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Effect of Prior Cancer on Outcomes in Advanced Lung Cancer: Implications for Clinical Trial Eligibility and Accrual

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Abstract

Background: Prior cancer is a common exclusion criterion in lung cancer trials. This practice reflects concerns that prior cancer may affect trial conduct or outcomes. However, the impact of prior cancer on survival in lung cancer is not known.

Methods: We identified patients older than age 65 years with stage IV lung cancer diagnosed between 1992 and 2009 in the Surveillance, Epidemiology, and End Results–Medicare linked registry. Prior cancer was characterized by type, stage, and timing. All-cause and lung cancer–specific survival were compared between patients with and without prior cancer using propensity score–adjusted Cox regression.

Results: Overall, 102 929 patients with stage IV lung cancer were identified, of whom 14.7% had a history of prior cancer. More than two-thirds (76.0%) of prior cancers were localized or regional stage; most were diagnosed five or fewer years prior to the lung cancer diagnosis. In propensity score–adjusted analysis, patients with prior cancer had better all-cause (hazard ratio [HR] = 0.93, 95% confidence interval [CI] = 0.91 to 0.94) and lung cancer–specific (HR = 0.81, 95% CI = 0.79 to 0.82) survival. In a simulated clinical trial–eligible population (age <75 years, no comorbidity, treated with chemotherapy), similar trends were noted. In subset analyses according to stage, type, and timing of prior cancer, no group of patients with prior cancer had inferior survival compared with patients without prior cancer.

Conclusion: Among patients with stage IV lung cancer, prior cancer does not convey an adverse effect on clinical outcomes, regardless of prior cancer stage, type, or timing. Broader inclusion in clinical trials of advanced lung cancer patients with a history of prior cancer should be considered.

Fewer than 5% of adults with cancer in the United States participate in clinical trials (1–4). Low accrual rates prolong study duration, limit generalizability, lead to premature study termination, limit the number of patients exposed to potentially beneficial experimental therapies, and leave important clinical questions unanswered (5,6). Barriers to clinical trial accrual include patient, clinician, trial, and system factors (1,3,7–15).

Among these, clinical trial eligibility criteria present a major barrier to study enrollment and represent one of the few accrual factors directly controlled by investigators and sponsors (6,13,116–19).

In cancer clinical trials, a history of prior cancer is a common exclusion criterion. For example, over 80% of lung cancer trials sponsored or endorsed by the Eastern Cooperative Oncology

Group (ECOG) exclude prior malignancy (20). Across trials, this restriction is variably defined, but is most commonly applied to patients with a prior cancer diagnosed within five years of the current cancer. For this reason alone, it is estimated that up to 18% of lung cancer patients are excluded from clinical trials (20). Given the near four-fold increase in the number of US cancer survivors over the past 30 years (21), the extent to which this practice limits trial accrual will likely increase.

The reflexive exclusion of patients with prior cancer from clinical trials presumably reflects concerns that a prior cancer diagnosis could interfere with study conduct or outcomes. However, studies evaluating the impact of prior cancer on lung cancer outcomes yield conflicting results, are predominantly small, single-center series, and primarily focus on resected, early-stage tumors (22–27). We therefore determined the prevalence and prognostic impact of prior cancers among patients with advanced lung cancer using a large, representative, population-based, clinically detailed dataset.

Methods

Data Sources

This study was approved by the University of Texas (UT) Southwestern Institutional Review Board. Data were obtained from the 1992–2009 National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program linked with 1991–2010 Medicare claims files from the Centers for Medicare and Medicaid. SEER is a nationally representative collection of population-based cancer registries (28). Linked SEER-Medicare data provide treatment and outcome information on SEER patients with Medicare. Data for this study were available from 17 registries, broadly representing approximately 28% of the US population (29).

Study Population

The study population included patients older than age 65 years with stage IV lung cancer diagnosed between 1992 and 2009. We used SEER historic stage to identify stage IV patients (30). We included only those older than age 65 years to allow for one year of complete Medicare claims data prediagnosis to determine comorbidity. We used data of patients diagnosed between 1992 and 2009 because Medicare claims were available as of 1991, and 2009 was the most recent year of data available at the time the present study was conducted. All patients had full coverage of Medicare Parts A and B from one year before and one year after the lung cancer diagnosis. We included only patients with non–small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) histology. To ensure complete claims data, we excluded members of health maintenance organizations and patients with only autopsy or death certificate records. We further excluded patients if they had incomplete diagnosis or death dates, or had a discrepancy between SEER and Medicare birth dates of a year or more.

Measures

We measured two primary outcomes: overall (all-cause) and cause-specific (lung cancer) mortality. Survival was measured as the interval in months between date of diagnosis (defined as the 15th of the month because SEER provides only month and year of diagnosis) and date of death provided by SEER. Patients were followed until respective dates of death (all-cause or lung cancer–specific) or censored at the end of 2009 (last date of death in 2011 SEER submission).

A history of prior cancer was determined as described in our previous study (20). In brief, the index lung cancer was defined as the first of any primary lung cancers diagnosed while the patient lived in a SEER registry area (see the Supplementary Methods, available online, for further details). Characteristics and number of of prior cancer(s) were recorded, including type, stage, and timing in relation to the index lung cancer.

We did not include patients with a prior primary lung cancer diagnosis in our analyses for a number of reasons. First, it is challenging to accurately identify same-site second primary cancers using registry data (31). Indeed, unless there is a clear difference in histology between the two lung cancers, it is difficult in clinical practice to determine if a patient has a second primary or recurrent disease. Second, in clinical trials of advanced lung cancer, a history of prior early-stage lung cancer that has subsequently recurred is generally permitted. This group appears to represent approximately 10% of trial populations (32).

We examined multiple SEER covariables associated with lung cancer prognosis as endorsed by earlier studies (33). For a full account of these covariables see the Supplementary Methods (available online). Surgery within 120 days of diagnosis, use of chemotherapy within 120 days, and use of radiotherapy within one year of diagnosis were identified using Medicare inpatient, outpatient, and physician claims (coded yes/no) following prior research. ICD-9 and CPT codes were used to identify these measures are listed in Supplementary Table 1 (available online) (34). Comorbidity was measured by searching inpatient, outpatient, or carrier claims for multiple chronic conditions occurring between 12 months prediagnosis using the Charlson Comorbidity Index–Klabunde adaptation (35,36). We classified comorbidity as none, one, or two or more following common practice. Patients with Medicaid were identified following common practice using the state buy-in variable (37).

Statistical Analysis

Using descriptive statistics, we reported the prevalence and correlates of stage IV lung cancer patients with prior cancer diagnosis. We quantified the type and stage of prior cancer in addition to time elapsed between the prior cancer diagnosis and index lung cancer diagnosis. We used unadjusted Kaplan-Meier analysis to compare survival functions for both all-cause and lung cancer–specific survival of no prior cancer diagnosis vs any prior cancer. Kaplan-Meier curves were also constructed according to characteristics of the most recent prior cancer, including timing, stage, and type of prior cancer. Associated *P* values were calculated. Propensity scores were constructed to adjust for observable differences (or potential confounders) between patients with and without a prior cancer diagnosis (see the Supplementary Methods, available online, for further details). Univariate, multivariable covariable-adjusted, and multivariable propensity score-adjusted Cox proportional hazards models were used to compare lung cancer–specific and all-cause mortality across patients with and without a prior cancer. We assessed the proportional hazard assumption using the SAS proportionality test (38). The assumption was not met, which is not surprising because in large datasets such as ours, very small departures from proportional hazards can be detected. To assess the impact of this violation of the assumption, we generated time by covariate interactions for all covariates in the model. In each model, the size, direction, and significance of hazard ratio demonstrating

the impact of prior cancer was virtually unchanged. We further examined outcomes by characersitics representative of common clinical trial eligbility criteria (20) as follows: 1) patients with no prior cancer, 2) patients with in situ/localized cancers diagnosed five or more years ago and who are likely to be eligible for clinical trials, and 3) all other patients with prior cancer and who are likely to be ineligible for clinical trials. In a sensitivity analysis, we compared multiple methods of propensity score adjustment (Supplementary Methods, available online). We also examined the robustness of our findings among a subsample of patients simulated to more closely resemble a clinical trial population: younger than age 75 years, no documented comorbidities, and received chemotherapy for the stage IV lung cancer diagnosis. Analyses were performed using SAS statistical software 9.3 (SAS Institute Inc., Cary, NC) and Stata 13.1 (StataCorp. LP., College Station, TX). All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

In all, 102 929 eligible stage IV lung cancer patients were identified, of whom 15 170 (14.7%) had a documented prior cancer. Baseline characteristics are listed in Table 1. Prior cancer differed across all measured covariables and was more common among older, male, non-Medicaid patients. After adjustment for

Table 1. Baseline patient characteristics of the stage IV lung cancer SEER-Medicare cohort (n = 102 929)

Patient characteristics	All patients No.	Prior malignancy No. (%)	*P**	Adjusted *P*†
Age, y			<.001	.74
<75	46 258	5622 (12.2)		
75–85	44 745	7496 (16.8)		
≥85	11 926	2052 (17.2)		
Sex			<.001	.95
Female	46 706	5749 (12.3)		
Male	56 223	9421 (16.8)		
Race			<.001	.95
White	87 800	13 219 (15.1)		
Black	8896	1295 (14.6)		
Other	5025	517 (10.3)		
Hispanic	1208	139 (11.5)		
Marital status			<.001	.93
Married	51 186	8224 (16.1)		
Sep/div/wid‡	40 390	5526 (13.7)		
Single	7970	954 (12.0)		
Unknown	3383	466 (13.8)		
Histology			<.001	.89
Adenocarcinoma	32 346	5031 (15.6)		
Squamous	14 952	2342 (15.7)		
Small cell	17 977	2410 (13.4)		
NSCLC§	37 654	5387 (14.3)		
Charlson Comorbidity Score			<.001	.94
0	36 485	5345 (14.6)		
1	31 651	4643 (14.7)		
2+	31 477	4866 (15.5)		
Not available	3316	316 (9.5)		
Medicaid			<.001	.10
Yes	18 678	2026 (10.8)		
No	84 251	13 144 (15.6)		
Lung cancer treatment			<.001	.33
Surgery only	1353	235 (17.4)		
Chemotherapy only	13 949	2257 (16.2)		
Radiation only	21 573	3251 (15.1)		
≥2 treatments	22 231	3227 (14.5)		
No surg/chemo/rad‖	43 823	6200 (14.1)		
Cause of death#			<.001	
Alive	4743	789 (16.6)		
Lung cancer specific	82 007	10 650 (13.0)		
All other causes	16 179	3731 (23.1)		
Total				
	102 929	15 170 (14.7)		

* Two-sided *P* value was calculated from logistic model Wald Chi-square. NSCLC = non–small cell lung cancer; SEER = Surveillance, Epidemiology, and Ends Results.
† Two-sided propensity score–adjusted *P* value: Groups are well balanced for covariables of interest if *P* values are not statistically significant.
‡ Separated/divorced/widowed.
§ Non–small cell lung carcinoma.
‖ No surgery/chemotherapy/radiation.
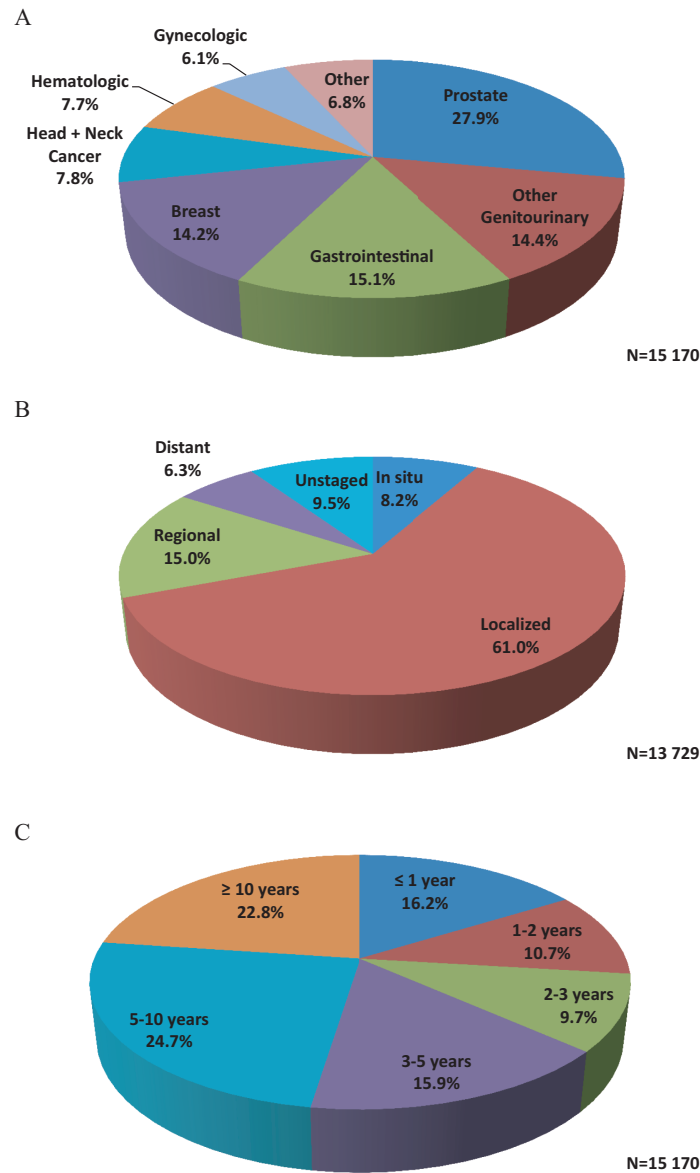# Dependent variable, no adjusted *P* value necessary.

A

B

C

Figure 1. Type **(A)**, stage **(B)**, and timing **(C)** of the most recent prior cancers. Cell sizes less than 11 are suppressed per the Surveillance, Epidemiology, and End Results–Medicare data use agreement; Denominators are not equal because of missing data. All statistical tests were two-sided.

propensity scores, all covariables were balanced among patients with and without a prior cancer.

Figure 1 depicts the type, stage, and timing of the most recent prior cancer. Prostate (27.9%), gastrointestinal (15.1%), other genitourinary (14.4%), and breast (14.2%) were the most common cancer types. Among women, the most common prior cancers were breast (37.0%), gastrointestinal (16.8%), and gynecologic (16.0%). For men, the most common prior cancers were prostate (44.8%), other genitourinary (17.8%), and gastrointestinal (14.0%). Localized and regional stages were most frequently observed, together accounting for 76% of cases. Only 6.3% of prior cancers were distant stage. The median times of diagnosis for prior cancers (measured from the index lung cancer date) were as follows: most recent, 4.7 years; second most recent, 8.3 years; third most recent, 10.9 years. Additional characteristics of second and third most recent prior cancers are provided in Supplementary Figure 1 (available online).

The Kaplan-Meier curves demonstrated statistically significantly different survival (P < .001) between patients with and without a prior cancer, demonstrating a favorable effect of prior cancer on all-cause and lung cancer–specific survival (Figure 2). Overall survival according to timing, stage, and type of prior cancer diagnosis is shown in Figure 3. In general, no subgroup of patients with prior cancer had inferior survival compared with patients with no prior cancer.

To analyze outcomes according to characteristics representative of common clinical trial eligibility criteria (20), we grouped patients according to both stage and timing of prior cancer. All-cause survival was similar among the groups, but again slightly favored those with prior cancer. The three groups and their hazard ratios for all-cause mortality are as follows: 1) patients with no prior cancer (referent), 2) patients with in situ/localized cancers diagnosed five or more years ago and who are likely to be eligible for clinical trials (hazard ratio [HR] = 0.96, 95%
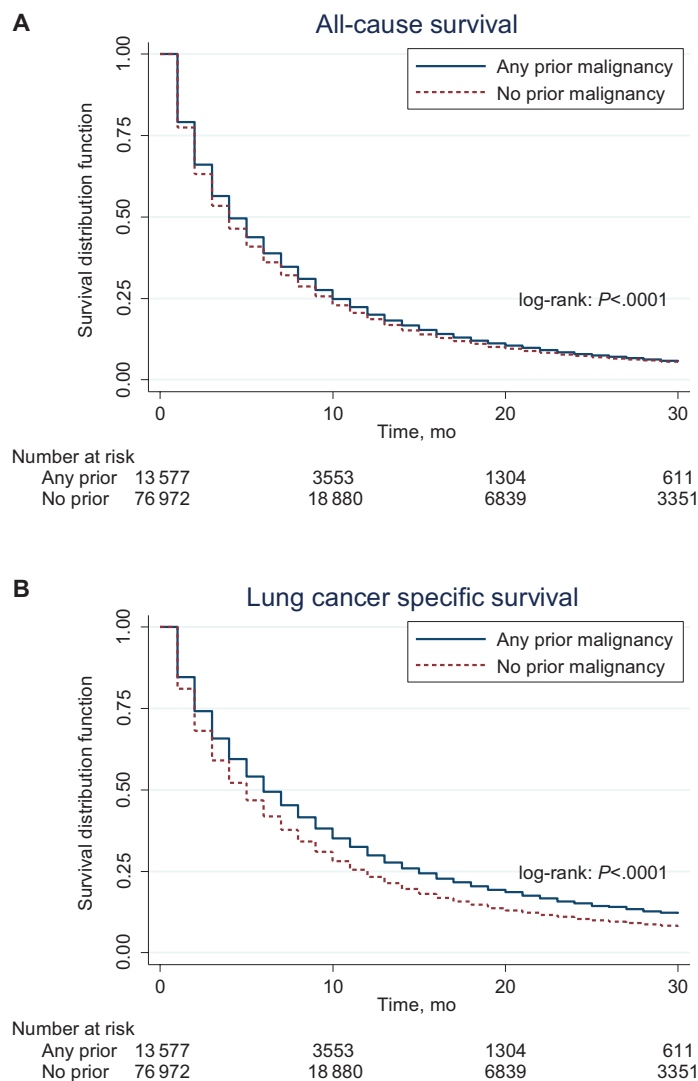
A

All-cause survival

Number at risk

Any prior	13 577	3553	1304	611
No prior	76 972	18 880	6839	3351

B

Lung cancer specific survival

Number at risk

Any prior	13 577	3553	1304	611
No prior	76 972	18 880	6839	3351

Figure 2. All-cause **(A)** and lung cancer–specific **(B)** survival for patients with and without any prior malignancy. All statistical tests were two-sided.

confidence interval [CI] = 0.93 to 0.99), and 3) all other patients with prior cancer and who are likely to be ineligible for clinical trials (HR = 0.94, 95% CI = 0.92 to 0.96).

In multivariable covariate-adjusted Cox models, prior cancer was associated with favorable all-cause (HR = 0.93, 95% CI = 0.91 to 0.94, $P < .001$) and lung cancer–specific (HR = 0.81, 95% CI = 0.79 to 0.82, $P < .001$) survival (Table 2). Non–small cell histology, female sex, younger age, lower comorbidity burden, and receipt of cancer-specific treatment were also associated with improved survival. In sensitivity analyses, effect size, direction, and statistical significance of the prior cancer effect on both outcomes was consistent across all three analyzed methods of propensity score adjustment (data not shown) and furthermore was consistent with the multivariable covariable-adjusted model. Thus for simplicity, we opted to present the multivariable covariable-adjusted model in Table 2. Univariate modeling recapitulated these results as well (data not shown).

Finally, we examined the effect of prior cancer among a subsample of patients who more closely resembled a clinical trial population. Among this subsample of patients who were younger than age 75 years, had no documented comorbidities, and received chemotherapy for the stage IV lung cancer diagnosis (n = 9024), prior cancer occurred in 13.0% of patients. Similar to the overall population, prior cancer did not convey an adverse effect on all-cause (HR = 0.95, 95% CI = 0.89 to 1.01, $P = .11$) or lung cancer–specific (HR = 0.82, 95% CI = 0.76 to 0.88, $P < .001$) mortality in propensity-score adjusted models (data not shown).

Discussion

The assumption that a prior cancer diagnosis may interfere with study conduct or outcomes has resulted in widespread and reflexive exclusion of patients with prior cancer from clinical trials across cancer types. In the present study of more than 100 000 stage IV lung cancer cases from the SEER-Medicare dataset, we found that 14.7% of patients with stage IV lung cancer had a history of prior malignancy. More than two-thirds of these prior cancers were in situ, localized, or regional stage. Prior cancers were diagnosed relatively close to the lung cancer diagnosis (median 4.7 years), and in the overall study population and every subgroup analyzed prior cancer did not adversely impact all-cause or lung cancer–specific survival.
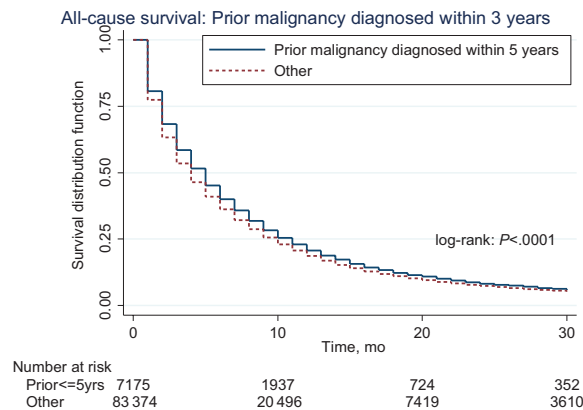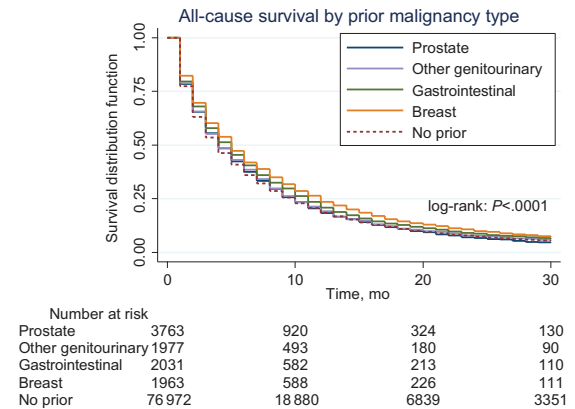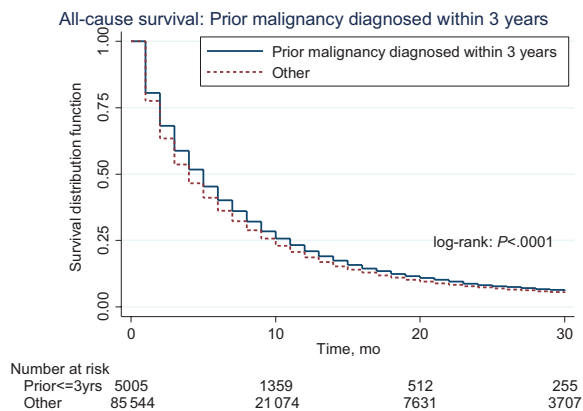
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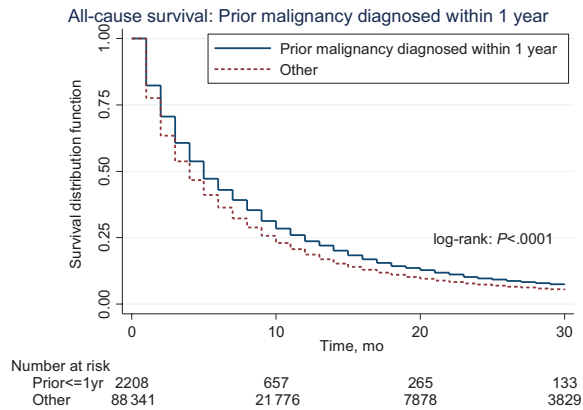
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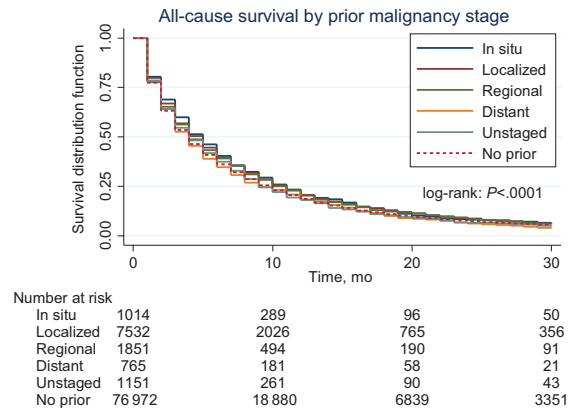
C

Figure 3. Overall survival according to type (**A**), stage (**B**), and timing (**C**) of prior cancer diagnosis. "Other" denotes patients with no prior malignancy or a history of prior malignancy diagnosed outside the referenced time frame. All statistical tests were two-sided.

Earlier studies investigating the impact of a prior cancer diagnosis on lung cancer outcomes yielded conflicting findings and primarily focused on resected, early-stage lung cancer (22–27,39). In a single-center series of 1914 lung cancer patients, of whom 228 (12%) had a history of at least one previous malignancy, no survival detriment was observed in the group with prior cancer (HR = 0.84, 95% CI = 0.70 to 1.01) (22). A number of smaller studies reported similar trends (24,26,27,39). Conversely, in a study of 2991 patients with resected stage I NSCLC, the

subset of 192 patients with prior cancer (6%) had statistically significantly inferior survival (HR = 1.44, 95% CI = 1.16 to 1.78) (23).

The 14.7% rate of prior cancer among patients with stage IV lung cancer suggests that prior cancer-related eligibility criteria may restrict clinical trial enrollment of a substantial proportion of patients. Indeed, in an earlier study, we determined that for some lung cancer clinical trials, up to 18% of patients may be excluded for this reason alone (20). As cancer

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Table 2. Multivariable covariate-adjusted hazard ratios for all-cause and lung cancer–specific mortality

Patient characteristics	All-cause HR* (95% CI†)	All-cause P‡	Lung cancer–specific HR* (95% CI†)	Lung cancer–specific P‡
Prior cancer diagnosis (vs none)				
Yes (any)	0.93 (0.91 to 0.94)	<.001	0.81 (0.79 to 0.82)	<.001
Age (vs 66–74), y				
75–85	1.09 (1.08 to 1.11)	<.001	1.08 (1.06 to 1.10)	<.001
>85	1.15 (1.12 to 1.17)	<.001	1.09 (1.07 to 1.12)	<.001
Sex (vs female)				
Male	1.13 (1.11 to 1.14)	<.001	1.13 (1.11 to 1.14)	<.001
Race (vs white)				
Black	0.94 (0.92 to 0.96)	<.001	0.92 (0.90 to 0.94)	<.001
Hispanic	0.84 (0.82 to 0.87)	<.001	0.85 (0.82 to 0.88)	<.001
Other	0.96 (0.91 to 1.02)	.19	0.94 (0.88 to 1.00)	.05
Marital status (vs married)				
Sep/div/wid§	1.06 (1.05 to 1.08)	<.001	1.06 (1.04 to 1.08)	<.001
Single	1.11 (1.08 to 1.13)	<.001	1.09 (1.06 to 1.12)	<.001
Unknown	1.04 (1.01 to 1.08)	.02	1.02 (0.99 to 1.07)	.22
Histology (vs other NSCLC)				
Small cell	1.04 (1.02 to 1.06)	<.001	1.10 (1.08 to 1.12)	<.001
Adenocarcinoma	0.87 (0.85 to 0.88)	<.001	0.89 (0.88 to 0.91)	<.001
Squamous	0.88 (0.87 to 0.90)	<.001	0.92 (0.90 to 0.94)	<.001
Comorbidity				
Comorbidities	1.16 (1.14 to 1.17)	<.001	1.11 (1.09 to 1.13)	<.001
Payer status				
Medicaid	0.99 (0.97 to 1.00)	.13	0.96 (0.94 to 0.98)	<.001
Treatment status (vs any treatment)				
No treatment	2.02 (1.99 to 2.05)	<.001	1.89 (1.86 to 1.92)	<.001

* HR denotes hazard ratio of all-cause and lung cancer–specific death for the above covariables. All statistical tests were two-sided. CI = confidence interval; HR = hazard ratio; NSCLC = non–small cell lung cancer.

† CI denotes confidence interval.

‡ P values were calculated from the Cox proportional hazard models.

§ Separated/divorced/widowed.

treatments improve and the number of survivors grows, this proportion will likely increase (22,49–42). Compared with other common exclusion criteria, prior cancer may be one of the most substantial factors limiting accrual. In a recent study of medical comorbidities among 460 patients with lung cancer, the proportion of patients with prior cancer was three times the proportion with renal disease, seven times the proportion with liver disease, and 14 times the proportion with human immunodeficiency virus (33). Furthermore, the observation that the majority of prior cancer cases are diagnosed within five years of the lung cancer diagnosis suggests that the common practice of excluding prior cancer within five years of enrollment still results in exclusion of a substantial proportion of patients (20).

The most common types of prior cancer in our cohort were prostate, gastrointestinal, other genitourinary, and breast. This histologic distribution resembles that reported in other series of prior malignancy among lung cancer patients (22–25,39). The high prevalence of prostate cancer in the cohort reflects its overall prevalence in the general population (43). Like lung cancer, other genitourinary malignancies such as bladder cancer are associated with smoking. Notably, bladder cancer has the highest rate of subsequent primary cancers of any malignancy (16%) (44). Given a predilection for early stage of diagnosis, indolent course, and excellent response to local treatments, it seems unlikely that antecedent bladder or prostate cancers would substantially impact outcomes in advanced lung cancer (45). Furthermore, across cancer types, more than two-thirds of prior cancers in our cohort were localized or regional stage, suggesting that these earlier diagnoses may not adversely impact advanced lung cancer outcomes.

In the overall study population and every subgroup analyzed, prior cancer diagnosis was not associated with inferior survival. By contrast, prior cancer diagnosis was generally associated with improved clinical outcomes, regardless of timing in relation to the lung cancer diagnosis. Similar trends have been identified in lymphoma and gastrointestinal malignancy populations (46–48). There are many potential explanations for these trends. Possibilities include differing patient biology or treatment responsiveness, more frequent engagement in healthcare systems, or a healthy survivor effect. Another possibility is lead-time bias: Although all cases in this study were stage IV, those occurring after a prior cancer may have been diagnosed earlier in the disease course because of more frequent and intensive clinical care related to the prior cancer. This hypothesis echoes earlier findings that increased comorbidity burden is associated with lung cancer diagnosis at an earlier stage (33).

Given what appears to be a slightly favorable prognostic effect of prior cancer, how might these cases be handled in lung cancer clinical trials? In general, clinical trials in lung cancer and other diseases have not excluded patients expected to have good outcomes. Such an approach, we believe, runs counter to goals of fair and equitable access to clinical research and cutting-edge therapies. Furthermore, to apply this approach in lung cancer trials, one would need to exclude women, Asians, and patients with the best functional status (ie, ECOG 0 vs 1), as each of these characteristics has been associated with improved clinical outcomes (32,49,50). Alternatively, one could consider stratifying patients according to prior cancer diagnosis, or including prior cancer in final Cox modeling.

One potential reason for excluding prior cancer from clinical trials is that exposure to prior cancer treatment may render

patients less likely to tolerate experimental therapies. Although we are not able to determine treatment toxicities in our current analysis, we believe this concern can be addressed in other ways. First, other eligibility criteria (such as organ function, blood counts, and functional status) may adequately screen for treatment intolerance. Second, prior cancer treatment (distinct from a prior cancer diagnosis) can be employed as an exclusion criterion. This practice is already employed in numerous lung cancer trials (20) and is likely to exclude far fewer patients than does prior cancer diagnosis exclusion.

This study has a number of limitations. Compared with individuals with other common malignancies, individuals with lung cancer are generally older and have greater smoking history. Both factors may influence the likelihood and nature of a prior cancer diagnosis, thereby limiting the generalizability of our findings to other cancer populations (43). Additionally, use of SEER-Medicare data limits our analysis to patients older than age 65 years. However, because of the advanced age at diagnosis of lung cancer (average 71 years), this restriction may exclude a smaller proportion of patients (approximately 30%) compared with other common cancers (51), Furthermore, in an analysis of the youngest and presumably healthiest patients in our cohort (simulated clinical trial-eligible population: age <75 years, no documented comorbidities, and received chemotherapy for the advanced lung cancer diagnosis), our findings were similar to those in the overall study population. Nevertheless, future research may be warranted on the prevalence and impact of prior cancers among younger patients with lung cancer.

In summary, among patients with advanced lung cancer, 14.7% have a history of prior cancer. Most of these cases occur within five years of the lung cancer diagnosis. More than two-thirds are in situ, localized, or regional stage (so presumably cured or at least not life-limiting in the context of advanced lung cancer). In general, prior cancer does not adversely impact all-cause or lung cancer–specific survival. If anything, patients with prior cancer do a little better. Together, these findings suggest that broader inclusion in clinical trials of advanced lung cancer patients with prior cancer could be considered without impacting study outcomes. Such policy modifications could lead to faster accrual, higher trial completion rates, and more generalizable results, ultimately providing better treatments to more patients sooner.

Funding

Notes

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