

Chapter 4

Epidemiological Evidence: IgE, Atopy, and Solid Tumors

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Abstract Epidemiological investigation into a potential relation between a history of allergic disorders, typically characterized by high levels of IgE, and cancer occurrence has been conducted for at least the past five decades. Recently, there is renewed interest in the field, and the literature is expanding rapidly. This chapter summarizes the epidemiological literature examining the potential relation between allergy and cancer, with a particular focus on the most recent contributions to the field. Although the majority of new and previously published studies evaluated self-reported history of specific allergic disorders (asthma, hay fever, eczema), there were also several new studies examining total or allergen-specific IgE antibodies, hospital discharges for allergic conditions, skin prick tested patients, and allergy-related gene polymorphisms in relation to cancer risk. Although there are a number of inverse relations reported, particularly with pancreatic cancer and glioma, there remain a number of methodological considerations. Further research is recommended in order to better understand the nature of a possible inverse relation and possible mechanisms of action with implications for cancer treatment and prevention. Multidisciplinary collaborations between the population and laboratory-based sciences would be particularly useful.

4.1 Introduction

Epidemiological investigation into a potential relation between a history of allergic disorders and cancer occurrence has been conducted for at least the past five decades [1]. Allergic disorders are typically characterized as an abnormal or hyperactive immune response in reaction to exposure to environmental agents or allergens [2]. High levels of immunoglobulin E (IgE) are defining characteristics of such a response [2, 3]. Although allergic disorders are associated with substantial

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morbidity and mortality, a prevailing theory exists to suggest that the presence of allergic disorders may in fact represent a manifestation of an enhanced capacity for immunosurveillance [4, 5].

Recently, there has been renewed interest in the field. Immunosuppressed patients have been found to experience greater cancer rates [6]. Concerns regarding the safety of anti-IgE therapy in the treatment of allergic asthma have also been raised. Due to suggestions of a possible increased cancer risk, it was recently suggested that omalizumab, the therapeutic anti-IgE antibody, not be used in asthma patients with a personal or family history of cancer [3]. Jensen-Jarolim et al. [7] have recently called for a role of IgE antibodies in cancer therapy and prevention. Fu et al. [8] have also suggested a potential therapeutic role for IgE in pancreatic cancer.

Although previous review articles have summarized the state of the epidemiological evidence [1, 9], the literature is expanding rapidly, and an updated synthesis is needed. The purpose of this chapter is to summarize the epidemiological literature examining the potential relation between allergy and cancer, with a particular focus on the most recent contributions to the field. Hematopoietic malignancies are examined separately in Chapter 5.

4.2 Methods

The search strategy was developed to identify previous observational epidemiological studies examining the relation between a personal history of allergic disorders and cancer (excluding hematopoietic malignancies). The search strategy used here served to update our previous review [1]. The OVID MEDLINE (2005 to September week 2 2008) database was searched using the following MeSH headings: 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, tumor, tumour, malignan\$, neoplasm\$, carcinoma, glioma, meningioma, neuroma, and risk. The search was restricted to human studies and papers written in English. The reference lists of all included original studies were also handsearched in order to identify additional studies not captured by the search strategy. A summary of previous epidemiological studies is presented below ordered by cancer site and study design.

4.3 Results

A total of 32 original epidemiological studies [10–41] and two meta-analyses [5, 42] were identified that were published since our previous review [1]. A total of eight original studies [43–50] were also identified here through handsearching the reference lists of new papers that were not captured previously. Although the majority of newly published studies were case-control studies, there were nine cohort studies [10, 12, 16, 17, 20, 22, 23, 25, 29] with most of size of approximately 20,000 participants or less. Studies were mainly conducted in North America and Europe, with

several publications from each of the United States, Germany, the United Kingdom, and Sweden. Although the majority of new and previously published studies evaluated self-reported history of specific allergic disorders (asthma, hay fever, eczema), there were also three new studies examining total or allergen-specific IgE antibodies [23, 28, 38], two new record linkage studies examining hospital discharges for allergic conditions [20, 25], one study extending follow-up of a cohort of skin prick tested patients [16], and five studies examining allergy-related gene polymorphisms [11, 26, 36, 37, 39] in relation to cancer risk.

4.3.1 All Cancer

Although early case-control and cross-sectional studies tended to report inverse associations between a history of allergy and the occurrence of all cancer combined [51–65], there are a number of potential limitations that limit the strength of their findings [1]. A summary of cohort studies is presented in Table 4.1.

Results from several large record linkage studies of discharge diagnoses databases have reported conflicting results. A Swedish study linking 64,346 people discharged from hospital with asthma to the Swedish Cancer Registry reported 4,520 incident cancer cases [66]. A significant inverse association between asthma and all cancers was observed with a standardized incidence ratio (SIR)¹ of 66 (95% confidence interval (CI)² = 64–68) reported. More recently, Hagstromer et al. [20] linked 15,666 people with a discharge diagnosis of atopic dermatitis with the Swedish Cancer Registry. Over a mean follow-up period of 15.4 years, a total of 331 incident cancers were identified. Overall, a significant positive association was observed for all cancers (SIR = 113, 95% CI 101–125), particularly among men (SIR = 130, 95% CI 110–154) and those diagnosed in the first 9 years of follow-up (SIR = 119, 95% CI 101–140). Upon further examination, it was revealed, however, that the association was driven mainly by several smoking- and alcohol-related cancers. In a similar study of 2,030 hospitalized in Denmark for atopic dermatitis, an excess of cancer cases were also observed (SIR = 150, 95% CI 120–190), driven mainly by keratinocyte carcinomas of the skin (see Section 4.3.7) [25].

Vesterinen et al. [67] linked 77,952 asthmatics from the Finnish Social Insurance Institution register with the Finnish Cancer Registry. A total of 3,842 incident cases were observed. Overall, a significant excess of incident cancers was observed among men (SIR = 112, 95% CI 107–117), driven mainly by excesses in lung cancer. No

¹The ratio of the number of new cancer cases observed in the population of interest (here subjects with a history of allergy) over a specified time period compared to that of a reference population, usually national cancer rates. An SIR of 100 indicates similar cancer incidence rates were observed in both the population of interest and in the reference population. SIRs above or below 100 indicate a higher than or lower than expected rate of cancer incidence respectively.

²The 95% confidence interval provides a range of values where the true value is found 95% of the time. 95% confidence intervals which exclude the null value of 1.0 (100 for standardized incidence/mortality ratios) indicate the result is “statistically significant”, and the null hypothesis can be rejected with less than a 5% chance that the association observed was due to chance.

Table 4.1 Previous cohort studies evaluating the association between a history of allergy and all cancer

References (country)	Study population (number of cancer cases)	Allergy indicator	Relative risk (95% CI)
Alderson [115] (England)	1,892 from asthma clinic, 63 all cancer deaths	PD asthma	71 ($p < 0.01$)
Polednak [116] (USA)	12,098 <i>men</i> from Harvard, 1,074 all cancer deaths	SR asthma	8.3 deaths per 100 asthma, 8.9 without (NS)
Kaaber [50] (Denmark)	326 atopic dermatitis patients, 9 incident cancer cases	PD atopic dermatitis (M,F)	23, 132 ($p > 0.05$)
Robinette and Fraumeni [117] (USA)	9,550 <i>men</i> with asthma in army hospitals, 328 all cancer deaths	PD asthma	128 ($p < 0.01$)
Hughes and Raitz [118] (USA)	500 allergic and 421 non-allergic patients, 26 incident cancer cases	Atopy (scratch test or intradermal skin test)	No association
Markowe et al. [119] (England)	2,547 asthmatic and non-asthmatic patients, 34 all cancer deaths	PD asthma	0.9 (0.5–1.5)
Reynolds and Kaplan [120] (USA)	6,848 in California, 472 incident cancer cases, 277 all cancer deaths	SR asthma (incidence M,F) (mortality M,F)	2.1 ($p < 0.05$) , 1.1 ($p > 0.05$) 2.4 ($p < 0.05$) , 0.5 ($p > 0.05$)
Mills et al. [69] (USA)	34,198 Seventh-Day Adventists, 1,102 incident cancer cases	SR PT any allergy (M,F) SR PT asthma SR PT hay fever SR PT reaction to medication SR PT reaction to chemicals SR PT reaction to bee sting SR PT reaction to poisonous plants PD asthma	1.13 (0.92–1.39), 1.00 (0.85–1.17) 0.78 (0.48–1.27), 0.96 (0.69–1.34) 1.06 (0.79–1.41), 1.15 (0.94–1.41) 1.33 (1.02–1.74), 0.79 (0.65–0.98) 0.67 (0.32–1.41), 0.80 (0.53–1.21) 0.67 (0.40–1.11), 1.06 (0.77–1.47) 1.13 (0.87–1.45), 0.98 (0.81–1.20) 66 (64–68)
Kallen et al. [66] (Sweden)	64,346 discharged from hospital with asthma, 4,520 incident cancer cases	PD asthma (M,F)	112 (107–117) , 103 (98–107)
Vesterinen et al. [67] (Finland)	77,952 asthmatics on Social Insurance Register, 3,842 incident cancer cases	SR asthma	1.0 (0.7–1.4)
Lange et al. [121] (Denmark)	13,540 from Copenhagen Heart Study, 1,338 all cancer deaths	PT asthma (M,F)	1.26 (0.68–2.34), 0.88 (0.38–2.02)
Knuiman et al. [122] (Australia)	4,277 in Busselton Health Study, 372 all cancer deaths		

Table 4.1 (continued)

References (country)	Study population (number of cancer cases)	Allergy indicator	Relative risk (95% CI)
Gergen et al. [123] (USA)	9,252 from NHANES II – Mortality Study, 998 all cancer deaths	Atopy (skin prick test)	0.89 (0.33–2.43) 30-to 44-year olds 0.78 (0.42–1.44) 45- to 59-year olds 1.13 (0.84–1.53) 60- to 75-year olds 1.04 (0.85–1.28)
Margolis et al. [101] (USA)	3,869 on Medicaid database, 165 incident cancer cases	PD severe eczema	
Vandentorren et al. [74] (France)	14,267 in PAARC Study, 932 all cancer deaths	SR asthma	1.06 (0.81–1.40)
Eriksson et al. [16] (Sweden)	13,811 patients from allergy clinic, 401 incident cancer cases	Atopy (skin prick test)	100 (83–120)
Hagstromer et al. [20] (Sweden)	15,666 discharged from hospital with atopic dermatitis, 331 incident cancer cases	PD atopic dermatitis (M,F)	130 (110–154) , 102 (88–188)
Lindelof et al. [23] (Sweden)	127,951 tested for total serum IgE or Phadiatop, 1,915 incident cancer cases	IgE highly elevated Positive Phadiatop	107 (82–137) 97 (82–114)
Olesen et al. [25] (Denmark)	2,030 discharged from hospital with atopic dermatitis, 67 incident cancer cases	PD atopic dermatitis	150 (120–190)
Turner et al. [70] (USA)	1,102,247 from CPS-II cohort, 81,114 all cancer deaths	SR PD asthma SR PD hay fever	1.06 (1.02–1.11) 0.92 (0.89–0.94)
Bellia et al. [10] (Italy)	1,233 elderly ambulatory patients, 59 all cancer deaths	SR PD asthma and hay fever PD asthma	0.88 (0.83–0.93) 17.3% of deaths with asthma versus 29.8% of deaths without (NS)

Eriksson et al. [16] extend cohort and follow-up from a previous publication [68]; standardized incidence ratios converted to base 100; NHANES II = Second National Health and Nutrition Examination Survey; PAARC = Air Pollution and Chronic Respiratory Diseases Study; CPS-II = Cancer Prevention Study – II; PD = physician diagnosed; SR = self-reported; M = male; F = female; PT = physician treated; IgE = immunoglobulin E; CI = confidence interval; NS = non-significant. See text for description of the various indicators of relative risk reported in individual studies. Statistically significant relative risk estimates are indicated by boldface type.

significant association with all incident cancers was observed in women. Recently, in an extended follow-up to a previous prospective study [68], Eriksson et al. [16] linked 13,811 skin prick tested patients to the Swedish Cancer Registry. A total of 119 incident cancer cases were observed among those with allergy with the same number expected (SIR = 100, 95% CI 83–120). Finally, in another recent prospective study, 70,136 patients for whom data on total serum IgE levels were known and 57,815 patients for whom data on allergen-specific IgE levels were known were followed up for cancer diagnosis according to the Swedish Cancer Registry [23]. No association with overall cancer incidence was reported for either measure (SIR IgE highly elevated = 107, 95% CI 82–137; SIR-positive Phadiatop = 97, 95% CI 82–114) among adults. Although an elevated SIR was observed among children with either a positive Phadiatop or elevated levels of total IgE (SIR = 262, 95% CI 131–469), these findings were based on only 11 childhood cancer cases.

There have also been several large cohort studies with data on individual level covariates. Mills et al. [69] evaluated the association between a history of allergy and cancer incidence in a cohort of 34,198 Seventh-Day Adventists. A total of 1,102 incident cases of cancer were observed over a 6-year follow-up period. No association was reported between a history of self-reported allergy, asthma, or hay fever, of sufficient severity to require treatment from a physician, and the occurrence of any type of cancer. In the largest prospective study conducted to date, over 1.1 million Cancer Prevention Study (CPS) – II study participants were followed up for 18 years with a total of 81,114 cancer deaths observed [70]. Overall, a significant inverse association was observed between a history of self-reported physician-diagnosed asthma and hay fever and all cancer mortality (hazard ratio (HR)³ = 0.88, 95% CI 0.83–0.93), driven mainly by lung and colorectal cancer mortality, with a similar, although slightly attenuated, relation observed with restriction to never smokers only (HR = 0.91, 95% CI 0.83–1.00). Although this study provides some of the strongest evidence for a potential relation between a history of allergy and cancer overall, the strength of the evidence remains limited.

4.3.2 Lung Cancer

A meta-analysis of studies published up to the year 2002 reported a combined odds ratio (OR)⁴ of 1.8 (95% CI 1.3–2.3) from previous case–control studies that evaluated the relation between asthma and lung cancer in never smokers [71].

³Here the survival experience of subjects in cohort studies with a history of allergy to those without is compared. Hazard ratios above 1.0 imply higher rates of cancer incidence (or death) in subjects with a history of allergy and hazard ratios below 1.0 imply lower rates of cancer incidence (or death) over the study follow-up period.

⁴Here an odds ratio denotes how much more likely cancer (or cancer death) occurs among study subjects with a history of allergy compared to those without in case-control studies. Odds ratios above 1.0 imply that cancer (or cancer death) was more likely to occur among study subjects with a history of allergy while odds ratios below 1.0 imply that cancer (or cancer death) was less likely to occur.

Similar findings were reported when combining the results for all previous studies that controlled for smoking history in the analysis. In contrast to the postulated protective effect of enhanced immunosurveillance among those with allergy, here it is thought that local mechanisms of inflammation and repair due to asthma may be responsible for a potential positive relation. Among the potential methodological limitations identified are misclassification and differential recall bias.

A number of subsequent studies have recently been published. Among case-control studies adjusting for smoking status, Schabath et al. [72] reported a positive association between self-reported physician-diagnosed asthma and lung cancer overall (OR = 1.25, 95% CI 0.99–1.57); however, upon exclusion of subjects with asthma diagnosis in the recent past (within 10 years of interview), the positive finding disappeared (OR = 1.06, 95% CI 0.80–1.40). An analysis of two large population-based case-control studies conducted in Montreal, Canada, reported no clear association between self-reported asthma and lung cancer overall, although there were some positive findings for specific lung cancer subtypes (below) [30]. In a case-control study nested in a cohort of asthmatic patients and the general population, a positive relation was observed (adjusted OR = 1.35, 95% CI 1.15–1.59) that weakened somewhat with the exclusion of asthma cases diagnosed within 1 year of lung cancer diagnosis (OR = 1.22, 95% CI 1.03–1.44) [18]. A positive, non-significant association was observed between allergen-specific IgE positivity and lung cancer (OR = 1.29, 95% CI 0.87–1.92) as well as self-reported physician-diagnosed asthma (OR = 1.40, 95% CI 0.71–2.77) in a case-control study nested in the ESTHER-I and -II prospective study by Wang et al. [38].

Two recent hospital-based case-control studies were conducted in never smokers (Table 4.2). In an extended analysis of the data collected as part of Schabath et al. [72], Gorlova et al. [19] reported a positive association between self-reported physician-diagnosed asthma and lung cancer overall (OR = 1.82, 95% CI 1.05–3.15); however, upon restriction to asthma only (and no hay fever), no association was reported (OR = 0.92, 95% CI 0.41–2.06). Seow et al. [37], in a study of never smoking Chinese women, reported a positive association between self-reported ever asthma/allergic rhinitis/atopic dermatitis and lung cancer overall (OR = 1.5, 95% CI 0.8–2.6) increasing to OR = 3.1 (95% CI 1.2–8.3) among those with an interleukin (IL) –6 CG/GG genotype, suggesting a role for inflammation in lung cancer. Brown et al. [13], in a case-control study nested in the Adverse Childhood Experiences (ACE) Study, reported an OR of 2.1 (95% CI 0.9–5.1) among non-smokers (including never and former smokers) with self-reported asthma.

Recent prospective studies controlling for smoking history reported mixed results [17, 73, 74]. In an analysis of 70 lung cancer deaths among the 6,144 non-smokers (including never and former smokers) in the second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, Brown et al. [12] reported a positive relation between a history of self-reported physician-diagnosed asthma and lung cancer (HR = 1.69, 95% CI 0.94–3.04), increasing with exclusion of those with a history of physician-diagnosed emphysema and/or chronic bronchitis. In the CPS-II cohort, no clear relation was observed between a history of self-reported

Table 4.2 Previous studies evaluating the association between a history of allergy and lung cancer in non-smokers

References (country)	Population (number of cancer cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Cohort Studies			
Brown et al. [12] (USA)	6,144 NHANES II, <i>non-smokers</i> , 70 lung cancer deaths	SR PD asthma	1.69 (0.94–3.04)
Turner et al. [70] (USA)	448,613 CPS-II <i>never smokers</i> , 1,539 lung cancer deaths	SR PD asthma SR PD hay fever SR PD asthma and hay fever SR PD rhinitis or sinusitis SR PD asthma/hay fever/atopy	1.11 (0.79–1.56) 1.02 (0.86–1.21) 0.83 (0.56–1.22) 1.84 (0.97–3.47) 1.04 (0.70–1.54)
Koh et al. [22] (China)	42,588 Singapore Chinese Health Study <i>never smokers</i> , 265 incident lung cancer cases		
Case-Control Studies			
Samet et al. [124] (USA)	Population-based, <i>never smokers</i> (26/285)	SR PD asthma	0.77 (0.10–6.13)
Alavanja et al. [76] (USA)	Population-based, <i>women, never smokers</i> (154/1,166)	SR PD asthma	2.7 (1.4–5.4)
Wu et al. [77] (USA)	Population-based, <i>women, never smokers</i> (412/1,253)	SR PD asthma	1.48 (1.0–2.2)
Mayne et al. [125] (USA)	Population-based, <i>non-smokers</i> (437/437)	SR PD asthma	1.97 (0.90–4.32)
Brenner et al. [81] (China)	Population-based, <i>never smokers</i> (253/540)	SR PD asthma	2.0 (0.9–4.2)
Castaing et al. [14] (Europe and UK)	Hospital-based, <i>never smokers</i> (223/1,039)	SR eczema	0.55 (0.28–1.08)
Brown et al. [13] (USA)	Nested in ACE Study, <i>non-smokers</i> (35/8,236)	SR asthma	2.1 (0.9–5.1)
Gorlova et al. [19] (USA)	Hospital-based, <i>never smokers</i> (280/242)	SR PD asthma SR PD hay fever SR asthma/allergic rhinitis/atopic dermatitis	0.92 (0.41–2.06) 0.50 (0.30–0.83) 1.5 (0.8–2.6)
Seow et al. [37] (Singapore)	Hospital-based, <i>women, never smokers</i> (132/163)		

Results for never smokers are presented where available; Gorlova et al. [19] re-analyze data in Schabath et al. [72] focussing on never smokers only; NHANES II = Second National Health and Nutrition Examination Survey; CPS-II = Cancer Prevention Study – II; ACE = Adverse Childhood Experiences Study; PD = physician diagnosed; SR = self-reported; CI = confidence interval; odds ratio and 95% CI for Samet et al. [124] calculated. See text for description of the various indicators of relative risk reported in individual studies. Statistically significant relative risk estimates are indicated by boldface type.

physician-diagnosed asthma and lung cancer mortality among nearly 450,000 never smoker participants (HR = 1.11, 95% CI 0.79–1.56) [70].

There are no consistent results for asthma associated with lung cancer subtypes. In case–control studies, Wu et al. [75] found that the risk of adenocarcinoma was not associated with self-reported physician-diagnosed asthma in women (OR = 1.0, 95% CI 0.5–2.1). Elevated ORs were reported for adenocarcinoma and other histological types of lung cancer in non-smoking women with a history of asthma by both Alavanja et al. [76] and Wu et al. [77]. Osann et al. [78] reported a positive relation between self-reported physician-diagnosed asthma and small cell lung cancer (OR = 4.8, 95% CI 1.0–22.8) in women. Ramanakumar et al. [30] reported an elevated, although imprecise, OR for the relation between a self-reported asthma history and adenocarcinoma (OR population controls = 2.0, 95% CI 0.8–4.8) but not squamous cell carcinoma (OR population controls = 1.2, 95% CI 0.6–2.5) in one study, with no positive findings in the other study.

In a cohort of 92,986 asthmatics in Sweden, a significant positive association was noted in both males and females for squamous cell carcinoma (SIR = 206, 95% CI 184–230) and small cell carcinoma (SIR = 234, 95% CI 160–331), but not for adenocarcinoma (SIR = 106, 95% CI 87–127) [79]. In a Finnish record linkage study, a significant positive association was noted for adenocarcinoma (SIR = 146) and squamous cell carcinoma (SIR = 117), but not for small cell carcinoma (SIR = 103), among individuals with a history of asthma [67]. Both of these studies were unable to control for individual-level variables. Lastly, no clear association was reported in heavy smokers with a self-reported physician-diagnosed asthma history and any lung cancer subtype [80].

Age at and timing of diagnosis of asthma may affect the association between asthma and lung cancer. One study showed a significant positive association among those with an asthma diagnosis at or prior to 20 years of age (OR = 1.95, 95% CI 1.1–3.6), and with a lapse of 11–20 years since first diagnosis of asthma (OR = 2.99, 95% CI 1.1–8.3) [77]. Both Brenner et al. [81] and Kallen et al. [66], however, reported significant positive associations for lung cancer within 1–5 years of an asthma diagnosis only.

In terms of other allergic disorders, Schabath et al. [72] reported an inverse association between self-reported physician-diagnosed hay fever and lung cancer overall (OR = 0.58, 95% CI 0.48–0.70) that was attenuated in never smokers (OR = 0.81, 95% CI 0.53–1.23). In a further examination of the never smokers [19] the inverse relation, however, was found to be fairly robust across categories of timing of diagnosis, duration of disease, and a history of hay fever only (with no asthma). Schabath et al. [72] also evaluated the influence of polymorphisms of matrix metalloproteinase-1 (MMP-1) and myeloperoxidase (MPO) genes and reported increasingly inverse associations between hay fever and lung cancer with increasing number of protective genotypes. A subsequent publication reported that cases with hay fever exhibited lower mutagen sensitivity in bleomycin and benzo[a]pyrene diol epoxide (BPDE) assays [41]. Another large case–control study by Castaing et al. [14] reported an inverse association between a history of self-reported eczema and lung cancer (OR = 0.61, 95% CI 0.48–0.76) that remained following stratification

by current age, sex, and smoking status (OR never smokers = 0.55, 95% CI 0.28–1.08) but was no longer significant. The OR was also seen to lower when cases with eczema further reported a history of asthma (OR = 0.45, 95% CI 0.19–1.08) or use of eczema medication (OR = 0.55, 95% CI 0.41–0.72). Upon stratification by histologic subtype, ORs tended to be lower for squamous cell carcinoma (OR = 0.51, 95% CI 0.36–0.73) and small cell carcinoma (OR = 0.54, 95% CI 0.34–0.85) (OR adenocarcinoma = 0.83, 95% CI 0.58–1.19). Wang et al. [38] reported an inverse association with self-reported physician-diagnosed hay fever (OR = 0.34, 95% CI 0.11–1.10), but not atopic dermatitis, in a nested case–control study.

No clear association between a positive skin prick test and lung cancer incidence was reported in three prospective studies [16, 73, 82]. Hagstromer et al. [20] reported a significant excess of lung cancer cases among females discharged from hospital with atopic dermatitis. Koh et al. [22], in a large Chinese prospective study, reported a positive association between self-reported physician-diagnosed allergic rhinitis/nonallergic rhinitis/sinusitis and lung cancer (HR = 1.59, 95% CI 1.06–2.37) that increased for females (HR = 2.32, 95% CI 1.23–4.39), adenocarcinoma cases (HR = 1.91, 95% CI 1.07–3.42), and never smokers (HR = 1.84, 95% CI 0.97–3.47). However, no association was reported between physician-diagnosed asthma, hay fever, allergic dermatitis, food allergy, or other allergy and lung cancer (HR = 1.11, 95% CI 0.90–1.36). Lindelof et al. [23] reported no association in participants who underwent testing for total and allergen-specific IgE levels in Sweden, although the precise SIR was not provided. In the CPS-II cohort, no clear relation was observed between a history of self-reported physician-diagnosed hay fever and lung cancer mortality among never smokers (HR = 1.02, 95% CI 0.86–1.21), although there was a non-significant inverse relation with a history of both asthma and hay fever (HR = 0.83, 95% CI 0.56–1.22) [70].

4.3.3 *Pancreatic Cancer*

A meta-analysis of studies published up to the year 2004 by Gandini et al. [4] reported significant inverse associations between pancreatic cancer and a history of any allergy (relative risk (RR)⁵ = 0.82, 95% CI 0.68–0.99) or atopy (RR = 0.71, 95% CI 0.64–0.80). Although a significant inverse association was also observed for respiratory allergy (RR = 0.63, 95% CI 0.52–0.76), no association was observed for asthma (RR = 1.01, 95% CI 0.77–1.31). Since then, at least six additional studies have been published with some similar findings reported [15, 16, 20, 24, 26, 70] (Table 4.3).

⁵Here the relative risk is the ratio of cancer risk (or death) among study subjects with a history of allergy to those without. Since most cancers are considered rare diseases, the various ratio measures (such as odds ratios and rate ratios) reported in individual studies approximate each other.

Table 4.3 Previous studies evaluating the association between a history of allergy and pancreatic cancer

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Cohort Studies			
Robinette and Fraumeni [117] (USA)	9,550 <i>men</i> with asthma in army hospitals, 17 pancreatic cancer deaths	PD asthma	17 deaths among asthmatics versus 5 for nasopharyngitis patients ($p \leq$ 0.05)
Mills et al. [126] (USA)	34,198 Seventh-Day Adventists, 40 pancreatic cancer deaths	SR PT asthma	0.87 (0.21–3.63)
		SR PT hay fever	0.66 (0.23–1.87)
		SR PT reaction to plants	0.99 (0.44–2.27)
		SR PT reaction to bee sting	0.43 (0.06–3.16)
		SR PT reaction to medication	0.67 (0.07–5.98)
		SR PT reaction to chemicals	1.53 (0.37–6.30)
Kallen et al. [66] (Sweden)	64,346 discharged from hospital with asthma, 160 incident pancreatic cancer cases	PD asthma	64 (55–75)
Vesterinen et al. [67] (Finland)	77,952 asthmatics on Social Insurance Register, 142 incident pancreatic cancer cases	PD asthma (M,F)	88 (67–113), 101 (80–124)
Stolzenberg- Solomen et al. [127] (Finland)	29,048 <i>male smokers</i> in ATBC study, 172 pancreatic cancer deaths	SR asthma	2.16 (1.17–3.98)
		SR allergic skin lesions	0.59 (0.29–1.20)
Eriksson et al. [16] (Sweden)	13,811 patients from allergy clinic, two incident pancreatic cancer cases	Atopy (skin prick test)	72 (9–260)
Hagstromer et al. [20] (Sweden)	15,666 discharged from hospital with atopic dermatitis, 11 incident pancreatic cancer cases	PD atopic dermatitis	190 (100–340)
Lindelof et al. [23] (Sweden)	70,136 tested for total serum IgE and 57,815 tested with Phadiatop	IgE highly elevated Positive Phadiatop	No association No association
Turner et al. [70] (USA)	1,102,247 from CPS-II cohort, 5,159 pancreatic cancer deaths	SR PD asthma	1.02 (0.85–1.23)
		SR PD hay fever	0.85 (0.77–0.95)
		SR PD asthma and hay fever	1.14 (0.94–1.38)
Case–Control Studies			
Lin and Kessler [128] (USA)	Hospital-based (109/109)	SR allergy/eczema/ dermatitis	2.56 (1.33–4.93)

Table 4.3 (continued)

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Gold et al. [129] (USA)	Hospital and population-based (201/201/201)	SR allergic disorders (HB, PB)	0.39 (0.22–0.71) , 0.97 (0.50–1.90)
Mack et al. [130] (USA)	Population-based (490/490)	SR asthma	0.7 (0.4–1.1)
		SR allergic skin reactions	0.2 (0.1–0.5)
		SR allergy to natural antigens	0.5 (0.3–0.9)
		SR allergy to commercial products	0.9 (0.5–1.6) 0.6 (0.4–0.8)
		SR any allergic disease	
Farrow and Davis [131] (USA)	Population-based, <i>men</i> (148/188)	SR asthma	1.1 (0.4–3.2)
		SR allergy to medication	1.7 (1.0–3.0)
		SR food allergy	2.1 (0.8–5.5)
		SR plant allergy	0.7 (0.3–1.8)
		SR animal allergy	1.2 (0.4–3.4)
La Vecchia et al. [132] (Italy)	Hospital-based (247/1,089)	SR drug allergy	0.94 (0.56–1.57)
Jain et al. [133] (Canada)	Population-based (249/505)	SR hay fever	0.47 (0.18–1.27)
		SR eczema	0.68 (0.30–1.51)
		SR asthma	0.52 (0.16–1.70)
		SR other allergies	1.26 (0.70–2.28)
Bueno de Mesquita et al. [134] (Netherlands)	Population-based (176 cases of exocrine cancer/487)	SR PT any allergy	0.57 (0.36–0.90)
		SR PT eczema	0.75 (0.42–1.32)
		SR PT other allergies	0.41 (0.21–0.82)
Kalapothiski et al. [135] (Greece)	Hospital-based (181/362)	SR allergic asthma	0.33 ($p = 0.28$)
		SR skin allergies	No association
Dai et al. [136] (China)	Population-based (108/275)	SR PD any allergic condition	0.7 (0.4–1.1)
		SR PD drug allergy	1.1 (0.5–2.4)
		SR PD food allergy	0.3 (0.0–2.6)
		SR PD contact dermatitis	0.5 (0.1–1.7)
		SR PD urticaria	0.5 (0.2–1.3)
		SR PD asthma	1.0 (0.3–3.2)
		SR PD allergic rhinitis	0.3 (0.1–1.4)
		SR moderate reaction to mosquito	0.7 (0.1–1.1) 1.0 (0.3–3.1)
		SR strong reaction to mosquito	
Silverman et al. [137] (USA)	Population-based (484/2,099)	SR PD any allergic condition	0.7 (0.5–0.9)
		SR PD hay fever	0.6 (0.5–0.9)
		SR PD asthma	1.0 (0.6–1.5)
		SR PD eczema	1.1 (0.7–1.9)
		SR PD animal allergy	0.5 (0.2–1.1)
		SR PD insect bite/sting allergy	0.8 (0.6–1.2)
		SR PD dust or mold allergy	0.6 (0.3–1.1)
		SR PD drug allergy	1.4 (1.1–1.9)
		SR PD household products allergy	1.5 (0.8–2.9)

Table 4.3 (continued)

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Holly et al. [138] (USA)	Population-based (532/1,701)	SR any allergy	0.77 (0.63–0.95)
		SR runny nose	0.84 (0.67–1.00)
		SR burning or watery eyes	0.80 (0.64–1.00)
		SR sneezing or congestion	0.75 (0.60–0.93)
		SR wheezing or asthma	0.53 (0.37–0.75)
		SR hives	0.92 (0.62–1.40)
		SR severe swelling	0.82 (0.54–1.20)
		SR anaphylactic shock	0.38 (0.11–1.30)
Lo et al. [24] (Egypt)	Hospital-based (194/194)	SR PD eczema	0.66 (0.46–0.93)
		SR allergy	0.8 (0.3–1.9)
Olson et al. [26] (USA)	Hospital-based (405/212)	SR any allergy	0.58 (0.40–0.84)
		SR hay fever	0.45 (0.29–0.70)
		SR medication	0.75 (0.46–1.19)
		SR animals	0.43 (0.23–0.80)
		SR any food	0.74 (0.39–1.40)
		SR dust	0.57 (0.29–1.12)
		SR mold	0.71 (0.31–1.65)
Eppel et al. [15] (Canada)	Population-based (276/378)	SR allergies/hay fever	0.43 (0.29–0.63)
		SR PD asthma	0.60 (0.31–1.16)

Eriksson et al. [16] extend cohort and follow-up from a previous publication [68]; standardized incidence ratios converted to base 100; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; IgE = immunoglobulin E; CPS-II = Cancer Prevention Study – II; PD = physician diagnosed; SR = self-reported; PT = physician treated; M = male; F = female; HB = hospital-based; PB = population-based; CI = confidence interval; odds ratio and 95% CI for Lin and Kessler [128] calculated. See text for description of the various indicators of relative risk reported in individual studies. Statistically significant relative risk estimates are indicated by boldface type.

Olson et al. [26] reported significant inverse associations between pancreatic cancer and a history of self-reported allergy (OR = 0.58, 95% CI 0.40–0.84), hay fever (OR = 0.45, 95% CI 0.29–0.70), and allergy to animals (OR = 0.43, 95% CI 0.23–0.80) in a US hospital-based case–control study. However, no exposure–response relationship was observed with increasing number of allergies reported. Olson et al. [26] also examined variants in IL-4 and IL-4R α genes with no overall association with pancreatic cancer reported. Eppel et al. [15] reported a significant 60% reduction in risk for pancreatic cancer associated with self-reported allergies or hay fever. The magnitude of the association was found to increase, however, with increasing age at onset. Lo et al. [24] reported no association between self-reported allergy and pancreatic cancer in a small hospital-based case–control study conducted in Egypt.

Among recent prospective studies, Turner et al. [70] reported a significant inverse association between a history of self-reported physician-diagnosed hay fever and pancreatic cancer mortality in the CPS-II cohort (HR = 0.85, 95% CI 0.77–0.95),

with a similar finding in never smokers ($HR = 0.86$, 95% CI 0.60–1.22). No association was found with asthma ($HR = 1.02$, 95% CI 0.85–1.23). Lindelof et al. [23] reported no association with total or allergen-specific IgE levels, although the precise SIR was not provided. An imprecise association among skin prick tested patients was reported by Eriksson et al. [16] with only two incident cases of pancreatic cancer observed. Hagstromer et al. [20] reported an excess of pancreatic cancer cases among patients discharged from hospital with atopic dermatitis.

4.3.4 Tumors of the Brain and Nervous System

A meta-analysis combining results from previous studies published up to the beginning of the year 2007, including 3,450 glioma patients and 1,070 meningioma patients, reported significant inverse associations between a history of allergy ($RR = 0.61$, 95% CI 0.55–0.67), asthma ($RR = 0.68$, 95% CI 0.58–0.80), eczema ($RR = 0.69$, 95% CI 0.5–0.82), and glioma [5]. No overall association was observed between allergy and meningioma ($RR = 0.93$, 95% CI 0.72–1.19). See Table 4.4 for a summary of previous studies. A subsequent case-control study combining data from five INTERPHONE study countries (UK and the Nordic countries) examined the relation between self-reported allergic status and glioma and meningioma [40]. Significant inverse associations were reported between a history of physician-diagnosed asthma, hay fever, eczema, and glioma of approximately 35%. Although, little change was observed with increasing duration of asthma, or age at onset, there was a significant trend with increasing number of allergies. Little change was observed with the exclusion of proxy respondents (a closest relative) where the case had died. A significant inverse association was observed between self-reported physician-diagnosed eczema and meningioma ($OR = 0.74$, 95% CI 0.60–0.91) but not asthma or hay fever. The inverse association was found to remain, however, only for current ($OR = 0.61$, 95% CI 0.47–0.79) as opposed to past ($OR = 1.05$, 95% CI 0.78–1.43) eczema.

In follow-up to epidemiological studies examining the potential relation between self-reported allergic status and glioma, recently, there have been some studies examining potential biological indicators of allergic status or polymorphisms in selected allergy-related genes. In 2004, significant inverse associations were reported by Wiemels et al. [83] between elevated total ($OR = 0.37$, 95% CI 0.22–0.64) and food-specific IgE ($OR = 0.12$, 95% CI 0.04–0.41) and glioma. The OR for respiratory-specific IgE was 0.76 (95% CI 0.52–1.10). IgE levels, however, were not found to be strongly related with allergic status based on self-report. In 2005, Schwartzbaum et al. [49] reported associations between IL-4RA and IL-13 polymorphisms and glioblastoma risk in Sweden. A subsequent follow-up study using data from the United Kingdom, Denmark, and Finland, however, failed to confirm these findings [36]. Wiemels et al. [39], in a California study, provided some evidence for a role of IL-4, IL-4R, and IL-13 polymorphisms in glioma risk. Finally, Brenner et al. [11], pooling data from two US studies, reported associations between IL-4 and IL-6 polymorphisms and risk of glioma.

Table 4.4 Previous studies evaluating the association between a history of allergy and glioma, meningioma, or acoustic neuroma

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)		
GLIOMA					
Cohort Studies					
Schwartzbaum et al. [139] (Sweden)	14,535 (C1) and 29,573 (C2) in Swedish Twin Registry (37 and 42 incident gliomas)	SR hay fever (C1)	0.74 (0.26–2.08)		
		SR eczema (C1)	0.52 (0.19–1.48)		
		SR allergic conditions (C1)	0.45 (0.19–1.07)		
		SR allergic conditions (C2)	1.09 (0.48–2.48)		
Case–Control Studies					
Hochberg et al. [140] (USA)	Hospital-based (160 glioblastoma cases/128)	SR PT allergies	0.6 (0.4–1.0)		
Schlehofer et al. [141] (International)	Population-based (1,178/1,987)	SR PD allergy	0.59 (0.49–0.71)		
		SR PD asthma	0.75 (0.55–1.03)		
		SR PD eczema	0.64 (0.47–0.86)		
		SR PD other allergies	0.59 (0.48–0.73)		
Brenner et al. [84] (USA)	Hospital-based (489/799)	SR any allergy	0.67 (0.52–0.86)		
		SR PD asthma	0.63 (0.43–0.92)		
		SR PD eczema	0.76 (0.45–1.27)		
		SR PD hay fever	0.97 (0.69–1.37)		
		SR allergy to medicine	0.79 (0.49–1.27)		
		SR allergy to insects	0.61 (0.36–1.05)		
		SR allergy to food	0.66 (0.25–1.74)		
		SR chemical allergy	0.23 (0.07–0.79)		
		SR other allergy	0.79 (0.32–1.96)		
		Wiemels et al. [83, 142] (USA)	Population-based (405/402)	SR any allergy	0.47 (0.33–0.67)
				SR runny nose	0.66 (0.49–0.88)
				SR watery eyes	0.66 (0.49–0.88)
SR sneezing	0.60 (0.45–0.80)				
SR wheezing	0.57 (0.38–0.86)				
SR rash/hives	0.85 (0.64–1.12)				
SR swelling	0.61 (0.45–0.83)				
SR anaphylactic shock	0.24 (0.08–0.73)				
Elevated total IgE	0.37 (0.22–0.64)				
Elevated respiratory IgE	0.76 (0.52–1.10)				
Elevated food IgE	0.12 (0.04–0.41)				
Schwartzbaum et al. [49] (Sweden)	Population-based (111/422)			SR PD asthma	0.64 (0.33–1.25)
		SR PD hay fever	0.98 (0.62–1.57)		
		SR PD eczema	0.67 (0.43–1.05)		
		SR PD contact allergy	1.02 (0.53–2.00)		
		SR PD food allergy	1.23 (0.61–2.49)		
Schoemaker et al. [33] (SE/N UK)	Population-based INTERPHONE study (965/1,716)	SR PD asthma	0.71 (0.54–0.92)		
		SR PD hay fever	0.73 (0.59–0.90)		
		SR PD eczema	0.74 (0.56–0.97)		
		SR PD any allergy	0.63 (0.53–0.76)		
Wigertz et al. [40] (SE UK and Nordic)	Population-based INTERPHONE study (1,527/3,309)	SR PD asthma	0.65 (0.51–0.82)		
		SR PD hay fever	0.66 (0.56–0.78)		
		SR PD eczema	0.65 (0.54–0.79)		
		SR PD any allergy	0.70 (0.61–0.80)		

Table 4.4 (continued)

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Harding et al. [21] (UK)	Population-based, <i>children</i> (326/6,292)	PR asthma PR eczema PR early-onset flexural rash PR asthma and eczema	0.90 (0.66–1.23) 0.89 (0.65–1.21) 1.17 (0.77–1.79) 0.55 (0.28–1.06)
MENINGIOMA			
Cohort Studies			
Schwartzbaum et al. [139] (Sweden)	14,535 (C1) and 29,573 (C2) in Swedish Twin Registry (41 and 42 incident meningiomas)	SR hay fever (C1) SR eczema (C1) SR allergic conditions (C1) SR allergic conditions (C2)	0.85 (0.33–2.17) 0.72 (0.30–1.70) 0.84 (0.42–1.68) 2.44 (1.08–5.51)
Case–Control Studies			
Schlehofer et al. [141] (International)	Population-based (331/1,123)	SR PD allergy SR PD asthma SR PD eczema SR PD other allergies	0.89 (0.65–1.22) 0.82 (0.46–1.44) 0.68 (0.42–1.08) 0.97 (0.67–1.41)
Brenner et al. [84] (USA)	Hospital-based (197/799)	SR any allergy SR PD asthma SR PD eczema SR PD hay fever SR allergy to medicine SR allergy to insects SR allergy to food SR chemical allergy SR other allergy	0.98 (0.70–1.38) 0.86 (0.53–1.40) 0.80 (0.42–1.53) 0.93 (0.58–1.50) 0.76 (0.40–1.46) 1.32 (0.72–2.43) 1.18 (0.40–3.48) 0.26 (0.06–1.16) 1.19 (0.41–3.42)
Schneider et al. [32] (Germany)	Population-based (118/7,466)	SR asthma	No association
Schoemaker et al. [35] (UK)	Population-based INTERPHONE study (475/1,716)	SR PD asthma SR PD hay fever SR PD eczema SR PD any allergy	0.85 (0.61–1.18) 0.81 (0.62–1.06) 0.72 (0.51–1.02) 0.76 (0.61–0.96)
Wigertz et al. [40] (SE UK and Nordic) ACOUSTIC NEUROMA	Population-based INTERPHONE study (1,120/3,309)	SR PD asthma SR PD hay fever SR PD eczema SR PD any allergy	0.94 (0.74–1.20) 0.93 (0.77–1.12) 0.74 (0.60–0.91) 0.95 (0.82–1.10)
Case–Control Studies			
Brenner et al. [84] (USA)	Hospital-based (96/799)	SR any allergy SR PD asthma SR PD eczema SR PD hay fever SR allergy to medicine SR allergy to insects SR allergy to food SR chemical allergy SR other allergy	1.02 (0.64–1.63) 1.34 (0.73–2.46) 0.92 (0.34–2.48) 2.36 (1.38–4.03) 0.53 (0.20–1.42) 1.12 (0.49–2.54) 3.01 (1.06–8.53) 0.79 (0.22–2.84) 3.81 (1.45–9.99)

Table 4.4 (continued)

References (country)	Population (number of cases or cases/controls)	Allergy indicator	Relative risk (95% CI)
Schoemaker et al. [34] (UK and Nordic)	Population-based INTERPHONE study (563/2,703)	SR PD asthma	1.1 (0.8–1.5)
		SR PD hay fever	0.9 (0.7–1.1)
		R PD Eczema	1.0 (0.8–1.3)
		SR PD any allergy	0.9 (0.8–1.1)
Schlehofer et al. [31] (Germany)	Population-based INTERPHONE study (97/194)	SR PD asthma	1.06 (0.40–2.82)
		SR PD hay fever	2.20 (1.09–4.45)
		SR PD eczema	1.11 (0.51–2.38)

Studies by Ryan et al. [143], Schlehofer et al. [144], and Cicuttini et al. [145] present preliminary findings from the international study of Schlehofer et al. [141] and are not presented here; results of studies examining allergy-related gene polymorphisms not presented here, but described in text [11, 36, 39, 49]; PD = physician diagnosed; SR = self-reported; PT = physician treated; PR = parental reported; C1 = cohort 1; C2 = cohort 2; IgE = immunoglobulin E; CI = confidence interval. See text for description of the various indicators of relative risk reported in individual studies. Statistically significant relative risk estimates are indicated by boldface type.

Recent cohort studies examining broader outcome categories have reported no clear findings. Two previous record linkage studies were conducted in Sweden with that of Kallen et al. [66] reporting an inverse association for incident tumors of the “eye and nervous system” among asthmatics (SIR = 75, 95% CI 64–88) while that of Hagstromer et al. [20] reported a positive association for incident brain tumors among men (SIR = 150, 95% CI 70–270) and women (SIR = 170, 95% CI 100–280) with atopic dermatitis. No association was observed between atopy defined by skin prick testing and incident brain tumors by Eriksson et al. [16], although the number of brain cancer cases observed was small. No association between a history of self-reported physician-diagnosed asthma or hay fever and brain cancer mortality was reported in the CPS-II cohort (HRs ranging from 0.96 to 0.97 overall) [70].

Three studies have examined the relation between allergic status and acoustic neuroma. Significant positive associations were noted by Brenner et al. [84] for self-reported physician-diagnosed hay fever (OR = 2.36, 95% CI 1.38–4.03), and self-reported allergy to food (OR = 3.01, 95% CI 1.06–8.53), or other substances (OR = 3.81, 95% CI 1.45–9.99). Schlehofer et al. [31] also reported a significant positive association between self-reported physician-diagnosed hay fever and acoustic neuroma (OR = 2.20, 95% CI 1.09–4.45) but not with asthma or eczema in the German arm of the INTERPHONE study. Findings from the UK and Nordic INTERPHONE case–control studies combined revealed no association between acoustic neuroma and any previous diagnosis of allergic disease (asthma, hay fever, eczema) nor with increasing duration or increasing number of allergic conditions ($p = 0.6$) [34].

There have also been four case–control studies in children. An early case–control study reported an inverse relation between asthma or allergy and childhood brain tumors [85]. In 2001, a population-based case–control study suggested an inverse

relation between a history of allergy and neuroblastoma in children less than 8 years of age (OR = 0.20, 95% CI 0.06–0.65), although there were only three cases with allergy [48]. A subsequent case–control study of neuroblastoma in patients under the age of 19 years conducted by the Children’s Oncology Group reported inverse associations between neuroblastoma and asthma, hay fever, and eczema ranging in magnitude from approximately 20–60% [45]. Finally, a UK study examining risk factors for childhood (less than 15 years of age) central nervous system (CNS) tumors reported a significant inverse association between parental-reported asthma and all CNS tumors (OR = 0.75, 95% CI 0.58–0.97) but no association with eczema [21]. Some inverse, non-significant, associations were reported for glioma and a significant inverse association reported between asthma and PNET/medulloblastoma of nearly 60%. Interestingly, when using physician notes to ascertain asthma status (as opposed to parental report) for a small subset of participants, no association with CNS tumors was observed (OR = 1.20, 95% CI 0.74–1.94).

4.3.5 Colorectal Cancer

A large hospital-based case–control study reported significant inverse associations between self-reported physician-diagnosed allergy and colon (OR = 0.76, 95% CI 0.59–0.97) and rectal (OR = 0.54, 95% CI 0.37–0.77) cancer [86]. Lower ORs were observed, however, with an age of diagnosis of at least 30 years (OR colon cancer = 0.71, 95% CI 0.52–0.96; OR rectal cancer = 0.42, 95% CI 0.26–0.68). Upon stratification by gender, the inverse association between allergy and colon cancer remained for males only (OR = 0.57, 95% CI 0.39–0.85). The remaining case–control studies report no significant findings [65, 87], although some inverse relations were noted [88–90]. Recently, Gonzalez-Perez et al. [18] reported an OR of 0.86 (95% CI 0.70–1.06) for colorectal cancer associated with asthma in a nested case–control study in the United Kingdom. However, in a nested case–control study in Germany, no association between allergen-specific IgE positivity and colorectal cancer (OR = 1.03, 95% CI 0.80–1.34) was observed [38].

In cohort studies, Talbot-Smith et al. [73] recently reported some imprecise inverse associations between a history of self-reported physician-diagnosed asthma or hay fever and colorectal cancer occurrence. For atopy, as defined by skin prick testing, ORs of 0.32 (95% CI 0.03–2.84) and 1.42 (95% CI 0.41–4.95) were reported for males and females, respectively. An analysis of 21,292 participants followed prospectively in the Iowa Women’s Health Study reported a significant 26% reduction in risk of colorectal cancer associated with self-reported physician-diagnosed allergy [29]. Similar findings were reported with examination of colon and rectal cancer separately (ORs = 0.77, 95% CI 0.60–0.99 and 0.63, 95% CI 0.36–1.12, respectively) and in never smokers (OR = 0.74, 95% CI 0.56–0.98). A significant exposure–response association was also observed with increasing number of allergies. In an analysis of the CPS-II cohort, a significant inverse association was observed between a history of both self-reported physician-diagnosed asthma and

hay fever and colorectal cancer mortality overall (HR = 0.76, 95% CI 0.64–0.91) [70]. The inverse association persisted, although was no longer significant, among never smokers (HR = 0.78, 95% CI 0.60–1.02).

The remaining cohort studies evaluated colon and rectal cancer separately with no clear findings [16, 20, 66–69]. Although a significant inverse association was reported by Kallen et al. [66] for both colon (SIR = 72, 95% CI 65–79) and rectal cancer (SIR = 59, 95% CI 52–68) in asthmatics, Vesterinen et al. [67] reported a significant positive association for rectal cancer among women with asthma (SIR = 142, 95% CI 117–169). Finally, imprecise inverse associations of approximately 30% were observed for colon cancer occurrence in studies by Hagstromer et al. [20] and Eriksson et al. [16], with no association reported for rectal cancer.

4.3.6 Reproductive Cancers

It is difficult to draw any conclusions regarding the potential association between a history of allergy and reproductive cancers with few significant and largely inconsistent findings. Several of the large cohort studies described above have evaluated cancer outcomes at multiple sites. In the study of Seventh-Day Adventists, Mills et al. [69] reported a significant inverse relation between an allergic reaction to poisonous plants requiring treatment by a physician and ovarian cancer (RR = 0.13, 95% CI 0.02–0.95). A significant trend was also observed with risk of ovarian cancer decreasing with increasing number of allergies reported. No other significant associations were found between any other allergy measure in this study and any of ovarian, uterine, cervical, breast, or prostate cancer, although there were some positive, non-significant associations observed. In the Swedish record linkage study of asthmatics by Kallen et al. [66], significant inverse associations were reported for ovarian cancer (SIR 52, 95% CI 42–63), cancer of the corpus uterus (SIR = 36, 95% CI 28–46) and uterus, not otherwise specified (NOS) (SIR = 58, 95% CI 32–104), as well as for cervical (SIR = 52, 95% CI 39–69), breast (SIR = 53, 95% CI 47–58), prostate (SIR = 72, 95% CI 67–78), and testicular cancer (SIR = 37, 95% CI 16–85). In contrast, the Finnish record linkage study by Vesterinen et al. [67] reported no significant findings with the exception of an inverse relation reported between asthma and cancer of the corpus uterus (SIR = 76, 95% CI 61–92). In an extended follow-up of a cohort of skin prick tested patients in Sweden, Eriksson et al. [16] reported no clear findings. Although in a previous analysis, an SIR of 250 (95% CI 101–516) was reported for breast cancer among atopic subjects [68], in the extended analysis, no association was found (SIR = 106, 95% CI 65–162) [16]. In an evaluation of the association between both self-reported physician-diagnosed allergy and atopy as defined by skin prick testing in the 1981 Busselton cohort, Talbot-Smith et al. [73] reported no association between asthma or hay fever and breast or prostate cancer, although there was a significant positive relation observed for prostate cancer in those with allergy to house dust mites (HR = 2.90, 95% CI

1.26–6.68). A recent Danish record linkage study following 2,030 adults hospitalized for atopic dermatitis tended to report an excess of male (SIR = 230, 95% CI 80–500) and female (SIR = 220, 95% CI 100–400) genital cancers, although the number of incident cancers was small [25]. No clear relation was reported for breast cancer. In a Swedish study of patients discharged with atopic dermatitis, no association was reported with endometrial, cervical, breast, or prostate cancer, although again the number of new cancer cases was also small [20]. Lindelof et al. [23] reported no association between total or allergen-specific IgE levels and cervical cancer occurrence. In two small, cancer site-specific prospective studies, significant positive associations were observed between non-atopic eczema and cervical cancer (OR = 3.27, 95% CI 1.95–5.49) [91] as well as asthma and prostate cancer (RR = 22.8, 95% CI 5.48–94.7) [92]. Finally, in an analysis of the CPS-II cohort, some inverse, although non-significant, findings were reported between a history of self-reported physician-diagnosed asthma and ovarian cancer mortality (HR = 0.79, 95% CI 0.56–1.11) as well as a history of both asthma and hay fever and uterine (HR = 0.59, 95% CI 0.33–1.05) and breast cancer mortality (HR = 0.86, 95% CI 0.71–1.05), with no clear relation reported between any indicator of allergic status and prostate cancer mortality [70].

Case-control studies also reported few significant findings. Vena et al. [65] reported a significant inverse relation between a history of self-reported physician-diagnosed hives and cervical (OR = 0.73), breast (OR = 0.75), and cancer of the corpus uterus (OR = 0.63) but no relation with other specific allergic disorders. A hospital-based case-control study reported significant positive relations between a history of atopy (OR = 1.8, 95% CI 1.1–3.1) and hay fever (OR = 2.6, 95% CI 1.2–5.6) and testicular cancer [93]. No relation was reported between a history of self-reported physician-diagnosed allergy and breast or prostate cancer in a case-control study nested in the first NHANES cohort [94]. Among more recent studies, Hedderston et al. [95] reported an OR of 0.77 (95% CI 0.60–0.99) for breast cancer among women aged older than 35 years with a history of self-reported physician-diagnosed allergies. Although no association was observed among women diagnosed with breast cancer less than 35 years of age (OR = 1.30, 95% CI 0.94–1.81), it was suggested that this finding may be due to the strong genetic aspect of the disease among younger women. A positive association was reported between allergen-specific IgE and breast cancer by Petridou et al. [28] (OR = 1.73, 95% CI 0.95–3.14) with no clear relation reported in the nested case-control study by Wang et al. [38]. Wang et al. [38] also reported a positive relation between allergen-specific IgE positivity and prostate cancer (OR = 1.35, 95% CI 1.00–1.83) with no clear relation observed for several self-reported physician-diagnosed allergic diseases. Recently, a population-based case-control study in Ontario, Canada, reported an inverse association between a history of self-reported physician-diagnosed allergies and prostate cancer (OR = 0.78, 95% CI 0.60–1.00) [44]. A UK-based nested case-control study reported some inverse, non-significant, findings between a history of asthma and breast (OR = 0.91, 95% CI 0.78–1.06) and prostate cancer (OR = 0.86, 95% CI 0.69–1.07) occurrence [18].

4.3.7 Other Cancer Sites

Few other specific cancer sites have received much study. Some inverse relations were reported between a history of allergies and esophageal cancer [63, 96]. More recently, an OR of 0.86 (95% CI 0.65–1.12) for gastro-esophageal cancer was reported in a nested case–control study of asthmatics in the United Kingdom [18]. Bosetti et al. [86] reported a non-significant inverse association between a history of self-reported physician-diagnosed allergy and esophageal cancer in an Italian case–control study (OR = 0.80, 95% CI 0.46–1.39). Although a Swedish record linkage study reported a greater than threefold increase in risk for esophageal cancer among those discharged from hospital with atopic dermatitis, this finding was based on only six incident cases and confounding by cigarette smoking and other factors could not be ruled out [20]. Conflicting results were reported in remaining cohort studies [66, 97].

No clear relation was reported between a history of allergy and stomach cancer in several prospective studies with few cases [16, 20, 68, 69] and in a prior hospital-based case–control study [65]. Although Ye et al. [97] reported an excess of gastric cardia adenocarcinomas among asthma patients (SIR = 140, 95% CI 100–190), Vesterinen et al. [67] reported an SIR of 85 (95% CI 71–100) for stomach cancer in men and 91 (95% CI 77–107) in women with asthma, and Kallen et al. [66] reported a 50% reduction in risk for stomach cancer in asthmatics. Although an inverse association was observed between a history of self-reported physician-diagnosed asthma and stomach cancer in the CPS-II cohort overall (HR = 0.72, 95% CI 0.51–1.01), it was not found to persist among never smokers (HR = 0.95, 95% CI 0.55–1.65) [70].

Several significant positive relations were observed between a history of asthma or allergy and bladder cancer. Urothelial cancer was positively associated with a history of allergic asthma (OR = 3.1, 95% CI 1.4–6.8) but not allergic dermatitis (OR = 0.8, 95% CI 0.4–1.6) or allergic rhinitis (OR = 0.9, 95% CI 0.5–1.6) in a Swedish case–control study [98]. Kim et al. [99] reported an OR of 4.15 (95% CI 1.61–10.75) for the relation between asthma and bladder cancer with risk increasing severalfold in those with glutathione *S*-transferase- μ (GSTM1) and glutathione *S*-transferase- θ (GSTT1) null genotypes in a hospital-based case–control study. Imprecise relations were reported in previous prospective studies [16, 68, 69], although an excess of male bladder cancer cases was reported in Finnish asthma patients (SIR = 125, 95% CI 100–150) [67].

A case–control study nested in the Finnish Adult Twin Cohort Study reported some imprecise positive associations between a history of atopic eczema (OR males = 1.10, 95% CI 0.47–2.59; OR females = 1.80, 95% CI 0.83–3.90) and urticaria (OR males = 3.00, 95% CI 0.31–28.8; OR females = 2.00, 95% CI 0.68–5.85) and basal cell carcinoma among 333 twin pairs discordant for the disease [46]. In a hospital-based case–control study in Italy, with 528 cases and 512 controls hospitalized for unrelated acute conditions, a significant inverse association was reported between self-reported physician-diagnosed asthma and basal cell carcinoma (OR = 0.45, 95% CI 0.24–0.82) [27]. Ming et al. [47] observed an inverse association between the UK Working Party diagnostic criteria for atopic dermatitis

(OR = 0.78, 95% CI 0.61–0.98) and nonmelanoma skin cancer, although ORs for self-reported history of dermatitis, atopic dermatitis, and eczema were 1.00 (95% CI 0.80–1.26), 0.92 (95% CI 0.68–1.26), and 0.85 (95% CI 0.67–1.08), respectively. No relation between allergy and malignant melanoma was reported in two early hospital-based case–control studies [65, 100].

Although no clear association between hospitalization for atopic dermatitis and melanoma (SIR = 60; 95% CI 30–120) or nonmelanoma (SIR = 150, 95% CI 80–260) skin cancer was reported by Hagstromer et al. [20] and Olesen et al. [25] reported a significant excess of keratinocyte carcinomas (SIR = 240, 95% CI 140–390) among hospitalized atopic dermatitis patients in Denmark, although the positive relation was observed only among those diagnosed in either the first four (SIR = 250, 95% CI 90–550) or five to nine (SIR = 380, 95% CI 160–740) years of follow-up and not those diagnosed with at least 10 years of follow-up (SIR = 90, 95% CI 10–340), suggesting that at least part of the observed association may be due to a potential detection bias. A US cohort study based on the Medicaid database reported a significant relation between a history of severe eczema and nonmelanoma skin cancer (RR = 2.14, 95% CI 1.50–3.05) [101]. No association between total or allergen-specific IgE levels and nonmelanoma skin cancer was reported by Lindelof et al. [23], although details regarding the precise nature of the association were not provided. Finally, no clear association between atopy defined through skin prick testing and melanoma was reported in two other recent prospective studies [16, 73].

An international case–control study reported an OR of 2.19 (95% CI 1.01–4.74) for the relation between a history of allergies and medullary thyroid carcinoma [102], although the authors suggested that reverse causality may be responsible for the association observed.

Finally, a small case–control study examining risk factors for juvenile bone tumors reported inverse associations with skin allergy (unadjusted OR = 0.76, 95% CI 0.37–1.55) and asthma/bronchitis (OR = 0.61, 95% CI 0.29–1.28) but not hay fever (OR = 1.49, 95% CI 0.65–3.43) [43]. This study examined incident and prevalent cases combined and recruited controls from the hospital, neighborhood, and family members.

4.4 Discussion

This chapter has summarized the epidemiological literature examining the potential relation between allergy and cancer, focusing on solid tumors. Although there are a number of inverse relations reported, particularly with pancreatic cancer and glioma, there remain a number of methodological considerations. Previous studies were largely based on self-reported allergy history. Although little is known regarding the reporting of allergic disorders throughout the life course, questionnaires ascertaining previous physician-diagnosed allergies may be preferred [1]. Recently, there have also been a number of studies that have attempted to improve on the predominance of self-reported exposure assessment in prior research by assessing biological indicators of allergic status including total or allergen-specific IgE antibodies, skin prick

tested patients, or allergy-related gene polymorphisms described above. Although it is unclear to what extent results of previous case-control studies examining current levels of IgE may be affected by either the developing tumor or its treatment, case-control studies examining allergy-related gene polymorphisms do not suffer the same potential limitation [49]. Although several associations have been observed between specific polymorphisms and glioma risk, additional research is needed to further clarify these findings [49]. Although there were some recent prospective studies following cohorts of either skin prick tested patients [16, 68, 73] or patients with data on total and allergen-specific IgE levels [23], few relations were observed, and there were small numbers of cancer cases. There are also several early studies (not described here) examining such indicators in cases and controls with no clear findings [52, 103–108].

Another key consideration relates to the timing of allergy diagnosis. As noted above, in the cohort study of patients hospitalized for atopic dermatitis by Olesen et al. [25], an excess of incident keratinocyte carcinomas was observed among patients diagnosed with cancer in the first several years of follow-up only, suggesting that a detection bias may have influenced study findings, whereby there may be enhanced monitoring of skin disorders among such patients. It is also possible that reverse causality may explain some positive associations between allergy and cancer, whereby the allergic symptoms or conditions reported may simply be a manifest of the developing cancer [102]. Indeed, in several studies, the positive association between asthma and lung cancer was found to weaken or disappear upon exclusion of those with a recent diagnosis [18, 66, 72, 81]. There were also some inverse relations at other cancer sites that were found to strengthen with increasing age at allergy diagnosis, possibly suggesting some non-atopic factor may be at play [1, 15, 86].

Similar to prior research, there are several recent studies that have reported significant trends with the strength of the inverse relation increasing with number of allergies reported [29, 40]. Although it is possible that this finding may be due to improvements in exposure ascertainment, whereby participants with multiple allergic disorders are more likely to truly be allergic, the possibility of some form of reporting bias remains.

There may also be a screening bias in studies of cancer mortality whereby, due to frequent contact with the medical profession, allergy patients may be diagnosed earlier, thereby improving cancer survival [70]. Some studies have also examined the possibility for differential cancer survival due to the presence or absence of asthma with mixed findings [109–112]. Recently, two studies have reported improved prognosis among those with allergic disorders [113], although subject selection is uncertain, as well as improved glioma survival associated with elevated IgE levels [114].

Confounding may also represent an important issue in such studies. Indeed, a variety of factors, including cigarette smoking and socio-economic status in particular, have been widely associated with both allergic status and cancer occurrence [1]. Although several large record linkage studies have been conducted, primarily in the Nordic countries, the strength of the evidence from such studies remains

limited due to the absence of data on such potentially confounding factors. Patients hospitalized for such disorders, and other clinic-based studies, may also represent a selected subsample of all allergy sufferers. Although studies with detailed data on sociodemographic and lifestyle variables, and studies in never smokers, particularly for smoking-related cancers, are preferred, residual confounding remains a possibility. In our analysis of the CPS-II cohort, there were differences in these and other variables, including diet, multivitamin use, and use of oral contraceptives or estrogen replacement therapy, among those with and without a self-report of physician-diagnosed asthma or hay fever [70]. Bellia et al., [10] in a prospective study of elderly asthmatics, recently, reported a clustering of mortality risk factors among asthmatics.

4.5 Conclusion

In conclusion, although there are a number of important methodological considerations, there remain a number of high-quality epidemiological studies that have pointed to a possible role of allergy in the occurrence of cancer, with potential implications for cancer treatment and prevention. Further research is recommended in order to better understand the nature of a possible inverse relation, and mechanisms of action, including further prospective studies using biological indicators of allergic status, studies validating allergic status based on self-report, and further examination of potential roles for IgE and Th2 cytokines in cancer treatment and prevention [1, 5, 7, 49]. Multidisciplinary collaborations between the population and the laboratory-based sciences would be particularly useful.

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