ORIGINAL ARTICLE

Tobacco Smoking and Risk of Second Primary Lung Cancer

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ABSTRACT

Introduction: Lung cancer survivors are at high risk of developing a second primary lung cancer (SPLC). However, SPLC risk factors have not been established and the impact of tobacco smoking remains controversial. We examined the risk factors for SPLC across multiple epidemiologic cohorts and evaluated the impact of smoking cessation on reducing SPLC risk.

Methods: We analyzed data from 7059 participants in the Multiethnic Cohort (MEC) diagnosed with an initial primary lung cancer (IPLC) between 1993 and 2017. Cause-specific proportional hazards models estimated SPLC risk. We conducted validation studies using the Prostate, Lung,

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Colorectal, and Ovarian Cancer Screening Trial (N = 3423 IPLC cases) and European Prospective Investigation into Cancer and Nutrition (N = 4731 IPLC cases) cohorts and pooled the SPLC risk estimates using random effects meta-analysis.

Results: Overall, 163 MEC cases (2.3%) developed SPLC. Smoking pack-years (hazard ratio [HR] = 1.18 per 10 pack-years, $p < 0.001$) and smoking intensity (HR = 1.30 per 10 cigarettes per day, $p < 0.001$) were significantly associated with increased SPLC risk. Individuals who met the 2013 U.S. Preventive Services Task Force's screening criteria at IPLC diagnosis also had an increased SPLC risk (HR = 1.92; $p < 0.001$). Validation studies with the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and European Prospective Investigation into Cancer and Nutrition revealed consistent results. Meta-analysis yielded pooled HRs of 1.16 per 10 pack-years ($p_{meta} < 0.001$), 1.25 per 10 cigarettes per day ($p_{meta} < 0.001$), and 1.99 ($p_{meta} < 0.001$) for meeting the U.S. Preventive Services Task Force's criteria. In MEC, smoking cessation after IPLC diagnosis was associated with an 83% reduction in SPLC risk (HR = 0.17; $p < 0.001$).

Conclusions: Tobacco smoking is a risk factor for SPLC. Smoking cessation may reduce the risk of SPLC. Additional strategies for SPLC surveillance and screening are warranted.

Keywords: Second primary lung cancer; Tobacco smoking; Smoking cessation; Surveillance; Screening

Introduction

Lung cancer has the second highest cancer incidence among women and men and continues to lead cancer-related mortality in the United States. Thus, lung cancer remains a major public health problem. However, the past decade saw a 26% improvement in 5-year survival rates,[1] indicating the number of lung cancer survivors is increasing. Multiple studies have revealed that survivors of an initial primary lung cancer (IPLC) are at high risk of developing a second primary lung cancer (SPLC),[2-5] with incidence rates after IPLC surgical resection ranging from 1% to 2% per patient-year.[2] Development of a SPLC can complicate a patient's clinical assessment and may require further aggressive intervention, adding to an already heavy burden for lung cancer survivors.

In 2013, the U.S. Preventive Services Task Force (USPSTF) established national guidelines for IPLC screening on the basis of age (55–80 y) and smoking history (≥30 pack-years, cessation ≤15 y)[6]—known risk factors for IPLC—which are currently under revision.[7] However, evidence-based guidelines for SPLC surveillance and screening are lacking,[8] in large part owing to an absence of established risk factors for SPLC.[9] Previous studies have sought to identify SPLC risk factors, but these have been limited to single institutions or population-based registries comprising selected patient populations without validation in independent cohorts.[10-13] Furthermore, these studies have used different methodological designs or statistical approaches for identifying SPLC risk factors and, accordingly, have reached conflicting conclusions. For example, although tobacco smoking is an established risk factor for IPLC, the association between smoking and SPLC risk has been controversial, with some studies reporting a positive association[5,10] and others revealing not significant relationships.[11,12] Our group previously used a risk stratification approach to distinguish between patients with IPLC at high versus low risk of SPLC using the Surveillance, Epidemiology, and End Results database.[13] However, this cohort did not contain data on potentially important risk factors such as tobacco smoking.

In this study, we leveraged data from the Multiethnic Cohort (MEC) to identify risk factors for SPLC among IPLC cases with a focus on tobacco smoking. We validated these findings with the following two additional cohorts: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Prospective Investigation into Cancer and Nutrition (EPIC). Finally, in a subset analysis in MEC, we evaluated the impact of smoking cessation on reducing SPLC risk.

Materials and Methods

MEC: Participants and Study Design (Discovery Cohort)

MEC is a population-based cohort that prospectively follows more than 215,000 California and Hawaii residents aged 45 to 75 years at enrollment (1993–1996).[14] In this study, we included all participants who were diagnosed with having an incident IPLC between 1993 and 2017 and who had nonmissing tobacco smoking data (see Supplementary Methods for details). Demographic and behavioral data were analyzed as self-reported in the baseline questionnaire; smoking-related variables were assigned values from the questionnaire nearest in time and before IPLC diagnosis: either the baseline (1993–1996) or 10-year follow-up questionnaire (2003–2008), if available (N = 1872; Supplementary Methods). Smoking-related variables included the following: smoking status, pack-years, intensity (i.e., cigarettes per day [CPD]), and quit years (i.e., years since cessation). Smoking intensity reflected the

average lifetime consumption of cigarettes. Incident IPLC and SPLC were identified through linkage to Surveillance, Epidemiology, and End Results registries together with IPLC age at diagnosis, stage, histology, and therapies. Lung cancer histology was classified on the basis of tumor ICD-O-3 morphology codes (Supplementary Methods). SPLC was defined according to Martini and Melamed criteria (Supplementary Methods).[15] Deaths were ascertained by means of linkage to the National Death Index and death certificate files.[14]

As primary analyses, we evaluated potential risk factors for SPLC focusing on smoking-related variables and clinical variables that have not previously been evaluated in the literature (i.e., body mass index [BMI], personal history of cancer, family history of lung cancer).[10-13] We also estimated the SPLC risk associated with meeting the 2013 USPSTF lung cancer screening criteria at IPLC diagnosis, as a composite smoking and age measure of individuals at particularly high risk of IPLC. We also conducted a set of confirmatory secondary analyses to evaluate the associations between SPLC and factors that were examined in previous studies (i.e., sex, race/ethnicity, education, IPLC therapies).[10,12,13]

Given the focus on the smoking-SPLC association, we conducted a subset analysis evaluating the impact of smoking cessation on SPLC risk using the longitudinal measurements of smoking at baseline and 10-year follow-up. Smoking cessation was defined as the change in smoking status from "current" at baseline to "former" at follow-up (versus "current" at baseline and "current" at follow-up). Participants included those who were current smoking at baseline, had 10-year follow-up smoking data, and were diagnosed with their IPLC before 10-year follow-up (N = 156; Supplementary Fig. 1). We evaluated the association between smoking cessation after IPLC diagnosis and SPLC after 10-year follow-up.

MEC: Statistical Analyses

Cause-specific proportional hazards models evaluated the associations between candidate risk factors and SPLC, accounting for the competing risk of death from all causes.[16] The cause-specific function was selected because it can estimate the effects of factors on SPLC risk with sustained power in multiple competing risk scenarios while minimizing type I error.[17] All models evaluated SPLC risk from the date of IPLC diagnosis. The proportional hazards assumption was confirmed for all models. In light of previous data indicating that IPLC age at diagnosis, stage, and histology are relevant predictors for SPLC,[13] we adjusted for these as covariates in all analyses. To account for multiple testing, we implemented a Bonferroni threshold for the primary analyses ($p = 0.05/9 = 0.005$). For all other analyses, statistical significance was defined at a two-sided p value less than 0.05. Cumulative incidences were calculated using Gray's method.[18] We handled missing data by performing multiple imputation[19,20] and evaluated the robustness of the findings using complete cases (Supplementary Methods).

We further evaluated the smoking-related variables in a subgroup analysis of early-stage IPLC cases to reduce potential noncausal effects from the competing risk of death[17] and to make the results comparable to previous data.[10-12] Additional sensitivity analyses evaluated the smoking-SPLC associations among ever smokers, within major IPLC histologic subtypes (i.e., adenocarcinoma, squamous cell carcinoma), and among advanced-stage IPLC cases. For continuous smoking variables (i.e., pack-years, CPD), we evaluated their potential nonlinear effects using natural cubic splines.[21] All analyses were performed using R version 4.0.2 (Vienna, Austria).

PLCO and EPIC: Validation Cohorts

We validated the SPLC associations using the following two additional epidemiologic cohorts: PLCO (N = 3423 IPLC cases with 110 SPLC) and EPIC (N = 4731 IPLC cases with 16 SPLC). Detailed information on these cohorts is included in the Supplementary Methods. As with the discovery cohort, cause-specific proportional hazards models evaluated the SPLC associations in PLCO and EPIC. To pool the SPLC associations across the three cohorts (discovery and validation), we used random effects meta-analysis.[22] Statistical significance was defined at a two-sided p value less than 0.05. Smoking cessation was not evaluated in these cohorts because longitudinal smoking data were unavailable for this collaborative study.

Results

MEC: Participant Characteristics

Among 7059 IPLC cases in MEC, the mean age at diagnosis was 74.3 years and a slight majority were of male sex (55.9%) (Table 1). Most IPLC cases were former or current smoking (87.8%), but prospective SPLC cases had particularly high mean smoking pack-years (31.2) and mean CPD (17.6). SPLC cases also had high frequencies of local IPLC stage (57.1%), adenocarcinoma IPLC (58.3%), previous IPLC surgery (73.6%), and meeting the USPSTF screening criteria (41.7%).

MEC: SPLC Incidence and Risk Factors

Median follow-up in the cohort was 10.0 months overall and 57.0 months among SPLC or censored cases (Table 1). Overall, 163 IPLC cases (2.3%) developed a SPLC (Supplementary Fig. 2), with a median time from

Table 1. MEC Participant Characteristics

Characteristics	Overall N = 7059	Outcome		
		SPLC n = 163	Deceased n = 5646	Censored n = 1250
Age at IPLC diagnosis (y), mean (SD)	74.3 (8.3)	72.2 (8.1)	74.0 (8.2)	76.2 (8.7)
BMI (kg/m^2),[a] mean (SD)	25.9 (4.7)	26.1 (4.6)	25.9 (4.7)	26.2 (4.8)
Sex, n (%)				
Male	3949 (55.9)	84 (51.5)	3297 (58.4)	568 (45.4)
Female	3110 (44.1)	79 (48.5)	2349 (41.6)	682 (54.6)
Race/ethnicity, n (%)				
African American	1798 (25.5)	37 (22.7)	1477 (26.2)	284 (22.7)
Japanese American	1603 (22.7)	37 (22.7)	1289 (22.8)	277 (22.2)
Latino	998 (14.1)	20 (12.3)	723 (12.8)	255 (20.4)
Native Hawaiian	573 (8.1)	14 (8.6)	481 (8.5)	78 (6.2)
White	1714 (24.3)	47 (28.8)	1382 (24.5)	285 (22.8)
Other	373 (5.3)	8 (4.9)	294 (5.2)	71 (5.7)
Education, n (%)				
High school or less	3592 (50.9)	71 (43.6)	2974 (52.7)	547 (43.8)
Some college or graduate	2811 (39.8)	77 (47.2)	2170 (38.4)	564 (45.1)
Postgraduate	626 (8.9)	15 (9.2)	481 (8.5)	130 (10.4)
Unknown	30 (0.4)	0 (0.0)	21 (0.4)	9 (0.7)
Personal history of cancer, n (%)				
Yes	1824 (25.8)	52 (31.9)	1429 (25.3)	343 (27.4)
No	5235 (74.2)	111 (68.1)	4217 (74.7)	907 (72.6)
Family history of lung cancer, n (%)				
Yes	622 (8.8)	14 (8.6)	483 (8.6)	125 (10.0)
No	6437 (91.2)	149 (91.4)	5163 (91.4)	1125 (90.0)
Smoking status, n (%)				
Never	863 (12.2)	19 (11.7)	607 (10.8)	237 (19.0)
Former	3243 (45.9)	72 (44.2)	2603 (46.1)	568 (45.4)
Current	2953 (41.8)	72 (44.2)	2436 (43.1)	445 (35.6)
Smoking pack-years,[b] mean (SD)	27.0 (20.0)	31.2 (21.3)	28.0 (20.0)	22.1 (19.5)
Cigarettes per day,[b] mean (SD)	15.5 (10.0)	17.6 (10.8)	16.0 (9.9)	13.3 (10.2)
Smoking quit years,[b,c] median (IQR)	0.5 (0–13)	0.3 (0–11)	0.5 (0–13)	4.0 (0–18)
IPLC stage, n (%)				
Local	1223 (17.3)	93 (57.1)	702 (12.4)	428 (34.2)
Regional	1583 (22.4)	51 (31.3)	1185 (21.0)	347 (27.8)
Distant	3811 (54.0)	17 (10.4)	3378 (59.8)	416 (33.3)
Unknown	442 (6.3)	2 (1.2)	381 (6.7)	59 (4.7)
IPLC histology, n (%)				
Adenocarcinoma	2832 (40.1)	95 (58.3)	2070 (36.7)	667 (53.4)
Squamous cell carcinoma	1401 (19.8)	36 (22.1)	1120 (19.8)	245 (19.6)
Large cell carcinoma	225 (3.2)	9 (5.5)	189 (3.3)	27 (2.2)
Small cell lung carcinoma	731 (10.4)	3 (1.8)	651 (11.5)	77 (6.2)
Other[d]	1870 (26.5)	20 (12.3)	1616 (28.6)	234 (18.7)
IPLC surgery, n (%)				
Yes	1512 (21.4)	120 (73.6)	830 (14.7)	562 (45.0)
No	4942 (70.0)	34 (20.9)	4264 (75.5)	644 (51.5)
Unknown	605 (8.6)	9 (5.5)	552 (9.8)	44 (3.5)
IPLC radiotherapy, n (%)				
Yes	2375 (33.6)	26 (16.0)	2050 (36.3)	299 (23.9)
No	4496 (63.7)	137 (84.0)	3443 (61.0)	916 (73.3)
Unknown	188 (2.7)	0 (0.0)	153 (2.7)	35 (2.8)
IPLC chemotherapy, n (%)				
Yes	2299 (32.6)	23 (14.1)	1906 (33.8)	370 (29.6)
No	4426 (62.7)	139 (85.3)	3454 (61.2)	833 (66.6)
Unknown	334 (4.7)	1 (0.6)	286 (5.1)	47 (3.8)

(continued)

Table 1. Continued

Characteristics	Overall N = 7059	Outcome		
		SPLC n = 163	Deceased n = 5646	Censored n = 1250
Met the USPSTF criteria, n (%)				
Yes	2058 (29.2)	68 (41.7)	1755 (31.1)	235 (18.8)
No	5001 (70.8)	95 (58.3)	3891 (68.9)	1015 (81.2)
Follow-up (mo), median (IQR)	10.0 (3-33)	46.0 (15-78)	7.0 (2-17)	59.0 (35-111)

Note: Demographic variables were collected from the baseline MEC questionnaire except smoking-related variables (see subsequent texts). Age at IPLC diagnosis, IPLC stage, IPLC histology, and IPLC therapies were obtained through linkage to SEER registries. The 2013 USPSTF lung cancer screening eligibility was calculated using age at IPLC diagnosis and smoking-related variables from the MEC questionnaires. Percentages may not sum to 100% owing to rounding.
BMI, body mass index; IPLC, initial primary lung cancer; IQR, interquartile range; MEC, Multiethnic Cohort; SEER, Surveillance, Epidemiology, and End Results; SPLC, second primary lung cancer; USPSTF, U.S. Preventive Services Task Force.
[a]BMI was unknown in 80 (1.1%) participants: 0 (0.0%) SPLC, 72 (1.3%) deceased, and 8 (0.6%) censored.
[b]Smoking-related variables are from the questionnaire closest in time and before the date of IPLC: at baseline or at 10-year follow-up, if available (n = 1872).
[c]Smoking quit years were evaluated only among ever smokers (n = 6196).
[d]Other histologies are listed in the Supplementary Methods and include histologies such as adenosquamous, lung neuroendocrine tumors, carcinoma not otherwise specified, and others.

IPLC diagnosis to SPLC diagnosis of 3.8 years (Supplementary Fig. 3). Smoking pack-years (hazard ratio [HR] = 1.18 per 10 pack-years, 95% confidence interval [CI]: 1.09–1.27, $p < 0.001$) and smoking intensity (HR = 1.30 per 10 CPD, 95% CI: 1.12–1.51, $p < 0.001$) were significantly associated with an increased risk of SPLC after adjusting for IPLC age at diagnosis, stage, and histology (Table 2 and Fig. 1*A*). Participants who met the USPSTF criteria had a nearly twofold increased risk of SPLC (HR = 1.92, 95% CI: 1.39–2.64, $p < 0.001$). Current smoking status and quit years trended toward having significant associations with SPLC but did not meet the Bonferroni threshold. Other primary variables (e.g., BMI) were not associated with SPLC. Sensitivity analyses using complete cases provided consistent results (Supplementary Table 1).

In the secondary analyses, only the treatment variables demonstrated significant associations with SPLC, including IPLC surgery which was associated with an increased risk of SPLC (HR = 1.89, 95% CI: 1.16–3.07, $p = 0.010$; Table 2). Other secondary variables such as sex, race/ethnicity, and education did not have significant associations with SPLC, consistent with previous assessments.[13] Distant IPLC stage was associated with a reduced risk of SPLC compared with local or regional IPLC (HR = 0.33, 95% CI: 0.20–0.56, $p < 0.001$), reflecting higher mortality before developing SPLC.

The subgroup analysis of early-stage IPLC cases revealed that the point estimates and statistical significance for almost all smoking-related variables were heightened (Fig. 1*B*). Among ever smokers, the SPLC risk estimates were consistent (Supplementary Fig. 4*A*). Stratified by IPLC histology, the effects of smoking remained largely consistent, although the significance was reduced among those with squamous IPLCs (N = 1401), possibly owing to a smaller sample size (Supplementary Fig. 4*B* and *C*). Among advanced-stage IPLC cases, none of the smoking variables had a significant association with SPLC, except for smoking intensity which had an inverted point estimate (HR = 0.57 per 10 CPD, 95% CI: 0.33–0.98; Supplementary Fig. 4*D*) compared with that in all-stage and early-stage IPLC cases; this inverse association potentially reflects a higher competing risk of mortality—and, hence, a reduced SPLC incidence—among advanced-stage IPLC cases.

Categorization of smoking pack-years and CPD revealed that the highest levels (≥30 pack-years and ≥30 CPD) conferred the greatest risk of SPLC (Fig. 2*A* and *B*). In applying smoothing splines, we confirmed that the linear models offered the best fit for both smoking pack-years and smoking intensity (Supplementary Fig. 5).

PLCO and EPIC: SPLC Validation Cohorts and Meta-Analysis

The validation PLCO cohort included 3423 IPLC cases and EPIC included 4731 IPLC cases (Supplementary Tables 2 and 3). In PLCO, smoking pack-years (HR = 1.10 per 10 pack-years, 95% CI: 1.04–1.15, $p < 0.001$), smoking intensity (HR = 1.20 per 10 CPD, 95% CI: 1.06–1.36, $p = 0.004$), and meeting the USPSTF criteria (HR = 2.09, 95% CI: 1.35–3.24, $p = 0.001$) were significantly associated with an increased risk of SPLC after adjusting for IPLC age, stage, and histology (Supplementary Table 4 and Fig. 3*A*–*C*). In EPIC, smoking pack-years (HR = 1.37 per 10 pack-years, 95% CI: 1.11–1.68, $p = 0.003$) was significantly associated with an increased risk of SPLC after adjusting for IPLC age and histology, whereas smoking intensity (HR = 1.52 per 10 CPD, 95% CI: 0.96–2.41, $p = 0.074$) and meeting the USPSTF criteria (HR = 2.34, 95% CI: 0.80–6.85; $p = 0.120$) both trended toward statistical significance in the same directions of the HRs in MEC.

Table 2. Associations Between SPLC and Participant Characteristics in the Multiethnic Cohort

Characteristics	HR (95% CI)	P
Primary analyses		
Smoking status		
Never	Reference	
Former	1.32 (0.79-2.20)	0.284
Current	1.80 (1.07-3.03)	0.028
Smoking per 10 pack-years	1.18 (1.09-1.27)	<0.001
Smoking per 10 cigarettes per day	1.30 (1.12-1.51)	<0.001
Smoking per 1 quit year[a]	0.97 (0.95-0.99)	0.010
Met the USPSTF criteria		
No	Reference	
Yes	1.92 (1.39-2.64)	<0.001
BMI (per 1 kg/m^2)	1.02 (0.99-1.05)	0.267
Personal history of cancer		
No	Reference	
Yes	1.30 (0.93-1.82)	0.120
Family history of lung cancer		
No	Reference	
Yes	0.82 (0.47-1.42)	0.472
Secondary analyses		
Sex		
Female	Reference	
Male	1.24 (0.91-1.70)	0.179
Race/ethnicity		
White	Reference	
African American	1.00 (0.65-1.55)	0.989
Japanese American	0.80 (0.52-1.24)	0.324
Latino	0.89 (0.53-1.51)	0.679
Native Hawaiian	1.09 (0.60-2.00)	0.769
Other	0.71 (0.33-1.50)	0.370
Education		
High school or less	Reference	
Some college or graduate	1.12 (0.81-1.55)	0.501
Postgraduate	0.93 (0.53-1.63)	0.799
IPLC surgery		
No	Reference	
Yes	1.89 (1.16-3.07)	0.010
IPLC radiotherapy		
No	Reference	
Yes	0.64 (0.41-0.98)	0.041
IPLC chemotherapy		
No	Reference	
Yes	0.55 (0.35-0.88)	0.013
Covariates		
Age at IPLC diagnosis (per 1 y)	1.00 (0.98-1.02)	0.841
IPLC stage		
Local/regional	Reference	
Distant	0.33 (0.20-0.56)	<0.001
Expanded IPLC stage		
Local	Reference	
Regional	0.68 (0.48-0.96)	0.028
Distant	0.28 (0.16-0.47)	<0.001
IPLC histology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	1.11 (0.76-1.64)	0.584
Large cell carcinoma	1.66 (0.80-3.46)	0.173
Small cell carcinoma	0.43 (0.13-1.40)	0.162
Other	0.65 (0.38-1.13)	0.130

Note: All cause-specific proportional hazards models accounted for the competing risk of death. Variables in the primary and secondary analyses were evaluated in individual cause-specific proportional hazards models adjusting for age at IPLC diagnosis, IPLC histology, and IPLC stage. Among covariates, age at IPLC diagnosis was adjusted for IPLC histology and stage, IPLC histology was adjusted for IPLC age and stage, and IPLC stage was adjusted for IPLC age and histology.

BMI, body mass index; CI, confidence interval; HR, hazard ratio; IPLC, initial primary lung cancer; SPLC, second primary lung cancer; USPSTF, U.S. Preventive Services Task Force

[a]Smoking quit years were evaluated only among ever smokers (n = 6196).

When pooling the SPLC associations across all three cohorts through random effects meta-analysis, smoking pack-years (HR = 1.16 per 10 pack-years, 95% CI: 1.06–1.26; $p_{meta} < 0.001$), smoking intensity (HR = 1.25 per 10 CPD, 95% CI: 1.14–1.38, $p_{meta} < 0.001$), and meeting the USPSTF criteria (HR = 1.99, 95% CI: 1.55–2.57, $p_{meta} < 0.001$) were all significantly associated with an increased risk of SPLC (Fig. 3). In contrast, the other primary and secondary variables did not exhibit significant associations with SPLC, with the exception of the IPLC therapies (Supplementary Fig. 6).

MEC: Smoking Cessation Analysis

To follow up on the smoking-SPLC association, we evaluated the effect of smoking cessation after IPLC diagnosis on SPLC risk in the MEC subset of 156 participants (Supplementary Fig. 1). Of these, 125 participants (80.1%) who were current smoking at baseline reported having quit smoking at the 10-year follow-up (Supplementary Table 5). Overall, 15 IPLC cases (9.6%) developed a SPLC after the 10-year follow-up (Fig. 4). When adjusting for age at IPLC diagnosis solely (to support model convergence in the small sample size), smoking cessation was associated with an 83% reduction in SPLC risk (HR = 0.17, 95% CI: 0.06–0.47, $p < 0.001$; Supplementary Table 6).

Discussion

In this study, we found that tobacco smoking is a prominent risk factor for SPLC among IPLC cases on the basis of three epidemiologic cohorts. We also revealed in a landmark analysis that smoking cessation after IPLC diagnosis is associated with a substantial reduction in the risk of SPLC. To the best of our knowledge, this is the first population-based study to leverage multiple epidemiologic cohorts in identifying and validating risk factors for SPLC, including tobacco smoking. We evaluated

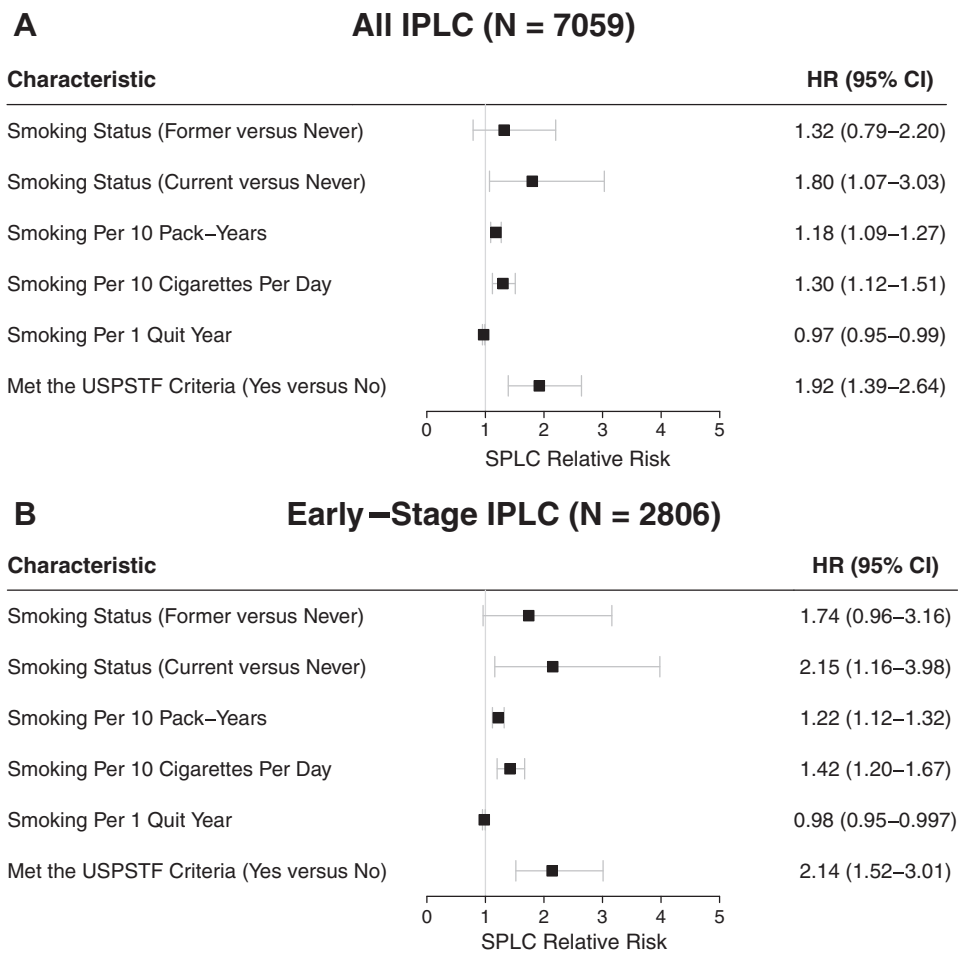

Figure 1. Forest plots of associations between smoking-related factors and SPLC in the Multiethnic Cohort. The smoking-SPLC associations were evaluated among (*A*) all IPLC cases (N = 7059) and (*B*) early-stage (I-III) IPLC cases (N = 2806). Smoking-related data were collected from the baseline questionnaire or 10-year follow-up questionnaire before IPLC diagnosis, if available. Meeting the 2013 USPSTF criteria was determined at IPLC diagnosis. All variables were evaluated in individual cause-specific proportional hazards models accounting for the competing risk of death. Models for all-stage IPLC cases adjusted for age at IPLC diagnosis, IPLC histology, and IPLC stage; models for early-stage IPLC cases adjusted for age at IPLC diagnosis and IPLC histology. CI, confidence interval; HR, hazard ratio; IPLC, initial primary lung cancer; SPLC, second primary lung cancer; USPSTF, U.S. Preventive Services Task Force.

several candidate SPLC risk factors that have not been previously examined (e.g., personal history of cancer, family history of lung cancer) and evaluated detailed smoking exposures through multiple measures, including smoking status, pack-years, intensity, and years since cessation.

Importantly, these data support tobacco smoking as a modifiable risk factor for SPLC, with smoking cessation after IPLC diagnosis associated with a significant reduction in SPLC risk. Although this effect was observed in a small subset analysis, it lends further support to smoking cessation efforts in patients even after an IPLC diagnosis or treatment. This finding further supports the relationship between tobacco smoking and SPLC,[23] though additional validation of the precise effect is required.

The smoking-SPLC associations in the literature have been inconsistent, possibly owing to a lack of appropriate statistical methods, small sample sizes, or heterogeneity in the smoking exposures evaluated across studies. The smoking-SPLC relationship was first detailed by Boyle et al.[10] who reported that smoking per 10 pack-years was associated with an 8% increased risk of SPLC in ever-smoking patients after definitive surgery. This is in contrast to two other studies which failed to find a smoking-SPLC association.[11,12] Notably, the latter two studies applied a Fine and Gray subdistribution model which may be underpowered to detect a smoking-SPLC effect,[17,24] as smoking is associated with both SPLC (the event of interest) and the competing risk of mortality.[25] In this analytical setting, a cause-specific hazard model may more accurately estimate the effect of

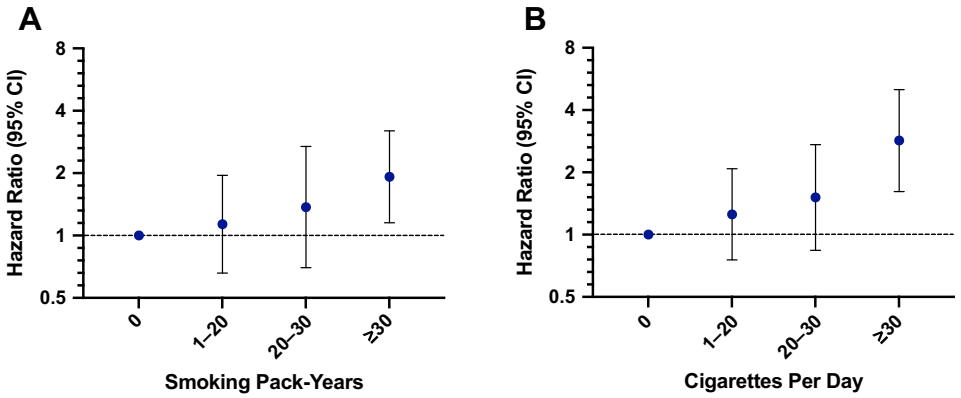

Figure 2. Sensitivity analyses for associations between categorical (*A*) smoking pack-years and (*B*) cigarettes per day and SPLC in the Multiethnic Cohort. All risk estimates were generated from cause-specific proportional hazards models adjusting for age at IPLC diagnosis, IPLC histology, and IPLC stage and accounting for the competing risk of death. CI, confidence interval; IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

smoking on SPLC risk and is the preferred approach for "causal" (i.e., risk-centered) analyses.[17,26] Accordingly, when we applied a Fine and Gray model to the MEC data, we found that the smoking effects, while still present, were attenuated (data not shown).

In stratifying the MEC population by IPLC stage at diagnosis, we found that the smoking effects were especially prominent among participants with an early-stage (I–III) IPLC. However, in participants who were diagnosed with having an advanced IPLC, most of the smoking-related variables did not have a significant association with SPLC, except for smoking intensity which had an inverted point estimate compared with that in all-stage and early-stage IPLC cases. This inverse association is likely owing to a higher competing risk of mortality and, hence, a reduced SPLC incidence among advanced-stage IPLC cases. As described previously, smoking is not only associated with an increased risk of SPLC but also with an increased risk of mortality,[25,27,28] and among participants with advanced IPLCs, the competing risk of mortality predominates. However, a definitive conclusion among these participants is precluded given the relatively few number of SPLC events. Regardless, smoking cessation efforts targeted to this population—while perhaps having less impact on the risk of SPLC—could potentially reduce the risk of smoking-associated mortality and should still be explored.[28]

Interestingly, the 2013 USPSTF criteria, a composite measure of smoking and age that identifies individuals at high risk of IPLC, were a significant indicator of a twofold increased risk of SPLC. This effect was largely driven by the risk conferred from a heavy smoking history, as observed in the categorical smoking plots. Although the smoking-SPLC associations were significant, the magnitude and significance of the smoking effects on SPLC are smaller than those reported for IPLC.[29-32] This attenuation is partly because the comparison of SPLC cases with non-SPLC cases among patients with lung cancer likely represents a comparison of heavier and lighter smoking histories, whereas the comparison of IPLC cases with non-cases more likely represents a comparison of ever-smoking and never-smoking histories. Furthermore, to develop a SPLC, an individual must first survive the IPLC long enough to develop another lung cancer, which itself can carry a long latency period.[33] Thus, although there is a biological rationale for tobacco smoke carcinogens inducing SPLC oncogenesis through similar DNA-damaging mechanisms as with IPLC,[34] it seems that the effect of tobacco smoking, while present, is modulated somewhat with SPLC.

BMI, personal history of cancer, and family history of lung cancer—while protective or risk factors for IPLC[35-38]—had negligible associations with SPLC, as did demographics including sex, race/ethnicity, and education. This study confirmed IPLC age at diagnosis, histology, and stage as relevant predictors of SPLC, which were previously identified in a large, population-based cohort.[13] IPLC surgery and chemotherapy had significant associations with SPLC as risk and protective factors, respectively, in the meta-analyses. However, these effects were driven largely by MEC and were not observed in PLCO. It is possible that these effects are not directly associated with the therapies themselves but perhaps mediated through mortality, as IPLC surgeries are typically performed in the early-stage setting and chemotherapies reserved for more advanced disease. Thus, these treatment effects should be interpreted with caution.

Despite its strengths, this study has several limitations. MEC includes a diverse population of subjects, but

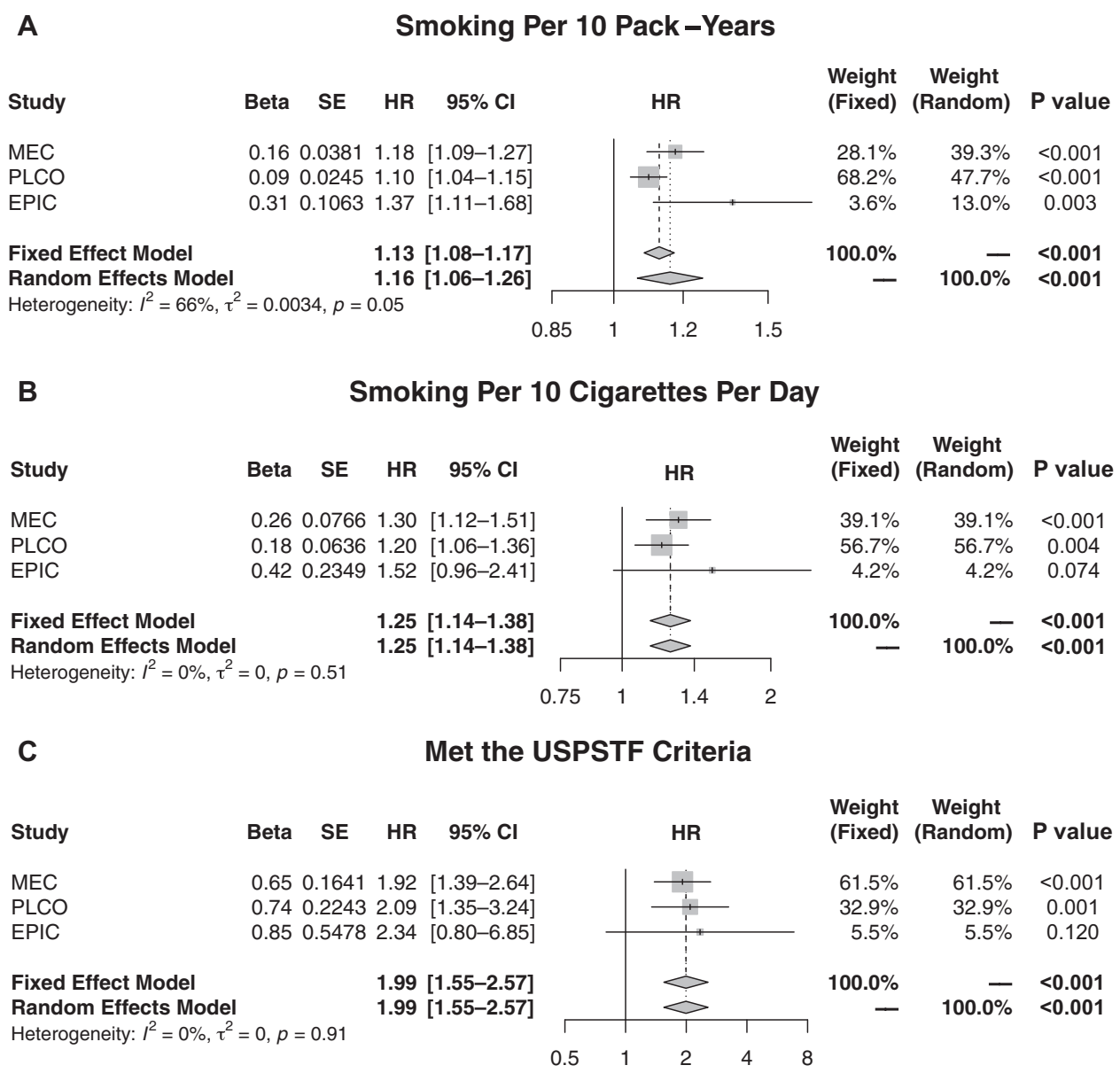

Figure 3. Meta-analyses of associations between smoking-related factors and SPLC across MEC, PLCO, and EPIC. Cause-specific proportional hazards models accounting for the competing risk of death from all causes were used to evaluate the risk of SPLC by (*A*) smoking per 10 pack-years, (*B*) smoking per 10 cigarettes per day, and (*C*) meeting the 2013 USPSTF screening criteria, adjusting for IPLC age at diagnosis, stage, and histology in MEC and PLCO and by IPLC age at diagnosis and histology in EPIC. CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; IPLC, initial primary lung cancer; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SPLC, second primary lung cancer; USPSTF, U.S. Preventive Services Task Force.

it enrolled lower rates of individuals with a current smoking status compared with national surveys at the time of enrollment,[14] though these rates were comparable to the general U.S. population in 2018.[39] Furthermore, validation of the smoking-related findings in two independent cohorts—which consisted of distinct study populations from various geographic regions—revealed consistent results. EPIC, although a sizable cohort, contained few SPLC events and lacked data on certain secondary variables. It is possible that SPLC cases were not fully captured owing to different cohort surveillance strategies between Europe and the United States. Nonetheless, these deficiencies were accounted for appropriately in the meta-analyses using random effects models. Demographic and environmental data were collected through self-reported questionnaires in all cohorts; thus, misclassification is possible, but the consistency of the SPLC associations strengthens these findings. The smoking cessation analysis consisted of a small subset of MEC participants and requires further

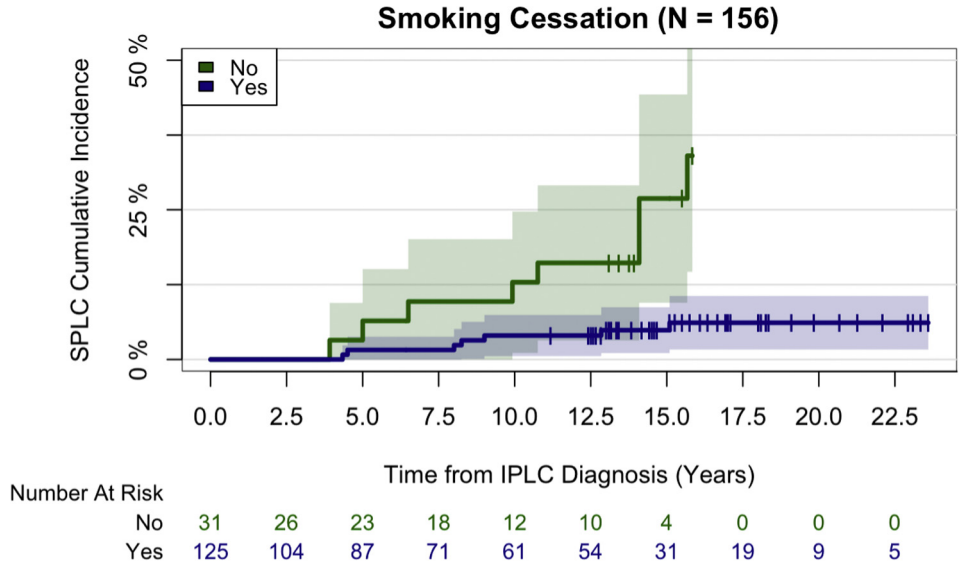

Figure 4. Smoking cessation and risk of SPLC in the Multiethnic Cohort (N = 156). Participants in this subset analysis were current smoking at baseline, had 10-year follow-up smoking data, and were diagnosed with an IPLC before follow-up. Participants who reported that they were "former" smoking at 10-year follow-up were classified as undergoing smoking cessation ("yes"), whereas those who reported that they were "current" smoking at 10-year follow-up were classified as not undergoing smoking cessation ("no"). Participants were followed for the development of SPLC after 10-year follow-up. This cumulative incidence plot was generated using Gray's method, accounting for the competing risk of death from all causes. IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

validation in independent cohorts, which is currently underway. Finally, one relevant question concerns the relationship between tobacco smoking and overall survival in patients with IPLC, specifically regarding the impact of SPLC on survival and how tobacco smoking contributes to survival differences. Future directions should aim to elucidate these relationships, which are beyond the scope of the present study.

In summary, tobacco smoking is a risk factor for SPLC among patients with lung cancer in multiple large epidemiologic cohorts with long-term follow-up. Smoking cessation after an IPLC diagnosis may reduce the risk of SPLC. Comprehensive risk models for SPLC that incorporate relevant risk factors, including tobacco smoking, are needed to identify IPLC cases at high risk of SPLC and guide the development of evidence-based SPLC surveillance and screening strategies.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.02.024

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