

Asthma and risk of lung cancer

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Abstract Asthma is a very common chronic disease that occurs in all age groups. Its high prevalence has significant health costs, which are even higher in the most severe disease forms. Lung cancer has the highest incidence of all cancers in the developed world and is an important cause of mortality. Patients with lung cancer are a big economic burden on health services, both in direct and indirect costs. Different authors suggest that atopic constitution, including different manifestations of allergy and asthma, are possible risk factors for lung cancer, above all in never-smokers. Given the high asthma prevalence and lung cancer incidence and mortality in developed countries, this association would have important public health implications. Uncertainties about the association and the underlying physiopathological mechanisms, however, seem to require further studies.

Keywords Asthma · Allergy · Lung cancer

Asthma is a very common chronic disease that occurs in all age groups [1]. Allergic mechanisms are present in about 80% of childhood asthma [2] and in 40–50% of the adult form [3]. The high prevalence of asthma means it has sig-

nificant health costs, increasing in the most severe disease forms [4].

Lung cancer has the highest incidence of all cancers in the developed world and is an important cause of mortality [5]. Patients with lung cancer are a big economic burden on health services, both in direct and indirect costs [6].

Although smoking has been identified as the major risk factor for lung cancer, approximately 10% of lung cancer deaths are not attributable to smoking [7]. Different authors suggest that atopic constitution, including different manifestations of allergy and asthma, are possible risk factors for lung cancer, above all in never-smokers [8–11]; other studies, however, do not find this association [12–14]. Some studies have even reported how the lung cancer risk was lower in patients with hay fever [13, 15]. Given the high asthma prevalence and lung cancer incidence and mortality in developed countries, an association between the two disorders would have important public health implications [8].

Asthma, allergic rhinitis and atopic dermatitis are clinical manifestations of atopy [16]. Atopic dermatitis and allergic rhinitis often precede [17] or accompany the development of asthma, so they seem to be influenced by common determinants. Even if the association between allergy and cancer risk is based on epidemiologic studies, the exact nature of the association is still controversial. Two different and opposing hypotheses have been suggested. Some studies defend the allergy protective effect, based on the “enhanced immune surveillance theory”, with stimulated immune systems being better able to detect and destroy malignant cells [18]. Other works, based on the theory of chronic antigenic stimulation, which would be a stem-cell pro-oncogenic mechanism, suggest, on the contrary, that allergy is associated with a higher cancer risk [8, 19].

The underlying pathology in atopic syndrome is the persistence of a chronic inflammatory condition. Chronic airway inflammation has been suggested to be a carcinogenesis mediator [20]; this could happen through different mechanisms. (1) The ongoing process of cell damage and repair seems to cause permanent abnormalities in the

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airway [8], and lung cancer can directly evolve from scar damage [21]. (2) Chronic inflammation results in a high cell turnover rate with a higher possibility of spontaneous mutation; it can reduce the clearance of inhaled toxins and carcinogens that are found in the bronchoalveolar epithelium [8] or it can cause greater susceptibility to oxidant-induced alterations [22]. Also, antioxidant levels in the respiratory tract of patients with asthma are low [23]; free radical-induced cell ageing and oxidants cause direct damage to DNA, which can contribute to lung carcinogenesis [11, 20]. (3) IL-6 plays a key role in the host defence mechanisms; it is the main cytokine detected in lung tumour tissue [24], and can be found at high levels in epithelial cells and peripheral blood of asthma patients [25]. (4) Asthma treatment with corticosteroids increases both the survival and the proliferation of basal epithelium cells, with high expression of Bcl-2 protein, an epithelial cell apoptosis inhibitor [26]. A slight increase of lung cancer risk was found in patients who used oral corticosteroids for periods not greater than 3 years; however, the chronic use of inhaled and oral corticosteroids was not associated with cancer, and the underlying physiopathological mechanisms remain unclear [27].

Lung cancer risk seems to be lower in patients with rhinitis, which could be justified by different mechanisms: Some authors state that IgE reactivity has a different effect in cancer regardless of the manifestations of atopy, defined as specific-IgE positivity, since they find that cancer risk is increasing in patients with asthma and decreasing in patients with allergic rhinitis [28]. Histamine, the main mediator in type 1 allergic reactions, seems to protect NK cells from oxidative reactions, as well as from inhibition and synergism with other cytokines to stimulate T-cell activity [29]. The addition of histamine to certain cancer immunotherapy regimes has shown improved survival results and extended remissions [29].

The differences found in the results could be due to different bias sources and confusion factors, apart from certain inconsistency in the study design. First, when defining allergy and atopy, the term allergy covers a wide range of symptoms, which include non-atopic conditions, as well as non-IgE-mediated reactions. Only a few studies determined the allergy condition with a skin test [18]. The incorrect asthma classification could explain the lung cancer risk increase observed. The definition of asthma used in some studies seems to have included patients affected by other lung, smoking-related conditions, especially chronic bronchitis and emphysema [30], since they can have similar medical manifestations; early lung cancer

symptoms could also have been misclassified as asthma [11, 30], hence unrealistically increasing the extent of the association. However, the risk increase did not change [8] in several case studies and controls which excluded the cases with an asthma diagnosis up to 5 years prior to the cancer diagnosis. On the other hand, a reduction in the risk estimation was found in other studies, when excluding the cases with an asthma diagnosis carried out within 5 years prior to the cancer diagnosis [31]. The vast majority of studies use patient assertion as an allergy status indicator and the validity of questionnaire-based diagnosis is still discussed; however, it seems acceptable in epidemiologic studies [32]. We have not found any data comparing lung cancer risk between patients suffering from allergic asthma and those suffering from non-allergic asthma.

Secondly, risk increase can show a memory bias. Regarding lung cancer, patients could more easily remember previous asthma symptoms due to the relevance of their current condition. In order to minimise bias, several studies used more objective measures, such as the asthma history confirmed by a medical doctor, patient age at the time of diagnosis, hospitalisation history and asthma drug use [8].

Thirdly, researchers using hospital records study selected populations [33], since the records include only those patients in need of consultation and treatment due to the symptom severity. Some authors obtained the community cohort and their results suggest there is no association between lung cancer and allergic conditions [18].

Since smoking is still a very common risk factor in lung cancer, and the habit is less widespread in patients with asthma [34], we could explain the lower incidence of lung cancer in those patients in this way. However, Santillan et al.'s meta-analysis reported a positive association between asthma and lung cancer, even in never-smoking patients [8].

Another potential confusion factor is the lifestyle-related exposures associated with asthma and lung cancer. However, they can have a lower effect than smoking, since patients with a history of asthma seem to tend to avoid other cancer-related exposures due to the symptoms, and the different preferences in food or lifestyle.

In conclusion, a relation between allergy conditions and a higher incidence of lung cancer seems possible. Uncertainties about the association and the underlying physiopathological mechanisms, however, seem to require further studies.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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