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Chronic rhinosinusitis and risk of lung cancer in the Singapore Chinese Health Study

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Abstract

Epidemiologic evidence suggests that chronic inflammatory conditions of the lung may increase lung cancer risk. These chronic conditions, such as chronic obstructive pulmonary disease and asthma, commonly coexist with chronic rhinosinusitis. We prospectively examined if chronic rhinitis or sinusitis was associated with lung cancer risk in the Singapore Chinese Health Study, a population-based cohort of 63,257 Singapore Chinese, who were aged 45–74 years when recruited between 1993 and 1998. Each subject completed a comprehensive interview on medical conditions, dietary and lifestyle factors at recruitment, and cancer occurrence and survival status were determined *via* linkage to population-based registries. As of 31 December, 2005, 954 cohort participants had developed lung cancer. Compared with subjects without such history, subjects who reported a history of physician-diagnosed rhinitis or sinusitis at baseline, whether allergic or nonallergic, had a statistically significant 59% increase in risk of lung cancer (hazard ratio [HR] = 1.59; confidence interval [CI] = 1.06–2.37). This association was significant and stronger in women (HR = 2.32; 95% CI = 1.23–4.39) compared to men, and for the adenocarcinoma cell type (HR = 1.91; 95% CI = 1.07–3.42) compared to other histologies. Overall, a history of asthma, hay fever, allergic dermatitis, food allergy or any other allergic conditions asked in a single question was not related to lung cancer risk (HR = 1.11; 95% CI = 0.90–1.36). Chronic rhinosinusitis may be a marker of pan-airway inflammation and its association with lung cancer risk provides evidence linking inflammation to lung carcinogenesis, especially among women.

Keywords

rhinosinusitis; lung cancer; rhinitis; sinusitis; Chinese

Lung cancer is among cancers with the highest incidence and mortality rates in many countries worldwide.[1] While cigarette smoking remains the most important risk factor, several epidemiologic studies have suggested that chronic inflammatory conditions of the lung, which can be triggered by allergenic, noxious or infective stimuli, may increase the risk of lung cancer. Among allergic conditions, bronchial asthma has been associated with a 2-fold increased risk of lung cancer in a meta-analysis of 4 cohort studies.[2] Severity of chronic bronchitis, which is a chronic inflammatory condition induced by cigarette smoking or pollution, has been associated with lung cancer risk in a dose-response relationship.[3] In lung infection, Chlamydia

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pneumoniae and Mycobacterium tuberculosis, both common respiratory pathogens, have been hypothesized to increase lung cancer risk.[4,5]

Although the nasal cavity, paranasal sinuses and lungs are considered separate organs of the respiratory tract, clinical epidemiologic and pathophysiologic studies suggest that a strong functional and immunological relationship exists among these 3 anatomical sites, and provide evidence for a combined upper and lower airway dysfunction that coexists in several prevalent respiratory conditions.[6] Nasal inflammation in rhinitis often coexists with sinus inflammation in sinusitis; these 2 conditions share the same prominent symptoms and are clinically indistinguishable.[7,8] Chronic rhinosinusitis, a term that combines these 2 conditions, in turn has been associated with clinically apparent asthma[6,9] or chronic obstructive lung disease (COPD).[10,11] Even in the absence of clinical symptoms, chronic rhinosinusitis is frequently associated with objective evidence of lower airway inflammatory involvement and bronchial hyperresponsiveness, suggesting that while the inflammatory process involving the upper airways is symptomatic, there is also chronic lower airway component of an overall lower severity that may not manifest clinically.[12] In this study, we prospectively examined if self-reported histories of physician-diagnosed chronic rhinitis or sinusitis were associated with lung cancer risk in the Singapore Chinese Health Study, a prospective cohort of 63,257 middle-aged and older Chinese men and women enrolled between 1993 and 1998.

Material and methods

Study population

The design of the Singapore Chinese Health Study has been described.[13] Briefly, the cohort was drawn from permanent residents or citizens of Singapore who resided in government-built housing estates (86% of the Singapore population resided in such facilities during the enrollment period). The age eligibility criterion was 45–74 years. We restricted recruitment to the 2 major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. Between April 1993 and December 1998, 63,257 subjects (about 85% of eligible subjects approached) were recruited. In the present study, we excluded 1,936 individuals with a baseline history of invasive cancer (except nonmelanoma skin cancer) or superficial, papillary bladder cancer from the analysis. Thus, the present study included 61,321 subjects. The study was approved by the Institutional Review Boards of the National University of Singapore and the University of Minnesota.

Baseline exposure assessment

At recruitment, an in-person interview was conducted in the home of the subject by a trained interviewer using a structured questionnaire. The questionnaire requested information on demographics, lifetime use of tobacco (cigarettes and water-pipe), current physical activity, menstrual/reproductive history (women only), occupational exposure, medical history, and family history of cancer. Information on current diet was assessed *via* a 165-item food frequency questionnaire that has been validated against a series of 24-hr dietary recall interviews[13] and selected biomarker studies[14,15] conducted on random subsets of cohort participants. The Singapore Food Composition Table, developed in conjunction with this cohort study, allows for the computation of intake levels of roughly 100 nutritive and nonnutritive compounds per study subject.[13]

The subjects were asked in 3 separate questions if they had a history of physician-diagnosed allergic rhinitis, nonallergic rhinitis or sinusitis. A subject with history of rhinosinusitis was one who said “yes” to any of the 3 conditions. In addition, in a single question, they were also asked if they had been diagnosed by a physician to have either asthma, hay fever, allergic dermatitis, food allergy or any other allergic conditions. For cigarette smoking, the study

population was divided into never, former and current smokers based on their choice of 3 possible responses to the following question, "have you ever smoked at least 1 cigarette a day for 1 year or longer." Subjects who answered "no" were classified as "never-smokers," those who answered "yes, but I quit smoking" were classified as "former smokers," and those who answered "yes, and I currently smoke" were classified as "current smokers." Ever smokers (former and current) were then asked about number of cigarettes smoked per day (6 categories from 6 or less to 43 or more); duration of smoking (5 categories from less than 10 years to 40 or more years); and number of years since quitting smoking (7 categories from less than 1 year to 20 years or more).

Case ascertainment

Identification of incident lung cancer cases and deaths among cohort members were accomplished by record linkage of the cohort database with databases from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases.[16] In our recent follow-up telephone/in-person interviews conducted between 1999 and 2004, among the 61,685 subjects (97.5%) that we had contact or follow-up information, only 17 subjects (0.03%) have migrated out of Singapore. This suggests that emigration is negligible among the subjects in the cohort. As of December 31, 2005, 954 cohort participants who were cancer-free at baseline had developed lung cancer. Eight hundred and thirty-two (87.2%) lung cancer cases were diagnosed histologically and their diagnoses were confirmed *via* manual review of pathology reports by a medically trained research staff. Eighty-nine (9.3%) cases were diagnosed clinically and 33 (3.5%) cases were identified through death certificates.

Data analysis

For each subject, person-years of follow-up, stratified simultaneously by calendar time and age at recruitment, were counted from the date of recruitment to the date of diagnosis of lung cancer, death, or December 31, 2005, whichever occurred first. Proportional hazards (Cox) regression methods were used to examine the associations between risk factors and risk of lung cancer.[17] All Cox regression models included age at recruitment (years), gender, dialect group (Hokkien, Cantonese), year of recruitment, level of education (no formal education, primary school, secondary or higher education), body mass index (kg/m^2 as continuous variable), number of cigarettes smoked per day (never smoker, 1–12, 13–22, or 23+), number of years of smoking (never smokers, 1–19, 20–39, or 40+), number of years since quitting smoking (continuous smokers, <1, 1–4, 5–19, 20+, or never smokers), dietary intakes of β-cryptoxanthin (mcg/1,000 kcal as continuous variable), and total isothiocyanates (μmol/1,000 kcal as continuous variable). These covariates were chosen because they were found to be associated with history of rhinosinusitis or incident lung cancer status (Table I), or established as factors associated with lung cancer risk in our previous studies among Chinese.[18,19]

Statistical computing was conducted using SAS version 9.1 (SAS Institute, Cary, NC) statistical software package. All *p* values quoted are 2-sided.

Results

In this population, 2.7% reported that they had been diagnosed to have either rhinitis or sinusitis. More males reported such conditions, and positive subjects were younger, more educated, less likely to be current smokers and more likely to report a history of asthma or other atopic/allergic conditions (Table I). As of December 31, 2005, among the 61,321 cohort members who were free of cancer at recruitment (601,529 total person-years of follow-up), after a mean follow-up time of 9.8 [standard deviation (SD), 2.5] years, 954 developed incident

lung cancer. Among the 954 lung cancer cases, 36.5% were adenocarinomas, 20.6% were squamous cell carcinomas, 10.4% were small cell carcinomas and the other 32.5% were either of other histological subtypes (14.6%) or of unknown histologies (17.9%). The mean age at diagnosis was 68.8 years for men and 69.0 years for women. Smoking was a very strong risk factor for lung cancer; 72.2% of subjects with lung cancer were ever smokers compared with 29.9% of those who remained free of lung cancer. Lung cancer cases were more likely to be males, older in age, and had lower level of education (Table I).

After adjustment for smoking history (including number of cigarettes smoked per day, number of years of smoking and number of years since quitting smoking), and other potential confounders including age, gender, education, body mass index and dietary intakes of beta-cryptoxanthin and isothiocyanates, subjects who reported a history of rhinitis or sinusitis, whether allergic or nonallergic, versus those without such a history at baseline, had a statistically significant 59% increase in risk of lung cancer (HR, 1.59; 95% CI, 1.06–2.37). This association was stronger for women than for men, for adenocarcinoma than for other cell types, and for never smokers than for ever smokers.

A total of 11.8% reported a history of physician-diagnosed asthma, hay fever, allergic dermatitis, food allergy or any other allergic conditions. The presence of 1 or more of these conditions, asked in a single question, was not related to lung cancer risk (HR, 1.11; 95% CI, 0.90–1.36) (Table II). Although there was an association among females (HR, 1.31; 95% CI, 0.94–1.84), the result was not statistically significant.

Discussion

Our results showed that chronic upper airway inflammation in the nasal or sinus mucosa may be associated with increased lung cancer risk. The association was stronger in women than men, for adenocarcinoma than for other cell types, and in never smokers than ever smokers. Conversely, we did not note any association between other allergic or atopic conditions and lung cancer risk.

The nasal cavity and paranasal sinuses are part of the upper airways and commonly thought of as a single clinical entity. Nasal and sinus inflammation coexist in rhinitis and sinusitis, and both conditions share the same prominent symptoms and are clinically indistinguishable. The term rhinosinusitis is often used to refer to an inflammatory process of the nasal cavity, which also includes the paranasal sinuses.[6–9] In our study, since our patients may not be able to distinguish rhinitis from sinusitis, we have defined a positive response to any of the conditions as having a history of rhinosinusitis. Prevalence of allergic rhinitis/rhinosinusitis differs by geographical regions.[20,21] In China, self-reported prevalence of allergic rhinitis ranges from 8.7 to 24.1% in 11 cities.[22] In another population-based study in Singapore, the rates of chronic rhinitis were highest (16.3%) in ages between 10 and 19 years and declined thereafter with age.[23] Furthermore, in this particular study, the prevalence of rhinitis, which was defined by self-reported presence of 2 or more nasal symptoms, was about 10% for those 40 years and above. However, only 53% with rhinitis sought medical help, suggesting that there is gross under-diagnosis of the condition in the community.[23] In our study, the low prevalence of rhinosinusitis is explained by our inclusion of only physician-diagnosed cases and the tendency for this non life-threatening condition to be under-diagnosed especially among older or less well-educated subjects. This hypothesis is supported by evidence that the prevalence of rhinosinusitis was positively associated with level of education in this cohort, and this association was not confounded by age, suggesting that the more educated subjects were more likely to seek consultation with the physician and obtain a diagnosis of rhinosinusitis from the doctor. Given that our study population was relatively uneducated (27.4% never received any formal education and 44.3% only had primary education), the low prevalence is therefore to

be expected. Nevertheless, since this is a prospective study, we have no evidence that this misclassification of exposure should be differential in terms of outcome. Hence, any impact on the results due to this under-reporting of rhinosinusitis would be an underestimation of the relative risk.

Both clinical observations and scientific evidence suggest that nasal/sinus passages are an integral part of the airways and pan-airway involvement of both the upper (nasal and sinuses) and lower (bronchi and lung) airways occurs through what has been described as "systemic cross-talk between the lung and the nose."[24] The association between rhinosinusitis and COPD is well described.[11] In a Swedish study involving both smokers and non-smokers, nasal symptoms were commonly reported with the bronchial disease in those with COPD.[10] In other studies, the prevalence of chronic nasal symptoms correlated with the clinical severity of COPD,[25] and therapy of the nasal and sinus disease was associated with improved pulmonary function.[26,27] In smokers with rhinosinusitis but without clinically apparent COPD, there was striking similarity in the inflammatory patterns with increased infiltration of CD8 T lymphocytes and squamous cell metaplasia in both the nose and bronchi.[28] The relationship between rhinitis and asthma is also well recognized,[29] and document based on the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines has recommended that a patient with rhinitis be evaluated for asthma, and vice versa.[30] In fact, rhinitis often precedes the onset of asthma and is associated with more severe asthmatic symptoms.[31,32]

Possible mechanisms underlying the shared pathophysiology between the upper and lower airway are the so-called nasal-bronchial reflex, inflammation caused by smoking, mouth breathing caused by nasal obstruction and pulmonary aspiration of nasal contents.[11] Regardless of the nature of the trigger, chronic rhinosinusitis may affect the lower airways by the aspiration of inflammatory exudates into the lower airways through aspiration and thus leading to deterioration of lung function and increased airway responsiveness. Another explanation is the nasal-lower airway interaction model from the work of Braunstahl *et al*.,[33] which suggested that the nasobronchial immunologic cross-talk in chronic rhinitis could lead to generalized airway inflammation through upregulation of adhesion molecules. Our study provides the first epidemiological evidence that rhinosinusitis is a risk factor for lung cancer, and another observation of a link between a disease of the upper airway in chronic rhinosinusitis and another disease of the lower airway in lung cancer.

The findings in this study are also consistent with the growing body of epidemiologic evidence that links inflammation with lung cancer etiology. Although tobacco contains a great number of chemical carcinogens that may directly induce damage to DNA, tobacco-induced lung damage can lead to dysregulated inflammatory response,[34,35] which in turn has been postulated as one of the mechanistic pathways of lung carcinogenesis among smokers.[35] Tobacco smoke contains high concentrations of oxidants and free radicals that can activate NF-κB and other inflammation-related genes, leading to a cascade of events (increased apoptosis, matrix degeneration, and intense inflammatory and immune responses) commonly described as the "hallmarks of COPD."[35] Among smokers, subjects with COPD versus those without possess a higher risk of lung cancer.[3,36] More recently, genes involved in the inflammation pathway have been linked to increased lung cancer risk among heavy smokers,[37] suggesting that chronic inflammation may be a cofactor to smoking in lung carcinogenesis. In lifetime nonsmokers, there is epidemiologic evidence that chronic inflammatory conditions of the lung from allergenic, infective or noxious stimulus, such as tuberculosis, chronic bronchitis, emphysema, pneumonia and asthma, increase risk of lung cancer.[4,38–41] Taken together, these studies demonstrate that aberrant and excessive inflammatory response in the lung, regardless of the nature of its initiation and maintenance, may lead to cancer development.

Interestingly, our data suggests that the association between rhinosinusitis and lung cancer was stronger in women compared with men. In general, women have higher immunoreactivity and are more prone to aberrant immune responses such as autoimmune diseases.[42] Hence, a possible explanation for the stronger association with lung cancer among women is that the rhinosinusitis may be more severe in women compared to men. Another biologically plausible explanation is that dysregulated immune response that promotes lung carcinogenesis is facilitated by an estrogen-driven pathway. A high prevalence of epidermal growth factor receptor (EGFR) gene mutation has been observed in lung cancer among Asian women, especially of the adenocarcinoma cell type, suggesting that this group may have distinct etiology.[43,44] EGFR has been implicated in both immunoreactivity of airway in asthma[45] and lung cancer carcinogenesis,[44,46] and there is evidence for an interaction between the estrogen receptor-signaling and the EGRF-signaling pathways in promoting mitogenesis in non-small cell lung cancer.[47,48] Adenocarcinoma is the histologic subtype of lung cancer most commonly associated with “scars” from previous episodes of chronic inflammation.[49,50] Hence, it is not surprising that the association between chronic rhinosinusitis and lung cancer in our study is stronger for adenocarcinoma versus other cell types.

Since rhinosinusitis commonly coexists with asthma, we would expect asthma to be associated with increased lung cancer risk. Asthma has been associated with a 2-fold increased risk of lung cancer in a meta-analysis.[2] However, systemic atopic conditions such as hay fever, allergic dermatitis and food allergies have shown null or negative associations with lung cancer risk.[51–54] This suggests that possible mechanism that may possibly link asthma to increased lung cancer risk is the chronic mucosal inflammation in the lung, and not the Th2-dominated hyperactivity of the immune system *per se*. Unfortunately, we were not able to differentiate between the effects of asthma and other systemic atopic conditions since we had asked about them in a single question.

The strengths of the present study include its population-based design, large number of genetically homogenous subjects, detailed information on cigarette smoking, comprehensive food frequency data, and information on medical history and lifestyle factors obtained through in-person interview at enrollment. We had highly complete follow-up for incidence of cancer and death among cohort participants through computer linkage to databases of the population-based death and cancer registries. Majority of lung cancer cases (96.5%) were verified through manual review of pathological reports and medical records. A major limitation is the self-reported nature of the medical conditions, and lack of information on the severity and duration of rhinosinusitis.

In conclusion, we report a novel finding that chronic rhinosinusitis may be associated with increased lung cancer risk, especially among women. This observed association is consistent with experimental and epidemiological data linking chronic airway inflammation with lung cancer development. Our findings also serve to better define the subpopulation at high risk for lung cancer.

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TABLE I

BASELINE CHARACTERISTICS OF COHORT MEMBERS (MEAN AND STANDARD DEVIATION OR NUMBER AND %) BY HISTORY OF RHINOSINSUSITIS AND INCIDENT LUNG CANCER STATUS, THE SINGAPORE CHINESE HEALTH STUDY

	Rhinosinusitis[1]		Lung cancer[2]	
	No (*n* = 59,683)	**Yes (*n* = 1,638)**	**No (*n* = 60,367)**	**Yes (*n* = 954)**
Age (years) at recruitment	56.5 (8.0)	54.1 (7.4)	56.3 (8.0)	62.6 (7.2)
Body mass index (kg/m^2)	23.1 (3.3)	22.8 (3.4)	23.1 (3.3)	22.3 (3.0)
Gender				
Males	26,439 (44.3%)	835 (51.0%)	26,622 (44.1%)	656 (68.8%)
Females	33,244 (55.7%)	803 (49.0%)	33,745 (55.9%)	298 (31.2%)
Dialect				
Cantonese	27,394 (45.9%)	952 (58.1%)	27,950 (46.3%)	374 (39.2%)
Hokkien	32,289 (54.1%)	686 (41.9%)	32,417 (53.7%)	580 (60.8%)
Level of education				
No formal education	16,472 (27.6%)	210 (12.8%)	16,359 (27.1%)	310 (32.5%)
Primary school (1–6 years)	26,559 (44.5%)	644 (39.3%)	26,743 (44.3%)	502 (52.6%)
Secondary and above	16,652 (27.9%)	784 (47.9%)	17,265 (28.6%)	142 (14.9%)
Cigarette smoking				
Never smokers	41,420 (69.4%)	1,168 (71.3%)	42,317 (70.1%)	265 (27.8%)
Former smoker	6,446 (10.8%)	247 (15.1%)	6,520 (10.8%)	138 (14.5%)
Current smokers	11,817 (19.8%)	223 (13.6%)	11,530 (19.1%)	551 (57.7%)
Age at starting to smoke[3]	20.2 (6.1)	20.2 (6.2)	20.3 (6.1)	18.8 (5.8)
Cigarettes/day[3]	17.3 (11.4)	17.7 (12.2)	17.2 (11.4)	19.1 (11.6)
Years of smoking[3]	33.1 (11.6)	28.8 (12.9)	32.7 (11.7)	40.3 (8.3)
Allergic/atopic condition				
No	52,939 (88.7%)	1,181 (72.1%)	53,244 (88.2%)	850 (89.1%)
Asthma, hay fever, skin allergy, food allergy or any other allergy	6,744 (11.3%)	457 (27.9%)	7,123 (11.8%)	104 (10.9%)

[1] All differences between subjects with rhinosinusitis and those without were statistically significant at 2-sided $p < 0.001$ except for age at smoking ($p = 0.963$) and number of cigarettes per day ($p = 0.417$) among the ever smokers.

[2] All differences between subjects with lung cancer and those without were statistically significant at 2-sided $p < 0.001$ except for association with allergic/atopic conditions ($p = 0.408$).

[3] Among ever smokers only.

TABLE II

HISTORY OF RHINOSINUSITIS OR ASTHMA/ALLERGY/ATOPY IN RELATION TO RISK OF LUNG CANCER, THE SINGAPORE CHINESE HEALTH STUDY

	Rhinosinusitis			Asthma/Allergy/Atopy		
	Person-years	Cases	HR (95% CI)[1]	Person-years	Cases	HR (95% CI)[1]
All subjects						
No	586,244	929	1.00	534,612	850	1.00
Yes	15,285	25	1.59 (1.06–2.37)	66,917	104	1.11 (0.90–1.36)
Males						
No	253,270	641	1.00	234,242	593	1.00
Yes	7,736	15	1.32 (0.79–2.21)	26,765	63	1.00 (0.77–1.30)
Female						
No	332,973	288	1.00	300,370	257	1.00
Yes	7,549	10	2.32 (1.23–4.39)	40,152	41	1.31 (0.94–1.84)
Adenocarcinoma						
No	582,844	336	1.00	531,507	314	1.00
Yes	15,227	12	1.91 (1.07–3.42)	66,564	34	0.97 (0.68–1.39)
Squamous/small cell carcinomas						
No	582,466	290	1.00	531,101	263	1.00
Yes	15,206	6	1.34 (0.59–3.01)	66,570	33	1.14 (0.79–1.64)
Never smokers						
No	414,568	255	1.00	378,178	237	1.00
Yes	11,042	10	1.84 (0.97–3.47)	47,432	28	1.04 (0.70–1.54)
Ever smokers						
No	171,675	674	1.00	156,434	613	1.00
Yes	4,244	15	1.43 (0.86–2.40)	19,486	76	1.14 (0.90–1.45)

[1] All HRs are adjusted for age at enrollment, year of enrollment, gender (for total sample), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, and secondary or higher education), body mass index (kg/m^2, continuous), number of cigarettes smoked per day (never smoker, 1–12, 13–22, or ≥23), number of years of smoking (never smokers, 1–19, 20–39, or ≥40), number of years since quitting smoking (continuous smokers, <1, 1–4, 5–19, ≥20, or never smokers), and dietary intakes of β-cryptoxanthin (mg/1,000 kcal) and total isothiocyanates (μmol/1,000 kcal).