

Reporting net survival in populations: a sensitivity analysis in lung cancer demonstrates the differential implications of reporting relative survival and cause-specific survival

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Background: Net survival is commonly quantified as relative survival (observed survival among lung cancer patients versus expected survival among the general population) and cause-specific survival (lung cancer-specific survival among lung cancer patients). These approaches have drastically different assumptions; hence, failure to distinguish between them results in significant implications for study findings. We quantified the differences between relative and cause-specific survival when reporting net survival of patients with non-small cell lung cancer (NSCLC).

Methods: Cases of NSCLC diagnosed between 2004 and 2014 were extracted from the Surveillance, Epidemiology, and End Results database. The net survival of each stage-by-age stratum was expressed as cause-specific survival (Kaplan-Meier approach) and relative survival (Ederer II approach); percentage-point (pp) differences between the survival estimates were quantified up to 10 years postdiagnosis.

Results: Analyses included 263,894 cases. Cause-specific survival estimates were higher than relative survival estimates across all strata. Although the differences were negligible at 1 year postdiagnosis, they increased with increasing years of follow-up, up to 9.3 pp at 10 years (eg, aged 60–74 with stage I disease: 53.0% vs 43.7%). Differences in survival estimates between the methods also increased by increasing age groups (eg, at 10 years postdiagnosis: 5.1 pp for ages 18–44, 8.8 pp for ages 45–59, and 9.3 pp for ages 60–74) but decreased drastically for those aged ≥ 75 (3.1 pp).

Conclusion: Relative survival and cause-specific survival are not interchangeable. The type of survival estimate used in cancer studies should be specified, particularly for long-term survival.

Keywords: biostatistics, cancer epidemiology, epidemiological methods, mortality, lung cancer

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Introduction

Communication of long-term survival probabilities to patients diagnosed with lung cancer is crucial and challenging. Unfortunately, the seemingly simple concept of survival is complicated by the use of different terminologies and survival measures to address different questions.^{1,2} Additionally, reporting of survival estimates is often incomplete or incorrect. For example, the “Lung Cancer Fact Sheet,” published by the American Lung Association,³ states that 5-year survival is 5% for late-stage lung

cancer. However, it is unclear whether this survival estimate was based on the relative or cause-specific approach. Furthermore, in a review examining variations in cancer survival across Europe,⁴ relative survival was reported as a proxy for cause-specific survival without assessment of resulting bias.

We differentiate between survival measures (net vs crude survival) and estimation frameworks (relative vs cause-specific approaches to estimate survival measures). When the object of interest is cancer deaths from lung cancer, net and crude survival are distinguished by the manner in which deaths from noncancer causes are considered. Net survival eliminates the impact from deaths from other causes and presents survival in a hypothetical world where lung cancer is the only cause of death. In contrast, crude survival accommodates deaths from other causes and presents cancer survival in the real world, where the patient may die of other causes.^{1,2}

The focus of this paper is net survival. Historically, net survival was developed to address whether patients have been cured (ie, the expected survival of cancer patients has returned to the level of the general population).⁵ Net survival is independent of death from noncancer causes, an important feature to appropriately track cancer survival across time and compare cancer burden between populations and countries with different life expectancies.

In population-based cancer studies, net survival can be estimated using different approaches, broadly categorized as relative survival and cancer-specific survival. In principle, both approaches estimate the same concept of net survival. However, these two constructs have drastically different assumptions: cancer-specific survival centers on deaths attributable to cancer, whereas relative survival does not differentiate between causes of death and instead considers all-cause deaths that are in excess of the mortality that would be expected in the general population without cancer.⁶ With different estimators to determine net survival, confusion arises in the comparability of the estimates from each approach. It is crucial to fully understand the underlying constructs of each method and the subtleties of each resulting estimate.

Relative survival is the ratio of the overall survival among patients diagnosed with cancer and the expected survival in a matched general population (the excess mortality attributable to cancer):

$$\frac{\text{Observed survival among patients with lung cancer}}{\text{Expected survival of a matched general population}}$$

“Matched general population” refers to a subset of the population with comparable characteristics (eg, sex and age) to the population of patients with lung cancer. Data for the derivation of observed survival and expected survival are generally extracted from cancer registries and state death files or national mortality registries. The main advantage of the relative survival approach is that it does not require information on cause of death, which is often difficult to obtain for every patient. However, the accuracy of the relative survival approach depends on how closely the composition of the general population matches the composition of the population of patients with lung cancer.

Cause-specific survival focuses on cancer-specific deaths and uses only the population of patients with lung cancer. Data for the calculation of cause-specific survival can be derived from institution-level cancer registries or population-based cancer registries. Unlike relative survival, cause-specific survival does not require population-level data; hence, it is not necessary to obtain mortality rates on the general population. However, credible cause-specific survival estimation assumes accurate cause-of-death classification.

As the methods are calculated differently, they provide different estimates of net survival probabilities. Howlander et al⁷ studied this topic in a range of cancer sites using a population-based cancer registry from the Surveillance, Epidemiology, and End Results (SEER) program.⁸ However, in their study, all subtypes of lung and bronchus diagnoses were presented as an aggregate group. In this study, we perform a comprehensive investigation specific to non-small cell lung cancer (NSCLC; by stage-and-age strata) and provide insights unique to the context of lung cancer. Through a series of sensitivity analyses, we herein quantify the extent of differences in net survival probability estimates when both relative and cause-specific survival methods are applied to the same registry data.

Methods

Study population

Cases of NSCLC were extracted from the SEER database issued in April 2017.⁸ SEER is a geographically-defined population-based cancer registry covering 34.6% of the US population. Patients diagnosed with NSCLC (no prior cancers and no second primaries) between 2004 and 2014 were selected for analysis. Histologic diagnoses were based on the morphologic codes from the International

Classification of Diseases for Oncology (ICD-O-3).⁹ Histologic types of NSCLC (ICD-O-3 topography code: C34) included squamous cell carcinoma (8051–2, 8070–6, 8078, 8083–4, 8090, 8094, 8120, 8123), adenocarcinoma (8015, 8050, 8140–1, 8143–5, 8147, 8190, 8201, 8211, 8250–5, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8440, 8470–1, 8480–1, 8490, 8503, 8507, 8550, 8570–2, 8574, 8576), large cell carcinoma (8012–4, 8021, 8034, 8082), adenosquamous carcinoma (8560), and other/not otherwise specified NSCLC (8022, 8030, 8031, 8032, 8033, 8035, 8046, 8200, 8230, 8430, 8441, 8551, 8562, 8575). For each patient, year of diagnosis, stage (based on the sixth edition of the AJCC Cancer Staging Manual,¹⁰ applicable to diagnoses made in 2004 or later), histologic type, age, sex, surgery (yes/no), cause of death, and survival duration (from diagnosis to death or last follow-up) were recorded. The final cohort comprised patients with NSCLC who were aged ≥ 18 years at the time of diagnosis.

Statistical analysis

Patients were categorized into 16 strata on the basis of stage (I, II, III, and IV) and age (18–44, 45–59, 60–74, and ≥ 75 years) at diagnosis. The survival measure of interest was net survival, expressed as relative survival and cause-specific survival within each stratum. Both methods were applied to the same cohort to calculate survival estimates up to 10 years postdiagnosis. Cause-specific survival was calculated using the Kaplan-Meier approach from the time of diagnosis to the time of lung cancer-specific death (patients were censored otherwise). Deaths due to cancer were identified by the SEER cause-specific death classification variable.^{7,8} Relative survival was calculated by dividing all-cause survival among the lung cancer patients by the expected survival of the matched general population using the Ederer II approach.¹¹ Expected survival was derived from life tables that matched the study population to the general population by sex, age, and calendar year of diagnosis. As a secondary assessment, the analyses were repeated in the subcohort of patients who underwent surgery. In all analyses, the differences between relative and cause-specific survival estimates at specific time points were quantified as percentage-points (pp).

A publicly available algorithm was adapted to estimate relative survival using SAS 9.4 (SAS Institute, Cary, NC, USA), incorporating the Ederer II approach.^{12,13} All other analyses were conducted using R 3.5.1 (R Core Team, Vienna, Austria), using the SEERaBomb package¹⁴ for data processing from the SEER database and the

demography package¹⁵ to extract life tables of the general population from the National Center for Health Statistics (NCHS).¹⁶

Results

Table 1 reports the number of patients in each stage-and-age stratum. Analyses included 263,894 patients with stage I (20%), stage II (5%), stage III (26%), or stage IV (49%) NSCLC, of whom 77% were aged ≥ 60 years and 46% were women. Figure S1A–D presents the crude probabilities of death from cancer and noncancer causes; Figure S2A–D presents these data for the subset of patients who underwent surgery.

Relative survival versus cause-specific survival

Among stage I patients, estimates of cause-specific survival were higher than estimates of relative survival in all age-by-stage strata, across all years of follow-up (Figure 1A). Differences between cause-specific and relative survival estimates were minimal in the short term (ie, 1 year postdiagnosis) but increased in magnitude with increasing years of follow-up (Table 1). For example, among those aged 60–74 years, cause-specific survival was 1.9 pp higher than relative survival at 1 year postdiagnosis (88.5% vs 86.6%). However, the difference increased to 5.7 pp at 5 years postdiagnosis (64.2% vs 58.5%) and 9.3 pp at 10 years postdiagnosis (53.0% vs 43.7%). Examining across increasing age groups, the differences between relative and cause-specific survival estimates increased with advancing age, except in the case of patients aged ≥ 75 years. For example, at 10 years postdiagnosis, cause-specific survival was 5.1 pp higher than relative survival among those aged 18–44 (74.1% vs 69.0%), 8.8 pp higher among those aged 45–59 (65.5% vs 56.7%), and 9.3 pp higher among those aged 60–74 (53.0% vs 43.7%), whereas the difference was 3.0 pp among patients aged ≥ 75 (37.3% vs 34.3%).

Overall, survival estimates were lower as stage increased (ie, stage II disease had worse survival estimates than stage I). Results for patients with stage II NSCLC mirrored those for patients with stage I disease: estimates of cause-specific survival were always higher than estimates of relative survival (Figure 1B). The differences between cause-specific and relative survival estimates were less drastic among patients with stage II disease than among those with stage I disease. For example, among those aged

Table 1 Summary of clinical data^a and survival estimates among patients with non-small cell lung cancer

Stage/Age ^b Stratum	Total, No.	Female, %	All-Cause Death, No.	Lung Cancer Death, No.	Relative Survival, %			Cause-Specific Survival, %		
					Years Since Diagnosis			Years Since Diagnosis		
					1	5	10	1	5	10
I/18-44	575	61	122	96	94.6	79.5	69.0	94.8	81.5	74.1
I/45-59	8266	54	2548	1838	91.0	67.9	56.7	92.4	73.1	65.5
I/60-74	25,942	50	10,813	7268	86.6	58.5	43.7	88.5	64.2	53.0
I/≥75	18,351	53	10,850	6943	79.8	47.8	34.3	80.2	49.8	37.3
Stage I total	53,134	52	24,333	16,145						
II/18-44	198	50	86	76	86.6	55.3	46.3	88.2	58.1	49.8
II/45-59	2740	44	1448	1231	81.7	42.7	32.6	81.8	46.6	39.1
II/60-74	6410	42	3942	3187	74.9	34.2	22.8	76.0	38.1	29.3
II/≥75	3697	47	2819	2245	61.3	23.3	13.6	60.9	24.9	17.3
Stage II total	13,045	44	8285	6739						
III/18-44	1264	47	900	844	64.3	22.2	16.1	62.8	23.8	18.6
III/45-59	14,337	41	10,600	9743	58.9	18.8	12.7	58.3	20.8	15.1
III/60-74	31,853	42	24,921	21,972	52.2	14.6	7.8	52.7	17.0	10.5
III/≥75	22,005	48	19,123	16,674	39.0	8.7	4.4	38.6	9.1	5.7
Stage III total	69,459	44	55,544	49,233						
IV/18-44	3237	50	2704	2563	40.0	7.2	3.7	39.0	7.7	4.5
IV/45-59	31,198	43	27,485	26,223	32.0	4.3	2.1	30.5	4.7	2.4
IV/60-74	58,898	42	52,671	49,445	27.5	3.5	1.4	26.5	4.0	1.9
IV/≥75	34,923	48	34,294	29,868	21.3	2.7	0.9	20.1	2.7	1.0
Stage IV total	128,256	44	115,154	108,099						

Notes: ^aClinical characteristics were extracted from the Surveillance, Epidemiology, and End Results data set. ^bAge, in years, at diagnosis.

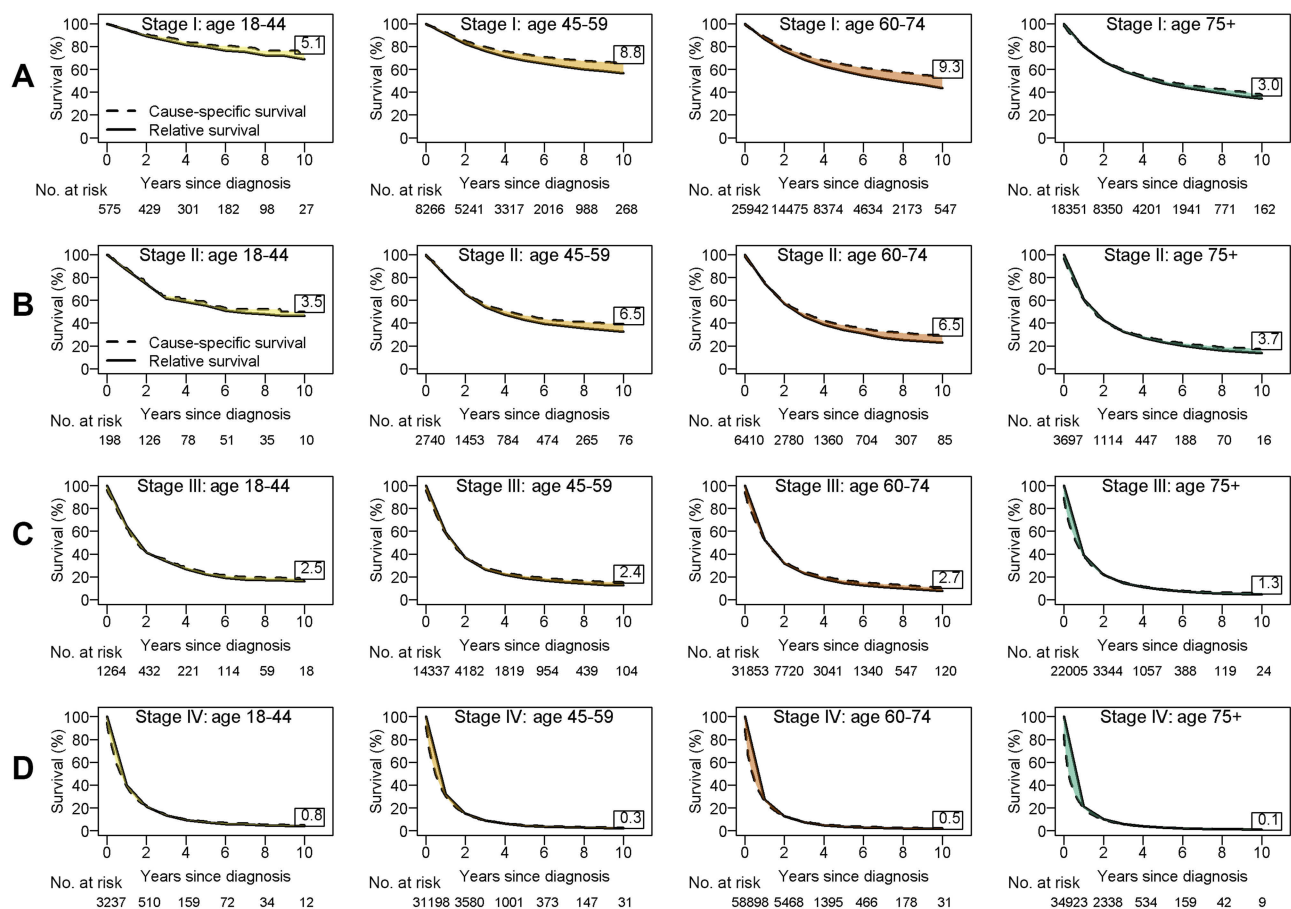


Figure 1 Relative and cause-specific survival estimates by age group for patients with stage I (A), stage II (B), stage III (C), and stage IV (D) non-small cell lung cancer. The value in each box reports the percentage-point difference at 10 years since diagnosis (the 10-year cause-specific survival estimate minus the 10-year relative survival estimate).

60–74 with stage II disease, cause-specific survival was 1.1 pp higher than relative survival at 1 year postdiagnosis (76.0% vs 74.9%) and 6.5 pp higher at 10 years postdiagnosis (29.3% vs 22.8%). These differences were less pronounced than those found in the corresponding patients with stage I disease (1.9 pp and 9.3 pp). The differences between cause-specific and relative survival estimates were <3 pp among all patients with stage III disease and <1 pp among all patients with stage IV disease (Figure 1C and D).

Subcohort analysis among surgical patients

Among the total cohort, 62,627 patients (24%) received surgery; most surgical patients had early-stage disease (69% of stage I and 64% of stage II disease groups, compared with 17% of stage III and 4% of stage IV disease groups). Overall, patients who underwent surgery had better survival than the overall cohort for corresponding strata. As observed

in the total cohort, estimates of cause-specific survival for patients who underwent surgery were always higher than estimates of relative survival (Table 2, Figure 2A–D). Among the stage I and II disease groups, the differences between cause-specific and relative survival estimates were similar to those in the overall cohort (in general, they were of a slightly smaller magnitude). As observed in the primary analyses, the difference between the two methods was negligible at 1 year postdiagnosis but increased as years of follow-up increased. For example, among those aged 60–74 with stage II disease, cause-specific survival was 0.9 pp higher than relative survival at 1 year postdiagnosis (85.1% vs 84.2%), 3.3 pp higher at 5 years postdiagnosis (48.1% vs 44.8%), and 6.5 pp higher at 10 years postdiagnosis (38.6% vs 32.1%).

Discussion

This study compares two competing conventional estimators of net survival. Applying both relative and cause-specific

Table 2 Summary of clinical data^a and survival estimates among patients with non-small cell lung cancer who received surgery

Stage/Age ^a Stratum	Total, No.	Female, %	All-Cause Death, No.	Lung Cancer Death, No.	Relative Survival, %					
					Years Since Diagnosis			Years Since Diagnosis		
					I	5	10	I	5	10
I/18-44	520	62	83	62	98.2	85.6	74.3	97.7	87.3	79.1
I/45-59	6915	56	1679	1160	95.1	75.8	65.0	96.0	79.8	72.9
I/60-74	19,386	52	6405	4003	92.8	70.8	54.8	93.9	74.4	62.6
I/≥75	9941	53	4791	2608	89.6	67.9	51.5	89.8	66.7	52.3
Stage I total	36,762	53	12,958	7833						
II/18-44	159	52	57	49	91.1	65.0	56.1	92.7	67.5	60.3
II/45-59	2078	46	975	818	87.5	50.0	38.8	87.6	53.6	45.3
II/60-74	4304	42	2271	1777	84.2	44.8	32.1	85.1	48.1	38.6
II/≥75	1811	46	1232	907	76.3	35.9	24.1	76.3	37.7	26.9
Stage II total	8352	44	4535	3551						
III/18-44	320	53	158	147	87.9	48.9	37.0	84.9	50.0	37.9
III/45-59	3204	47	1732	1539	82.5	42.2	31.0	81.7	44.5	34.9
III/60-74	6070	45	3576	2995	78.1	37.2	24.3	78.3	39.4	28.6
III/≥75	2391	49	1677	1324	70.3	31.1	16.2	69.8	30.9	20.8
Stage III total	11,985	47	7143	6005						
IV/18-44	220	59	157	145	61.0	21.9	15.4	60.9	24.0	19.5
IV/45-59	1557	51	1112	1047	62.2	21.8	12.0	61.3	23.3	13.9
IV/60-74	2613	48	1863	1682	60.8	21.2	10.9	60.3	22.1	13.1
IV/≥75	1138	49	894	782	51.4	18.3	11.3	49.7	17.8	10.6
Stage IV total	5528	49	4026	3656						

Notes: ^aClinical characteristics were extracted from the Surveillance, Epidemiology, and End Results data set. ^bAge, in years, at diagnosis.

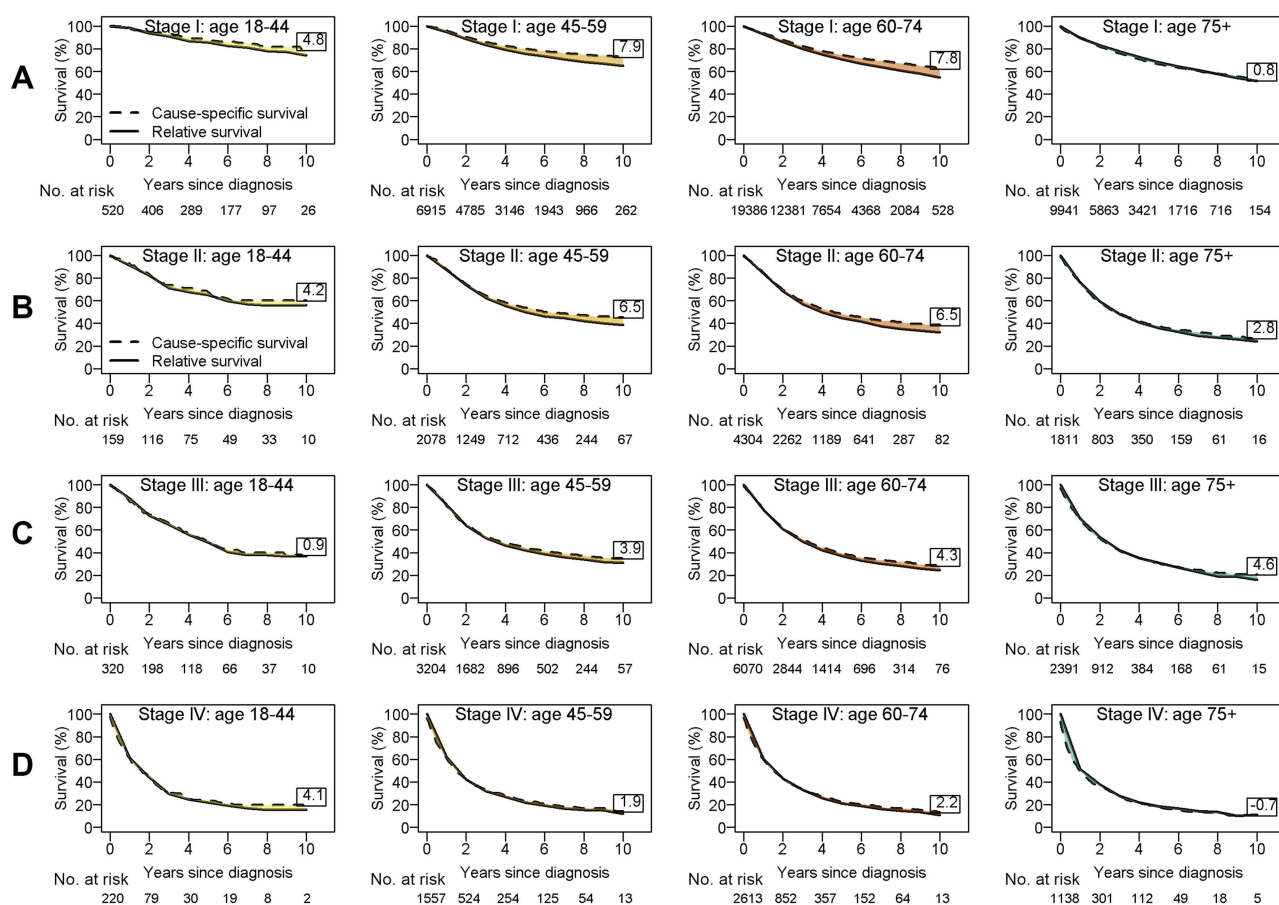


Figure 2 Relative and cause-specific survival estimates by age group for patients who underwent surgery with stage I (A), stage II (B), stage III (C), and stage IV (D) non-small cell lung cancer. The value in each box reports the percentage-point difference at 10 years since diagnosis (the 10-year cause-specific survival estimate minus the 10-year relative survival estimate).

survival methods to the same data, we quantified the differences in net survival estimates between the methods in the context of NSCLC. Results demonstrates that in most situations, relative survival and cause-specific survival provided similar estimates of net survival. Negligible differences between the two frameworks in certain scenarios implies that both approaches can be reliably used to estimate net survival in subgroups where cancer survival is poorer (eg, among late-stage disease or older patients) and the interest is in short-term survival. However, our study also highlights situations with major discrepancies between the two methods and cautions against using the two terminologies interchangeably, especially when focused on long-term follow-up, as both frameworks are vulnerable to errors.

For cause-specific survival, accurate cause-of-death coding in cancer registries is crucial. The degree of bias in cause-specific survival estimates depends on the degree of misclassification of cancer-specific cause of death on death certificates. Results from lung cancer screening trials

estimated up to 15% under-reporting of lung cancer deaths due to misclassification.^{17–19} In this set of analyses, it is reasonable to assume that the potential for bias due to misclassification is greater among older patients (among whom the overall incidence of death is much greater than among younger patients) and lower among those with late-stage disease (among whom a greater proportion of deaths can be assigned to lung-cancer causes, with greater confidence).

In addition to misattribution of the cause of death, cause of death may have been recorded as “unknown” (ie, death cannot be ascribed to lung cancer or to other causes with certainty). Gamel and Vogel²⁰ proposed partitioning these deaths by the ratio of lung cancer–specific deaths to deaths attributable to other causes. We conducted sensitivity analyses on the basis of this approach (results not shown); owing to the small number of deaths attributable to unknown causes in this context, the conclusions were similar.

The primary source of error for relative survival is non-comparability between the study population and the general population used to estimate underlying mortality.² Comparability implies that if the patient did not have cancer, then the patient's survival experience (or background mortality) is assumed to match the general population. This assumption is undoubtedly violated in the current context of lung cancer, where patients are more likely to be smokers than the general population. Smoking is a major risk factor for developing lung cancer and consequently dying from lung cancer.²¹ More importantly, smoking increases the risk of comorbidities such as chronic respiratory disease, cardiovascular disease and other smoking-related cancers.^{22–24} Lung cancer patients are therefore more likely to die from other smoking-related comorbidities, so their true background mortality may not be comparable to the general population. In reality, the potential biases resulting from noncomparability could likely explain the differences between relative and cause-specific survival estimates observed here: since the life tables used in this study do not account for tobacco-use or smoking-related comorbidities, the expected survival may have been overestimated, resulting in underestimation of the relative survival. This potential explanation is further highlighted in the subgroup analysis among surgical patients, where we observed greatly diminished or negligible differences between relative and cause-specific survival estimates. Patients who are eligible for surgery tend to have lower rates of comorbidities, therefore their background mortality is more comparable to the general population. Few studies have quantified the impact of tobacco-use on relative survival estimates.²⁵ Using the Finnish Cancer Registry, Hinchliffe et al²⁶ showed that the bias in relative survival due to the non-comparability of smoking patterns was negligible. However, reporting of tobacco-use is often unreliable. Thorough investigation of the impact of noncomparability requires using smoking-adjusted life tables, as attempted by several researchers,^{27,28} but such adaptations of life tables are difficult to implement because the necessary population-level smoking data linked to mortality data are rarely available. Because the SEER registry does not capture data on tobacco-use or smoking-related comorbidities, we cannot fully address this issue in our current analysis. Future studies should confirm that the differences in estimates between the two frameworks can indeed be reduced by using smoking-adjusted life tables or by stratifying analyses by smoking-related comorbidities.

In theory, relative survival requires a comparison group free of the cancer under study. In practice, expected survival is typically calculated from general-population life tables, which include people previously diagnosed with cancer. With the inclusion of people previously diagnosed with cancer, the expected survival in the general population would be underestimated and hence lead to overestimation of relative survival. Studies have examined this issue in the general populations of Finland²⁹ and Canada.³⁰ These studies concluded that adjustment for cancer mortality is warranted if relative survival is estimated for all cancer sites combined but that the proportion of deaths attributable to specific cancers, particularly lung cancer, is too small to affect the relative survival estimates. Although we did not extract lung cancer mortality from the comparison cohort by excluding individuals with lung cancer, we believe that the magnitude of the bias in relative survival estimation is negligible for lung cancer.³¹

We assessed two classical methods to estimate net survival; however, other methods with different properties exist and have been examined,^{32–34} including a proposed method by Perme et al.³⁵ In addition, the net survival estimates we present in this study are in the context of a hypothetical world where cancer is the only cause of death.^{1,36} However, specific questions of interest may require consideration of other causes of death. Hence, instead of net survival, it is more appropriate to present crude survival in those cases. Formal comparisons between these two survival measures can be found elsewhere.²

Last, the use of the SEER registry allowed us to evaluate long-term survival among patients with lung cancer. However, such a large, multi-institutional database is subject to the typical limitations associated with any retrospective registry-based data involving a group of heterogeneous patients not treated uniformly. Important covariates such as significant comorbidities, tumor locations, radiographic results, and treatment of subsequent cancer recurrences were not captured in the SEER registry. Hence, the lack of adjustment for factors associated with prognosis is a limitation we cannot overcome in this study.

Conclusion

Relative survival and cause-specific survival are complementary but not interchangeable. In general, both frameworks provide similar estimates of net survival. However, differences between the two estimates may still be considerable in certain situations, particularly when the focus

is on early-stage disease and long-term survival probability estimation. Hence, it is crucial to detail the type of survival estimates presented or communicated. With a deliberate focus on obtaining a well-matched comparison cohort and accurate cause-of-death coding, population-based studies should present results from both approaches and identify differences in study findings, along with the limitations specific to each method.

Data availability

This paper utilized publicly available data through the Surveillance, Epidemiology, and End Results (SEER) program.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

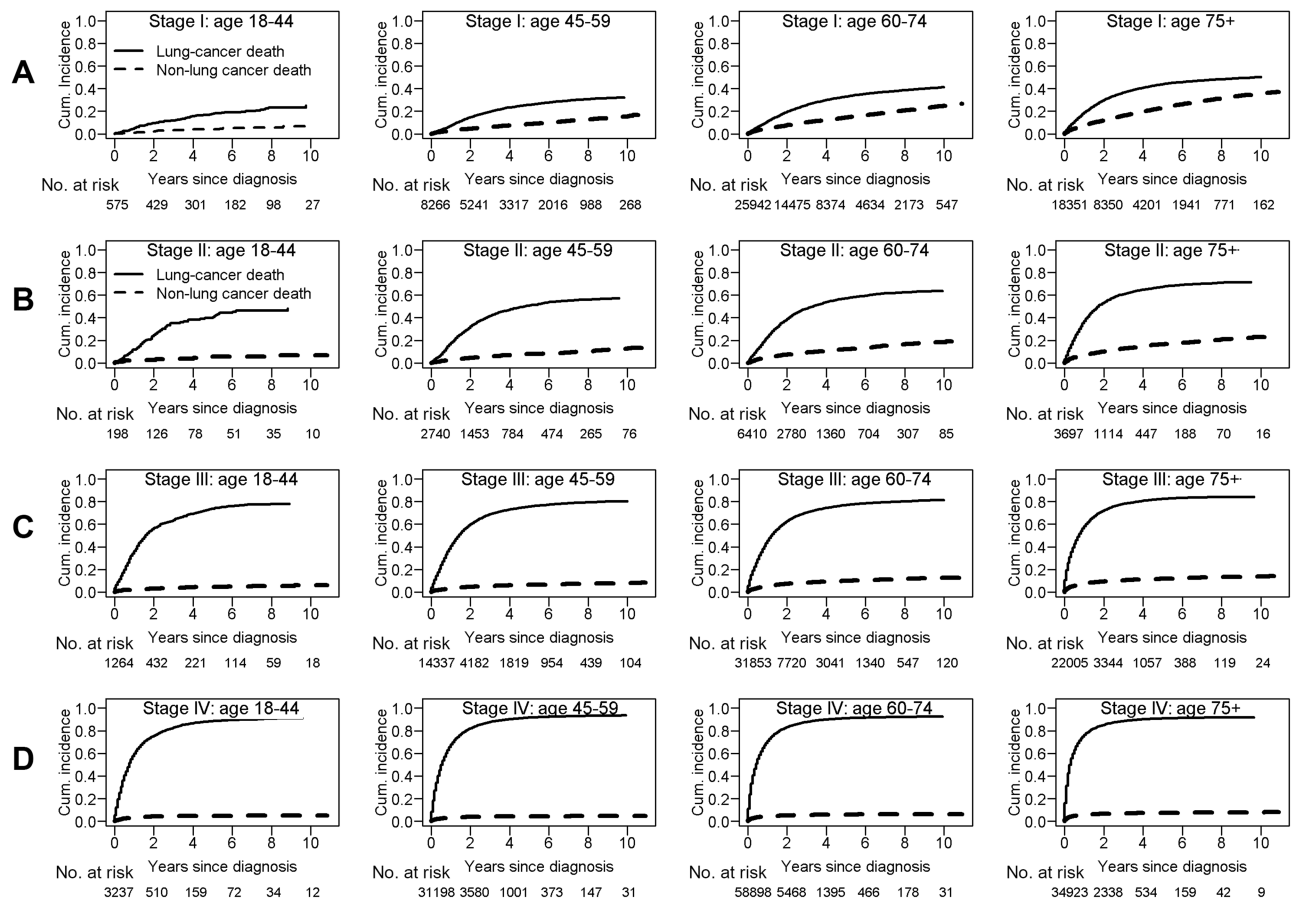


Figure S1 Crude mortality from cancer and noncancer causes by age group for patients with stage I (A), stage II (B), stage III (C), and stage IV (D) non-small cell lung cancer. Cumulative incidence of lung-cancer deaths (LC-CID) and cumulative incidence of nonlung-cancer deaths (non-LC-CID) were generated using a competing risk approach. Overall, LC-CID increased with advancing age and stage; similarly, non-LC-CID increased with advancing age and stage. Even though the total number of deaths increased with age, the proportion of deaths attributable to cancer in the older age group decreased because of increased competing causes of death.

Abbreviation: Cum. incidence, cumulative incidence.

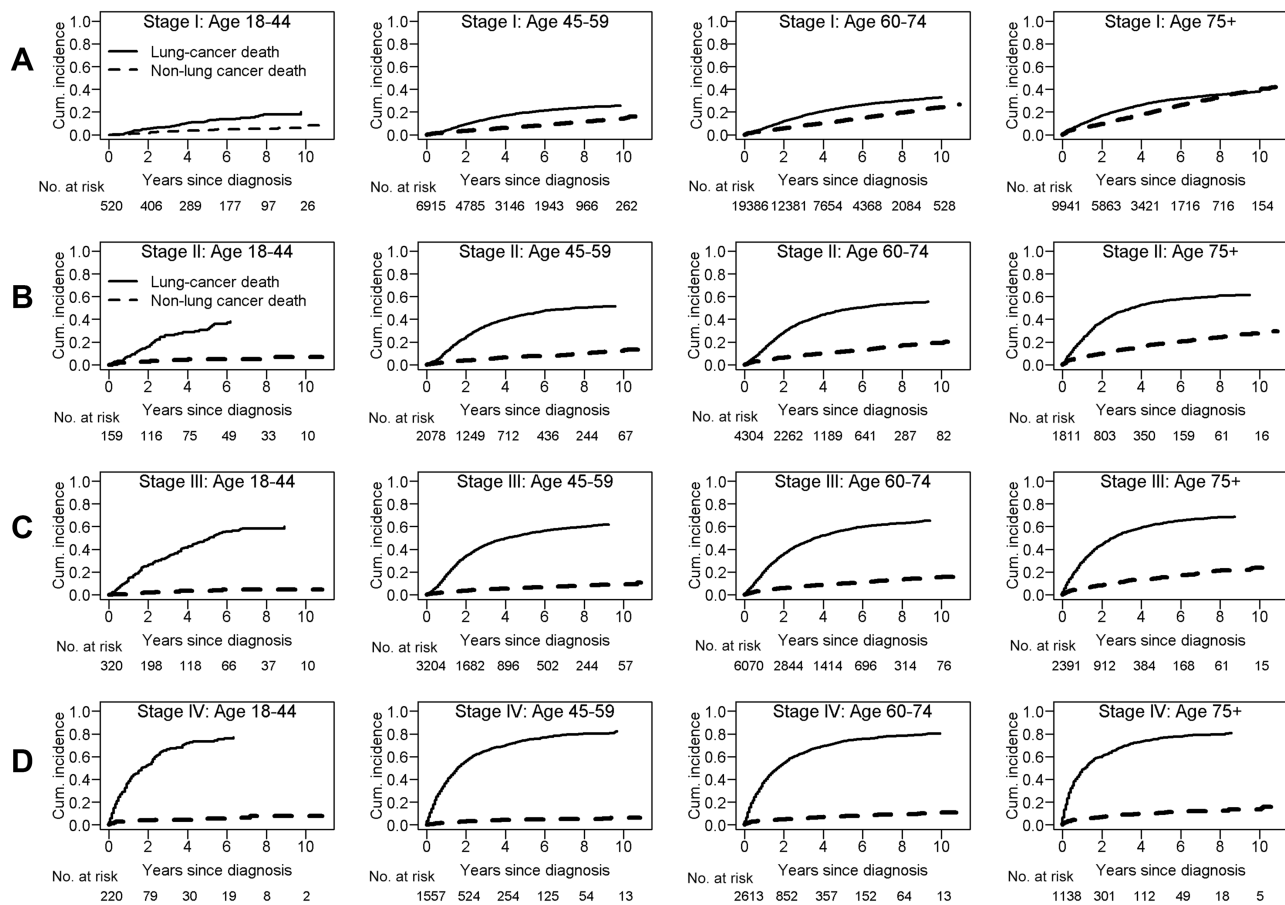


Figure S2 Crude mortality due to cancer and noncancer causes by age group for patients with stage I (A), stage II (B), stage III (C), and stage IV (D) non-small cell lung cancer among patients who underwent surgery.

Abbreviation: Cum. incidence, cumulative incidence.

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