Cancer Causes & Control (2019) 30:465–475
https://doi.org/10.1007/s10552-019-01161-7

ORIGINAL PAPER

Second primary lung cancer in United States Cancer Survivors, 1992–2008

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Received: 24 September 2017 / Accepted: 10 February 2019 / Published online: 21 March 2019

Abstract

Purpose Lung cancer is common and lethal, and can occur in survivors of previous cancers. We sought to describe the incidence and mortality attributable to second primary lung cancers (SPLC) among survivors of other cancers, and to identify survivors at highest risk.

Methods We identified adults diagnosed with a localized malignancy from non-pulmonary cancer sites from surveillance, epidemiology, and end results (SEER) data from 1992 to 2008. We explored factors associated with the incidence and death from SPLC using bivariable and multivariable models. Finally, we compared standardized incidence rates for SPLC in our cohort with the control arm of the National Lung Screening Trial (NLST), a randomized lung cancer screening trial.

Results We identified 1,450,837 survivors of non-pulmonary cancers, of whom 25,472 developed SPLC at a mean (SD) follow-up of 5.7 (3.6) years. Over half (57%) of patients with SPLC died of the disease. Survivors of cancer of the hypopharynx, oropharynx, tonsil, and larynx, experienced SPLC at standardized incidence rates which greatly exceeded that observed in the control arm of the NLST (572/100,000 person-years). Additionally, survivors of bladder and esophageal cancer had rates that approached the NLST control arm rate. Increasing age and being divorced/widowed/separated were independent risk factors for SPLC in most primary cancer types.

Conclusion The incidence of SPLC in survivors of certain primary cancers greatly exceeds the rate observed in the control arm of the NLST. Further study could help determine if screening for lung cancer in these cancer survivors could prevent death from lung cancer.

Keywords SEER program · Lung neoplasms · Second primary neoplasms · Epidemiology · Survivors · Screening

Introduction

In the last 30 years, 5-year survival following a diagnosis of cancer has increased over 20% points in the United States, with a concomitant steady decline in the cancer death rate. These gains have resulted in 1.7 million deaths averted as of 2012 [1]. The population of cancer survivors in the United States continues to grow, and is estimated to exceed 20 million by 2026 [2]. Many of these survivors will live in excess of 10 years following their diagnosis. It has been estimated that cancer survivors have a 14% higher risk of developing a second malignancy than would be expected in the general population [3]. We recently reported that in a United States population-based cohort of cancer survivors, 8% of cancer survivors developed a second primary malignancy [4]. Second primary lung cancer (SPLC) was the most common, representing 25% of these second primary malignancies, and was the cause of death in 12% of our cohort of cancers survivors.

Lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death among women worldwide [5]. While the 5-year survival rate in the United States for lung cancer is only 19% [6], early-stage

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10552-019-01161-7) contains supplementary material, which is available to authorized users.

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disease demonstrates far more favorable outcomes, owing to the strong association between stage at diagnosis and survival [6]. In an attempt to identify early-stage disease when interventions may be curative, various lung cancer screening strategies have been evaluated. In 2011, the National Lung Screening Trial (NLST), a randomized, prospective screening trial of patients with a strong smoking history, demonstrated a 20% relative reduction in death from lung cancer in patients who underwent screening with three annual chest CTs [7]. Based on these results, most clinical guidelines including those from the American Cancer Society, National Comprehensive Cancer Network, and United States Preventative Services Task Force now recommend annual screening for specified populations of current and former heavy smokers.

In our practice, we have observed a high rate of SPLC in survivors of bladder cancer. This observation, along with the well-established relationship between tobacco smoke exposure and both pulmonary and non-pulmonary malignancies [8], prompted our interest in exploring the incidence rate and mortality attributable to SPLC in survivors of cancer. This investigation was undertaken in light of the demonstrable survival gains attained by the NLST lung cancer screening protocol in high-risk patients. We sought to explore SPLC incidence rates within our cancer survivor population in order to evaluate whether any sub-populations of cancer survivors demonstrate incidence rates of SPLC sufficiently high to consider lung cancer screening in that sub-population.

Materials and methods

Dataset

We obtained data from the April 2013 release of the publicly available SEER database. This release from the SEER program compiled information on cancer incidence and survival rate from 18 population-based cancer registries throughout the United States and covered approximately 28% of the general population [6].

Patient cohort

We identified all patients diagnosed with a primary malignancy among eight of the highest-incident non-pulmonary cancer sites in both genders (i.e., prostate, breast, colon, rectum, bladder, uterus, kidney, and melanoma) as well as additional sites known to be strongly associated with tobacco smoke (oropharynx, hypopharynx, larynx, tonsil, esophagus) [1]. We excluded cases of locally advanced or metastatic disease ($n = 989{,}989$ excluded) so as to avoid misclassification of pulmonary metastases as SPLC. While data were available through 2011, we limited our cohort to patients diagnosed from 1992 to 2008 ($n = 1{,}438{,}093$ excluded) in order to ensure 3 years of follow-up after a cancer diagnosis. We subsequently excluded cases in which the second primary malignancy was diagnosed within 1 year of the first malignancy ($n = 4{,}774$ excluded) in order to prevent misclassification of metastatic primary malignancies as second primary malignancies. Finally, we limited our analysis to patients ≥ 18 years of age ($n = 11{,}315$ excluded). From this cohort, individuals with a pathologic diagnosis of primary lung cancer were identified and denoted as the SPLC group. Cancer cases were categorized by site using International Classification of Diseases for Oncology, Second Edition (ICD-O-2) codes [9].

Primary outcome and co-variates of interest

Our primary outcome was the diagnosis of a SPLC, based on a diagnosis of one of the incident cancer types followed by a diagnosis of lung cancer. Our secondary outcomes of interest were death from a primary malignancy or SPLC, and standardized incidence rate of SPLC (weighted for age, sex, and race based on the distributions of these variables present in the NLST). Patient demographics included age in years (18–50, 51–65, 66–80, and > 80), marital status (single, married/domestic partner, divorced/widowed/separated, unknown), race (white, black, unknown, and other—includes American Indian, Alaskan Native, Asian/Pacific Islander), gender (male, female), and year of diagnosis (1992–1996, 1997–2000, 2001–2004, 2005–2008). SEER merged ZIP code level data for education level and annual household income from 2008 United States Census data. Individual-level data were imputed from the percentage of patients holding a bachelor's degree and the median annual household income in each patient's ZIP code, which was then stratified into quartiles. Tumor characteristics included grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, unknown/not applicable) and stage (in situ and/or localized, regional, distant, unstaged, and unknown).

Statistical analysis

We generated descriptive statistics for our cohort and evaluated the association between co-variates of interest and development of SPLC using Chi-square and two-sided t tests. Next, we employed a competing risk regression analysis to generate cumulative incidence estimates of

Table 1 Cohort demographics stratified by second lung cancer ($n = 1{,}450{,}837$)

Characteristic	Second primary lung		No second primary lung		p value
	$n = 25{,}472$		$n = 1{,}425{,}365$		
	No	%	No	%	
Age at diagnosis					
18–50	963	3.8	235,342	16.5%	< 0.0001
51–65	8,198	32.2	513,293	36.0%	
66–80	14,553	57.1	536,458	37.6%	
80 +	1,758	6.9	140,272	9.8%	
Sex					
Male	16,863	66.2	793,925	55.7%	< 0.0001
Female	8,609	33.8	631,440	44.3%	
Race					
White	21,698	85.2	1,189,929	83.5%	< 0.0001
Black	2,726	10.7	131,968	9.3%	
Other	1,041	4.1	80,315	5.6%	
Unknown	7	0.0	23,153	23,153	
SEER location by census region					
West	12,066	47.4	759,266	53.3%	< 0.0001
South	4,413	17.3	248,027	17.4%	
Northeast	4,250	16.7	235,237	16.5%	
Midwest	4,743	18.6	182,835	12.8%	
Marital status					
Single	2,136	8.4	151,097	10.6%	< 0.0001
Married/domestic partner	15,878	62.3	884,806	62.1%	
Divorced/widowed/separated	5,759	22.6	275,007	19.3%	
Unknown	1,699	6.7	114,455	8.0%	
Year of diagnosis					
1992–1996	5,482	21.5	181,346	12.7%	< 0.0001
1997–2000	6,838	26.8	270,179	19.0%	
2001–2004	8,743	34.3	471,946	33.1%	
2005–2008	4,409	17.3	501,894	35.2%	
Primary cancer					
Prostate	9,861	38.7	511,486	35.9%	< 0.0001
Breast	4,723	18.5	341,394	24.0%	
Colorectal	2,810	11.0	149,970	10.5%	
Bladder	3,986	15.6	107,963	7.6%	
Melanoma	1,155	4.5	120,591	8.5%	
Endometrial	819	3.2	74,082	5.2%	
Kidney	850	3.3	55,114	3.9%	
Thyroid	273	1.1	46,727	3.3%	
Tonsil	61	0.2	1,350	0.1%	
Oropharynx	27	0.1	262	0.0%	
Hypopharynx	20	0.1	292	0.0%	
Esophagus	117	0.5	8,001	0.6%	
Larynx	770	3.0	8,133	0.6%	
Grade					
Well differentiated	3,398	13.3	185,288	13.0%	< 0.0001
Moderately differentiated	12,396	48.7	624,732	43.8%	

Table 1 (continued)

Characteristic	Second primary lung		No second primary lung		*p* value
	n = 25,472		*n* = 1,425,365		
	No	%	No	%	
Poorly differentiated	5,475	21.5	319,606	22.4%	
Undifferentiated	511	2.0	23,172	1.6%	
Unknown/not applicable	3,692	14.5	272,567	19.1%	

Also available but not displayed

No. number

%Received degree, %household income, and metro/suburban/rural location

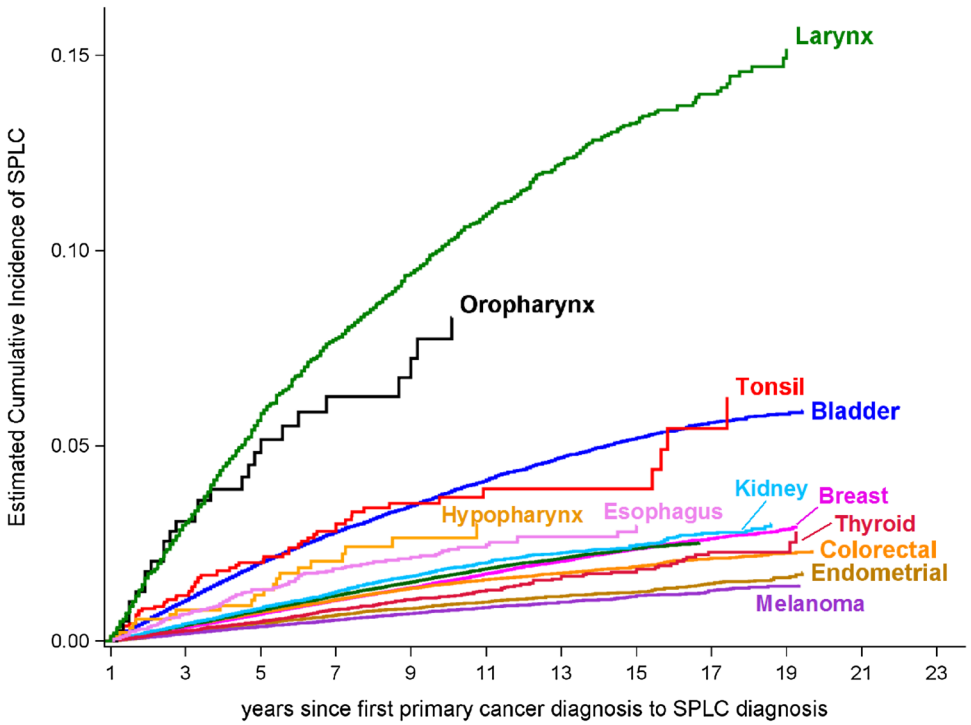

Fig. 1 Estimated cumulative incidence of second primary lung cancer with death from other causes as competing risk, by primary cancer site (*n* = 1,450,837). Figure 1 depicts the estimated cumulative incidence of second primary lung cancer following a diagnosis of a primary cancer, by each of the primary cancer sites. Performed as a competing risk analysis, with death from any cause as competing risk. Events occurring during the first year of follow-up were excluded in order to prevent misclassification of metastatic primary malignancies as second primary malignancies

SPLC in the population, with death from any other cause as the competing risk. Those without SPLC or the competing risk during the follow-up period were right censored, and because all patients were followed until the end of data collection in 2011, this censoring was non-informative. For death from SPLC, we displayed the survival rate distribution estimate using the Kaplan–Meier method. We then estimated hazard ratios using a separate multivariable Cox proportional hazard model for each primary cancer site that incorporated our co-variates of interest (age, race, marital status, tumor grade, stage, % with bachelor's degree, and median annual household income). We also calculated distributions of cause of death in all patients, and in patients with multiple malignancies, stratified by first cancer site, and whether cause of death was due to primary or secondary malignancy. We calculated standardized incidence rates for the entire cohort, as well as stratified by primary tumor site. Crude rates were then weighted for age, race, and gender based on the distribution of these variables in the NLST. In addition, we generated incidence rates of SPLC for each primary tumor type in an index individual who, based on the hazard ratios calculated in the Cox multivariable model, would be considered the average risk for SPLC. All statistical tests were performed at the 5% significance level and conducted in SAS 9.4 (SAS Institute Inc., Cary, NC). This

Table 2 Proportional sub-distribution of probability (CI) of second primary lung cancer by each primary cancer location

Primary site	Prostate $n=465,136$	Breast $n=332,642$	Colorectal $n=143,973$	Melanoma $n=87,792$	Bladder $n=104,980$	Thyroid $n=44,712$	Kidney $n=53,459$	Endometrial $n=71,669$
Age at diagnosis								
18–50	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
51–65	**3.66 (2.90–4.63)**	**2.96 (2.65–3.30)**	**4.10 (3.14–5.35)**	**6.06 (4.66–7.90)**	**3.73 (3.01–4.63)**	**5.62 (3.93–8.02)**	**3.52 (2.65–4.68)**	**2.87 (2.07–3.98)**
66–80	**6.49 (5.15–8.19)**	**3.86 (3.46–4.31)**	**6.13 (4.72–7.96)**	**9.72 (7.49–12.60)**	**4.69 (3.80–5.80)**	**10.61 (7.28–15.45)**	**5.30 (3.99–7.03)**	**4.65 (3.34–6.47)**
> 80	**3.93 (3.07–5.03)**	**1.47 (1.25–1.72)**	**2.53 (1.90–3.37)**	**5.29 (3.77–7.43)**	**1.81 (1.43–2.30)**	**4.52 (1.87–10.92)**	**2.35 (1.54–3.59)**	**2.52 (1.64–3.86)**
Sex								
Male	–	**1.68 (1.23–2.31)**	**1.49 (1.37–1.62)**	**1.32 (1.15–1.53)**	**1.12 (1.03–1.21)**	**1.36 (1.02–1.80)**	**1.19 (1.03–1.38)**	–
Female	–	Reference	Reference	Reference	Reference	Reference	Reference	–
Race								
White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Black	**1.31 (1.24–1.39)**	1.01 (0.91–1.13)	0.94 (0.82–1.07)	1.95 (0.92–4.12)	1.08 (0.92–1.26)	1.26 (0.81–1.95)	0.89 (0.71–1.13)	1.02 (0.76–1.36)
Other	0.92 (0.83–1.02)	**0.66 (0.57–0.76)**	0.86 (0.73-1.00)	0.91 (0.38–2.21)	**0.80 (0.67–0.97)**	0.70 (0.43–1.16)	0.69 (0.47-1.00)	**0.60 (0.41–0.87)**
Marital status								
Married/domestic partner	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Divorce/widow/separated	**1.19 (1.13–1.26)**	**1.33 (1.25–1.43)**	**1.13 (1.03–1.25)**	**1.25 (1.04–1.50)**	1.05 (0.97–1.15)	**1.51 (1.12–2.03)**	1.08 (0.90–1.29)	1.15 (0.98–1.35)
Single	1.01 (0.94–1.09)	1.06 (0.95–1.17)	1.08 (0.95–1.24)	0.84 (0.66–1.07)	0.92 (0.81–1.04)	1.01 (0.68–1.52)	0.88 (0.69–1.13)	0.94 (0.74–1.19)

Primary site	Tonsil $n=1330$	Oropharynx $n=281$	Hypopharynx $n=300$	Esophagus $n=7767$	Larynx $n=8490$
Age at diagnosis					
18–50	Reference	Reference	Reference	Reference	Reference
51–65	**2.59 (1.14–5.87)**	4.44 (0.53–36.95)	0.63 (0.15–2.72)	1.52 (0.72–3.21)	**2.84 (2.05–3.94)**
66–80	**3.08 (1.27–7.47)**	4.78 (0.58–39.15)	**0.16 (0.03–0.77)**	1.30 (0.62–2.74)	**2.42 (1.73–3.37)**
> 80	1.08 (0.13–8.74)		0.19 (0.03–1.43)	**0.21 (0.05–0.79)**	1.09 (0.66–1.81)
Sex					
Male	1.34 (0.73–2.47)	1.10 (0.46–2.62)	0.65 (0.24–1.72)	0.79 (0.51–1.23)	0.74 (0.62–0.89)
Female	Reference	Reference	Reference	Reference	Reference
Race					
White	Reference	Reference	Reference	Reference	Reference
Black	1.93 (0.96–3.90)	1.36 (0.41–4.58)	0.22 (0.03–1.58)	1.15 (0.67–1.96)	0.95 (0.76–1.20)
Other	0.32 (0.04–2.42)			0.36 (0.09–1.47)	0.77 (0.50–1.18)
Marital status					
Married/domestic partner	Reference	Reference	Reference	Reference	Reference
Divorce/widow/separated	1.70 (0.94–3.07)	1.56 (0.61–4.03)	**3.10 (1.06–9.09)**	0.64 (0.39–1.05)	0.94 (0.79–1.13)
Single	0.70 (0.29–1.67)	1.08 (0.35–3.32)	1.42 (0.38–5.29)	0.85 (0.50–1.44)	0.86 (0.67–1.10)

Adjusted for mean age (63.8), white race, married, well-differentiated grade, highest quartile of education and highest quartile of household income; and female for except for prostate and endometrial cancer. Also included in the models were % received college degree to % household income to primary tumor grade—associations between these variable strata and cumulative incidence were inconsistent across primary tumor sites and were thus omitted from the table for display for simplicity

Bolded results are statistically significant to the < 0.05 level

study was deemed to be exempt by the IRB of the University of California, Los Angeles (UCLA).

Results

We identified 1,450,837 patients with first incident cancers diagnosed between 1992 and 2008 that met our inclusion criteria, amongst whom 25,472 developed a SPLC (Table 1). Mean (SD) follow-up was 7.7 (4.2) years and 5.7 (3.6) years for those who did and did not develop a SPLC, respectively ($p < 0.0001$). Competing risk analysis demonstrated that survivors of hypopharynx, oropharynx, larynx, tonsil, bladder, and esophageal cancers demonstrated the highest estimated cumulative incidence of SPLC (Fig. 1). For example, we estimated that at 10-years of follow-up, approximately 10% of laryngeal cancer survivors will have developed a SPLC, while just over 2.5% of bladder cancer survivors will have developed SPLC. Multivariable models generated for each first cancer site demonstrated that increasing age was an independent risk factor for the development of SPLC in all of the first cancer sites evaluated except oropharynx and esophagus (Table 2). Other variables did not consistently demonstrate independent increased risk for the development of SPLC across all first cancer sites; however, male gender and being divorced/widowed/separated both conferred an increased risk for developing a SPLC in the majority of the primary sites evaluated. When comparing the characteristics between those that developed a SPLC and those that were censored, we found differences in age, sex, and marital status across the majority of the primary cancer sites, and their subsequent cumulative incidences from inclusion in the competing risks models were also significant.

Of the 25,472 patients who developed SPLC, 19,938 died during follow-up, and of these, 14,476 died of lung cancer (Supplemental Table 1). Thus, 57% of the patients who developed SPLC died of the disease, and SPLC represented 73% of the deaths in cohort of patients who developed SPLC. For those who did not develop SPLC, the most common cause of death was a non-cancer cause of death, with 62% of deaths accounted for by non-cancer etiologies. Figure 2 demonstrates Kaplan–Meier survival estimates in patients with SPLC. Multivariable models generated for each first cancer site demonstrated that while across many of the first cancer sites, age > 80 years old was a risk factor for death from SPLC, this was not consistent amongst all first cancer sites and was not demonstrated in any of the head and neck cancers, and the remaining co-variates demonstrated either no or an inconsistent association with the risk of death from SPLC (Table 3).

Standardized incidence rates were calculated for the entire cohort, as well as stratified by primary tumor site. These incidence rates were then weighted separately for age, sex, and race based on the distributions of those variables found in the study participants of the National Lung Screening Trial (NLST) [7]. The crude and adjusted standardized incidence rates are summarized in Fig. 3. We observed that survivors of cancers of the hypopharynx, oropharynx, larynx, and tonsil demonstrated standardized incidence rates far exceeding those seen in the control arm of the NLST. Survivors of bladder and esophageal cancer exhibited incidence rates that approached those observed in the control arm of the NLST.

Discussion

In this population-based cohort study of cancer survivors, we made several notable observations. First, there was significant variation in the incidence of SPLC in survivors of cancer when stratifying by site of first malignancy. Survivors of cancer of the larynx, oropharynx, bladder, tonsil, hypopharynx, and esophagus developed SPLC at higher rates than survivors of other cancers. For virtually all primary cancer types, increasing age predicted an increased risk for developing SPLC. Secondly, more than three-quarters of the patients who developed SPLC died during follow-up, with SPLC responsible for almost three-quarters of these deaths. For those patients who developed SPLC, the site of their primary tumor did not appear to strongly influence survival rate from SPLC. Finally, and most importantly, when comparing the standardized incidence rate of lung cancer in our cohort with those in the NLST, we found that survivors of cancer of the tonsil, oropharynx, hypopharynx, and larynx, demonstrated standardized incidence rates that exceeded those seen in the control arm of the NLST, which screened for lung cancer in a high-risk population with a significant smoking history [7]. Bladder and esophageal cancer survivors, while not exceeding the rate seen in the NLST (572 per 100,000 person-years), had rates that were comparable (512 and 450, respectively). These findings suggest that there may be identifiable sub-populations of cancer survivors who may be at extremely high risk for the development of SPLC, and in whom screening may prevent death from lung cancer.

While both genetic predisposition and the subsequent carcinogenic effects of cancer treatments have both been cited as potential mechanisms to explain epidemiologic clustering of multiple primary cancer types, the predominant explanation for the excess risk of SPLC in cancers of the head and neck and urinary bladder is the well-established risk factor implicated in all of these cancers, namely, tobacco smoke. Carcinogenic agents within tobacco smoke are known to be the predominant cause of lung cancer in the United States, and are estimated to be responsible for approximately 65% of bladder cancer risk in men and 20–30% in women [10]. Prior studies of SEER data have estimated that tobacco/

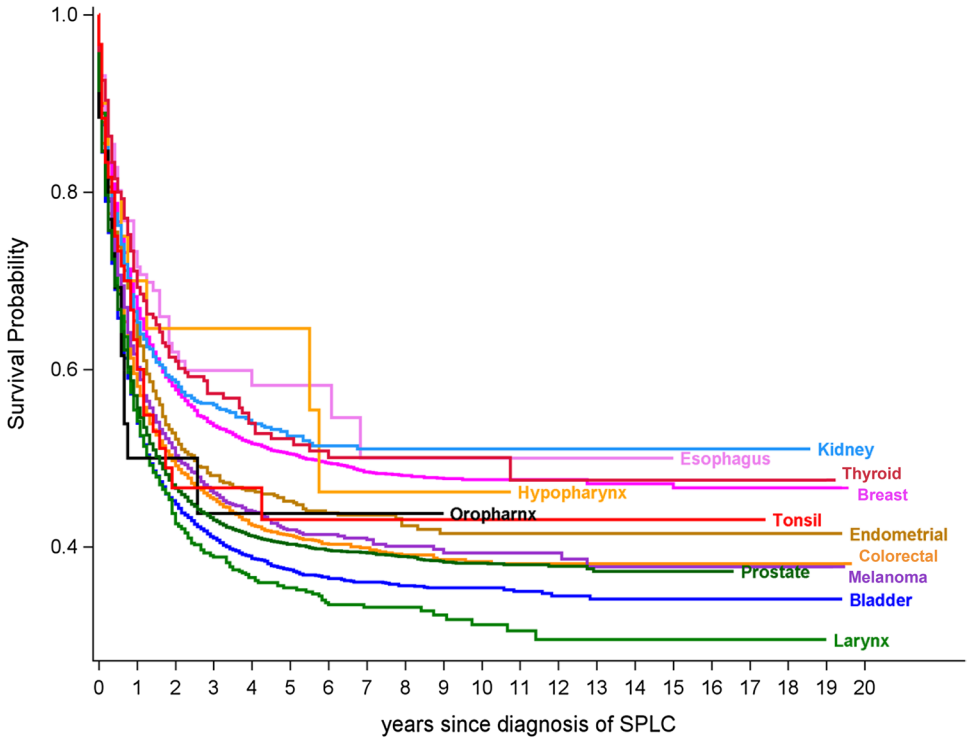

Fig. 2 Kaplan–Meier survival estimates in patients with second primary lung cancer* ($n = 25{,}472$). *Note the *Y*-axis begins at 0.3. Figure 2 depicts Kaplan–Meier survival estimates in patients with second primary lung cancer, by primary cancer site. Events were considered death from second primary lung cancer. Time zero calculated as year of second primary lung cancer diagnosis

alcohol-related cancer sites accounted for over 35% of the total excess subsequent cancers [3]. The present study places this epidemiologic association between tobacco smoke, cancers of the head and neck, and lung cancer within the context of the findings of the NLST, in which screening using three annual low-dose chest CTs reduced the risk of death from lung cancer by 20% in current and former heavy smokers, when compared to three annual chest radiographs [7]. This finding demonstrates that screening interventions in a population at sufficiently high risk produced a mortality reduction, likely owing to the strong stage-dependent survival rate exhibited by lung cancer [6]. Because of the known relationships between smoking intensity (cigarettes per day), duration (number of years smoking), time since quitting, and lung cancer risk [11], the NLST inclusion criteria utilized pack-years, time since quitting, and age as criteria for identifying a high-risk cohort. The cohort identified with these criteria developed lung cancer at 572 cases per 100,000 person-years when screened with radiographs, and 645 cases per 100,000 person-years when screened with chest CT. In our cohort of survivors of head and neck cancers, in whom no information regarding either smoking history or lung cancer screening was available, the incidence of lung cancer vastly exceeded that observed in the NLST.

Whether this incidence rate in our population could have been entirely accounted for by smoking history alone cannot be determined by SEER data, which do not include smoking history. Further investigation will be required to determine whether a history of head and neck or bladder cancer, independent of tobacco smoke exposure, is an independent risk factor for the development of SPLC. If this is the case, survivors of head and neck cancers or bladder cancer who also have a strong history of smoking could represent an extremely high-risk group, in which screening could be especially beneficial. At present, the American Cancer Society recommends that survivors of head and neck cancer be screened for second primary lung cancer according to National Comprehensive Cancer Network recommendations with low-dose annual chest CT based on smoking history [12]. However, the guidelines acknowledge that there are individuals who would not have met the NLST criteria but are at similar risk, and that these individuals be screened as well [13]. Investigators have demonstrated that accurate lung cancer prediction models are significantly more sensitive in identifying individuals who will be diagnosed with lung cancer and would save more lives than the NLST criteria [14, 15]. Tammemagi et al. [16] have published a risk calculator for clinical use which can predict individuals at the highest risk, and while it incorporates a personal history of cancer, it is not specific for cancers of the head and neck or urinary bladder [14]. The findings of our study suggest that patients with a history of head and neck cancer, particularly in those aged 66–80, may be at sufficiently high risk to warrant lung cancer screening independent of the details of their smoking history.

Several other risk factors, increasing age, male gender, and being divorced/widowed/separated were found to independently predict an increased risk for SPLC in many

Table 3 Adjusted hazard ratios (CI) for death from lung cancer by each primary cancer location

Primary site	Prostate	Breast	Colorectal	Melanoma	Bladder	Thyroid	Kidney	Endometrial
	n = 8,943	*n* = 4,516	*n* = 2,637	*n* = 879	*n* = 3,761	*n* = 257	*n* = 815	*n* = 784
Age at diagnosis								
18–50	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
51–65	1.20 (0.86–1.68)	1.32 (1.10–1.58)	1.33 (0.88–2.01)	0.79 (0.56–1.12)	1.07 (0.80–1.43)	1.29 (0.75–2.22)	1.19 (0.74–1.91)	1.84 (1.07–3.14)
66–80	1.43 (1.02-2.00)	1.85 (1.55–2.21)	1.75 (1.16–2.62)	1.03 (0.74–1.45)	1.29 (0.97–1.71)	1.73 (0.98–3.05)	1.56 (0.98–2.50)	1.94 (1.14–3.30)
> 80	1.71 (1.20–2.43)	1.96 (1.55–2.49)	1.91 (1.24–2.95)	1.36 (0.88–2.10)	1.87 (1.38–2.53)	1.47 (0.19–11.59)	1.83 (0.97–3.44)	1.99 (1.05–3.78)
Sex								
Male	–	–	1.11 (0.99–1.24)	1.15 (0.94–1.40)	1.02 (0.92–1.13)	1.19 (0.79–1.80)	**1.29 (1.03–1.62)**	–
Female	–	–	Reference	Reference	Reference	Reference	Reference	–
Race								
White	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Black	1.04 (0.96–1.12)	0.97 (0.82–1.14)	0.89 (0.74–1.08)	0.37 (0.09–1.49)	0.93 (0.76–1.14)	1.52 (0.82–2.81)	0.78 (0.53–1.14)	1.18 (0.80–1.73)
Other	0.96 (0.84–1.10)	**0.65 (0.51–0.83)**	0.93 (0.75–1.15)	1.03 (0.33–3.26)	0.97 (0.76–1.23)	1.10 (0.54–2.26)	1.13 (0.64–1.99)	0.90 (0.51–1.59)
Marital status								
Married/domestic partner	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Divorce/widow/ separated	1.07 (0.99–1.15)	**1.10 (1.00-1.20)**	1.05 (0.93–1.19)	0.86 (0.67–1.09)	1.04 (0.93–1.15)	1.36 (0.88–2.10)	**1.29 (1.00-1.66)**	1.23 (1.00-1.52)
Single	0.93 (0.84–1.03)	1.09 (0.94–1.27)	1.04 (0.87–1.24)	1.12 (0.81–1.53)	0.90 (0.77–1.06)	0.94 (0.49–1.79)	1.35 (0.93–1.95)	1.07 (0.77–1.48)

Primary site	Tonsil *n* = 57	Oropharynx *n* = 25	Hypopharynx *n* = 20	Esophagus *n* = 114	Larynx *n* = 739
Age at diagnosis					
18–50	Reference*	Reference*	Reference*	Reference*	Reference*
51–65					
66–80	1.01 (0.45–2.26)*	1.02 (0.30–3.40)*	0.90 (0.16–5.14)*	0.83 (0.45–1.51)*	1.12 (0.93–1.34)*
> 80					
Sex					
Male	–†	–†	–†	–†	–†
Female	–†	–†	–†	–†	–†
Race					
White	Reference	Reference	–†	Reference	Reference

Table 3 (continued)

Primary site	Tonsil $n=57$	Oropharynx $n=25$	Hypopharynx $n=20$	Esophagus $n=114$	Larynx $n=739$
Black	0.35 (0.09–1.43)*	0.19 (0.02–1.53)*	–†	2.09 (0.92–4.75)*	0.92 (0.70–1.20)*
Other			–†		
Marital status					
Married/domestic partner	Reference	Reference	Reference	Reference	Reference
Divorce/widow/separated	1.95 (0.80–4.80)	1.27 (0.36–4.48)	0.88 (0.19–4.10)	0.92 (0.42–2.01)	**1.24 (1.01–1.53)**
Single	0.46 (0.05–4.10)	2.28 (0.47–11.02)	1.33 (0.23–7.66)	0.51 (0.19–1.36)	1.03 (0.74–1.42)

Also included in the models were % received college degree to % household income to primary tumor grade. Associations between variable strata and hazard ratios were inconsistent across primary tumor sites and were thus omitted for simplicity

Bolded results are statistically significant to the <0.05 level

*Strata have been combined due to small numbers of events. Cell borders are used to highlight combined strata

†Insufficient number of events to perform analysis

of the first cancer types we examined. The most probable explanation for these findings is the association of these risk factors with exposure to tobacco smoke, for which we were unable to control. Males in both the United States and abroad smoke at higher rates than females [17, 18], and demonstrated higher incidence rates of lung cancer in the United States during the timeframe of our study. Americans who are divorced/widowed/or separated smoke at higher rates than those who are married [17, 19, 20] and as such marital status may also have served as a surrogate marker for smoking in our study. The incidence of lung cancer is known to demonstrate an age-dependent incidence pattern, with those ≥ 70 demonstrating the highest incidence rates [1], an observation which was recapitulated in our study.

Bladder cancer is predominantly a localized, superficial disease with excellent treatment options for the majority of patients, with 5-year survival rates exceeding 75% [6]. Many of these patients will live for decades following their diagnosis [21]. Those patients who are actively smoking at the time of their bladder cancer diagnosis represent a high-yield opportunity for smoking cessation intervention, which if successful will reduce the risk of bladder cancer recurrence [22], but also their risk of developing lung cancer, both of which demonstrate progressive decrease in risk over time following smoking cessation [3, 23]. A diagnosis of bladder cancer is known to be a teachable moment in which smoking cessation intervention can increase both the number of attempts to quit as well as the 1-year quit rate [24].

Our study findings must be considered in light of inherent data and study design limitations. First, the rate of the development of SPLC was ascertained by identifying patients diagnosed with lung cancer amongst survivors of other common non-pulmonary malignancies. Misclassification of a metastasis from the primary as an SPLC could have occurred. We attempted to avoid this by limiting the cohort to cases of SPLC that occurred >1 year from the diagnosis of the primary tumor, and by limiting our cohort to those with exclusively localized first cancers. Taken in total, we believe these exclusions likely lead to an overall underestimate of SPLC incidence for the following reason: a diagnosis of cancer is typically accompanied by a brief period of intensive diagnostic intervention, during which it is likely that an unknown number of synchronous primary lung cancers would be diagnosed. These SPLC, while representative of the phenomena we sought to describe, were excluded from our analysis in order to provide a conservative estimate. Given the nature of SEER data, we were unable to evaluate for several important co-variates that were likely related to both the development of first and second cancers. Smoking status is the most notable of these; however, prior cancer treatments such as chemotherapy and radiation therapy should also be considered.

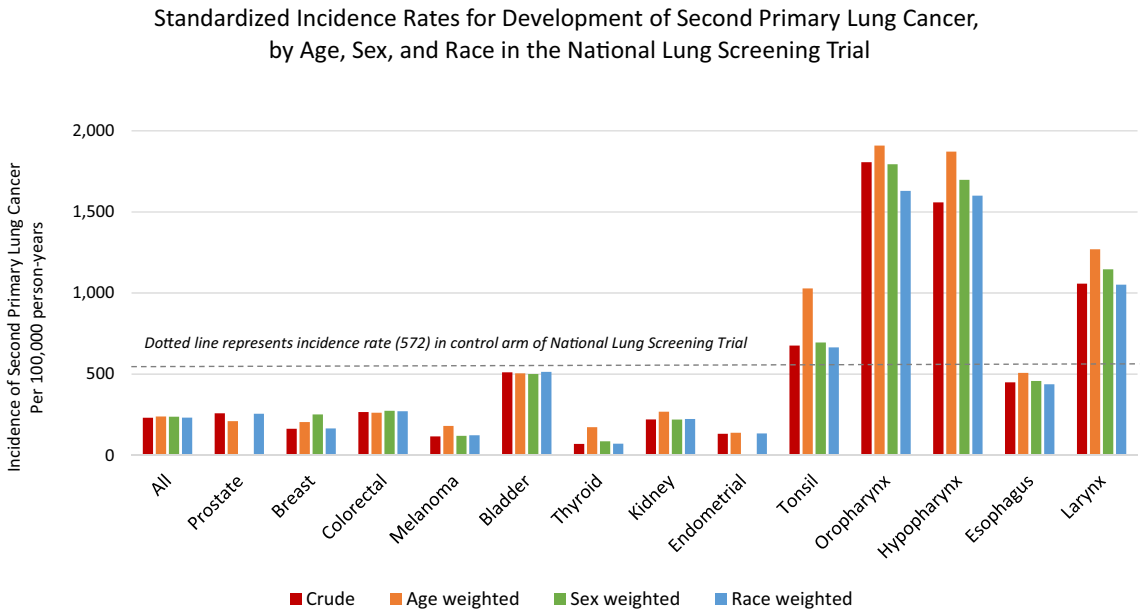

Fig. 3 Standardized incidence rates for development of second primary lung cancer, by age, sex, and race in the National Lung Screening Trial. Figure 3 depicts standardized incidence rates for the development of second primary lung cancer of each primary cancer during the study period, by each primary cancer site. Incidence rates are displayed as crude rates, as well as rates that have been standardized for the age, sex, and race distributions that were present in the National Lung Screening Trial. The dotted line represents the incidence rate of lung cancer (572 per 100,000 person-years) that was observed in the radiograph-screened arm of the trial

Conclusions

In this population-based study of US cancer survivors, those with a prior diagnosis of cancer of the hypopharynx, oropharynx, larynx, and tonsil demonstrated standardized incidence rates that far exceeded those seen in the control arm of the NLST. In addition, those with a prior diagnosis of bladder or esophageal cancer exhibited incidence rates that approached those observed in the control arm of the NLST. Whether tobacco smoke exposure could account entirely for this risk is unknown, and warrants further study. Further efforts to identify those patients at highest risk for lung cancer may consider a personal history of head and neck cancer or bladder cancer as a potential candidate risk factor for evaluation.

Acknowledgements This work was supported in part by the STOP Cancer Foundation and the Flax Family Foundation (KC).

Compliance with ethical standards

Conflict of interest All authors report no financial conflicts of interest.

Informed consent Dr. Nicholas M. Donin and Dr. Karim Chamie take ultimate responsibility for the integrity of the content contained herein.

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