



# Impact of prior cancer history on the overall survival of younger patients with lung cancer

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## ABSTRACT

**Background** Patients with a history of prior cancer are frequently excluded from cancer trials. Previous studies indicated that prior cancer does not adversely impact clinical outcomes for patients with lung cancer older than 65 years. However, it remains unknown whether these results are applicable to patients with lung cancer aged younger than 65 years old. The study aimed to investigate the impact of prior cancer history on younger patients with lung cancer.

**Methods** We identified younger patients with lung cancer (<65 years) diagnosed between 2004 and 2009 in the Surveillance, Epidemiology, and End Results database. Propensity score matching was performed to balance differences in baseline characteristics between groups. Kaplan-Meier method and the Cox proportional hazards model were used to evaluate the impact of prior cancer on overall survival (OS).

**Results** Among 103 370 eligible patients with lung cancer, 15.18% had a history of prior cancer. Lung and bronchus (25.83%), breast (14.13%), prostate (8.85%) and cervix uteri (4.74%) were the most common prior cancer types. Of prior cancers, 61.56% are localised and regional stages. More than 67.98% of prior cancers were diagnosed within 5 years of the index lung cancer diagnosis. The median times of diagnosis for prior cancers were 38 months. Patients with prior cancer had the same/non-inferior OS as that of patients without a prior cancer diagnosis (propensity score-adjusted HR=1.01, 95% CI=0.99 to 1.04, p=0.324). Subgroup analyses stratified by timing of prior cancer displayed almost the same tendency (p>0.05). Interestingly, early-stage patients with a history of prior cancer had adverse survival curves (p<0.05). Advanced-stage patients with prior cancer had non-inferior survival (p>0.05).

**Conclusions** A prior cancer diagnosis has a heterogeneous effect on the survival of patients with lung cancer aged <65 years across different stages, but further prospective studies are still warranted.

## INTRODUCTION

Lung cancer is one of the most common causes of cancer-related mortality, accounting for 25% of all cancer deaths. Compared to other cancer types, advanced improvement of survival for lung cancer is very slow, for which

## Key questions

### What is already known about this subject?

▶ Previous studies indicated that a prior cancer history does not impact the overall survival of lung cancer patients older than 65 years.

### What does this study add?

▶ Our study further investigated whether prior cancer could impact the clinical outcomes of patients with lung cancer younger than 65 years.

### How might this impact on clinical practice?

▶ Our finding indicated that a prior cancer history had a heterogeneous effect on the survival of lung cancer patients aged <65 years across different stages, which could help clinicians to decide whether a prior cancer history should be adopted as an exclusion criteria for younger lung cancer patients.

the 5-year survival rate is 18%.<sup>1</sup> To improve the diagnosis and treatment of lung cancer, numerous clinical trials are warranted to test whether new medical approaches work and how well they work. However, the enrolment rate and the completion rate of cancer clinical trials are unable to keep pace.<sup>2,3</sup> In the USA, fewer than 5% of patients with cancer are included in clinical trials.<sup>4,5</sup> The low accrual rate has been attributed to many factors, among which increasingly complex eligibility criteria are a major barrier.<sup>6,7</sup> What's worse, some eligibility criteria are applied in clinical trials just because similar protocols have been applied in a similar population, without scientific validation.<sup>7</sup>

A prior cancer diagnosis has been adopted as an exclusion criterion due to the belief that a prior cancer diagnosis could adversely affect the outcomes of clinical trials. Up to 18% of potential participants were excluded from lung cancer clinical trials for this reason alone.<sup>8</sup> Little evidence has been found to support this assumption. Instead, previous



studies based on Surveillance, Epidemiology, and End Results (SEER)–Medicare database indicated that prior cancer does not adversely impact clinical outcomes for patients with lung cancer older than 65 years across different stages.<sup>9,10</sup> Due to the restrictions of SEER–Medicare data, the findings of these studies were limited to elderly patients. However, patients with lung cancer aged <65 years are also a significant proportion of the whole population, which accounts for 30.3%.<sup>11</sup> The clinical characteristics of younger patients, such as treatment tolerance and effectiveness, are different from those of older patients.<sup>12,13</sup> It remains unknown whether a prior cancer diagnosis impacts the survival of younger patients with lung cancer. To address these assumptions, we determined the characteristics and prognostic impact of prior cancer among patients with lung cancer using the SEER database.

## METHODS

### Data source and study population

All the data used in our study were extracted from the SEER database through SEER\*Stat software V.8.3.5, which covers approximately 34.6% of the population in the USA (<https://seer.cancer.gov/>, accession numbers 13693–Nov2015 and lh8N7912).<sup>14,15</sup> Patients younger than 65 years old who were diagnosed with lung cancer from January 2004 to December 2009 were included in the study. Exclusion criteria were listed as follows: (1) <18 years of age at diagnosis, (2) patients with unknown follow-up information and survival data, (3) and patients with only death certificates or autopsy records. We extracted demographic and clinical characteristics from the SEER database, including age, sex, race, marital status, TNM stage (American Joint Committee on Cancer [AJCC] sixth edition), pathology grade, surgery records and radiotherapy records. The survival data were recorded in months. To include those who died within 1 month after the cancer diagnosis, we transformed 0-month survival into 0.5-month survival.<sup>16</sup>

### Measures

As described in our previous study, we determined a prior cancer diagnosis according to SEER sequence numbers, which reflects the order of diagnosis time of all primary reportable neoplasms.<sup>17</sup> We calculated the timing of prior cancer by subtracting the diagnosis date of the most recent prior cancer from the diagnosis date of the index lung cancer. The primary endpoint of the study was overall survival (OS). The cut-off date was set as 31 December 2014 to ensure at least 5 years of follow-up time for all included patients.

### Statistical analysis

Patients included in our study were categorised into two groups: with a prior cancer diagnosis and without a prior cancer diagnosis. We assessed differences in the characteristics of these two groups of patients, with t-test for continuous variables and Pearson  $\chi^2$  analysis for categorical

variables. Propensity score matching (PSM) method was employed to reduce the bias due to observed confounding variables in baseline characteristics.<sup>18</sup> Propensity scores were calculated based on age, sex, race, marital status, TNM stage (AJCC sixth edition), pathology grade, surgery records and radiotherapy records. We performed a one-to-one PSM with a calliper of 0.2 and used these PSM pairs in subsequent analyses. With the Kaplan–Meier method, we estimated the OS of the patients and compared the differences between the two groups using log-rank tests. A multivariate Cox proportional hazards model was also built to identify whether prior cancer impacts the prognosis independently. The common demographic and clinical characteristics, including age, sex, race, marital status, TNM stage (AJCC sixth edition), pathology grade, surgery records and radiotherapy records, were entered as covariates. We set the significance level at 0.05 (two-sided). All the analyses were performed using R V.3.4.2 (Institute for Statistics and Mathematics, Vienna, Austria; [www.r-project.org](http://www.r-project.org)).

## RESULTS

In all, 103 370 eligible patients with lung cancer were identified, of whom 15 696 (15.18%) had a history of prior cancer. A prior cancer diagnosis was more common among women (53.9% vs 43.7%,  $p<0.001$ ), the elderly (58.55 years vs 56.86 years,  $p<0.001$ ), Caucasians (83.1% vs 78.6%,  $p<0.001$ ) and married individuals (55.6% vs 53.0%,  $p<0.001$ ). Other baseline patient characteristics are shown in [table 1](#).

Lung and bronchus (25.83%), breast (14.13%), prostate (8.85%) and cervix uteri (4.74%) were the most common prior cancer types ([figure 1](#)). Among patients with prior cancer, distant stages were the most frequently observed, accounting for 45.1%. More than 67.98% of prior cancers were diagnosed within 5 years of the index lung cancer diagnosis. The median times between the index lung cancer date and the most recent diagnosis for prior cancers were 38 months. After propensity matching, the covariables were mostly balanced.

The unadjusted Kaplan–Meier curves in [figure 2](#) showed an adverse effect of prior cancer on OS, compared with patients without a prior cancer diagnosis (log-rank tests,  $p=0.029$ ). However, in Cox regression analysis, patients with prior cancer had the same/non-inferior OS as that of patients without a prior cancer diagnosis (HR=1.01, 95% CI=0.99 to 1.04,  $p=0.324$ ). Subgroup analyses stratified by timing of prior cancer displayed almost the same tendency ( $p>0.05$ ). Interestingly, early-stage patients with a prior cancer diagnosis had adverse survival than those without a history of prior cancer ( $p<0.05$ ), while advanced-stage patients with and without a prior cancer had similar OS ( $p>0.05$ ) ([figure 3](#)).

## DISCUSSION

Our current study suggested that a prior cancer diagnosis was not rare among younger patients with lung cancer. On

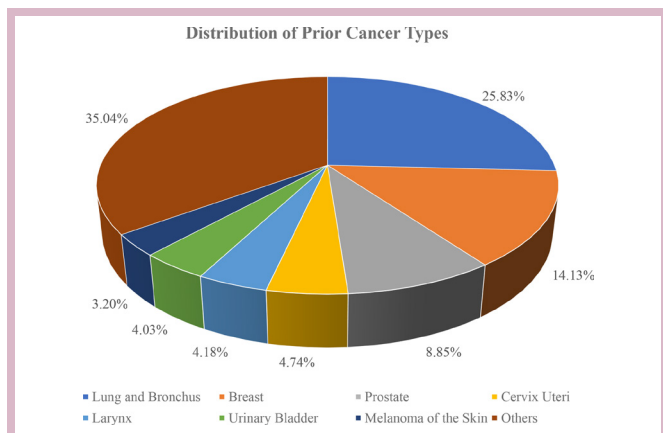
**Table 1** Baseline characteristics of patients with lung cancer in the original/matched data sets (N=15 696).

Characteristics	Original data set		P value	Matched data set		P value
	No prior cancer N=87674 (%)	With prior cancer N=15 696 (%)		No prior cancer N=15 696 (%)	With prior cancer N=15 696 (%)	
Age (years), mean (SD)	56.86 (6.64)	58.55 (5.91)	<0.001	58.74 (5.64)	58.55 (5.91)	0.005
Race (%)			<0.001			0.301
Black	13230 (15.1)	2003 (12.8)		1937 (12.3)	2003 (12.8)	
Unknown/others	5552 (6.3)	649 (4.1)		615 (3.9)	649 (4.1)	
White	68892 (78.6)	13044 (83.1)		13144 (83.7)	13044 (83.1)	
Gender			<0.001			0.892
Male	49396 (56.3)	7242 (46.1)		7255 (46.2)	7242 (46.1)	
Female	38278 (43.7)	8454 (53.9)		8441 (53.8)	8454 (53.9)	
Marital status			<0.001			0.699
Unmarried	41228 (47.0)	6962 (44.4)		6997 (44.6)	6962 (44.4)	
Married	46446 (53.0)	8734 (55.6)		8699 (55.4)	8734 (55.6)	
Primary site			<0.001			0.532
Main bronchus	5534 (6.3)	733 (4.7)		734 (4.7)	733 (4.7)	
Upper lobe	44914 (51.2)	8097 (51.6)		8240 (52.5)	8097 (51.6)	
Middle lobe	3535 (4.0)	732 (4.7)		686 (4.4)	732 (4.7)	
Lower lobe	18213 (20.8)	3777 (24.1)		3705 (23.6)	3777 (24.1)	
Overlapping lesion	1274 (1.5)	179 (1.1)		164 (1.0)	179 (1.1)	
Lung, NOS	14204 (16.2)	2178 (13.9)		2167 (13.8)	2178 (13.9)	
AJCC group			<0.001			0.020
I	12420 (14.2)	4290 (27.3)		4152 (26.5)	4290 (27.3)	
II	3728 (4.3)	777 (5.0)		805 (5.1)	777 (5.0)	
III	21389 (24.4)	3596 (22.9)		3714 (23.7)	3596 (22.9)	
IV	44175 (50.4)	5649 (36.0)		5765 (36.7)	5649 (36.0)	
Unknown	5962 (6.8)	1384 (8.8)		1260 (8.0)	1384 (8.8)	
Surgery			<0.001			0.934
Yes	19232 (21.9)	5457 (34.8)		5465 (34.8)	5457 (34.8)	
No/unknown	68442 (78.1)	10239 (65.2)		10231 (65.2)	10239 (65.2)	
Radiotherapy			<0.001			0.850
Yes	39779 (45.4)	5525 (35.2)		5508 (35.1)	5525 (35.2)	
No/unknown	47895 (54.6)	10171 (64.8)		10188 (64.9)	10171 (64.8)	
Grade			<0.001			0.667
Well differentiated	3069 (3.5)	950 (6.1)		897 (5.7)	950 (6.1)	
Moderately differentiated	11510 (13.1)	2864 (18.2)		2820 (18.0)	2864 (18.2)	
Poorly differentiated	22875 (26.1)	4131 (26.3)		4190 (26.7)	4131 (26.3)	
Undifferentiated	5055 (5.8)	680 (4.3)		682 (4.3)	680 (4.3)	
Unknown	45165 (51.5)	7071 (45.0)		7107 (45.3)	7071 (45.0)	
Stage			<0.001			0.033
Distant	53977 (61.6)	7078 (45.1)		7162 (45.6)	7078 (45.1)	
Localised	10937 (12.5)	3976 (25.3)		3822 (24.4)	3976 (25.3)	
Regional	19995 (22.8)	4011 (25.6)		4142 (26.4)	4011 (25.6)	
Unknown/unstaged	2765 (3.2)	631 (4.0)		570 (3.6)	631 (4.0)	

AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

the whole, a prior cancer diagnosis did not convey a distinguishing affect on the survival of the patients, which was consistent with the research that focused on patients older than 65 years and our previous study.<sup>9 10 17 19</sup> However, in

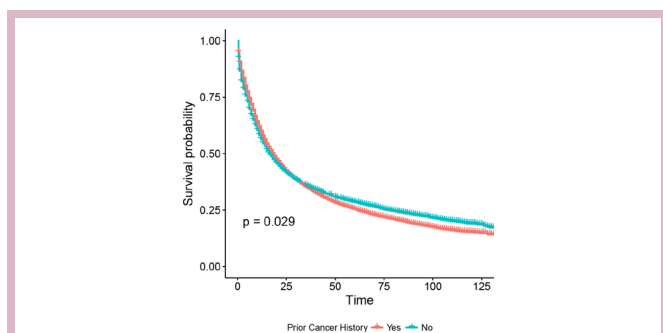
patients aged  $\geq 65$  years, the impact of prior cancer did not vary across different stages of lung cancer, which was distinguished from the heterogeneous effect of tumour stage in our study. We found that a prior cancer diagnosis adversely



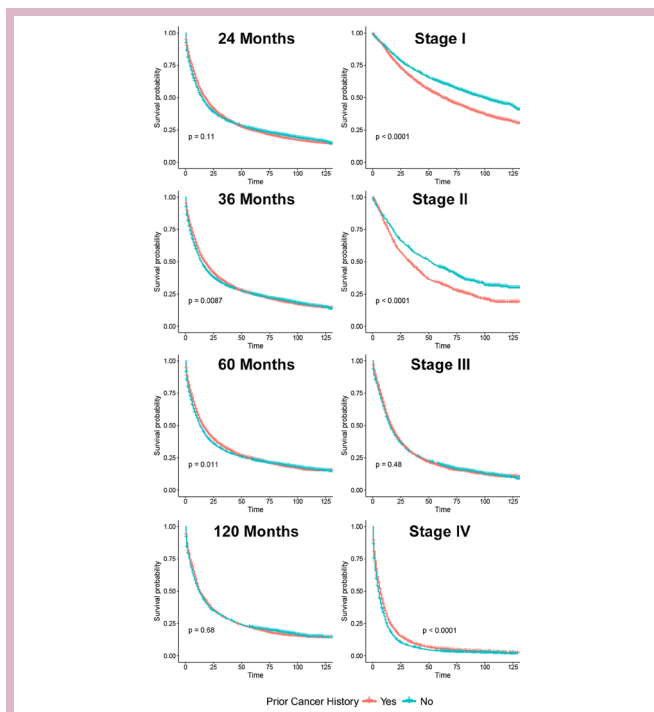
**Figure 1** Distributions of prior cancer types.

affected the OS of the early-stage patients but had no significant influence on the survival of the advanced-stage patients. The unique impact of a prior cancer diagnosis on younger patients with lung cancer may result from their unique clinical characteristics. Younger patients with lung cancer tend to have better prognosis than older patients, especially in patients with early-stage non-small cell lung cancer (NSCLC). Nevertheless, the OS of younger patients with advanced-stage NSCLC is only marginally better than that of the older patients, although the younger patients have fewer comorbidities.<sup>20</sup> Younger patients with early-stage lung cancer are more likely to be cured than those with advanced disease and older patients. Therefore, the risks of increasing treatment intolerance due to prior cancer treatment are more likely to worsen the survival of younger patients with early-stage lung cancer. While older patients and advanced-stage patients are more likely to die from the progression of lung cancer,<sup>21</sup> the impact of prior cancer is relatively neglectable. Our study indicated that the heterogeneous survival impact of a prior cancer diagnosis might need to be taken into consideration when recruiting younger volunteers for lung cancer clinical trials.

In most lung cancer trials, the time interval must be at least 5 years if patients who have prior cancer diagnosis want to be enrolled in.<sup>9</sup> In our study, more than 67.98% of prior



**Figure 2** The unadjusted Kaplan-Meier survival curves of prior cancer impact on the OS in younger patients with lung cancer. The OS of younger patients with lung cancer with a prior cancer was marginally better than that of patients without a prior cancer ( $p < 0.05$ ). OS, overall survival.



**Figure 3** Subgroup analysis of prior cancer impact on the overall survival stratified by the timing of prior cancer and American Joint Committee on Cancer (AJCC) stage in younger patients with lung cancer. The younger patients with lung cancer with prior cancer showed a similar survival with patients without a prior cancer, regardless of the timing of a prior cancer diagnosis. Early-stage patients with a history of prior cancer had adverse survival curves ( $p < 0.05$ ). Advanced-stage patients with prior cancer had non-inferior survival ( $p > 0.05$ ).

cancer were diagnosed within the 5-year interval in relation to the index lung cancer diagnosis. Our findings suggested that the timing of a prior cancer diagnosis relative to the index lung cancer did not convey an appreciable adverse effect on patients' OS, suggesting that the impact of prior cancer history on younger patients' OS was independent of follow-up time. In addition, the median times of diagnosis for prior cancers were 38 months, which indicated that active surveillance was necessary for cancer survivors.

In addition to concerns about the survival impact of prior cancer diagnosis, there is another reason why patients with prior cancer are usually excluded. The treatment they received might lower the patient's tolerance or decrease the efficacy of further treatment for the current lung cancer. Although treatment toxicities cannot be determined in our current analysis due to data restriction, we believe this concern can be allayed in other ways. For example, we can restrict the enrolment according to organ function so that we could exclude patients who are intolerant of treatment. Moreover, prior cancer treatment can be employed as an exclusion criterion, which is different from prior cancer diagnosis exclusion. This strategy has been adopted in many lung cancer trials.<sup>9</sup>

There are also several limitations in our study. First, detailed characteristics of a prior cancer cannot be achieved through the SEER database. We defined a prior cancer history according to the documented order, and we could only include the type and the timing of prior cancer in our study. Other information such as the efficacy and toxicity of treatment on prior cancer could not be considered due to lack of relevant data. Second, in our PSM analyses and regression models, comorbidities were not included because there were no relevant data in the SEER database. PSM analysis could not adjust for unobservable differences between groups. Therefore, hidden bias resulting from unobservable confounders remained after the PSM process. Finally, further study is warranted to confirm the generality of our findings since SEER data only cover approximately 34.6% of the total US population, thus making it necessary to confirm the generality of our findings.

## CONCLUSIONS

In conclusion, a prior cancer diagnosis has a heterogeneous effect on the survival of patients with lung cancer aged <65 years across different stages. For younger patients with early-stage lung cancer, a prior cancer history might need to be cautiously considered when deciding the exclusion criteria, while for younger patients with advanced lung cancer, broader inclusion trial criteria could be adopted in terms of prior cancer diagnosis, which could increase the accrual rate and enable the outcomes of the clinical trials to benefit more patients.

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**Contributors** JL, HZ, and YZ contributed equally to this work and should be regarded as cofirst authors. LZ, JL, HZ and YZ and were responsible for the conception and design of the study, the interpretation of data, drafting and writing of the article; WF, YY, SH, GC and SZ were responsible for acquisition, analysis and interpretation of data and drafting the text, and also participated in the drafting of the article; JS, WX, ZZ and XC were responsible for the interpretation of the data and drawing the figures. HZ and YH were responsible for the revision of the intellectual content. All authors participated in the final approval of the article and agreed to be accountable for all aspects of the work.

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