Family History of Cancer and Risk of Lung Cancer among Nonsmoking Chinese Women

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Abstract

The relationship between family cancer history in first-degree relatives and risk of lung cancer was evaluated among a population-based cohort of 71,392 female nonsmokers in Shanghai, China. A total of 179 newly diagnosed lung cancer patients were identified during 441,410 person-years of follow-up. Lung cancer risk was not elevated among those with a family history of lung cancer. However, risk of lung cancer was increased among subjects who had two or more first-degree relatives with any type of cancers {rate ratio [RR], 1.95 [95% confidence intervals (95% CI), 1.08-3.54] for two relatives with any cancers and RR, 3.17 [95% CI, 1.00-10.03] for three or more relatives with any cancer}. Having a family history of colorectal cancer (RR, 2.38; 95% CI, 1.21-4.70) and having siblings with stomach cancer (RR, 2.16; 95% CI, 1.01-4.65) and pancreatic cancer (RR, 4.19; 95% CI, 1.04-16.95) were also found to be associated with lung cancer risk. This cohort study indicated a moderate association of lung cancer risk with a family cancer history in general, but not with a family history of lung cancer specifically. The associations were stronger when a sibling, rather than a parent, was affected. The apparent link between lung cancer risk and a family history of colorectal, stomach, and pancreas cancers may be worth further investigation. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2432–5)

Introduction

Lung cancer is the leading cancer in incidence and mortality worldwide (1). Tobacco smoking is a major established risk factor for lung cancer, contributing to 10-fold or higher risks in long-term smokers (2, 3). Despite a relatively low prevalence of smoking (3.8%; ref. 4), Chinese women nevertheless have among the world's highest incidence of lung cancer (1). As such, uncovering the role of other potential risk factors, including environmental exposures, other lifestyle and occupational factors, and family history of cancers, is particularly important to understand the etiology of lung cancer in these nonsmoking women.

The role of family history of cancer as a risk factor has been the subject of numerous lung cancer studies (5-13). Most of the evidence has been derived from case-control studies (5), which are more prone to recall and selection biases. Whereas several cohort studies have examined the relationship between family history and lung cancer risk in Western populations (6-9), no cohort study has investigated the relationship in an Asian population. To fill this gap, we analyzed lung cancer risk in a large population-based cohort of women in China, the Shanghai Women's Health Study. The relatively large number of lung cancer cases in nonsmoking women in this study presents an opportunity to more clearly evaluate family history as a risk factor.

Received 5/1/07; revised 8/15/07; accepted 9/12/07.

Grant support: NIH research grant R01 CA70867 and by Intramural Research Program contract N02 CP1101066.

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doi:10.1158/1055-9965.EPI-07-0398

Methods and Materials

Study Population. A detailed description of the Shanghai Women's Health Study population has been published elsewhere (10). Briefly, a roster of 81,170 women, ages 40 to 70 years, was obtained from the resident offices in seven communities located in urban Shanghai, China. A total of 75,221 (92.7%) women participated in the study and completed baseline surveys between 1996 and 2000. Of those, we excluded 279 women who were found to be younger than age 40 years or older than age 70 years, 1,490 women who had a prevalent cancer, and 10 women who did not accrue any follow-up time. The remaining cohort of 73,442 women was followed through December 2004. A total of 197 lung cancer patients were diagnosed during the follow-up period, with 24 patients being diagnosed within the first year of follow-up.

At baseline, 2,050 (2.8%) participants reported having ever smoked at least 1 cigarette per day for more than 6 months. Of these participants, 18 were newly diagnosed with lung cancer (9.1% of incident lung cancer cases) during the follow-up. These participants and cases were excluded from the current analysis.

Data Collection and Follow-up. Information on family cancer history in first-degree relatives was collected at baseline survey. Each subject was asked

whether their family members, including parents, siblings, and children, had ever been diagnosed with cancer. For those who reported a positive family cancer history, further information on the affected family members, types of cancer, and ages at diagnosis was elicited. In addition, information on active and passive smoking, dietary intakes, and demographic factors was also collected at the baseline and first follow-up survey. Subjects who had ever been exposed to passive smoking were identified based on their husband's smoking status and/or passive smoke exposure at work or home. Information on active and passive smoking and other covariates was not collected for first-degree relatives.

The first follow-up interview was conducted in 2000-2002 and the second was conducted in 2002-2004. Standardized and structured questionnaires were used to update information on environmental and lifestyle factors, as well as interim health history including cancer. Newly diagnosed cancer cases were also ascertained through the Shanghai Cancer Registry, which is legally mandated in Shanghai, China. Information on date and hospital of diagnosis was collected. Medical charts and pathology slides were collected from diagnostic hospital and reviewed by two study cancer pathologists to verify the diagnosis. In addition, the death certificate data from the Shanghai Vital Statistics Unit were collected to identify causes of death for deceased participants.

Table 1. Selected characteristics of the cohort and incident lung cancer patients

Characteristics	Cohort (n = 71,392)	Lung cancer (n = 179)
	n (%)	n (%)
Age (y)		
40-44	20,396 (28.6)	17 (9.5)
45-49	15,059 (21.1)	22 (12.3)
50-54	10,205 (14.3)	21 (11.7)
55-59	7,250 (10.2)	23 (12.8)
60-64	8,956 (12.5)	37 (20.7)
65+	9,526 (13.3)	59 (33.0)
Educational level		
Elementary school or less	14,562 (20.4)	70 (39.1)
Middle school	26,759 (37.5)	52 (29.1)
High school	20,206 (28.3)	33 (18.4)
College or graduate school	9,856 (13.8)	24 (13.4)
Missing	9 (0.01)	0 (0.0)
Family income		
<¥10,000	11,190 (15.7)	36 (20.1)
¥10,000-	27,290 (38.2)	65 (36.3)
¥20,000-	20,213 (28.3)	46 (25.7)
¥30,000	12,683 (17.8)	31 (17.3)
Missing	16 (0.02)	1 (0.6)
Passive smoking		
No	9,053 (12.7)	28 (15.6)
Yes	57,334 (80.3)	127 (70.9)
Missing	5,005 (7.0)	24 (13.4)
Alcohol consumption		
No	70,008 (98.1)	177 (98.9)
Yes	1,384 (1.9)	2 (1.1)
No. siblings		
0	3,974 (5.6)	16 (8.9)
1	6,157 (8.6)	15 (8.4)
2	11,368 (15.9)	34 (19.0)
3	15,570 (21.8)	36 (20.1)
4	14,429 (20.2)	32 (17.9)
5+	19,894 (27.9)	46 (25.7)
No. children		
0	2,360 (3.3)	7 (3.9)
1	40,121 (56.2)	55 (30.7)
2	15,268 (21.4)	50 (27.9)
3	7,432 (10.4)	41 (22.9)
4	4,041 (5.7)	17 (9.5)
5+	2,172 (3.0)	9 (5.1)

Statistical Analysis. Person-years for each subject were calculated from the date of enrollment to the primary end point (diagnosis of first primary cancer), death, or December 31, 2004, whichever came first. Cox proportional hazard models were used to compute incidence rate ratio (RR) and 95% confidence intervals (95% CI). Potential confounding variables, including age at baseline (<45, 45-49, 50-54, 55-59, 60-64, ≥65), passive smoking (yes, no, missing), number of siblings (<3, 3-4, ≥4), and number of children (<2, 2, >2), were controlled in the final model. Adjustment for education, family income, alcohol consumption, age at menarche, age at first birth, menopausal status, ever exposed to coal cooking fumes, and major occupational exposures did not result in any material changes of the observed associations and were therefore not included in the final model. Women who reported having no family members with any cancers were treated as reference group. Testing for linear trend was done by including the number of affected relatives into the model as a continuous variable. All analyses were done in SAS 9.1 (SAS Institute, Inc.). All tests were two sided, with a significance level of 0.05.

Results

As shown in Table 1, lung cancer patients were generally older and had more children as compared with the cohort. The percentage reporting ever exposure to passive smoking at home and/or at work was lower in lung cancer patients than in the cohort. A higher percentage of lung cancer patients had <8 years of education than the cohort. The distributions of other selected factors, including family income and number of siblings, were similar in lung cancer patients and those in the cohort.

A family history of cancer overall or a history of cancer in parents was not associated with lung cancer risk [RR, 1.06 (95% CI, 0.76-1.48) for any cancer in first-degree relatives and 0.97 (95% CI, 0.65-1.45) for any cancer in parents], but having siblings with any cancer was associated with a 70% increased risk (RR, 1.70; 95% CI, 1.10-2.63; Table 2). The risk was higher, albeit statistically insignificant, when only tobacco-related cancers in siblings were considered (RR, 1.81; 95% CI, 0.88-3.72).

The numbers of cases with a history of specific types of cancer in relatives were small (Table 2). Having a family history of lung cancer was not related to risk of lung cancer (RR, 0.89; 95% CI, 0.42-1.91). However, lung cancer risk was elevated among those with a family history of colorectal cancer overall (RR, 2.38; 95% CI, 1.21-4.70), including a cancer history in both parents (RR, 2.33; 95% CI, 1.02-5.28) and siblings (RR, 2.63; 95% CI, 0.84-8.31). An excess lung cancer risk was also observed among women having siblings with cancer of the stomach (RR, 2.16; 95% CI, 1.01-4.65) and pancreas (RR, 4.19; 95% CI, 1.04-16.95). When we stratified the analyses by age, similar results were observed for women who were under age 55 years and for those

Table 2. Family history of selected cancer sites and risk of lung cancer among nonsmokers

	Cases	Person-years	RR* (95% CI)
Any cancers	46	147.50	1.06 (0.76-1.48)
Parents †	30	86.05	0.97 (0.65-1.45)
Siblings ‡	25	85.26	1.70 (1.10-2.63)
Tobacco-related cancers§	18	67.57	1.13 (0.69-1.85)
Parents †	12	40.65	1.02 (0.56-1.84)
Siblings ‡	8	34.57	1.81 (0.88-3.72)
Lung	7	24.58	0.89 (0.42-1.91)
Parents †	4	10.36	0.69 (0.25-1.86)
Siblings ‡	3	14.22	1.46 (0.46-4.59)
Esophagus	8	29.48	1.80 (0.88-3.67)
Parents †	7	24.53	1.96 (0.92-4.19)
Siblings ‡	1	4.95	0.97 (0.14-6.97)
Stomach	14	37.06	1.34 (0.77-2.33)
Parents †	7	17.01	0.97 (0.45-2.08)
Siblings ‡	7	20.05	2.16 (1.01-4.65)
Colorectum	9	31.81	2.38 (1.21-4.70)
Parents †	6	16.21	2.33 (1.02-5.28)
Siblings ‡	3	15.60	2.63 (0.84-8.31)
Liver	7	18.92	1.20 (0.56-2.57)
Parents †	4	10.04	1.13 (0.42-3.05)
Siblings ‡	3	8.87	1.32 (0.42-4.15)
Pancreas	3	13.51	1.93 (0.62-6.07)
Parents †	1	5.75	0.95 (0.13-6.83)
Siblings ‡	2	7.76	4.19 (1.04-16.95)
Breast	5	10.05	1.54 (0.63-3.76)
Parents †	1	0.21	0.67 (0.09-4.77)
Siblings ‡	4	9.85	2.45 (0.90-6.65)

*Adjusted for age, passive smoking, number of siblings, and number of children.
† Adjusted for age and passive smoking.
‡ Adjusted for age, passive smoking, and number of siblings.
§ Tobacco related cancers including cancer of the lung, oral cavity, pharynx, esophagus, pancreas, bladder, and kidney.

who were aged 55 years or older (data not shown). Exclusion of the small percentages of cases (n = 28) and cohort members (n = 9053) who reported never having been exposed to passive smoke did not materially alter the findings (data not shown).

Lung cancer risk increased further with increasing number of family members with cancer (P_{trend} = 0.0016; Table 3). The excess RR was restricted to women with multiple family members diagnosed with cancer, from 1.95 (95% CI, 1.08-3.54) for women with two affected family members to 3.17 (95% CI, 1.00-10.03) for those with three or more affected family members. The risk did not significantly increase with increasing number of family members diagnosed with tobacco-related cancers (P_{trend} = 0.4606). Exclusion of the first year of follow-up seemed to strengthen the results in general (data not shown).

Discussion

In this cohort study, lung cancer risk was elevated among women who had two or more first-degree relatives with any cancers, and the risk further increased with increasing number of affected family members. For most cancer types in relatives, as well as cancer overall or tobacco-related cancers, the association seemed to be stronger when the affected member was a sibling. No association was observed for a family history of lung cancer.

A number of studies have reported a positive association between lung cancer and a family history of lung cancer (6-9, 11-31). It has been suggested that this relationship largely reflects shared environmental factors, such as tobacco smoking, although inherited genetic susceptibility may play a role in familial lung cancers (14). To disentangle the role of genetic or other environmental or lifestyle factors from tobacco smoking in risk of family lung cancers, researchers have taken an approach to study familial aggregations among nonsmokers. The results, however, have been inconsistent. Whereas a few studies reported a significantly increased risk associated with a family history of lung cancer among lifetime nonsmokers (12, 15, 30), others including our study did not observe such an association (16, 20, 24, 28, 31-34). Although a meta-analysis indicated a significant increase in familial aggregation of lung cancers among nonsmokers, there was a significant heterogeneity among contributing studies (5).

We found an excess risk of lung cancer among those with relatives affected by most cancer types but not lung cancer. The associations were mostly restricted to those having an affected sibling but not a parent. This observation may suggest that shared environmental or lifestyle factors are more likely to play a key role in the development of lung cancer than inherited genetic susceptibility. To date, very few studies have investigated the risk of lung cancer in relation to family history of specific cancer types other than lung cancer. The significant associations we found with family histories of several digestive tract cancers, including cancers of the stomach, colorectum, and pancreas, in this nonsmoking population are intriguing. Several earlier studies have also reported an elevated risk of lung cancer associated with a family history of stomach/abdominal cancer (21), colorectal cancer (21), and digestive tract cancers (26, 34), although the relationships with the type of relatives (siblings or parents) have been inconsistent. If a consistent pattern is confirmed in further studies, it could present opportunities for identifying environmental and host genetic factors that may not have been previously considered for lung cancer etiology. To this end, studies among nonsmokers and prospective studies that collected exposure data, including active and passive smoke exposures, in both index subjects and

Table 3. Number of first-degree relatives with cancer and risk of lung cancer among nonsmokers

	Cases	Person-years	RR* (95% CI)
Any cancer			
1	31	105.88	0.86 (0.58-1.27)
2	12	29.14	1.95 (1.08-3.54)
3+	3	12.48	3.17 (1.00-10.03)
P_{trend}			0.0016
Tobacco-related cancers †			
1	16	59.93	1.07 (0.64-1.79)
2	2	7.64	2.03 (0.50-8.19)
3+	0		
P_{trend}			0.4606

*Adjusted for age, passive smoking, number of siblings, and number of children.
† Tobacco related cancers including cancer of the lung, oral cavity, pharynx, esophagus, pancreas, bladder, and kidney.

their relatives may provide an enhanced opportunity for discoveries of new etiologic factors.

Several strengths and potential limitations of this study should be considered in interpreting our findings. The high participation rate minimized selection bias. The large proportion of nonsmokers (97%) provided an opportunity to investigate the potential risk for non–smoking-related lung cancer, the etiology of which is poorly understood. Although the detailed information on passive smoking helps to minimize the potential confounding effect from passive smoking, residual confounding from passive smoking cannot be ruled out. Chance explanation may also play a role given the relatively small number of cases. Information on family history of cancer was collected from subjects' recall and no further efforts have been made to contact the relatives to verify the diagnosis. Because the information was collected before the disease onset, if there is a bias resulting from subjects' inaccurate recall, it is likely to be nondifferential and bias the results toward null. Because it is possible that some of the subjects are members of the same families, there may be some degree of nonindependence among individual observations. Information on tobacco smoking among first-degree relatives was not collected in this study. Previous studies showed similar results for the relationship between family cancer history and lung cancer risk before and after adjusting for tobacco smoking in relatives (28, 34), which argues against confounding by smoking among the relatives as an explanation for the observed associations.

In conclusion, the current study supports a moderate association of lung cancer risk with a family cancer history in general, but not with a family history of lung cancer specifically. The associations were stronger when a sibling rather than a parent was affected. The apparent link between lung cancer risk and a family history of colorectal, stomach, and pancreas cancers may warrant further investigation.

Acknowledgments

We thank the Shanghai residents who participated in the study and thank the research staff of the Shanghai Women's Health Study for their dedication and hard work.

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Cancer Epidemiol Biomarkers Prev 2007;16:2432-2435.