**Carcinogenesis** vol.27 no.6 pp.1240–1244, 2006
doi:10.1093/carcin/bgi309
*Advance Access publication December 12, 2005*

# Joint effect of asthma/atopy and an IL-6 gene polymorphism on lung cancer risk among lifetime non-smoking Chinese women

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**Recent evidence suggests that inflammatory pathways are important mediators of carcinogenesis. Asthma, allergic rhinitis and atopic dermatitis are clinical manifestations of a systemic atopic disorder, which is associated with airway hyper-responsiveness and inflammation. We examined the effect of a history of asthma/atopy among 132 lung cancer cases (of which 72% were adenocarcinomas) and 163 controls, all of whom were non-smoking Chinese women, in combination with a single nucleotide polymorphism (−634C/G) in the interleukin-6 (IL-6) gene which regulates secretion of a pro-inflammatory cytokine found to be predominant in lung tumour tissue. We observed a slight increase in risk of lung cancer [odds ratio, OR = 1.5, 95% confidence interval (95% CI) = 0.8–2.6] and of adenocarcinoma (OR = 1.6, 95% CI = 0.9–3.1) with asthma/atopy alone. There was no effect of the IL-6 CG/GG genotype on lung cancer risk on its own. Among individuals with both asthma/atopy and the IL-6 −634 G allele, however, risk was increased at least 3-fold (OR = 3.1, 95% CI = 1.2–8.3 for all cancers and OR = 4.2, 95% CI = 1.5–11.6 for adenocarcinomas) relative to individuals with no asthma/atopy and the CC genotype. On stratified analysis, a significant increase in risk with asthma/atopy was restricted to those with the at-risk genotype ($P_{int} < 0.05$). Our findings are consistent with the role of chronic inflammation as an aetiologic factor among non-smoking Asian women, and suggest that asthma/atopy is a risk marker for susceptibility to the development of lung cancer.**

## Introduction

There is a growing recognition that inflammatory pathways play an important role in malignant transformation (1–4). Chronic inflammation is likely to be a key factor in the development of lung cancer, as attested to by genetic and molecular studies of inflammatory markers such as cytokines and COX-2 in lung tumour tissue (5–7) and gene polymorphisms in peripheral blood (8). Although this has recently been established in smoking-induced lung tumours (9), there is evidence that this may also be a key pathway among non-smokers (10), for whom the aetiology is incompletely understood. Epidemiologic studies have shown that tuberculosis, chronic bronchitis, emphysema, pneumonia and asthma increase risk of lung cancer among lifetime non-smokers in the United States and in China (11–15).

Asthma, allergic rhinitis and atopic dermatitis are closely associated manifestations of a systemic atopic disorder which may be either allergic or non-allergic in origin (16), and is characterized by both acute and chronic inflammatory processes (17–20). Longitudinal studies document a progression in clinical signs of this disorder between the skin and the upper and lower airways over time (21). While asthma has been shown to increase risk of lung cancer by ∼80%, based on a recent meta-analysis of epidemiologic studies (22), the association between lung cancer and other forms of atopy is much less clear (23).

Cytokines are important mediators of the inflammatory response. Interleukin-6 (IL-6) is a pro-inflammatory cytokine which plays a central role in host defense mechanisms (24). It induces the expression of acute-phase inflammatory response elements such as COX-2, NFκβ and C-reactive protein, which in turn result in the production of reactive oxygen species (ROS) by activated leukocytes (25,26). ROS are potent inducers of oxidative DNA damage in the surrounding cells, and have been implicated as part of the mechanism by which chronic inflammation enhances risk of carcinogenesis (27). IL-6 has been found to be the predominant cytokine detected at elevated levels in lung tumour tissue (5,28,29), in sera of lung cancer patients relative to controls (30), and appears to be an independent mediator of C-reactive protein levels in lung cancer patients (31). Several single-nucleotide polymorphisms in the IL-6 gene have been described, the most well-studied of which is a −174G→C polymorphism in the promoter region. While individuals with the G allele at this position exhibit an increased inflammatory response (32), there is also evidence that transcriptional regulation of IL-6 is governed by cooperative influence of several polymorphic sites (33). The −174 C allele polymorphism is extremely rare in Asian populations (34,35), among whom a more common and potentially useful marker has been reported at position −634 (C→G) in the promoter region of the gene (36). The −634 G allele is associated with an elevated production and secretion of IL-6 by peripheral blood mononuclear cells *in vitro* (37).

In the light of the current understanding of inflammation as a key pathway in carcinogenesis, we sought to examine if risk of lung cancer was influenced by a prior history of asthma or atopy, in combination with the IL-6 −634 C→G polymorphism, in a population of non-smoking Singapore Chinese women.

**Abbreviations:** CI, confidence interval; IL-6, interleukin-6; OR, odds ratio.

 

## Materials and methods

Participants were drawn from a hospital-based case–control study on lung cancer among Chinese women, which has been described elsewhere (38). Briefly, incident cases were primary lung cancers diagnosed at one of three major hospitals in Singapore between April 1996 and September 1998. Controls were patients admitted to the same hospitals, not for malignant or chronic respiratory conditions. Cases and controls were frequency-matched by 10 year age groups, and the response rate among eligible cases and controls were 95.0 and 96.9%, respectively; written consent was obtained from all participants.

Demographic information, data on smoking and other relevant exposures were obtained by in-person interview with a trained nurse. A lifetime non-smoker was one who responded negatively to the question: 'Have you ever smoked a cigarette or any other form of tobacco, at least once a day for 1 year?' Intake frequencies (per week) and portion size (in multiples of a standard serving) of 20 vegetables and 13 varieties of fruit commonly eaten in this country were used to compute an index of fruit and vegetable consumption in the 3 years preceding admission or diagnosis. As part of their medical history, participants were asked if they ever had any of the following illness: tuberculosis, chronic bronchitis, asthma and allergic rhinitis/allergic skin disorder; uncertain responses were coded as 'no'. For each of the conditions, interviews were trained to use standardized translations which were in common use and would be easily understood by respondents who spoke Mandarin or local dialects.

A consecutive sub-sample of 420 participants in the study (233 cases and 187 controls) consented to donate a blood specimen for genotyping. Of these, 295 (132 cases and 163 controls) were lifetime non-smokers, and form the study population for this report. This study was approved by the Institutional Review Board of the National University of Singapore.

Among the cases included in the analysis, >90% (122, 92.4%) were pathologically confirmed. We were able to review and confirm the histological subtype for 107 (87.7%) of these individuals whose material was available to us. In addition, clinical records of all cases were reviewed 3 years after the close of the study, to ascertain that there was no subsequent evidence of an occult primary tumour which was undiagnosed at the time of recruitment.

Isolation of genomic DNA from peripheral lymphocytes was carried out using the standard proteinase K-phenol–choloroform procedure (39) and DNA was stored at −30°C till analysis. The IL6-634 GC polymorphism was determined by PCR followed by restriction fragment-length polymorphism analysis. The PCR product (180 bp) was amplified using forward primer 5′-GAGACGCCTTGAAGTAACTG-3′ and reverse primer 5′-AACCAAA-GATGTTCTGAACTGA-3′ with *Taq* Polymerase (Promega, USA) in the presence of 1.5 mM $Mg^{2+}$. Cycling parameters were: denaturation at 95°C (45 s), annealing at 48°C (45 s), extension at 72°C (60 s) for 40 cycles with final extension at 72°C for 10 min. Digestion was performed with *Bsr*BI (New England Biolabs, USA), at 37°C for 3 h. The C allele has no *Bsr*BI cleavage site, whereas the PCR product is cleaved into two fragments of 120 and 60 bp in the presence of the G allele.

We used unconditional logistic regression to compute adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for the association between lung cancer risk and history of asthma/atopy and IL6-634 genotype. These were adjusted for age, fruit and vegetable intake, place of birth and exposure to environmental tobacco smoke. The interaction between the asthma/atopy and the IL-6 −634 polymorphism was evaluated using a full model containing the first level and interaction terms, adjusted for the same confounders. All analysis were performed on the SPSS Win 13.0 statistical package (SPSS, Chicago, IL).

## Results

Table I provides a comparison of selected characteristics among cases and controls—cases were more likely to be born in China and their fruit and vegetable consumption was lower than among controls (Mann–Whitney *U*-test $P < 0.01$). Differences in reported exposure to environmental tobacco smoke were not statistically significant.

A total of 124 cases and 162 controls were successfully genotyped. The prevalence of the G allele was 22.6%, and distribution of the genotype frequencies conformed to that expected under the Hardy–Weinberg equilibrium.

**Table I.** Distribution of selected characteristics among cases and controls, Singapore Chinese women non-smokers ($N = 288$)

| | Cases ($n$, %) $N = 126$ | Controls ($n$ ,%) $N = 162$ |
|---|---|---|
| Age in years[a] (mean, SD) | 62.0 ± 13.7 | 63.4 ± 12.3 |
| Years of formal education (mean, SD) | 3.52 ± 4.18 | 3.80 ± 4.75 |
| Birthplace | | |
| Singapore/Malaysia | 82 (65.1) | 130 (80.2) |
| China/other | 44 (34.9) | 32 (19.8) |
| Servings of fruit and vegetable per week | | |
| Mean, SD | 30.5 ± 47.4 | 34.3 ± 21.8 |
| Median | 24.4 | 29.5 |
| Exposure to environmental tobacco smoke at home | | |
| Daily | 46 (36.5) | 72 (44.4) |
| Weekly < daily | 16 (12.7) | 15 (9.3) |
| Less than weekly | 64 (50.8) | 75 (46.3) |
| Self-reported history of | | |
| Asthma only | 7 (5.6) | 4 (2.5) |
| Allergic rhinitis or atopic dermatitis | 26 (20.6) | 23 (14.2) |
| Both of the above | 3 (2.4) | 6 (3.7) |
| IL6-634 genotype | | |
| *CC* | 70 (56.5) | 97 (59.9) |
| *CG* | 46 (37.1) | 55 (34.0) |
| *GG* | 8 (6.5) | 10 (6.2) |
| Histological subtype | | |
| Squamous/small cell carcinoma | 14 (11.9) | |
| Adenocarcinoma | 85 (72.0) | |
| Large cell undifferentiated/not otherwise specified | 19 (16.1) | |

All participants are Chinese women, cases and controls frequency-matched for age.
[a]Refers to age at diagnosis (cases) and age at interview (controls).

Approximately one-fifth of our participants (23.0% of cases and 17.9% of controls) reported a history of atopy, manifested either as allergic rhinitis or atopic dermatitis. The corresponding figures for asthma were 7.9 and 6.2%, respectively. The number of participants reporting a past history of tuberculosis ($n = 15$) or chronic bronchitis ($n = 3$) was too small for further analysis.

A history of asthma or atopy conferred a 45% increase in risk of lung cancer for all histological types combined (Table II); when adenocarcinomas were considered separately, the adjusted OR was 1.6—in both cases this was not statistically significant. There was no association between lung cancer risk and the presence of the IL-6 −634 G allele (adjusted OR 1.1 for all histological types and for adenocarcinomas). However, individuals with both asthma/atopy and the CG/GG genotype had a significantly elevated risk; 3-fold for all histologies (adjusted OR = 3.1, 95% CI = 1.2–8.3) and 4-fold for adenocarcinoma (adjusted OR = 4.2, 95% CI = 1.5–11.6), relative to individuals with no history of asthma/atopy and who were of the IL6-634 CC genotype. When stratified by history of asthma or atopy; CG/GG genotype did not significantly influence risk among individuals negative for these conditions. However, among those who were positive, the OR for lung cancer associated with a CG/GG genotype was 3.8 (95% CI = 1.3–11.8) and for adenocarcinoma the corresponding OR was 8.0 (95% CI = 2.3–27.3). In both cases, the multiplicative interaction term was statistically significant (Table II).

**Table II.** Odds ratios and 95% CI for association between asthma/atopy, IL6-C634G polymorphism and lung cancer among Singapore Chinese women non-smokers

| | | All histological types | | Adenocarcinoma only | |
|---|---|---|---|---|---|
| | | Cases/controls | OR[a] | Cases/controls | OR[a] |
| History of asthma, allergic rhinitis or atopic dermatitis | | | | | |
| None | | 90/129 | 1.0 | 58/129 | 1.0 |
| One or more | | 36/33 | 1.5 (0.8–2.6) | 27/33 | 1.6 (0.9–3.1) |
| IL6-634 genotype | | | | | |
| *CC* | | 70/97 | 1.0 | 46/97 | 1.0 |
| *CG*/*GG* | | 54/65 | 1.1 (0.7–1.8) | 37/65 | 1.1 (0.6–2.0) |
| History of asthma, allergic rhinitis or atopic dermatitis | IL6-634 genotype | | | | |
| None | *CC* | 53/71 | 1.0 | 37/71 | 1.0 |
| One or more | *CC* | 17/26 | 0.8 (0.4–1.7) | 9/26 | 0.5 (0.2–1.3) |
| None | *CG*/*GG* | 36/58 | 0.8 (0.5–1.4) | 20/58 | 0.6 (0.3–1.1) |
| One or more | *CG*/*GG* | 18/7 | 3.1 (1.2–8.3) | 17/7 | 4.2 (1.5–11.6) |
| None | *CC* | 53/71 | 1.0 | 37/71 | 1.0 |
| | *CG*/*GG* | 36/58 | 0.8 (0.5–1.4) | 20/58 | 0.6 (0.3–1.1) |
| One of more | *CC* | 17/26 | 1.0 | 9/26 | 1.0 |
| | *CG*/*GG* | 18/7 | 3.9 (1.3–11.8) | 17/7 | 8.0 (2.3–27.3) |
| | | | $P_{int} = 0.013$ | | $P_{int} < 0.001$ |

$P_{int} = P$ for interaction between asthma/atopy and IL6-634 genotype.
[a]Adjusted for age and fruit and vegetable intake (standard servings per week), place of birth (Singapore/Malaysia, China/Other) and exposure to environmental tobacco smoke (daily/less often than daily).

## Discussion

To our knowledge, this is the first report to demonstrate an interaction between asthma/atopy and a cytokine gene polymorphism in influencing risk of lung cancer among non-smokers. Our observation that a positive association between lung cancer and a past history of asthma or atopy is enhanced in persons who also possess the IL-6 CG/GG genotype supports the role of inflammation as a mediator for lung carcinogenesis, and for adenocarcinomas in particular, in these individuals.

The current understanding of the patho-biology of asthma and other allergic conditions is that atopy is a systemic disorder that may be manifest in the skin or airways or both (19,40,41). Airway hyper-reactivity and allergic skin inflammation occur concurrently in response to the same stimuli *in vivo* (42), and atopic dermatitis and allergic rhinitis are often the first steps towards the development of asthma (40–42). It has been reported that 39% of patients with allergic rhinitis have concomitant bronchial asthma, and 48% have atopic dermatitis (43), suggesting these may be governed by common determinants, including subsets of genes (44). The underlying pathology in the atopic syndrome is that of a persistent chronic inflammatory state, with episodes of acute inflammation corresponding to clinical exacerbations (17,19). Indeed, the asthmatic lung appears to be more susceptible to oxidant injury as a result of these inflammatory processes (45).

The emerging picture from epidemiologic studies of asthma and lung cancer is of a consistent elevation in risk that does not appear to be confounded by smoking. Wang and Diepgen (23) reviewed published studies on this topic since 1985, and concluded that despite mixed results for other sites, the data pointed consistently to a positive association. This is generally, although not uniformly, borne out by large prospective studies (46–50). A recent meta-analysis examined this association in 18 studies, and found a combined relative risk of 1.7 (95% CI = 1.3–2.2) for asthmatics among studies which controlled for smoking history; for analyses restricted to non-smokers, the combined estimate was 1.8 (95% CI = 1.3–2.3) (22). On the other hand, the relationship between other forms of atopy, and cancer is controversial. Although early studies on atopy found an inverse relationship between hay fever and lung cancer (51,52), recent reports show that the effect is absent when non-smokers were considered alone (46,53), or after adjustment for smoking (54).

The limitations of the present study should be borne in mind. The most important of these is the use of self-reports for asthma and for other manifestations of the atopic syndrome. In administering the questionnaire, we used both their conventional translations as well as lay terms adopted by medical professionals for each of these conditions, that are widely understood by middle-aged and elderly Chinese to mean allergic conditions manifest as wheezing, running nose and skin rashes, respectively. As with all case–control studies, there is a potential for differential recall bias, with cases more likely to recall a history of these medical conditions as a result of their lung cancer. This may be less severe in a hospital-based study, given that controls are also patients with medical conditions. Another possible source of bias is misdiagnosis of asthma, or symptoms that were actually indicative of other chronic bronchitis or emphysema, or even lung cancer. The current study population of non-smokers would be least susceptible to this bias; although we cannot rule out early lung cancer as a cause for symptoms as we did not record the length of time by which diagnosis of asthma preceded occurrence of lung cancer.

The strengths of the study are that it is conducted in an ethnically homogenous population, among which close to 90% of cancers were histologically confirmed. Since all participants were women, there is less likelihood of confounding by unmeasured exposures, e.g. in the workplace. Importantly, we demonstrate that a significant association between atopy and lung cancer is restricted to individuals who also possess the IL-6 634 G allele. It is unlikely that a spurious relationship between atopy and lung cancer, including one arising through recall bias, would demonstrate this specificity.

Our results are provocative in the light of recent findings that activating mutations in the epidermal growth factor receptor (EGFR) are more prevalent among non-smokers, Asians and females, and are characteristically found in adenocarcinomas (55,56). EGFR is a trans-membrane receptor tyrosine kinase which mediates cellular responses to many external stimuli (57). EGFR activation is also known to play an important role in allergic airway inflammation and remodelling (58,59), and there is evidence that a persistent pro-inflammatory state in severe asthma is a result of disordered tyrosine kinase pathways (60,61).

A unique feature of this report is that we have attempted to include all clinical manifestations of the atopic syndrome, as an indicator of a systemic propensity to inflammation, which, even if not clinically recognizable in the lung, are likely to be indicative of airway sensitivity and responsiveness. Close to 20% of women in this consecutive series of non-smoking lung cancer patients had both asthma/atopy and the at-risk genotype. While these findings need to be replicated in larger, prospective studies, they support the role of chronic inflammation as an aetiologic factor in this population, and suggest that asthma and atopy may be risk markers for vigilance in prevention or early detection of lung cancer.

## Acknowledgements

We are grateful to the participants of the study on Lung Cancer in Chinese Women, and to the Medical Boards of the National University Hospital, Singapore General Hospital and Tan Tock Seng Hospital. This work was funded by the National Medical Research Council, Singapore (NMRC1996/0155).

*Conflict of Interest Statement*: None declared.

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*Received September 23, 2005; revised October 30, 2005; accepted December 6, 2005*