

An overview of the association between allergy and cancer

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Numerous epidemiological studies have evaluated some aspect of the association between a history of allergy and cancer occurrence. In this article, an overview of the epidemiological evidence is presented with a discussion of a number of methodological issues important in this area of study. Literature searches were conducted using the MEDLINE database from 1966 through to August 2005 to identify articles that explored a personal history of allergic disorders as a risk factor for cancer. Although it is difficult to draw conclusions between allergy and cancer at many sites because of insufficient evidence or a lack of consistency both within and among studies completed to date, strong inverse associations have been reported for pancreatic cancer and glioma, whereas lung cancer was positively associated with asthma. Additional studies are needed to confirm these findings and to address the limitations of previous studies, including the validity and reliability of exposure measures and control for confounding. Further, large prospective studies using cancer incidence would be particularly useful, including studies using biological markers of allergic status to reduce potential misclassification and to confirm the results of previous studies based on self-report. There is also a need for further basic research to clarify a potential mechanism, should an association exist.

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Cancer is a major threat to population health and is currently the second leading cause of death in Canada and the United States.^{1,2} Cancer researchers have attempted to describe a role for various biological, lifestyle, and environmental factors in cancer development, including a potentially important role for the immune system.^{3–5} The concept of immune surveillance, first proposed almost a century ago,^{6,7} suggests that the immune system is continuously searching for and destroying tumor cells as they arise. Although historically controversial, recent scientific advancements have led to renewed interest in the immune surveillance theory.^{3,7–9}

It has been suggested that those with a history of allergy, in particular atopic disorders, may possess an enhanced capacity for immune surveillance.^{10–13} Although it has been commonly assumed that the atopic immune response offers little benefit to individuals, recently, it has been argued that it may offer a valuable evolutionary advantage.^{14,15} This immune response may also be related to cancer development.

Numerous epidemiological studies have evaluated some aspect of the association between a history of allergy and cancer occurrence. In this article, we provide an overview of the epidemiological evidence and discuss a number of methodological issues important in this area of study. A critical assessment of the literature in this area is important to clarify previous conflicting reports and to determine future research directions.

Methods

Literature searches were conducted using the MEDLINE database from 1966 through August 2005, using standard search procedures.^{16–19} Articles that explored a personal history of allergic disorders as a risk factor for cancer were sought. The following MeSH headings and key words were used: allerg\$, atop\$, hypersensitivity, asthma, hay fever, rhinitis, eczema, dermatitis, hives, skin test\$, cancer, tumor, tumour, malignancy, neoplasm, leukemia, leukaemia, lymphoma, myeloma, hodgkin, and glioma.

Study selection was restricted to human and papers written in English. Case reports and descriptive studies were excluded. Additional studies were identified through hand searching reference lists. For multiple publications, only the most relevant article was included. The studies were categorized by cancer site and study design, and the overall and subgroup results were examined while taking into account possible study limitations, including sample size, exposure measurement, confounding, and other methodological issues. Relative risks were rounded to one decimal place, and all standardized mortality ratios (SMR) and standardized incidence ratios (SIR) were converted to base one hundred for consistency.

A total of 148 epidemiological studies were identified that evaluated some aspect of the association between a history of allergy and cancer occurrence. The studies took place largely throughout North and South Americas, Asia, and Europe. This overview provides a brief historical perspective and a detailed discussion of the most relevant epidemiological studies published by cancer site.

All cancers

A number of early case-control studies reported an inverse association between allergy and cancer all sites combined.^{20–27} These early studies were hospital-based, and many of which involved small sample sizes^{20,21,24} and little control for potential confounders.^{20–27} The results from early cohort studies were not consistent and also involve small numbers of cancer cases and have little or no control for possible confounders.^{12,28–32}

Several large cohort studies have recently examined this association. Results from large record linkage studies of asthmatics have reported conflicting results. In Sweden, a record linkage study of 64,346 people treated in hospital for asthma found a significant inverse association for all cancer mortality (standardized mortality ratio (SMR) = 66, 95% confidence interval (CI) = 64–68) and for site-specific cancer mortality.³³ Another study linking 77,952 people on the Finnish Social Insurance Institution Register who had received reimbursement for asthma medication with the Finnish Cancer Registry reported a significant positive association for all cancer in men (standardized incidence ratio (SIR) = 112, 95% CI = 107–117) but not women (SIR = 103, 95% CI = 98–107).³⁴ Both of these large record linkage studies were unable to control for individual level covariates in analysis. We recently analyzed data from the American Cancer Society (ACS) prospective cohort of nearly 1.2 million participants.³⁵ A significant inverse association was reported for all cancer mortality in participants who reported a history of both asthma and hay fever (relative risk (RR) = 0.9, 95% CI = 0.8–0.9). The estimate attenuated slightly upon restriction to never smokers (RR = 0.9, 95% CI = 0.8–1.00). The remaining out of all cohort studies revealed few significant findings,^{36–40} including 3 studies using skin prick testing as an indicator of allergic status.^{11,41,42} Overall, the studies conducted to date provide little clear evidence that allergies are associated with cancer overall.

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Lung cancer

Several case-control studies that did not control for smoking found significant inverse associations between lung cancer and a history of allergies, atopy, or asthma.^{43–47} Since smoking is a major risk factor for lung cancer, adequate control for smoking is critical. Recently, a meta-analysis estimated a combined odds ratio (OR) of 1.8 (95% CI = 1.3–2.3) from previous case-control studies that evaluated lung cancer risk in never smokers with asthma versus those without asthma.⁴⁸ A RR of 1.7 (95% CI = 1.3–2.2) was found when combining the results for all case-control and cohort studies that controlled for smoking history in the analysis. It was concluded that asthmatics are at increased risk of lung cancer; however, potential misclassification and differential recall bias in previous studies are still of concern. The potential positive association between asthma and lung cancer may be due to various mechanisms, including: (i) elevated levels of free radicals and reduced levels of antioxidants in the respiratory tract,^{49,50} (ii) continual stimulation of cell regeneration to repair inflammatory lung damage,^{49,51} and/or (iii) an increased sensitivity to carcinogens.³⁴

Pancreatic cancer

Population-based case-control studies and cohort studies have generally reported no association between a history of asthma and pancreatic cancer.^{10,34,52–54} Previous studies that evaluated hay fever in relation to pancreatic cancer risk all reported an inverse association with point estimates ranging from 20–70% reductions in risk with some findings significant.^{10,53–55} Recently, a meta-analysis reported a significant inverse association between a history of any allergy (RR = 0.8, 95% CI = 0.7–0.99), respiratory allergy (RR = 0.6, 95% CI = 0.5–0.8), and atopy (RR = 0.71, 95% CI = 0.6–0.8) and pancreatic cancer risk.⁵⁶ No association was found with a history of asthma. The most recent case-control study, which did not use any proxy data, reported numerous inverse associations for pancreatic cancer in relation to various allergies, allergic conditions, and symptoms.⁵⁷ A significant exposure-response relationship was also found with risk decreasing with increasing number of allergies and severity of symptoms. In our recent analysis, we also recently reported a significant inverse association for pancreatic cancer mortality in the overall ACS cohort among participants with a history of hay fever (RR = 0.85, 95% CI = 0.77–0.95) but not asthma.³⁵ Similar results were found among never smokers (RR hay fever = 0.84, 95% CI = 0.71–1.0).

Neoplasms of lymphatic and hematopoietic tissue

Non-Hodgkin's lymphoma (NHL). Although case-control studies have generally reported inverse associations of NHL with a history of asthma or hay fever, conflicting results for other indicators of allergic status (specific allergies or eczema) have been reported^{58–69} and few prospective studies exist. Unstable risk estimates were reported in 3 prospective studies with few cases.^{11,12,39} Of the remaining cohort studies, one large record linkage study reported a decreased risk of fatal NHL in asthmatics (SMR = 61, 95% CI = 51–74),³³ with no significant findings reported in the others.^{34,35,70} Notably, one case-control study that evaluated risk for NHL in HIV positive men found a significant inverse association with an allergy to grass, hay, leaves, plants, and pollen.⁶⁴ It was suggested that this inverse association may be due to the continual capacity for differentiation of B-cells.⁶⁴

Hodgkin's disease (HD). There is no convincing evidence to support an association between a history of allergy and HD. All cohort studies involve very small numbers of cases.^{11,28,32,33} Virtually all case-control studies, with the exception of those by Vineis *et al.*⁶⁹ and McKinney *et al.*,⁶⁶ reported no significant relationships.^{68,71–73} Vineis *et al.*⁶⁹ reported that a reduced risk of HD was significantly associated with a history of hay fever (OR = 0.5, 95% CI = 0.3–0.8), but not with eczema (OR = 0.7, 95% CI = 0.4–1.3) or allergies (OR = 0.9, 95% CI = 0.5–1.4). McKinney *et al.*⁶⁶ reported HD to be positively associated with a history of

eczema (OR = 1.9, 95% CI = 1.2–3.0), but reported no association with a history of allergies.

Leukemia. In adults, it remains unclear whether a history of allergy is associated with leukemia. The majority of case-control studies are relatively small in size, few are population-based, and few consistent or significant results have been reported.^{60,66,74–78} Two case-control studies did note inverse relationships between specific forms of leukemia and number of allergies or allergic conditions.^{76,77} Few cohort studies have evaluated leukemia as an outcome. Two cohort studies were based on very small numbers of cases.^{11,12} Both Mills *et al.*³⁹ and Söderberg *et al.*⁷⁰ reported non-significant results for leukemia in relation to a variety of indicators of allergic status. Two large record linkage studies both reported inverse associations for incident and fatal leukemia with a 14–45% decrease in risk in asthmatics.^{33,34} We also reported a significant inverse association of leukemia mortality with asthma (RR = 0.8, 95% CI = 0.6–0.98) in the ACS cohort but not with any other indicator of allergic status.³⁵

Some inverse associations were reported in studies of childhood leukemia. Wen *et al.*⁷⁹ found that acute lymphatic leukemia (ALL) in children was inversely related to a variety of allergic conditions, as well as an inverse relationship between ALL and number of allergies. Nishi and Miyake⁸⁰ reported a significant inverse association for childhood ALL of the non T cell type in relation to a history of atopy (OR = 0.3, 95% CI = 0.1–0.8). A 60% reduction in risk for childhood leukemia was associated with a history of previous hospitalization for allergic disease.⁸¹ A large case-control study of childhood leukemia in Germany also reported significant inverse associations of ALL in children with a history of allergies and atopic conditions.⁸² Spector *et al.*,⁸³ however, reported a 2-fold increase in risk for ALL among children with a medical record of atopy or hives.

Multiple myeloma. Overall, little evidence exists for a relationship between allergy and multiple myeloma, with the majority of studies reporting no association.^{33–35,39,60,69,70,84–95} Williams *et al.*⁹⁵ restricted cases to light chain myeloma and found no association with a history of allergy. A large case-control study by Lewis *et al.*⁹² evaluated risk of a multiple myeloma by immunoglobulin (Ig) subtype. Although no overall association was found, a significant positive association was reported between IgG myeloma in whites and a history of eczema (OR = 2.1, 95% CI = 1.1–4.2) or any allergic condition (OR = 1.6, 95% CI = 1.1–2.3). Another study examining risk factors for multiple myeloma by Ig subtype reported no association with a history of allergy.⁹⁰ An increasing risk for multiple myeloma with increasing number of allergies was reported by Bourguet and Logue⁸⁵; the results, however, were nonsignificant and based on a very small number of cases.

Brain cancer

Case-control studies have consistently reported inverse associations between a history of allergy and the occurrence of glioma^{96–98}; however, few prospective studies exist with which to confirm an association and limitations such as the use of proxy respondents and the potential for reporting biases in cases remain a concern. A large international case-control study examined various potential risk factors for brain cancer among adults in 8 centers.⁹⁷ Upon pooling of the data, inverse associations were found between glioma and a history of any allergic disease (OR = 0.6, 95% CI = 0.5–0.7), asthma (OR = 0.8, 95% CI = 0.6–1.0) and eczema (OR = 0.6, 95% CI = 0.5–0.9). Brenner *et al.*⁹⁶ reported significant inverse associations between glioma and various allergy measures, including a history of any allergy (OR = 0.7, 95% CI = 0.5–0.9), asthma (OR = 0.6, 95% CI = 0.4–0.9) and a chemical allergy (OR = 0.2, 95% CI = 0.1–0.9), but not hay fever (OR = 1.0, 95% CI = 0.7–1.4). Wiemels *et al.*⁹⁸ reported a significant 50% reduction in risk for glioma in relation to a history of any allergy, with other significant findings noted for specific allergies and allergic symptoms. A significant trend in risk was also noted, with risk

decreasing as the number of allergies increased. Recently, Wiemels *et al.*⁹⁹ in another case-control study measured IgE levels in glioma cases and controls as a biomarker of allergic status. An OR of glioma risk in those with elevated IgE levels compared to normal levels of 0.3 (95% CI = 0.2–0.6) was reported. IgE levels were, however, not found to be strongly related with self-reported allergy. A small prospective study based on the Swedish Twin Registry reported an inverse association between allergies and glioma in a cohort of same gender twins born between 1886 and 1925 (hazard ratio (HR) = 0.4, 95% CI = 0.2–1.1).¹⁰⁰ Allergies were associated with a reduced risk for high grade (HR = 0.4, 95% CI = 0.1–1.9) but not low-grade glioma (HR = 2.6, 95% CI = 0.9–7.8) in a cohort of same gender twins born between 1926 and 1958. It has been suggested that those with an allergic history may be better able to mount a successful immunological anti-glioma response.^{98,101}

No significant association was reported between meningioma and a history of allergy in previous case-control studies.^{96,97,102} The Swedish Twin Registry study reported a doubling in risk for meningioma among those with any allergic condition.¹⁰⁰ Brenner *et al.*⁹⁶ reported that acoustic neuroma was significantly and positively associated with hay fever (OR = 2.4, 95% CI = 1.4–4.0), allergy to food (OR = 3.0, 95% CI = 1.1–8.5) and allergy to other substances (OR = 3.8, 95% CI = 1.4–10.0). In the ACS cohort, we found no association between a history of any asthma or hay fever and brain cancer mortality.³⁵

Reproductive cancers

The association between a history of allergy and reproductive cancers has received less attention. Although certain inverse associations have been reported, particularly among the record linkage studies, in general, results have been inconsistent, and no clear evidence exists.

Ovarian cancer. Mills *et al.*³⁹ reported an 87% reduction in the risk of ovarian cancer in relation to a history of reaction to poisonous plants, as well as a significant inverse relationship with a number of allergies. No other significant associations were found with other allergy measures in this study. Except for the study by Kallen *et al.*,³³ all other studies have reported no significant association between ovarian cancer and atopy, asthma or hay fever.^{27,34,35}

Uterine cancer. Previous case-control studies have reported no association between a history of allergy, asthma, or hay fever and uterine cancer.^{27,103} Previous record linkage studies in asthmatics reported inverse associations ranging from 24–64%.^{33,34} Mills *et al.*,³⁹ however, reported inconsistent results for risk of endometrial cancer in those with asthma or hay fever in the Seventh-Day Adventist cohort. We noted a nonsignificant inverse association between mortality of cancer of the corpus and uterus, not otherwise specified and a history of asthma and hay fever in the ACS cohort (RR = 0.6, 95% CI = 0.3–1.1); however, the results were based on only 12 cases with both disorders.³⁵

Cervical cancer. A case-control study reported a significant inverse association between cervical cancer and a history of hives (OR = 0.6), but not asthma or hay fever.²⁷ Recently, a tripling in risk for cervical cancer was reported among those with eczema, although this was considered to be likely of the nonatopic type.¹⁰⁴ The same study also reported no association between a history of hay fever and cervical cancer.

Breast cancer. A reduction in the risk of breast cancer by nearly half was reported among asthmatics in a case-control study of women in Montreal.¹⁰⁵ Kallen *et al.*³³ reported a reduction in risk of a similar magnitude for breast cancer mortality among individuals diagnosed with asthma in Swedish hospitals. Although inverse associations were also reported in several other case-control studies,^{103,106} all remaining studies, including several prospective studies, reported no significant association between a variety of indicators of allergic status and breast cancer.

Prostate cancer. A 5-year cohort study in Japan reported an elevated risk of prostate cancer among those with asthma (RR = 22.8, 95% CI = 5.5–94.7).¹⁰⁸ The results were based on only 10 cases and were subject to potential biases related to screening or hospital-based recruitment. A larger population-based cohort study also reported a positive association between prostate cancer and asthma (HR = 1.9, 95% CI 1.0–3.6), but no association with hay fever (HR = 1.1, 95% CI 0.6–2.0).¹⁰⁷ A sub-cohort of participants in this study who were also skin-prick-tested demonstrated a significantly increased risk of prostate cancer among those with allergy to house dust mites (HR = 2.9, 95% CI = 1.3–6.7). The remaining cohort studies^{12,34,35,39} reported no significant association, with the exception of the study by Kallen *et al.*³³ who reported a SMR of 72 (95% CI = 67–78).

Testicular cancer. Swerdlow *et al.*¹⁰⁹ reported increased risks for testicular cancer in relation with a history of atopy (OR = 1.8, 95% CI = 1.1–3.1), hay fever (OR = 2.6, 95% CI = 1.2–5.6), eczema (OR = 3.1, 95% CI = 1.0–10.0) and asthma (OR = 1.7, 95% CI = 0.8–3.6). All remaining studies that examined the association between testicular cancer and allergy, again with the exception of Kallen *et al.*,³³ reported no association.^{110,111}

Colorectal cancer

Results from previous case-control and cohort studies have not been entirely consistent^{27,39,112}; however, some inverse nonsignificant^{107,113,114} and significant findings have been observed.^{33–35} A nonsignificant inverse association between colorectal cancer and a history of allergies was reported in large case-control studies by Negri *et al.*¹¹⁴ and Kune *et al.*¹¹³ A prospective study by Talbot-Smith *et al.*¹⁰⁷ recently reported a reduced risk of colorectal cancer in association with a history of asthma or hay fever, although none were significant. We reported a significant inverse association between a history of both asthma and hay fever and colorectal cancer mortality (RR = 0.8, 95% CI = 0.6–0.9) in the overall ACS cohort, and a similar finding in never smokers (RR = 0.8, 95% CI = 0.6–1.0).³⁵ Kallen *et al.*³³ also reported a significant inverse association for colon and rectal cancer mortality in asthmatics; however, Vesterinen *et al.*³⁴ reported a significantly increased risk for rectal cancer in relation to asthma in women (SIR = 142, 95% CI = 117–169).

Esophageal and stomach cancer

Inconsistent results were reported in studies of esophageal and stomach cancer risk. Elevated risks were reported for esophageal and gastric cardia adenocarcinomas in asthma patients by Ye *et al.*,¹¹⁵ which were attributed to excess gastro-esophageal reflux in that population. Several, mostly small, case-control studies have reported inverse associations between esophageal cancer and a history of allergy.^{103,116,117} Kallen *et al.*³³ reported a 50% reduction in risk for stomach cancer mortality in asthmatics; however, remaining cohort studies reported no significant relationships.^{34,39}

Medullary thyroid carcinoma

The association between a history of allergies and medullary thyroid carcinoma was evaluated in a pooled analysis of 14 international case-control studies.¹¹⁸ Upon analysis of 48 cases and 240 controls, a doubling in risk was found for medullary thyroid carcinoma in those with a history of allergies. The authors suggested, however, that the positive association observed may be due to the release of vasoactive compounds by the tumor causing allergic-like symptoms to be reported in cases.

Bladder cancer

An early hospital-based case-control study noted that a history of allergy was associated with an increased risk of bladder cancer in men (OR = 1.7), but a reduced risk in women (OR = 0.3).¹¹⁹

More recent case-control studies have reported positive associations between a history of asthma and both urothelial cancer (OR = 3.1, 95% CI = 1.4–6.8)¹²⁰ and bladder cancer (OR = 4.2, 95% CI = 1.6–10.8)¹²¹ with risk increasing for bladder cancer in asthmatics with the glutathione S-transferase-[mu] (GSTM1) (OR = 9.2, 95% CI = 2.3–37.8) or glutathione S-transferase-[theta] (GSTT1) (OR = 19.2, 95% CI = 2.3–160.1) null genotypes. This finding was suggested to be due to a deficiency in the detoxification of reactive asthma medication intermediates through a lack of these enzymes.¹²¹ Among cohort studies, Mills *et al.*³⁹ reported no significant findings, while Vesterinen *et al.*³⁴ reported a significantly increased risk for bladder cancer in asthma patients among men (SIR = 125, 95% CI = 103–149) but not women (SIR = 90, 95% CI = 60–128).

Discussion

Although many studies have suggested a relationship between a history of allergy and cancer occurrence. It is difficult to draw conclusions between allergy and cancer at many sites because of insufficient evidence or a lack of consistency both within and among studies completed to date. The nature of the relationship may also depend on the cancer site studied. Despite conflicting research, strong inverse associations have been reported for pancreatic cancer and glioma, whereas lung cancer was positively associated with asthma. A number of important methodological issues are apparent in previous studies. Limitations associated with exposure assessment, confounding and bias are critical and should be considered when evaluating studies of this type.

Methodological issues

Measurement of allergy. The vast majority of previous studies use self-reported history of allergic conditions as an indicator of allergic status. An important problem in ascertaining an accurate history of allergy in epidemiological studies is differentiating between disorders that are allergic in origin and other conditions that exhibit similar symptomology, such as difficulties in distinguishing between asthma and various smoking-related lung diseases.^{122–124} Similarly, the etiology of conditions such as asthma is variable, involving a number of immunological and nonimmunological factors, including allergy.¹²⁵ For example, asthma development in childhood is more likely to be allergic compared with adult-onset asthma.

Relatively few questionnaires that have attempted to measure a history of allergy have been validated. Validating asthma questionnaires is particularly difficult because of the absence of a universally accepted definition. In adults, physician-diagnosed asthma questions are preferable to symptom-based questions or questions asking whether they have ever had the disease, as they demonstrate high reliability, specificity and positive predictive values.^{123,126} The combination of more objective diagnostic measures such as a bronchial hyperresponsiveness test or exercise test in conjunction with questionnaire responses does not appear to improve asthma classification accuracy in population-based studies of adults or children.^{127–131} A questionnaire using physician-diagnosed hay fever has been validated.¹²⁶ This physician-diagnosed hay fever question resulted in the most accurate diagnosis among different questions assessing a history of hay fever. A score-based questionnaire to distinguish between allergic rhinitis and other similar conditions has also been validated.¹²²

Little is known about the accuracy of reporting of lifetime allergic history. Possible reporting differences may exist based on recentness or severity of allergic symptoms. A study evaluating consistency of respiratory questionnaire responses after a 4-year period found that the concordance of reporting of current asthma was only 76.6%, likely due to variability in symptom presentation.¹³² One study validating a questionnaire for atopic dermatitis reported that those most likely to be classified as false negatives were those with mild symptoms.¹³³ Similarly, the low to moderate

sensitivities found for physician-diagnosed asthma can also be attributed to underdiagnosis in those with mild symptoms not seeking medical consultation.¹²⁶ Studies using registries of hospital discharge codes or allergy medication history may have studied select populations, as the registries covered only those whose symptoms were severe enough to require treatment.^{33,34}

Following a detailed symptom history, measurement of specific IgE antibodies through skin testing or a radioallergen sorbent test (RAST) could be performed to confirm allergic status. In case-control studies, however, such information from cases may be affected by the developing cancer.⁵⁷ In large cohort studies, moreover, this technique may not always be feasible. Another concern with the use of such biological information is the potential modifying effects of gender or cigarette smoking status.^{57,134–136} Obtaining a history of other atopic conditions and assigning allergic status when a history of other atopic disorders exists has also been suggested to reduce misclassification.¹³³ Significant trends of cancer risk in relation to allergy have been reported, with the risk of cancer decreasing as the number of allergies increases.^{39,57,76,77,79,85,98} A possible reason for this is that the accuracy of classification of individuals into allergic *versus* nonallergic categories is improved as those reporting a greater number of allergies are more likely to truly be allergic. However, in case-control studies, it could also result from a positive bias in the reporting of allergies by cases.

Another important issue related to exposure assessment is the use of proxy respondents for children or for those with highly fatal cancers. A high confirmatory rate (98%) of parental reporting of physician-diagnosed asthma in children was previously reported.¹³⁷ Good agreement between parental reporting of asthma and medical records for children one to thirteen years of age was found for asthma occurrence within the past year (91%) and lifetime asthma occurrence (87%).¹³⁸ It has been suggested that a proxy effect is likely, however, in parents reporting allergic symptoms.¹³⁹

In adults, few studies have attempted to assess the accuracy of proxy respondents in reporting prior medical history. Linet *et al.*¹⁴⁰ measured agreement in reporting of medical history, including allergy, between interview data and medical records in self and proxy respondents. No improvement in accuracy was seen in self as opposed to proxy respondents. Another study evaluated the concordance of reporting of medical history in surrogate respondents for those who had died 5 years prior to the initial interview.¹⁴¹ It was suggested that detailed information regarding medical history may need to be confirmed through medical records when using proxy respondents.^{141,142}

Few studies have attempted to determine if an effect due to respondent type exists. Schwartzbaum *et al.*¹⁰⁰ examined the effect of proxy respondents in case-control studies of glioma risk. Odds ratios were found to decrease across studies, as the number of proxy respondents increased (Pearson correlation coefficient = −0.9, 95% CI = −1.0 to −0.6). The possibility of reporting bias in brain cancer cases due to cognitive impairment in these studies is also difficult to assess. Given these potential source of bias, as well as the distinct possibility for recall bias in case-control studies due to underreporting of minor allergies, the findings from large prospective studies may be particularly useful.

Symptoms of certain developing malignancies may be mistaken as being allergic in origin, and may result in misdiagnosis and misclassification of allergy.^{143–153} This could produce a positive bias because of the greater number of cancer cases reporting previously diagnosed allergic symptoms, such as was suggested for the positive association observed between medullary thyroid carcinoma and allergy.¹¹⁸ The influence of excluding cases with recent allergic diagnoses has not been subject to in-depth examination. In lung cancer studies, a reduction in risk estimates has been seen when excluding those with an asthma diagnosis 1–5 years prior to cancer diagnosis.^{34,154}

Outcome assessment. In mortality-based studies, cancer incidence as well as factors affecting survival influences the outcome.

Few studies examining differential prognosis or survival from cancer due to the presence of asthma or hay fever have been reported in the literature. The prognosis of asthmatic and nonasthmatic lung cancer patients in one study was found not to differ.¹⁵⁵ Another study reported, however, that asthma exerted a negative impact on survival from lung cancer.¹⁵⁶ Asthma was also associated with a 2-fold increase in risk for breast cancer death 30 months postdiagnosis in postmenopausal women over 55 years of age.¹⁵⁷ Lastly, Yancik *et al.*¹⁵⁸ concluded that asthma did not impact the survival experience of those with colorectal cancer. Inferences from mortality-based studies are thought to represent less of a problem when studying highly lethal cancers, as nearly all incident cases are soon fatal.

A screening bias may exist in those with frequent contact with the medical profession due to allergic symptoms increasing the opportunity for cancer detection.³⁹ This may lead to a negative bias if the cancer diagnoses were occurring at an earlier stage among people with allergies, hence improving survival because of earlier detection.¹

Other methodological issues. The majority of the earlier studies did not take into account important covariates such as age, sex and smoking, which may modify or confound the association between allergy and cancer. Only the most recent studies have considered other important site-specific cancer risk factors.

Cigarette smoking status is a particularly important factor for a number of reasons. Smoking is an important risk factor for cancer at many sites. Those with asthma or allergy may be less likely to smoke due to an exacerbation of respiratory symptoms^{12,35,41,46,159}; however, this remains controversial. Similarly, those with a history of asthma and/or hay fever have been reported to be more likely to quit smoking.¹⁶⁰ As a consequence, it might be expected that the risk for smoking-related cancers among those with asthma and/or hay fever could decline over time.⁴⁸ As well, greater misclassification of asthma may occur, particularly in studies using symptom-based questionnaires, in those who smoke as symptoms of other chronic respiratory diseases may mimic those of asthma. The evaluation of cancer risk in never smokers for smoking-related cancers may address these concerns.⁴⁸

Socio-economic status is another important factor that has not often been taken into consideration. Socio-economic status has been associated both with allergy^{161–164} and with cancer occurrence and survival.^{165,166} Early birth order and reduced sibship size (as possible indicators of environmental exposures such as reduced exposure to infectious agents or exposures in the intrauterine environment) have been positively associated with allergy occurrence^{167–169} and inversely associated with risks of NHL,⁶² AML,¹⁷⁰ and HD in children,¹⁷¹ but positively associated with ALL¹⁷⁰ and HD in young adults.^{171,172} There is a possibility that asthma and allergy medications are related to cancer; however, there exists little evidence to date.^{54,67,76,90–92,94,95,97,102,105,173–178} Those with a history of asthma and allergy may also tend to avoid other exposures related to cancer due to their allergy symptoms such as certain occupational exposures or exhibit different dietary or lifestyle preferences.^{179–182}

Biological plausibility. At this point in time, no precise explanation has been put forward to explain an overall inverse association between a history of allergy and cancer risk. Although potential biological mechanisms exist for associations at specific sites (such as the positive association observed between asthma and lung cancer), evidence for a global mechanism is limited. Enhanced immune surveillance is often cited as a biological mechanism when inverse associations are reported. Evidence for the immune surveillance theory in humans derives from the observation that those who are immunosuppressed exhibit a higher incidence of malignancy.^{7–9} The infiltration of developing tumors by various immune cells and the immune system evading behaviour of tumors further strengthens the evidence for this theory.³

The atopic diseases are characterized by an atypical, Th2-dominated immune response to innocuous environmental agents.^{183,184}

These diseases are characterized by large amounts of IgE antibody production by the β cells stimulated by the Th2 cytokines upon allergen exposure.¹⁸⁵ The resulting response is an inflammatory reaction mediated by the IgE-mast cell release of histamine, leukotrienes, chemotactic factors, platelet-activating factor and proteases.^{125,184} The early inflammatory response is comprised of smooth muscle contraction, mucus secretion, vasodilation and a loss of microvascular integrity.^{125,184} The infiltration and activation of eosinophils, neutrophils, Th2-type CD4⁺ cells and macrophages occur during the late inflammatory response.^{125,184} It remains unclear, however, how this immune response is related to cancer development.

Although controversial, certain immunological findings may provide clues for a potential mechanism. For example, higher numbers of natural killer (NK) cells have been observed in asthmatics.¹⁸⁶ Those with allergic asthma were found to possess significantly stronger NK cell activity against the K-562 leukemic cell line¹⁸⁷ and U937 cell growth.¹⁸⁸ Children with atopic dermatitis were found to possess greater NK cell activity against Burkitt's lymphoma cells.¹⁸⁹ NK cell activity may also be related with total serum IgE levels.¹⁹⁰ A large cohort study with 11 years of follow-up demonstrated that low NK cell activity was associated with an enhanced risk of cancer at all sites.¹⁹¹

Th2-type cytokines such as IL-10 and IL-4 have been found to demonstrate antitumor properties.^{192–197} Low blood and tissue levels of histamine were related to reduced antitumor activity and with tumor occurrence.¹⁹⁸ Histamine may protect NK cells from reactive oxygen species inhibition and synergize with other cytokines to stimulate antitumor NK and T cell activity.¹⁹⁹ The addition of histamine to certain cancer immunotherapy regimes has shown results improving survival and prolonging remission.¹⁹⁹

Eosinophils may play a role in the initiation of the antitumor response.²⁰⁰ Eosinophil recruitment to the tumor may be related to a Th2 type response and IL-4.^{201–203} Lastly, IgE-driven immune reactions have also been shown to be effective in inhibiting tumor growth.^{204,205}

Overall, although it is plausible that enhanced immune surveillance in individuals with a history of allergy may be associated with reduced cancer risk, specific evidence remains limited and controversial. A formal model for an allergy–cancer association remains to be developed.

Conclusions and future directions

A history of allergy has been inversely associated with risk for cancer at a number of sites; however, it is difficult to draw conclusions at many sites because of inconsistent findings and limitations of previous studies. For many cancer sites, few large prospective studies evaluating cancer incidence exist, and few have been able to adjust for potential cancer site-specific confounders, in particular cigarette smoking. Further study is needed in the validation of indicators of allergic status for use in large epidemiological studies, including biomarkers to reduce potential misclassification of allergic status and to confirm the results of previous studies based on self-report. The use of skin-prick testing and IgE levels were examined in few studies. More importantly, in advance of additional expenditure in epidemiological studies of this type, there is a need for further basic research to clarify the mechanisms behind an association, should one exist. Although great advances have been made, the role of the immune system in cancer development as well as relevant differences between allergic and nonallergic individuals require further clarification. Laboratory studies of gene knock out mice may help to determine individual genes that are involved in the allergy and cancer processes and delineate if they are related. Gene chip microarray studies may also help to determine specific animal gene targets and whether such targets can be extrapolated to human homologues that would then be applicable to population health studies.

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