Cancer Immunol Immunother (2012) 61:1493–1510
DOI 10.1007/s00262-011-1180-6

SYMPOSIUM-IN-WRITING PAPER

Epidemiology: allergy history, IgE, and cancer

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Received: 14 July 2011 / Accepted: 1 December 2011 / Published online: 20 December 2011

Abstract Numerous epidemiological studies have investigated potential associations between allergy history and cancer risk with strong inverse associations reported in studies of pancreatic cancer, glioma, and childhood leukemia. Recently, there has been a rapid expansion of the epidemiological literature both of studies evaluating self-reported allergy history in relation to cancer risk and of studies evaluating biological indicators of allergy history and immune function including levels of immunoglobulin (Ig) E. However, there are several potential methodological limitations associated with prior studies, and further research is required to clarify associations observed. This paper summarizes the recent epidemiological literature examining associations between allergy history and cancer risk. From 2008, a total of 55 epidemiological studies were identified that examined some aspect of the association between allergy and cancer. Although the majority of studies examined self-reported allergy history in relation to cancer risk, there were also studies examining allergy diagnoses or discharges as captured in existing administrative databases, levels of IgE, polymorphisms of allergy, inflammatory- or allergy-related cytokine genes, and concentrations of immune regulatory proteins. The most frequently studied cancer sites included brain and lymphatic and hematopoietic cancers. Potential methodological sources of bias are discussed as well as recommendations for future work.

Keywords Allergy · Cancer · Epidemiology · IgE · AllergoOncology symposium-in-writing

Introduction

Numerous epidemiological studies have investigated potential associations between allergy history and cancer risk with strong inverse associations reported in studies of pancreatic cancer, glioma, and childhood leukemia. Although findings may reflect a state of enhanced immune surveillance and anti-tumor defense among those with atopic allergic disorders (allergic asthma, allergic rhinitis, atopic dermatitis), they may also be due to methodological sources of bias in previous work. Conversely, chronic stimulation of the immune system may be associated with increased cancer risk at selected sites.

An overview of the epidemiological literature published from 1966 to 2005 was provided by Turner et al. [1] and updated through mid-2008 [2]. There are also other published reviews [3–5]. Subsequently, there has been a rapid expansion of the epidemiological literature both of studies evaluating self-reported allergy history in relation to cancer risk and of studies evaluating biological indicators of allergy history and immune function including levels of immunoglobulin (Ig) E in order to address potential reporting biases in allergy history by study participants. Jensen-Jarolim et al. [6] recently defined the field of AllergoOncology and suggested a role for IgE antibodies in

This paper is part of the Symposium in Writing: AllergoOncology: The role of Th2 responses in cancer.

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natural tumor surveillance as well as in active and passive immunotherapy.

The purpose of this paper is to summarize the recent epidemiological literature examining associations between allergy history and cancer risk, with a particular focus on brain, lymphatic and hematopoietic, and pancreatic cancers. Potential methodological sources of bias will be described as well as recommendations for future work. Selected findings of particular relevance from the earlier epidemiological literature will also be discussed.

Methods

The search strategy updated that of previous work [1, 2]. In brief, the OVID MEDLINE database was searched (2008 to November week 3 2011) to identify previous epidemiological studies examining some aspect of the association between allergy and cancer according to the following MeSH headings: Hypersensitivity/, exp Hypersensitivity, Immediate/, exp IgE/, exp Neoplasms by Histologic Type/, exp Neoplasms by Site/, and key words: allerg$, atop$, hypersensitiv$, asthma$, hay fever, rhinitis, conjunctivitis, eczema, dermatitis, hives, skin test$, IgE, cancer, tumo?r, malignan$, neoplasm$, carcinoma, leuk?emia, lymphoma, myeloma, hodgkin$, glioma, meningioma, neuroma, and risk. Only human studies and studies written in English were considered. The reference lists of identified studies were also hand-searched.

Results

From 2008, a total of 55 epidemiological studies were identified, including 45 original publications [7–51], four review articles [2, 4, 52, 53], and five meta-analyses [54–58] that examined some aspect of the association between allergy and cancer (Table 1). There was also one article that presented both original and meta-analytic findings [59]. Thirty original publications were of a case–control design [7, 9, 10, 13–16, 20–22, 24, 27–32, 34, 36–40, 42, 43, 46–49, 51] and 14 were either of a cohort design or were nested case–control studies [8, 11, 12, 17–19, 23, 25, 26, 33, 41, 45, 50, 59]. Two studies examined cancer progression/survival [35, 44]. Studies were conducted throughout the world including several European countries, North America, Australia, and Asia. As were previous studies, the majority of recent publications examined self-reported allergy history in relation to cancer risk. However, there were several studies examining allergy diagnoses or discharges as captured in existing administrative databases [8, 11, 16, 23, 26, 27, 59]. There were also eight recent studies that captured data on Ig levels, including levels of IgE [10, 12, 20, 41, 48–50, 59], four studies that examined polymorphisms of allergy, inflammatory- or allergy-related cytokine genes [14, 24, 29, 38], and one study that examined concentrations of immune regulatory proteins (soluble CD23 and CD14) [51] in relation to cancer risk. Two studies examined interactions between allergy history and genotype for glioma risk [28, 43]. One study examined mRNA expression levels of allergy- or inflammatory-related genes in relation to cancer progression [44]. The most frequently studied cancer sites included brain [9, 12–14, 20–22, 28, 31, 32, 38, 40–44, 48, 49, 51] and lymphatic and hematopoietic cancers [10, 11, 17, 26, 27, 34, 36, 39, 46].

All cancer

Several large prospective studies examined associations between allergy history and overall cancer risk with little clear evidence for an association observed. Among earlier studies examining self-reported allergy history, there was no association between a history of self-reported physician-diagnosed allergy, asthma, or hay fever and overall cancer occurrence in the Adventist Health Study; however, a history of reaction to medication was positively associated with overall cancer occurrence in men (relative risk (RR) = 1.33; 95% confidence interval (CI), 1.02–1.74) and inversely associated in women (RR = 0.79; 95% CI, 0.65–0.98) [60]. There was no clear association between self-reported asthma history and overall cancer mortality in three smaller studies [61–63]. In the Cancer Prevention Study-II (CPS-II), a cohort of nearly 1.1 million participants followed up for 18 years (1982–2000), a significant inverse association was observed between a self-reported history of both physician-diagnosed asthma and hay fever, since reporting of allergy history may be improved in participants with multiple allergic conditions, and overall cancer mortality (hazard ratio (HR) = 0.88; 95% CI, 0.83–0.93) but not for either asthma or hay fever alone [64]. However, in an attempt to minimize potential residual confounding by cigarette smoking, the association attenuated somewhat in never smokers (HR = 0.91; 95% CI, 0.83–1.00).

There are also several record linkage studies that have examined associations between allergy history as captured in hospital discharge databases or insurance registries and overall cancer risk to address potential reporting biases in allergic status based on self-report, with conflicting findings observed [23, 65–69]. A Swedish study followed 64,346 hospitalized asthma patients (1969–1983) for cancer incidence through 1987 [66]. A total of 4,520 cancer cases were observed. There was a significant deficit in overall cancer incidence (standardized incidence ratio (SIR) = 66; 95% CI, 64–68) as well as at many sites.

Table 1 Previous studies examining the association between allergy and cancer by cancer site and study design (2008–2011)

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
All cancer, case–control studies						
El-Zein et al. [15], Canada	3,300 incident male cancer cases from major Montreal hospitals (1979–1985)	512 population controls	Self-reported diagnosis of asthma, eczema	Asthma	0.85 (0.6–1.3)	Age, family income, respondent status
				Eczema	0.70 (0.4–1.1)[a]	
All cancer, cohort studies						
Arana et al. [8], UK	4,518,131 patients from THIN database (1992–2006), 129,972 incident cancer cases	–	Atopic dermatitis diagnosis from THIN database	Atopic dermatitis	1.49 (1.39–1.61)[b]	Age, sex
Ji et al. [23], Sweden	140,425 hospitalized asthma patients from Swedish Hospital Discharge Register (1965–2004), 7,421 incident cancer cases	–	Asthma hospitalization	Asthma	1.36 (1.33–1.39)[b]	Age group, gender, period, SES, residential area
Van Hemelrijck et al. [59], Sweden	24,820 in the AMORIS study with IgE measurements (1985–1996), 862 incident cancer cases	–	IgE concentrations	IgE (4th vs. 1st quartile)	0.90 (0.74–1.10)[c]	SES, age, gender
Brain tumors, case–control studies						
Berg-Beckhoff et al. [9], Germany	366 incident glioma cases and 381 meningioma cases from neurosurgical clinics (2000–2003), INTERPHONE study	1,494 population controls	Self-reported physician-diagnosed asthma, hay fever, eczema		Glioma	Center, sex, SES, urban/rural, smoking, age at diagnosis
				Any	0.92 (0.70–1.22)	
				Asthma	0.65 (0.36–1.19)	
				Eczema	0.91 (0.65–1.27)	
				Hay fever	0.96 (0.67–1.38)	
					Meningioma	
				Any	0.87 (0.66–1.14)	
				Asthma	0.78 (0.47–1.28)	
				Eczema	0.84 (0.61–1.15)	
				Hay fever	0.98 (0.67–1.39)	
Harding et al. [21], UK	575 incident central nervous system tumors from the UK Childhood Cancer Study (1991–1996)	6,292 population controls	Maternal-reported ever asthma, wheezing or whistling in the chest, eczema, early-onset flexural rash, physician-diagnosed asthma from medical records	Asthma	0.75 (0.58–0.97)	Age, sex, region, Townsend deprivation category
				Wheezing (moderate)	0.72 (0.55–0.97)	
				Wheezing (severe)	0.77 (0.53–1.13)	
				Eczema	0.94 (0.74–1.18)	
				Early-onset flexural rash	0.95 (0.68–1.34)	
				Asthma (medical records)	1.20 (0.74–1.94)	
Scheurer et al. [40], USA	325 incident glioma cases from 15 Texas counties (2001–2006)	600 population controls	Self-reported asthma, allergy history, regular antihistamine use for 6 months or more	Antihistamines	1.37 (0.87–2.14)	Age, gender, race
				Antihistamines + asthma/allergy	2.54 (1.28–5.03)	
				Asthma/allergy	0.34 (0.23–0.51)	
Schoemaker et al. [42], England	299 incident pituitary gland tumors from neurosurgical centers, oncology units, and Thames Cancer Registry (2000–2005)	630 population controls	Self-reported ever diagnosis of asthma, hay fever, eczema	Any	0.8 (0.6–1.1)	Sex, age, region, interview year, Townsend deprivation score
				Asthma	0.9 (0.6–1.5)	
				Hay fever	0.7 (0.5–1.0)	
				Eczema	1.0 (0.6–1.6)	
				Other allergy	0.8 (0.5–1.1)	

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Wiemels et al. [48], USA	535 incident glioma cases from the Northern California Rapid Case Ascertainment program (2001–2004)	532 population controls	Self-reported reaction to various allergens, allergy symptoms, history of asthma and eczema, total, food, and respiratory IgE	Any Respiratory allergy Food allergy ln(total IgE) Elevated total IgE Elevated food IgE Elevated respiratory IgE	0.50 (0.36–0.70) 0.63 (0.49–0.81) 0.88 (0.65–1.18) 0.89 (0.82–0.98) 0.79 (0.55–1.12) 0.58 (0.33–1.03) 0.80 (0.60–1.06)	Age, gender, ethnicity, education, smoking
Gousias et al. [20], Greece	49 glioma patients operated on in the University Hospital of Ioannina (2005–2008)	30 hospital controls	Total IgE	Total IgE	No significant difference	–
Schoemaker et al. [43], International	1,029 incident glioma cases from treating clinics and cancer registries in Denmark, Finland, Sweden, UK from INTERPHONE study (2000–2004)	1,668 population controls	Self-reported physician-diagnosed asthma, hay fever, eczema, TERT (rs2736100), CCDC26 (rs4295627), CDKN2A/B (rs4977756), PHLDB1 (rs498872), RTEL1 (rs6010620)	Any Asthma Hay fever Eczema Interactions between asthma and PHLDB1 (rs498872), any allergy and CDKN2A/B (rs4977756), RTEL1 (rs6010620)	0.66 (0.55–0.78) 0.79 (0.60–1.04) 0.77 (0.63–0.95) 0.66 (0.51–0.84)	Study center, sex, age
Zhou et al. [51], USA	1,079 incident glioma cases from the San Francisco Bay Area Adult Glioma Study, and the UCSF Neuro-Oncology Clinic (1997–2006)	736 population controls	Self-reported diagnosed allergy, asthma, eczema, sCD14, sCD23, total IgE	sCD14 (4th vs. 1st quartile) sCD23 (1st vs. 4th quartile)	3.94 (2.98–5.21) 2.5 (1.89–3.23)	Age, gender, ethnicity, education, smoking
Claus et al. [13], USA	1,124 incident meningioma cases from Rapid Case Ascertainment systems and state cancer registries in Connecticut, Massachusetts, North Carolina, the San Francisco Bay Area, and 8 Houston counties (2006–2010)	1,000 population controls	Self-reported allergy, asthma, eczema	Allergy Asthma Eczema	0.6 (0.5–0.7) 0.7 (0.6–0.9) 0.8 (0.6–1.1)	Age, sex
Dobbins et al. [14], UK/USA	1,878 incident glioma cases from the UK INTERPHONE study and the M.D. Anderson Cancer Center, Texas	3,670 birth cohort controls	ORMDL3 (rs7216389), PDE4D (rs1588265), C11orf30 (rs7130588), IL1RL1 (rs1420101)	ORMDL3 (rs7216389) PDE4D (rs1588265) C11orf30 (rs7130588) IL1RL1 (rs1420101)	1.10 (1.01–1.19) 0.97 (0.89–1.06) 0.99 (0.91–1.06) 1.05 (0.97–1.14)	–

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Lachance et al. [28], USA	855 incident high-grade glioma cases from a referral-based practice (Mayo Clinic, Rochester, Minnesota), the Northern California Rapid Case Ascertainment Program and the UCSF Neurooncology Clinic (University of California, San Francisco), and the Duke University Medical Centre (Raleigh, North Carolina) and the North Shore University Medical Centre (University of Illinois, Chicago)	1,160 clinic and population controls	Self-reported physician-diagnosed allergy, TERT (rs2736100), CCDC26 (rs4295627), CDKN2A/B (rs1063192, rs1412829, rs2157719, rs4977756), PHLDB1 (rs498872), RTEL1 (rs6089953, rs4809324, rs6010620)	Allergy	0.62 (0.51–0.76) Interactions between allergy and CDKN2A/B (rs4977756) and RTEL1 (rs4809324)	Age, gender, medical center
McCarthy et al. [32] and Il'yasova et al. [22], USA	419 incident glioma cases from the Duke University Medical Centre, North Carolina, and the North Shore University Health System, Illinois (2006–2008)	612 hospital controls	Self-reported diagnosed allergies: seasonal, pets, medications, foods, other up to 2 years ago and antihistamine use	Allergy Seasonal allergy Medication allergy Pet allergy Food allergy Other allergy Antihistamines	0.60 (0.46–0.79) 0.55 (0.42–0.73) 0.68 (0.49–0.93) 0.60 (0.44–0.88) 0.58 (0.35–0.97) 0.34 (0.22–0.54) 0.76 (0.59–0.99)	Age, gender, race, education, study site
McCarthy et al. [31], International	617 incident oligodendroglial tumor cases from 7 hospital- and population- based case–control studies conducted in the USA, Sweden, and Denmark	1,260 controls	Self-reported allergies/hay fever and ever use of allergy medication	Asthma Allergies Eczema	0.4 (0.2–0.7) 0.9 (0.7–1.3) 0.5 (0.3–1.0)	Age, gender, site
Ruan et al. [38], China	677 incident glioma cases from Neurosurgery Department at Huashan Hospital, Fudan University (2004–2006)	698 hospital controls	IL-13 (rs20541), IL-4Ra (rs1801275), STAT6 (rs1059513), STAT6 (rs324015)	IL-13 (rs20541) IL-4Ra (rs1801275) STAT6 (rs324015) STAT6 (rs1059513)	0.96 (0.81–1.13) 0.92 (0.75–1.13) 1.16 (0.99–1.35) 1.01 (0.73–1.39)	Age, sex, family history of cancer, smoking status
Wiemels et al. [49], USA	1,065 incident meningioma cases from Rapid Case Ascertainment in five states, and hospital pathology and tumor registries (2006–2009)	634 population controls	Self-reported diagnosed allergy, asthma, eczema, total IgE	Allergy Asthma Eczema ln(total IgE)	0.64 (0.51–0.80) 0.65 (0.50–0.86) 0.95 (0.67–1.34) 0.85 (0.75–0.98)	Age, smoking, gender, race, SES
Brain tumors, cohort studies						
Schwartzbaum et al. [44], USA	Tissue samples from 142 glioblastoma patients from the National Cancer Institute's Cancer Genome Atlas	–	mRNA expression of allergy and inflammatory-related genes	mRNA expression of allergy and inflammatory-related genes	Inverse correlation between CD133 and 69% of allergy-/inflammatory-related genes	–

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Calboli et al. [12], USA	Nested case–control study of 169 glioma cases and 520 control subjects from four prospective cohorts (Physicians' Health Study, Nurses' Health Study, Women's Health Study, Health Professionals Follow-Up Study)	520 controls	Self-reported asthma history/self-reported physician-diagnosed asthma, total, food, and respiratory IgE	Asthma	0.60 (0.21–1.70)	–
				Borderline elevated total IgE	0.63 (0.42–0.93)	
				Elevated total IgE	0.98 (0.61–1.56)	
				Elevated food IgE	1.03 (0.54–1.98)	
				Elevated respiratory IgE	1.12 (0.77–1.62)	
Schlehofer et al. [41], International	Nested case–control study of 275 glioma, 175 meningioma, 49 acoustic neuroma cases and 963 controls from the European Prospective Investigation into Cancer and Nutrition (EPIC)	963 controls	Respiratory IgE	Elevated respiratory IgE	0.73 (0.51–1.06) glioma	Education, smoking
					0.96 (0.61–1.51) meningioma	
					0.80 (0.32–1.99) acoustic neuroma	
Lymphatic and hematopoietic cancers, case–control studies						
Biggar et al. [10], International	200 incident NHL patients from the SCALE study (1999–2002), Sweden and Denmark	200 population controls	Total IgE	Total IgE	B-cell NHL patients had lower immunoglobulin levels, including total IgE than controls	–
Mirabelli et al. [34], Italy	2,290 incident lymphoma cases diagnosed at 11 medical centers (1991–1993)	1,771 population controls	Asthma-specific job exposure matrix applied to lifetime occupational history to assess occupational exposure to high molecular weight allergens	Any	0.78 (0.63–0.97)	Age, sex, study center, education
				Animal	0.73 (0.53–0.99)	
				Enzymes	0.94 (0.52–0.99)	
				Flour	0.82 (0.51–1.32)	
				Latex	0.53 (0.30–0.95)	
				Mite and insect	0.82 (0.56–1.19)	
				Plant	1.69 (0.64–0.44)	
Pawha et al. [36], Canada	316 incident male Hodgkin's lymphoma cases from five provincial cancer registries, and hospital ascertainment (Quebec) (1991–1994)	1,506 population controls	Self-reported diagnosis of asthma, hay fever, allergies, allergy desensitization shots, patch skin test for allergy	Asthma	0.90 (0.53–1.54)	Age, province
				Hay fever	0.68 (0.43–1.07)	
				Allergies	0.81 (0.60–1.11)	
				Allergy desensitization shots	0.55 (0.30–0.99)	
				Patch skin test	1.14 (0.59–2.20)	
Vajdic et al. [46], International	13,535 incident NHL cases from 13 case–control studies from the InterLymph Consortium (1983–2005)	16,388 hospital and population controls	Self-reported history of asthma, hay fever, eczema, any specific allergy, food allergy	Asthma	0.90 (0.83–0.99)	Age, sex, study center
				Hay fever	0.82 (0.75–0.89)	
				Eczema	1.06 (0.91–1.25)	
				Specific allergy	0.80 (0.71–0.90)	
				Food allergy	0.75 (0.58–0.96)	

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Kristinsson et al. [27], Sweden	2,470 incident lymphoplasmacytic lymphoma–Waldenstrom macroglobulinemia cases from Swedish Cancer Registry, major treatment centers, and Swedish Inpatient Registry (1958–2005)	9,698 population controls	Previous discharge of allergic alveolitis, rhinitis, erythema, urticaria, atopic eczema	Any allergic or chronic inflammatory condition	1.2 (1.0–1.4)	Year of birth, year of diagnosis, sex, county
Rudant et al. [39], France	634 incident acute lymphoblastic leukemia and 86 acute myeloblastic leukemia cases from the French National Registry of Childhood Blood Malignancies, ESCALE study (2003–2004)	1,494 population controls	Maternal-reported history of asthma, eczema, wheezing bronchitis	Asthma Eczema Wheezing bronchitis	0.7 (0.4–1.0) ALL 0.6 (0.3–1.6) AML 0.7 (0.6–0.9) ALL 1.1 (0.7–1.9) AML 0.7 (0.6–1.0) ALL 1.0 (0.6–1.8) AML	Age, gender, parental professional category, urbanization
Lymphatic and hematopoietic cancers, cohort studies						
Brown et al. [11], USA	4,501,578 hospitalized male veterans from US Veterans Affairs hospitals (1969–1996), 4,641 incident multiple myeloma cases	–	Previous discharge diagnosis of allergic rhinitis, asthma, eczema and dermatitis, erythema, urticaria	Allergic rhinitis Asthma Eczema and dermatitis Erythema Urticaria	1.45 (0.93–2.25) 0.98 (0.79–1.22) 1.11 (0.91–1.35) 1.03 (0.72–1.48) 1.13 (0.64–1.99)	Visits, attained age, calendar time, latency, race
Erber et al. [17], USA	193,050 African American, Caucasian, Japanese American, Latino and Native Hawaiian from the Multiethnic Cohort (1993–2003), 939 incident NHL cases	–	Self-reported physician-diagnosed asthma, hay fever skin allergy, food allergy, other allergy and ever use of antihistamines at least two times per week for at least 1 month	Allergies Caucasian African Am. Japanese Am. Latino Antihistamines (current) Caucasian African Am. Japanese Am. Latino	 1.17 (0.90–1.52) 0.86 (0.58–1.27) 1.02 (0.75–1.38) 1.46 (1.07–2.00) 1.21 (0.78–1.86) 1.00 (0.52–1.91) 0.93 (0.49–1.75) 1.80 (1.09–2.97)	Sex, education, BMI, alcohol
Koshiol et al. [26], USA	4,501,578 hospitalized male veterans from US Veterans Affairs hospitals (1969–1996), 9,496 incident NHL cases	–	Previous discharge diagnosis of asthma, allergic alveolitis, dermatitis, erythema, rhinitis, urticaria	Any allergy Asthma Allergic alveolitis Dermatitis Erythema Rhinitis Urticaria	1.4 (1.3–1.5) 0.90 (0.77–1.1) 4.2 (1.8–10.1) 1.6 (1.5–1.8) 2.7 (2.3–3.2) 0.81 (0.56–1.2) 1.2 (0.85–1.7)	Age, calendar time, race, latency, number of hospital visits
Pancreatic cancer, case–control studies						
Anderson et al. [7], Canada	422 incident pancreatic cancer cases from Ontario Cancer Registry (2003–2007)	312 population controls	Self-reported ever allergy or hay fever up to 1 year ago	Allergies	0.40 (0.26–0.59)	Age, education, BMI, smoking family history, fruit, alcohol, caffeinated beverages

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Maisonneuve et al. [30], International	823 incident pancreatic cancer cases from hospitals and Cancer Registries in Toronto, Utrecht, Opole, Adelaide, and Montreal (1982–1988)	1,679 population controls	Self-reported ever medical treatment for asthma, eczema, hay fever, other	Any Asthma Eczema Hay fever Other allergy	0.64 (0.50–0.82) 0.57 (0.34–0.97) 0.60 (0.42–0.88) 0.76 (0.47–1.24) 0.72 (0.49–1.07)	Smoking, schooling, age, gender, interview type
Pancreatic cancer, cohort studies						
Olson et al. [35], USA	475 incident pancreatic cancer cases from Memorial Sloan-Kettering Cancer Center (2004–2008) followed for survival for 48 months	–	Self-reported ever allergy to foods, animals, pollen or hay fever, plants, bee stings, molds, medicine, vaccines, other	Any allergies Medication allergy Hay fever	0.72 (0.43–1.23) (R) 0.68 (0.49–0.95) 0.66 (0.33–1.31) (R) 0.68 (0.45–1.04) 1.20 (0.65–2.22) (R) 0.88 (0.59–1.31)	BMI, lymph nodes, tumor stage
Lung cancer, case–control studies						
Wang et al. [47], Hong Kong	212 incident never-smoking female lung cancer cases from oncology center (2002–2004)	292 population controls	Self-reported physician-diagnosed asthma	Asthma	4.78 (1.23–18.63)	Age, employment, yellow/orange and green vegetables, multivitamins
Lim et al. [29], Singapore	433 incident never-smoking female lung cancer cases from five public sector hospitals (1996–1998, 2005–2008)	1,375 hospital controls	Self-reported history of asthma, allergic rhinitis, atopic eczema	Asthma Allergic rhinitis/atopic eczema	1.01 (0.66–1.56) 0.93 (0.69–1.26)	Age, family history, fruit/vegetables, country of origin, dialect, housing type, education, environmental tobacco smoke
Lung cancer, cohort studies						
Frostad et al. [19], Norway	19,998 randomly selected Oslo adults (1972–2002), 352 incident lung cancer cases	–	Self-reported physician-diagnosed asthma	Asthma	1.9 (1.1–3.4) (men)	Age, smoking, occupational exposure
Koh et al. [25], Singapore	63,257 in the Singapore Chinese Health Study (1993–2005), including 42,588 never smokers, 954 incident lung cancer cases, 265 in never smokers	–	Self-reported physician-diagnosed allergic rhinitis, nonallergic rhinitis, sinusitis, asthma, hay fever, allergic dermatitis, food allergy, or other	Rhinosinusitis Asthma/allergy/atopy Asthma/hay fever/allergic dermatitis/food allergy/other	1.59 (1.06–2.37) 1.84 (0.97–3.47) (N) 1.11 (0.90–1.36) 1.04 (0.70–1.54) (N) 1.11 (0.90–1.36)	Age, enrollment year, gender, dialect, education, BMI, smoking, β-cryptoxanthin, total isothiocyanate
Fan et al. [18], China	9,295 tin miners in the Yunnan Tin Corporation, China (1992–2001), 502 incident lung cancer cases	–	Self-reported physician-diagnosed asthma	Asthma	1.27 (0.96–1.68)	Gender, age, education, smoking status, pack-years, occupational radon and arsenic exposure, prior pulmonary disease

Table 1 continued

Reference, country	Subjects/study population	Controls	Allergy assessment	Allergy indicator	RR (95% CI)	Variables in model
Other cancers, case–control studies						
Pelucchi et al. [37], Italy	528 incident basal cell carcinoma cases from hospital centers (1995–1996)	512 hospital controls	Self-reported physician-diagnosed asthma	Asthma	0.45 (0.24–0.82)	Age, sex, study center, education, eye, hair and skin color, sunlight exposure, severe sunburn
Elmasri et al. [16], USA	1,582 women discharged from Florida hospitals with an ovarian cancer diagnosis (2001)	4,744 fracture and 21,830 acute MI controls	Presence of asthma as secondary diagnosis	Asthma	0.73 (0.52–1.03) fracture controls 0.73 (0.54–1.01) acute MI controls	Age, race-ethnicity, Medicaid, obesity, smoking
Johnson et al. [24], USA	561 invasive squamous cell cervical cancer cases from the Cancer Surveillance System in Seattle (1986–1998)	1,258 population controls	Self-reported ever allergies to foods, pollens/plants/grasses/trees, medications/drugs/immunizations, inhalants/molds/dust/animals/tobacco, other	Any allergy Airborne allergy Antibiotic allergy Food allergy Animal allergy	0.7 (0.6–0.9) 0.6 (0.5–0.7) 0.9 (0.7–1.1) 0.7 (0.5–0.9) 0.7 (0.5–1.0)	Age, smoking, number of lifetime sex partners
Other cancer, cohort studies						
Meinhold et al. [33], USA	90,713 US radiologic technologists (1983–2006), 282 incident thyroid cancer cases	–	Self-reported history of asthma	Asthma	1.68 (1.00–2.83) women 1.49 (0.33–6.62) men	Age, sex, smoking, BMI, benign thyroid conditions, personal radiographs to head/neck, occupational radiation thyroid dose
Severi et al. [45], USA	16,934 men in the Melbourne Collaborative Cohort Study (1990–2007), 1,179 incident prostate cancer cases	–	Self-reported physician-diagnosed asthma or wheezy breathing and current medications	Asthma Inhaled glucocorticoids Systemic glucocorticoids Topical glucocorticoids Antihistamines Bronchodilators	1.25 (1.05–1.49) 1.39 (1.03–1.88) 1.71 (1.08–2.69) 0.95 (0.49–1.83) 0.78 (0.45–1.35) 1.36 (1.05–1.76)	Country of birth
Wiemels et al. [50], USA	Nested case–control study of 112 patients with squamous cell carcinoma of the skin and 227 controls from a multicenter randomized control trial on the prevention of subsequent squamous cell carcinoma diagnoses in nonmelanoma skin cancer patients	227 controls	Total, respiratory, food IgE	ln(total IgE) ln(respiratory IgE) ln(food IgE)	1.08 (0.92–1.26) 1.40 (1.07–1.84) 1.27 (0.36–4.54)	Gender, smoking status, age

ALL acute lymphoblastic leukemia, *AML* acute myeloblastic leukemia, *AMORIS* Apolipoprotein MOrtality RISk, *BMI* body mass index, *ESCALE* Etude sur les cancers de l'enfant, *MI* myocardial infarction, *N* never smokers, *R* resected patients, *SCALE* Scandinavian Lymphoma Etiology Study, *SES* socioeconomic status, *THIN* The Health Improvement Network, University of California San Francisco

[a] Inverse associations also observed for specific cancer sites

[b] Positive associations also observed for specific cancer sites

[c] No significant association for specific cancer sites

However, a 2009 study following 140,425 hospitalized asthma patients in Sweden (1965–2004) for cancer incidence through 2004 noted significant excesses in cancer incidence (SIR = 1.36; 95% CI, 1.33–1.39) overall and at most sites [23]. Other recent studies of individuals either diagnosed [8] or discharged [65, 68] with atopic dermatitis have also reported some evidence for an excess in cancer cases; however, in one study [65], findings were driven mainly by smoking- or alcohol-related cancers, suggesting that results were likely confounded by smoking and alcohol consumption, which were not accounted for in analysis. Patient populations may also represent a selected group of those with underlying disease including hospitalized atopic dermatitis patients who may experience increased comorbidity [65].

Biological indicators of allergy history have also been examined in relation to overall cancer risk. No clear associations with either overall cancer incidence or mortality were observed in cohorts of skin prick–tested individuals [70, 71]. In a prospective study of 70,136 allergy-tested patients (1988–2000), there was no association between elevated total serum (SIR = 107; 95% CI, 82–137) or respiratory-specific (SIR = 97; 95% CI, 82–114) IgE and overall cancer incidence [72]. More recently, 24,820 healthy individuals from the AMORIS study were followed up for 11 years (1985–1996) [59]. No association was observed between IgE concentrations and cancer incidence overall (HR highest vs. lowest quartile = 0.90; 95% CI, 0.74–1.10) or with cancer originating in epithelial, lymphatic or hematopoietic, mesenchymal, or nervous tissues.

Numerous studies have examined possible associations between allergy history and cancers of the brain, lymphatic and hematopoietic system, and pancreas specifically due to strong inverse associations reported in previous work.

Brain tumors

Inverse associations between allergy history and glioma have been consistently reported in case–control studies based on self-report as well as in studies examining biological indicators of allergic status. However, there remain questions regarding the directionality of the observed associations, and results from prospective studies are unclear.

A 2007 meta-analysis of 3,450 glioma and 1,070 meningioma cases reported significant inverse associations between a self-reported history of any allergy (RR = 0.61; 95% CI, 0.55–0.67), asthma (RR = 0.68; 95% CI, 0.58–0.80), or eczema (RR = 0.69; 95% CI, 0.5–0.82) and glioma with no association observed for meningioma [73]. The significant inverse association remained in studies with direct, as opposed to proxy, patient interviews (RR any allergy = 0.66; 95% CI, 0.58–0.75). A subsequent analysis of 1,527 glioma cases and 3,309 controls from five INTERPHONE study countries (UK and Nordic countries) reported significant inverse associations between a self-reported prior diagnosis of asthma, hay fever, eczema, and glioma risk (~35%) [74]. There was also a significant inverse trend in glioma risk with increasing number of allergies. A history of current (odds ratio (OR) = 0.61; 95% CI, 0.47–0.79) but not previous (OR = 1.05; 95% CI, 0.78–1.43) eczema was inversely associated with meningioma.

More recently, nonsignificant inverse associations between allergy history and both glioma and meningioma were reported in the German INTERPHONE study [9]. Significant inverse associations between a self-reported prior diagnosis of allergy and glioma risk (~25–65%) were reported in a recent US case–control study with no proxy interviews [22, 32]. However, there was no association with age or years since diagnosis. In contrast, Scheurer et al. [40] reported a positive association between a self-reported history of long-term antihistamine use (at least 10 years) and glioma risk in those with a history of asthma or allergy (OR = 3.56; 95% CI, 1.56–8.14). Although there were no data on dosage, specific timing, or reason for use, findings may indicate either a direct or indirect effect of antihistamine medication on glioma risk. Claus et al. [13] reported a significant inverse association between a self-reported history of allergy (OR = 0.6; 95% CI, 0.5–0.7) and asthma (OR = 0.7; 95% CI, 0.6–0.9) and meningioma risk but not eczema (OR = 0.8; 95% CI, 0.6–1.1).

A history of self-reported allergy and/or asthma was significantly inversely associated with risk of anaplastic oligodendroglioma (OR = 0.6; 95% CI, 0.4–0.9) in a pooled analysis of data from seven studies [31]. A history of asthma alone was also inversely associated with risk of both oligodendroglioma (OR = 0.5; 95% CI, 0.3–0.9) and anaplastic oligodendroglioma (OR = 0.3; 95% CI, 0.1–0.9).

Due to the potential for recall bias in brain cancer patients due to the developing tumor, there have also been studies examining biological indicators of allergic status with similar findings observed. However, it remains unclear whether results may be due to enhanced immune status in allergy patients, treatment-related effects, or reverse causality.

In 2004, Wiemels et al. [75] reported significant inverse associations between elevated total (OR = 0.37; 95% CI, 0.22–0.64) and food-specific (OR = 0.12; 95% CI, 0.04–0.41) IgE and glioma risk in US case–control study. However, IgE levels were not correlated with self-reported allergy history, and in a more recent analysis, the inverse association remained only when considering temozolomide-treated patients, raising questions regarding the utility

of IgE as a biomarker in retrospective studies [48]. Post-diagnosis total IgE levels were inversely associated with meningioma [49]. Elevated IgE levels have also been associated with improved glioma survival [76].

In order to better understand the balance of humoral and innate immune function in glioma, Zhou et al. [51] recently examined concentrations of immune regulatory proteins, soluble CD23 (a marker of humoral immunity) and soluble CD14 (a marker of innate immunity) in a US case–control study. Significantly lower levels of sCD23 and significantly higher levels of sCD14 were observed in glioma cases compared to control subjects. Although neither marker was related to total levels of IgE, cases and controls with an allergy history had higher levels of sCD23.

Schwartzbaum et al. [44] reported an inverse association between mRNA expression levels of a variety of inflammatory- and allergy-related genes (including Th2 cytokine and IgE-binding genes) and CD133 mRNA (as an indicator of tumor progression) in a cross-sectional study of 142 glioblastoma patients, possibly suggesting widespread immunosuppression in glioma progression.

There are also several studies that have investigated germline polymorphisms in asthma- or allergy-related genes in relation to glioma risk in order to further address potential concerns surrounding recall bias in previous studies based on self-report as well as reverse causality in previous studies measuring levels of IgE or other immune parameters. However, results are not entirely consistent, and further research is required.

Schwartzbaum et al. [77] noted associations between polymorphisms in IL-4Rα (rs1805015, rs1801275), IL-13 (rs1800925) genes and glioblastoma risk in a Swedish study. However, the polymorphisms were not associated with self-reported allergy history among controls, and results were not replicated in a subsequent study [78]. Wiemels et al. [79] reported no clear association between polymorphisms in IL-4, IL-4R, or IL-13 genes and glioma risk; however, there was some suggestion of an association with some haplotypes. Associations between IL-4 (rs2243248) and IL-6 (rs1800795) polymorphisms and glioma risk were noted in a pooled analysis of two studies [80]. Ruan et al. [38] observed no overall association between polymorphisms in IL-4Rα (rs1801275), IL-13 (rs20541), and STAT6 (rs1059513, rs324015) genes and glioma risk in a recent Chinese study.

In contrast to previous studies noting inverse associations between allergy and glioma risk, Dobbins et al. [14] recently reported a significant positive association between a ORMDL3 (rs7216389) polymorphism, associated with childhood asthma, and glioma risk in an analysis of two genomewide association studies. Schoemaker et al. [43] reported that the inverse association between allergy history and glioma risk was modified by genotype. In particular, the inverse association between asthma and glioma strengthened with increasing number of PHLDB1 (rs498872) risk alleles as did the inverse association between any allergy and glioma with increasing number of RTEL1 (rs6010620) risk alleles. Conversely, the inverse association between any allergy and glioma weakened with increasing number of CDKN2A/B (rs4977756) risk alleles. Lachance et al. [28] reported that the inverse association between allergy history and high-grade glioma weakened in those with one or two CDKN2A/B (rs4977756) risk alleles but strengthened in those with one or two RTEL1 (rs4809324) risk alleles.

In other retrospective studies, Schoemaker et al. [42] recently reported an inverse association between a past diagnosis of hay fever and pituitary tumor risk (OR = 0.7; 95% CI, 0.5–1.0). However, findings strengthened in those with a hay fever diagnosis of <10 years (OR = 0.4; 95% CI, 0.2–1.0). Previous studies of acoustic neuroma reported findings ranging from no association to significant positive associations with specific allergies observed [82–84].

Results from studies with prospectively collected data on allergy history are unclear. Schwartzbaum et al. [81] reported some evidence for an inverse association between a history of self-reported allergy and glioma in a 1886–1925 cohort from the Swedish Twin Registry (HR any allergy = 0.45; 95% CI, 0.19–1.07). However, in a 1926–1958 cohort, there was no association observed (HR any allergy = 1.09; 95% CI, 0.48–2.48). In the CPS-II, there was no association between a self-reported history of physician-diagnosed asthma (HR = 0.97; 95% CI, 0.73–1.30), hay fever (HR = 0.96; 95% CI, 0.83–1.11), or both asthma and hay fever (HR = 0.96; 95% CI, 0.71–1.30) and brain cancer mortality overall [64].

There are also two recent studies with prospectively collected data on serum IgE levels. In a case–control study nested in four US prospective studies, including 169 glioma cases and 520 control subjects, borderline elevated total IgE levels were significantly inversely associated with glioma (OR = 0.63; 95% CI, 0.42–0.93) but not elevated total IgE levels (OR = 0.98; 95% CI, 0.61–1.56) [12]. There was also no association observed between elevated food- (OR = 1.03; 95% CI, 0.54–1.98) or respiratory-specific IgE (OR = 1.12; 95% CI, 0.77–1.62) and glioma risk. The concordance between self-reported asthma and elevated IgE levels was 48%. Another case–control study nested in the European Prospective Investigation into Cancer and Nutrition, including 275 gliomas, 175 meningiomas, 49 acoustic neuromas and 963 control subjects, reported some evidence for an inverse association between elevated respiratory-specific IgE and glioma risk (OR = 0.73; 95% CI, 0.51–1.06), but not meningioma (OR = 0.96; 95% CI, 0.61–1.51), or acoustic neuroma (OR = 0.80; 95% CI, 0.32–1.99) [41]. There was also a

significant inverse linear trend in risk for high-grade glioma with increasing categories of respiratory-specific IgE concentrations.

Among children, a significant inverse association between parental-reported asthma (OR = 0.75; 95% CI, 0.58–0.97) but not eczema (OR = 0.94; 95% CI, 0.74–1.18) and childhood central nervous system (CNS) tumors was recently reported in a UK case–control study, driven by a strong inverse association with PNET/medulloblastoma (OR = 0.43; 95% CI, 0.23–0.81) [21]. However, upon examination of associations with asthma diagnosis from primary care records in a subset of participants, which are not subject to potential parental recall bias, no overall association was observed (OR = 1.20; 95% CI, 0.74–1.94). Upon examination of associations with 'adult-type tumors' (approximately 31% of child CNS cases), nonsignificant inverse associations with parental-reported asthma (OR = 0.86; 95% CI, 0.56–1.31), severe wheeze (OR = 0.55; 95% CI, 0.25–1.20) and eczema (OR = 0.89; 95% CI, 0.58–1.35) were observed.

Lymphatic and hematopoietic cancers

Although case–control studies based on self-report have reported inverse associations between allergy history and lymphoma risk, particularly for non-Hodgkin's lymphoma (NHL), results from cohort studies and studies measuring specific IgE levels have not supported a link [1, 53]. Inverse associations have also been reported between allergy history and childhood leukemia. However, potential parental reporting biases in self-reported allergy history may account for the associations observed.

In case–control studies of all lymphomas combined, results from the Epilymph study, an international collaborative study of 2,480 lymphoma cases and 2,540 largely hospital-based controls, reported significant inverse associations between a self-reported history of asthma (OR = 0.72; 95% CI, 0.58–0.89), food allergies (OR = 0.67; 95% CI, 0.52–0.85) and total lymphoma risk [85]. Significant inverse associations were also observed between food allergy and Hodgkin's lymphoma (OR = 0.55; 95% CI, 0.31–0.99), NHL (OR = 0.69; 95% CI, 0.53–0.90), and B-NHL (OR = 0.70; 95% CI, 0.53–0.91) as well as between respiratory allergy and multiple myeloma (OR = 0.65; 95% CI, 0.43–0.98).

Soderberg et al. [86] examined 39,908 hematological malignancies from the Swedish Cancer Registry (1987–1999) and 149,344 population-based controls. Asthma diagnosis was identified through the Swedish Hospital Discharge Registry (1969–1999). ORs below unity were observed for all hematological malignancies combined (OR = 0.9; 95% CI, 0.8–1.0), including NHL (0.9; 95% CI, 0.8–1.0), and leukemia (OR = 0.9; 95% CI, 0.7–1.1) specifically. Upon restriction to asthma diagnosed at least 10 years in the past, ORs of 0.9 (95% CI, 0.7–1.1) and 0.6 (95% CI, 0.4–0.9) were observed for NHL and leukemia, excluding CLL, respectively. Conversely, Arellano et al. [87] reported a significant positive association between atopic dermatitis severity and all lymphomas combined (OR = 2.4; 95% CI, 1.5–3.8) in the PharMetrics database of atopic dermatitis patients.

Most recently, Mirabelli et al. [34] in a large multicenter population-based case–control study reported significant inverse associations between occupational exposure to high molecular weight allergens and total (OR = 0.78; 95% CI, 0.63–0.97) and B-cell (OR = 0.75; 95% CI, 0.59–0.94) lymphoma. Significant inverse associations for lymphoma risk were also observed with exposure to animal (OR = 0.73; 95% CI, 0.53–0.99) and latex (OR = 0.53; 95% CI, 0.30–0.95) allergens specifically; however, there was no exposure–response relationship according to duration of exposure. Limitations include potential self-selection in employment history, including whether high molecular weight–sensitized individuals may avoid such occupational exposures, as well as potential confounding by another underlying factor.

Previous case–control studies have also reported significant inverse associations between self-reported allergy history and NHL risk [88–90]. More recently, results from the Interlymph study, an international collaborative case–control study of 13,535 NHL cases and 16,388 hospital- and population-based controls, reported significant inverse associations between a self-reported history of any specific allergy (OR = 0.80; 95% CI, 0.68–0.94) and NHL overall adjusting for other atopic diseases [46]. There was also a significant inverse association between hay fever (OR = 0.85; 95% CI, 0.77–0.95), any specific allergy (OR = 0.84; 95% CI, 0.76–0.93), and B-cell NHL. Significant inverse associations were also observed for specific allergic conditions (asthma, hay fever, allergies) among individuals with at least one other allergic condition.

Notably, Melbye et al. [91] examined associations between self-reported allergic status, respiratory-specific IgE, and NHL in a large Nordic study. Significant inverse associations between self-reported allergic rhinitis (OR = 0.86; 95% CI, 0.77–0.98), specific IgE positivity (OR = 0.68; 95% CI, 0.58–0.80), and NHL risk were observed. There was also a significant linear trend of decreasing NHL risk with increasing specific IgE concentration. However, according to degree of disease dissemination, the strongest inverse associations were observed in those with more advanced disease. Additionally, in a case–control study nested in a cohort of approximately 400,000 pregnant women, there was an inverse association between specific IgE levels and NHL in those with an NHL diagnosis near to the date of serum collection. It was concluded

that findings did not support a causal association between allergy and NHL risk and that previously observed inverse associations were likely due to reverse causality, due to NHL-related immune suppression.

In support of this, a Spanish hospital-based case–control study reported significant inverse associations between respiratory-specific IgE and total lymphoma risk (OR upper tertile = 0.39; 95% CI, 0.28–0.54) as well as with NHL (OR upper tertile = 0.54; 95% CI, 0.36–0.81) and B-cell lymphoma specifically (OR upper tertile = 0.34; 95% CI, 0.23–0.48) [92]. However, nonsignificant inverse associations were also observed across all other histologic subgroups, and specific IgE levels were found to be lower pre-treatment as were all immunoglobulins (specific IgE and total IgM, IgA, IgG) with more advanced disease. Subsequently, Biggar et al. [10] examined Ig subclass levels (total IgM, IgD, IgA, IgE, IgG, IgG_4) in 200 NHL patients and 200 age- and sex-matched population controls. B-cell NHL patients exhibited lower levels of all Ig subclasses compared to controls, suggesting that the inverse association observed between NHL and IgE is likely due to generalized immune suppression in the disease.

No association was observed between allergy history and lymphoplasmacytic lymphoma–Waldenstrom macroglobulinemia in a Swedish case–control study [27]. Prior allergy desensitization shots were significantly inversely associated with Hodgkin's lymphoma in a case–control study in Canada [36].

In cohort studies, a positive association between self-reported childhood eczema and incident NHL (RR = 2.3; 95% CI, 1.0–5.3) was observed in a Swedish study of twins born from 1886 to 1925 as well as a positive association between hives and incident leukemia (RR = 2.1; 95% CI, 1.0–4.5); however, there were few exposed cancer cases [93]. In the CPS-II, there was no association between a history of self-reported physician-diagnosed asthma or hay fever and either NHL or multiple myeloma mortality; however, there was a significant inverse association between asthma and leukemia mortality overall (HR = 0.75; 95% CI, 0.58–0.98) [64].

More recently, Koshiol et al. [26] in a record linkage study of over four million hospitalized US veterans reported a significant positive association between allergy and NHL risk (RR = 1.4; 95% CI, 1.3–1.5). The association was somewhat stronger in black compared to white veterans and among those diagnosed with allergy two to four, as compared to 5 years or more, in the past. No association was observed between allergy and multiple myeloma [11]. Erber et al. [17], in the Multiethnic Cohort, reported a significant positive association between a self-reported history of physician-diagnosed allergies (HR = 1.46; 95% CI, 1.07–2.00), antihistamine use (HR = 1.80; 95% CI, 1.09–2.97), and NHL risk in Latino participants with no association observed for other ethnic groups.

Inverse associations have also been reported between allergy history and childhood leukemia [94–98]. A 2010 meta-analysis reported significant inverse associations between a history of allergy (OR = 0.69; 95% CI, 0.54–0.89), eczema (OR = 0.74; 95% CI, 0.58–0.96), and hay fever (OR = 0.55; 95% CI, 0.46–0.66) and childhood/adolescent acute lymphoblastic leukemia (ALL) but not acute myeloid leukemia (AML) [56]. However, results attenuated upon restriction to nested case–control studies, allergy history obtained from medical records (as opposed to parental report), and studies with a latency period, suggesting that bias associated with parental-reported allergy ascertainment may have accounted for the inverse associations observed. Results also attenuated in studies with response rates of 80% of greater, possibly suggesting some form of selection bias. The most recent ESCALE study also noted inverse associations between maternal-reported asthma (OR = 0.7; 95% CI, 0.4–1.0), eczema (OR = 0.7; 95% CI, 0.6–0.9), and childhood ALL [39].

Pancreatic cancer

Allergy history has been associated with reduced pancreatic cancer risk in case–control studies based on self-report as well as with improved survival. A 2005 meta-analysis including 3,040 pancreatic cancer cases reported significant inverse associations between a history of any allergy (RR = 0.82; 95% CI, 0.68–0.99) or atopy (RR = 0.71; 95% CI, 0.64–0.80) and pancreatic cancer risk [99]. Results strengthened in studies with direct, as opposed to proxy, patient interviews (RR any allergy = 0.70; 95% CI, 0.51–0.97). No association was observed with asthma (RR = 1.01; 95% CI, 0.77–1.31).

Similar results were reported in more recent studies. Olson et al. [100] reported significant inverse associations between a history of any self-reported allergy (OR = 0.58; 95% CI, 0.40–0.84), hay fever (OR = 0.45; 95% CI, 0.29–0.70), or allergy to animals (OR = 0.43; 95% CI, 0.23–0.80) and pancreatic cancer risk in a US hospital-based case–control study. However, there was no exposure–response relationship with increasing number of allergies. There was also no association with polymorphisms of IL-4 and IL-4Rα genes. In a subsequent analysis of 475 incident pancreatic cancer patients, a self-reported allergy history was associated with a significantly improved survival in patients without resection (n = 315) (median survival time = 13.3 months vs. 10.4 months; HR = 0.68; 95% CI, 0.49–0.95) [35]. In patients with resection (n = 160), a nonsignificant survival advantage was observed (median survival time = 33.1 months vs. 21.8 months; HR = 0.72; 95% CI, 0.43–1.23).

In the Ontario Pancreas Cancer Study, a self-reported history of allergies or hay fever was associated with a 60% (95% CI, 41–74%) reduction in pancreatic cancer risk [7]. Similar results were observed in never smokers (OR = 0.45; 95% CI, 0.24–0.82) and when excluding proxy respondents. However, there may be some form of selection bias due to low response rates as well as a survival bias due to the rapidly fatal nature of the disease. A large multicenter population-based case–control study reported a 36% (95% CI, 18–50%) reduction in pancreatic cancer risk in those with a self-reported history of any allergy [30]. For specific allergies, significant inverse associations were observed for asthma (OR = 0.57; 95% CI, 0.34–0.97) and eczema (OR = 0.60; 95% CI, 0.42–0.88). Similar results were observed for both direct and proxy interviews.

In prospective studies, there was a significant inverse association observed between a self-reported history of physician-diagnosed hay fever and pancreatic cancer mortality in the CPS-II (HR = 0.85; 95% CI, 0.77–0.95), with a similar, although nonsignificant, finding observed in never smokers (HR = 0.86; 95% CI, 0.60–1.22) [64]. There was no association with asthma (HR = 1.02; 95% CI, 0.85–1.23). There was also no association between either total or allergen-specific IgE levels or positive skin prick testing and pancreatic cancer occurrence in prospective studies, although there were few pancreatic cancer cases observed [70, 72].

Other cancer sites

There are also other recent studies of cancer at other sites. Although some previous studies have suggested a positive association between asthma and lung cancer, due to local mechanisms of inflammation and repair, results are not entirely consistent and there are few prospective studies or studies of never smokers [2]. More recently, Wang et al. [47] reported a significant positive, although imprecise, association between a history of self-reported physician-diagnosed asthma and lung cancer risk (OR = 4.78; 95% CI, 1.23–18.63) in never-smoking women. Koh et al. [25] reported HRs of 1.04 (95% CI, 0.70–1.54) and 1.84 (95% CI, 0.97–3.47) for incident lung cancer associated with a self-reported history of physician-diagnosed asthma/hay fever/atopy and rhinosinusitis, respectively, in never smokers in the Singapore Chinese Health Study. Lim et al. [29] reported interactions between a self-reported asthma and atopy history and polymorphisms in inflammatory-related genes for lung cancer risk.

There are also fewer studies at other cancer sites, and it remains unclear whether prior allergies may either be positively or negatively associated with cancer at other sites. In case–control studies, significant inverse associations were observed between a self-reported history of any allergy, airborne allergies, food allergies, and animal allergies and cervical cancer risk (~30–40%) [24]. The inverse association for pollen allergy strengthened in more advanced disease as well as in HPV18+ compared to HPV16+ disease. Variation in an allergy-related cytokine gene, CSF2RB (rs16997517), was associated with both pollen allergy (in controls) and reduced cervical cancer risk. An inverse association between asthma and ovarian cancer (~27%) was reported in a Florida study using hospital discharge data [16]. An Italian study reported a significant inverse association between a self-reported prior asthma diagnosis and basal cell carcinoma (OR = 0.45; 95% CI, 0.24–0.82) [37]. In a Montreal study, significant inverse associations between a self-reported prior diagnosis of asthma and stomach cancer risk (OR = 0.27; 95% CI, 0.1–0.9) as well as between eczema and lung cancer risk (OR = 0.34; 95% CI, 0.2–0.7) were observed with non-significant inverse associations observed for cancer at other sites [15].

In prospective studies, Severi et al. [45] reported significant positive associations between self-reported physician-diagnosed asthma (HR = 1.25; 95% CI, 1.05–1.49) and current asthma medication use, in particular systemic glucocorticoids (HR = 1.71, 95% 1.08–2.69), and prostate cancer incidence in the Melbourne Collaborative Cohort Study. A self-reported asthma history was positively associated with incident thyroid cancer in the US Radiologic Technologists Study [33]. Wiemels et al. [50] observed a positive association between total and specific IgE concentrations and risk of a subsequent squamous cell carcinoma of the skin in patients with a previous nonmelanoma skin cancer.

Conclusion

In summary, although results from retrospective studies have consistently reported strong, inverse associations between a self-reported history of allergy and cancer risk, particularly for pancreatic cancer, glioma, and childhood leukemia, results from studies with medical record-defined allergy, or from prospectively designed studies, are less clear. Although retrospective studies with biological indicators of allergy history, including levels of IgE, have also pointed to inverse associations with cancer risk, findings may be due to reverse causality and/or treatment-related effects. Prospective studies with data on IgE levels or skin prick-tested participants have observed few consistent associations with cancer risk and were generally small in size. There are also several studies that examined associations between polymorphisms in allergy-related genes and cancer risk; however, further research is required to replicate such findings.

Further epidemiological research is required to better understand possible associations between prior allergy and cancer risk including validation studies to better understand allergy reporting, including both parental reporting of childhood allergies and self- or proxy-reported allergic status, as well as the use of medical records for allergy ascertainment; further assessment of the impact of possible selection biases in participant recruitment, including self-selection and low response rates; further studies with detailed allergy indicators including information on allergy history and treatment throughout the life course including data on the timing of allergy onset; further studies with prospectively collected allergy information to address possible reporting biases in retrospective studies; and further studies with biological indicators of allergic status, including total and specific levels of IgE and other relevant immune markers, particularly in large-scale, prospectively based designs, to avoid possible tumor- and treatment-related effects. Zennaro et al. [101] recently described a microarray approach to examining immune response to tumor antigens in a cancer and allergy population. Finally, to examine the possible impact of publication bias, pooled analyses involving consortia of previous or ongoing studies may also be informative.

Conflict of interest No conflict of interest to declare.

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