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Incidence of Smoking-Related Second Primary Cancers After Lung Cancer in Germany: An Analysis of Nationwide Cancer Registry Data

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ABSTRACT

Introduction: Approximately 80% of lung cancer cases in Germany are attributable to smoking. Patients with a lung cancer diagnosis may remain at increased risk of developing smoking-related second primary cancers (SPCs).

Methods: Anonymous data from 11 population-based cancer registries covering approximately 50% of the German population were pooled for the analysis. Included patients were diagnosed with having an index lung cancer between 2002 and 2013, aged 30 to 99 years old at diagnosis, and survived for at least 6 months. We calculated standardized incidence ratios (SIRs)—stratified by age, sex, region, and period—comparing the incidence of smoking-related and other SPCs to the general population.

Results: Of the 135,589 lung cancer survivors (68.2% male; mean follow-up 30.8 mo) analyzed, 5298 developed an SPC. In males, the risk was particularly high for SPCs of the larynx (SIR = 3.70, 95% confidence interval [CI]: 3.14–4.34), pharynx (3.17, 2.61–3.81), and oral cavity (2.86, 2.38–3.41). For females, SIRs were notably elevated for the esophagus (4.66, 3.15–6.66), oral cavity (3.14, 2.03–4.63), and urinary tract (2.68, 2.04–3.45). When combining all smoking-related cancer sites, SIR was 1.41 in males (95% CI: 1.36–1.47) and 1.81 in females (95% CI: 1.68–1.94). We observed that males had a 1.46-fold (95% CI: 1.37–1.56) and females a 1.33-fold (95% CI: 1.20–1.47) increased risk for smoking-related compared with other cancers.

Conclusions: Patients with primary lung cancer were at increased risk for developing a smoking-related SPC. Therefore, the advantages of increased patient surveillance and the benefits of smoking cessation strategies should be considered.

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Introduction

Tobacco smoking is the leading cause of lung cancer worldwide. In Germany—where smoking rates declined in the past two decades but remain high at 24% for males and 19% for females[1]—current estimations reveal that more than four in five lung cancer cases are attributable to smoking.[2] Still, a large proportion of patients with a lung cancer diagnosis continue smoking after therapy.[3,4] These patients may remain at increased risk of developing second primary cancers (SPCs), defined as a new independent cancer diagnosis.[5]

Previous research using U.S. and U.K. cancer registry data reported that lung cancer survivors have an increased risk for developing SPC in sites with direct contact to tobacco smoke or its metabolites, such as the head and neck, larynx, small intestine, and urinary tract.[6,7] A pooled analysis of North American cohort studies revealed that patients who quit smoking at the time of their first cancer diagnosis had a reduced risk for SPC after primary bladder, kidney, head and neck, and

lung cancers.[8] This indicates that apart from genetic susceptibility, radiation and chemotherapy exposure, other lifestyle-related risk factors, and increased patient surveillance, there is an independent contribution of continuous smoking to SPC risk. Therefore, we hypothesize an elevated risk predominantly in cancer sites for which a causal link to tobacco smoking has been previously established.

In the past two decades, cancer registration in Germany was largely improved by establishing regional population-based cancer registries (PBCRs) in all 16 states. Analyses of risk for multiple primary cancers after lymphoma, endometrial cancer, and unknown primary in Germany have been published,[9–11] but so far, none with regard to smoking-related cancers.

Our objective was to present the absolute and relative incidences of smoking-related SPC in patients who have survived lung cancer in Germany using cancer registry data.

Material and Methods

Data

The German Centre for Cancer Registry Data (ZfKD) provided a data set with lung cancer cases (International Classification of Diseases—10 codes C33 and C34) from all PBCRs in Germany.[12] We restricted data to include all patients with a primary lung cancer diagnosed between January 2002 and December 2013 who were between 30 and 99 years old at the time of diagnosis. The ZfKD collected anonymous data comprising basic patient information, such as year and month of birth, sex, region of residence, vital status, year, month and data on type of diagnosis, location, morphology, staging, and grading of the tumor.[13] Data from 11 German states (Bavaria, Brandenburg, Bremen, Hamburg, Mecklenburg-Western Pomerania, Lower Saxony, Muenster district, Saarland, Saxony, Schleswig-Holstein, Thuringia) covering approximately 50% of the German population were pooled for this study (Supplementary Fig. 1). The selected registries fulfilled the basic quality parameter of covering at least 90% of incident cancer cases in the registry area as recommended by the Association of PBCR in Germany[14] and had started cancer registration in 2002 or earlier, allowing for sufficient follow-up time. Patients with benign or unusual histologic types of lung cancer were excluded. This exclusion was based on a histologic classification of first lung cancers into subtypes (Supplementary Table 2). For the main analyses, we further excluded patients with a diagnosis on the basis of a death certificate only (DCO) and less than 6 months of survival. More details on case exclusion and data modifications are provided in the Supplementary Tables 3 and 4.

Definition of SPC and Smoking Relatedness

We restricted our analysis to lung cancer as index cancer on the basis of sound evidence for the high proportion of disease incidence attributable to smoking.[2,15] Patients younger than 30 years were excluded because this is the earliest age in which lung cancer is likely to be caused by smoking.[16]

All included PBCRs applied the International Agency for Research on Cancer (IARC) definition of multiple primaries.[17] For calculating the incidence of SPC, we considered independent cancer diagnoses that occurred after the index lung cancer and before the end of the observation period on December 31, 2014, in the same patient (excluding nonmelanoma skin cancers C44 and nonmalignant tumors D00–D48).

Inherently, PBCR data do not provide information on patients' smoking history. To summarize SPC incidence in smoking-related sites, we used the definition by the IARC to specify sites where tobacco smoking has an established carcinogenic effect.[18] In addition, we aggregated data for sites categorized as smoking-related by Barclay et al.[6] and Boakye et al.[7] to allow for comparison. Supplementary Table 5 lists the sites considered to be smoking-related according to the three definitions, the relative risk of current smokers versus never smokers, and the percentage of those cancers attributable to smoking.

Statistical Analysis

We described the absolute incidence of SPC by summing up all observed cases within the follow-up periods of 6 to 12 months, 1 to 5 years, 5 to 10 years, and more than 10 years after a lung cancer diagnosis. To estimate the relative incidence, we calculated standardized incidence ratios (SIRs) comparing the observed number of cases among lung cancer survivors to the expected number of cancers in the general German population. The expected number of cases was calculated on the basis of age-, sex-, region-, and period-specific reference rates including DCO cases provided by ZfKD and person-years at risk until the date of SPC, date of death, or end of follow-up on 31 December 2014, whatever event occurred first. In addition, we calculated the ratio between the overall SIR for smoking-related sites and the SIR for other cancer sites (Smo-R) and exact 95% confidence intervals (CIs) as proposed by Breslow and Day.[19] For our main analyses, we presented the results stratified by follow-up time and excluded the first 6 months of follow-up, to allow for comparability with previously published data from England and the United States.[6,20]

For sensitivity analyses, we excluded SPCs reported as DCO from our observed counts and calculated SIRs

using national reference rates without DCO. In an additional sensitivity analysis, we restricted our data to registries with DCO rates of less than 10%, assuming a low percentage of DCO diagnoses indicates higher registration quality.

All analyses were conducted in R[21] with data management using the tidyverse and tidytable packages.[22,23] Figures were created with ggplot2[24] and tables with gt.[25] The routines to calculate and summarize stratified SIRs are publicly available in the R package msSPChelpR,[26] and all scripts used to create our analyses are published online.[27]

Results

Description of the Study Population

A total of 263,921 patients fulfilling the inclusion criteria were identified in the data. We observed a high, though declining age-standardized incidence of lung cancer among men (from 63.7 per 100,000 in the year 2002 to 50.0 per 100,000 population in 2013) and an increasing incidence among women (from 18.2 to 23.4 per 100,000). Almost half of the patients had either a DCO diagnosis, a cancer-free survival of less than 6 months (48.6%), or unclear information on follow-up time (0.1%) and were therefore disregarded in further analyses (Table 1).

The main analysis cohort comprised 135,589 lung cancer survivors, 68.2% males, and 31.8% females, with a mean follow-up period of 30.8 months. From January 2002 to December 2014, a total of 72.2% of the patients had died after lung cancer without developing an SPC, another 23.9% were alive without an event at the end of 2014, and 3.9% developed an SPC.

Incidence of SPC

A total of 5298 SPCs were observed, of which 3806 occurred in men and 1492 in women. The absolute incidence rate of any SPC for men was 1650.8 per 100,000 person-years and considerably higher than that for women (1270.9 cases per 100,000 person-years) (Table 1).

In absolute terms, the most frequent SPCs were prostate, colorectal, lung, urinary tract, and breast cancers (Supplementary Table 6). The relative incidence compared with the general male population was particularly high for laryngeal cancers (SIR = 3.70, 95% CI: 3.14–4.34), pharyngeal cancers (SIR = 3.17, 95% CI: 2.61–3.81), and cancers of the oral cavity (SIR = 2.86, 95% CI: 2.38–3.41). For females, overall SIRs were particularly high for the esophagus (SIR = 4.66, 95% CI: 3.15–6.66), oral cavity (SIR = 3.14, 95% CI: 2.03–4.63), and urinary tract (SIR = 2.68, 95% CI: 2.04–3.45). For both sexes, cancer sites of the head and

neck region and the respiratory tract had a consistently increased risk regardless of follow-up time (Fig. 1). The risk for prostate cancer, however, was 19% lower than in the general male population (SIR = 0.81, 95% CI: 0.76–0.87; Supplementary Table 7), whereas the risk of female breast cancer was elevated (SIR = 1.35, 95% CI: 1.22–1.49; Supplementary Table 8).

When combining all smoking-related cancer sites, we observed an increased relative incidence of 1.37 for males within 6 to 12 months, 1.39 for 1 to 5 years, 1.52 for 5 to 10 years, and 1.41 (95% CI: 1.36–1.47) for the entire follow-up. For females, the SIRs were even higher: 1.90 for 6 to 12 months, 1.74 for 1 to 5 years, 1.87 for 5 to 10 years, and 1.81 (95% CI: 1.68–1.94) for the complete follow-up (Fig. 1 and Table 2).

In contrast, the risk for male lung cancer survivors to develop SPC in non-smoking-related sites did not differ from that of the general population with an SIR of 0.96 (95% CI: 0.91–1.02; Table 2). For women, the risk for other cancers was elevated compared with the general population (SIR = 1.36, 95% CI: 1.26–1.46) but was considerably lower than for smoking-related sites.

We found that SIRs for SPC were particularly elevated for younger people aged 30 to 64 years across all follow-up time (Table 2). For the age group 65 to 69 years, the SIRs were similar to the overall SIR of the study population; for 70- to 74-year-olds, the risk was approximately 1, and for all patients above the age of 75 years, incidence of SPC was below the expected rates in the general population. This age group also had a decline of SIRs with increasing survival time. For example, for patients who were 75 to 79 years old at their first cancer diagnosis, SIR was 1.07 (95% CI: 0.92–1.24) for 6 to 12 months of survival time, 0.95 (95% CI: 0.86–1.05) for 1 to 5 years of survival, 0.78 (95% CI: 0.63–0.97) for 5 to 10 years, and 0.30 (95% CI: 0.06–0.87) for more than 10 years of survival (Table 2).

Stratification by histologic type of lung cancer revealed similar SPC risks. For patients diagnosed with having adenocarcinoma, the SIR was 1.31 (95% CI: 1.25–1.37), with squamous cell carcinoma 1.33 (95% CI: 1.27–1.39), small cell carcinoma 1.24 (95% CI: 1.14–1.35), and other NSCLC 1.20 (95% CI: 1.10–1.30).

We did not identify any time trend in SPC incidence regarding the calendar year of diagnosis. Patients diagnosed with having lung cancer between 2002 and 2005 had an SIR of 1.34 (95% CI: 1.28–1.39) compared with 1.27 (95% CI: 1.19–1.34) for patients diagnosed between 2010 and 2013.

We observed strong regional differences in SPC risk depending on where the index lung cancer was registered (Table 2). The lowest incidence of SPC was found in Saarland, where the overall SIR was 0.77 (95% CI:

0.64–0.92). Bavaria, Lower Saxony, Hamburg, and Schleswig-Holstein had SPC rates above the national average. The most populous regions in the sample—Bavaria (SIR = 1.39, 95% CI: 1.31–1.46) and Lower Saxony (SIR = 1.40, 95% CI: 1.33–1.48)—considerably added to the excess of observed cases because these states also contributed more than one-third of the total population at risk.

Table 1. Characteristics of Analyzed Study Population With Primary Lung Cancer

Observed Cases of Primary Lung Cancer (All Independent of Survival)[a]	Total N = 263,921 (100.0%)	Male n = 184,156 (68.2%)	Female n = 79,765 (31.8%)
Age-standardized incidence rate of lung cancer			
ASIR in 2002 (per 100,000) (95% CI)	38.0 (37.4-38.5)	63.7 (62.7-64.7)	18.2 (17.7-18.7)
ASIR in 2006 (per 100,000) (95% CI)	37.6 (37.1-38.1)	59.4 (58.5-60.4)	20.1 (19.6-20.7)
ASIR in 2010 (per 100,000) (95% CI)	36.3 (35.8-36.8)	53.3 (52.5-54.2)	22.3 (21.8-22.9)
ASIR in 2013 (per 100,000) (95% CI)	35.5 (35.0-36.0)	50.0 (49.2-50.8)	23.4 (22.8-23.9)
Follow-up time			
DCO or less than 1 mo,[b] n (%)	55,814 (21.1)	39,022 (21.2)	16,792 (21.1)
1-6 mo,[b] n (%)	72,355 (27.4)	52,570 (28.5)	19,785 (24.8)
6-12 mo, n (%)	43,949 (16.7)	31,331 (17.0)	12,618 (15.8)
1-5 y, n (%)	71,858 (27.2)	48,289 (26.2)	23,569 (29.5)
5-10 y, n (%)	15,537 (5.9)	10,050 (5.5)	5487 (6.9)
10+ y, n (%)	4245 (1.6)	2775 (1.5)	1470 (1.8)
Unknown,[b] n (%)	163 (0.1)	119 (0.1)	44 (0.1)
Observed cases of primary lung cancer (at least 6 mo survival)			
n (% of total)	135,589 (100.0)	92,445 (68.2)	43,144 (31.8)
Age at diagnosis of LC, n (%)			
30-54	20,820 (15.4)	12,454 (13.5)	8366 (19.4)
55-59	16,333 (12.0)	10,664 (11.5)	5669 (13.1)
60-64	21,999 (16.2)	15,205 (16.4)	6794 (15.7)
65-69	25,684 (18.9)	18,486 (20.0)	7198 (16.7)
70-74	23,995 (17.7)	17,494 (18.9)	6501 (15.1)
75-79	16,374 (12.1)	11,506 (12.4)	4868 (11.3)
80-84	7860 (5.8)	5182 (5.6)	2678 (6.2)
85+	2524 (1.9)	1454 (1.6)	1070 (2.5)
Year of diagnosis of LC, n (%)			
2002-2005	42,167 (31.1)	30,246 (32.7)	11,921 (27.6)
2006-2009	46,213 (34.1)	31,515 (34.1)	14,698 (34.1)
2010-2013	47,209 (34.8)	30,684 (33.2)	16,525 (38.3)
Histology of LC, n (%)			
Small-cell carcinoma	24,361 (18.0)	15,821 (17.1)	8540 (19.8)
Adenocarcinoma	46,899 (34.6)	28,026 (30.3)	18,873 (43.7)
Squamous cell carcinoma	38,812 (28.6)	31,912 (34.5)	6900 (16.0)
Carcinoid	2046 (1.5)	753 (0.8)	1293 (3.0)
Other NSCLC	15,377 (11.3)	10,479 (11.3)	4898 (11.4)
Unspecified lung cancer	8094 (6.0)	5454 (5.9)	2640 (6.1)
Person-years at risk			
Mean follow-up (mo)	30.8	29.9	32.7
Sum of PYAR	347,949	230,550	117,399
Patient status, n (%)			
SPC developed	5298 (3.9)	3806 (4.1)	1492 (3.5)
Dead after LC	97,883 (72.2)	68,607 (74.2)	29,276 (67.9)
No event until end of follow-up	32,408 (23.9)	20,032 (21.7)	12,376 (28.7)
Absolute incidence rate of SPC			
IR (per 100,000 person-years) (95% CI)	1522.6 (1481.9-1564.2)	1650.8 (1598.8-1704.1)	1270.9 (1207.2-1337.0)

Note: Number of patients with primary index lung cancer, ASIR of primary lung cancer, follow-up time, characteristics of patients included in the main analysis with at least 6 months of survival, and absolute incidence of SPC by sex. ASIR based on the European Standard Population 1976 for the population aged 30+ years.
[a]After exclusion by age and morphologic classification of unusual, benign, or sarcoma.
[b]DCO cases and cases with unknown or less than 6 mo follow-up time are excluded from further analyses.
ASIR, age-standardized incidence rate; CI, confidence interval; DCO, death certificate only; IR, incidence rate; LC, primary lung cancer; PYAR, person-years at risk; SPC, second primary cancer.
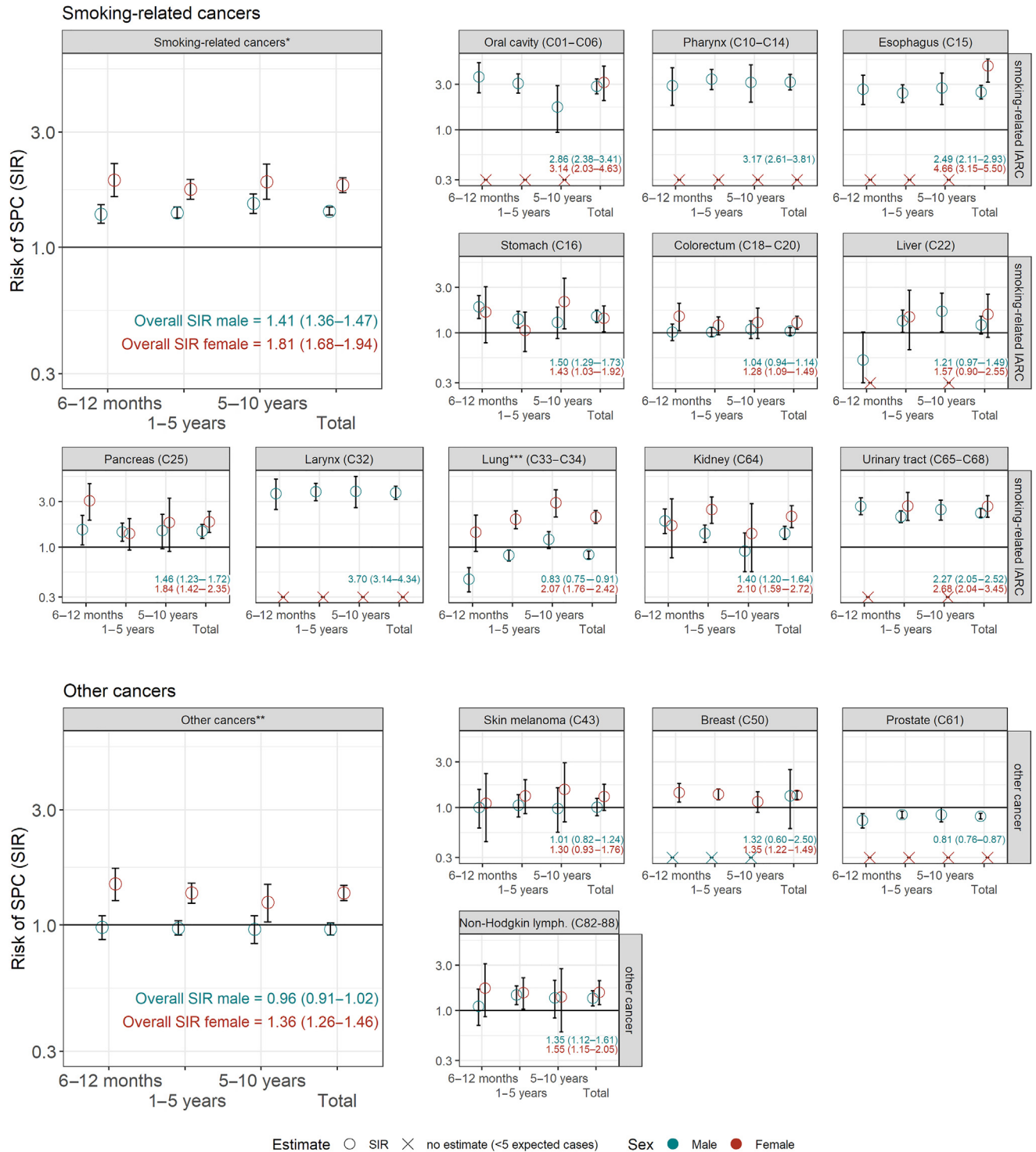
Figure 1. Incidence of SPC in smoking-related and other cancer sites (N = 135,589). Site-specific SIRs stratified by sex on the log-transformed y axis (for males in green and for females in red) and stratified by follow-up time on the x axis. Notes: SIR is only calculated for strata with at least five expected cases. Numeric SIR values are given for total follow-up time (6 mo to 10+ y). All sites with at least 70 observed or expected cases for males or 30 observed or expected cases for females for total follow-up time. *Total for "Smoking-related cancers" includes all SPCs with locations C01–C06, C10–C14, C15-16, C18-20, C22, C25, C30, C31, C32, C33-34, C53, C56, C64, C65-68, and C92. **Total for "Other cancers" includes all other locations. ***The registration of a second primary lung cancer followed the IARC international rules for multiple primary cancers. SIR for lung cancer may be underestimated owing to the histology-dependent registration of SPC with the same location as the first cancer. IARC, International Agency for Research on Cancer; SIR, standardized incidence ratio; SPC, second primary cancer.

Smoking-Related Versus Other SPC

In our analysis cohort, 59.6% of SPCs after lung cancer occurred in smoking-related sites when applying the IARC definition of smoking relatedness, whereas 51.6% would have been expected if the distribution was equal to the general population. The overall SIR for smoking-related cancers was 1.41 (95% CI: 1.36–1.47) in males and 1.81 (95% CI: 1.68–1.94) in females. When applying the definition of smoking relatedness (that excludes the larynx, ovary, and myeloid leukemia from smoking-related sites) of Boakye et al.,[7] we observed a similar estimate of 1.37 (95% CI: 1.32–1.43) in males and 1.85 (95% CI: 1.71–2.00) in females. In contrary, when applying the definition of smoking relatedness of Barclay et al.[6]—which focuses on cancers of the lung, larynx, esophagus, urinary bladder, and head and neck—to the German data, we obtained a considerably higher ratio for females (SIR = 2.44, 95% CI: 2.17–2.74) and a slightly higher SIR for males (SIR = 1.56, 95% CI: 1.47–1.65) (Fig. 2). Independent of the definition, the risk for an SPC in smoking-related sites was always higher than the risk for other cancers. Males had a 46% and females a 33% higher risk for smoking-related than for other cancers (Smo-R males = 1.46, 95% CI: 1.37–1.56; Smo-R females = 1.33, 95% CI: 1.20–1.47).

Sensitivity Analyses

In the sensitivity analyses, removing all DCO cases from the count as SPC resulted in 894 (16.9%) fewer observed cancers. When recalculating SIR using national reference rates also omitting DCO, we obtained results similar to the main analysis. In general, SIRs excluding DCO cases in SPC were approximately 0.10 lower than those including DCO in observed counts were. The reduction was more pronounced for other cancers (0.28 lower in females, 0.10 lower in males) than for smoking-related cancers (0.11 lower in females, 0.05 lower in males) so that the difference between the SIRs of smoking-related versus other cancers was slightly increased (Supplementary Table 9).

When restricting analyses to a subset of PBCR with DCO rates of less than 10%, only six registries (Brandenburg, Bremen, Hamburg, Mecklenburg-Western Pomerania, Saarland, and Saxony) fulfilled this criterion for part of the observation period. Total person-years at risk were reduced to 59,639 resulting in small observed and expected counts (O = 950, only 17.9% of the main analysis set), and thus, no reliable estimations of site-specific SIRs were possible (Supplementary Table 10). The overall SIRs were considerably reduced both for smoking-related cancers (0.52 lower in females, 0.24 lower in males) and for other cancers (0.20 lower in females, 0.21 lower in males).

Discussion

In this first nationwide analysis of the incidence of SPCs using PBCR data, we found an increased risk of SPCs among German lung cancer survivors compared with the general population. The risk of being diagnosed with having an SPC in a smoking-related site was 1.41-fold for men and 1.81-fold for women, whereas the risk for other cancers was not elevated for men and 1.36-fold for women. An increased risk of smoking-related cancers versus other cancers was found across different definitions of smoking relatedness and for both sexes across all follow-up periods (even after more than 5 y of survival). This indicates that, after surviving lung cancer, patients are susceptible to develop another malignancy associated with tobacco smoking.

Similar findings have been reported by previous registry-based studies from other countries.[6,7,28–32] In an analysis of all lung cancer cases in England diagnosed between 2000 and 2014, Barclay et al.[6] found an elevated risk for smoking-related cancers for at least 10 years after the lung cancer diagnosis. The SIRs of 1.36 for men and 1.98 for women are slightly lower than what we found for Germany when applying the same definition of smoking relatedness (Fig. 2). Several studies analyzed data from the U.S. Surveillance, Epidemiology, and End Results (SEER) Program.[7,20,28,29] The most comparable analysis was performed by Boakye et al. using the SEER-18 data set. They included primary cancers diagnosed between 2000 and 2014 and found an overall SIR of 1.62 for both sexes after lung cancer.[7] Furthermore, 3 studies evaluated the risk of a second lung cancer after an index lung cancer and found a significantly higher risk for both men and women.[20,28,29] In summary, SPC risk after lung cancer seems to be higher in the United States. This might, however, partly be explained by methodological differences in registration, such as applying the SEER rules of multiple primaries, instead of the IARC definition as discussed subsequently.

In this study, the risk for most tobacco-related cancers after lung cancer was significantly elevated, especially for the larynx, pharynx, oral cavity, and esophagus, as found in previous research.[6,7,30] The particularly high SIRs for cancer in tobacco-related sites, which are 1.3- to 1.7-fold the estimate for other cancers, indicate that smoking could explain the increased risk for lung cancer survivors. For these sites, consistent positive dose-response relationships between duration of smoking and risk of cancer have been described.[33] In addition, these are the sites for which risk of cancer is particularly high among smokers compared with nonsmokers.[34] Tabuchi et al.[31] have revealed that in 30,000 patients with lung cancer from a hospital registry in Osaka, Japan, ever smokers had increased SIRs of 2.69 for laryngeal,

Table 2. Relative Incidence of SPC Stratified by Follow-Up Time

All Sites Combined	Total						6-12 mo		1-5 y		5-10 y		10+ y	
	O	E	SIR	95% CI	PYAR	N	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
Overall	5298	4116	1.29	1.25-1.32	280,155	135,589	1.29	1.22-1.37	1.28	1.23-1.32	1.32	1.24-1.41	1.20	0.97-1.47
Female	1492	962	1.55	1.47-1.63	95,827	43,144	1.66	1.48-1.85	1.52	1.42-1.62	1.51	1.33-1.70	1.77	1.22-2.49
Male	3806	3153	1.21	1.17-1.25	184,327	92,445	1.19	1.11-1.28	1.20	1.15-1.25	1.26	1.17-1.36	1.02	0.78-1.32
Age at LC diagnosis														
30-54	528	191	2.77	2.54-3.01	49,577	20,820	2.92	2.37-3.54	2.67	2.37-3.00	2.81	2.33-3.36	3.48	2.06-5.49
55-59	534	292	1.83	1.68-1.99	36,067	16,333	2.18	1.81-2.61	1.71	1.52-1.91	1.83	1.50-2.21	2.02	1.11-3.40
60-64	966	605	1.60	1.50-1.70	48,821	21,999	1.37	1.16-1.60	1.63	1.50-1.77	1.71	1.49-1.95	1.59	1.04-2.33
65-69	1262	955	1.32	1.25-1.40	55,471	25,684	1.31	1.15-1.48	1.34	1.24-1.43	1.30	1.15-1.48	1.18	0.74-1.78
70-74	1008	983	1.03	0.96-1.09	46,389	23,995	1.05	0.92-1.20	1.01	0.93-1.10	1.08	0.93-1.25	0.67	0.34-1.21
75-79	665	705	0.94	0.87-1.02	29,015	16,374	1.07	0.92-1.24	0.95	0.86-1.05	0.78	0.63-0.97	0.30	0.06-0.87
80-84	260	306	0.85	0.75-0.96	11,799	7860	0.97	0.77-1.21	0.90	0.77-1.05	0.44	0.26-0.71	0.00	0.00-0.91
85+	75	80	0.93	0.74-1.17	3017	2524	1.20	0.81-1.72	0.88	0.63-1.20	0.49	0.13-1.25	0.00	0.00-6.67
Year of LC diagnosis														
2002-2005	2245	1679	1.34	1.28-1.39	115,984	42,167	1.39	1.25-1.54	1.33	1.26-1.41	1.33	1.23-1.44	1.20	0.97-1.47
2006-2009	1942	1559	1.25	1.19-1.30	103,795	46,213	1.30	1.17-1.43	1.21	1.15-1.28	1.30	1.17-1.45	NA	NA
2010-2013	1111	877	1.27	1.19-1.34	60,376	47,209	1.20	1.08-1.33	1.30	1.21-1.40	NA	NA	NA	NA
Regional cancer registry														
Bavaria	1353	975	1.39	1.31-1.46	71,827	33,357	1.43	1.27-1.61	1.39	1.30-1.49	1.28	1.11-1.46	1.92	1.30-2.75
Brandenburg	304	288	1.06	0.94-1.18	19,329	9740	0.69	0.50-0.93	1.04	0.90-1.21	1.55	1.21-1.94	1.61	0.65-3.32
Bremen	135	112	1.20	1.01-1.42	7427	3214	1.08	0.68-1.61	1.23	0.98-1.53	1.21	0.81-1.74	1.46	0.40-3.73
Hamburg	304	208	1.46	1.30-1.64	14,070	6926	1.75	1.38-2.18	1.38	1.18-1.61	1.37	1.01-1.81	1.71	0.63-3.71
Mecklenburg-Western Pomerania	223	191	1.17	1.02-1.33	12,362	6536	0.85	0.60-1.18	1.14	0.96-1.36	1.74	1.31-2.27	0.65	0.08-2.35
Lower Saxony	1227	875	1.40	1.33-1.48	57,884	28,735	1.59	1.42-1.78	1.36	1.26-1.47	1.41	1.23-1.61	0.60	0.32-1.03
Muenster	400	305	1.31	1.19-1.45	20,048	10,001	1.17	0.92-1.46	1.35	1.18-1.53	1.42	1.12-1.78	0.60	0.12-1.75
Saarland	120	156	0.77	0.64-0.92	10,460	4741	0.67	0.41-1.03	0.85	0.67-1.07	0.71	0.45-1.05	0.00	0.00-1.14
Saxony	466	429	1.09	0.99-1.19	27,578	13,561	1.09	0.89-1.33	1.05	0.93-1.18	1.16	0.93-1.44	1.63	0.84-2.84
Schleswig-Holstein	531	352	1.51	1.38-1.64	23,363	11,405	1.61	1.34-1.93	1.50	1.34-1.68	1.39	1.12-1.71	1.61	0.83-2.81
Thuringia	235	225	1.04	0.91-1.19	15,805	7373	0.87	0.62-1.19	1.05	0.88-1.24	1.21	0.90-1.58	1.18	0.38-2.75
Histology of LC														
Adenocarcinoma	1826	1397	1.31	1.25-1.37	101,649	46,899	1.40	1.26-1.54	1.28	1.20-1.35	1.28	1.14-1.43	1.64	1.18-2.23
Carcinoid	135	99	1.37	1.15-1.62	9775	2046	1.83	1.12-2.82	1.32	1.05-1.65	1.43	1.01-1.97	0.00	0.00-1.30
Other NSCLC	553	462	1.20	1.10-1.30	32,560	15,377	1.08	0.88-1.31	1.27	1.14-1.41	1.11	0.90-1.37	1.04	0.48-1.97
Small-cell carcinoma	532	428	1.24	1.14-1.35	32,404	24,361	1.20	1.02-1.40	1.27	1.13-1.42	1.29	1.02-1.60	0.98	0.39-2.02
Squamous cell carcinoma	1988	1493	1.33	1.27-1.39	89,795	38,812	1.30	1.17-1.43	1.31	1.23-1.39	1.47	1.33-1.61	1.11	0.77-1.56
Unspecified lung	264	238	1.11	0.98-1.25	13,972	8094	1.27	1.00-1.59	1.09	0.92-1.27	0.99	0.69-1.37	0.81	0.22-2.08
Site of SPC														
Smoking-related cancers—total	3158	2123	1.49	1.44-1.54	280,155	135,589	1.47	1.36-1.59	1.46	1.39-1.53	1.59	1.47-1.72	1.57	1.21-2.00
Other cancers—total	2140	1993	1.07	1.03-1.12	280,155	135,589	1.11	1.01-1.21	1.08	1.02-1.14	1.04	0.94-1.15	0.80	0.54-1.15
Smoking-related cancers—male	2414	1711	1.41	1.36-1.47	184,327	92,445	1.37	1.26-1.50	1.39	1.32-1.47	1.52	1.38-1.66	1.39	1.02-1.86
Other cancers—male	1392	1443	0.96	0.91-1.02	184,327	92,445	0.98	0.87-1.09	0.97	0.91-1.04	0.96	0.84-1.09	0.57	0.32-0.93
Smoking-related cancers—female	744	412	1.81	1.68-1.94	95,827	43,144	1.90	1.62-2.22	1.74	1.58-1.91	1.87	1.58-2.21	2.31	1.37-3.65
Other cancers—female	748	550	1.36	1.26-1.46	95,827	43,144	1.48	1.26-1.72	1.36	1.23-1.49	1.24	1.03-1.47	1.39	0.78-2.29

Note: Number of observed and expected SPCs in the main analysis (N = 135,589) and standardized incidence ratios overall, by sex, by index lung cancer diagnosis, and for grouped smoking-related and grouped other cancers, stratified by follow-up time.

CI, confidence interval; E, number of cases expected according to age-, sex-, region-, and period-specific reference rates for the general population; LC, primary lung cancer; NA, not applicable; O, number of cases observed in the data; PYAR, person-years at risk; SIR, standardized incidence ratio; SPC, second primary cancer.

	Total			Male			Female		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
SIR smoking-related cancer									
SIR (IARC def. - 18)	**1.49**	1.44–1.54		**1.41**	1.36–1.47		**1.81**	1.68–1.94	
SIR (Boakye def. - 7)	**1.46**	1.40–1.51		**1.37**	1.32–1.43		**1.85**	1.71–2.00	
SIR (Barclay def. - 6)	**1.67**	1.59–1.75		**1.56**	1.47–1.65		**2.44**	2.17–2.74	
SIR other cancer									
SIR other (IARC def. - 18)	**1.07**	1.03–1.12		**0.96**	0.91–1.02		**1.36**	1.26–1.46	
SIR other (Boakye def. - 7)	**1.14**	1.10–1.19		**1.04**	0.99–1.09		**1.39**	1.30–1.48	
SIR other (Barclay def. - 6)	**1.17**	1.14–1.21		**1.08**	1.04–1.13		**1.43**	1.35–1.51	
Smo-R: Ratio SIR vs. SIR other									
Smo-R (IARC def. - 18)	**1.39**	1.31–1.46		**1.46**	1.37–1.56		**1.33**	1.20–1.47	
Smo-R (Boakye def. - 7)	**1.28**	1.21–1.35		**1.32**	1.23–1.41		**1.33**	1.20–1.48	
Smo-R (Barclay def. - 6)	**1.42**	1.34–1.51		**1.44**	1.34–1.54		**1.71**	1.50–1.95	

Figure 2. Impact of smoking-relatedness definition on SIR estimates and risk for smoking-related versus other second primary cancers. SIR estimate and respective 95% CI for smoking-related cancers (orange tones) according to three different definitions of smoking relatedness, then SIR for other cancers in the middle (blue tones), and the ratio of smoking-related versus other cancer SIRs (Smo-R) at the bottom (gray tones). The first column reveals the total estimates for the complete analysis data set (N = 135,589). The second column for males and the last column for females. For smoking-related cancers, the Barclay definition results in higher SIR estimates than the IARC and Boakye definitions, especially for females. Estimates for other cancers only reveal marginal differences. The ratio Smo-R is consistently above one for all definitions, indicating a 1.3- to 1.7-fold SIR for smoking-related cancers compared with other cancers. Notes: Smoking-relatedness definition by IARC includes C00, C01-C06, C09-14, C15-16, C18-20, C22, C25, C30-34, C53, C56, C64-68, and C92. Boakye definition is based on Boakye et al.[7] and includes C00-14, C15-16, C18-20, C22, C25, C30-31, C33-34, C53, C64, and C67. Barclay definition is based on Barclay et al.[6] and includes C00-14, C15, C31, C33-34, and C67. SIRs and Smo-R for Germany are calculated by the authors using the three different definitions of smoking relatedness. CI, confidence interval; def., definition; IARC, International Agency for Research on Cancer; SIR, standardized incidence ratio; Smo-R, ratio between the overall SIR for smoking-related sites and the SIR for other cancer sites.

3.41 for pharyngeal, and 3.94 for esophageal cancers, whereas never smokers had no risk increase. Another explanation besides smoking behavior could be shared environmental or genetic risk factors for developing lung cancer and other cancers in the upper respiratory tract. Our observation that SIRs for smoking-related cancers remain consistently high—not only for the first years after the lung cancer diagnosis but also for more than 5 years of follow-up—corroborates the assumption that a considerable amount of patients continue smoking after their first cancer diagnosis.

The comparably low SIRs for lung cancer that we found in our analysis are affected by the IARC definition of multiple primaries that is routinely applied by all German PBCRs.[14] A second primary lung cancer is only registered if the tumor has a different histology group than the index lung cancer and unspecified histology types are excluded from SPC count. Because we compared this limited observed count to the expected general lung cancer risk independent of histology, our SIRs for the site lung underestimate the true incidence ratio. Other analyses that used the IARC definition of multiple primaries also found lower SIRs for second lung cancer[30,31] than studies using the SEER definition.[20,28,29] Weir et al.[35] have revealed that applying SEER rules for multiple primaries instead of the IARC rules results in

higher incidence estimates, especially for paired organs and organs with a large surface, such as the lung and bronchus.

For females, the risk of smoking-related cancers was significantly higher compared with males across follow-up time, in line with previous findings.[6] The lower baseline cancer risk in the general female population than in the male population in Germany[36] results in higher SIRs even if the absolute effect of smoking was the same in men and women. In addition, epidemiologic evidence indicates that women have higher risk of tobacco-related disease than men with comparable smoking behavior.[37,38] Various molecular hypotheses have been presented[5,33,39]; however, the reason for this finding is not fully understood and deserves further investigation.

Within the context of substantial legal and organizational changes in cancer registration in Germany since 2013,[13] it remains unclear whether follow-up time and the actual application of multiple primary definition play an important role in SIR estimations. We observed largely increased rates for less than 6 months follow-up time that might be due to increased patient surveillance during the treatment period or registration of non-independent second cancers; however, we excluded this follow-up period from our main analysis (Supplementary Fig. 11 and Supplementary Table 12). Additional research is needed to investigate whether this is due to a large number of SPCs developing simultaneously with the primary lung cancer or whether data quality, such as high DCO rates or limited information on second cancers, also affects SIR estimates.

Our research is the first to provide absolute and relative incidence rates for smoking-related SPC after lung cancer in Germany. We used the most comprehensive data set of pooled PBCR for the analysis cohort, covering half of the German population. Furthermore, we applied the most accurate methodology for calculating SIRs by using age-, sex-, region-, and period-specific reference rates. We reported our analyses stratified by follow-up time to avoid bias and data artifacts, especially for the first year of follow-up. In addition, we report site-specific SIRs to allow comparison of SIRs for smoking-related and other SPCs independent of the definition of smoking relatedness, for which we used an established classification by the IARC.

This analysis is subject to the inherent limitations of PBCR data that do not contain information on individual lifestyle factors. First, there is no information on the actual smoking status of patients. All conclusions on the association between cancer diagnosis and smoking were made on a population level. Although for the index lung cancer, we can be sufficiently certain that the disease was caused by tobacco smoking in most observed patients owing to the high population-attributable fraction,[2] the definition of smoking-relatedness in other sites is more ambiguous. Second, regional variations of SIR rates within the German PBCR suggest that there might be differences in cancer registration practices, especially with regard to how the IARC criteria of multiple primaries are applied when no histologic verification of the second cancer is available. In addition, misclassification of metastases, especially for tumors with no histologic verification, could have led to an overestimation of SIRs. Last, we might have overestimated the follow-up time for some patients because of DCO cases and incomplete record linkage to death registries. The actual date of diagnosis for DCO cases is unknown, and therefore, the date of diagnosis is replaced by the date of death, although cancer must have occurred before death. Incomplete record linkage of PBCR with death registries leads to immortal time bias.[13] Both effects increase follow-up time for the expected count, therefore underestimating the true SIR.

For the growing number of long-term survivors, our findings imply the possibility of lowering the risk for subsequent cancer by quitting smoking after their lung cancer diagnosis. Observational studies have revealed that many smokers continue or restart smoking after lung cancer,[3,4,8] whereas smoking cessation decreases SPC risk in patients with cancer and improves survival.[5,40] Thus, smoking cessation may result in a lower SPC incidence with all its associated individual and societal benefits. Future analyses will reveal whether decreasing smoking rates also reduce the incidence of smoking-related SPC. Moreover, even patients who have survived lung cancer for 5 years and longer could benefit from continuous medical surveillance, because they remain at increased risk particularly for smoking-related cancers.

This comprehensive analysis of data from 11 German PBCR revealed an increased risk for second cancers among lung cancer survivors compared with the general population. The risk was notably increased for developing a smoking-related SPC compared with non–smoking-related SPC. Males had a 46% and females a 33% higher risk for smoking-related than for other cancers. This research indicates that a large burden of disease is related to subsequent tobacco smoking-associated cancers. Therefore, the advantages of increased patient surveillance and smoking cessation efforts should be considered, especially for long-term lung cancer survivors.

CRediT Authorship Contribution Statement

Marian Eberl: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing—

original draft, Writing—review and editing, Visualization.

Luana F. Tanaka: Validation, Resources, Writing—original draft, Writing—review and editing.

Klaus Kraywinkel: Methodology, Validation, Resources, Writing—review and editing, Supervision.

Stefanie J. Klug: Conceptualization, Validation, Writing—review and editing, Supervision.

Data Availability Statement

Because of legal restrictions, the individual-level raw data used for this analysis are only available by means of request to the German Centre for Cancer Registry Data (ZfKD) that can provide a scientific use file. More information on the application process is provided on the ZfKD website (https://www.krebsdaten.de/Krebs/EN/Content/ScientificUseFile/scientificusefile_node.html).

The authors of this article strongly support open science and have therefore published both the analysis code and the newly programmed software to review and download under a GPL-3 license.

Repository for analysis code: https://github.com/marianschmidt/pub_spc_lung_cancer_jto.

Repository for software code: https://doi.org/10.5281/zenodo.5055870.

Ethics Approval and Consent to Participate

This study analyzed the scientific use file (SUF) of the German Centre for Cancer Registry Data (ZfKD). Data collection is mandated and regulated by the German Federal Law on Cancer Registration (BKRG), and secondary data analysis of the anonymous SUF—as used in this study—does not require ethics approval or consent by patients (Section 3 and Section 5 BKRG).

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.2021.11.016.

References

1. Seitz N-N, Lochbühler K, Atzendorf J, Rauschert C, Pfeiffer-Gerschel T, Kraus L. Trends in substance use and related disorders. *Dtsch Arztebl Int*. 2019;116:585-591.
2. Mons U, Gredner T, Behrens G, Stock C, Brenner H. Cancers due to smoking and high alcohol consumption. *Dtsch Arztebl Int*. 2018;115:571-577.
3. Walker MS, Vidrine DJ, Gritz ER, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. *Cancer Epidemiol Prev Biomark*. 2006;15:2370-2377.
4. Park ER, Japuntich SJ, Rigotti NA, et al. A snapshot of smokers following lung and colorectal cancer diagnosis. *Cancer*. 2012;118:3153-3164.
5. Warren GW, Sobus S, Gritz ER. The biological and clinical effects of smoking by patients with cancer and strategies to implement evidence-based tobacco cessation support. *Lancet Oncol*. 2014;15:e568-e580.
6. Barclay ME, Lyratzopoulos G, Walter FM, Jefferies S, Peake MD, Rintoul RC. Incidence of second and higher order smoking-related primary cancers following lung cancer: a population-based cohort study. *Thorax*. 2019;74:466-472.
7. Boakye EA, Buchanan P, Hinyard L, et al. Trends in the risk and burden of second primary malignancy among survivors of smoking-related cancers in the United States. *Int J Cancer*. 2019;145:143-153.
8. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. *J Clin Oncol*. 2014;32:3989-3995.
9. Baras N, Dahm S, Haberland J, et al. Subsequent malignancies among long-term survivors of Hodgkin lymphoma and non-Hodgkin lymphoma: a pooled analysis of German cancer registry data (1990-2012). *Br J Haematol*. 2017;177:226-242.
10. Chen T, Brenner H, Fallah M, et al. Risk of second primary cancers in women diagnosed with endometrial cancer in German and Swedish cancer registries. *Int J Cancer*. 2017;141:2270-2280.
11. Liu H, Hemminki K, Sundquist J, et al. Second primary cancers after cancer of unknown primary in Sweden and Germany: efficacy of the modern work-up. *Eur J Cancer Prev*. 2013;22:210-214.
12. Zentrum für Krebsregisterdaten (ZfKD) im Robert Koch-Institut. Datensatz des ZfKD auf Basis der epidemiologischen Landeskrebsregisterdaten Epi2016_2, verfügbare Diagnosejahre bis 2014 auf dem Stand von Epi2016_2). - Population-based cancer registry dataset from the German Center for Cancer Registry Data. https://www.krebsdaten.de/Krebs/DE/Content/Scientific_Use_File/Versionen/epi2016_2/epi2016_2_node.html. Accessed October 15, 2021.
13. Arndt V, Holleczek B, Kajüter H, et al. Data from population-based cancer registration for secondary data analysis: methodological challenges and perspectives. *Gesundheitswesen*. 2020;80:S62-S71.
14. Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID). Atlas der Krebsinzidenz und Krebsmortalität der Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID). Lübeck, Germany: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. 2021. https://atlas.gekid.de/CurrentVersion/Methoden%20GEKID%20Atlas.pdf. Accessed October 15, 2021.
15. Wienecke A, Barnes B, Lampert T, Kraywinkel K. Changes in cancer incidence attributable to tobacco smoking in Germany, 1999-2008. *Int J Cancer*. 2014;134:682-691.
16. Liu B, Quan X, Xu C, et al. Lung cancer in young adults aged 35 years or younger: a full-scale analysis and review. *J Cancer*. 2019;10:3553-3559.

17. International Agency for Research on Cancer. International rules for multiple primary cancers (ICD-O third edition). http://www.iacr.com.fr/images/doc/MPrules_july2004.pdf; 2004. Accessed October 15, 2021.

18. Secretan B, Straif K, Baan R, et al. A review of human carcinogens—part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol*. 2009;10:1033-1034.

19. Breslow NE, Day NE. Statistical methods in cancer research volume II: the design and analysis of cohort studies. International Agency for Research on Cancer. http://publications.iarc.fr/Book-And-Report-Series/Iarc-Scientific-Publications/Statistical-Methods-In-Cancer-Research-Volume-II-The-Design-And-Analysis-Of-Cohort-Studies-1986; 1987. Accessed October 15, 2021.

20. Thakur MK, Ruterbusch JJ, Schwartz AG, Gadgeel SM, Beebe-Dimmer JL, Wozniak AJ. Risk of second lung cancer in patients with previously treated lung cancer: analysis of surveillance, epidemiology, and end results (SEER) data. *J Thorac Oncol*. 2018;13:46-53.

21. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org/. Accessed October 15, 2021.

22. Fairbanks M. Tidytable: tidy Interface to 'data.table'. https://CRAN.R-project.org/package=tidytable. Accessed October 15, 2021.

23. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4:1686.

24. Wickham H. *Ggplot2: elegant graphics for data analysis*. Berlin, Germany: Springer; 2016.

25. Iannone R, Cheng J, Schloerke B. Gt: easily create presentation-ready display tables. The Comprehensive R Archive Network. https://CRAN.R-project.org/package=gt. Accessed October 15, 2021.

26. Eberl M. MsSPChelpR: helper functions for second primary cancer analyses. The Comprehensive R Archive Network. https://CRAN.R-project.org/package=msSPChelpR. Accessed October 15, 2021.

27. Eberl M. Code for Paper "Incidence of smoking-related second primary cancers after lung cancer in Germany: an analysis of nationwide cancer registry data" submitted to JTO - marianschmidt/pub_spc_lung_cancer_jto. GitHub. https://github.com/marianschmidt/pub_spc_lung_cancer_jto. Accessed October 15, 2021.

28. Abdel-Rahman O, Cheung WY. Subsequent thoracic cancers among patients diagnosed with lung cancer: a SEER database analysis. *Curr Med Res Opin*. 2017;33:2009-2017.

29. Khanal A, Lashari BH, Kruthiventi S, et al. The risk of second primary malignancy in patients with stage Ia non-small cell lung cancer: a U.S. population-based study. *Acta Oncol*. 2018;57:239-243.

30. Jégu J, Colonna M, Daubisse-Marliac L, et al. The effect of patient characteristics on second primary cancer risk in France. *BMC Cancer*. 2014;14:94.

31. Tabuchi T, Ito Y, Ioka A, Nakayama T, Miyashiro I, Tsukuma H. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. *Ann Oncol*. 2013;24:2699-2704.

32. Youlden DR, Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. *BMC Cancer*. 2011;11:1-12.

33. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100 E, Personal Habits and Indoor Combustions*. Lyon, France: International Agency for Research on Cancer; 2012. http://publications.iarc.fr/_publications/media/download/3059/2a872fb83cc036dc80eebbbf097a85d5044ad708.pdf. Accessed October 15, 2021.

34. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer*. 2008;122:155-164.

35. Weir HK, Johnson CJ, Ward KC, Coleman MP. The effect of multiple primary rules on cancer incidence rates and trends. *Cancer Causes Control*. 2016;27:377-390.

36. Robert Koch-Institut and Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Cancer in Germany in 2015/2016. https://edoc.rki.de/bitstream/handle/176904/8320/cancer_germany_2015_2016_2.pdf; 2020. Accessed October 15, 2021.

37. Hansen MS, Licaj I, Braaten T, Langhammer A, Le Marchand L, Gram IT. Sex differences in risk of smoking-associated lung cancer: results from a cohort of 600,000 Norwegians. *Am J Epidemiol*. 2018;187:971-981.

38. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378:1297-1305.

39. Fidler-Benaoudia MM, Torre LA, Bray F, Ferlay J, Jemal A. Lung cancer incidence in young women vs. young men: a systematic analysis in 40 countries. *Int J Cancer*. 2020;147:811-819.

40. Osazuwa-Peters N, Adjei Boakye E, Chen BY, Tobo BB, Varvares MA. Association between head and neck squamous cell carcinoma survival, smoking at diagnosis, and marital status. *JAMA Otolaryngol Head Neck Surg*. 2018;144:43-50.