.41
Esophageal	4	11.5	0.35	0.94	0.72	0.45
Bladder	3.4	20.9	0.16	0.79	0.3	0.41
Uterine	2.6	39.2	0.07	0.78	0.16	0.3
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

Average annual incidence and 5-year cumulative probability of cancer death for cancers diagnosed at metastasis (stage IV) and overall, by cancer type category, for persons aged 50–79 years, SEER18, 2006–2015.
**Crude average annual rates per 100,000.*
***Includes unknown/unstaged cancers.*
****Estimated from multiplying stage-specific incidence and 5-year probabilities of death.*

Stage Shift IV to III Scenario

- If all stage IV cancers were instead diagnosed at stage III, 22% fewer cancer deaths would be expected (representing an absolute reduction of 71 deaths) (Table 2).
- The greatest absolute reductions in deaths were estimated for lung, colorectal, and prostate cancers, but comparable reductions were estimated for the other cancer types cumulatively.
- Few deaths were estimated to be averted for liver and pancreatic cancer.

Table 2. Stage IV to III: Stage IV Cancers Assumed Outcome Similar to Stage III

	Cancer diagnoses in first year	Deaths after 5 years	Deaths after hypothetical stage shift	Absolute deaths averted	Proportion deaths averted
All cancers	1,078	325	254	71	0.22
Selected cancers					
Lung	147	107	95	12	0.11
Colorectal	94	28	18	11	0.38
Pancreatic	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
Esophageal	12	8	8	1	0.1
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

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 survival rates for persons aged 50–79 years from SEER18 2006–2015. All calculations include cancers of unknown stage. Estimated deaths are rounded up to the nearest integer while proportion based on division of estimates with 2 decimal places.

Stage Shift IV to III/II/I Scenario

- If all persons diagnosed with stage IV cancers had the same probability of cancer deaths as those diagnosed in stages III, II, and I (assuming one-third each), then 34% fewer cancer deaths would be expected (representing an absolute reduction of 110 deaths) (Table 3).
- The greatest absolute reductions in deaths were estimated for lung, colorectal, breast and prostate cancers, but similar reductions were estimated for the other cancer types cumulatively.
- Pancreatic and liver cancer had the least (6–11%) estimated reductions in deaths.

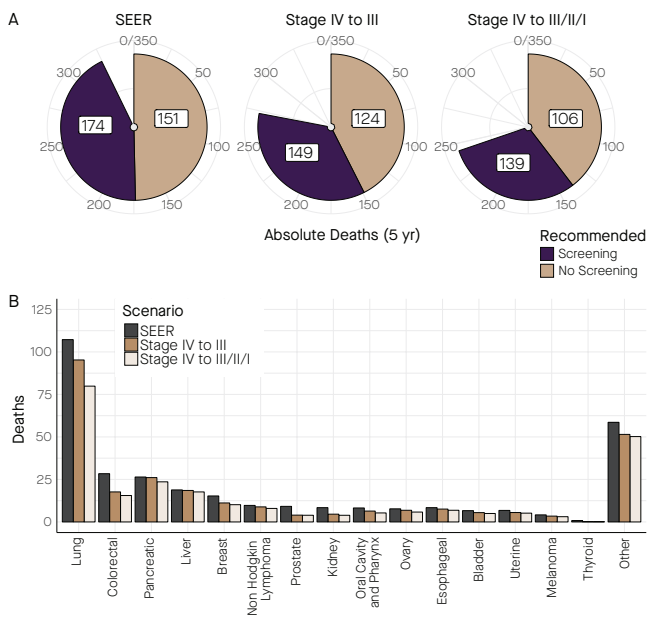
Table 3. Stage IV to III/II/I: Stage IV Cancers Assumed Outcomes Similar to Equal Parts Stages III, II, and I

	Cancer diagnoses in first year	Deaths after 5 years	Deaths after hypothetical stage shift	Absolute deaths averted	Proportion deaths averted*
All cancers	1,078	325	215	110	0.34
Selected cancers					
Lung	147	107	80	27	0.26
Colorectal	94	28	16	13	0.45
Pancreatic	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
Esophageal	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	0.8

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 survival rates for persons aged 50–79 years from SEER18 2006–2015. All calculations include cancers of unknown stage. All calculations include cancers of unknown stage. Estimated deaths are rounded up to the nearest integer while proportion based on division of estimates with 2 decimal places.

- Under all schemes (standard SEER diagnosis, and stage shift IV to III and IV to III/II/I scenarios), the cancer types that contributed to approximately half of the expected cancer deaths within 5 years (ie, the potential survival benefit) were those with USPSTF-recommended screening programs (lung, colorectal, breast) (Figure 1A).
- The individual cancer contribution to the overall expected cancer deaths within 5 years are shown for each scheme in Figure 1B.

Figure 1. Contributions to Five-year Cancer Deaths by Cancer Types

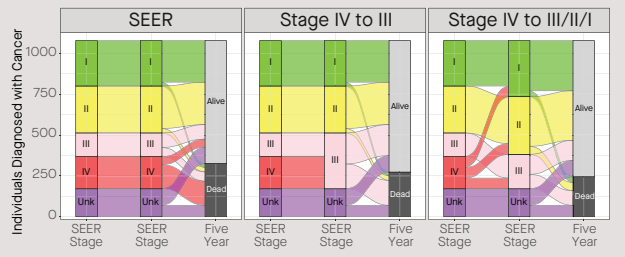


Contributions to the total number of expected cancer deaths in the hypothetical cohort divided by cofactors: A) Expected number of deaths within 5 years in SEER, Stage IV to III, and Stage IV to III/II/I scenarios were divided between selected cancers where a USPSTF recommended screening paradigm exists for at-risk individuals (lung, colorectal, breast), and the remaining cancers. B) Individual cancer contribution to absolute deaths under each scheme. 'Other cancers' is described in Methods.

CONCLUSIONS

- Although single cancers, especially lung and colorectal cancer, represent important contributors to overall cancer mortality, multi-cancer approaches may have greater potential impact to reduce cancer deaths.
- Cancer diagnosed at stage IV represents a major contributor to the overall cancer burden (Figure 2).
  - Detecting cancer before stage IV, even modest shifts to stage III, would offer substantial benefit in terms of reducing cancer deaths.

Figure 2. Hypothetical Reduction of Cancer Burden Assuming Earlier Cancer Detection



"Unk" includes cancers of unknown stage, including all cancer types for which AJCC staging information was not provided by SEER.

References

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2. Etzioni R, Urban N, Ramsey S, et al. The case for early detection. Nat Rev Cancer 3:243–252, 2003.
3. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) – Linked To County Attributes Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.
4. United States Preventive Services Task Force; USPSTF A and B Recommendations https://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/. Accessed May 13, 2019.

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