EUROPEAN JOURNAL OF CANCER 45 (2009) 3047–3053

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Cancer diagnosis in first-degree relatives and non-small cell lung cancer risk: Results from a multi-centre case–control study in Europe

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ARTICLE INFO

Article history:
Received 6 February 2009
Received in revised form 1 May 2009
Accepted 6 May 2009
Available online 29 May 2009

Keywords:
Family history
Non-small cell lung cancer
Genetic susceptibility

ABSTRACT

Because aggregation of cancers at different sites can occur in families, cancer could be considered as a broad phenotype with shared genetic factors. Here, we report results from a multi-centre case–control study of non-small cell lung cancer (NSCLC), with particular emphasis on a history of cancer in first-degree relatives and the risk of lung cancer. From 2002 to 2006, 733 NSCLC patients treated surgically were recruited in 8 European countries and matched to 1312 controls, by centre, sex and age. We used multivariate conditional logistic regression models to test the association between a history of cancer in first-degree relatives and risk of NSCLC. A family history of lung cancer was associated with an odds ratio (OR) for early-onset (54 years or younger) NSCLC of 4.72 (95% confidence interval [CI] = 1.02–21.90). A family history of gastric cancer was associated with an OR for NSCLC of 1.82 (95% CI = 1.08–3.06) and for late-onset (55 years or older) NSCLC of 2.92 (95% CI = 1.10–7.75). Our findings provide further evidence of a familial predisposition to lung cancer and support the hypothesis that family history is a significant risk factor for the disease. Because of the inherent potential for bias in familial case–control study design, cautious interpretation is warranted.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.05.006

1. Introduction

Lung cancer is the most common cancer in the world with 1.3 million new cases diagnosed every year. The highest rates of lung cancer are found in Europe and Northern America.[1] Although lung cancer is largely attributable to cigarette smoking, the disease also has an important heritable component. Numerous studies have found an increased risk of lung cancer in individuals who have a first-degree relative with the disease. Familial clustering can also occur between cancers at different sites, suggesting that cancer could be considered a broad phenotype with shared genetic factors.[2] For instance, it has been reported that oestrogen-related genes may serve as a link between a maternal history of breast cancer and an increased risk of lung cancer.[3–5]

In 1963, Tokuhata and Lilienfeld[6] provided the first epidemiologic evidence of familial aggregation of lung cancer, suggesting the interaction of genes, shared environment and common lifestyle factors in the aetiology of the disease. Since then, researchers have compared the concordance of lung cancer between monozygotic and dizygotic pairs of twins to quantify the extent to which an observed familial pattern is due to genetic or shared environmental factors.[7] The largest of these studies suggested a limited heritability of lung carcinoma, though none of the studies had statistically significant findings.[8] More recently, population-based studies in Iceland demonstrated that a familial factor for lung cancer extended beyond the nuclear family, strongly suggesting a genetic predisposition to the disease.[2,7] Major lung cancer susceptibility loci have since been mapped to chromosome 15q25,[9–13] 6p21[12] and 5p15,[12,13] further indicating that genetic factors play a role in an individual's susceptibility to lung cancer. However, the genetic variants the studies identified explain only a small part of the heritable risk, thus implying the presence of other genetic factors that increase the risk for lung cancer.

Because interactions with the environment can substantially modify genetic effects, epidemiological studies of familial aggregation play an important role in elucidating the interplay between genes and the environment. Using the results from a multi-centre case–control study of non-small cell lung cancer (NSCLC) in Europe we investigated the association between a family history of cancer and lung cancer risk, taking into account environmental factors, tobacco use and family size.

2. Materials and methods

2.1. Participants

The European Early Lung Cancer study was conducted in 12 areas of 8 countries: France, Germany, Ireland, Italy, the Netherlands, Poland, Spain and the United Kingdom. The study's main objective was to identify genetic alterations in the respiratory epithelium that could be used to detect NSCLC at its early stages. Between 2002 and 2006, NSCLC patients with surgically resected primary tumours confirmed either histologically or cytologically were recruited and matched to 1 or 2 controls. Most centres recruited controls from the same hospitals as the patients or general public hospitals serving the same areas as the patients. In the United Kingdom, controls were selected from population registers of general practitioners. To be eligible, controls had to be hospitalised for a disease that was not attributable to smoking and have no history of cancer or respiratory disease. Controls were matched to patients based on treatment centre, gender and age (±5 years). The study protocol was approved for each centre by its institutional and local ethics committees, and written informed consent was obtained from all participants. Overall, the response rate was 79.4% for NSCLC patients and 89.1% for controls.

2.2. Data collection

All participants were interviewed by a research interviewer. A standardised lifestyle questionnaire was used to collect detailed information about patients' and controls' socioeconomic and demographic characteristics, medical history, family history of cancer, history of tobacco use and occupational exposure to asbestos. Data collection was identical for all participants.

Extensive information about participants' tobacco smoking, including participants' age at the start and end of all periods of consumption and the number of cigarettes smoked per day, was recorded. All periods of consumption were counted towards total exposure. Individuals who had smoked at least 100 cigarettes during their lifetimes were defined as ever-smokers; this category included current smokers, former smokers (patients who had quit smoking at least 1 year before diagnosis or controls who had quit smoking at least 1 year before their interviews) and recent quitters (those who had quit within the previous year). Information about the history of cancer among first-degree relatives (parents, siblings and biological children), including age of diagnosis, site of cancer and relation to the participant, was recorded. A family history positive for cancer was defined as a self-report of at least 1 first-degree relative with a malignant tumour.

2.3. Statistical analysis

We used univariate conditional logistic regression to compare patients' and controls' demographic and lifestyle characteristics. Family history of cancer was categorised as any cancer, lung cancer, smoking-related cancer (excluding lung cancer) and cancers unrelated to smoking to more easily distinguish between an environmental or genetic component of risk. Smoking-related cancers included cancers of the bladder, head and neck, kidney, pancreas, larynx and oesophagus. Continuous variables that did not meet the log-linearity assumption were transformed into categorical variables, and plausible two-way interactions were checked. Because the rate of cancer diagnosed in first-degree relatives is proportional to the number of relatives, we performed systematic adjustment for family size. Multivariate analyses were conducted to control for factors imbalanced between patient and control groups; using backward selection, factors significant at the 0.05 level were included in the final model.

To study the association between family history and NSCLC, we applied conditional logistic regression modelling. All models were adjusted for age, sex, study centre, family

size, pack-years of tobacco consumption, occupational exposure to asbestos and education level. Stratified analyses were performed for sex, smoking status, age at lung cancer diagnosis (defined as 54 years or younger for early-onset and 55 years or older for late-onset), first-degree relative (parents, siblings and children) and histological subtype of tumour. Heterogeneity in risk estimates among these strata was then assessed. Statistical analyses were performed using SAS 9.1.3 software (SAS Institute, Cary, NC). Results were recorded as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). All tests were two-sided, and p values less than 0.05 were considered statistically significant.

3. Results

Patients' and controls' baseline characteristics are summarised in Table 1. The final study population consisted of 2045 Caucasian participants: 733 NSCLC patients and 1312 cancer-free controls. The majority of patients and controls were men (73.0% and 72.8%, respectively). The patients' mean age was 63.9 years (standard deviation [SD], 9.1 years), and the controls' mean age was 63.2 years (SD, 9.0 years) ($p = 0.06$). Adenocarcinoma (46.7%) and squamous cell carcinoma (42.3%) were the dominant histological subtypes of NSCLC.

We found significant differences between patients and controls in education level ($p < 0.0001$), occupational exposure to asbestos ($p < 0.0001$) and all measures of cigarette smoking. Patients who were ever-smokers reported significantly more cigarette consumption than controls who were ever-smokers (40.7 mean pack-years for patients *versus* 22.7 mean pack-years for controls; $p < 0.0001$).

Family history data were available for 5137 first-degree relatives of patients (mean, 7.9) and 10,265 first-degree relatives of controls (mean, 7.6) ($p = 0.94$). There was no significant difference in patients' and controls' numbers of first-degree relatives with a history of cancer ($p = 0.12$). Furthermore, no heterogeneity was observed for family history of cancer between countries ($p = 0.99$).

We next examined the association between a family history of cancer and NSCLC risk (Table 2). Overall, a family history of cancer was significantly associated with NSCLC risk (OR = 1.16, 95% CI = 1.02–1.33). We also observed borderline associations between a family history of lung cancer and NSCLC risk (OR = 1.33, 95% CI = 0.97–1.81), and a family history of cancers unrelated to smoking and NSCLC risk (OR = 1.23, 95% CI = 0.97–1.57). Further investigation of cancers unrelated to smoking revealed that a family history of gastric cancer was associated with an elevated risk of NSCLC (OR = 1.82, 95% CI = 1.08–3.06). We did not observe any association between a family history of smoking-related cancers and NSCLC risk.

Table 3 shows the association between a family history of cancer and risk of early-onset and late-onset NSCLC. After adjusting for age, gender, study centre, family size, pack-years of tobacco use, occupational exposure to asbestos and education level, we found that a history of lung cancer among first-degree relatives was significantly associated with an increased risk for early-onset NSCLC (OR = 4.72, 95% CI = 1.02–21.90). A family history of gastric cancer was associated with an increased risk of late-onset NSCLC (OR = 2.92, 95% CI = 1.10–7.75).

Table 1 – Characteristics of the study population.

Characteristic	Patients, $n = 733$	Controls, $n = 1312$	p-value[a]
Country			
France	155 (21.1)	279 (21.3)	
Germany	97 (13.2)	160 (12.2)	
Ireland	65 (8.9)	129 (9.8)	
Italy	63 (8.6)	119 (9.1)	
The Netherlands	108 (14.7)	207 (15.8)	
Spain	84 (11.5)	160 (12.2)	
United Kingdom	159 (21.7)	255 (19.4)	
Sex			
Male	535 (73.0)	955 (72.8)	
Female	198 (27.0)	357 (27.2)	
Smoking status			<0.0001
Never	50 (7.1)	368 (28.2)	
Former	534 (75.4)	898 (68.8)	
Current	124 (17.5)	40 (3.0)	
Occupational asbestos exposure			<0.0001
No or unsure	546 (79.3)	1160 (89.4)	
Yes	143 (20.8)	137 (10.6)	
Education level			<0.0001
Low	464 (69.5)	769 (59.3)	
High[b]	204 (30.5)	527 (40.7)	
Number of first-degree relatives			0.94
2–4	116 (17.9)	205 (16.2)	
5–6	165 (25.4)	346 (27.4)	
7–9	198 (30.5)	385 (30.4)	
⩾10	170 (26.2)	329 (26.0)	
Continuous variables			
Mean age, years (SD)	63.9 (9.07)	63.2 (9.0)	0.06
Mean tobacco consumption, pack-years (SD)	40.7 (25.61)	22.7 (24.3)	<0.0001
Mean total smoking duration, years (SD)	36.5 (16.76)	23.4 (19.7)	<0.0001

SD, standard deviation.
a *P* values were derived from conditional logistic regression.
b First degree, higher degree, professional qualification or university entrance. Data are numbers of patients or controls (%) unless otherwise specified.

An analysis of the data by histological subtype of lung cancer revealed a significant association between family history of cancer and risk of squamous cell lung carcinoma (Table 4). We found that a family history of cancers unrelated to smoking was associated with an increased risk of squamous cell lung carcinoma (OR = 1.62, 95% CI = 1.10–2.39) and that a family history of gastric cancer was associated with a significantly increased risk of squamous cell lung carcinoma (OR = 2.18, 95% CI = 1.01–4.02).

4. Discussion

An early onset is one of the hallmarks of heritable cancer.[14] We found that patients had a 4.6-fold higher OR (95% CI = 1.02–21.90) for early-onset NSCLC if a first-degree relative

Table 2 – Odds ratios for risk of lung cancer by history of cancer among first-degree relatives, European early lung cancer study, 2002–2006.

Cancer type and no. of first-degree relatives affected	No. of patients (%)[a]	No. of controls (%)[a]	OR[b]	95% CI[b]	*p*-value	OR[c]	95% CI[c]	*p*-value
Any cancer								
0	336 (48.5)	671 (51.7)						
⩾1	357 (51.5)	628 (48.3)	1.29	1.05–1.58	0.02	1.16	1.02–1.33	0.03
Lung cancer								
0	562 (81.1)	1123 (86.5)						
⩾1	131 (18.9)	176 (13.5)	1.55	1.19–2.03	0.001	1.33	0.97–1.81	0.08
Smoking-related cancers[d]								
0	622 (89.7)	1192 (91.8)						
⩾1	71 (10.3)	107 (8.2)	1.24	0.84–1.84	0.28	1.23	0.83–1.80	0.30
Non-smoking-related cancers								
0	444 (64.1)	853 (65.7)						
⩾1	249 (35.9)	446(34.3)	1.17	0.95–1.45	0.14	1.23	0.97–1.57	0.09
Gastric cancer								
0	651 (93.9)	1249 (96.2)						
⩾1	42 (6.1)	50 (3.8)	1.69	1.08–2.64	0.02	1.82	1.08–3.06	0.02

OR, odds ratio; CI, confidence interval.
a Missing values were not included in percentage calculations.
b ORs and 95% CIs calculated by conditional logistic regression adjusted for family size.
c ORs and 95% CIs calculated by conditional logistic regression adjusted for family size, tobacco consumption in pack-years, occupational asbestos exposure and education level.
d Head and neck, oesophagus, pancreas, larynx, bladder and kidney cancers.

had been diagnosed with lung cancer. Despite the small sample size and wide confidence intervals, our results are consistent with those of previous reports and support the hypothesis that a genetic component to risk likely exists in this group. For instance, Bromen and colleagues[15] reported a 4.75-fold increase in risk of lung cancer among relatives of probands who were diagnosed with lung cancer before 50 years of age. Moreover, a history of lung cancer in a first-degree relative was previously reported to be associated with a 2.6-fold increase in risk of early-onset lung cancer (i.e. before 46 years of age), with no elevated risk observed in the older group.[16]

Our findings also suggest that individuals with first-degree relatives who have a history of gastric cancer have an increased risk of NSCLC (OR = 1.82, 95% CI = 1.08–3.06), of late-onset NSCLC (OR = 2.92, 95% CI = 1.10–7.75) and of squamous cell lung carcinoma (OR = 2.18, 95% CI = 1.01–4.02). Our findings agree in part with those of a large population-based cohort study of non-smoking Chinese women in which having a sibling with gastric cancer was associated with an elevated risk of lung cancer (relative risk = 2.16, 95% CI = 1.01–4.65).[17]

We cannot rule out the possibility that the observed association between a family history of gastric cancer and NSCLC risk in our study could be related to tobacco smoking because of the known familial aggregation of smoking habits,[7,18,19] nor can we discount the possibility of chance finding. It is also biologically plausible that the association we observed between a family history of gastric cancer and an increased risk of NSCLC could be linked by *Helicobacter pylori* infection via upregulation of gastrin and cyclooxygenase-2, which may account for tumour growth and angiogenesis.[20] Although *H. pylori* seroprevalence was reported in one study to be significantly higher in lung cancer patients than in controls, suggesting an association between *H. pylori* infection and the risk of lung cancer,[21] a more recent study did not confirm this finding.[22]

Another plausible explanation for our finding that a family history of gastric cancer increases NSCLC risk could be that an interaction between common environmental risk factors such as smoking or diet and genetic factors induces several types of cancers.[23] Familial aggregation has been shown to occur between some cancers at different sites, suggesting that cancer might be considered a broad phenotype with shared genetic factors that are not site-specific.[2] Although it is not possible to conclude whether this finding is due to genetic susceptibility or shared dietary or smoking habits within the family setting, we believe that shared tobacco consumption habits are unlikely to account for all of the association because the elevated risk persisted even after we controlled for confounding factors such as age, gender, study centre, family size, pack-years of tobacco use, occupational exposure to asbestos and education level in our analyses.

With regard to histological type, an elevated risk of squamous cell lung carcinoma was associated with a family history of cancers unrelated to smoking, whereas no clear increase in risk of adenocarcinoma was observed. These findings are supported by those in a large prospective study of two Japanese cohorts in which a family history of cancer was more strongly associated with the risk of squamous cell lung carcinoma than with other histological types (hazard ratio = 2.79, 95% CI = 1.37–5.68).[24] Although a link between tobacco smoking and squamous cell carcinoma is well established, our results

Table 3 – Odds ratios for risk of lung cancer by history of cancer in first-degree relatives and age at diagnosis, European early lung cancer study, 2002–2006.

Patient age at lung cancer diagnosis	Number of cancers in cancer site and no. of first-degree relatives affected	No. of patients (%)[a]	No. of controls (%)[a]	OR[b]	95% CI[b]	*p*-value	OR[c]	95% CI[c]	*p*-value
<55 years	*Any cancer*								
	0	94 (77.0)	191 (78.6)						
	⩾1	28 (23.0)	52 (21.4)	1.08	0.61–1.91	0.80	0.92	0.47–1.81	0.81
	Lung cancer								
	0	112 (91.8)	239 (98.4)						
	⩾1	10 (8.2)	4 (1.6)	5.58	1.51–20.67	0.01	4.72	1.02–21.90	0.05
	Smoking-related cancers[d]								
	0	117 (95.9)	233 (95.9)						
	⩾1	5 (4.1)	10 (4.1)	0.83	0.28–2.49	0.75	0.39	0.10–1.51	0.17
	Non-smoking-related cancers								
	0	101 (82.8)	195 (80.3)						
	⩾1	21 (17.2)	48 (19.8)	0.78	0.41–1.47	0.45	0.73	0.36–1.50	0.39
	Gastric cancer								
	0	123 (98.4)	242 (98.8)						
	⩾1	2 (1.60)	3 (1.22)	1.09	0.18–6.60	0.92	1.27	0.18–8.93	0.81
⩾55 years	*Any cancer*								
	0	459 (82.4)	883 (84.4)						
	⩾1	98 (17.6)	163 (15.6)	1.19	0.88–1.59	0.26	1.17	0.83–1.64	0.38
	Lung cancer								
	0	537 (96.4)	1009 (96.5)						
	⩾1	20 (3.6)	37 (3.5)	0.99	0.54–1.82	0.96	0.82	0.42–1.61	0.57
	Smoking-related cancers								
	0	550 (98.7)	1032 (98.7)						
	⩾1	7 (1.3)	14 (1.3)	1.08	0.42–2.76	0.86	0.87	0.30–2.55	0.80
	Non-smoking-related cancers								
	0	474 (85.1)	912 (87.2)						
	⩾1	83 (14.9)	134 (12.8)	1.23	0.90–1.70	0.20	1.24	0.86–1.79	0.25
	Gastric cancer								
	0	551 (97.4)	1044 (99.1)						
	⩾1	15 (2.65)	10 (0.95)	2.96	1.27–6.86	0.01	2.92	1.10–7.75	0.03

OR, odds ratio; CI, confidence interval.

a Missing values were not included in percentage calculations.

b ORs and 95% CIs calculated by conditional logistic regression adjusted for family size.

c ORs and 95% CIs calculated by conditional logistic regression adjusted for family size, tobacco consumption in pack-years, occupational asbestos exposure and education level.

d Head and neck, oesophagus, pancreas, larynx, bladder and kidney cancers.

suggest that genetic factors may also play a role in the development of squamous cell carcinoma of the lung.

Because our study was designed to recruit NSCLC patients with surgically resected primary tumours (stages IA–IIB), these patients represent only a small proportion (20–25%) of all NSCLC patients, introducing potential selection bias. Ascertaining lifestyle data from lung cancer patients also introduces the possibility of recall bias, and we acknowledge that the use of self-reported family history of cancer in our study may have resulted in imprecise risk estimates. When Bondy and colleagues[25] evaluated the validity of proband-reported family history of cancer using medical records and death certificates, they found that 85% of probands correctly identified primary lung cancer in first-degree relatives. However, a cancer registry study that linked individuals to their first-degree relatives suggested that in case–control studies of a specific cancer type, patients are more likely than controls to report both true-positive and false-positive family histories of their particular cancer, resulting in inflated estimates of the relative risk.[26] Because the age at onset among relatives was reported by the lung cancer patients in our study, inaccuracies may have led to information bias.

Table 4 – Odds ratios for risk of lung cancer by history of cancer in first-degree relatives and histological subtype, European early lung cancer study, 2002–2006.

Histological subtype	Cancer site and no. of first-degree relatives affected	No. of patients (%)[a]	No. of controls (%)[a]	OR[b]	95% CI[b]	*p*-value	OR[c]	95% CI[c]	*p*-value
Adenocarcinoma									
	Any cancer								
	0	159 (49.8)	280 (47.2)						
	⩾1	160 (50.2)	313 (52.8)	0.91	0.67–2.14	0.56	1.01	0.72–1.43	0.95
	Lung cancer								
	0	265 (80.6)	528 (85.7)						
	⩾1	64 (19.5)	88 (14.3)	1.63	1.10–2.41	0.02	1.45	0.93–2.25	0.10
	Smoking-related cancers[d]								
	0	291 (88.5)	570 (92.5)						
	⩾1	38 (11.6)	46 (7.5)	1.76	1.11–2.82	0.02	1.42	0.82–2.43	0.21
	Non-smoking-related cancers								
	0	226 (68.7)	393 (63.8)						
	⩾1	103 (31.3)	223 (36.2)	0.84	0.61–1.14	0.27	0.85	0.59–1.21	0.36
	Gastric cancer								
	0	314 (95.4)	593 (96.3)						
	⩾1	15 (4.6)	23 (3.7)	1.32	0.64–2.48	0.45	1.92	0.82–4.46	0.13
Squamous cell carcinoma									
	Any cancer								
	0	119 (42.7)	262 (49.3)						
	⩾1	160 (57.4)	269 (50.7)	1.42	1.04–1.96	0.03	1.40	0.94–2.07	0.10
	Lung cancer								
	0	238 (82.6)	472 (86.3)						
	⩾1	50 (17.4)	75 (13.7)	1.24	0.82–1.88	0.33	1.04	0.62–1.75	0.87
	Smoking-related cancers[d]								
	0	262 (91.0)	498 (91.0)						
	⩾1	26 (9.0)	49 (9.0)	1.08	0.64–1.82	0.80	0.96	0.52–1.76	0.88
	Non-smoking-related cancers								
	0	176 (61.1)	371 (67.8)						
	⩾1	112 (38.9)	176 (32.2)	1.57	1.14–2.18	0.008	1.62	1.10–2.39	0.01
	Gastric cancer								
	0	265 (92.0)	528 (96.5)						
	⩾1	23 (8.0)	19 (3.5)	2.74	143–5.24	0.003	2.18	1.01–4.02	0.05

OR, odds ratio; CI, confidence interval.
a Missing values were not included in percentage calculations.
b ORs and 95% CIs calculated by conditional logistic regression adjusted for family size.
c ORs and 95% CIs calculated by conditional logistic regression adjusted for family size, tobacco consumption in pack-years, occupational asbestos exposure and education level.
d Head and neck, oesophagus, pancreas, larynx, bladder and kidney cancers.

Recruiting controls from hospitals can result in potential selection bias because such individuals are not necessarily representative of non-affected subjects. To be eligible for our study, controls had to attend hospital for a disease that was not attributable to smoking, which gave rise to differences in smoking behaviour between patients and controls. This inclusion criterion may have led to selection bias if controls' smoking habits differed from those of the whole population. However, analyses of a subset of participating and non-participating controls indicated that there were no differences in age, sex and smoking status between the two groups (data not shown). Furthermore, hospital controls have the advantage of being able to better remember cancer cases that occurred among their relatives, which may counterbalance the potential recall bias inherent in retrospective case–control studies.[27]

Because elevated relative risks could have been generated by shared smoking habits within families, familial effects on lung cancer risk should be interpreted cautiously.[28] Although it has been shown that most familial cases of lung cancer cannot be attributed to shared smoking habits,[18] it is difficult to prove that the accumulation of lung cancer risk has a genetic origin. We attempted to compensate for this difficulty by collecting smoking information from patients and controls, thus allowing a detailed adjustment in the analyses. We also controlled for the number of first-degree relatives,

occupational exposure to asbestos and education level. Strict adherence to matching criteria also ensured homogeneity between patients and controls for age and sex, which are strong confounding factors.

Taken together, our findings provide further evidence of a familial predisposition to lung cancer in some individuals and support the hypothesis that family history is a significant risk factor for the disease. Furthermore, the observed association between a family history of gastric cancer and an increased risk of NSCLC could be due to *H. pylori* infection, lifestyle habits, genetic factors, or a combination thereof. However, further research is required to confirm the validity of this finding.

5. Conflict of interest statement

None declared.

Acknowledgements

We thank the individuals who participated in this research and the clinicians and support staff who made this study possible. The European Early Lung Cancer study was supported by a Framework V grant from the European Union (QLG1-CT-2002-01735).

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