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Current status and perspectives regarding the association between allergic disorders and cancer

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Abstract

Whilst activation of immune system may lead to a lower risk of some diseases, it has been shown that a history of atopic allergic disorders such as asthma, hay fever, eczema and food allergies could be related to several types of cancer. However, the evidence is not entirely conclusive. Two proposals suggest a possible mechanism for the association between allergic disorders and cancers: immune surveillance and the antigenic stimulation. The association of allergy and cancer may vary by cancer site and the type of exposure. The aim of current review was to summarize the current knowledge of the association between allergic diseases and the risk of cancers with particular emphasis on case-controls and cohort studies to estimate the cancer risk associated with allergy.

Key words: Allergy; Atopy; Asthma; Cancer; Tumor; Rhinitis
1. Introduction

Allergic disorders such as asthma, eczema, hay fever, allergic rhinitis and food allergies are common health problems and increasing in prevalence globally. They are a result of inappropriate immune system response to innocuous environmental antigens and are mainly mediated by T helper cell Type 2 ‘Th2’ response, as defined below. In contrast to Th2 cells, ‘Th1’ cells produce pro-inflammatory cytokines and are the major player in immunity against infections, elimination of cancerous cells as well as autoimmune disorders. An imbalance in the Th1/Th2 pathways is responsible for multiple immunological disorders, including allergies, autoimmune disorders and hypersensitivity reactions. Consequently altering the balance of these pathways may be a promising approach in the management of many immune-associated or immune-treatable disorders, although there are some controversies.

Because Th1 and Th2 cells can have an inhibitory effect, on each other, over activation of one system may exacerbate or relieve symptoms caused by the other. In this regard, inverse relationships between atopic dermatitis (AD) and insulin-dependent diabetes mellitus as well as different cancers have been reported. There is currently controversy about the relationship between allergy and cancers. Some evidence supported a protective role of allergy against glioma (GM), pancreatic cancer (PC), and hematological malignancies. In contrast, a positive association has been demonstrated between allergy and lung cancer (LC) risk while for allergy and gastrointestinal (GI) cancers, the results have been inconclusive.

Two proposals have suggested plausible mechanisms for the relationship between allergic disorders and cancers: immune surveillance and the antigenic stimulation. The immune surveillance theory is frequently invoked to rationalize inverse relationships between atopic diseases and some cancers. It has been shown that Th2 cytokines, which participate in the pathophysiology of atopic disorders, may contribute in antitumor immunity by attracting and activating eosinophils, macrophages, natural killer (NK) cells, and Type 2
CD8+ T cells. IgE is an essential player in the allergic response, and has the pivotal role in response to allergens and up-grading allergic symptoms, but recently researchers have noted potential anti-cancer properties of IgE, and several studies have demonstrated high tumoricidal effects of IgE.\textsuperscript{14,15}

On the other hand, the antigenic induction hypothesis suggests that overactive immune conditions stimulate chronic cellular inflammation, causing DNA mutation in dividing cells and consequently tumor initiation and propagation.\textsuperscript{16} In addition, cytokines originating from Th2 cells such as interleukin 4 (IL-4), and IL-13 can mediate some biological effects, such as tumor proliferation, cell adhesion, cell survival and lymph node-metastasis.\textsuperscript{17,18}

Studies published before 1985 provided evidence for reduced risk of cancer in allergic diseases.\textsuperscript{19} Findings of epidemiological studies since the 1980s are more complicated, suggesting that associations might be dependent on the particular allergies and affect specific organ cancer types providing a more mechanistic explanation.

In this review, we discuss the existing data on the association between allergy and different type of cancers. A critical evaluation of the literature in this matter is essential to clarify previous controversial findings and to determine future research directions.

1.1. Methods

Scientific databases were searched and all epidemiological studies that explored the relationship between allergic disorders and any cancer, published before January 2020, were retrieved, and were classified according to cancer site. Studies which investigated several cancer types were included for assessment if tumor-specific analyses were undertaken, and if so, these data were classified by site. The tables show a classification for exposure using 3 common subtypes: atopy, asthma, or allergy. Atopy was defined if the study particularly
recruited atopic-specific increased IgE values as the exposure. Allergy is recorded if the exposure attributed to the study was one or combined with the following allergies: eczema, nasal, plants, dust, mold, insect, animal, food, plant, as well as hay fever. Asthma is recorded if the study comprised a unique analysis by using asthma as the exposure. Information about study design, cancer-site, number of cases, country, type of exposure, adjustment of potential confounders, and estimates of relationships were gathered via two independent expert researchers (A.B. and M.F.).

2. Allergy and cancer risk

2.1. Hematological malignancies

2.1.1. Acute leukemia

Allergy has been assessed as a protective factor for several cancers including childhood leukemia. Evaluation of 1842 children with acute lymphoblastic leukemia (ALL) reported that a history of eczema was associated with a significantly reduced risk of cancer (odds ratio (OR)=0.7, 95% CI:0.5 to 0.9)20. In an old case-control study conducted in USA, prior diagnosis of asthma was protective against ALL (OR=0.9, 95%CI:0.4–1.9) and acute myeloid leukemia (AML) (OR=0.7, 95%CI:0.5–1.2) 21. In another survey, a history of allergic disease was related to a significant 50% lower risk for ALL but a not-significant 20% decrease in the risk of AML 22. In contrast, a study of 180 childhood ALL patients demonstrated no significant association of childhood ALL with history of eczema (OR=1.1, 95% CI:0.6 to 2.0) 23. A case-control record and population-based study reported that any type of allergy and asthma was related to a greater odds of childhood ALL 24. In a meta-analysis performed in 2010 on childhood/adolescent with ALL, the risks of atopy/allergies, asthma, hay fever and eczema were 0.7, 0.8, 0.5, and 0.7 (95% CI: 0.5 to 0.9; 95% CI: 0.6 to 1.0; 95% CI:0.4 to 0.5; and 95% CI:0.6 to 0.9), respectively 8.
Overall, it appears that the risk of ALL is possibly decreased in allergic patients.

2.1.2. Chronic leukemia

Studies evaluating the association in adult leukemia have yielded mixed results. A non-significant risk of chronic lymphocytic leukemia (CLL) in adults with a history of eczema was reported in the US population \(^{25}\). Recently in a cohort population-based study atopy, is linked with a 50\% lower risk of CLL (relative risk (RR)=0.5, 95 \% CI: 0.3 to 0.8)\(^{26}\). Reports on the relationship between allergic diseases and CLL are restricted; although protective role is stronger.

2.1.3. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)

Hodgkin lymphoma (HL), is a malignancy of B-cells, and is one of the most prevalent cancers in younger adults \(^{27}\). It has been proposed that allergy might be related to an increased risk of HL, particularly in younger cases \(^{28}\). It has reported that history of allergic rhinitis was correlated with a non-significantly lower risk of HL (OR=0.8, 95\% CI:0.6 to 1.0)\(^{29}\).

As for non-Hodgkin (NHL), self-reported hay fever was associated with a 14\% lower risk in a large population-based study \(^{30}\). Another study showed overall 1.4 odds of NHL in patients with allergic diseases\(^{31}\). In children, the negative relationship was found between allergic diseases and NHL (OR: 0.5; 95\%CI: 0.3 to 0.9). \(^{32}\)

Totally, obtained results did not support any connection between allergic disorders and lymphoma.

2.2. Breast cancer
Breast cancer (BC) is the second most frequent cause of cancer related mortality among women worldwide [33]. In 1985s, a study reported no association between BC risk and hay fever, but the risk of BC was rather decreased in women with history of hives or other allergies [19]. But in other study, a history of allergies or hay fever was related to a non-significant 20% lower risk of BC (95% CI: 0.7 to 0.9) [34]. Also, among young American women, an allergic disorders was associated with a lower risk of BC [35]. Although some studies represented no association between allergies and BC risk possibly not had enough power to evaluate this association [36-38]. Case control studies evaluating the relationship of allergy and BCs are shown in table1. Petridou and colleagues found serum IgE levels were positively associated with BC in a Greek population sample [39].

In Canadian individuals, asthma was not related to BC risk overall; but, a significant decrement in BC risk was observed only in premenopausal women [34]. The reason may be explained by difference in pattern of asthma among pre- and postmenopausal women, as allergic asthma is usually occur earlier compared to non-allergic asthma [40, 41] which affects older people [42-45].

Another approach to evaluate the relationship between allergies and cancer is “Mendelian Randomization”, which uses a functional genetic variation as an instrumental variable to investigate the association between modifiable exposures and disease [46]. A Mendelian randomization study did not show any causal relationship between allergic disease and risk of BC overall (OR=1.00; 95% CI: 0.96–1.04) or by subtype (estrogen receptor (ER) positive [OR=0.99; 95% CI: 0.95–1.04]), and ER negative [OR=1.05; 95% CI: 0.99–1.10]) [47].

In conclusion, the current evidence does not support the proposal that allergic conditions can affect the susceptibility to develop BC in women (Table 1 and 2).

2.3. Pancreatic cancer
PC as a fourth most common cause of cancer related mortality worldwide, and has an extremely poor prognosis. A meta-analysis of 14 PC studies showed the 30% and 45% lower risk in subjects with history of any allergies and nasal allergies, respectively. Another review of 11 published studies reported a reduced risk of PC in respiratory allergy conditions such as allergies to plants or pollen or hay fever. In the PanGenEU study conducted on 1297 pancreatic ductal adenocarcinoma (PDAC) cases and 1024 normal controls above 18 years old revealed that asthma was related to 40% reduced risk of PDAC (95% CI: 0.5 to 0.9) which consist with a result of meta-analysis of 10 case–control studies (OR=0.7, 95% CI: 0.6 to 0.9). Nasal allergies and associated symptoms were protective factor for PDAC (OR=0.7, 95% CI: 0.5 to 0.8 and OR= 0.6, 95% CI: 0.5 to 0.8, respectively) which confirmed by a meta-analysis of nasal allergy studies (OR=0.6, 95% CI: 0.5 to 0.7). However, cohort studies performed in different countries have reported no association between PC risk and serum Ig E levels, history of allergy, or the results of skin prick tests for allergy (SPT). These inconclusive results may be attributed to the young age of the studied population and short follow up, resulting to only a small number of cases; Furthermore, data were not adjust for potentially confounding factors.

The underlying mechanisms of association between allergy and PDAC risk are unclear. It has been proposed that hyperactive immune system involved in subjects with allergy. Furthermore, susceptibility and severity of asthma and allergies are known to be affected by genetic factors and interactions between gene and environment. Further researches are needed to clarify the role of genetics in these relationships. In addition, it has been found that cromolyn as an anti-allergic agent can suppress proliferation and propagation of human PC cells in both vitro and in vivo models.
Immune surveillance is an important aspect of the immune system, because of the possibility of destroying preneoplastic cells and, therefore safeguarding the body from cancer via an IFN-γ–dependent way. The immune cells that have been implied in surveillance are NK cells, NK-T cells, CTLs, as well as γδ T cells. These cells related to the both the innate (NK and NK-T cells) and adaptive, antigen-specific (γδ, αβ T cells) immune system. These cells have the potential to manage the pancreas; most of these cells are active within allergic responses.48

According to the above studies, allergic diseases are mainly related with a lower risk of PC.

2.4. Gastrointestinal (GI) cancers

2.4.1. Colorectal cancer

Studies reporting the association of allergy and GI cancers have reported inconsistent results.10 Allergy was described to be protective factors in a case–control studies on CRC patients.58, 59 Although, these studies used a self-reported history of atopy, and did not distinguish between different types of allergies; so, it may be lead to misclassification. In contrast, cohort studies did not support the protective effect of atopy against CRC.37, 60 A prospective data analysis of first National Health and Nutrition Examination Survey (NHANES I) showed non-significant higher risk (RR=1.7, 95% CI: 0.9 to 3.1) among CRC patients regarding to any type of allergy.38 Cohort studies investigating the association between allergy and CRCs are shown in table 2.

A meta-analysis of 16 studies in 2009 found no association between allergy and CRC risk.61 A study among patients with colon and rectum cancer, reported an inverse association between allergic rhinitis and only rectum cancer.62 The Iowa Women’s Health study highlighted history of two or more atopic conditions correlated with a 42% decrement in
CRC risk. More recent cohort study among different ethnic population explained that allergy had a protective effect against CRC among both men and women (RR = 0.9, 95% CI: 0.8 to 0.9) in all populations except Latinos. Also, allergy cases had a 20% fewer CRC-related mortality. Therefore based on the presented studies, the risk of CRC is probably decreased in patients suffering from allergic disorders (Table 1 and 2).

2.4.3. Esophageal and Gastric cancer

In a cross-sectional survey among 24,089 Korean cases, a history of AD was related to a reduced risk of gastric cancer, but only in men (OR=0.16; 95% CI: 0.03–0.75). Ye et al. reported that higher risk of esophageal and gastric cancers in asthmatic patients which may be due to the more gastro-esophageal reflux in these patients. In a Canadian study, a 27% lower risk of gastric cancer (95%CI, 0.1–0.9) was found in patients with a self-reported history of asthma. Kallen et al. reported a 50% lower risk of stomach cancer mortality among asthmatics; but, cohort studies reported no significant relationships.

With respect to esophageal cancer, several case-control studies have reported inverse relationships between esophageal tumor and history of allergy. In a case-control study among 304 cases with esophagus cancer and 4999 healthy controls, the negative associations was found between history of any allergy and cancer of esophagus (OR= 0.80; 95%CI: 0.46–1.39). Another population-based case-control study including 163 esophageal cancer patients and 275 controls, a history of allergy was linked with 60% decrement of esophageal cancer risk (95% CI:0.4–0.9).

This evidence indicates that allergic disorders are associated with a significantly lower risk of esophageal and gastric cancer.
The biological mechanism for the correlation of allergy with GI malignancies is not well understood but one common route for allergen exposure is digestive system, where mast cells and eosinophils are abundant. This can trigger a type I IgE-mediated hypersensitivity reactions, and activation of eosinophils and mast cells and interaction of IgE and cancer cell, causes degranulation and release of different mast cells mediator which promote permeability and inflammation. Studies have shown that eosinophils have cytotoxic effects and antitumor activity on precancerous cells which drive from high proliferating tissues, such as the gut lining. Due to the high presence of eosinophils and degranulation of mast cell in the respiratory mucosal lining of asthmatic cases, leukocytes in the gut of subjects with atopic conditions is more. Another theory, termed the prophylaxis hypothesis proposed that immune responses and inflammation in mucosal layer can cause to further rapid clearance of mutagenic stimulators.

2.5. Brain cancer

Since early 1990s, many studies have reported that allergy may be related to a lower risk of brain tumors. A case–control study in Boston showed an inverse association of glioblastoma with medications for any kind of allergies (RR= 0.6, 95% CI: 0.4–1.0). In a multicenter international case–control research among 1178 patients, history of allergy was a protective factor (OR=0.4, 95% CI: 0.5–0.7) for GM. Several case–control and cohort studies highlighted the protective effect of allergy against GM (Table1 and 2). A lower risk of GM among people with a history of allergy was confirmed in Swedish twins cohort and hospital discharges cohort. A meta-analysis published in 2009 disclosed that meningioma (a low-grade tumor) did not display inverse relationship with allergy in adults.

INTERPHONE is a large population based case–control study performed among 13 country included 2103 patients with different type of brain tumor, as well as 2520 normal controls.
Finding of this study indicated a significant inverse association between a history of any allergy and GM (OR=0.7, 95% CI: 0.6 to 0.9), acoustic neuroma (OR=0.6, 95% CI:0.5 to 0.8), and meningioma (OR=0.8, 95% CI: 0.6 to 0.9), but not parotid gland tumors (OR=1.2, 95% CI: 0.7 to 2.0) \(^8^9\). Also, it has been shown that an inverse relationship between prediagnostic IgE levels and GM risk \(^8^1,^9^0\). Recently, Porcelli *et al.* in a cross sectional study reported that allergic disorders may protect against pediatric brain tumors (PBT) development in individuals with Neurofibromatosis type 1 (NF1). In another study a non-significant inverse relationships between asthma and PBTs was reported, although, this association was more strong in the younger than in the older age group \(^9^1\). Brenner *et al.* in a multicenter hospital-based study among adults reported a 2.4-fold increased risk of having a history of hay fever for acoustic neuroma (95% CI:1.4 to 4.0)\(^8^8\). Overall, the evidence, suggests that allergic diseases appear to be associated to a lower risk of brain tumors (Table 1 and 2).

### 2.6. Lung cancer (LC)

Almost all scientific findings indicated that history of allergic disease related to greater risk of LC. Multiple case–control studies among never-smoker reported risks of LC associated with asthma to be up to 2.8 \(^9^2-^9^5\).

A population-based case–control study among Missouri woman found the asthma was a non-significant risk factor (OR=1.2, 95% CI: 0.8 to 2.1) in smokers and significant risk factor (OR=2.7, 95% CI: 1.4 to 5.4) in non-smokers for primary LC after adjustment for duration or intensity of exposure \(^9^3\). A study in 98 female cases of small cell lung cancer (SCLC) and 204 controls reported history of asthma related to statistically significant increased risk of LC after adjustments for age, education, and smoking \(^9^6\). A study in China reported the increased risk of asthma (OR=2.0, 95% CI: 0.9 to 4.2) among nonsmokers even adjusting for smoking history \(^9^5\).
In a case–control study including 437 LC cases and 437 controls, asthma was not an important risk factor for LC in never-smokers (OR=1.10; 95% CI: 0.47-2.59), although was related with higher risk in subjects with history of smoking (OR=4.3; 95% CI:1.2-15.2)\(^97\). In two studies in USA were not observed any association between history of asthma and adenocarcinoma of the lung after adjusting age and smoking history \(^98,99\). It have been shown a 50% reduced risk for LC among 217 case–control pairs women with asthma or hay fever from the Californian nested case–control study after adjustment for education and smoking \(^100\). Similarly, prospective cohort studies showed a higher risk of LC among asthmatic patients. In a prospective study on a Finnish twin cohort, the risk of LC-mortality was higher in men with asthma (HR= 3.2; 95% CI:1.4- 7.3, adjusted for smoking) \(^101\). In a large study of 78000 participants, the risk of LC was increased (Standardized Incidence Ratio (SIR) = 1.3 in men and SIR = 1.7 in women) among asthmatic patients \(^102\). In Swedish patients which hospitalized for asthma \(^103\), the SIR of LC was 1.6 (95% CI: 1.5–1.7; covariate: duration of follow-up, calendar year at entrance, age, comorbidities, emphysema, chronic bronchitis) during 8.5-years follow up.

In contrast, two case-control studies performed by El-Zein et al have reported an inverse association between eczema and LC (OR: 0.34, 0.73; 95% CI: 0.2-0.7, 0.48–1.12) after adjustment for age, sex, education, ethnocultural origin, fruit and vegetable intake, and smoking \(^67,104\). In a retrospective population-based cohort study in Taiwan, the population with eczema had a 2.80-fold greater risk of developing LC after adjusting for age and comorbidity than controls (95% CI: 2.59–3.03) \(^105\). A meta-analysis including 18 studies among 16375202 individuals showed 1.44 fold higher risk of LC in asthmatics (95% CI: 1.31–1.59). In addition, never-smoker asthmatics patients also had the elevated LC risk (OR = 1.28, 95% CI: 1.10–1.50) \(^106\). A more recent meta-analysis by karim et al, reported that asthma is associated with an higher risk of LC, while atopy without asthma may be have a
Asthma patients generally have other subtypes of LC other than adenocarcinoma. In asthmatic patients, different inflammatory cells (i.e. T and B lymphocytes, mast cells, basophils, eosinophils, neutrophils and dendritic cells) are recruited to the lung and with structural cells (epithelial and mesenchymal cells) participate in airway inflammation. Prolonged inflammation may trigger tumor development due to oxidative damage which can promote mutations in tumor suppressor gene. Accumulating evidence has highlighted a close association between chronic airway inflammation and LC. Additionally, chronic inflammation-enhances the generation of reactive oxygen or nitrogen species in the lung that can increase susceptibility to LC. Moreover, prolong use of glucocorticoids as a fundamental treatment in asthma, lead the general suppression of immune system which consequently may increase the risk of cancer development.

Conclusively, studies strongly supported that asthma is positively associated with risk of LC even after adjustment for potential confounders.

### 2.7. Bladder cancer (BIC)

An early case-control study reported that a history of atopy was associated with a higher risk of BIC in men, but with a lower risk in women. Other case-control studies have demonstrated positive relationships of having history of asthma and either urothelial tumor or BIC. Interestingly, risk of BIC increased in asthmatics with the glutathione S-transferase (GSTM1) or glutathione S-transferase (GSTT1) null genotypes. This finding was speculated to be as a result of a lack of the detoxification of reactive asthma medication intermediates by a deficiency of these enzymes. However, in population-based case-control study in the Netherlands, history of skin disease was inversely associated with BIC risk (OR = 0.74, 95% CI: 0.61–0.90). Recently, in a multicenter and hospital-based study among 936 urothelial bladder cancer (UBIC) patients and 1022 controls, asthma had a
protective effect for UBIC (OR=0.54, 95% CI: 0.37, 0.79)\textsuperscript{117}. Asthma has consistently been associated with a reduced risk of UBIC (OR=0.54, 95% CI: 0.37-0.79) in Spanish population\textsuperscript{118}. Tumor-related tissue eosinophilia has been connected with favorable prognosis in bladder cancer\textsuperscript{119}. Furthermore, experimental evidences demonstrated that eosinophils are tumoricidal in BlC\textsuperscript{120}. Higher concentrations of IgE and eosinophils have been found in other diseases i.e. helminthic infections, for which the lethal complication is BlC\textsuperscript{121}. Overall, most of the studies indicate an inverse association between allergic diseases and BLC.

2.8. Prostate cancer

Prostate cancer (PrC) is one of most frequent malignancy in men\textsuperscript{122}. There are several studies exploring possible effect of systemic inflammation conditions on prostate carcinogenesis. In a study was assessed single-nucleotide polymorphisms (SNP) between patients with PrC and normal controls revealed that 4 genes (TLR1, TLR6, OAS1, and OAS2) participate in innate inflammation pathways were associated to higher risk of PrC\textsuperscript{123}. It has also been found that increased white blood cell count, as a marker of systemic inflammation, was significantly associated with advance PrC risk\textsuperscript{124}. Results from large-scale cohort study including 16,934 men by Severi and coworker revealed a small increment in PrC risk in asthmatic patients compared to controls (HR: 1.2, 95% CI: 1.05 to 1.5)\textsuperscript{125}. Furthermore, the risk was further elevated in cases allocating anti-asthma medications such as inhaled glucocorticoids, systemic glucocorticoids, and bronchodilators. Glucocorticoids are a very potent anti-inflammatory agent which frequently prescribed for not only for asthmatic patients but also for other types of allergic disorders such as allergic rhinitis and eczema. Rather than the anti-inflammatory effects, glucocorticoids can suppress different aspects of immune system and therefore consider as an immune-suppressive drug\textsuperscript{126}. And so their prolong use can increase the risk of tumorigenesis due to immunosuppressive and anti-apoptotic features\textsuperscript{127, 128}.
A prospective questionnaire-based cohort study reported that men with a history of asthma had a 30% low risk of lethal PrC\textsuperscript{122}. In contrast, Zhao et al reported 86 of 1552 asthmatics were diagnosed PrC during follow-up\textsuperscript{37}. In the large nationwide study, asthma was an independent risk factor for PrC and was associated to a 136% higher risk after adjustment. Also, there was no direct relationship between history of glucocorticoids consumption and PrC diagnosis. Glucocorticoids joined with mutated androgen receptors which may lead to development and progression of androgen-independent PrC\textsuperscript{129}. Although, there is inadequate document to establish this theory associated to prostate carcinogenesis.

In a large, population-based case-cohort study including 4124 cases with asthma and 8248 full-matched healthy control subjects, asthma was significantly associated with PrC (OR= 2.4, 95% CI: 1.2 to 4.6) and its independent risk factors were age and hypertension\textsuperscript{130}. But, in seven studies, no significant association was detected between allergic diseases and PrC\textsuperscript{36-38, 60, 101, 131, 132}. In a recent meta-analysis included case-control (n=5) and cohort studies (n=15), the RR for developing PrC risk was 1.04 (95%CI: 0.9–1.2) for asthma, 1.04 (95%CI: 0.9–1.1) for hay fever, 1.2 (95%CI: 0.7–2.1) for atopy, and 0.96 (95%CI: 0.8–1.1) for any allergy. When adjusted for potential confounders, i.e. smoking, alcohol drinking, age, BMI and race, identical results were yielded\textsuperscript{133}. In contrast, findings of a Mendelian randomization study did not provide any evidence to support association of allergic disease with PrC (OR=1.00 ; 95%CI: 0.94–1.05)\textsuperscript{47}. Conclusively, it seems that allergic disorders do not have any protective or enhancer role in development of PrC.

2.9. Head and neck cancer (HNC)

Head and neck cancer (HNC) (tumors of the oral cavity, larynx, oropharynx and hypopharynx) is the fifth most frequent cancer worldwide. A meta-analysis of 14 studies showed a protective effect for allergic symptoms in HNC (OR=0.8, 95% CI: 0.6 to 0.9)\textsuperscript{134}. In
contrast, cohort study showed that higher serum IgE levels were related to a higher risk of HNC \(135\). In a cohort study with 14,849 participants, subjects with positive tests for serum specific IgE against inhalant allergens had a higher risk of HNC (OR=1.7, 95 % CI: 1.0–3.1). In other cohort including 37747 subjects, high IgE levels was linked with an 1.4-fold higher risk of oral and pharyngeal cancer (95 % CI:1.0 to 1.8) \(^{26}\). In a hospital-based case-control study among 252 HNC cases and 236 healthy controls, having any allergy was a protective factor against developing of HNC (OR = 0.41, 95% CI: 0.27–0.62) particularly in oral cancer (OR = 0.4, 95% CI: 0.2–0.6) and oropharyngeal cancer (OR = 0.5, 95% CI: 0.2–0.9) \(^{136}\).

The results of a meta-analysis by Hsiao et al demonstrated a negative relationship between allergies and HNC which was stronger among the case-control studies (RR\(_{\text{meta}}\) = 0.6, 95% CI: 0.4–0.8) than cohort studies (RR\(_{\text{meta}}\) = 0.9, 95% CI: 0.7–1.2) \(^{136}\).

It has been shown that elevated the number of IgE-positive cells in the tissue of squamous cell carcinoma of head and neck than normal tissue \(^{137}\).

Liao et al have recently reported that elevated serum total IgE levels were related to a significantly 1.7-fold higher incidence of HNC. Symptomatic allergy was related to a significantly 40% decrement of HNC risk. Notably, asymptomatic atopic cases had a higher risk of HNC than subjects with normal serum IgE level and no allergy symptoms which supported the “prophylaxis hypothesis.” \(^{138}\). Although the investigations on the association between allergic diseases and HNC are limited, they tend to support a protective role of allergies.

### 2.10. Squamous cell carcinoma (SCC) and early onset basal cell carcinoma (BCC)

There are limited data about the contribution of atopic and allergic disorders in the etiology of keratinocyte tumors. In 2003, Twin Cohort study reported that females with a history of
AD prone to be more likely to affect a basal cell carcinoma (BCC), but it was non-significant (OR=1.8, 95% CI:0.8 to 3.9) \(^{139}\). Results from a nested case–control study of skin cancer patients demonstrated that cases who developed a new primary cutaneous squamous cell carcinoma (SCC) had higher prediagnostic IgE levels than controls who did not \(^{140}\). Similarly, a higher risk of SCC was reported in asthmatics subjects compared with non-asthmatics subjects (Table2) \(^{141}\). Other studies presented positive \(^{141}\), negative \(^{19}, 62, 68, 142\), and null association between BCC and SCC and allergic disorders \(^{19, 142, 143}\). In a population-based case–control study including 375 early onset BCC patients and 251 controls, as well as 254 SCC patients and 432 controls, an overall inverse association was reported between an allergic disorders and risks of early onset BCC but not SCC. Interestingly, reduced risks of either early onset BCC or SCC related to atopic history was noticed only in women \(^{144}\). In a recent report from Minnesota, the odds ratio for SCC development in patients with history of AD compared to cases without was 1.75 (95% CI: 1.05–2.93) \(^{145}\). Although, almost all studies was discussed above had limited data about possible modifying factors, for instance age at onset, type of allergy and its severity, as well type of medications.

In general, there the results are controversies but it seems that allergic diseases may decrease the keratinocyte tumors risk.

2.11. Cervical Cancer (CC)

Cervical cancer (CC) is a malignant cancer of the cervix with nearly 277,000 new diagnosed cases and 266,000 deaths annually \(^{146}\). A case-control study among USA individuals reported that an odds of history of any allergy was 0.7 (95 % CI: 0.6 to 0.9) for squamous cell SCC. Also, they estimated the risk of CC related to SNPs in the chromosome 5 cytokine cluster genes \(^{147}\). Also, they estimated the risk of CC related to SNPs in the chromosome 5 cytokine cluster genes including IL4, IL9, and IL13 \(^{147}\). Montgomery and coworker found significant
association between eczema during childhood and susceptibility to CC among two combined British cohorts (OR=3.27, 95% CI:1.95 –5.49)\textsuperscript{148}. It is plausible that patients with seborrhoeic eczema, which is as a result of high yeast colonization, have suppressed T-cell function. Despite the scarce of data in this regard, the role of allergic disease in CC is protective.

3. Discussion

Despite the limited results, the current available data from case-control and cohort studies indicate that allergy is associated with a lower risk of cancer although the exact mechanism is not well understood. Studies on serum total IgE and allergen-specific IgE supported the negative associations with the development of melanoma, BC, gynaecological cancers and GM\textsuperscript{149}.

Indeed, the association of allergy and cancer varies with cancer site. The inconsistent results of the studies showed that the association between atopy and carcinoma risk is regulated not only via the specific-cancer site but also by the type of allergic exposure as well. For instance, LC risk was remarkably elevated particularly in patients with history of asthma, but not other atopic diseases. Recently it has been reported that in patients with any type of cancer, the ORs for allergic rhinitis, AD, and bronchial asthma were 0.7 (95%CI: 0.5–0.8), 0.9 (95%CI: 0.8–0.99), and 1.03 (95%CI: 0.9–1.1) than normal cases, respectively\textsuperscript{150}.

Prophylaxis hypothesis may be the more probably explain the inverse association between Allergy and certain cancers. Concerning to the “prophylaxis hypothesis,” allergic reaction is the body’s way of throw outing carcinogens, and so, allergy contributed in protection against cancer\textsuperscript{151}. Actually, relationship between cancer risk and allergy symptoms was more commonly highlighted in malignancies of tissues or organs which interface the external environment such as GI cancers than others such as breast and prostate tumors.
Natural T cells, and in particular the CD4+ is associated to atopy and total IgE concentrations \(^{152}\). Besides, the population of IFN-\(\gamma\)-generating CD8+ T cells is correlated to asthma intensity, to bronchial hyper-responsiveness, as well as to blood eosinophilia\(^{153}\). In several cancer types, such as CRC or gallbladder carcinoma, immunohistochemical characterization of tumor-infiltrating Type 2 CD8+ T cells has been found to relate to a higher overall survival \(^{154,155}\). Understanding the protective role of IgE and Th2 immunity against cancer formation would also participate to understanding whether asthmatic patients who admitted to receive anti-IgE therapy may be vulnerable to developing tumor.

Many of previous reports above collected data of allergy symptoms retrospectively; so recall bias is plausible. Also, study participants may mistake non-allergic symptoms and over-estimated the allergy symptoms. Additionally, an ongoing chemoradiotherapy may influence the manifestation of allergy \(^{156}\), which could affect recall when subjects declaring history of atopic diseases. In addition, little knowledge exists on risk of cancer in association to some specific allergies, i.e. foods and drugs or the effect of treatment for allergies.

Confounding variables also contributed in the association between allergic diseases and tumor risk. Whereas all studies mentioned in this review were adjusted for smoking, several other potential confounders have not been considered. Alcohol use is a risk factor for CRC, liver cancer and BC and has been correlated with SPT reactivity and IgE levels \(^{157,159}\). Obesity is associated to both asthma and some site-specific tumors \(^{160,161}\). Socioeconomic condition has also linked with both allergy and human malignancies \(^{162-165}\). The nature of atopy assessment (i.e. self-completed questionnaires, interviews, SPTs, serum total and allergen-specific IgE levels) as well as participants selection bias can causes a negative impact on causality and treatment-associated effects \(^{166}\). Furthermore, little is known about the effect of age at onset of allergies or the frequency of allergies and risk of developing cancer.
If potential confounders were not considered in the data analysis, the associations have prone to be skewed.

In this review we summarize the current knowledge about association between allergic diseases and the risk of cancers and it seems that in many cancers, allergic disorders have a protective effect while in some others allergies may have a predisposing role but in spite of a huge body of epidemiological studies, the exact mechanism which allergy may prevent or promote a malignancy is not well understood.

Considering the inconsistent results and the uncertainty about the causal relationship and exact mechanisms, the European Academy of Allergy and Clinical Immunology in 2014 announced Task Force status in the inter-disciplinary field of AllergoOncology for better characterization and understanding of the interface between allergic responses and human malignancies, utilized immune surveillance, immunomodulation as well as the actions of IgE-mediated immune responses opposed to cancer, to acquire novel approaches for development of potential new effective treatments for cancers¹⁶⁷.

Further large-scale prospective studies should focus on a more carefully defined atopy status, manifestation of different atopic diseases, and repeated measurements over time respected to potential confounders, to advance our understanding of the role that allergies might play in the risk of developing cancer.

**Funding:** This work supported by grant from Birjand University of Medical Sciences (Code: 4891).
### Table 1. Case-control studies of association between atopy/asthma/allergy and different cancers

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<th>Type of cancer</th>
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<th>Type of study</th>
<th>OR</th>
<th>95% CI</th>
<th>Year/Country</th>
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Acute lymphoblastic leukemia (ALL); Breast cancer (BC); Cervical cancer (CC); Colorectal cancer (CRC); Gastric cancer (GC); Glioma (GM); Head and neck cancer (HNC); Lung cancer (LC); Non-Hodgkin Lymphoma (N-HL); Pancreatic cancer (PC); Prostate cancer (PrC); Squamous cell carcinoma (SC); Urothelial bladder cancer (UBIC).

*Adjusting for smoking
Table 2. Cohort studies of association between atopy/asthma/allergy and different cancers

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<tr>
<th>Type of cancer</th>
<th>Number of cases</th>
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**Abbreviations**: relative risk (RR); Chronic lymphoblastic leukemia (CLL); Breast cancer (BC); Cervical cancer (CC); Colorectal cancer (CRC); Lung cancer (LC); Non-Hodgkin Lymphoma (N-HL); Pancreatic cancer (PC); Prostate cancer (PrC).

*Adjusting for smoking*
References:


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