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Association of Bronchial Asthma with Lung Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

The purpose of this study was to systematically examine the association between bronchial asthma and lung cancer. Research on the correlation between bronchial asthma and lung cancer was retrieved from the database. Literature was screened based on inclusion and exclusion criteria, and the number of patients in the included studies was extracted and analyzed. This study used Stata statistical software version 16.0 and Cochrane Review Manager version 5.4 for meta-analysis. In our study, 19 articles were selected. Without considering other influencing factors, the risk of lung cancer in asthma patients was relative risk (RR)=1.40 (95% CI: 1.17-1.67, I2=55.7%), and after correcting for risk factors such as smoking and age, it was found that the risk of small-cell lung cancer in asthma patients was RR=2.11 (95% CI: 1.45-3.24). Asthma may increase the risk of developing lung cancer, with an even higher likelihood for small cell lung cancer.

Keywords: Association; Bronchial asthma; Lung cancer; Meta-analysis; Systematic review

INTRODUCTION

Primary bronchopulmonary cancer is a life threatening disease. Its etiologic factors are numerous and complex, and it is affected by different risk factors such as age, gender, race, occupation, and living habits. Moreover, its epidemiological characteristics vary in different countries and even in different regions of the same country. The incidence and death rate of lung cancer have remained high for a long time, and tend to increase year by year in China.[1] The latest epidemiological estimation shows that by 2050 there may be at least 1.4 million new cases of lung cancer and at least 1.2 million deaths worldwide.[2] In order to promote tertiary prevention of lung cancer, it is important to identify risk factors associated with the disease and strengthen early diagnosis and treatment of tumors accordingly. Bronchial asthma is one of the most common chronic diseases of the respiratory tract, and the global prevalence of asthma has fluctuated from 1% to 18% in recent years.[3] Epidemiologic surveys have shown that there are about 30 million patients with bronchial asthma in China.[4] The incidence of bronchial asthma is increasing worldwide, and more than half of the patients with asthma fail to achieve bronchial asthma control; therefore, it is clear that global asthma prevention and treatment is facing quite serious problems.[5] The economic pressure and medical burden of bronchial asthma on individuals,

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families, and governments are enormous, and it will gradually become a prominent problem affecting public health and social development.

Some studies have pointed out the correlation between asthma and lung cancer.[6-10] In a large-sample study in Taiwan that included more than 7 million female respondents over the age of 20 years, it was found that the hazard ratio (HR) of developing lung cancer in people with asthma compared with those without asthma was 1.50 (95% confidence interval [CI]: 1.21–1.85).[11] However, in another study, in which asthma patients were followed prospectively for 20 years, asthma was not found to increase the risk of unfavorable prognostic events related to lung cancer, and the actual number of asthmatics with lung cancer was lower than the expected number of asthmatics with lung cancer, which led to the conclusion that allergic asthma may be a protective factor against lung cancer.[12-15] Therefore, the relationship between asthma and lung cancer needs to be further investigated. Therefore, the relationship between asthma and lung cancer needs to be further investigated. Thus, we conducted a meta-analysis to comprehensively analyze the association of bronchial asthma with lung cancer and its tumor markers.

MATERIALS AND METHODS

Scope of Literature Search

We performed a comprehensive literature search using the following databases: Wanfang, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature, VIP, Embase, PubMed, Cochrane Library, and Web of Science. Our search terms included "asthma," "bronchial asthma," "lung adenocarcinoma," "non-small cell lung cancer," "lung cancer," "small cell lung cancer," "tumor markers," "squamous cell carcinoma," and "alveolar carcinoma." Advanced search methods were employed to ensure the inclusion of relevant studies. All kinds of literatures on patients with bronchial asthma or lung cancer that were published until June 2023 after the establishment of the database were searched.

Inclusion and Exclusion Criteria of Literature

1) The type of study was a prospective cohort study and the literature could be extracted directly from the relative risk (RR) or HR with 95% CI or be calculated from the data in the text; 2) population-based study on the association between asthma and lung cancer, with a follow-up period of ≥3 years; 3) the exposure factor was asthma and the outcome indicator was the occurrence of lung cancer or death due to lung cancer; 4) the observation group was the population with asthma, and the control group was the population without asthma; 5) less than 10% loss-to-follow-up rate in the study cohort.

Exclusion criteria: 1) no clear control group or total population data as control; 2) in vitro experiments, animal experiments, etc.; 3) observation group suffered from allergic diseases other than asthma; 4) the content of the literature was reviewed, pathology, etc. Low-quality research reported, republished and reviewed by experts.

Literature Screening and Data Extraction

The literature screening process of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) process (Figure 1). When screening the literature, irrelevant articles were excluded through reading the article titles, and further screening was conducted by reading the abstracts and full texts to determine the inclusion of the literature. The extracted data included: author, publication date, study design type, number of cases, sample size, and relevant outcome indicators. The screening process was independently conducted by two researchers strictly following the standard process, and in case of any disagreements or opinions, a third reviewer was invited to resolve the issue through discussion among the three.

Statistical Methods

This study used Stata statistical software version 16.0 and Cochrane Review Manager version 5.4 for conducting the meta-analysis. For binary variables, the RR and 95% CI were used as statistical measures for efficacy analysis. Heterogeneity analysis of the included study results was first conducted using the chi-square test and combined with p value to determine the size of heterogeneity. If $p>0.1$ or $I^2 \leq 50\%$, it indicates no heterogeneity or small heterogeneity among the studies, and a fixed-effect model is used for analysis. If $p<0.1$ or $I^2>50\%$, it indicates heterogeneity among the studies, and a random-effect model is used. If significant heterogeneity is found after combining the studies, sensitivity analysis was conducted by omitting one study at a time to evaluate if a single study significantly affects the results or subgroup analysis is performed to explore

the source of heterogeneity. The funnel plot was used to assess potential publication bias. Descriptive analysis may also be used. The significance level for meta-analysis is set at α=0.05.

RESULTS

Basic Information Included in the Study

A total of 5304 relevant articles was retrieved from the databases of CNKI, PubMed, Cochrane Library, Embase, and Web of Science. After removing duplicate articles, 296 articles remained. Through reading the titles, abstracts, and keywords, a further selection was made, resulting in a total of 19 articles.[16-34] (Figure 1).

Systematic Review

Table 1 lists the characteristics of the studies included in the experiment. Among these 19 studies, 10 were conducted in Europe, 3 in Asia, and 6 in North America. The follow up ranged from 2 to 39 years. Figure 2 demonstrates the risk of bias (Figure 2).

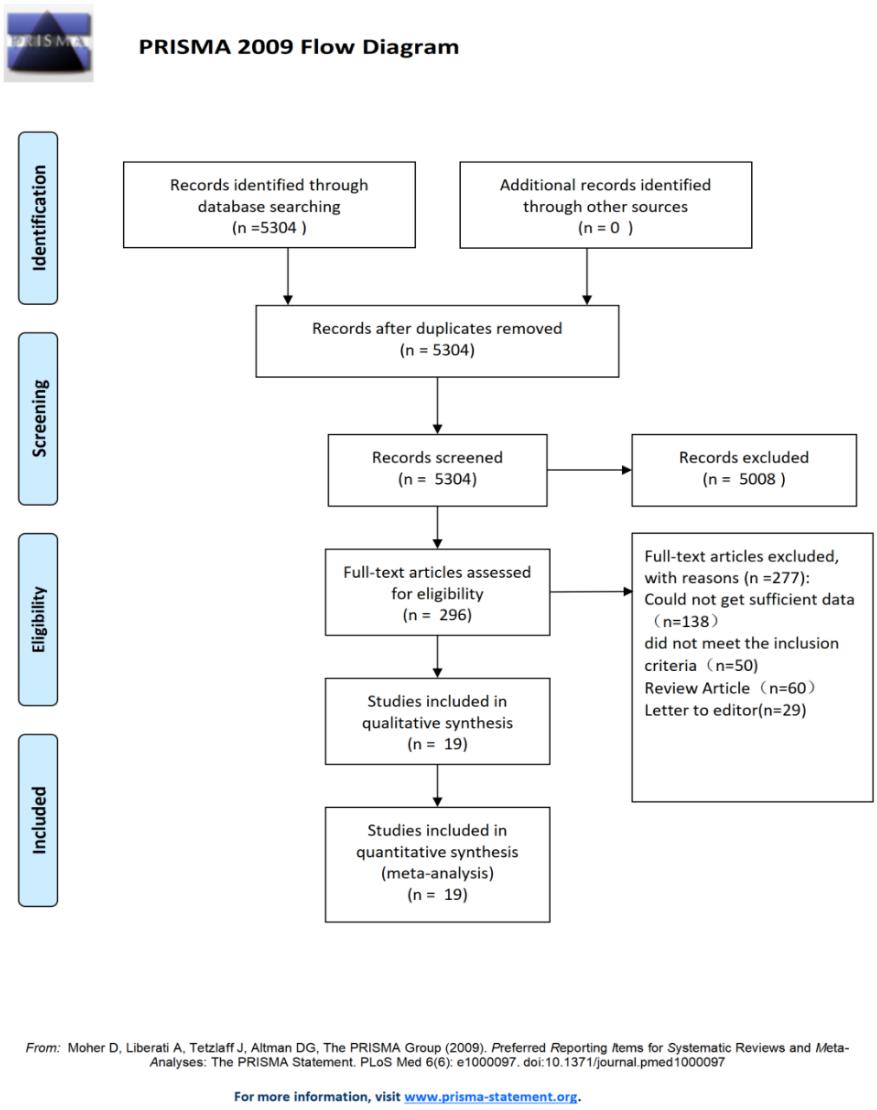

Figure 1. Flow diagram of literature search process

Pooled Analysis

Fourteen studies[16, 17, 22, 23, 25-29, 31, 33, 34] provided data on the correlation between asthma and lung cancer risk. The results showed that the risk value of lung cancer in patients with asthma was RR=1.40 (95% CI: 1.17-1.67, I^2=55.7%, p=0.006) (Figure 3).

Nine studies provided data on the correlation between asthma and the risk of death from lung cancer. The results of the meta-analysis demonstrated that the risk value of death due to lung cancer in asthma patients was RR= 1.07 (95% CI: 0.93-1.24, p=0.168, I^2=34.1%) (Figure 4). This indicates that no correlation between asthma and the risk of death due to lung cancer was found.

Subgroup Analysis

Subgroup analysis according to gender, race, smoking history, duration of follow-up, lung cancer type, and quality of literature factors (Figure 5). Moreover, after correcting for risk factors such as smoking and age, the risk of small cell lung cancer in asthmatics was RR=2.11 (95% CI: 1.45-3.24, p<0.05), while the risk of non-small cell lung cancer was RR=1.11 (95% CI: 0.87-1.43). There was no publication bias, which is shown in the funnel plots (Figure 6).

Table 1. Basic characteristics of the included literature

First author/year	Country	Subjects	NOS score	Outcome indicators	follow up (Years)
Alison 2003[16]	Western Australia	124	5	incidence rate morbidity	7
Alyson 2004[17]	American	17698	7	incidence rate	8
Antonio 2006[18]	Spain	8896	8	incidence rate	9
Charlotte 1995[19]	Denmark	2150	7	morbidity	19
David 2005[20]	American	9087	8	morbidity	4
Elisa 1997[21]	Finland	14652	7	morbidity	16
Elizabeth 2019[22]	New York	64170	8	incidence rate	7
Fan 2016[23]	China	9295	7	Morbidity incidence rate	7
Gao 2010[24]	China	61500	6	incidence rate	4
Humairat 2022[25]	USA	23523	8	incidence rate	3
Ji 2009[26]	Swedish	14025	8	incidence rat	39
Jiang 2021[27]	China	62791	7	incidence rate	22
Laila 2021[28]	United Kingdom	4289	7	incidence rate	2
Liu 2015[29]	Swedish	10649	8	incidence rate	6
Michelle 2005[30]	Canada	1102247	8	Morbidity	2
Paolo 2002[31]	Sweden	92986	7	incidence rate	29
Stéphanie 2003[32]	France	14267	8	Morbidity	2
Yi 2023[33]	USA	90021	8	incidence rate	8
Yunus 2015[34]	Denmark	94079	8	Morbidity incidence rate	4.5

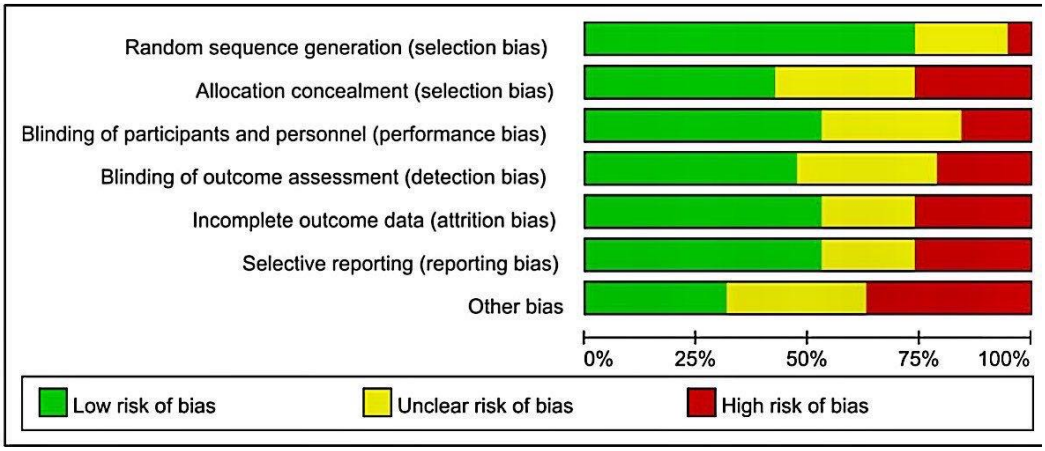

Figure 2. The risk of bias of included in the meta-analysis

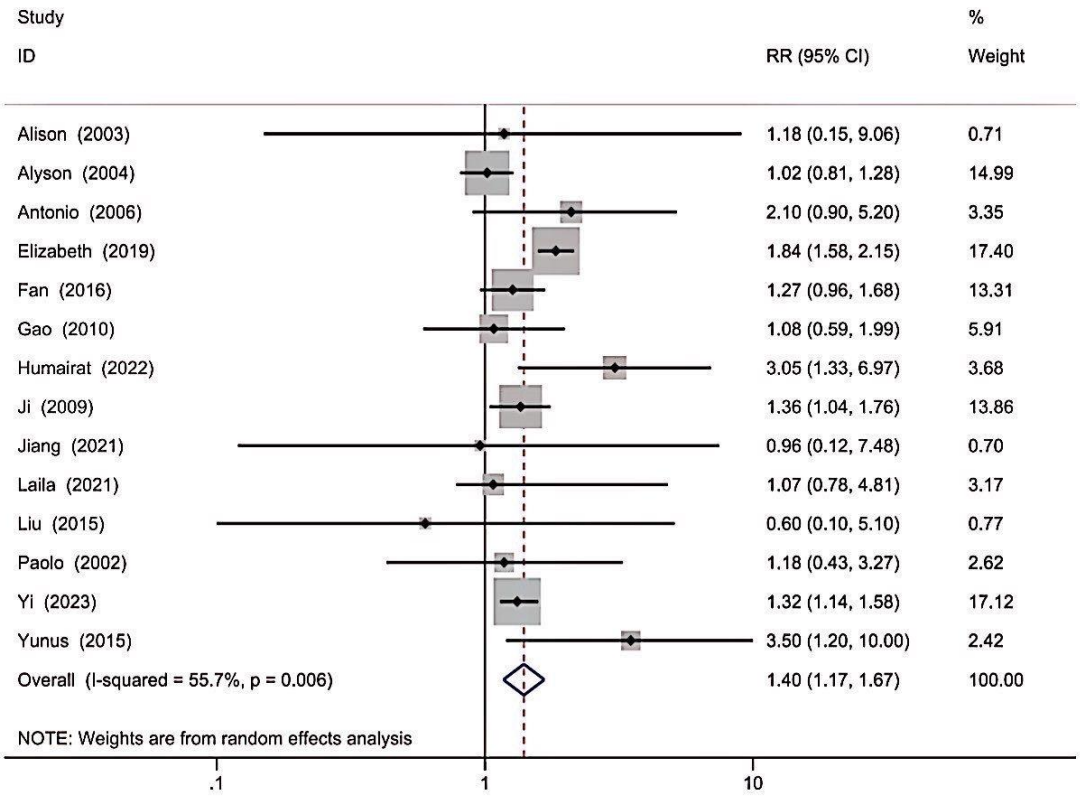

Figure 3. Forest plot of the correlation between asthma and lung cancer risk. RR: relative risk

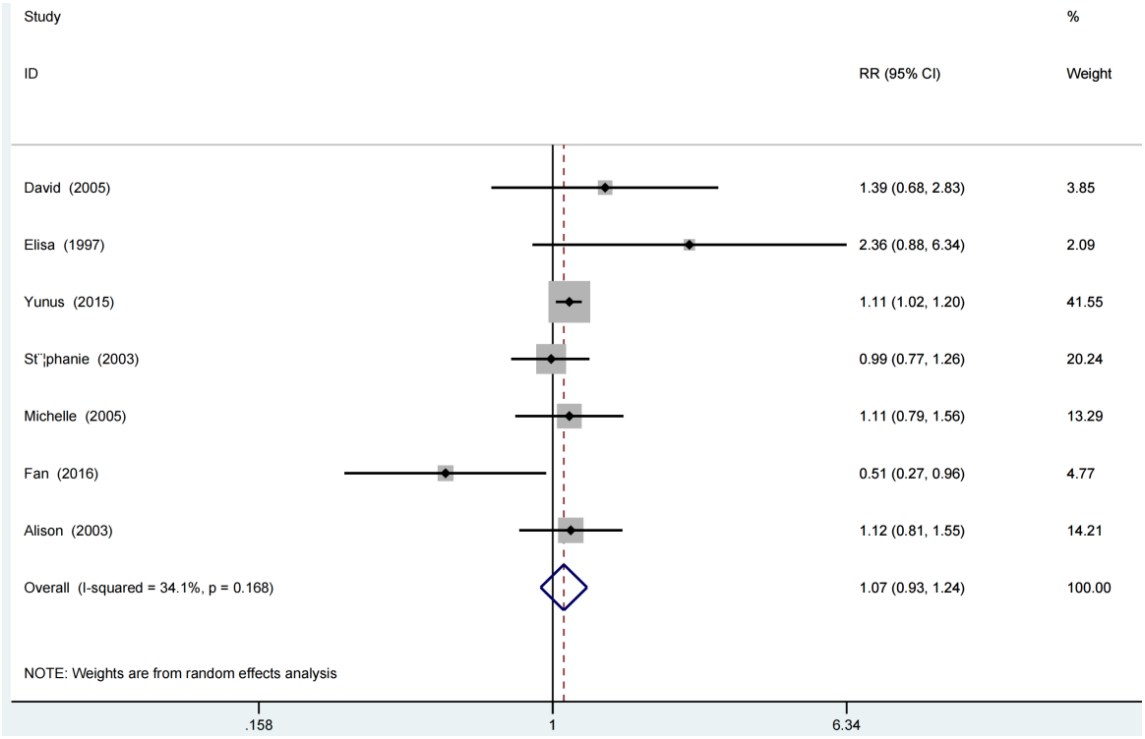

Figure 4. Forest plot of correlation between asthma and risk of death from lung cancer. RR: relative risk

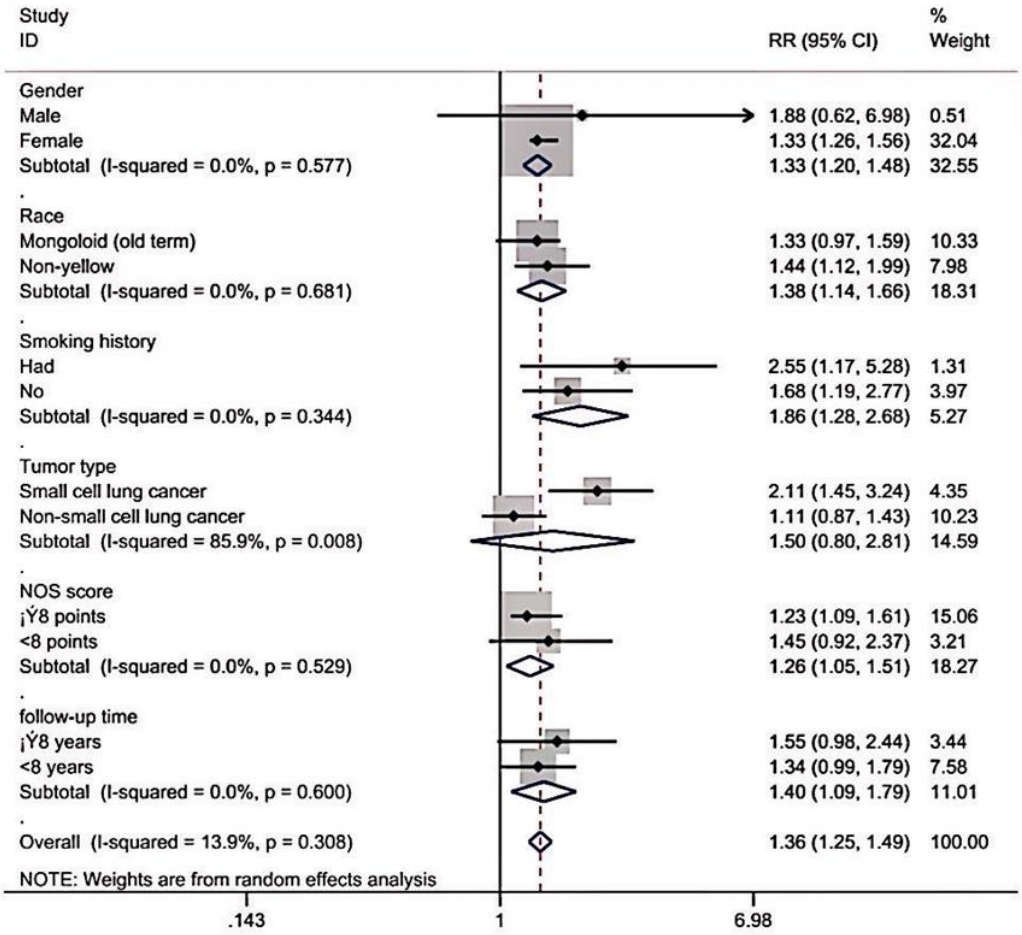

Figure 5. Subgroup analysis of the correlation between asthma and the risk of lung cancer development. RR: relative risk

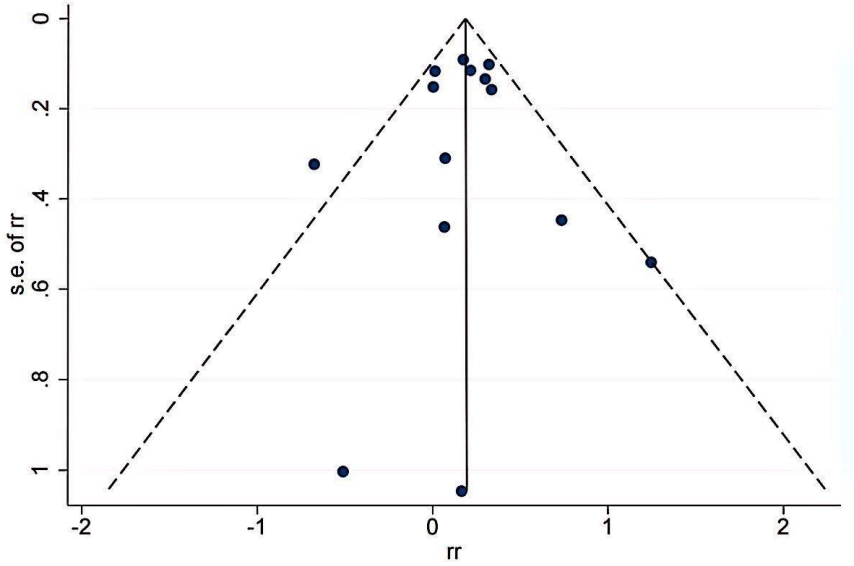

Figure 6. The funnel plots. Funnel plot with pseudo 95% confidence limits

DISCUSSION

The mechanisms that increase the risk of lung cancer in asthma may be as follows: 1) repeated damage to airway cells in inflammation forms airway scar tissue, which is more prone to cancer;[35] 2) chronic inflammation accelerates the turnover of new and old cells in the airway, increasing the risk of spontaneous malignant transformation of cells;[36] and 3) chronic inflammation reduces the ability of the airway epithelial cells to remove inhaled toxins and tumor cells and increases the susceptibility of the cells to toxin-induced mutations.[37] However, some have questioned this view, based on the theory that chronic inflammation can activate the body's immune response and therefore, the immune system's "self-monitoring" of cancer cells can be improved, so that malignant cells can be eliminated on time, and the results of some clinical studies have shown that asthma does not affect the risk of lung cancer, and even reduces the risk of lung cancer.[38,39] Some studies have shown that patients with high asthma control levels may have increased risk of lung cancer due to long-term hormone inhalation, which suppresses immunity and reduces the body's ability to recognize and remove malignant cells; in addition to hormones, long-term use of other kinds of anti-asthma drugs, such as long-acting muscarinic antagonist (LAMA), is also a good choice for patients with asthma. LAMA may also increase the risk of lung cancer.[40] Asthma is not the only cause of chronic inflammation of the airways, chronic bronchitis, emphysema, chronic obstructive pulmonary disease and other diseases can also leave the airways in a state of chronic inflammation for a long time. The risk of information bias in retrospective studies is high, and there is a great risk of misdiagnosing other lung diseases as asthma, which affects the credibility of the study results. In this paper, a systematic evaluation of prospective cohort studies showed that asthma increased the risk of lung cancer, and small cell lung cancer was more likely to occur, regardless of other influences. However, the Dutch hypothesis suggests that asthma and chronic lung disease may be different stages of the same disease, and that asthmatics may have an increased risk of chronic lung disease, so it cannot be ruled out that asthma may increase the risk of lung cancer as well as chronic lung disease, and that correcting for a history of lung disease as a risk factor may result in the incorrect categorization of some of the positive results as negative; nor can it be ruled out that the results of the subgroups of patients with asthma were not statistically significant, although they were 1.11 times higher than those of non-asthmatics;[41,42] it cannot be ruled out that the sample size of each group was reduced after grouping according to the subgroup factors, which reduced the efficacy of the test and led to false-negative results. A systematic evaluation of studies investigating the association between asthma and the risk of lung cancer deaths showed that asthma did not affect the risk of lung cancer deaths, but false-negative results could not be excluded because of a decrease in the power of the test due to an insufficient number of included studies. Based on the fact that the level of asthma control in Asian populations is lower than that in Europe and the United States, and that standardized treatment of asthma has been shown to improve the prognosis of lung cancer in relevant domestic studies.[8] The present study concludes that, although this systematic evaluation did not find that the risk of death from lung cancer was increased by the development of asthma, due to the small number of included studies and the lack of sample size, it is difficult to deny the correlation between the risk of death from asthma and that of lung cancer based on this negative result.

In conclusion, the results of this systematic review indicate that asthma can increase the risk of developing lung cancer, and the likelihood of developing small cell lung cancer is even greater. The relationship between asthma and the risk of death from lung cancer is currently unclear. The correlation between asthma and lung cancer does not differ among different genders, races, and smoking status. However, more well-designed, adequately powered, prospective, multicenter, and controlled studies are needed to explore and verify the specific mechanisms with less bias.

STATEMENT OF ETHICS

The protocol was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital. All the methods were carried out in accordance with the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable

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