

## Atopic Diseases Correlated with the Incidence of Cancer

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### Abstract

In our previously study, we demonstrated an association between eczema and the risk of glioma. Our results revealed that eczema significantly reduced the risk of glioma. Here, we review related published data to investigate the association between allergic diseases and the risk of cancer. We also discuss the potential mechanism of how allergic diseases might modify the risk of cancer.

**Keywords:** Cancer Risk; Allergic Disease; Eczema; Allergy

### Introduction

In 2016, we studied the relation between eczema and the risk of primary glioma based on 66,978 subjects. Our results showed that patients with a history of eczema had a 0.69-fold lower risk of glioma than patients without eczema [1]. These findings revealed significant protective effects of allergic disease in terms of susceptibility to cancer. However, there was room for further investigations of correlations between allergic diseases and the risk of malignancies.

Although underlying related mechanisms of allergy diseases as a probable protection factor against the development of some malignant tumors remain unclear, this subject has been widely studied in human and experimental models [2]. In this article, we review related published data to investigate the association between allergic diseases and the risk of cancer. In addition, we present immunological surveillance as a further sustainment of a mechanism active in IgE levels and eosinophil in the anti-tumor response.

### Epidemiological Studies of Eczema and the Risk of Cancer

An inverse relation between eczema and the incidence of malignancies at many sites has been reported in several epidemiological studies. A case-control study involving 3812 subjects in Canada based on a questionnaire interview found a significant inverse association between eczema and stomach cancer (OR, 0.27; 95% CI, 0.10-0.90) and lung cancer (OR, 0.34; 95% CI, 0.20-0.70) [3]. Our previous study revealed an inverse relation between eczema and the risk of glioma (OR, 0.69, 95% CI, 0.61-0.78), suggesting that eczema may modify the risk of glioma by modulating the immune system [1]. A population-based case-control study conducted in the United States by Wen et al. reported that eczema had a significant protective effect against acute lymphoblastic leukemia among children (OR, 0.70, 95% CI, 0.50-0.90) [4]. Series studies have noted the same results that atopic diseases reduce the risk of malignancies (Table 1).

On the other hand, these correlations varied significantly among different studies. A follow-up study involving 4,518,131 patients showed that the incidence risk of skin melanoma and non-melanoma skin cancer increased after adjusting for age and sex. Another retrospective population-based cohort study by Juan et al. in a Chinese population revealed that individuals with eczema had a 2.80-fold higher risk of lung cancer compared with the controls [5]. This finding was attributed to chronic inflammation resulting in genomic instability in local airways.

However, one limitation of published data should be noted. Most studies did not assess confounding factors, such as age, sex and complications at the patient level and incorporate them into the analysis. Future well-designed with risk adjusted studies are warranted, and then lead to a more accurate correlation between atopic diseases and cancer.

### The Association between Allergic Diseases and Cancer Development

Allergic diseases may affect the development of cancer. This inverse association may result from reverse causality. Because the tumor itself can suppress the immune system [6], patients with malignant tumors often exhibit immunological defects (e.g., a delayed hypersensitivity response or a reduced number of circulating T cells) [7]. Eczema is considered to be a chronic state of inflammation in certain tissues, which makes it responsible for the positive associations observed with cancer risk. Females with a history of eczema tended to be more likely to develop a basal cell carcinoma [8]. The skin is an organ that is directly exposed to the environment and therefore very susceptible to allergens as well as carcinogens [9]. The connection between lung cancer and asthma is quite similar to the one between eczema and skin risk. It can be concluded that immune surveillance is subordinate because inflammation dominates these localized diseases, promoting cancer development. Allergy treatment is also capable of affecting tumor outcome [10]. Glucocorticoids used for the treatment of atopic diseases have been shown to increase cancer risk due to immunosuppressive condition [11].

Study	Type of cancer	Types of study	No. of Subjects	Risk estimate [OR /RR, with 95% CI]	Terminology used for atopic diseases
Wen (2000)	Acute Lymphoblastic Leukemia	Case-control, population based	1842	0.70 (0.50-0.90)	Eczema (allergic, in the context of hay fever, asthma; unknown physician-diagnosed or self-assessment)
Schuz (2003)	Acute Lymphoblastic Leukemia)	Case-control, population based	1294	0.50 (0.30-0.70)	Physician-diagnosed neurodermatitis in children
Fabbro-Peray (2001)	Non Hodgkin Lymphoma	Case-control, population based	445	0.50 (0.30-0.70)	Eczema (any type; unknown physician-diagnosed or self-assessment)
Melbye (2007)	Non Hodgkin Lymphoma	a population-based case-control study and in a prospective study	6242	0.32 (0.20-0.42)	questionnaire information on allergy
Schlehofer (1999)	Glioma	Case-control, population based	1178	0.60 (0.50-0.90)	Physician-diagnosed eczema (allergic)
Wigertz (2007)	Glioma	A large population-based case-control study	6046	0.70 (0.61-0.80)	any of asthma, hay fever, eczema, or other type of allergy
Holly (2003)	Pancreatic cancer	Case-control, population based	532	0.77 (0.63-0.95)	Self-assessment eczema (allergic)
Eppel (2007)	Pancreatic cancer	A population-based case-control study	654	0.43 (0.29-0.63)	allergies or hay fever
Olson (2010)	Pancreatic cancer	A hospital based case-control study	475	0.68 (0.49-0.95)	self-reported allergies
Cotterchio (2014)	Pancreatic cancer	A population-based case-control study	1630	0.68 (0.52-0.89)	questionnaires collected lifetime allergy history
Negri (1999)	Rectal cancer	A multicentric case-control study	4882	0.64 (0.44-0.92)	history of allergy
Bosetti (2004)	Colon	A case-control studies	8314	0.76 (0.59-0.97)	history of allergy
Prizment (2007)	Colorectal cancer	A case-control studies	21292	0.70 (0.49-0.98)	self-reported questions about physician-diagnosed asthma, hay fever, eczema
Hwang (2012)	Colorectal cancer	A prospective cohort study	367179	0.82 (0.69-0.79)	
Turner (2005)	Colorectal cancer	A prospective cohort study	1102247	0.76 (0.64, 0.91)	asthma and hay fever
	overall cancer	A prospective cohort study	1102247	0.88 (0.83-0.93)	asthma and hay fever
El-Zein (2014)	lung cancer	A population-based case-control study	2655	0.37 (0.24-0.59)	self-reported history of eczema
Jensen (2012)	Malignant melanoma	A large cohort study	31330	0.46 (0.19-0.95)	atopic dermatitis patients

**Table 1:** Representative studies on negative association between allergy and cancer.

### Underlying Mechanism of Eczema on Cancer

The potential mechanism between eczema and cancer is not yet clear. It has been widely admitted that atopic diseases are hyper-reactive states of the immune system. This hyper-reactive state might result in enhanced immune surveillance that is capable of detecting and destroying tumor cells before the development of clinically detectable malignancies. As an example, natural killer cells are important innate immunity cells playing the role of immune surveillance, and they are more prevalent and more active in people suffering from atopic diseases [12]. Eosinophils should be emphasized because eczema is often accompanied by increased levels of eosinophil.

These increased eosinophils have been repeatedly shown to be associated with better prognoses in cancer patients [13]. Recently, several studies also found that eosinophilia possibly prevents the development of cancer [14-16]. Eosinophils can always be found surrounding solid tumors, and they might directly destroy tumor cells via cell lysis due to the cytotoxicity mediated by granule proteins such as eosinophil cationic protein [16,17]. Carretero reported that activated eosinophils were essential for tumor rejection in the presence of tumor-specific CD8(+) T cells and initiated substantial changes in the tumor microenvironment, such as macrophage polarization and normalization of the tumor vasculature [18]. It should be noted that

above studies presented a new concept for eosinophils in cancer that may lead to novel therapeutic strategies and allow patents to combat cancer directly. The level of IgE is also thought to be a better way of detecting the association between allergy and cancer [15,19]. IgE is produced and regulated by the B cells as well as T helper type2 (Th2) and type 17 (Th17) cells. Additional evidence for protection against glioma afforded by the immune system is lower antibody titers to varicella zoster virus and the reported fewer number of cases of chicken pox infections compared with controls [20]. Our previous study provided evidence that the germ-line polymorphism increased the risk of cancer [21]. Similar results have been demonstrated that single nucleotide polymorphisms (SNPs) and haplotypes in genes encoding IL-4, IL-4R and IL-13 play a critical role in allergies and IgE production [22]. Several studies have found that SNPs in IL-4, IL-4R and IL-13 are inversely correlated with the incidence of glioma [23-25]. The data obtained from an animal experiment suggest that a concomitant allergic condition reduces tumor progression via increased tumor cell apoptosis [26].

Although several studies have demonstrated that eczema significantly reduces the risk of glioma, two outstanding aspects of these studies should be addressed. First, the majority of these studies investigating this association have been retrospective case-control studies; only a small proportion used prospective methods. Allergy symptoms are prone to be confounded with symptoms of other diseases due to confabulation memory. Another aspect that must be noted is the definition of atopic diseases. Most of the studies pertaining to allergic diseases were questionnaire based and used imprecise terminology [4,27], although the diagnosis was made by physicians in several studies [28,29]. The variational results regarding different types of cancer are multifactorial. In addition, cancer prevalence is not affected by a history of eczema. Therefore, results should not be overstated.

Above all, given that allergic inflammations possess an enhanced tumor immune surveillance, it is possible that a history of allergies might reduce the risk of malignancies. The evidence from epidemiological studies suggests this possibility, although most of these studies were characterized by confounding factors. Therefore, the results might have been biased and the underlying mechanisms were not clear. It is accordingly reasonable to speculate about an inverse association between allergies and cancer risk. In addition, numerous valid patents pertaining to allergy-related proteins or cytokines for the treatment of cancer have been filed or awarded [16]. However, there is a long way to go to illuminate the potential biological mechanisms between allergic diseases and cancer risk. These findings will help to explore targeted therapies with allergy related cytokines as a promising novel perspective to combat cancer.

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