

Relationship between Allergy and Cancer: An Overview

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Key Words

Allergy · Cancer · Inflammation · Immunosurveillance

Abstract

Allergic diseases and malignancies cause a lot of morbidity, mortality and high costs for healthcare systems. An inverse association between allergy and cancer has been suspected for a long time, but even despite extensive research no general relationship has been determined. This review comprises 32 epidemiological studies published between 1960 and 2011 and draws conclusions regarding relationships between specific types of cancer and allergic diseases. On the one hand, inflammatory reactions in the course of allergy can support carcinogenesis but are limited to specific areas, whereas on the other hand systemic effects in terms of enhanced immunosurveillance can prevent cancer.

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Introduction

Worldwide, but especially in developed countries, allergies and cancer cause a lot of morbidity and mortality, and high costs for healthcare systems. In 2008, 12.7 million people were diagnosed with cancer and 7.6 million people died of cancer worldwide, with incidences in industrialized countries nearly twice as high as in developing countries [1]. In Germany, as well as in the USA and

other developed countries, cancer is the second leading cause of death after cardiovascular diseases [2, 3]. As the population is increasingly aging and lifestyle is changing, rates of cancer are rising [1]. Allergies, however, are even more prevalent, but mortality is much lower. In Germany about 40% of all adults have ever suffered from any type of allergy, and about 300 million people in the world are suffering from asthma [4, 5].

This overview comprises 32 epidemiological studies published between 1960 and 2011 which were selected from the MEDLINE database by an electronic search. Additionally, cited references were checked manually. All studies were either case-control studies comparing subjects who have a condition/disease with patients who do not have the condition/disease retrospectively, or prospective cohort studies measuring a variety of variables in a group of people over a period of time to see whether they develop the outcome of interest [6]. Results were grouped by the individual types of cancer and allergy. Only statistically significant results were considered, statistical values were: odds ratio (OR), relative risk (RR), risk odds ratio (ROR), hazard ratio (HR), incidence rate ratio (IRR), standardized incidence ratio (SIR) or standard morbidity ratio (SMR). OR describes the degree of association between two variables, in this case the incidence of allergy and cancer, whereby an OR of 1 is equivalent to no association. RR, HR and IRR give the ratio of the incidence of cancer in allergic patients to that in non-allergic patients. SIR and SMR are ratios between ob-

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Table 1. Studies on association between allergy and cancer

Type of cancer	Type of allergy	Negative	Positive
Cancer in general	Any allergy	[9–11, 25]	[16]
	Asthma	[12]	[17]
	Atopic dermatitis		[19–21]
	Allergic rhinitis	[12, 15]	[15]
	Other allergies	[13, 14]	[14]
Pancreatic cancer	Any allergy	[26–29]	
	Atopic dermatitis		[20]
	Allergic rhinitis	[12, 28]	
	Other allergies	[28]	
Lung cancer	Asthma		[12, 15, 18]
	Atopic dermatitis		[20]
	Allergic rhinitis	[12]	
	Other allergies	[13]	
Colorectal cancer	Any allergy	[12, 31–33]	
	Asthma		[17]
	Atopic dermatitis	[33]	
	Allergic rhinitis	[12, 15]	
Other digestive cancers	Any allergy	[32]	
	Asthma	[17]	
	Atopic dermatitis		[20]
	Allergic rhinitis	[13, 15]	
Skin cancer	Asthma	[15]	
	Atopic dermatitis		[19, 21]
	Allergic rhinitis	[15]	[34]
Brain cancer	Any allergy	[35–39]	
	Asthma	[35–37]	[20]
	Atopic dermatitis	[36, 37]	[15, 20]
	Allergic rhinitis	[36, 37]	[35]
	Other allergies	[35]	[35]
Lymphatic and hematopoietic cancers	Any allergy		[16]
	Asthma	[12, 17]	
	Atopic dermatitis		[20, 21]
	Allergic rhinitis		[15]
Reproductive cancers	Any allergy		[34, 40]
	Asthma	[17]	[34]
	Allergic rhinitis		[15]
	Other allergies	[13, 14]	
Other cancers	Any allergy	[32]	
	Asthma	[17]	[15, 17]
	Allergic rhinitis	[15]	[15]

served cases of cancer among allergic patients and the expected number in a reference population [7, 8]. This review intends to give a brief overview of current studies and draw conclusions regarding the relationships between specific types of cancer and allergic diseases.

Results

Table 1 summarizes the evaluated studies, sorted by types of cancer and allergy. Table 2 and 3 show information about studies on cancer sites which were found to clearly correlate, either positively or negatively, with allergies.

Cancer in General

Study results are very inconsistent considering the association between all types of cancer and a history of allergy. In 1960, Fisherman [9] identified a significantly lower incidence of atopic diseases in cancer patients than in noncancerous subjects (3.2 vs. 12.9%), which implicates atopy as a protective factor for cancer development. Mackay [10] could prove this only for female but not for male cancer patients. Skin-tested atopy was 15-fold less prevalent in cancer patients in a case-control study in 1976 [11]. A more recent study that investigated more than 1.1 million US Americans within the Cancer Prevention Study II, resulted in an inverse association between cancer and hay fever (RR = 0.92, 95% CI 0.89–0.94), asthma and hay fever (RR = 0.88, 95% CI 0.83–0.93) and asthma and/or hay fever (RR = 0.94, 95% CI 0.92–0.96). These associations were not significant in never smokers [12]. Women suffering from hives were related to a reduced risk of cancer in general (OR = 0.76) [13]. A cohort study of 34,198 Seventh-day Adventists, who do not smoke cigarettes, drink alcohol or eat meat, found an increased risk of cancer for males (RR = 1.33) and a decreased risk for females (RR = 0.79) suffering from allergic reactions to medications [14]. Another cohort study in Taiwan reported a decreased risk of cancer for men (SIR = 0.93), but an increased risk for women with allergic rhinitis (SIR = 1.13). For both sexes combined there was no alteration in the risk of overall cancer [15]. A prospective study, based on the First National Health and Nutrition Examination Survey (NHANES I) of the USA, analyzed the incidence of cancer among 6,108 adults. Subjects who reported physician-diagnosed asthma, hay fever, hives, food allergy or another allergy were found to be at a higher risk (ROR = 1.40) of developing cancer. The highest risk was reported for patients with hives (ROR = 1.50) [16]. Vesterinen et al. [17] evaluated the correlation between a history of asthma and cancer by linking two Finnish registers. They found a slightly increased risk of cancer for asthmatic men (SIR = 1.12), whereas González-Pérez et al. [18] reported no association. A positive association between atopic dermatitis and cancer risk was observed in a prospective

Table 2. Studies on negative association between allergy and cancer

Type of cancer	Type of allergy	Study design	Number of subjects	Value (95% CI)	Reference	Year
Pancreatic cancer	Any allergy	cc	2,233	OR = 0.77 (0.63–0.95)	[26]	2003
		cc	654	OR = 0.43 (0.29–0.63)	[27]	2007
		cc	617	OR = 0.58 (0.40–0.84)	[28]	2007
		cc	475	HR = 0.68 (0.49–0.95)	[29]	2010
	Allergic rhinitis	pc	1,102,247	RR = 0.85 (0.77–0.95)	[12]	2005
		cc	617	OR = 0.45 (0.29–0.70)	[28]	2007
	Other allergies	cc	617	OR = 0.43 (0.23–0.80)	[28]	2007
Colorectal cancer	Any allergy	cc	6,107	OR = 0.88 (0.63–1.00)	[31]	1999
		cc	8,314	OR = 0.76 (0.59–0.97) (colon) OR = 0.54 (0.37–0.77) (rectum)	[32]	2004
		pc	1,102,247	RR = 0.76 (0.64–0.91)	[12]	2005
		pc	21,292	HR = 0.74 (0.59–0.94)	[33]	2007
	Atopic dermatitis	pc	21,292	HR = 0.70 (0.49–0.98)	[33]	2007
	Allergic rhinitis	pc	1,102,247	RR = 0.92 (0.85–0.99)	[12]	2005
		pc	367,179	SIR = 0.82 (0.69–0.79)	[15]	2011
	Brain cancer (glioma)	Any allergy	cc	1,581	OR = 0.67 (0.52–0.86)	[35]
cc			2,681	OR = 0.63 (0.53–0.76)	[36]	2006
cc			1,067	OR = 0.59 (0.63–0.70) (reported) OR = 0.89 (0.82–0.92) (IgE)	[38]	2009
Asthma		cc	1,581	OR = 0.63 (0.43–0.92)	[35]	2002
		cc	2,681	OR = 0.71 (0.54–0.92)	[36]	2006
		cc	6,046	OR = 0.65 (0.51–0.82)	[37]	2007
Atopic dermatitis		cc	2,681	OR = 0.74 (0.56–0.97)	[36]	2006
		cc	6,046	OR = 0.65 (0.54–0.79)	[37]	2007
Allergic rhinitis		cc	2,681	OR = 0.73 (0.59–0.90)	[36]	2006
		cc	6,046	OR = 0.66 (0.56–0.78)	[37]	2007
Other allergies		cc	1,581	OR = 0.23 (0.07–0.79)	[35]	2002

cc = Case-control study; pc = prospective cohort study.

Table 3. Studies on positive association between allergy and cancer

Type of cancer	Type of allergy	Study design	Number of subjects	Value (95% CI)	Reference	Year
Lung cancer	Asthma	pc	78,000	SIR = 1.32 (1.22–1.42) (men)	[17]	1993
				SIR = 1.66 (1.39–1.94) (women)		
		pc	1,102,247	RR = 1.11 (1.02–1.20)	[12]	2005
		pc	129,860	OR = 1.35 (1.15–1.95)	[18]	2006
		pc	367,179	SIR = 1.42 (1.31–1.54)	[15]	2011
Skin cancer	Atopic dermatitis	pc	6,275	SMR = 2.4 (1.4–3.9)	[19]	2005
		pc	4,518,131	IRR = 1.74 (1.25–2.41) (melanoma)	[21]	2010
				IRR = 1.46 (1.27–1.69) (nonmelanoma)		

pc = Prospective cohort study.

study in Denmark (SMR = 1.5) as well as in a retrospective cohort study in Sweden observing 15,666 patients hospitalized for atopic dermatitis (SIR = 1.13), and a study in the UK (IRR = 1.49) [19–21]. Three further studies could not describe any correlation between a history of allergy and either cancer in general or any specific cancer site [22–24]. A different kind of research was done by Pompei et al. [25] who monitored 1,055 patients after primary tumor therapy. Among allergic individuals the probability of being cured was about 20% higher than in nonallergic subjects, and they were at a 50% lower risk of tumor progression.

Pancreatic Cancer

Association between a history of allergy and pancreatic cancer seems to be more definite. Only one study found a 90% increased risk of pancreatic cancer in patients with atopic dermatitis (SIR = 1.9, 95% CI 1.0–3.4) [20]. Five further surveys could demonstrate an inverse association (table 2). Holly et al. [26] reported a decreased prevalence of any self-reported allergy among pancreatic cancer patients. This correlation was available for multiple allergens like house dust, plants, mold, animals and food. Furthermore, risk decreased with increasing numbers of allergies and increasing severity of symptoms. It should be noted that allergic patients still showed a reduced risk even after receiving hyposensitization therapy. Hay fever was correlated with a reduced risk of pancreatic cancer in a prospective study by Turner et al. [12]. Eppel et al. [27] found a risk of pancreatic cancer in allergic patients that was scaled down by more than 50%, but this did not apply to asthmatics. For males separately, the risk was even lower. Another study that additionally investigated a possible association between variants in IL-4 and IL-4 receptor α genes and cancer prevalence found a negative correlation for any allergy, hay fever and reaction to animals. But variants in the above-mentioned genes were not correlated to cancer [28]. A more recent study detected a significantly increased survival of non-resected pancreatic cancer patients with self-reported allergies. In the cohort that had undergone a resection, results were nonsignificant [29].

Lung Cancer

Examining risk factors for the development of lung cancer, control of smoking is of great importance as tobacco is demonstrably the major oncogenic substance causing tumors of the lung [30]. Nevertheless, all of the evaluated studies suggest a positive association between a history of asthma and lung cancer (table 3). Without

controlling for smoking, a study of 78,000 asthmatic patients found an increased risk for women as well as for men [17]. Another study observed on the one hand a positive association with asthma only, but on the other hand negative associations with hay fever only, both asthma and hay fever, and either of these conditions. After restricting the results to cancer mortality among never smokers, there was no longer a significant association [12]. A 2-fold risk was determined for patients with atopic dermatitis [20]. A further survey calculated a lower but still elevated risk for asthma when controlling for smoking. An additional analysis of the effect of respiratory drugs taken for the treatment of asthma showed no connection to cancer development [18]. In a Taiwanese study, asthma was the only type of allergy associated with risk of lung cancer [15]. Vena et al. [13] reported decreased risks in males with hives or other allergies (OR = 0.52 and 0.53, respectively, significant at the 0.05 α -level).

Colorectal Cancer

Cancers of the colon and rectum are less prevalent among individuals who show a history of allergy. Only one study has reported an increased risk of rectum cancer in asthmatic women (SIR = 1.42) and an increased risk of colon cancer for both sexes (SIR = 1.17) [17]. Five further studies identified allergies to be inversely associated with colorectal cancer (table 2). The probability of developing colorectal cancer with any self-reported allergy in an Italian study was lowered, whereas the association was stronger when allergy was diagnosed at the age of 35 years or older. Regarding colon and rectum cancer separately, the risk of rectum cancer was lower than that of colon cancer whereas the latter was statistically not significant [31]. Another case-control study found a protective effect of any allergy on cancer development. Self-reported allergy was inversely associated with both colon and rectum cancer [32]. The risk of colorectal cancer calculated by Turner et al. [12] was reduced by more than 20% among patients suffering from both asthma and hay fever and less reduced among patients suffering from hay fever only. A prospective study from Iowa involving only women noted an inverse correlation for allergy in general, which was strongest in patients with skin allergies. Moreover, risk decreased with an increasing number of allergies – the HR for more than two allergies was 0.58 compared to 0.75 for only one allergy [33]. Allergic rhinitis was associated with an SIR of 0.82 for rectal cancer among Taiwanese patients and the association was stronger for males than for females [15].

Further Digestive Cancers

Excluding colorectal cancer there have only been a few surveys considering digestive organs. Regarding oral cancer, two studies have presented allergies as protective factors. The first reported an OR of 0.49 for males with hay fever [13], whilst the second reported an OR of 0.44 for a self-reported history of any allergy [32]. Esophageal cancer risk was increased in atopic dermatitis patients (SIR = 3.5, 95% CI 1.3–7.7), but at the same time decreased in patients with allergic rhinitis (SIR = 0.68, 95% CI 0.50–0.90) [15, 20]. Asthma was inversely associated with tumors of the stomach (SIR = 0.88) as well as allergic rhinitis with cancer of the small intestine (SIR = 0.39) [15, 17].

Skin Cancer

The prevalence of skin cancer has predominantly been examined among subjects suffering from atopic dermatitis (table 3). For other types of allergy there is only little evidence available. Hwang et al. [15] showed a negative association between nonmelanoma skin cancer and both allergic rhinitis (SIR = 0.40) and asthma (SIR = 0.39). Conversely, Talbot-Smith et al. [34] reported an excess risk of malignant melanoma for patients with a history of hay fever (HR = 2.39, 95% CI 1.00–5.70), which was only relevant for men. Atopic dermatitis was associated with a clearly increased risk of keratinocyte carcinoma, which made up half of all observed excess cancers. Among 6,275 hospitalized atopic dermatitis patients, not a single case of malignant melanoma was found [19]. Another study involving patients with atopic dermatitis found an increased risk of melanoma as well as of nonmelanoma skin cancer [21].

Brain Cancer

Most studies agree about a decreased risk of tumors of the brain (glioma) being associated with atopic diseases (table 2). Two studies have indicated a positive correlation. A Swedish retrospective study identified atopic dermatitis as a risk factor for brain cancer (SIR = 1.6) [20] and the same was inferred by a Taiwanese cohort study (SIR = 2.52) [15, 20]. The latter additionally mentioned physician-diagnosed asthma (SIR = 1.95) and allergic rhinitis (SIR = 1.53) as risk factors. In contrast, in a hospital-based case-control study the prevalence of glioma was reduced in combination with physician-diagnosed history of any allergy and asthma as well as with a self-reported allergy to chemicals. Meningioma risk was not associated with any type of allergy and the risk of acoustic neuroma was positively associated with hay fever, allergy to food and allergy to other substances [35]. One further

case-control study found hospitalized glioma cases to be less likely to suffer from asthma, as well as hay fever, atopic dermatitis or allergy in general. Moreover, there was a stronger risk reduction in conjunction with the use of any allergic medication (OR = 0.48) such as nasal spray or antihistamines [36]. Wigertz et al. [37] contrasted the prevalence of allergy among glioma and meningioma cases with noncancerous individuals. They showed a decreased risk of glioma among subjects with asthma, atopic dermatitis and hay fever. Treatment of hay fever with nasal spray or eye drops was associated with lower risks than nontreated disease (OR = 0.64 and 0.68, respectively). Meningioma risk was only reduced among atopic dermatitis patients (OR = 0.74) [37]. One case-control study used immunoglobulin E (IgE) levels for the measurement of allergy besides a self-reported history of allergy. OR for glioma risk varied as IgE levels generally did not confirm self-reported allergies, although both implicated a decreased risk [38]. A few years later the same research group reported similar risks for meningioma development. OR was 0.64 for self-reported allergy and 0.85 for IgE measurement [39].

Lymphatic and Hematopoietic Cancer

There are no consistent statements concerning the association between allergic diseases and tumors of lymphatic and hematopoietic tissues. While McWhorter [16] suggested a highly elevated risk of lymphoma, leukemia and myeloma for individuals with any allergy (ROR = 3.84, 95% CI 1.55–9.51), Vesterinen et al. [17] observed an SIR of 0.55 (95% CI 0.34–0.85) for leukemia among asthmatics. The latter study also showed a reduced risk of multiple myeloma in asthmatic women (SIR = 0.53). A significant inverse association between asthma and leukemia was also reported by Turner et al. [12] (RR = 0.75), whereas two further studies showed a positive association between lymphoma and atopic dermatitis; one calculated an SIR of 2.0 whilst the other presented an IRR of 2.21 [20, 21]. In a further study, where hematological malignancy was not specified, allergic rhinitis turned out to be a risk factor too (SIR = 1.23) [15]. Mills et al. [14] reported an RR of 6.53 (95% CI 2.21–19.92) for sarcoma associated with reaction to medication.

Reproductive Cancer

On the one hand, prostate cancer tends to be more common among atopic patients. In an Australian prospective study, individuals with any atopy (HR = 2.49, 95% CI 1.04–5.93), asthma (HR = 1.89, 95% CI 1.00–3.60) and reaction to house dust mites (HR = 2.90, 95% CI

1.26–6.68) were found to be at an elevated risk of prostate cancer. This study found no association between allergy and breast cancer [34]. A German study, which used allergen-specific IgE for the definition of atopy, reported a positive correlation between atopic disease and risk of prostate cancer (OR = 1.35), but not of breast cancer [40]. In another retrospective study an increased risk of breast cancer for subjects suffering from allergic rhinitis was observed (SIR = 1.20) [15]. On the other hand, further reproductive cancers including tumors of the uterus, cervix and ovary are less prevalent among allergic patients. Uterine cancer and asthma indicated an inverse association (SIR = 0.76) as well as ovarian cancer and reaction to poisonous plants (RR = 0.13), where there was also significant evidence of a decreasing risk with an increasing number of allergies [14, 17]. The prevalence of female reproductive system tumors in general was reduced for hives (OR = 0.75). In this case the greatest reduction was found for cervical cancer (OR = 0.63) [13].

Other Cancer Sites

In addition to the results presented so far, studies have reported inverse associations between larynx cancer and asthma (SIR = 0.63 in men) as well as any allergy (OR = 0.33) and allergic rhinitis and both hypopharyngeal cancer (SIR = 0.62) and tongue cancer (SIR = 0.71) [15, 17, 32]. Positive associations have been observed between kidney cancer and both allergic rhinitis (SIR = 2.64) and asthma (SIR = 2.66), thyroid gland cancer and allergic rhinitis (SIR = 1.47), urinary bladder cancer and both allergic rhinitis (SIR = 1.23) and asthma (SIR = 1.23), tumors of the nasal cavities and allergic rhinitis (SIR = 2.74), nasopharyngeal cancer and allergic rhinitis (SIR = 1.31) and urinary bladder cancer and asthma (SIR = 1.25 in men) [15, 17].

Discussion

This overview supports the assumption that there is no general relationship between allergy and cancer. Nevertheless, by considering different types of cancer separately, certain trends can be observed. Regarding pancreatic cancer, colorectal cancer and glioma, all types of allergy were shown to be a protective factor (table 2). Conversely, asthma is a risk factor for lung cancer as is atopic dermatitis for skin cancer (table 3). For other types of cancer, results are counterbalanced or too few patients were available to draw a conclusion.

Most of the studies are retrospective case-control studies, only a small proportion used prospective methods. As tumors affect the immune system, e.g. by suppressing immune responses, this could be misinterpreted in the assessment of allergic diseases in case-control studies, describing a reverse causality [41]. Generally, categorizing participants as allergic or nonallergic is a shortcoming of many studies. Most of the presented studies used self-reported allergy, registrations in cases of atopic dermatitis or reported medical diagnoses for categorizing, rather than skin prick testing or measurement of IgE levels. Apparent allergy symptoms might be confounded with symptoms of other diseases, e.g. chronic obstructive pulmonary diseases with asthma. Most of the studies that used skin prick testing or measurement of IgE reported a higher risk of cancer or no correlation at all [23, 24, 34, 40]. Furthermore, diagnoses may be falsified as IgE levels, for instance, might be influenced by alcohol consumption, cigarette smoking or developing tumors [40]. The difficulties in assessing allergy status were partly compensated by calculating risks for increasing numbers of allergies, because individuals reporting multiple allergies were regarded as having at least one allergy [42]. Those studies which evaluated the number of allergies consistently reported decreasing risks with increasing numbers [14, 26, 33, 37, 39]. These results strengthen an inverse correlation between allergy and cancer.

Allergy treatment is also capable of affecting tumor outcome. Glucocorticoids used for the treatment of asthma were shown to increase cancer risk due to immunosuppressive and antiapoptotic properties [30, 43]. The same active substances are present in ointments for treatment of atopic dermatitis [19]. In contrast, nonsteroidal anti-inflammatory drugs and cromoglicic acid were reported to decrease cancer risk [44, 45]. So there are rather inconsistent indications concerning the influence of antiallergic agents which might explain the missing consideration of medication in many of the presented studies. Two of the three studies which evaluated allergy medication reported stronger risk reductions among treated patients compared to nontreated patients, whilst the other study found no connection [15, 36, 37].

There are two hypotheses for the different effects of allergies on cancer development. A reason for a protecting effect of allergies might be the enhancement of a mechanism called immunosurveillance (fig. 1). The hypothesis of immunosurveillance states that to a certain degree the immune system is able to detect and destroy tumor cells before they can arise to clinically detectable malignancies. For example, natural killer (NK) cells play

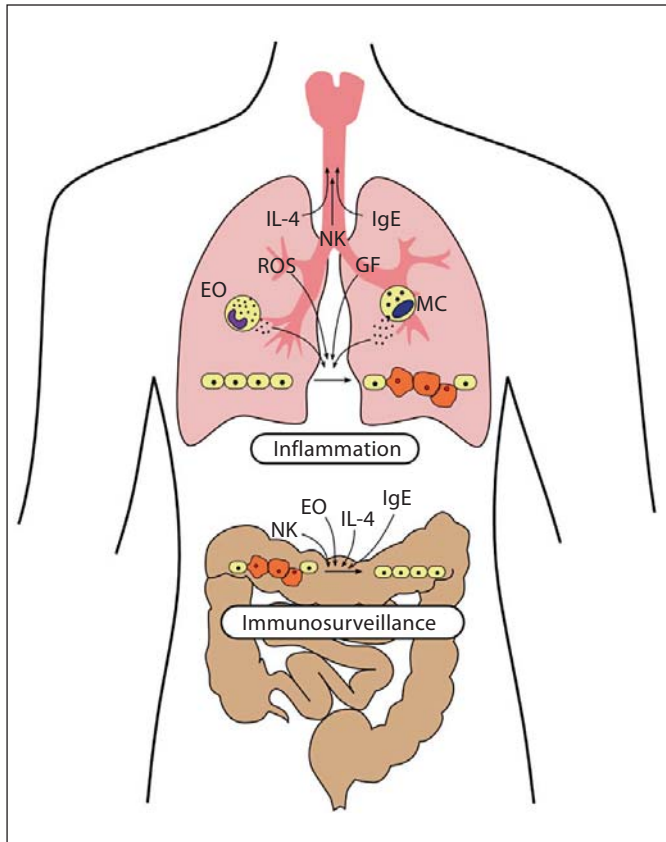


Fig. 1. Local and systemic effects of allergies using the example of asthma. EO = Eosinophil; MC = mast cell; ROS = reactive oxygen species; GF = growth factor.

an important role in immunosurveillance and they have been demonstrated to be more prevalent and more active in people suffering from asthma or allergic rhinitis [46]. NK cells can recognize tumor cells by altered or insufficient expression of major histocompatibility complex molecules via specific receptors [47]. Tumor cells are then directly destroyed through the release of perforin and granzyme which cause lysis and apoptosis [48]. In addition, NK cells produce interferon- γ which is capable of increasing the immunogenicity of tumor cells [49]. Further attention should be given to immune cells which usually do not occur in noticeable numbers in other than allergic conditions and which could make the difference in the effectiveness of antitumor responses. Eosinophils have to be particularly emphasized, since their abundance has repeatedly been associated with better prognoses in tumor patients [50]. Due to the cytotoxicity mediated by granule proteins like eosinophil cationic protein, tumor cells can be directly destroyed through cell lysis

[51]. In addition to the higher appearance, they also show an advanced cytotoxic potential under allergic conditions [52]. Tumor-promoting effects, however, were observed by means of release of vascular endothelial growth factor [53]. Additionally, it should be noted that eosinophils also release reactive oxygen species which exert harmful effects on healthy cells and are able to damage DNA [50]. Taken together, study results tend to prove a clear antitumor effect of eosinophils which should predominate possible tumor-promoting effects. However, it should be kept in mind that most of the results are based on *in vitro* studies and the effects of other allergic mediators were not considered.

IgE usually occurs in tissues bound to its receptors, but in allergic individuals levels are elevated in tissues as well as in the serum meaning systemic effects are possible [54]. Depending on the type of receptor it engages to, different effector functions such as antibody-dependent cellular cytotoxicity or phagocytosis are triggered [51]. IgE from allergic donors is, like eosinophils, more effective than that from healthy donors, and a stronger effect than with immunoglobulin G has also been observed [55, 56]. One may ask whether allergen-specific IgE is able to direct effector cells against tumor cells by binding to tumor antigens. Maybe there are similar molecular patterns and, as not only specific but also total IgE levels are elevated in allergic individuals, the probability of the occurrence of tumor-specific IgE is elevated [54]. For the isotype switch in B cells and the differentiation into IgE-producing plasma cells, IL-4 is the inducing mediator. Additionally, IL-4 acts in an antiangiogenic way, thus it does not destroy tumor cells directly, but limits their further growth [57]. The combined effects of IL-4, IgE and eosinophils might be decisive, which would finally lead to an increased rate of apoptosis of tumor cells, as has been proven in animal experiments [58].

The tumor-promoting effects of allergies can be limited to inflammation-induced carcinogenesis. Inflammatory reactions constitute an environment rich in possible mutagenic substances and growth factors which establish the required conditions for initiation, promotion and progression of tumors [59]. This connection is largely accepted and supported by a great number of trials [60]. Allergy-induced inflammation is usually limited to the site of entry of the respective allergens, thus inflammation-induced cancer occurs primarily at sites which are exposed to the environment.

The varying results regarding different types of cancer are reasonable in so far as there are different etiologies and types of affected tissue. Cancer prevalence in general

is not affected by a history of allergy, or more precisely, studies report negative as well as positive or no associations. When regarding the results for the particular types of cancer, this becomes plausible, because there are some clear inverse as well as positive correlations. Furthermore, values for risk reduction were rather low, so results should not be overstated. Pancreatic cancer, however, was more definitely reduced among allergic patients, regardless of the type of allergy. Risk reductions were more distinct for this cancer site, by up to more than 50%. The pancreas is accessible to all of the cells required for a successful immunosurveillance, so the hypothesis of enhanced immunosurveillance seems to apply for this type of cancer [61]. The protective effect should be ascribed to the systemic effect of allergies, and not to any local reaction which takes place at the entry location of allergens. However, as pancreatic cancer is one of the most disastrous types of cancer with very poor survival rates, the evidence of enhanced immunosurveillance may play a rather minor role.

In contrast to the pancreas, the lung is an organ which is directly exposed to the environment and thus very susceptible to allergens as well as carcinogens. Here, immunosurveillance is secondary since inflammation dominates this location, promoting cancer development. The connection between skin cancer and atopic dermatitis is quite the same as the one between lung cancer and asthma. Atopic dermatitis causes large areas of inflammation on the skin which provide access to carcinogens and the required microenvironment [20]. Consequently, skin cancer prevalence was twice as high among atopic dermatitis patients compared to nonallergic controls. The colon and rectum are also exposed tissues; nevertheless, they were associated with a lower prevalence of every type of allergy. One reason might be that allergic reactions to food were rarely assessed. Asthma, allergic rhinitis or atopic dermatitis do not affect gut tissues, consequently there is no local inflammation which would foster tumor

growth. Additionally, the gut-associated lymphoid tissue contains the largest accumulation of lymphocytes [62]. This should imply an effective immunosurveillance, possibly enhanced by allergic conditions, supported by high curing rates in the case of early detection [3].

Findings of an apparent effect of allergies on the brain are rather unexpected. Immune cell invasion into the brain is strictly regulated through the blood-brain barrier [63]. Nevertheless, at least for glioma, there is growing evidence of a role of allergies as a protective factor as studies report significantly reduced risks. Tumor-induced inflammation causes changes in the blood-brain barrier, altering the accessibility of immune cells. Thus, the nascent tumor itself enables immunosurveillance in a usually 'immunologically privileged' organ [64].

Conclusion

A connection between allergy and cancer has been suspected for a long time, but even despite extensive research, no definite relationship has been determined. Regarding cancer in general, no clear relationship, either positive or negative, to allergies can be observed. However, asthma was identified as a risk factor for the development of lung cancer. Equally, atopic dermatitis increases the risk of skin cancer. Conversely, allergies decrease the risk of pancreatic cancer, colorectal cancer and glioma. The fact that allergies are accompanied by inflammatory reactions which constitute an optimal environment for carcinogenesis explains a positive association. These inflammations are limited to specific areas, whereas systemic effects in terms of enhanced immunosurveillance can likewise be evoked, thus preventing cancer. Nevertheless, these results should not be overstated due to some weaknesses in the studies. Further research is needed to clearly understand the relationship between allergy and cancer on the molecular level.

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