



Disparity in age at lung cancer diagnosis between current and former smokers

Barbara G. Campling¹ · Zhong Ye² · Yinzhi Lai² · Ling Li² · Voichita Bar-Ad³ · Maria Werner-Wasik³ · Bo Lu³ · Scott W. Cowan⁴ · Nathaniel R. Evans⁴ · Inna Chervoneva⁵ · Chun Wang²

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Abstract

Purpose In a previous study of smoking cessation in veterans with lung cancer, we noted as an incidental finding that current smokers were much younger than former smokers at diagnosis. To confirm and extend this observation, we analyzed the association of smoking status with age at diagnosis and survival of lung cancer patients.

Methods The Jefferson Cancer Registry collects information on all cancer patients registered at this hospital. Information on smoking status has been recorded since 1995. We determined age at diagnosis and survival of current and former smokers with lung cancer.

Results 5111 lung cancer cases were identified in the registry from 1995 to 2011 inclusive. Smoking status was recorded in 4687 cases (91.7%). Of these, 1859 (39.7%) were current, 2423 (51.7%) were former, and 405 (8.6%) were never smokers. There was a 6-year difference in median age at lung cancer diagnosis between the current (63 years) and former smokers (69 years) ($P < 0.0001$). The median survival was 12.1 months for current versus 14.5 months for former smokers ($P < 0.0001$).

Conclusions These results confirm and extend our observation that among patients diagnosed with lung cancer, current smokers are younger than former smokers. The possible explanations include higher competing causes of death and increased risk of lung cancer among current smokers as well as increasing proportions of former smokers in older populations. Ongoing exposure to tobacco carcinogens may accelerate the development of lung cancer in continuing smokers. This provides more incentive for smokers to quit at the earliest age possible.

Keywords Lung neoplasms · Smoking · Smoking cessation · Age disparity · Cancer registry

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✉ Barbara G. Campling
Barbara.Campling@bccancer.bc.ca

✉ Chun Wang
Chun.Wang@jefferson.edu

¹ BC Cancer, Sindi Ahluwalia Hawkins Centre for the Southern Interior, 399 Royal Avenue, Kelowna, BC V1Y 5L3, Canada

² Department of Medical Oncology, Thomas Jefferson University, 1025 Walnut Street, Suite 727, Philadelphia, PA 19107, USA

Introduction

Most lung cancers are caused by smoking. Although the prevalence of smoking is declining in the United States (Jamal et al. 2015), those who have smoked heavily in the past continue to be at risk for lung cancer for years

³ Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA

⁴ Department of Surgery, Thomas Jefferson University, Philadelphia, PA, USA

⁵ Division of Biostatistics, Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA, USA

after quitting. Consequently, the proportion of lung cancer patients who are former smokers is increasing relative to current smokers (Mong et al. 2011; Tong et al. 1996). Numerous studies in lung cancer (Bhatt et al. 2015; Ferretich et al. 2013; Tammemagi et al. 2004; Videtic et al. 2003) and other cancers (Browman et al. 1993; Fleshner et al. 1999; Mayadev et al. 2018) have shown that survival of patients who continue to smoke is shorter than for those who have quit.

In a previous study of spontaneous smoking cessation in veterans with lung cancer, we interviewed patients with lung cancer about their smoking habits and cancer symptoms preceding diagnosis (Campling et al. 2011). As an incidental and unexpected finding, we noted that the median age at diagnosis was 57.8 years for current ($n = 60$) compared to 68 years for former smokers ($n = 55$). Other groups have also reported significant age differences between current and former smokers with lung cancer indicating that our observation was not spurious (Bhatt et al. 2015; Tammemagi et al. 2004; Toh et al. 2006). However, none of these studies explored possible implications of this age disparity. We postulate that smoking cessation may extend the life of those who quit, not only by reducing the risk of developing lung cancer, but also by delaying the onset of lung cancer in those who develop the disease.

To confirm and extend our observation of an age disparity between current and former smokers with lung cancer, we conducted a registry-based study to determine age at diagnosis in current and former smokers with lung cancer. We also determined all-cause mortality according to smoking status.

Materials and methods

Patients and data collection

Thomas Jefferson University Hospital maintains a registry of all newly diagnosed cancer patients seen there. 5111 lung cancer cases were identified in the registry from 1995 to 2011. Smoking status was recorded in 4687 of them, including 1859 current and 2423 former smokers. The 405 never smokers were excluded. The Institutional Review Board of Thomas Jefferson University approved the study.

Certified tumor registrars collected information from clinical records within 6 months of diagnosis. Demographic variables included age, gender and ethnicity; clinical variables included stage, histologic subtype, smoking status and date of death or last follow-up. Tumor stage was classified by AJCC staging criteria, using the 6th Edition of the AJCC Staging Manual up until 2009 (American Joint Commission on Cancer 2007), and the 7th Edition thereafter (American Joint Commission on Cancer 2009). Histologic subtypes of lung cancer included adenocarcinoma, squamous cell, large

cell, non-small cell lung cancer-not otherwise specified (NSCLC-NOS), small cell lung cancer (SCLC), and others (including carcinoid, sarcomatoid, and miscellaneous carcinomas). Mesotheliomas and in situ carcinomas were excluded.

Information on smoking status has been recorded in the registry since 1995. The US Centers for Disease Control and Prevention defines a “never smoker” as an individual who has smoked < 100 cigarettes in their lifetime (Centers for Disease Control and Prevention 2019). However, it was not possible to obtain this information from retrospective chart reviews and, thus, patients who were recorded as having never smoked were categorized as never smokers. Subjects who were recorded as smokers at diagnosis were categorized as current smokers and those who had smoked, but had quit prior to diagnosis, were categorized as former smokers.

Additional information on smoking was then obtained from original medical records, including amount smoked and duration of smoking among ever smokers, as well as duration of cessation among former smokers. Data obtained included smoking intensity (packs/day), age at smoking initiation, age at smoking cessation, years smoked, and pack-years smoked [obtained either directly from charts or calculated using smoking intensity (packs/day \times years smoked)]. Duration of cessation was obtained directly from medical records or calculated according to the information on age/date at smoking cessation and date of diagnosis. All charts were reviewed and detailed smoking information was available in a subset of patients.

Subgroup analyses

To assess the impact of reclassifying recent quitters as current smokers on the age difference between current and former smokers, we conducted analyses in the subgroup of former smokers with information on duration of smoking cessation. The duration of cessation was available for a subgroup of 979 (40.4%) of the 2423 former smokers. Former smokers were then reclassified based on the duration of cessation (quit anytime, quit ≥ 30 days, or ≥ 1 year before diagnosis). The reclassified current smokers then included these recent quitters. The median age was recalculated for current and former smokers and compared between these two groups. We further categorized 862 former smokers who quit for ≥ 1 year according to cessation duration (1–4, 5–9, 10–19, ≥ 20 years) and compared the age of former smokers according to duration of cessation.

We also investigated the relationship between tobacco exposure on the age disparity in another subgroup of current and former smokers with information available on smoking intensity and/or total tobacco exposure. This information was available for 824 current and 819 former smokers (quit ≥ 1 year before lung cancer diagnosis). Among these

patients, 491 current and 476 former smokers had information on smoking intensity (packs/day), 435 current and 451 former smokers had information on smoking duration (years), and 772 current and 745 former smokers had information on total tobacco exposure (pack-years). We compared differences in smoking intensity, duration, and total tobacco exposure between current and former smokers. We also compared the age difference between current and former smokers who had similar levels of tobacco exposure.

Validation analysis

We conducted an independent internal validation, using lung cancer patients in the Jefferson Cancer Registry from 2012 to 2015. The same variables as in the 1995–2011 analysis were collected and analyzed. In this new dataset, including 465 current and 791 former smokers, the median age at lung cancer diagnosis was calculated and compared for current and former smokers.

Statistics

Comparisons between current and former smokers were made with a *t* test for continuous variables and chi square test for categorical variables. Overall survival was defined as time from initial diagnosis to death from any cause. The last date with known vital status was considered the date of last follow-up, and patients alive at last follow-up were censored. Kaplan–Meier survival curves were used to compare the survival of current and former smokers, and the log rank test was used to test this difference. To control for potential confounding and interactions, both stratified analyses and multivariate Cox proportional hazards analyses were conducted. Multivariate linear regression modeling was used to study the association between age at diagnosis and smoking status while adjusting for other clinical and demographic characteristics. The statistical software packages SAS (Version 9.2, SAS Institute, Cary, NC, USA) and Stata (Version 12.0, Stata Corp, College Station, TX, USA) were used for data analysis. All statistical tests were two sided. A *p* value of <0.05 was considered significant.

Results

Patient characteristics

There were 5111 lung cancer cases identified in the Jefferson Cancer Registry from 1995 to 2011 inclusive. Smoking status was recorded in 4687 cases (91.7%). Of these, 1859 (39.7%) were current, 2423 (51.7%) were former, and 405 (8.6%) were never smokers at diagnosis. Never smokers were excluded. As shown in Table 1, there was

a difference in gender distribution between current and former smokers with slightly more women among current smokers ($P=0.05$). About half of both male and female subjects were former smokers. There was a significant difference in racial distribution of current vs. former smokers, with a higher proportion of current smokers among blacks than whites ($P<0.0001$). A higher proportion of former smokers presented with localized cancer (Stage I and II) (28.2% of former vs. 21.4% of current smokers), whereas a higher proportion of current smokers presented with stage IV disease (47.2% of current vs. 36.6% of former smokers). The histologic subtype distribution was significantly different between current and former smokers, with more former smokers having adenocarcinomas (39.1% of former vs. 33.3% of current smokers), and more current smokers having small cell lung cancer (13.7% of current vs. 10.4% of former smokers).

Age at lung cancer diagnosis between current and former smokers

The median age at lung cancer diagnosis was younger among current than former smokers (63 vs. 69 years) ($P<0.0001$, Table 1). This age difference was observed for each cancer stage (data not shown). To assess the effect of reclassifying recent quitters as current smokers, we examined a subgroup of 979 former smokers with information on duration of cessation. The median age difference between current and former smokers (7 years) was similar to that in all patients. In this subgroup, when former smokers were defined as those who quit smoking ≥ 30 days or ≥ 1 year before diagnosis, the median age difference remained 7 years (Table 2). Furthermore, when former smokers who quit smoking ≥ 1 year were categorized according to their cessation duration, we noted a gradient of increasing age at lung cancer diagnosis along with increasing duration of cessation (Table 2).

Age distribution of current and former smokers

The absolute number of current and former smokers in each 5-year age category is shown in Fig. 1a, and the proportion is shown in Fig. 1b. The age range with the highest number of subjects for both current and former smokers was 66–70 years. Before age 61, the absolute number of current smokers exceeded that of former smokers whereas at age 61 and thereafter, the number of former smokers exceeded that of current smokers (Fig. 1a). The proportion of current smokers within each age category was highest in the youngest age range and declined gradually with increasing age, whereas the proportion of former smokers was lowest in the youngest age range and increased steadily with age (Fig. 1b).

Table 1 Characteristics of current and former smokers with lung cancer, Jefferson Cancer Registry, 1995–2011

Variables	Current	Former	P value
	Number of patients (%)		
	1859 (43.4)	2423 (56.6)	
Age (years)			
Mean (SD) ^a	63.1 (10.8)	68.0 (10.4)	<0.0001
Median (range)	63 (29–92)	69 (32–100)	<0.0001
Gender			
Female	953 (51.3)	1168 (48.2)	0.05
Male	906 (48.7)	1255 (51.8)	
Race			
White	1359 (73.1)	1928 (79.6)	<0.0001
Black	394 (21.2)	375 (15.5)	
Asian	33 (1.8)	31 (1.3)	
Other	73 (3.9)	89 (3.7)	
Disease stage			
I	299 (16.1)	507 (20.9)	<0.0001
II	98 (5.3)	177 (7.3)	
III	437 (23.5)	607 (25.1)	
IV	877 (47.2)	887 (36.6)	
Unknown	148 (8.0)	245 (10.1)	
Histology			
Adenocarcinoma	619 (33.3)	948 (39.1)	0.0001
Squamous	383 (20.6)	507 (20.9)	
Large cell	66 (3.6)	66 (2.7)	
NSCLC NOS ^b	496 (26.7)	587 (24.2)	
Small cell	255 (13.7)	252 (10.4)	
Other ^c	40 (2.2)	63 (2.6)	
Survival			
Median (months) (95% CI) ^d	12.1 (11.4–13.1)	14.5 (13.7–15.5)	<0.0001
2-year, % (95% CI) ^d	31.4 (29.2–33.5)	36.2 (34.2–38.2)	0.0001
5-year, % (95% CI) ^d	16.5 (14.8–18.4)	19.0 (17.4–20.7)	0.0004

^aSD standard deviation^bNSCLC NOS non-small cell lung cancer, not otherwise specified^cOther includes carcinoid, sarcomatoid, and miscellaneous^dCI confidence interval

Age difference between current and former smokers in relation to tobacco exposure

When we compared smoking intensity and/or total tobacco exposure in 824 current and 819 former smokers, no significant difference was observed between current and former smokers in smoking intensity (mean of 1.3 vs. 1.4 packs/day, $P=0.26$) (Supplementary Table 1). However, current smokers had smoked longer than former smokers (mean of 38.4 vs. 31.6 years, $P<0.0001$) and, thus, had a greater total tobacco exposure (mean of 50.8 vs. 46.2 pack-years, $P=0.0039$). We further stratified the analysis of age difference according to total tobacco exposure. Current smokers were still significantly younger than former smokers who had similar tobacco exposure (Supplementary Table 1). The

only exception was the 61–70 pack-year category, but this was not statistically significant and is likely an unstable estimation due to small sample size.

Multivariate linear regression analysis

To determine whether the age difference of current vs. former smokers was independent of differences in other variables, we performed multivariate linear regression to determine which factors were associated with age at diagnosis. After adjustment for these variables, current smokers were on average 4.76 years younger than former smokers (Table 3). This analysis also showed that patients with squamous cell lung cancer were on average 3.61 years older

Table 2 Subgroup analysis of age difference between current and former smokers according to the time from smoking cessation to lung cancer diagnosis

	<i>N</i>	Median age (range)
Current smokers	1859	63 (29–92)
Former smokers (quit any time before diagnosis)	979	70 (32–96)
Age difference (years)		7
		<i>P</i> < 0.0001
Current smokers ^a	1891	63 (29–92)
Former smokers (quit ≥ 30 days before diagnosis)	947	70 (32–96)
Age difference (years)		7
		<i>P</i> < 0.0001
Current smokers ^a	1976	63 (29–92)
Former smokers (quit ≥ 1 year before diagnosis)	862	70 (32–96)
Age difference (years)		7
		<i>P</i> < 0.0001
Duration of smoking cessation (years)		
1–4	176	65.5 (37–89)
5–9	150	67.5 (38–86)
10–19	241	70 (32–91)
≥ 20	295	74 (42–96)
		<i>P</i> < 0.0001

SD standard deviation

^aIncluding recent quitters

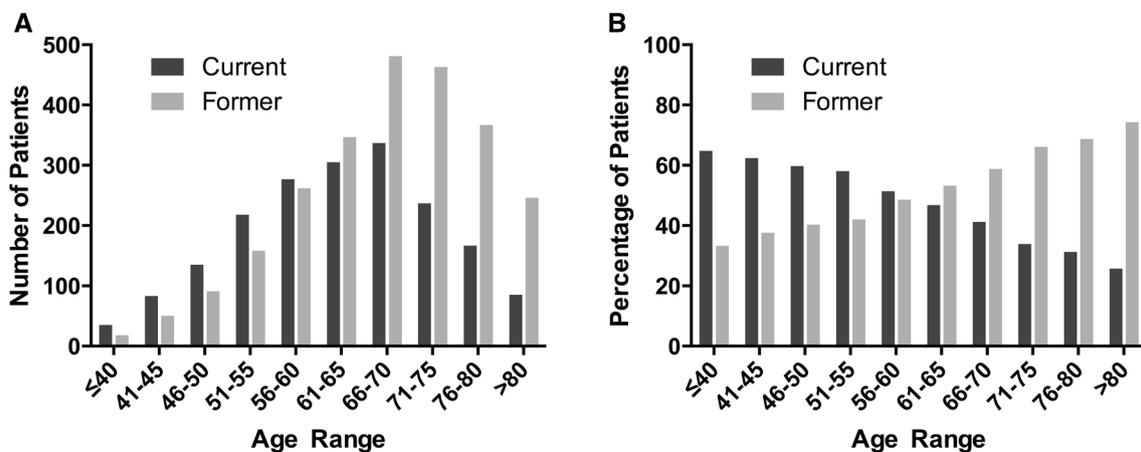


Fig. 1 Age distribution of current and former smokers. Subjects were grouped into 5-year age categories for those between ages 41–80 years, flanked by those ≤ 40 and > 80 years. The absolute number of patients in each age category is shown in **a**, and the percentage is shown in **b**

than those with adenocarcinoma, and black patients were 2.62 years younger than whites.

Survival analysis

2-year survival was significantly better for former than current smokers (36.2% vs. 31.4%, *P* = 0.0001), as was the 5-year survival (19.0% vs. 16.5%, *P* = 0.0004, Table 1). Median survival of current smokers was 12.1 months, compared to 14.5 months for former smokers (*P* < 0.0001, Fig. 2). After adjusting for age, gender, race, stage, and

histology, current smoking status was an independent predictor of survival, conferring a 1.16-fold increased risk of death (*P* < 0.0001, Table 4).

Validation analysis

Using Jefferson Cancer Registry data from 2012 to 2015, we developed a new dataset of 465 current and 791 former smokers. We again found that current smokers were diagnosed at a younger age than former smokers (64 vs. 70 years, Supplementary Table 2). After adjustment for

Table 3 Multivariate linear regression for age at diagnosis

Variable	Regression coefficient (years)	P value
Gender		
Male	Reference	
Female	-0.48	0.14
Race		
White	Reference	
Black	-2.62	<0.0001
Asian	-1.00	0.45
Other	0.61	0.47
Stage		
I	Reference	
II	-2.87	<0.0001
III	-2.34	<0.0001
IV	-1.96	<0.0001
Unknown	-2.71	<0.0001
Histology		
Adenocarcinoma	Reference	
Squamous	3.61	<0.0001
Large cell	-0.58	0.54
NSCLC-NOS ^a	1.34	0.002
Small cell	1.26	0.02
Other	0.53	0.62
Smoking status		
Former	Reference	
Current	-4.76	<0.0001

Table 4 Multivariate Cox model for survival after diagnosis of lung cancer

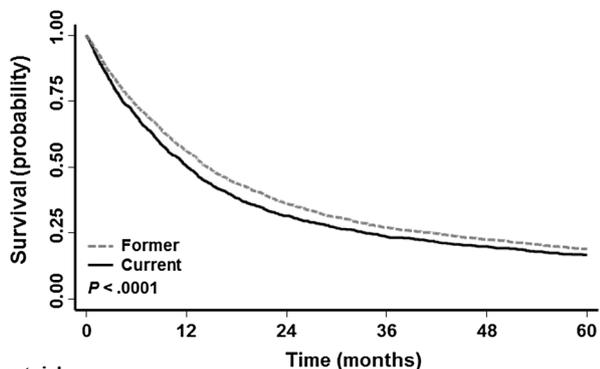
Variable	HR ^a (95% CI ^b)	P value
Age ^c	1.03 (1.02–1.03)	<0.0001
Gender		
Male	Reference	
Female	0.85 (0.80–0.91)	<0.0001
Race		
White	Reference	
Black	1.05 (0.96–1.15)	0.26
Asian	0.89 (0.66–1.19)	0.42
Other	1.10 (0.93–1.30)	0.28
Stage		
I	Reference	
II	1.76 (1.49–2.08)	<0.0001
III	2.78 (2.48–3.12)	<0.0001
IV	5.82 (5.21–6.50)	<0.0001
Unknown	2.57 (2.23–2.97)	<0.0001
Histology		
Adenocarcinoma	Reference	
Squamous	1.05 (0.96–1.15)	0.30
Large Cell	1.04 (0.86–1.26)	0.70
NSCLC-NOS ^d	1.16 (1.06–1.27)	0.001
Small cell	1.15 (1.03–1.29)	0.01
Other	0.74 (0.58–0.95)	0.02
Smoking status		
Former	Reference	
Current	1.16 (1.09–1.25)	<0.0001

^aHR hazard ratio (risk of death after lung cancer diagnosis)

^bCI confidence interval

^cAssociation with age (as a continuous variable) is with survival after diagnosis

^dNSCLC-NOS non-small cell lung cancer, not otherwise specified



No. at risk	0	12	24	36	48	60
Former	2423	1299	786	558	433	330
Current	1859	903	519	358	281	220

Fig. 2 Kaplan–Meier estimates of survival of current vs. former smokers after diagnosis of lung cancer. Median survival time for current smokers was 12.1 months compared to 14.5 months for former smokers

covariates, the age at diagnosis in current smokers was 4.74 years younger than in former smokers (Supplementary Table 3), similar to our main analysis (4.76 years, Table 3).

Discussion

Our results confirm our prior observation that among patients with newly diagnosed lung cancer, current smokers are younger than former smokers (Campling et al. 2011). The 6-year difference in median age at diagnosis contributes to many more years of life lost for current smokers than the 2.4-month survival difference after diagnosis. The age difference between current and former smokers with lung cancer is not widely recognized, but it has been found in other studies, although not discussed (Bhatt et al. 2015; Tammemagi et al. 2004; Toh et al. 2006).

Former smokers remain at risk for lung cancer even many years after cessation. While many studies have examined survival of current and former smokers after diagnosis of lung cancer, few have examined age at diagnosis of lung cancer according to the smoking status. Furthermore, most

tumor registries, including the Surveillance, Epidemiology, and End Results (SEER) database, do not currently collect information on smoking. The age difference found in the current study, although smaller than in our prior study (Campling et al. 2011), was very close to that reported in a recent retrospective analysis of 61,440 lung cancer cases in the Veteran's Affairs Comprehensive Cancer Registry (Bhatt et al. 2015).

Initiation and promotion of lung cancer are multistage processes that begin many years before clinical presentation. A number of factors influence the length of time for cancers to become clinically apparent. The incidence of lung cancer in both current and former smokers increases with age (Halpern et al. 1993; Thun et al. 2013), while the prevalence of smoking decreases with age (Jha et al. 2013). The risk of lung cancer is higher among continuing smokers than among those who quit (Halpern et al. 1993). Smokers at any age have a higher overall risk of death than former smokers, and current smokers lose more than 10 years of life compared to never smokers (Jha et al. 2013). Quitting smoking at any age lowers the risk of smoking-related diseases, including lung cancer (Jha et al. 2013). Among former smokers, the earlier they quit, the greater the increase in life expectancy (Jha et al. 2013). Current smokers may not live long enough to develop lung cancer in old age. Thus, the observed age disparity is likely related to higher competing causes of death and increased risk of lung cancer among current smokers, as well as increasing proportions of former smokers in older populations.

Genetic factors are involved in predisposition to both nicotine addiction and lung cancer. Several genome-wide association studies demonstrate a strong link between lung cancer risk and a locus on chromosome 15q14-15.1 which contains a nicotinic acetylcholine receptor gene cluster (Amos et al. 2008; Hung et al. 2008; Liu et al. 2008; Spitz et al. 2008; Thorgeirsson et al. 2008). A variant allele at this locus is associated with a higher prevalence of current smoking (Thorgeirsson et al. 2008). Subjects with this high-risk allele are likely to develop lung cancer at an earlier age, with a median age at diagnosis of 61 years for homozygous carriers of the high risk variant, 64 years for heterozygotes and 66 years for subjects with wild-type genotype (Spitz et al. 2008). Approximately, 42% of people of European ancestry carry at least one copy of the high risk allele (Saccone 2007). The genetic predisposition to both nicotine addiction and lung cancer may contribute to the earlier age of onset of lung cancer in continuing smokers.

In our original study, we found that the median interval from smoking cessation to diagnosis was 2.7 years, much less than the median age difference of 10.2 years between current and former smokers with lung cancer (Campling et al. 2011). Many of these former smokers likely harbored their cancer at the time they quit smoking. Continuing

smoking may accelerate the growth of latent lung cancers by ongoing exposure to cancer growth-promoting and angiogenic effects of nicotine and tobacco carcinogens (Cattaneo et al. 1993; Dasgupta et al. 2006; Heeschen et al. 2001; Maneckjee and Minna 1990; Mousa and Mousa 2006; Schuller 1989; Song et al. 2003).

Another possible contributor to the age difference is "lead time bias". Current smokers may be more likely to undergo health examinations, which could lead to earlier diagnosis. We have no information on timing of diagnostic investigations or presenting symptoms for the patients in this retrospective study. However, lung cancer is an aggressive malignancy and the interval from symptoms to diagnosis is usually short (only 2.3 months in our prior study) (Campling et al. 2011). More importantly, if lead time bias was a significant contributor to the age difference, one would expect current smokers to present with earlier-stage disease. However, in this study, we found that a higher proportion of current smokers presented with stage IV disease (Table 1). In view of the expected short interval between symptoms and diagnosis in lung cancer patients, and the fact that more current smokers presented with advanced disease, lead-time bias is unlikely to account for the age disparity between current and former smokers at lung cancer diagnosis.

Cancer registries provide valuable information for descriptive epidemiologic and clinical studies. However, registry-based studies are limited by their retrospective nature. Recall and information bias related to smoking status may have occurred in the current study. Moreover, due to lack of information on lifetime tobacco exposure or duration of smoking cessation for many patients, the results from subgroup analyses need to be validated. Future independent prospective studies are warranted to validate the findings of our study. It would also be interesting to compare the age at diagnosis of current and former smokers with other malignancies as well as non-malignant conditions.

A randomized study has shown that screening for lung cancer using low dose spiral CT scanning decreases lung cancer mortality by 20% (The National Lung Screening Trial Research Team 2011). Many clinical practice guidelines now recommend lung cancer screening beginning at age 55 for both current and former smokers with at least a 30-pack year smoking history (Canadian Task Force on Preventive Health Care 2016; Detterbeck et al. 2013; Jaklitsch et al. 2012; Moyer et al. 2014; Wender et al. 2013; Wood 2015). Given that subjects who continue to smoke are likely to be diagnosed with lung cancer at a younger age, it may be worth initiating lung cancer screening earlier than age 55 in subjects who are active smokers.

In summary, we found that current smokers were significantly younger at lung cancer diagnosis (median 63 years) than former smokers (median 69 years). The 6-year difference in age at diagnosis accounts for many more years of life

lost than the 2.4-month difference in survival after diagnosis. Our results provide more incentive for smokers to quit at the earliest age possible.

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Compliance with ethical standards

Conflict of interest All the listed authors declare no potential conflicts of interest related to this research.

Research involving human participants This study was reviewed and approved by the Institutional Review Board of Thomas Jefferson University.

Informed consent Informed consent was not required by the Institutional Review Board of Thomas Jefferson University.

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