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ORIGINAL ARTICLE

Clinical characteristics and survival in non-small cell lung cancer patients by smoking history: a population-based cohort study

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ABSTRACT

Introduction: Approximately, 10–15% of lung cancer patients have never smoked. Previous epidemiological studies on non-tobacco associated lung cancer have been hampered by selected data from a small number of hospitals or limited numbers of patients. By use of data from large population-based registers with national coverage, this study aims to compare characteristics and survival of patients with non-small cell lung cancer (NSCLC) with different smoking histories.

Methods: Swedish national population-based registers were used to retrieve data on patients diagnosed with primary NSCLC between 2002 and 2016. The Kaplan–Meier method and Cox proportional hazard models were used to estimate overall survival and lung cancer-specific survival by smoking history.

Results: In total, 41,262 patients with NSCLC were included. Of those, 4624 (11%) had never smoked. Never-smokers were more often women and older compared to ever smokers (current and former). Adenocarcinoma was proportionally more common in never-smokers (77%) compared to current (52%) and former smokers (57%). Stage IV disease was more common in never-smokers (57%) than in current (48%) and former smokers (48%). Epidermal growth factor receptor mutation was observed more in never-smokers (37%) compared to current (5%) and former smokers (9%). Both lung cancer-specific and overall survival were higher for never-smokers compared to current smokers.

Conclusions: The observed differences in characteristics between never-smokers and smokers, and the higher survival in never-smokers compared to smokers from this large population-based study provide further evidence that lung cancer in never-smokers is clinically different to tobacco-associated lung cancer. The findings from this study emphasise the need for an improved understanding of genetics, pathogenesis, mechanisms and progression of non-tobacco associated lung cancer that may help prevent lung cancer or identify individually targeted treatments.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide with approximately 1.5 million deaths globally each year [1,2]. In Sweden, about 3800 incident cases of lung cancer are reported each year, representing the fourth and sixth most common malignancy in men and women, respectively [1].

Although tobacco smoking is the primary cause of lung cancer [3–6], around 10–15% of lung cancer patients in Western countries have never smoked [7,8]. Thus, lung cancer also represents an important health issue for never-smokers. Risk factors for lung cancer in never-smokers include exposure to cooking fumes, radon, asbestos, outdoor pollution and environmental tobacco smoke [6,7,9].

Several studies of different size and design have compared clinical lung cancer characteristics in never-smokers with that of ever-smokers, including assessments of survival [6–26]. Most of these studies were hospital-based with data from only a small number of hospitals and the majority included less than 2000 lung cancer patients [8,10,12,15–18,20–22,24,26]. Despite inconsistencies between studies, the collective evidence indicates that the pathogenesis and tumour biology of lung cancer differ by smoking history.

The aim of the present study was to compare clinical characteristics, management and survival in never-smokers and ever smokers (current and former) diagnosed with non-

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Supplemental data for this article can be accessed here.

small cell lung cancer (NSCLC) by the use of large population-based registers.

Material and methods

The National Lung Cancer Register and Lung Cancer Database Sweden

Data on NSCLC patients diagnosed in Sweden between 2002 and 2016 were retrieved from the Lung Cancer Database Sweden (LCBaSe). LCBaSe is a research database generated by record linkage between the National Lung Cancer Register (NLCR) and the Swedish Cancer Register (SCR), the Cause of Death Register (CDR), the National Patient Register (NPR), the Prescribed Drug Register (PDR), the Longitudinal Integration Database for Health, Insurance and Labour Market Studies (LISA) and the National Population Register [27].

The NLCR was established in 2002 and includes more than 95% of all patients registered with a lung cancer diagnosis in the SCR, to where reporting is mandated by law [28]. The NLCR is a prospective, population-based register, which contains information on sex, age at diagnosis, smoking history (self-reported by the patient to the medical doctor), World Health Organisation (WHO) performance status (0–4) (PS), mode of detection, histopathology, stage at diagnosis, epidermal growth factor receptor (EGFR) mutation status and planned primary treatment. The NLCR is continuously updated against the National Population Register to monitor the current vital status of registered patients.

Information on the highest attained educational level was obtained from the LISA database at Statistics Sweden and collapsed into three groups based on the number of years of formal education at the end of the year before the diagnosis; low ($\leq$9 years), middle (10–12 years) and high ($\geq$13 years).

Charlson Comorbidity Index (CCI) was calculated based on information retrieved from the NPR and the SCR during a 10-year period prior to the lung cancer diagnosis. The index was summed to obtain an overall score, resulting in three comorbidity levels; 0 for no, 1 for mild and $\geq$2 for severe comorbidity.

For a more detailed description of the variables and grouping of the variables, see Supplementary Material S1.

The unique personal identity number, assigned to all Swedish residents at birth or permanent residency allowed individual level record linkage between different registers [29].

Survival and cause of death

Overall survival and lung cancer-specific survival were estimated. Survival time for each patient was defined from the date of diagnosis to the date of death (attributed to any cause in the overall analysis and to lung cancer (International Classifications of Diseases (ICD) 9 code 162, and ICD10 code C34) in the cause-specific analysis), emigration, or 31 December 2016, whichever occurred first. Information on the cause of death was obtained from the CDR [30,31]. The CDR covers all deaths in Sweden since 1961 and is based on information from death certificates. Less than 1% of all reported deaths lack information on the cause of death and the validity, comparing the death certificate and information from medical records, for malignant tumours has been estimated to be over 90% [31].

Statistical analysis

Possible differences in characteristics by smoking history (current, former and never) were tested using the χ^2-test for categorical variables and the Kruskal–Wallis test for continuous variables. All statistical tests were two-sided.

Overall survival and lung cancer-specific survival were estimated at one year, two years and five years after diagnosis, by use of the Kaplan–Meier method. Differences between groups by smoking history were univariately tested using the log-rank test.

Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer-specific mortality and all-cause mortality with current smokers as the reference group. Time since lung cancer diagnosis was used as the underlying time scale. The models were adjusted for age, histopathology, CCI, PS, planned primary treatment and educational level, with further stratification for stage and sex. The proportional hazard assumption was tested using the scaled Schoenfeld residuals. If the proportional hazard assumption was not met, an interaction term between smoking history and the underlying time scale was added to the model.

Statistical analyses were performed using Stata and R statistical software packages [32,33].

Ethical approval

The study was approved by the Regional Ethical Review Board in Stockholm (2012/1162-31/4;2016/1137-32;2017/445-32).

Results

Patient characteristics

Between 2002 and 2016, 52,264 lung cancer cases were registered in the NLCR. After excluding patients with records of negative survival time ($n = 157$), and patients with other histopathology ($n = 10{,}845$), 41,262 patients with NSCLC were included in the study of which 19,853 (48%) were women and 21,409 (52%) men (Table 1). Of the included patients, 17,878 (43%) were classified as current smokers, 17,966 (44%) as former smokers, 4624 (11%) as never-smokers and 794 (2%) as missing. The proportion of women was higher among never-smokers (66%) than current smokers (49%) and former smokers (43%). Never-smokers were older at the time of diagnosis (median age 73 years, inter quartile range (IQR)=63–80) than current smokers (median age 67 years, IQR = 61–73) and former smokers (72, IQR = 66–78). More than one quarter (27%) of the never-smokers were 80 years or older at diagnosis compared to current smokers

Table 1. Baseline characteristics of non-small cell lung cancer (NSCLC) patients in Sweden diagnosed during 2002–2016.

	Smoking status at diagnosis									Total	
	Current smokers (*N* = 17,878, 43.3%)		Former smokers (*N* = 17,966, 43.5%)		Never-smokers (*N* = 4624, 11.2%)		Missing (*N* = 794, 1.9%)		*p* Value[a]	(*N* = 41,262)	
Sex (%)											
Men	9104	(50.9)	10,330	(57.5)	1564	(33.8)	411	(51.8)	<.001	21,409	(51.9)
Women	8774	(49.1)	7636	(42.5)	3060	(66.2)	383	(48.2)		19,853	(48.1)
Age at diagnosis (years)											
Median (IQR)	67	(61–73)	72	(66–78)	73	(63–80)	71	(63–79)	<.001	70	(63-76)
Age at diagnosis (years) (%)											
<40	40	(0.2)	21	(0.1)	94	(2.0)	4	(0.5)	<.001	159	(0.4)
40–49	519	(2.9)	188	(1.0)	253	(5.5)	21	(2.6)		981	(2.4)
50–59	3034	(17.0)	1366	(7.6)	483	(10.4)	105	(13.2)		4988	(12.1)
60–69	7163	(40.1)	5432	(30.2)	1025	(22.2)	218	(27.5)		13,838	(33.5)
70–79	5708	(31.9)	7499	(41.7)	1521	(32.9)	257	(32.4)		14,985	(36.3)
≥80	1414	(7.9)	3460	(19.3)	1248	(27.0)	189	(23.8)		6311	(15.3)
Basis of diagnosis (%)											
Clinical diagnosis	18	(0.1)	14	(0.1)	7	(0.2)	2	(0.3)	<.001	41	(0.1)
Cytology	6403	(35.8)	6587	(36.7)	1771	(38.3)	377	(47.5)		15,138	(36.7)
PAD	11,402	(63.8)	11,322	(63.0)	2830	(61.2)	406	(51.1)		25,960	(62.9)
Missing	55	(0.3)	43	(0.2)	16	(0.3)	9	(1.1)		123	(0.3)
Histopathology (%)											
Squamous	5094	(28.5)	4621	(25.7)	419	(9.1)	184	(23.2)	<.001	10,318	(25.0)
Adenocarcinoma	9286	(51.9)	10,312	(57.4)	3546	(76.7)	417	(52.5)		23,561	(57.1)
Large cell/undiff. NSCLC	2728	(15.3)	2291	(12.8)	434	(9.4)	134	(16.9)		5587	(13.5)
Adenosquamous	202	(1.1)	198	(1.1)	43	(0.9)	11	(1.4)		454	(1.1)
Sarcomatous/pleomorf comp.	73	(0.4)	61	(0.3)	32	(0.7)	3	(0.4)		169	(0.4)
Unclassified cancer	495	(2.8)	483	(2.7)	150	(3.2)	45	(5.7)		1173	(2.8)
EGFR (%)[b]											
Not taken	1574	(43.3)	1815	(39.9)	303	(27.8)	47	(53.4)	<.001	3739	(40.0)
Taken, results positive	85	(2.3)	222	(4.9)	281	(25.8)	3	(3.4)		591	(6.3)
Taken, results negative	1637	(45.0)	2144	(47.2)	448	(41.1)	25	(28.4)		4254	(45.5)
Taken, results inconclusive	108	(3.0)	163	(3.6)	40	(3.7)	4	(4.5)		315	(3.4)
Missing	230	(6.3)	203	(4.5)	17	(1.6)	9	(10.2)		459	(4.9)
Stage (%)											
IA	1824	(10.2)	1877	(10.4)	505	(10.9)	55	(6.9)	<.001	4261	(10.3)
IB	1430	(8.0)	1508	(8.4)	284	(6.1)	62	(7.8)		3284	(8.0)
IIA	383	(2.1)	473	(2.6)	76	(1.6)	9	(1.1)		941	(2.3)
IIB	753	(4.2)	739	(4.1)	103	(2.2)	17	(2.1)		1612	(3.9)
IIIA	1753	(9.8)	1759	(9.8)	287	(6.2)	48	(6.0)		3847	(9.3)
IIIB	2812	(15.7)	2677	(14.9)	655	(14.2)	117	(14.7)		6261	(15.2)
IV	8642	(48.3)	8675	(48.3)	2635	(57.0)	425	(53.5)		20,377	(49.4)
Missing	281	(1.6)	258	(1.4)	79	(1.7)	61	(7.7)		679	(1.6)
M-stage among stage IV (%)[c]											
M1 (a/b missing)	23	(0.5)	31	(0.6)	4	(0.3)	0	(0.0)	<.001	58	(0.5)
M1a	1183	(26.8)	1641	(31.6)	594	(38.8)	32	(23.9)		3450	(30.6)
M1b	3208	(72.7)	3513	(67.8)	931	(60.9)	102	(76.1)		7754	(68.9)
WHO performance status (%)											
WHO 0	3636	(20.3)	3915	(21.8)	1235	(26.7)	106	(13.4)	<.001	8892	(21.6)
WHO 1	6849	(38.3)	6758	(37.6)	1637	(35.4)	202	(25.4)		15,446	(37.4)
WHO 2	3867	(21.6)	3745	(20.8)	836	(18.1)	157	(19.8)		8605	(20.9)
WHO 3	2150	(12.0)	2236	(12.4)	557	(12.0)	131	(16.5)		5074	(12.3)
WHO 4	771	(4.3)	738	(4.1)	200	(4.3)	72	(9.1)		1781	(4.3)
Missing	605	(3.4)	574	(3.2)	159	(3.4)	126	(15.9)		1464	(3.5)
Charlson Comorbidity Index (%)											
0	10,301	(57.6)	8845	(49.2)	2851	(61.7)	387	(48.7)	<.001	22,384	(54.2)
1	3000	(16.8)	3315	(18.5)	586	(12.7)	136	(17.1)		7037	(17.1)
2+	4577	(25.6)	5806	(32.3)	1187	(25.7)	271	(34.1)		11,841	(28.7)
In-patient register diagnosis within 10 years before cancer diagnosis, no. (%)											
COPD	2248	(12.6)	2409	(13.4)	60	(1.3)	74	(9.3)	<.001	4791	(11.6)
CVD	6079	(34.0)	8436	(47.0)	1720	(37.2)	340	(42.8)	<.001	16,575	(40.2)
Dementia	64	(0.4)	95	(0.5)	23	(0.5)	12	(1.5)	<.001	194	(0.5)
Education level (%)											
Low	7856	(43.9)	7801	(43.4)	1706	(36.9)	385	(48.5)	<.001	17,748	(43.0)
Middle	7566	(42.3)	6997	(38.9)	1618	(35.0)	279	(35.1)		16,460	(39.9)
High	2118	(11.8)	2880	(16.0)	1175	(25.4)	109	(13.7)		6282	(15.2)
Missing	338	(1.9)	288	(1.6)	125	(2.7)	21	(2.6)		772	(1.9)

[a] *p* Value for the hypothesis of no difference in distribution between smoking status groups.
[b] Presented for patients diagnosed 2014–2016.
[c] Presented for stage IV patients diagnosed 2010–2016.

(8%) and former smokers (19%). Also, a higher proportion of the never-smokers (8%) were younger than 50 years compared to current smokers (3%) and former smokers (1%). A PS of 0 was proportionally more common in never-smokers (27%) than in current smokers (20%) and former smokers (22%). Similarly, the proportion of patients with a CCI score of 0 was highest in never-smokers. In an assessment by specific concomitant medical conditions, a record of a diagnosis of chronic obstructive pulmonary disease (COPD) was less common in never-smokers (1%) than in current smokers (13%) and former smokers (13%). One quarter (25%) of never-smokers were classified as having a high education compared to 12% and 16% in current smokers and former smokers, respectively.

Occurrence

During the study period, the proportion of NSCLC patients categorised as never-smokers fluctuated between 10% and 13% with no apparent temporal trend (Figure 1). However, the absolute number of never-smokers diagnosed with NSCLC increased twofold between 2002 and 2016, from approximately 200 to 400 patients. The corresponding increase in current smokers was from about 1000 to 1200, and from approximately 750 to 1500 in former smokers.

Tumour characteristics

Adenocarcinoma was the most common histological type in all groups, constituting 77% of lung cancer in never-smokers, 52% in current smokers and 57% in former smokers (Table 1). Conversely, squamous cell carcinoma was less common in never-smokers (9%) than in current smokers (29%) and former smokers (26%).

There were only minor differences in the distribution of early-stage disease by smoking history (Table 1). However, a higher proportion of never-smokers were diagnosed with stage IV disease (57%) compared to current smokers (48%) and former smokers (48%). In all smoking history groups, the proportion of stage IV disease was higher from 2010, the year when the TNM-system was re-classified. However, the largest increase was observed in never-smokers (51% vs. 63%) compared to current smokers (46% vs. 51%) and former smokers (44% vs. 52%). From 2010 onwards, the proportion of stage IV patients diagnosed with the new TNM subcategory M1a (local metastases) was higher in never-smokers (39%) than in current smokers (27%) and former smokers (32%). Consequently, the proportion of M1b (distant metastases) was lower in never-smokers (61%) compared to current smokers (73%) and former smokers (68%).

From 2014 onwards, EGFR testing was recorded as performed in 71% of never-smokers, compared to 50% in current smokers, and 56% in former smokers (Table 1). The highest proportion of positive EGFR tests (in relation to both tested and non-tested) was observed in never-smokers (26%) compared to current smokers (2%) and former smokers (5%). Also, when only related to those tested, the highest proportion of positive EGFR tests was observed in never-smokers (37%) compared to current smokers (5%) and former smokers (9%).

Primary treatment

In patients with early-stage disease (I–II), the most common primary treatment was surgery (S2). In stage III NSCLC, combined radio-chemotherapy was the most common treatment in both current smokers and former smokers, while chemotherapy alone was the most common treatment in never-smokers. Regardless of smoking history, chemotherapy was

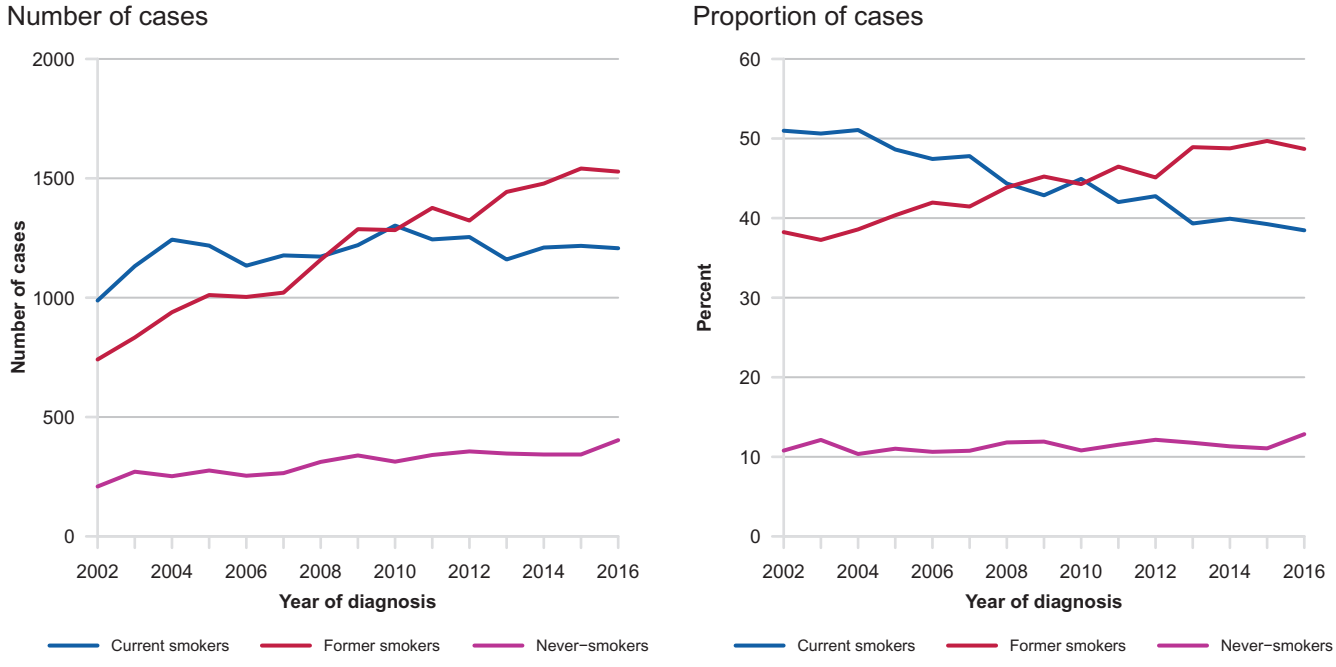

Figure 1. Number of cases and proportion of cases, by calendar year and smoking history.

the most common therapy in late-stage disease (IV). The proportion of patients without an assigned active treatment was similar in the different smoking history groups.

Survival

For all stages combined, the unadjusted cause-specific survival estimate at one year for never-smokers, current smokers and former smokers were 53%, 44% and 47%, respectively (Figure 2, Table 2). Similarly, the highest cause-specific survival at two and at five years post-diagnosis was observed in never-smokers. Unadjusted overall survival estimates were also higher in never-smokers compared to current smokers and former smokers (Table 2, S3).

In the adjusted Cox regression models, the risk of lung cancer-specific death during the first two years following diagnosis was consistently lower in never-smokers compared to current smokers (Table 3). A similar general overall pattern was observed for men and women separately, and also following the stratification by stage. The unadjusted HRs are presented in S4. The HRs for all-cause mortality followed a similar pattern as the HRs for cause-specific mortality (S5).

Discussion

Main findings

The findings of this large population-based study provide further evidence of differences between never-smokers and

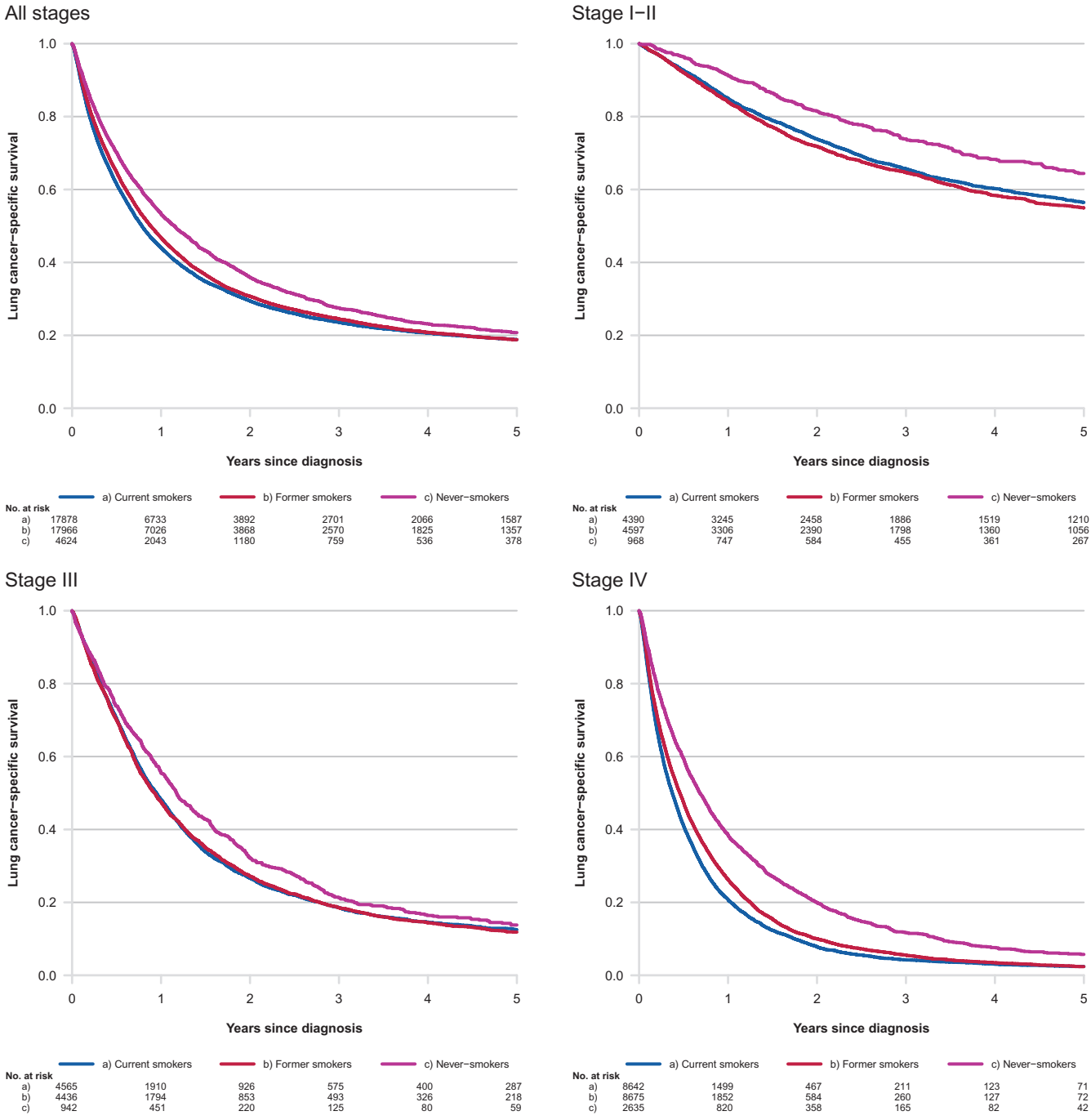

Figure 2. Lung cancer-specific survival, by stage and smoking history.

Table 2. Lung cancer-specific and overall survival, in percent, with 95% confidence limits.

	1-Year lung cancer-specific survival						2-Year lung cancer-specific survival						5-Year lung cancer-specific survival					
	Current smokers		Former smokers		Never-smokers		Current smokers		Former smokers		Never-smokers		Current smokers		Former smokers		Never-smokers	
Stage at diagnosis																		
All	44.0	(43.3–44.8)	46.8	(46.0–47.5)	53.2	(51.8–54.8)	29.4	(28.7–30.2)	30.7	(30.0–31.4)	35.9	(34.4–37.5)	18.8	(18.2–19.5)	18.8	(18.1–19.5)	20.7	(19.4–22.2)
I–II	85.0	(83.9–86.1)	84.0	(82.9–85.1)	91.3	(89.4–93.2)	73.8	(72.5–75.3)	71.9	(70.5–73.3)	81.5	(78.9–84.2)	56.4	(54.7–58.2)	54.9	(53.2–56.7)	64.4	(60.8–68.2)
III	48.2	(46.7–49.7)	47.5	(46.0–49.1)	55.5	(52.3–58.9)	26.7	(25.3–28.1)	27.2	(25.7–28.6)	32.2	(29.1–35.7)	12.5	(11.4–13.7)	11.9	(10.7–13.1)	13.8	(11.3–16.8)
IV	20.7	(19.9–21.7)	26.3	(25.3–27.3)	38.4	(36.4–40.4)	7.8	(7.2–8.5)	10.0	(9.3–10.7)	20.0	(18.3–21.8)	2.4	(2.0–2.9)	2.4	(2.0–2.9)	5.7	(4.6–7.1)
1-Year overall survival							2-Year overall survival						5-Year overall survival					
	Current smokers		Former smokers		Never-smokers		Current smokers		Former smokers		Never-smokers		Current smokers		Former smokers		Never-smokers	
Stage at diagnosis																		
All	40.7	(40.0–41.4)	43.1	(42.3–43.8)	48.9	(47.4–50.4)	25.8	(25.2–26.5)	26.8	(26.1–27.5)	31.5	(30.1–32.9)	14.6	(14.1–15.2)	14.4	(13.8–15.0)	16.4	(15.2–17.7)
I–II	80.8	(79.6–82.0)	80.0	(78.8–81.2)	87.5	(85.4–89.7)	67.3	(65.9–68.8)	65.2	(63.8–66.7)	75.3	(72.5–78.3)	45.5	(43.9–47.2)	43.8	(42.2–45.5)	55.6	(52.1–59.4)
III	44.4	(43.0–45.9)	43.7	(42.3–45.3)	50.4	(47.3–53.7)	23.3	(22.0–24.6)	23.5	(22.2–24.8)	27.9	(25.0–31.0)	9.9	(9.0–10.9)	9.1	(8.2–10.1)	10.5	(8.4–13.0)
IV	18.8	(18.0–19.7)	23.6	(22.7–24.6)	34.8	(32.9–36.7)	6.6	(6.1–7.2)	8.5	(7.9–9.1)	17.1	(15.7–18.7)	1.7	(1.4–2.1)	1.8	(1.4–2.2)	4.1	(3.2–5.2)

Non-small cell lung cancer (NSCLC) patients in Sweden diagnosed during 2002–2016.

ever smokers (current and former) diagnosed with NSCLC. The differences were apparent for the patient- and clinical characteristics, for management of the disease and survival. Also, the absolute number of cases of NSCLC occurring in never-smokers increased twofold during the period under study. Age at diagnosis and the proportion of women were higher among never-smokers, and adenocarcinoma and EGFR-mutations were proportionally more common. Even though, never-smokers were more often diagnosed with stage IV disease, the overall and lung cancer-specific survival were consistently higher.

Interpretation and comparison to other studies

Patient characteristics

The overrepresentation of women in this group is also confirmed [7–12,14–18,20–22,24,26], and supports the notion of the presence of sex-based differences either in vulnerability to non-tobacco associated lung cancer or in exposure to other risk factors, such as environmental tobacco smoke. Due to observed sex imbalances, there has been considerable interest surrounding the possible role of oestrogen [6,9,34,35]. Stimulation of oestrogen receptors has been shown to increase cell proliferation and cancer cell growth. In both men and women, oestrogen receptors are present in normal lung tissue and in tissue with lung cancer. The β-receptor is the predominant subtype and studies have reported that the oestrogen β-receptor is more common in lung cancer patients with no history of smoking than in current smokers. Among never-smokers with lung cancer, the β-receptor is more common in women than in men, which may imply that sex-hormones are involved in the development of lung cancer in never-smokers, but data on these findings are inconsistent [9,35].

In line with results from most previous studies [7,11,12,16,19,26], never-smokers were older at diagnosis compared to current smokers and former smokers. The observed higher proportion of both younger (<50 years) and older patients (≥80 years) among never-smoking has, to the best of our knowledge, never been observed before. However, there have also been reports of no differences in age and also the opposite, i.e., a younger age at diagnosis among never-smokers [7–10,14,15,17–22,26]. None of the studies reporting an older age for never-smokers included an East Asian population. Review articles have reported that never-smokers in Asian populations are younger at lung cancer diagnosis compared to ever-smokers, and vice versa in Western populations [7,36]. The higher proportion of never-smokers diagnosed after the age of 80 compared with smokers could be explained by a higher risk of death due to other causes in smokers. Thus, competing risks alter the probability of lung cancer at old ages. The higher proportion of younger patients among the never-smokers may reflect an influence of heredity, because a family history of lung cancer has been associated with an earlier onset of lung cancer [37–39].

Some 30–40% of the Swedish general population aged 25–74 years during the period under study had attained a high education (post-secondary school degree) [40]. The

Table 3. Adjusted hazard ratios (HR) with 95% confidence limits (95% CI) for the outcome lung cancer-specific mortality.

	Stage at diagnosis											
	I–II			III			IV			All stages combined (adjusted for stage)		
	HR[a]	(95% CI)	*p* Value	HR[a]	(95% CI)	*p* Value	HR[a]	(95% CI)	*p* Value	HR[a]	(95% CI)	*p* Value
Both sexes combined												
Current smokers	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–
Former smokers	0.95	(0.88–1.01)	.121	0.94	(0.89–0.99)	.012	0.90	(0.87–0.93)	<.001	0.92	(0.89–0.94)	<.001
Never-smokers	0.81	(0.71–0.93)	.002									
≤0.5 years since diagnosis				0.78	(0.67–0.90)	.001	0.65	(0.61–0.70)	<.001	0.67	(0.62–0.71)	<.001
>0.5, ≤1 years since diagnosis				0.70	(0.59–0.83)	<.001	0.69	(0.62–0.76)	<.001	0.71	(0.65–0.77)	<.001
>1, ≤2 years since diagnosis				0.88	(0.75–1.05)	.150	0.63	(0.56–0.71)	<.001	0.73	(0.67–0.80)	<.001
>2 years since diagnosis				1.01	(0.83–1.22)	.953	0.91	(0.77–1.06)	.218	0.92	(0.83–1.02)	.115
Men												
Current smokers	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–
Former smokers	0.94	(0.86–1.04)	.217	0.97	(0.91–1.04)	.395	0.87	(0.83–0.91)	<.001	0.91	(0.88–0.95)	<.001
Never-smokers	0.80	(0.64–1.01)	.063									
≤0.5 years since diagnosis				0.69	(0.53–0.90)	.006	0.65	(0.58–0.72)	<.001	0.66	(0.59–0.73)	<.001
>0.5, ≤1 years since diagnosis				0.56	(0.41–0.77)	<.001	0.59	(0.50–0.70)	<.001	0.59	(0.51–0.68)	<.001
>1, ≤2 years since diagnosis				0.86	(0.65–1.12)	.263	0.55	(0.45–0.67)	<.001	0.65	(0.56–0.75)	<.001
>2 years since diagnosis				1.16	(0.85–1.59)	.356	1.02	(0.79–1.32)	.854	1.03	(0.87–1.22)	.748
Women												
Current smokers	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–	1.00	(ref.)	–
Former smokers	0.94	(0.84–1.05)	.274	0.88	(0.82–0.96)	.002	0.93	(0.88–0.98)	.004	0.92	(0.89–0.96)	<.001
Never-smokers	0.84	(0.71–0.99)	.038									
≤0.5 years since diagnosis				0.83	(0.69–1.01)	.060	0.64	(0.58–0.70)	<.001	0.66	(0.61–0.72)	<.001
>0.5, ≤1 years since diagnosis				0.78	(0.63–0.97)	.024	0.79	(0.70–0.90)	<.001	0.81	(0.72–0.90)	<.001
>1, ≤2 years since diagnosis				0.91	(0.73–1.12)	.362	0.71	(0.61–0.82)	<.001	0.79	(0.70–0.88)	<.001
>2 years since diagnosis				0.92	(0.72–1.18)	.509	0.87	(0.71–1.07)	.186	0.86	(0.75–0.98)	.021

Non-small cell lung cancer (NSCLC) patients in Sweden diagnosed during 2002–2016. An interaction between smoking status and time since diagnosis was included in the model if tests indicated non-proportional hazards.

[a]Adjusted for sex (in models with both sexes combined), age, histopathology, WHO performance status, treatment, Charlson Comorbidity Index and education level.

proportion with a high educational level among those younger than 50 years in the general population ranged between 35% and 46%, 29–36% for individuals aged 50–59 years, 20–33% for those 60–69 years and 14–27% for those 70–74 years. Considering the higher age range for lung cancer patients, never-smokers were in level with those in the two higher age groups of the general population while current smokers had a lower proportion with a high educational level compared to the general population.

Occurrence

In accordance with the findings in this study, previous studies from Europe and the United States of America found that around 10% of all lung cancers occur in never-smokers [7,8,26]. The corresponding proportion in Asian populations has been reported to be between 30% and 40% [7,18,26]. A higher occurrence of non-tobacco smoking risk factors (e.g., air pollution, occupational exposure and genetic factors) in Asian countries compared to Western countries is often proposed as an important reason for the higher proportion of never-smokers with lung cancer [36].

Tumour characteristics

The present study confirms the findings from previous studies that adenocarcinoma and EGFR-mutations are overrepresented among lung cancer patients without a history of smoking [6,7,9,11,14–22,24–26,41–43]. To the best of our knowledge, this was the first nationwide Nordic population-based study finding a higher proportion of EGFR-mutations in never-smokers compared to ever smokers.

It remains unclear if smoking history is associated with tumour stage at diagnosis [7,9,10,12,15–18,20,21]. In this study, stage IV was more common in never-smokers than in ever smokers. In a study from Portugal, it was observed that the time from onset of symptoms to a medical appointment was longer in never-smokers than in ever-smokers (3 vs. 2 months), possibly explaining a higher proportion of stage IV patients in never-smokers [20]. However, there was no difference in the prevalence of symptoms between the smoking groups. A higher proportion of stage IV patients in never-smokers could also reflect a lower awareness and delayed diagnosis in nonsmokers among both the patients and health care providers [16]. It may also reflect an effect of the re-classification of the TNM-system in 2010. The proportion of stage IV patients diagnosed from 2010 with non-distant metastases (M1a) was higher in never-smokers compared to smokers, and consequently, distant metastases (M1b) were more common in smokers [44]. Before 2010, patients with pleural effusion (included in non-distant metastasis) were classified as stage IIIB disease, possibly explaining the difference in the proportion of stage IV NSCLC compared to a study by Clement-Duchene et al. which only included data on patients diagnosed prior to re-classification [16]. However, a study by Toh et al. from 2006 also observed a higher proportion of never-smokers with stage IV compared to ever smokers [15].

Primary treatment

As expected, and in accordance with current Swedish and international guidelines [45,46], surgery was the treatment of

choice in early-stage disease, while combined radio-chemotherapy and chemotherapies were more common in more advanced disease. However, a relative overrepresentation of chemotherapy in never-smokers with stage III disease was a surprise finding, possibly reflecting that pleural effusions, categorised as stage III disease before 2010, was more common in never-smokers. According to current recommendations, patients with pleural effusions should be treated with chemotherapy, similar to stage IV patients. The finding of a lower comorbidity burden in never-smokers was expected and confirmed results from previous studies [47,48].

Survival

At one year and two years post-diagnosis, both cause-specific survival and overall survival were higher in never-smokers than in ever smokers. This pattern was observed overall and for all stages. At five years, there were no survival differences in all stages combined, and in stage III disease. Higher survival in never-smokers, both cause-specific and overall, remained in stages I–II and IV disease. These findings of higher unadjusted survival in never-smokers confirm results from previous studies conducted in different populations and settings [10–12,15,17,22,26]. The lower adjusted hazards for never-smokers also confirms the findings of previous studies [11,15,17,26]. In general, studies that failed to estimate a significant difference in survival between the groups had a smaller study population [18,21].

There are several possible explanations for the difference in prognosis between never-smokers and patients with a history of smoking.

A high burden of comorbidity has been found to negatively affect the prognosis in patients with NSCLC [23]. Thus, a lower comorbidity burden in never-smokers is likely to play a role, either directly or mediated by a lower treatment intensity in frail patients with many coexisting conditions [49]. Differences in tumour characteristics and biology between smokers and never-smokers could also explain observed differences in survival. While stage IV disease overall was more common among never-smokers, the proportion of stage IV disease with distant metastases was lower in non-smoking patients compared to smokers. Also, a notable discrepancy in tumour biology is a higher rate of EGFR-mutation in never-smokers, a difference that may explain the better prognosis in never-smokers following treatment with therapies targeting the EGFR-gene [50]. Mutations in the TP53-gene represent another possible reason for differences in survival. TP53-mutations have been associated with a worse prognosis, and are less common in never-smokers [51,52]. A meta-analysis including 19 studies with a total of 1406 NSCLC patients with a TP53-mutation and 1965 patients without a TP53-mutation estimated a 26% higher overall survival for those lacking the mutation [52].

Strengths and limitations

Strengths of the present study include its large study population and the population-based study design. Further, the use of population-based registers with high coverage and high validity minimises the risk of selection bias and misclassification bias.

One weakness was that smoking history was self-reported, by the patient to the physician, possibly resulting in misclassification in various ways; the patient's self-report is incorrect or that the physician is entering incorrect information in the medical record or when reporting to the register. A systematic review of the association between self-reported and cotinine-assessed (the predominant metabolite of nicotine) smoking status concluded that self-reported status tends to underestimate the true smoking prevalence [53]. A Swedish study assessed the concordance between self-reported smoking status and cotinine levels in plasma and carbon monoxide level in expiration air in patients with ischaemic heart disease who reported that they were former smokers. Less than 10% of the former smokers were considered to be current smokers. Therefore, the results of this study may have underestimated the true association (i.e., survival in never-smokers is higher than what was estimated). A potential limitation is that lung cancer is incorrectly registered as the cause of death on the death certificates despite no evidence of disease progression or relapse. This may result in lower estimated lung cancer-specific survival compared to the true survival. However, the consistency between the death certificate and relevant case information in medical records has been estimated to be over 90% for malignant tumours in the CDR [31]. Other limitations include the absence of information on exposure to environmental tobacco smoke, and occupational exposures, which are difficult to quantify.

Conclusions

The observed differences in clinical characteristics in EGFR-mutation, cancer stage, age and sex distribution, and histopathology between never-smokers and smokers, and the higher survival in never-smokers from this large nationwide population-based study provide further evidence that lung cancer in never-smokers is clinically different from tobacco-associated lung cancer. The findings from this study emphasise the need for an improved understanding of genetics, pathogenesis, mechanisms and progression of non-tobacco associated lung cancer that may help prevent lung cancer or identify individually targeted treatments.

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