

A meta-analysis of asthma and risk of lung cancer (United States)

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Abstract

Objective: To review epidemiologic evidence that asthma is a risk factor for lung cancer, with particular attention to the role of smoking on this association.

Methods: Through MEDLINE computer searches (January 1966 to April 2002) and a review of references, we identified studies with quantitative data on the relation of asthma to lung cancer. Summary estimates of relative risks (RR) were calculated using the fixed-effects model or the random-effects model as appropriate.

Results: The combined results from five case-control studies – that presented data limited to individuals who had never smoked – showed a 1.8-fold increase in lung cancer risk among asthmatics (95% confidence interval (CI) = 1.3–2.3). The results from six case-control and four cohort studies, which controlled for smoking history also were significant (RR = 1.7; 95% CI = 1.3–2.2). Finally, to illustrate the potential confounding by tobacco, we combined data from seven cohort studies that did not control for smoking history and found an overall RR of 1.4 (95% CI = 1.2–1.6).

Conclusions: The increased risk of lung cancer among never smoking individuals with asthma supports a direct relation between asthma and lung cancer. There is biological evidence to support this association.

Abbreviations: CI – confidence interval; RR – relative risk

Introduction

Lung cancer is the second most commonly occurring noncutaneous cancer in the United States and the leading cause of cancer death [1]. Worldwide, lung cancer kills over one million people each year [2]. Although smoking has been identified as the major risk factor for lung cancer [3, 4], approximately 10% of lung cancer deaths are not attributable to smoking [5–7]. Despite its large public health impact, the aetiology of lung cancer among nonsmokers is poorly defined. Over the past decade, several epidemiological studies have

established previous nonmalignant lung disease (such as emphysema, chronic bronchitis, pneumonia or tuberculosis) as a risk factor for lung cancer among nonsmokers [8–12]. However, the association between asthma and risk of lung cancer is uncertain.

Initial studies relating asthma and risk of lung cancer reported an inverse association [13–18]. Asthma may decrease the risk of lung cancer by increasing immunological surveillance of cancer cells [17]. Alternatively, although many asthmatics smoke, asthmatics could be protected from lung cancer because of the somewhat lower prevalence of current smoking found in these patients compared to the general population [12, 15, 16]. More recent studies, however, reported a positive association between asthma and risk of lung cancer, even among nonsmoking asthmatics [10–12, 19–21]. Asthma may increase the risk of lung cancer by reducing the clearance of toxins and carcinogens in the

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bronchoalveolar epithelium [10–12], by chronic inflammation of the airways [11, 12] or *via* the immune system [11]. Given the high prevalence of asthma and the high incidence and mortality of lung cancer in developed countries, an association between these two disorders would have important public health implications. Thus, we reviewed the medical literature and conducted a meta-analysis to estimate the magnitude of any association between asthma and lung cancer risk. The primary objective was to disentangle the role of smoking on the relation of asthma to risk of lung cancer.

Materials and methods

Literature review

We searched the MEDLINE database (US National Library of Medicine) from January 1966 to April 2002 to obtain all publications with quantitative data regarding the association between asthma and risk of lung cancer; we identified articles using the Medical Subject Headings term ‘asthma’ or textword terms ‘asthma’, ‘allergy’ and ‘atopy’, and the Medical Subject Headings terms ‘neoplasm’ and ‘lung neoplasms’ or the textword terms ‘cancer’ and ‘lung cancer’. We conducted secondary searches for additional studies of previous lung disease and lung cancer risk, using the Medical Subject Headings terms ‘respiratory tract diseases’ or ‘lung diseases’ and ‘lung neoplasms’. The search was followed by manual examination of the reference lists of included articles, review articles and standard texts.

A total of 29 articles were reviewed to determine eligibility for the meta-analysis [10–38]. We excluded studies that did not provide estimates of risk of lung cancer in relation to asthma and a measure of precision (*i.e.*, a standard error or CI) or sufficient information to calculate such a measure [36, 37]. All studies included in the meta-analysis were unique contributions; if an investigator had published more than one study or if results concerning similar populations were reported several times [10, 29, 33, 38], then the other studies would be included only if all study populations were independent [10, 29]. In studies that met our inclusion criteria but lacked important data, we attempted to contact the authors for the needed information [12]. We excluded six potentially relevant studies [13, 15, 17, 18, 34, 35] for a variety of reasons. The study of Osann [17] was excluded, because the case definition required asthma and hay fever, and hay fever was found to have a protective effect against lung cancer in one study [19]. We excluded the study by Samet *et al.* [34] because 71% of asthmatics also had chronic bronchitis or emphy-

sema. The studies of Gabriel *et al.* [13] and Polednak [35] were excluded, because the definition of asthma was unclear. Finally, we excluded the studies by Ford and Eriksson [15, 18] because the number of cases with lung cancer was very small (two and one, respectively). Thus, for the present meta-analysis, we summarized results of eight case-control studies [10–12, 19–24], in which lung cancer cases and controls free from this malignancy are identified and information on asthma history before diagnosis is obtained and compared, and 10 cohort studies [14, 16, 25–32], in which individuals with or without asthma are followed up for subsequent occurrence of lung cancer. Several studies with more than one set of results presented their findings for subgroups of smoking history (never smokers, former smokers, adjusted for smoking history).

Statistical methods and analysis

We abstracted odds ratios, relative risks (RR), standardized mortality ratios, standardized incidence ratios, and 95% confidence intervals (CI) from all studies; for simplicity, however, we use RR to refer to measures for case-control and cohort studies in this paper.

To convert CI's from the different studies into estimates of the variance of the log RR, we transformed the interval to the log scale. Under the assumption that the CI had been constructed by adding and subtracting 1.96 times the standard error of the log RR, interval length is divided by 3.92 to obtain an approximate standard error, which was then squared to estimate the variance. For several studies, only a RR and a *p* value were provided. The *p* value was first converted to the corresponding two-sided *z* statistic (from a table of standard normal variates). Assuming that the log RR is approximately normally distributed, we set the calculated *z* statistic equal to the log RR divided by its unreported standard error, to solve for the standard error.

To combine data we used the meta-analysis routine in Stata 7.0 (Stata Corp, College Station, TX). We calculated pool estimates of the RR's according to: (1) the fixed-effects model, weighted average using the inverse of the variance as weight; and (2) the random-effects model, weighted average using the sum of the inverse of the variance and the moment estimator of the variance among studies as weight [39]. The random-effects model does not assume homogeneity of RR's (*i.e.*, uniformity of the association) across studies. This method is conservative and produces a relatively larger variance (and hence wider CI) than the methods that assume homogeneity of risk. For our analyses, we used the random-effects routine when the Cochran Q statistic was greater than the degrees of freedom [40]. We did not

attempt to weight studies by quality criteria. We also evaluated publication bias through methods described by Begg and Mazumdar [41] and Egger *et al.* [42]. The attributable risk percentage for the population was calculated as described by Schlesselman [43].

To disentangle the role of smoking in the association between asthma and lung cancer risk separate analyses were performed according to estimates adjusted for smoking history: (1) studies that included risk estimates among never smokers, defined as persons who do not currently smoke and report smoking <100 cigarettes in their lifetime [10–12, 19–21]; (2) studies that controlled for smoking history (*e.g.*, by adjusting for pack-years) [10, 12, 19–28], and (3) studies that did not control for smoking [14, 16, 28–32]. Moreover, to determine whether asthma affects the risk of specific lung cancer cell types, we performed subanalyses by pathologic type of lung cancer: (1) adenocarcinomas and (2) nonadenocarcinomas, which are represented by squamous, small, and large cell carcinomas. Because no different effect by gender has been reported in several studies [12, 21, 28, 29], we combined the results on the two genders.

Results

Never smokers

We identified five case-control studies that presented data limited to men and women who had never smoked (Table 1). The RR of lung cancer among asthmatics ranged from 1.1 to 2.7. Among these five studies we observed little heterogeneity ($Q = 3.0$ on 4 df; $p = 0.55$) and the fixed-effects combined RR was 1.8 (95% CI = 1.3–2.3) comparing risk of lung cancer among asthmatics with that among controls.

Alavanja *et al.* [10] and Mayne *et al.* [12] both presented results for additional subsets of cases that shed light on this overall relation. In these two case-

control studies, estimates of the association between asthma and lung cancer also were estimated among former smokers, defined as subjects who had smoked no more than 100 cigarettes in the 10 or 15 years prior to diagnosis of lung cancer. We combined these data and studies limited to never smokers ($Q = 5.5$ on 6 df; $p = 0.48$) and observed that, among nonsmoker subjects, asthma continued to have a significantly increased risk of lung cancer (RR = 1.8; 95% CI = 1.4–2.3). Since passive smoking might still confound the association between asthma and lung cancer we combined the estimates of four studies among nonsmokers that adjusted for lifetime environmental tobacco smoke exposure [10–12, 21]; the combined fixed-effects estimate from these studies was 1.9 (95% CI = 1.4–2.5).

Studies adjusted for smoking history

We next combined data from seven case-control studies and four cohort studies that controlled for smoking history, usually by modelling pack years (Table 2). When data from case-control studies that presented RR adjusted for smoking history were combined, there was a statistically significant increase in risk of lung cancer (RR = 1.6; 95% CI = 1.3–1.9). The cohort studies also suggested a positive association (RR = 2.0; 95% CI = 1.3–2.9). Finally, combining data across all 11 studies, we observed a significant relation between asthma and risk of lung cancer (RR = 1.7; 95% CI = 1.3–2.2). Heterogeneity among all studies was present ($Q = 18$ on 10 df; $p = 0.05$). The test for heterogeneity was no longer significant after removing the two most extreme studies from the analysis ($p = 0.18$) [24, 25]; after removing these studies a significant RR of 1.6 was still present (95% CI = 1.4–2.0).

Misclassification of early diagnosis of lung cancer can be present since asthma may be an early manifestation of lung cancer. This bias could artificially increase the

Table 1. Case-control studies of asthma and lung cancer among men and women who never smoked

Study	Years of study	Gender	Country	Origin of controls	Total cases	Hystologic type adeno-carcinoma (%)	RR	95% CI
Vena <i>et al.</i> [19, 20]	1957–1965	Men	USA	Hospital	91	NS ^a	1.6	0.7–3.6 ^b
Alavanja <i>et al.</i> [10]	1986–1991	Women	USA	Population	432	67	2.7	1.4–5.4
Wu <i>et al.</i> [11]	1985–1990	Women	USA	Population	397	70	1.7	1.1–2.5
Mayne <i>et al.</i> [12]	1982–1984	Men, women	USA	Population	197	51	1.1	0.5–2.6
Brenner <i>et al.</i> [21]	1994–1998	Men, women	China	Population	253	NS	2.0	0.9–4.2

^a Histologic type not separately presented in published report.

^b Standard error calculated from data.

Table 2. Case-control and cohort studies that adjusted for smoking history included in the meta-analysis of lung cancer risk

Study	Years of study	Gender	Country	Study type	Cases	Hystologic type adenocarcinoma (%)	RR	95% CI
Vena <i>et al.</i> [19, 20]	1957–1965	Men	USA	Case-control	1052	NS ^a	1.6	1.1–2.5 ^b
Wu <i>et al.</i> [24]	1983–1986	Women	USA	Case-control	336	100	1.0	0.5–2.1
Alavanja <i>et al.</i> [10]	1986–1991	Women	USA	Case-control	618	62	1.3	0.8–2.1
Mayne <i>et al.</i> [12]	1982–1984	Men, women	USA	Case-control	436	51	2.1	1.0–4.1
Brownson <i>et al.</i> [22]	1993–1994	Women	USA	Case-control	676	33	1.1	0.7–1.7
Osann <i>et al.</i> [23]	1990–1993	Women	USA	Case-control	98	0 ^c	4.8	1.0–22.8
Brenner <i>et al.</i> [21]	1994–1998	Men, women	China	Case-control	885	NS	2.1	1.5–3.0
Reynolds <i>et al.</i> [25]	1965–1983	Men	USA	Cohort	102	NS	5.2	2.0–13.5
Mills <i>et al.</i> [26]	1977–1982	Men, women	USA	Cohort	2188	NS	1.2	0.4–3.3
Lange <i>et al.</i> [27]	1976–1995	Men, women	Denmark	Cohort	315	NS	1.3	0.7–2.3
Huovinen <i>et al.</i> [28]	1976–1991	Men, women	Finland	Cohort	471	NS	2.8	1.2–6.8

^a Histologic type not separately presented in published report.

^b Standard error calculated from data.

^c Study restricted to small cell lung cancer only.

magnitude of any association between asthma and lung cancer. The majority of the case-control studies in this analysis restricted the data to asthma diagnosed more than three or five years before the time of interview of cases and controls to minimize this bias. However, misclassification could still be present since previous analyses have found that with increasing latency exclusion the significance of the estimates are diluted for other pulmonary diseases [12, 22]. On the other hand, a decrease in risk might also be because the prevalence of smoking among subjects with asthma decreases with time [29]; the prevalence of former smokers is greater among subjects with asthma than the general population [44]. Therefore, we combined studies in which asthma preceded the diagnosis of lung cancer by 11–20 years and more than 20 years [11, 21]. We observed a borderline significant increased risk of lung cancer when asthma was diagnosed 11–20 years prior to interview (RR = 1.8; 95% CI = 1.0–3.4, $p = 0.05$). When studies were restricted to those with more than 20 years since diagnosis of asthma, there was a significant increase in risk of lung cancer (RR = 1.6; 95% CI = 1.1–2.4).

Studies not adjusted for smoking history

To illustrate the potential confounding by tobacco use among subjects with asthma, we combined data from seven cohort studies that reported estimates of the association but did not control for smoking history [14, 16, 28–32]. Heterogeneity among studies was substantially higher ($Q = 16.4$ on 6 df, $p = 0.01$), and the overall RR of lung cancer was 1.4 (95% CI = 1.2–1.6). The cohort studies were slightly influenced by a large

significant study from Sweden [29]. If this study were omitted from the analysis then the estimated risk of lung cancer would still be significant (RR = 1.3; 95% CI = 1.1–1.6). These final studies suggested that the association between asthma and lung cancer was weakly attenuated by cigarette smoking.

Histology of lung cancer

Because the risk of lung cancer associated with asthma exposure may vary by specific lung cancer histology, we considered differences between the risk of adenocarcinoma and nonadenocarcinoma of the lung. Five case-control studies reported estimates by histology of lung cancer adjusted for smoking history [10–12, 23, 24]. These studies suggested a significant increase risk of adenocarcinoma of the lung (RR = 1.5; 95% CI = 1.1–2.8). A stronger association was found when we pooled estimates related to nonadenocarcinoma (RR = 2.5; 95% CI = 1.5–4.1). Overall, when the estimates stratified by histology type were combined we found a consistent increased risk of lung cancer due to asthma exposure (fixed-effects combined RR = 1.8; 95% CI = 1.3–2.3).

Publication bias

For case-control studies that restricted the analysis to never smokers, case-control and cohort studies that adjusted for smoking, and cohort studies that did not control for smoking the Egger's regression asymmetry test ($p = 0.76, 0.64, 0.39$, respectively) and the Begg's adjusted rank correlation test ($p = 0.76, 0.47, 0.76$, respectively) did not demonstrate any substantial evidence of publication bias.

Discussion

In this meta-analysis of asthma and risk of lung cancer, we identified studies and performed analysis to reduce the bias related to incomplete control for cigarette smoking (Table 3). When we limited the analysis to never smokers, we observed a statistically significant 1.8-fold increase in risk of lung cancer among adults with asthma. The pattern of results observed across studies that control for confounding by cigarette smoking is consistent.

Several sources of bias should be considered in the interpretation of our results. First, misclassification of asthma could explain the increased lung cancer risk observed. The asthma case definition used in the published epidemiological studies may have included individuals that may suffer from other pulmonary diseases, especially chronic bronchitis and emphysema, which are positively related with smoking [45]. The problem of misclassification between reported asthma and these pulmonary diseases was largely overcome by studying asthma as a risk factor for lung cancer in never smokers, which is the approach that is least susceptible to such bias. However, misclassification could still explain the positive association between asthma and lung cancer since history of chronic bronchitis and emphysema also were positively associated with lung cancer among subjects who never smoked [10–12].

Moreover, an increase in the RR could reflect differential recall bias, which is a major problem in case-control studies. As a result of lung cancer, cases are more likely to recall previous history of asthma because of their current illness. To minimize this bias, several studies ascertained asthma by asking about history of asthma that were diagnosed by a physician, the age at which they were first diagnosed, history of hospitalization, and use of antiasthma medications. However, recall bias remains as a plausible explanation of the increased risk of lung cancer among subjects with asthma in case-control studies. Also, several studies relied on direct and next-of-kin interviews. When next-of-kin interviews were excluded from the analyses, the risk due to asthma history increased [10, 12, 22] or

remained unchanged [21]. In contrast, cohort studies overcome this limitation of case-control studies and misclassification, if present, would be related to a self-reported physician diagnosis of asthma. Lack of validity of questionnaires to ascertain asthma has been reported [46], and given the nature of the study design nondifferential misclassification could arise in the exposure, so that any true association between asthma and lung cancer will be diluted or underestimated. As a result, the observed association would be biased towards the null. Our findings of a significant increased risk when estimates were pooled from cohort studies suggest that misclassification of asthma diagnosis was minimal.

Another possibility is that the lung cancer cases from the published case-control studies have had early symptoms of lung cancer that could have been diagnosed incorrectly as asthma prior to the lung cancer diagnosis, which could artificially increase the magnitude of the association between asthma and lung cancer. However, all case-control studies excluded cases if the diagnosis of asthma was made during one [11, 21], three [10, 22], or five [12, 19, 20] years before the diagnosis of lung cancer. Moreover, a significant increase in risk of lung cancer was present even more than 20 years since diagnosis of asthma.

Second, confounding by a factor common to asthma and lung cancer could also explain the positive association observed. The increased lung cancer risk observed among never smokers with asthma might be due to confounding by lifetime environmental tobacco smoke. Long-term exposure to environmental tobacco smoke increases risk of lung cancer in individuals who have never personally used tobacco [47]. However, the results of the analysis among studies that controlled for environmental tobacco smoke in nonsmokers provide direct evidence that the increased risk of lung cancer is not due to confounding by tobacco. Other confounders such as occupational exposure and respiratory tract infections should be taken into account in the interpretation of our findings. It is likely, however, that any confounding would be small in comparison with that of tobacco smoking.

Table 3. Meta-analysis of asthma and risk of lung cancer: summary of results

	No. of studies	Weighted model	RR	95% CI
Never smokers [10–12, 19–21]	5	Fixed-effects	1.8	1.3–2.3
Never and former smokers [10–12, 19–21]	5	Fixed-effects	1.8	1.4–2.3
Controlled for smoking history [10, 12, 19–28]	11	Random-effects	1.7	1.3–2.2
Case-control studies [10, 12, 19–24]	7	Fixed-effects	1.6	1.3–1.9
Cohort studies [25–28]	4	Fixed-effects	2.0	1.3–2.9
Not controlled for smoking history [14, 16, 28–32]	7	Random-effects	1.4	1.2–1.6

Confounding could also explain the modest increase in lung cancer risk found among studies that did not control for smoking. Several studies have shown that current smoking is less common among asthmatics than other adults from the general population [15, 37, 44, 48]; furthermore, asthmatics voluntarily abstain from using tobacco and stopped smoking more commonly than the general population [44, 49]. Therefore, the association between asthma and lung cancer will be underestimated since smoking is negatively associated with asthma, and asthma is a risk factor for lung cancer.

We found that the RR was higher for nonadenocarcinomas compared to adenocarcinomas. These results are consistent with previous reports of the association between asthma and histology of lung cancer. However, confounding due to tobacco may explain the increased risk found in nonadenocarcinomas since it is consistent with the strength of the carcinogenic value of tobacco on different histological types of lung cancer [50].

Third, publication bias is an important problem in medicine and occurs when the chance that a study is published depends, to some extent, on the significance of the reported association; this bias could have occurred if investigators who found no association did not bother to submit their data for publication or if null findings were of little interest to journal editors. In our analyses, no evidence of publication bias was found with standard tests. However, caution in the interpretation of these results should be considered given the small number of studies in the subanalyses according to smoking history. We are aware that at least two form of publication bias in our analyses may have artificially inflated the pooled RRs. For instance, there are published cohort studies that explored the association between asthma and mortality which do not mention lung cancer or no estimates of the association were presented, and also there are published case-control studies on lung cancer and previous pulmonary diseases which do not mention asthma history as exposure. Probably, analyses of the association between asthma and lung cancer were performed in some of these studies, however the results were not reported because of null results. In the second form of publication bias, four [13, 15, 18, 34] of the six studies that were excluded in our analyses provided evidence against a relation between asthma and lung cancer but could not be included in our pooled analyses for the reasons previously mentioned. The further inclusion of these results would have decreased the pooled RR observed in studies that did not control for smoking history.

While the possibility that bias or uncontrolled confounding accounts for increased risk of lung cancer among subjects with asthma cannot be excluded, at least

three plausible biological mechanisms are worthy of consideration. First, asthma may increase the risk of lung cancer by reducing the clearance of inhaled toxins and carcinogens that are found in the bronchoalveolar epithelium. The presence of mucociliary dysfunction in asthma is suggested by clinical observations and has been confirmed by pathological and physiological studies [51, 52]. Furthermore, asthma is typically associated with an obstructive pulmonary impairment that is reversible [53]; impaired pulmonary function is also associated with a defective elimination of noxious agents from the airway and is associated with increased risk of neoplasms of the lung irrespective of smoking [54]. Another potential mechanism is based on cellular mechanisms involved in the airway inflammation that characterizes asthma. An imbalance between generation and elimination of free radicals has been implicated in the pathogenesis of asthma [55]. Antioxidant levels in the respiratory tract of subjects with asthma are reduced [56]. These oxidants cause direct damage to DNA, proteins, and lipids and may play a direct role in lung carcinogenesis [57]. At the same time, chronic inflammation can cause chronic mitogenesis that can be indirectly mutagenic (and consequently carcinogenic) because it increases the probability of converting endogenous DNA damage into mutations. Moreover, a persistent level of cell damage and an ongoing repair process characterize chronic inflammation in asthma, changes that may cause permanent abnormalities in the airway [58]. A combination of tissue damage and carcinogen exposure has been shown to be required for experimental induction of lung cancer [59]. Finally, asthma may affect risk of lung cancer through corticosteroid treatment. Lung cancer has been associated with suppression of the cellular immune system [60]. Glucocorticoid treatment in patients with asthma is associated with cellular and humoral immunosuppression [61, 62] and thereby may facilitate carcinogenesis in the lungs. Furthermore, asthma treatment with corticosteroids augments survival and proliferation of basal epithelial cells, an effect associated with a high expression of Bcl-2, an inhibitor of programmed cell death or apoptosis in epithelial cells [63]. A dysregulation of the balance between cell death and cell growth has been involved in the pathogenesis of cancer [64]. Moreover, the protein Bcl-2 has been demonstrated in 25% of nonsmall-cell lung cancer [65].

Assuming that the prevalence of self-reported lifetime asthma in adults who do not smoke is around 9% and among adults who smoke is around 12% [66], and if the association between asthma and lung cancer risk is causal, then the proportion of lung cancer cases attributable to asthma among never smokers and smokers is

estimated to be 6.7 and 7.7%, respectively. It has been estimated that the proportion of lung cancer cases attributable to previous nonmalignant pulmonary disease among nonsmokers is 10–20% [10, 12, 33]. Since asthma affects up to 15 million Americans and is the most common chronic disease in childhood and a disease of considerable morbidity in adults [66, 67], the positive association between asthma and lung cancer is a subject of considerable public health importance. For instance, individuals with asthma should take extra precautions to reduce exposure to other known lung carcinogens such as smoking, environmental tobacco smoke, and radon.

In summary, numerous studies have found an increased risk of lung cancer among adults with asthma. The presence of a strong association when analysis is limited to never smokers supports a direct relation between asthma and lung cancer. Presently, the most likely explanations of the increased risk of lung cancer among asthmatics are that asthmatics have increased susceptibility to carcinogens because of their impaired mucociliary system and pulmonary function, chronic airway inflammation, altered immune system or apoptosis dysregulation. Clarification of these potential mechanisms is a topic for future experimental or clinical research. Furthermore, prospective cohort studies among nonsmokers with a large group of cases of lung cancer are needed to overcome sources of bias that could explain the association between asthma and lung cancer.

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