

Supplemental Figures and Tables

Appendix 1. Lung cancer morphology groups

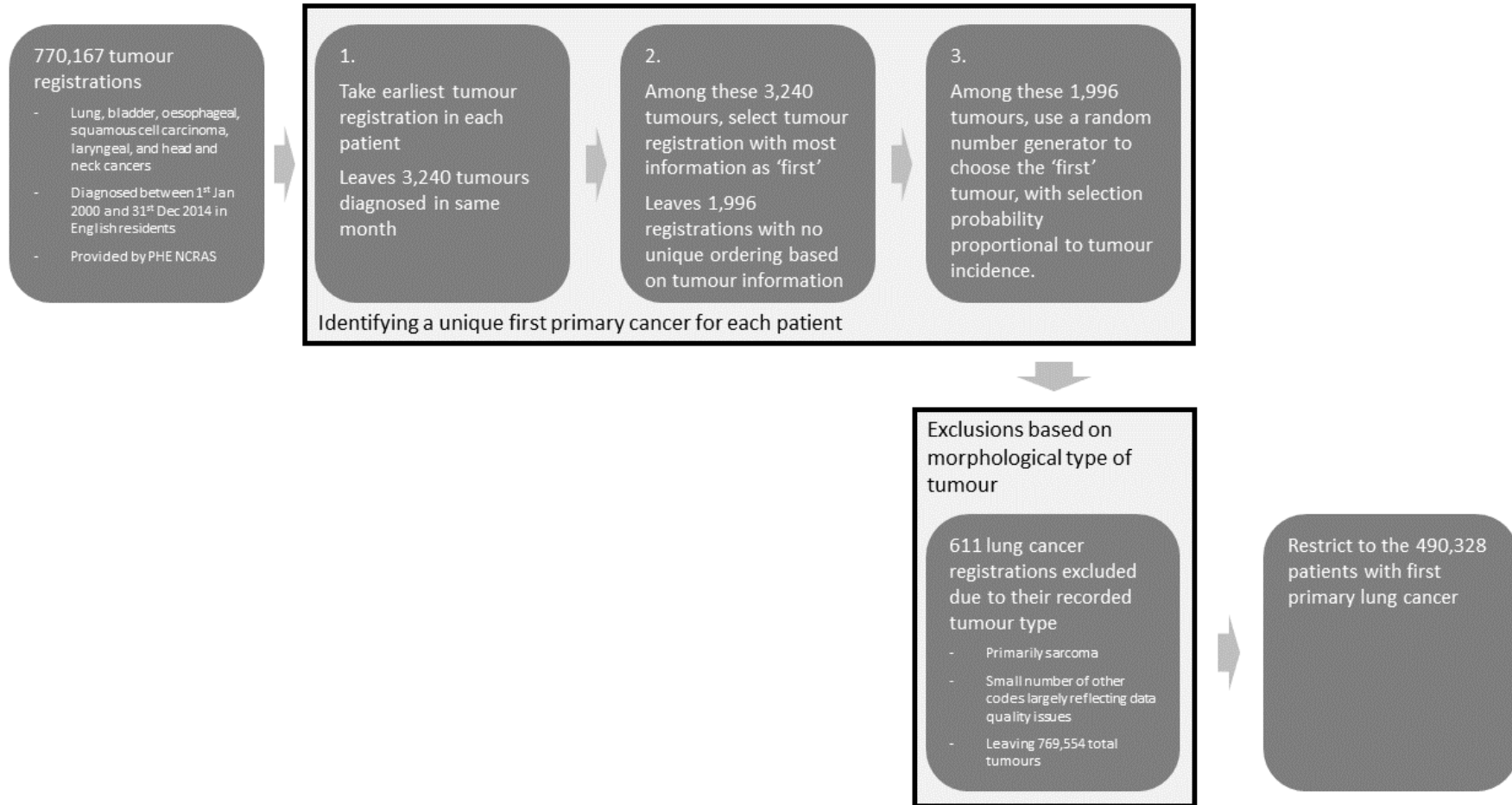
Table 1. Lung cancer morphology groups and associated ICD10-O2 morphology codes, along with incidence counts observed for all primary lung cancers in 2000 to 2014. Counts between 0 and 5 have been suppressed.

Broad group	Specific group	ICD10 O2 morphology code	Description	Count
SCLC	Small cell carcinoma	8041	Small cell carcinoma NOS	54,388
SCLC	Small cell carcinoma	8042	Oat cell carcinoma	3,069
SCLC	Small cell carcinoma	8045	Small cell-large cell carcinoma	453
SCLC	Small cell carcinoma	8044	Small cell carcinoma, intermediate cell	48
SCLC	Small cell carcinoma	8043	Small cell carcinoma, fusiform cell	35
SCLC	Small cell carcinoma	8002	Malignant tumour, small cell type	11
NSCLC	Adenocarcinoma	8140	Adenocarcinoma NOS	95,311
NSCLC	Adenocarcinoma	8250	Bronchiolo-alveolar adenocarcinoma	2,896
NSCLC	Adenocarcinoma	8480	Mucinous adenocarcinoma	1,540
NSCLC	Adenocarcinoma	8481	Mucin-producing adenocarcinoma	872
NSCLC	Adenocarcinoma	8260	Papillary adenocarcinoma NOS	768
NSCLC	Adenocarcinoma	8550	Acinar cell carcinoma	664
NSCLC	Adenocarcinoma	8251	Alveolar adenocarcinoma	254
NSCLC	Adenocarcinoma	8310	Clear cell adenocarcinoma NOS	200
NSCLC	Adenocarcinoma	8490	Signet ring cell carcinoma	114
NSCLC	Adenocarcinoma	8323	Mixed cell adenocarcinoma	72
NSCLC	Adenocarcinoma	8570	Adenocarcinoma with squamous metaplasia	27
NSCLC	Adenocarcinoma	8211	Tubular adenocarcinoma	22
NSCLC	Adenocarcinoma	8141	Scirrhus adenocarcinoma	6
NSCLC	Adenocarcinoma	8440	Cystadenocarcinoma NOS	6
NSCLC	Adenocarcinoma	8143	Superficial spreading adenocarcinoma	<6
NSCLC	Adenocarcinoma	8144	Adenocarcinoma, intestinal type	<6
NSCLC	Adenocarcinoma	8147	Basal cell adenocarcinoma	<6
NSCLC	Adenocarcinoma	8190	Trabecular adenocarcinoma	<6
NSCLC	Adenocarcinoma	8201	Cribiform carcinoma	<6
NSCLC	Adenocarcinoma	8252	Bronchioalveolar carcinoma non mucinous	<6
NSCLC	Adenocarcinoma	8320	Granular cell carcinoma	<6
NSCLC	Adenocarcinoma	8401	Apocrine adenocarcinoma	<6
NSCLC	Adenocarcinoma	8470	Mucinous cystadenocarcinoma NOS	<6
NSCLC	Adenocarcinoma	8572	Adenocarcinoma with spindle cell metaplasia	<6
NSCLC	Adenocarcinoma	8574	Adenocarcinoma with neuroendocrine differentiation	<6
NSCLC	Squamous cell carcinoma	8070	Squamous cell carcinoma NOS	93,142
NSCLC	Squamous cell carcinoma	8071	Squamous cell carcinoma, keratinising NOS	5,946
NSCLC	Squamous cell carcinoma	8072	Squamous cell carcinoma, large cell, non-keratinising	1,102
NSCLC	Squamous cell carcinoma	8073	Squamous cell carcinoma, small cell, non-keratinising	91
NSCLC	Squamous cell carcinoma	8074	Squamous cell carcinoma, spindle cell	80
NSCLC	Squamous cell carcinoma	8052	Papillary squamous cell carcinoma	27
NSCLC	Squamous cell carcinoma	8083	Basaloid Squamous Cell carcinoma	25
NSCLC	Squamous cell carcinoma	8076	Squamous cell carcinoma, microinvasive	6
NSCLC	Carcinoid	8240	Carcinoid tumour NOS	3,451
NSCLC	Carcinoid	8249	Atypical carcinoid tumour	23
NSCLC	Carcinoid	8241	Carcinoid tumour, argentaffin, malignant	18
NSCLC	Carcinoid	8244	Composite carcinoid	17
NSCLC	Carcinoid	8243	Goblet cell carcinoid	<6
NSCLC	Carcinoid	8245	Adenocarcinoid tumour	<6
NSCLC	Other NSCLC	8046	Non-small cell carcinoma, NOS	62,241
NSCLC	Other NSCLC	8012	Large cell carcinoma NOS	7,225
NSCLC	Other NSCLC	8246	Neuroendocrine carcinoma	3,736
NSCLC	Other NSCLC	8560	Adenosquamous carcinoma	2,036
NSCLC	Other NSCLC	8032	Spindle cell carcinoma	390
NSCLC	Other NSCLC	8022	Pleomorphic carcinoma	354
NSCLC	Other NSCLC	8033	Pseudosarcomatous carcinoma	272
NSCLC	Other NSCLC	8200	Adenoid cystic carcinoma	212
NSCLC	Other NSCLC	8980	Carcinosarcoma NOS	210
NSCLC	Other NSCLC	8430	Mucoepidermoid carcinoma	98

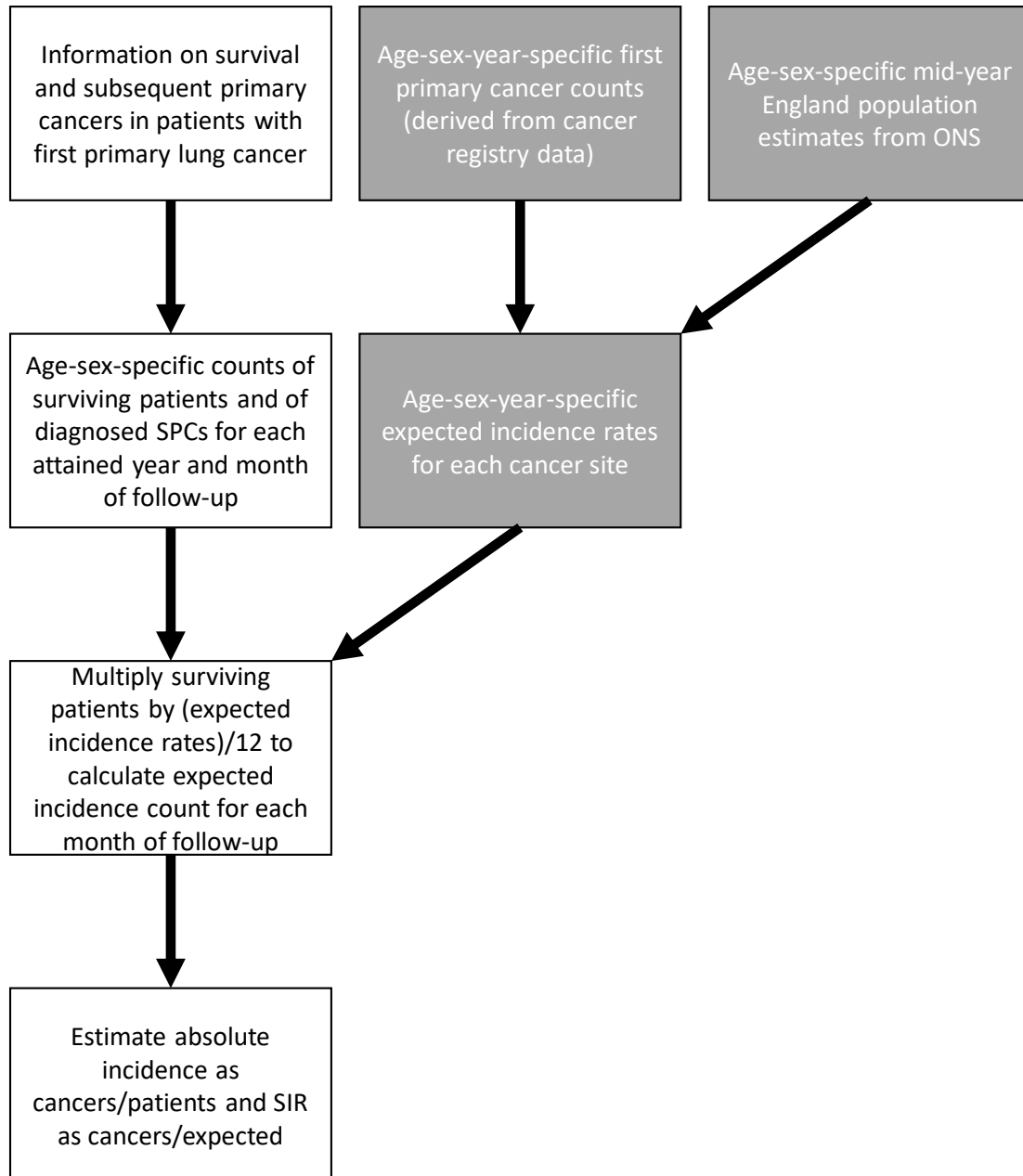
NSCLC	Other NSCLC	8031	Giant cell carcinoma	93
NSCLC	Other NSCLC	8050	Papillary carcinoma NOS	47
NSCLC	Other NSCLC	8972	Pulmonary blastoma	31
NSCLC	Other NSCLC	8013	Large cell neuroendocrine	19
NSCLC	Other NSCLC	8123	Basaloid carcinoma	15
NSCLC	Other NSCLC	8940	Mixed tumour, malignant NOS	13
NSCLC	Other NSCLC	8075	Adenoid squamous cell carcinoma	10
NSCLC	Other NSCLC	8230	Solid carcinoma NOS	6
NSCLC	Other NSCLC	8255	Adenocarcinoma with mixed cell types	6
NSCLC	Other NSCLC	8030	Giant cell and spindle cell carcinoma	<6
NSCLC	Other NSCLC	8034	Polygonal cell carcinoma	<6
NSCLC	Other NSCLC	8082	Lymphoepithelial carcinoma	<6
NSCLC	Other NSCLC	8145	Carcinoma, diffuse type	<6
NSCLC	Other NSCLC	8562	Epithelial-myoepithelial carcinoma	<6
NSCLC	Unspecified lung	8010	Carcinoma NOS	109,420
NSCLC	Unspecified lung	8000	Neoplasm, malignant	48,258
NSCLC	Unspecified lung	8020	Carcinoma, undifferentiated NOS	879
NSCLC	Unspecified lung	8021	Carcinoma, anaplastic type NOS	301
NSCLC	Unspecified lung	8001	Tumour cells, malignant	250
NSCLC	Unspecified lung	8004	Malignant tumour, fusiform cell type	32
NSCLC	Unspecified lung	8003	Malignant tumour, giant cell type	10
Exclude	Excluded - sarcoma	8800	Sarcoma NOS	191
Exclude	Excluded - sarcoma	8801	Spindle cell sarcoma	69
Exclude	Excluded - sarcoma	8890	Leiomyosarcoma NOS	68
Exclude	Excluded - sarcoma	8810	Fibrosarcoma NOS	48
Exclude	Excluded - sarcoma	9120	Haemangiosarcoma	28
Exclude	Excluded - sarcoma	9040	Synovial sarcoma NOS	26
Exclude	Excluded - sarcoma	8803	Small cell sarcoma	19
Exclude	Excluded - sarcoma	8900	Rhabdomyosarcoma NOS	13
Exclude	Excluded - sarcoma	8802	Giant cell sarcoma (except of bone M9250/3)	10
Exclude	Excluded - sarcoma	8830	Fibrous histiocytoma, malignant	8
Exclude	Excluded - sarcoma	8804	Epithelioid sarcoma	<6
Exclude	Excluded - sarcoma	8811	Fibromyxosarcoma	<6
Exclude	Excluded - sarcoma	8850	Liposarcoma NOS	<6
Exclude	Excluded - sarcoma	8851	Liposarcoma, well differentiated	<6
Exclude	Excluded - sarcoma	8852	Myxoid liposarcoma	<6
Exclude	Excluded - sarcoma	8854	Pleomorphic liposarcoma	<6
Exclude	Excluded - sarcoma	8894	Angiomyosarcoma	<6
Exclude	Excluded - sarcoma	8901	Pleomorphic rhabdomyosarcoma	<6
Exclude	Excluded - sarcoma	8910	Embryonal rhabdomyosarcoma	<6
Exclude	Excluded - sarcoma	8920	Alveolar rhabdomyosarcoma	<6
Exclude	Excluded - sarcoma	8933	Adenosarcoma	<6
Exclude	Excluded - sarcoma	8963	Rhabdoid sarcoma	<6
Exclude	Excluded - sarcoma	9170	Lymphangiosarcoma	<6
Exclude	Excluded - sarcoma	9180	Osteosarcoma NOS	<6
Exclude	Excluded - sarcoma	9220	Chondrosarcoma NOS	<6
Exclude	Excluded - sarcoma	9260	Ewing's sarcoma	<6
Exclude	Excluded - unusual	9133	Epithelioid haemangioendothelioma, malignant	17
Exclude	Excluded - unusual	8720	Malignant melanoma NOS	15
Exclude	Excluded - unusual	8040	Tumourlet (uncertain malignancy)	11
Exclude	Excluded - unusual	8011	Epithelioma, malignant	8
Exclude	Excluded - unusual	8146	Monomorphic adenoma	8
Exclude	Excluded - benign	8333	Microfollicular adenoma	6
Exclude	Excluded - unusual	9364	Peripheral neuroectodermal tumour	6
Exclude	Excluded - unusual	8120	Transitional cell carcinoma NOS	<6
Exclude	Excluded - unusual	8263	Adenocarcinoma in tubulovillous adenoma	<6
Exclude	Excluded - unusual	8520	Lobular carcinoma NOS	<6
Exclude	Excluded - unusual	8815	Solitary fibrous tumour	<6
Exclude	Excluded - unusual	8982	Myoepithelioma	<6
Exclude	Excluded - unusual	9050	Mesothelioma, malignant	<6
Exclude	Excluded - unusual	9071	Endodermal sinus tumour	<6
Exclude	Excluded - unusual	9080	Teratoma, malignant NOS	<6
Exclude	Excluded - unusual	9130	Haemangioendothelioma, malignant	<6
Exclude	Excluded - unusual	9473	Primitive neuroectodermal tumour	<6

* Descriptions sourced from <http://www.celsius.lshhtm.ac.uk/dataDict/appendices/MorphologyofNeoplasmsICDO2.html> and <http://codes.iarc.fr/codegroup/2>

Appendix 2 Figure 1. Flow chart showing exclusions and processing to produce the final analysis cohort of patients with first primary lung cancer



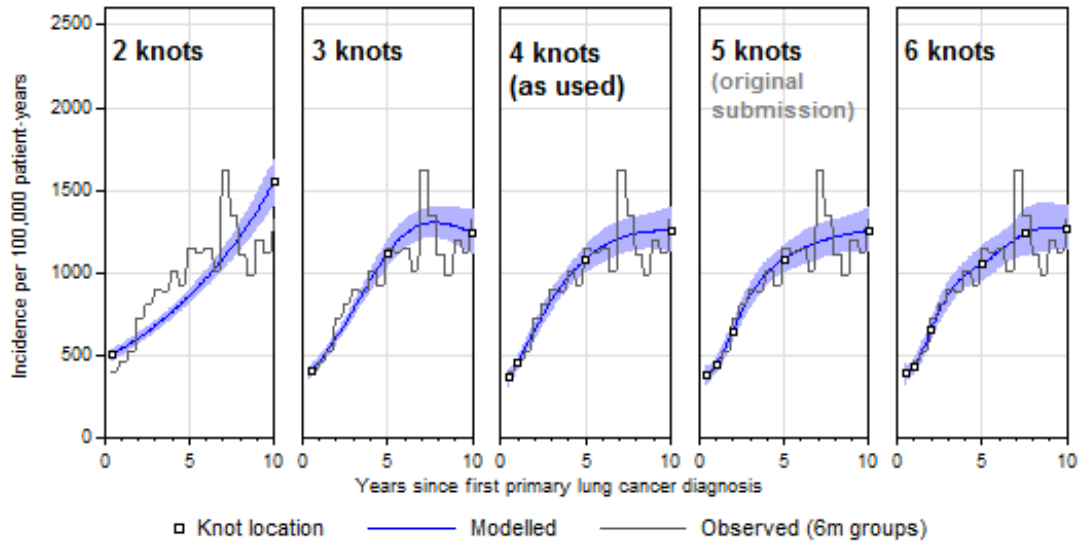
Appendix 2 Figure 2. Flow chart showing additional processing to calculate expected incidence of smoking-related second and higher order primary cancers in patients with first primary lung cancer



Appendix 3. Sensitivity analysis for parametrisation of elapsed follow-up time

Appendix 3 Figure 1. Demonstration that number of knots has minimal impact on results, as long as the impact of follow-up time is not treated as linear

Overall absolute incidence rate modelled with different knot locations



Appendix 3 Table 1. AIC and SBC for models with follow-up time as the only covariate

Knot locations (months)	SIR model		Absolute incidence model	
	AIC	SBC	AIC	SBC
6, 120	969	975	928	934
6, 60, 120	841	951	835	844
6, 12, 60, 120	827	839	828.58	841
6, 12, 24, 60, 120	825	841	828.57	844
6, 12, 24, 60, 90, 120	826	845	830	849

Appendix 3 Table 2. AIC and SBC for models including age and sex

Knot locations (months)	SIR model		Absolute incidence model	
	AIC	SBC	AIC	SBC
6, 120	3793	3880	3767	3854
6, 60, 120	3692	3812	3678	3798
6, 12, 60, 120	3678	3830	3676	3829
6, 12, 24, 60, 120	3683	3868	3683	3869
6, 12, 24, 60, 90, 120	3686	3904	3687	3906

Appendix 3 Table 3. AIC and SBC for models split by first primary cancer

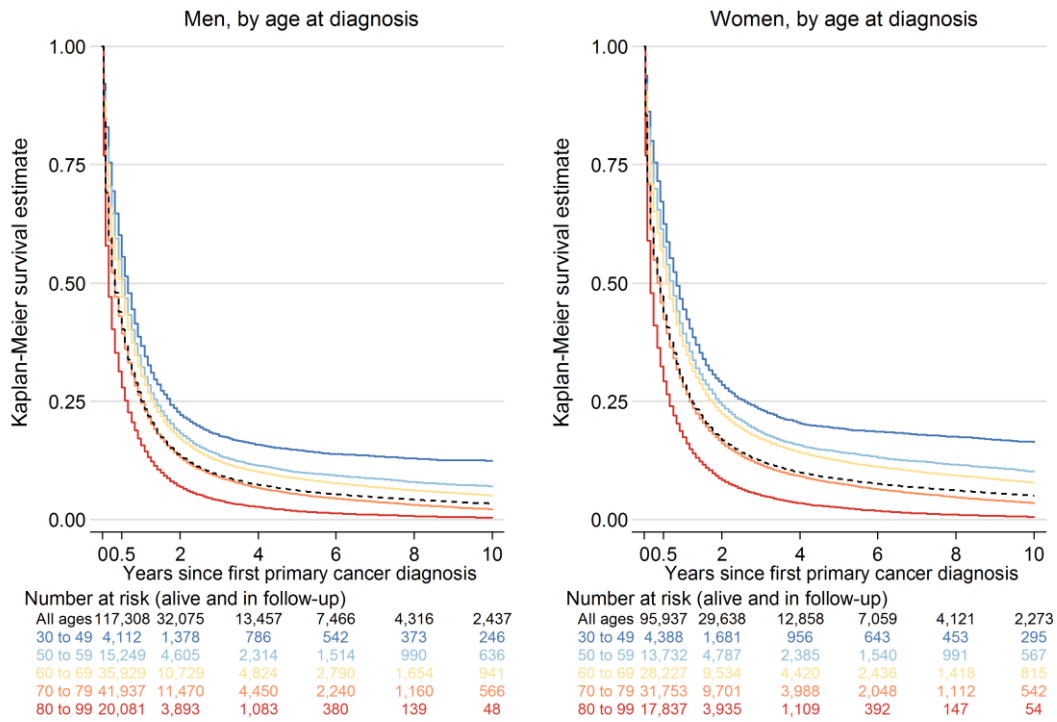
Knot locations (months)	SIR model		Absolute incidence model	
	AIC	SBC	AIC	SBC
6, 120	1316	1331	1272	1288
6, 60, 120	1191	1215	1185	1208
6, 12, 60, 120	1179	1210	1181.4	1211
6, 12, 24, 60, 120	1179	1217	1182	1221
6, 12, 24, 60, 90, 120	1178	1224	1181.5	1228

Appendix 3 Table 4. AIC and SBC for models with follow-up time as the only covariate, “default” knot locations

Number of knots at “default” locations	SIR model		Absolute incidence model	
	AIC	SBC	AIC	SBC
2	969	975	928	934
3	862	872	849	858
4	837	850	833	846
5	831	846	832	848
10	834	872	836	874
15	840	893	841	895

Appendix 4. Additional results

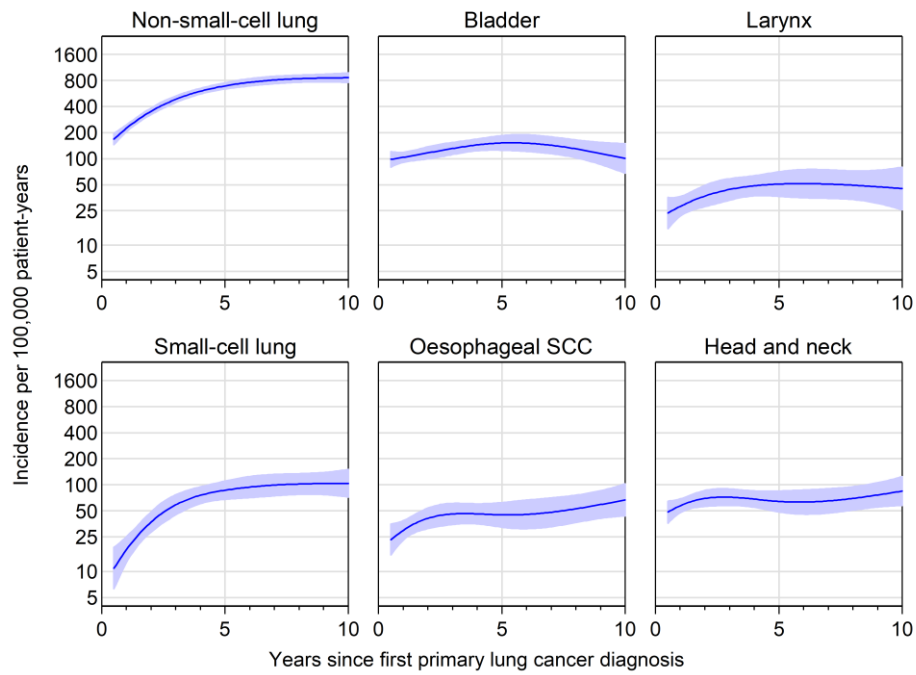
Appendix 4 Figure 1. Kaplan-Meier estimate of overall survival from lung diagnosis to ten years follow-up, by sex and age group. Joint log-rank tests of equality of age-specific survival functions stratified by sex and of equality of sex-specific survival functions stratified by age all give $p < 0.001$.



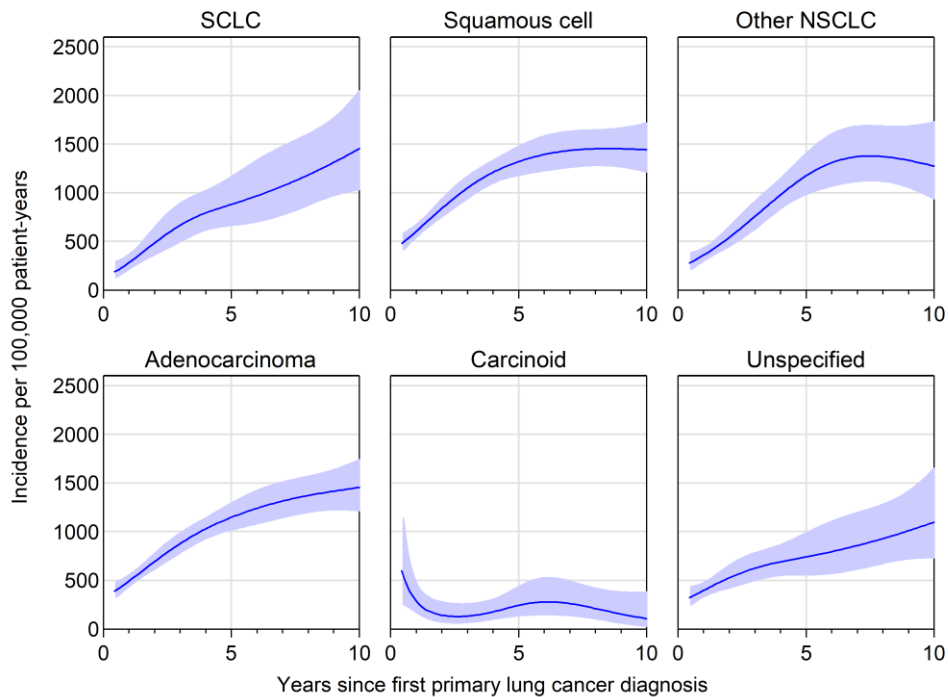
Appendix 4 Table 1. 'Spotlight' milestone (1-, 3-, 5-, 7- and 10-year) estimates of absolute incidence rates per 100,000 and standardised incidence rate ratios for second and higher order primary cancers following lung diagnosis, by sex and age at diagnosis

Sex	Age at diagnosis	Year of follow-up	Absolute incidence rate per 100,000 patient-years		Standardised incidence rate ratio	
				(95% CI)		(95% CI)
Men	30 to 49	1	385.6	(252.4, 589.2)	3.2	(2.1, 4.8)
		3	337.4	(202.8, 561.5)	2.8	(1.7, 4.7)
		5	349.7	(210.9, 580.0)	3.2	(1.9, 5.2)
		7	369.5	(209.8, 651.0)	3.0	(1.7, 5.4)
		10	396.9	(219.4, 718.2)	2.3	(1.3, 4.1)
	50 to 59	1	373.3	(297.8, 467.9)	1.5	(1.2, 1.8)
		3	718.0	(577.7, 892.4)	2.8	(2.3, 3.5)
		5	895.1	(731.4, 1095.5)	2.9	(2.4, 3.5)
		7	969.3	(773.0, 1215.3)	2.6	(2.1, 3.3)
		10	998.7	(769.9, 1295.6)	2.2	(1.7, 2.9)
	60 to 69	1	530.3	(463.7, 606.5)	1.1	(1.0, 1.3)
		3	1093.9	(961.7, 1244.3)	2.4	(2.1, 2.7)
		5	1423.6	(1254.4, 1615.7)	2.7	(2.4, 3.1)
		7	1555.2	(1345.6, 1797.5)	2.6	(2.3, 3.0)
		10	1562.1	(1293.9, 1885.9)	2.4	(2.0, 2.9)
	70 to 79	1	597.1	(528.8, 674.3)	0.8	(0.7, 0.9)
		3	1152.7	(1017.1, 1306.4)	1.5	(1.3, 1.7)
		5	1435.4	(1249.7, 1648.8)	1.8	(1.6, 2.1)
		7	1553.6	(1323.8, 1823.2)	1.9	(1.6, 2.2)
		10	1602.6	(1269.1, 2023.7)	1.9	(1.5, 2.3)
80 to 99	1	591.0	(489.7, 713.3)	0.7	(0.5, 0.8)	
	3	925.1	(728.1, 1175.5)	1.0	(0.8, 1.3)	
	5	1381.8	(993.3, 1922.1)	1.5	(1.1, 2.1)	
Women	30 to 49	1	266.4	(168.4, 421.5)	3.7	(2.3, 5.8)
		3	223.2	(130.7, 381.2)	3.1	(1.8, 5.3)
		5	249.1	(147.5, 420.6)	3.7	(2.2, 6.3)
		7	288.2	(162.2, 512.3)	3.9	(2.2, 7.0)
		10	353.6	(196.4, 636.6)	3.4	(1.9, 6.0)
	50 to 59	1	355.7	(282.4, 448.2)	2.4	(1.9, 3.1)
		3	655.1	(525.6, 816.4)	4.4	(3.5, 5.5)
		5	879.3	(719.7, 1074.4)	4.9	(4.0, 6.0)
		7	1042.8	(835.0, 1302.3)	4.9	(3.9, 6.1)
		10	1227.3	(960.8, 1567.7)	4.7	(3.7, 6.0)
	60 to 69	1	388.8	(331.4, 456.2)	1.5	(1.3, 1.8)
		3	767.7	(659.5, 893.6)	3.0	(2.6, 3.5)
		5	1075.8	(929.9, 1244.6)	3.7	(3.2, 4.3)
		7	1287.1	(1092.4, 1516.5)	4.0	(3.4, 4.7)
		10	1476.6	(1208.3, 1804.5)	4.1	(3.3, 5.0)
	70 to 79	1	394.6	(338.0, 460.8)	1.0	(0.9, 1.2)
		3	729.3	(623.7, 852.8)	1.9	(1.6, 2.2)
		5	977.9	(831.8, 1149.6)	2.4	(2.1, 2.9)
		7	1159.2	(965.9, 1391.1)	2.8	(2.3, 3.3)
		10	1365.7	(1072.1, 1739.8)	3.2	(2.5, 4.0)
80 to 99	1	322.9	(252.5, 412.9)	0.8	(0.7, 1.1)	
	3	483.8	(362.0, 646.7)	1.2	(0.9, 1.6)	
	5	778.2	(540.0, 1121.3)	2.0	(1.4, 2.8)	

Appendix 4 Figure 2. Incidence rate per 100,000 patient-years of second and higher order smoking-related primary cancers after lung cancer diagnosis up to ten years follow-up, by site of second primary cancer



Appendix 4 Figure 3. Incidence rate per 100,000 patient-years of second and higher order smoking-related primary cancers after lung cancer diagnosis up to ten years follow-up, by sub-site of first primary lung cancer



Appendix 4 Figure 4. Standardised incidence rate ratio for second and higher order smoking-related primary cancers after lung cancer diagnosis up to ten years follow-up, by sub-site of first primary lung cancer

