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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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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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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