ORIGINAL ARTICLE

Incidence of second and higher order smoking-related primary cancers following lung cancer: a population-based cohort study

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ABSTRACT

Background Lung cancer 5-year survival has doubled over 15 years. Although the risk of second primary cancer is recognised, quantification over time is lacking. We describe the incidence of second and higher order smoking-related primary cancers in lung cancer survivors, identifying high-incidence groups and how incidence changes over time from first diagnosis.

Methods Data on smoking-related primary cancers (lung, laryngeal, head and neck, oesophageal squamous cell carcinoma and bladder) diagnosed in England between 2000 and 2014 were obtained from Public Health England National Cancer Registration and Analysis Service. We calculated absolute incidence rates and standardised incidence rate ratios, both overall and for various subgroups of second primary cancer for up to 10 years from the initial diagnosis of lung cancer, using Poisson regression.

Results Elevated incidence of smoking-related second primary cancer persists for at least 10 years from first lung cancer diagnosis with those aged 50 and 79 at first diagnosis at particularly high risk. The most frequent type of second malignancy was lung cancer although the highest standardised incidence rate ratios were for oesophageal squamous cell carcinoma (2.4) and laryngeal cancers (2.8) and consistently higher in women than in men. Over the last decade, the incidence of second primary lung cancer has doubled.

Conclusion Lung cancer survivors have increased the incidence of subsequent lung, laryngeal, head and neck and oesophageal squamous cell carcinoma for at least a decade from the first diagnosis. Consideration should be given to increasing routine follow-up from 5 years to 10 years for those at highest risk, alongside surveillance for other smoking-related cancers.

Key messages

What is the key question?
► What are the age and sex-specific absolute and relative risks of developing smoking-related second and higher order primary cancers following lung cancer?

What is the bottom line?
► Our population-based approach shows that lung cancer survivors, particularly women, have increased the incidence of smoking-related primary cancers for at least a decade from the time of their first primary lung cancer diagnosis, with those aged 50–79 at first diagnosis at particularly high risk.

Why read on?
► With improving lung cancer survival rates consideration should be given to extending lung cancer follow-up from 5 years to 10 years and to undertaking surveillance for other smoking-related cancers including head and neck, laryngeal and oesophageal squamous cell carcinoma.

risk and evaluate how incidence changes over time following diagnosis. We have focused on cancers of the lung, larynx, head and neck, oesophagus (squamous cell carcinoma) and urinary bladder as these cancers have the largest proportion of deaths attributable to cigarette smoking.[7] We assessed the incidence of developing an SPC at different time points after initial diagnosis to inform clinicians about optimal follow-up periods and surveillance regimens after lung cancer treatment with curative intent.

METHODS
Smoking-related primary cancers
Data from the National Cancer Registration and Analysis Service of Public Health England (the organisation responsible for cancer registration in England) provided information on first, second and higher order smoking-related primary cancers diagnosed in English residents aged 30–99 between 1 January 2000 and 31 December 2014. This included all diagnoses of the lung (ICD-10, C33–C34), bladder (C67), oesophageal squamous cell

INTRODUCTION
Five-year survival of patients with lung cancer has doubled in England during the past 15 years leading to increasing numbers of survivors.[1,2] Lung cancer survivors are thought to be at an increased risk of second primary cancer (SPC).[3–6] However, neither the way in which incidence of subsequent malignancy changes during follow-up nor patient characteristics associated with increased risk of SPC are well understood. We have estimated the incidence of smoking-related second and higher order primary cancers following a primary diagnosis of lung cancer to determine which groups are at higher

carcinoma (OSCC) (C15, morphology codes 8070–8074, 8094, 8123, 8560), laryngeal (C32) and head and neck cancers (C00–C14, C31). The cancer registry captures at least 98% of primary cancer diagnoses in England[8] and records multiple primary cancers following International Agency for Research on Cancer and European Network of Cancer Registries' rules.[9] Cases classified as recurrence of first primary lung cancer were excluded. Data were available on tumour type (site, morphology), month of diagnosis as well as patient information including age at diagnosis, sex, income deprivation quintile and vital status (whether a patient was alive, dead or lost to follow-up).[10] Lung cancers were divided into small cell lung cancer (SCLC) and non-SCLC (NSCLC), and NSCLC was split into adenocarcinoma, squamous cell carcinoma, other NSCLC, carcinoid and unspecified lung (online supplementary appendix 1 table 1).

Estimating expected incidence of smoking-related primary cancers

To evaluate whether lung cancer survivors were at an increased risk of SPC compared with those with no diagnosis of lung cancer, we estimated the number of cancers we would expect in people without lung cancer (online supplementary appendix 2 figure 2). We obtained midyear population estimates for England from 2000 to 2014 from the Office for National Statistics and matched these with first primary cancers in our dataset to calculate the expected age-sex-year-specific incidence rates.[11] We matched these rates with person-years of follow-up in the cancer registry dataset stratified by sex, attained age and attained year. We multiplied the person-years of follow-up by the expected age-sex-year-specific incidence rates to calculate the number of expected cancers. We compared the number of observed and expected cancers to calculate standardised incidence rate ratios (SIRs).

Statistical analysis
Analysis cohort
After restriction (online supplementary appendix 2 figure 1), the analysis cohort included 490 328 patients with first primary lung cancer. Most patients (489 740, 99.9%) had complete survival follow-up to death or censoring at 31 December 2014. Follow-up for the remaining 588 patients was censored on the day they were last known to be alive.

Our analyses exclude primary cancers diagnosed within 6 months of the first primary cancer as such tumours were deemed likely to represent 'synchronous' diagnoses.

Descriptive analysis
We described absolute incidence rates and SIRs for the cohort from 6 months to 10 years follow-up, including by sex, age at diagnosis and deprivation group, as well as by the site of the SPC. We provide a brief summary of the incidence of subsequent smoking-related SPC up to 10 years from diagnosis for those diagnosed in 2000–2004, with complete follow-up, as other descriptive results may be affected by variable follow-up periods.

The choice to limit at 10 years follow-up was informed by the results of Kaplan-Meier survival analyses, presented in online supplementary appendix 4 figure 1.

Describing how risk changes over follow-up
We investigated how absolute incidence rates (second and higher order primary cancers diagnosed per 100 000 patient-years) and SIRs changed during follow-up. We plotted age-sex-specific incidence rate and SIR against months of follow-up and modelled

how the incidence rate or SIR changed over time using Poisson models with patient-years (incidence rate) or expected cancers (SIR) as exposure. We modelled elapsed follow-up time using restricted cubic splines allowing us to avoid the disadvantages of categorisation while providing for potentially non-linear associations between elapsed follow-up and SPC risk.[12 13] Exploratory modelling guided the choice and number of knots and the interaction terms used in the model. The final models included pairwise interactions between age and follow-up, sex and follow-up, and age and sex, and parameterised follow-up using splines with knots at 6, 12, 60 and 120 months. Further interaction terms were not included as they decreased model fit measured using the Akaike information criterion.[14] We used the same approach to evaluate changes in SIR over follow-up by the site of SPC and by the morphology of first primary lung cancer, removing age at diagnosis and sex from the model. Results were not sensitive to the exact knot locations (online supplementary appendix 3 figure 1).

Describing how risk changes by year of first primary lung cancer diagnosis

We extended our initial approach to evaluate how the risk of SPC changed during different study periods, limiting observations to 6–60 months of follow-up. Based on exploratory analyses, we split SPC into second primary lung cancers and other smoking-related primary cancers. We initially described the observed changes in absolute risk of second primary lung and other smoking-related primary cancers in patients diagnosed with first primary lung cancer in 2005–2009 and 2010–2014 compared with 2000–2004. We then used the Akaike information criterion to select an adjusted model,[14] considering patient age, sex, deprivation and elapsed follow-up (modelled as above using restricted cubic splines with knots at 6, 12 and 60 months follow-up) and all two-way interactions. This provided a check that apparent differences were not explained by changes in patient casemix or improvements in survival.

RESULTS
Description of analysis cohort
Between 2000 and 2014, 490 328 patients were diagnosed with first primary lung cancer (table 1). We have a priori focused on the 213 245 patients (43%) surviving 6 months after diagnosis, contributing 335 436 patient-years of follow-up (table 1; online supplementary appendix 4 figure 1). The median follow-up was 10 months per patient (IQR 4–28 months). Despite low survival rates, 4710 patients diagnosed in 2004 or before were still alive at 10 years follow-up (table 1). Survival rates were higher for women than men and for younger than older patients (online supplementary appendix 4 figure 1). Lung cancer was more common in patients from more deprived areas and more deprived patients had worse survival.

Around 1.1% (2328 of 213 245) of patients alive at 6 months had SPCs during follow-up, some of whom had higher order (ie, third or fourth) primary cancers as well. Restricting to patients diagnosed in 2000–2004 who survived to 6 months and have 10 years complete follow-up gives similar results.

Overall incidence of second and higher order primary cancers
Over the entire length of follow-up, SIRs for second and higher order primary cancer were highest for those aged 30–49 (SIR 3.4, 95% CI 2.6 to 4.4) or 50–59 at diagnosis (SIR 2.7, 2.5 to 3.1), for women (SIR 2.0, 1.9 to 2.1) and for the most deprived patients (SIR 1.8, 1.7 to 2.0) (table 2). Patients whose first primary lung

Table 1 Number of patients alive and in follow-up at the start of interval and absolute incidence rate within interval periods within the first 10 years after diagnosis with first primary lung cancer, by patient and tumour characteristics. The period 'diagnosis to 6 months' was discarded from all other analyses

		Diagnosis to 6 months			6–12 months			1–5 years			5–10 years			10 years
			Absolute incidence rate per 100 000			Absolute incidence rate per 100 000			Absolute incidence rate per 100000			Absolute incidence rate per 100 000		
		Patients	Estimate	(95% CI)	Patients	Estimate	(95% CI)	Patients	Estimate	(95% CI)	Patients	Estimate	(95% CI)	Patients
Overall		490328	1338	(1276 to 1402)	213245	399	(358 to 443)	128128	683	(647 to 720)	19280	1184	(1093 to 1280)	4710
Subsite of first primary cancer	Small cell carcinoma	57179	534	(427 to 660)	26896	213	(133 to 322)	13224	495	(388 to 622)	1275	995	(697 to 1378)	335
	Adenocarcinoma	100395	1461	(1330 to 1601)	55363	422	(342 to 514)	36524	738	(672 to 809)	6063	1275	(1106 to 1461)	1394
	Squamous cell carcinoma	97253	1672	(1532 to 1822)	56077	552	(461 to 656)	35960	864	(790 to 943)	6120	1398	(1227 to 1586)	1568
	Other non-small cell lung cancer	75505	1226	(1083 to 1382)	35004	295	(212 to 400)	20008	590	(505 to 686)	2826	1310	(1062 to 1598)	592
	Carcinoid	3422	1930	(1260 to 2827)	3074	539	(233 to 1061)	2834	146	(75 to 255)	1368	253	(126 to 453)	484
	Unspecified lung	156574	1341	(1212 to 1479)	36831	332	(244 to 441)	19578	515	(428 to 614)	1628	853	(594 to 1187)	337
Age at diagnosis	30–49	13890	925	(667 to 1251)	8500	452	(258 to 733)	5484	262	(172 to 381)	1429	340	(194 to 551)	541
	50–59	51944	1075	(921 to 1247)	28981	283	(196 to 396)	18168	579	(497 to 670)	3728	1006	(832 to 1206)	1203
	60–69	125462	1412	(1293 to 1538)	64156	404	(331 to 488)	40145	746	(681 to 816)	6898	1396	(1234 to 1574)	1756
	70–79	173884	1552	(1440 to 1670)	73690	426	(355 to 506)	44198	766	(701 to 836)	5934	1339	(1160 to 1538)	1108
	80–99	125148	1104	(983 to 1234)	37918	418	(320 to 537)	20133	596	(502 to 703)	1291	1037	(671 to 1530)	102
Sex	Male	278006	1540	(1452 to 1633)	117308	460	(401 to 526)	68811	806	(752 to 863)	9814	1316	(1183 to 1460)	2437
	Female	212322	1081	(998 to 1169)	95937	325	(271 to 387)	59317	549	(503 to 599)	9466	1045	(924 to 1177)	2273
Deprivation quintile	1-least deprived	68084	1335	(1175 to 1512)	31084	378	(279 to 502)	19002	601	(516 to 695)	3017	1033	(828 to 1273)	777
	2	85982	1266	(1126 to 1419)	38313	362	(273 to 469)	22840	639	(558 to 729)	3426	1195	(983 to 1440)	859
	3	98660	1372	(1234 to 1520)	42644	451	(356 to 562)	25703	649	(572 to 734)	3867	1211	(1011 to 1438)	947
	4	111788	1363	(1234 to 1503)	47560	354	(275 to 448)	28445	685	(609 to 768)	4239	1074	(894 to 1280)	1024
	5-most deprived	125814	1339	(1218 to 1470)	53644	437	(353 to 534)	32138	790	(713 to 874)	4731	1354	(1159 to 1572)	1103
Year of diagnosis	2000	31289	750	(573 to 966)	12610	258	(137 to 441)	7335	432	(324 to 565)	1615	857	(640 to 1124)	918
	2001	30924	743	(566 to 959)	12567	316	(181 to 513)	7371	714	(573 to 880)	1632	977	(746 to 1258)	911
	2002	29999	885	(689 to 1121)	12386	301	(169 to 497)	7332	511	(392 to 656)	1591	1008	(771 to 1294)	899
	2003	30071	670	(501 to 879)	12352	477	(306 to 710)	7484	519	(402 to 661)	1749	899	(684 to 1159)	981
	2004	30543	971	(767 to 1211)	12957	342	(202 to 540)	7859	497	(384 to 632)	1763	1506	(1225 to 1832)	1001
	2005	30850	1124	(906 to 1379)	13244	258	(141 to 433)	8126	546	(430 to 683)	1867	1438	(1160 to 1761)	–
	2006	32075	857	(672 to 1077)	13841	389	(244 to 589)	8468	671	(544 to 819)	1940	1371	(1080 to 1716)	–
	2007	32236	1207	(987 to 1461)	14332	426	(275 to 628)	8831	700	(575 to 845)	2152	1122	(840 to 1468)	–
	2008	32994	1466	(1225 to 1739)	14837	311	(187 to 486)	9270	662	(543 to 798)	2290	1496	(1103 to 1984)	–
	2009	33244	1160	(951 to 1402)	15509	297	(179 to 463)	9877	853	(726 to 997)	2681	1570	(984 to 2377)	–
	2010	33772	1754	(1497 to 2043)	15900	271	(161 to 428)	10340	771	(649 to 909)	–	–		–
	2011	34651	1710	(1460 to 1989)	16802	454	(310 to 640)	11070	803	(672 to 953)	–	–		–
	2012	35838	2277	(1995 to 2587)	18068	612	(450 to 814)	12276	962	(802 to 1145)	–	–		–
	2013	35900	1771	(1524 to 2046)	18351	617	(455 to 818)	12489	843	(621 to 1117)	–	–		–
	2014	35942	2150	(1848 to 2488)	9489	602	(337 to 994)	–			–	–		–

Table 2 Observed and expected second and higher order primary cancers over the entire 335 436 patient-years of follow-up from 6 months after diagnosis to 10 years follow-up or the 31 December 2014, overall, by subsite of first primary lung cancer and by patient characteristics. Italics denotes the lung sub-sites

		Observed SPCs	Expected SPCs	Absolute incidence rate per 100 000 person-years		Standardised incidence rate ratio	
				Estimate	(95% CI)	Estimate	(95% CI)
Overall		2313	1491.9	689.6	(661.7 to 718.2)	1.55	(1.49 to 1.61)
Subsite of first primary lung cancer	Small cell carcinoma	131	109.0	455.3	(380.7 to 540.2)	1.20	(1.00 to 1.43)
	Adenocarcinoma	759	407.0	752.4	(699.8 to 807.9)	1.86	(1.73 to 2.00)
	Squamous cell carcinoma (SCC)	873	497.9	882.8	(825.2 to 943.3)	1.75	(1.64 to 1.87)
	Other NSCLC	312	223.0	619.4	(552.6 to 692.1)	1.40	(1.25 to 1.56)
	Carcinoid	31	41.7	219.4	(149.1 to 311.4)	0.74	(0.51 to 1.06)
	Unspecified lung	207	213.2	488.3	(424.0 to 559.5)	0.97	(0.84 to 1.11)
Site of SPC	Lung	1460	993.8	435.3	(413.2 to 458.2)	1.47	(1.39 to 1.55)
	Small cell carcinoma	142	94.3	42.3	(35.7 to 49.9)	1.51	(1.27 to 1.78)
	NSCLC	1318	899.5	392.9	(372.0 to 414.7)	1.47	(1.39 to 1.55)
	Adenocarcinoma	485	187.8	144.6	(132.0 to 158.0)	2.58	(2.36 to 2.82)
	Squamous cell carcinoma	400	190.9	119.2	(107.8 to 131.5)	2.10	(1.90 to 2.31)
	Other NSCLC	216	143.5	64.4	(56.1 to 73.6)	1.51	(1.31 to 1.72)
	Carcinoid	13	4.4	3.9	(2.1 to 6.6)	2.98	(1.59 to 5.10)
	Unspecified lung	204	372.9	60.8	(52.8 to 69.8)	0.55	(0.47 to 0.63)
	Bladder	397	299.9	118.4	(107.0 to 130.6)	1.32	(1.20 to 1.46)
	Oesophageal SCC	124	52.1	37.0	(30.7 to 44.1)	2.38	(1.98 to 2.84)
	Laryngeal	122	43.5	36.4	(30.2 to 43.4)	2.81	(2.33 to 3.35)
	Head and neck	210	102.6	62.6	(54.4 to 71.7)	2.05	(1.78 to 2.34)
Age at diagnosis	30–49	59	17.5	316.1	(240.6 to 407.8)	3.38	(2.57 to 4.35)
	50–59	332	121.0	608.3	(544.6 to 677.3)	2.74	(2.46 to 3.05)
	60–69	862	428.0	779.0	(727.8 to 832.7)	2.01	(1.88 to 2.15)
	70–79	833	658.9	751.4	(701.2 to 804.2)	1.26	(1.18 to 1.35)
	80–99	227	266.4	558.1	(487.9 to 635.6)	0.85	(0.74 to 0.97)
Sex	Male	1398	1030.7	792.7	(751.7 to 835.4)	1.36	(1.29 to 1.43)
	Female	915	461.1	575.2	(538.5 to 613.7)	1.98	(1.86 to 2.12)
Deprivation quintile	1-least deprived	315	234.4	616.1	(549.9 to 688.0)	1.34	(1.20 to 1.50)
	2	391	273.5	653.7	(590.5 to 721.8)	1.43	(1.29 to 1.58)
	3	464	303.2	688.4	(627.2 to 754.0)	1.53	(1.39 to 1.68)
	4	492	325.1	663.9	(606.5 to 725.2)	1.51	(1.38 to 1.65)
	5 - most deprived	651	355.6	784.5	(725.4 to 847.2)	1.83	(1.69 to 1.98)
Period of first diagnosis	2000–2004	762	535.8	633.3	(589.2 to 680.0)	1.42	(1.32 to 1.53)
	2005–2009	941	575.2	724.6	(679.1 to 772.5)	1.64	(1.53 to 1.74)
	2010–2014	610	380.9	715.4	(659.8 to 774.5)	1.60	(1.48 to 1.73)
Elapsed follow-up time	6–12 months	390	450.9	401.4	(362.5 to 443.3)	0.87	(0.78 to 0.96)
	1–5 years	1302	804.8	698.9	(661.4 to 737.9)	1.62	(1.53 to 1.71)
	5–10 years	621	236.2	1194.9	(1102.7 to 1292.6)	2.63	(2.43 to 2.84)

cancer was adenocarcinoma (SIR 1.9, 1.7 to 2.0) or squamous cell carcinoma (SIR 1.8, 1.6 to 1.9) were at highest risk of SPC, while those with carcinoid tumours were not at increased risk (SIR 0.7, 0.5 to 1.1) (table 2; online supplementary appendix 4 figure 4).

The most common smoking-related second SPC in this cohort was NSCLC, with 1318 SPCs (table 2), primarily adenocarcinoma (485 SPCs) or squamous cell carcinoma (400 SPCs). Bladder cancers were next most common (397

SPCs) followed by head and neck cancers (210 SPCs). However, there were many more laryngeal cancers (SIR 2.8, 95% CI 2.3 to 3.4 and OSCC, SIR 2.4, 95% CI 2.0 to 2.8) than would be expected given incidence rates in the general population, although absolute numbers of these rarer cancers remained small (122 laryngeal and 124 OSCC). Additional results on risk by the site of SPC and by histological type of first primary lung cancer are shown in online supplementary appendix 4.
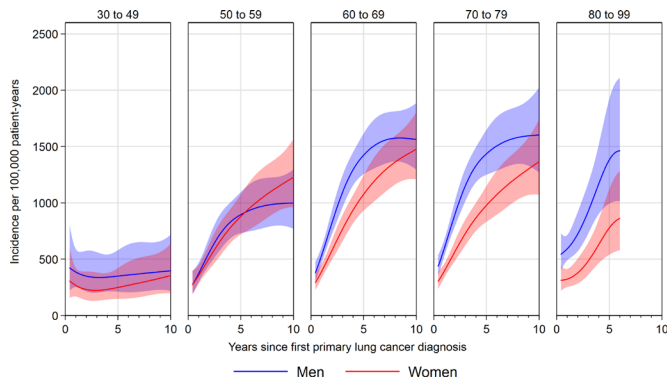
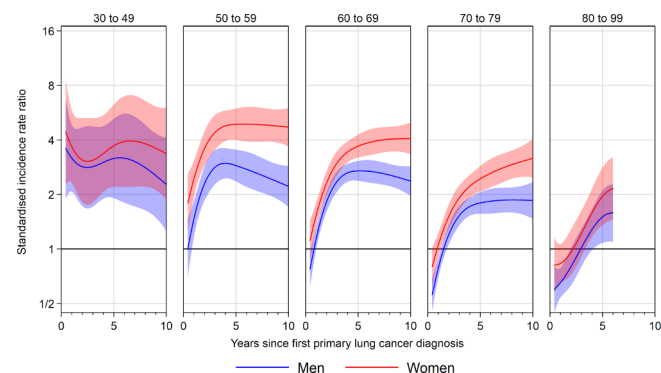**Figure 1** Absolute incidence of second and higher order smoking-related primary cancers after lung diagnosis up to 10 years follow-up, by sex and age group.

Variation in SPC incidence rates over follow-up

Absolute incidence rate

For patients aged 50–59, 60–69 or 70–79 at first cancer diagnosis, absolute incidence of SPC increased sharply from 6 to 36 months follow-up, and then increased more slowly or remained stable up to 10 years after first cancer (figure 1; online supplementary appendix 4 table 1). For example, at 1 year after first primary in men aged 50–59, incidence of SPC was 373 per 100 000 patient-years (95% CI 298 to 468), rising to 718 (578 to 892) at 3 years and 895 (731 to 1096) at 5 years, with the rate at 10 years being 999 (770 to 1296). For younger patients, aged 30–49 at first cancer, incidence rates remained relatively low throughout follow-up. For those aged 80–99, small sample size prevents meaningful long-term examination of SPC risk. In contrast to incidence in the general population, absolute incidence was relatively similar for men and women with NSCLC in most age groups (figure 1).

Standardised incidence rate ratio

Patients aged 50–59, 60–69 and 70–79 at first lung cancer diagnosis had a higher-than-expected incidence of smoking-related SPCs from 3 to at least 10 years follow-up, when compared with the general population without lung cancer (figure 2; online supplementary appendix 4 table 1). Similar to absolute incidence rates, SIRs increased rapidly from 6 months to 3 years follow-up, but then remained stable or slightly decreased as

Figure 2 Standardised incidence rate ratios for second and higher order smoking-related primary cancers after lung diagnosis up to 10 years follow-up, by sex and age group. Results for the 30–49 age group are imprecise due to the small number of cancers expected in this group.
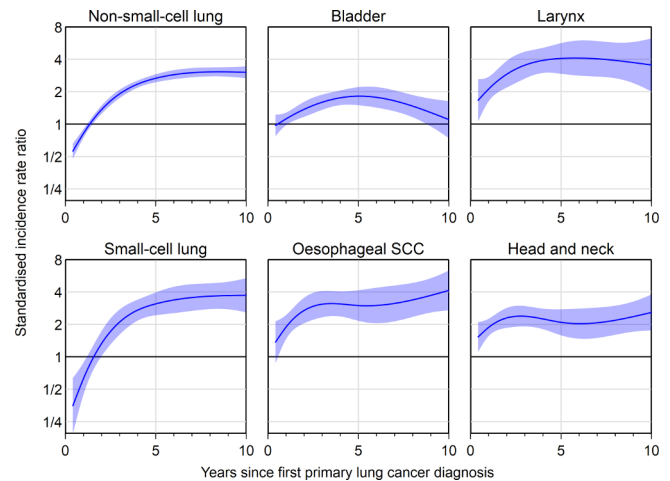

Figure 3 Standardised incidence rate ratios for second and higher order smoking-related primary cancers after lung diagnosis up to 10 years follow-up, by site of second primary cancer. SCC, squamous cell carcinoma.

follow-up continued. For example, the SIR for SPC in men diagnosed with first primary lung cancer aged 50–59 was 1.5 (95% CI 1.2 to 1.8) at 1-year follow-up, increasing to 2.8 (2.3 to 3.5) at 3 years. From 3 years, the SIR decreased slightly but remained higher than the risk in the general population over the entire follow-up (eg, SIR 2.9 at 5 years, 2.6 at 7 years, 2.2 at 10 years, online supplementary appendix 4 table 1). Results for those aged 30–49 were highly variable due to the smaller number of cancers than expected in this group, and similarly to the absolute results, meaningful estimation of long-term SPC risk was not possible for those aged 80–99.

Of note, women had higher SIR for smoking-related SPC than men, with SIR for women aged 60–69 at diagnosis being 3.7 (95% CI 3.2 to 4.3) at 5 years follow-up compared with 2.7 (2.4 to 3.1) for men (figure 2). Similar differences were seen in other age groups.

Analysis of different cancer sites revealed that they followed one of three patterns. SIRs for second primary NSCLC and SCLC followed the same pattern as the overall SIRs, beginning with reduced risk but increasing over time (figure 3). SIRs for second primary OSCC, laryngeal cancer and head and neck cancer were elevated across the entire period of follow-up. SIRs for second primary bladder cancer were similar to the general population at the start and end of follow-up, appearing to peak at around 5 years from first primary lung cancer diagnosis, with an SIR at 5 years of 1.8 (95% CI 1.5 to 2.2) (figure 3).

Trends in incidence by year of first primary lung cancer diagnosis

Patients with more recent first primary lung cancers had higher rates of second primary lung cancers. The incidence rate among patients first diagnosed with lung cancer in 2010–2014 was 715 per 100 000 patient-years (95% CI 660 to 775, table 2), higher than among those first diagnosed in 2000–2004 (633, 589 to 680). Given differences in elapsed follow-up, we would have anticipated higher incidence rates among those diagnosed in earlier periods. A more detailed examination, limiting to data between 6 months and 5 years from diagnosis, showed that patients with first primary lung cancer diagnosed in 2010–2014 had double the rate of second primary lung cancers compared with those with first primary diagnosis in 2000–2004 (figure 4A) even though most patients diagnosed in 2010–2014 had not
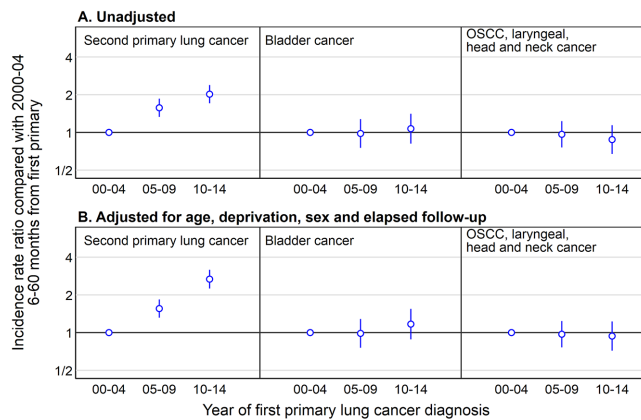
Figure 4 Incidence rate ratio for incidence of second primary cancers between 6 and 60 months after first primary lung cancer diagnosis in patients diagnosed with first primary lung cancer in 2005–2009 and 2010–2014 compared with 2000–2004, split into lung cancer, bladder cancer and OSCC, laryngeal, head and neck cancer. Note that most patients diagnosed in 2010–2014 have less than 5 years follow-up in our analysis dataset. OSCC, oesophageal squamous cell carcinomas.

reached 5 years follow-up. In contrast, rates of other smoking-related SPCs remained stable between 2000 and 2014 (figure 4A). Adjusting for patient age, sex, deprivation and elapsed follow-up did not meaningfully change these results (figure 4B).

DISCUSSION

There is strong evidence that elevated incidence of second and higher order primary cancers prevails for at least 10 years from first lung cancer diagnosis for patients aged 50–59, 60–69 and 70–79 at first cancer diagnosis. Oesophageal squamous and laryngeal cancers are associated with the greatest excess incidence in lung cancer survivors, although the most frequent type of subsequent malignancy is another lung cancer. We have also identified that the incidence of second primary lung cancer has doubled between 2000–2004 and 2010–2014.

Some recent studies have reported an increased risk of SPC after lung cancer compared with the general population.[3–6 15–18] One large cohort study in the USA found the incidence of second primary lung cancer was 1% per patient-year,[18] with higher SIRs for women and for younger patients, but did not explore changes in incidence over follow-up from the first primary cancer diagnosis. The majority of other studies had relatively small samples of patients with lung cancer,[4 5 15 16] preventing detailed analysis of incidence by patient characteristics or site of SPC. Other work focuses on describing factors associated with higher risk or incidence of SPC among patients with lung cancer.[19–21] These show that risk varies by patient demographics and behaviour and are similar, if not more important, than tumour factors. These studies are broadly in agreement with our results that incidence is highest in patients aged between 50 and 79 at first lung cancer diagnosis with relatively small differences between the main histological subtypes of lung cancer.[19] They confirm that continued smoking is associated with higher risk of SPC and adverse outcomes,[22] with smoking cessation reducing the incidence of SPC among lung cancer survivors.[20]

Our observation that the incidence rate of SPC is lower in the first 2 years of follow-up may be explained by the fact that many tumours, which would have been diagnosed during this period, were diagnosed during initial investigation for lung cancer and were excluded from analysis because we a priori excluded subsequent registrations within the first 6 months from diagnosis of an index smoking-related cancer. The second possibility is that patients with an SPC diagnosed early in follow-up may have been mislabelled as a recurrence of the first primary cancer by their treating clinicians rather than as a true SPC. This is a particularly plausible explanation given that the risk of non-lung SPCs was not reduced at the beginning of follow-up.

Major strengths of our study are its large sample size and population-based nature including all English residents diagnosed with first primary lung cancer between 2000 and 2014. This has allowed us to estimate age-specific and sex-specific incidence for several strata and given sufficient numbers of cancer survivors for meaningful estimation of incidence rates even 10 years after the first lung cancer diagnosis. The flexible parameterisation of follow-up time avoids arbitrary categorisation (and associated loss of statistical power) and enables the assessment of variation in incidence during the time from diagnosis.

The main study limitation is the lack of information on smoking status before and after diagnosis, both of which are moderators of SPC risk.[20] Additionally, we have not been able to investigate the impact of tumour factors, such as stage at diagnosis, because this information is incomplete for most study years. Staging information is much more complete for patients diagnosed from 2013 onwards, but these patients do not yet have any meaningful length of follow-up for analysis.

The key implication of this work is that incidence rates for second and higher order primary cancers continue to rise beyond the end of routine specialist 5-year follow-up after an initial lung cancer diagnosis. Given the incidence of SPC varies substantially by age at first diagnosis, consideration should be given to extending routine follow-up from 5 to 10 years, particularly for patients aged 50–79 at first diagnosis. In addition, this evidence can be used to inform lung cancer survivors and their families about the level and nature of risk of other organ cancers; this prognostic information is important for patients and clinicians and may facilitate patient education about possible symptoms of subsequent cancers and, given previous evidence of associations between continued smoking and incidence of further primary cancers, enhance smoking cessation among lung cancer survivors.

Surveillance efforts to promote early detection of subsequent smoking-related primary cancers should focus equally on both men and women. SIRs for second and higher order primary cancers are much higher in female survivors than male survivors. This is due to absolute incidence rates of subsequent primary cancers being similar for both men and women, despite incidence of first primary cancers being higher among men.

Survival rates, particularly for early-stage disease, are expected to improve further which will lead to an increasing population of patients alive 5, 10 or more years from their diagnosis. Our findings suggest a stable increase in the incidence of smoking-related cancers among lung cancer survivors, which will lead to an increasing number of diagnoses of SPC. The observation that the incidence of second primary lung cancer has doubled between 2000–2004 and 2010–2014 indicates that this issue is becoming increasingly important. The reasons behind this rapid change require further investigation but may be related to the changes in incidence of multifocal adenocarcinoma, particularly in women and to an increasing recognition of the issue of SPCs.

The optimal follow-up schedules and investigations to manage this expanding pool of cancer survivors will need to be determined by guideline development groups and policy-makers. Patient and clinician education about risks of SPC will be required to promote prompt diagnosis thereby achieving the best possible longer term outcomes.

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