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TURNER, Michelle Catherine

AUTEUR DE LA THÈSE - AUTHOR OF THESIS

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Yue Chen / Daniel Krewski

DIRECTEUR DE LA THÈSE - THESIS SUPERVISOR

EXAMINATEURS DE LA THÈSE - THESIS EXAMINERS

R. Dales

I. Neutel

J.-M. De Koninck, Ph.D.

LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

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ALLERGY AND CANCER: ANALYSIS OF THE AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II PROSPECTIVE COHORT

by

MICHELLE CATHERINE TURNER

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ABSTRACT

The presence of allergy may reduce cancer risk. Literature searches identified 142 epidemiological studies on this association. Data from the American Cancer Society Cancer Prevention Study-II cohort were used to explore the relationship between self-reported asthma and/or hay fever and cancer mortality in 508 318 men and 483 079 women who were cancer-free at baseline. During 18 years of follow-up from 1982-2000, there were 44 524 cancer deaths in men and 36 567 in women. Cox proportional hazards models were used to obtain adjusted relative risks for overall cancer mortality and for cancer mortality at 12 sites. There was approximately a 10% reduction in overall cancer mortality among people with asthma and hay fever. Asthma and/or hay fever were also associated with a reduced risk of cancer at a number of other sites, and some of the associations were modified by gender and smoking status.

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INTRODUCTION

Cancer is a major threat to population health. It is currently the second leading cause of death in Canada and the United States[1;2]. In the year 2003, it is estimated that 139 900 new cases of cancer and 67 400 deaths from cancer will occur in Canada[3]. Lung cancer and colorectal cancer are responsible for the largest number of cancer deaths in the Canadian population, followed by prostate cancer in men and breast cancer in women[4]. Recently, overall cancer mortality rates have been seen to decline. Since 1988, the age-standardized all cancer death rate has decreased by 12% in men and 13% in women (lung cancer excluded)[3]. This decrease has been attributed to a number of factors including improved screening practices, improved treatments, and changes in individual behaviors[4]. A decline in cancer mortality rates has not been observed at all sites. Significant increases in the mortality rate were noted between 1991 and 1999 for melanoma and non-Hodgkin's lymphoma in men, and lung cancer in women[4].

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 [5-7]. The concept of immune surveillance, first proposed almost a century ago, suggests that the immune system is continuously searching for and destroying tumor cells as they arise [8;9]. Although historically controversial, recent scientific advancements have led to renewed interest in immune surveillance theory[9].

Evidence for the immune surveillance theory in humans derives from the observation that those who are immunosuppressed exhibit a higher incidence of malignancy[9-11]. The infiltration of developing tumors by various immune cells and the immune system evading behaviour of tumors further strengthens the evidence for this theory[7]. Certain groups may possess an enhanced capacity for immune surveillance. Specifically, it has been suggested that those with a history of allergy, in particular atopic disorders (allergic asthma, allergic rhinitis, and atopic dermatitis), may display enhanced immune competency and an enhanced capacity for immune surveillance[12-15].

It has been commonly assumed that the atopic immune response offers little benefit to individuals[16]. Recently, it has been argued however, that an atopic immune system may offer a valuable evolutionary advantage[16]. Although at this time, understanding of the role of the immune system in cancer development remains unclear, there have been some intriguing findings, which support a generalized protective effect of an allergic history on cancer development. These findings support possible roles for natural killer (NK) cells, cytokines, IgE, histamine and eosinophils in modulating cancer risk.

A review of the current epidemiological evidence indicates that the relationship between allergy and cancer remains controversial. A number of early case-control studies examining the association between allergy and cancer of all sites have reported a negative association [17-21]. Other early case-control studies reported either no association or an increased cancer risk in relation to an allergic history[22-25]. The majority of these

early studies are hospital-based, and are limited by very small sample sizes, lack of control for potential confounders, or possible selection biases.

Suggestions of a possible relationship between allergy and cancer have been examined in 26 cohort studies and 116 other cancer site-specific case-control studies. Unfortunately, many of these cohort studies also have little control for confounding and involve small numbers of cancer cases. Additionally, no comprehensive review of these studies exists upon which to base conclusions and future research efforts.

Objectives

The overall objective of this thesis is to examine the association between allergy and cancer. The specific objectives are as follows:

(1) to conduct a detailed literature review of previous studies exploring the relationship between allergy and cancer;

(2) to perform a thorough analysis of American Cancer Society – Cancer Prevention Study II (ACS – CPS II) data to examine the association between a history of asthma and/or hay fever and overall and site-specific cancer mortality; and

(3) to develop and offer new insight into the possible relationship between allergy and cancer, taking into account possible biological mechanisms that may contribute to such an association.

Research Questions

This thesis will address these specific research questions:

(1) Do previous epidemiological studies indicate an association between allergy and overall cancer occurrence or cancer at specific sites?

(2) Is a history of allergy (as measured by asthma and/or hay fever) associated with overall or site-specific cancer mortality in the ACS – CPS II cohort?

(3) How is the association between a history of allergy and overall or site-specific cancer mortality modified by cigarette smoking status or age at baseline in the ACS-CPS II cohort?

Significance of Proposed Study

This investigation of cancer mortality among individuals with allergic disorders is an important area of study. Specifically, it is important to clarify previous conflicting reports on the association between allergy and cancer. It is also important to further understand the role of the immune system in cancer development, and how this may relate to allergy.

This thesis has the potential to contribute to this area through both the literature review and the analysis of a large dataset. A comprehensive literature review on the subject of allergy and cancer has, to my knowledge, never been published. Although several limited reviews exist, a lack of detail and non-inclusion of a large proportion of

previous studies limit their contributions. The analysis of the ACS – CPS II data will address many of the limitations of previous studies. It will not only offer the largest sample size of any study conducted to date, it is one of only a few prospective cohort studies with the ability to control for numerous potential site-specific covariates that may modify or confound the effects of allergic status during analysis, and affords an opportunity to examine multiple cancer sites.

Outline of Thesis

This thesis is composed of 5 chapters. Following this introductory chapter, the second chapter provides a review of previous studies that have examined the relationship between a history of allergy and cancer occurrence. The methods used to identify previous studies are described, followed by a summary of previous findings organized by cancer site. A discussion of the difficulties associated with ascertaining allergic status in epidemiological studies is also provided. The third chapter describes the dataset and methods used for the data analysis. Chapter 4 presents the results of the data analysis by cancer site. Chapter 5 integrates the findings of the literature review and data analysis. Potential biological mechanisms that may motivate an association between allergy and cancer are also explored. Directions for further work based on this research are also suggested.

LITERATURE REVIEW

Methods

Literature searches were conducted using the MEDLINE and Biological Abstracts databases through to September 2003, and the CancerLIT database through to October 2002. Articles which explored a personal history of allergic disorders as a risk factor for cancer were identified through this search.

MeSH headings were used when searching the MEDLINE and CancerLIT databases. The MeSH headings of "Hypersensitivity" and "Neoplasms" were selected, with subheadings of "Hypersensitivity, Immediate", "Neoplasms by Histologic Type", and "Neoplasms by Site" exploded. A free-text search was also performed in all databases using the following keywords: "allerg$", "atop$", "hypersensitiv$", "asthma$", "hay fever", "rhinitis", "conjunctivitis", "eczema", "dermatitis", "hives", "urticaria", "angioedema" or "skin test", combined with "cancer", "tumor", "tumour", "malignan$", "neoplasm$", "carcinoma", "leukemia", "leukaemia", "lymphoma", "myeloma", "hodgkin", "glioma", and "risk". The Boolean operator OR was used to independently group allergic terms and cancer terms. The Boolean operator AND was used to group allergic, cancer, and risk search terms. The search was restricted to human studies and papers written in English. Case reports and descriptive studies were excluded. Additional studies were identified by manually searching reference lists and communicating with an

investigator working in the area. Only the most relevant article was included when there were multiple publications on the same study.

Studies were categorized by cancer site and study design. Overall and subgroup results were examined, while taking into account possible study limitations including sample size, control for confounding, exposure measurement, and other methodological issues. Relative risks were rounded to one decimal place. All standardized mortality ratios (SMR) and standardized incidence ratios (SIR) were converted to base one hundred for consistency.

Results

A total of 142 epidemiological studies were identified, including 26 cohort studies and 116 case-control or cross-sectional studies that evaluated some aspect of the association between a history of allergy and cancer occurrence. A summary of these studies organized by cancer site can be seen in Appendix 1. The studies took place in the United States, Canada, China, Japan, Korea, Australia, New Zealand, Brazil, Venezuela, Kuwait, and throughout Europe. Studies evaluating this association have been conducted for approximately five decades. A variety of study populations, study designs, and exposure measures have been used.

All Cancers

A number of early case-control and cross-sectional studies were conducted that evaluated the association between a history of allergy and the occurrence of all cancer combined [17-24;26-32]. Many of these studies were summarized by Vena et al. [32]. The majority of these early studies reported an inverse association between allergy and cancer of any type. These early studies were primarily hospital-based, and suffer from limitations of very small sample sizes, a lack of control for potential confounders, or possible selection biases.

The results from early cohort studies were not consistent [14;33-37]. Many of these studies have little or no control for possible confounders and involve small numbers of cancer cases. Several large cohort studies have recently examined this association. A large record linkage study of 64 346 people treated in hospital for asthma in Sweden found significantly reduced risks for all cancers (SMR = 66, 95% confidence interval (CI) = 64-68) and for site-specific cancers [38]. Another large cohort study linked 77 952 people in the Finnish Social Insurance Institution register who had received reimbursement for asthma medication with the Finnish Cancer Registry[39]. A total of 3 842 cancer cases were observed, along with a significantly increased risk for all cancer in men with asthma (SIR = 112, 95% CI = 107-117) but not women (SIR = 103, 95% CI = 98-107). Both of these large record linkage studies were unable to control for individual level covariates in analysis. Mills et al. [40] evaluated the association between a history of allergy and cancer in a cohort of 34 198 Seventh-Day Adventists. A total of 1 102 cases of cancer were observed. No association was reported between a history of any allergy (hazard ratio (HR) = 1.1, 95% CI = 0.9-1.4 in men, HR = 1.0, 95% CI = 0.8-1.2 in women), asthma

(HR = 0.8, 95% CI = 0.5-1.3 in men, HR = 1.0, 95% CI = 0.7-1.3 in women), or hay fever (HR = 1.1, 95% CI = 0.8-1.4 in men, HR = 1.2, 95% CI = 0.9-1.4 in women) and the occurrence of any type of cancer. The remaining cohort studies revealed no significant associations between allergy and all cancer occurrence[41-44], including three prospective studies utilizing skin testing as an indicator of allergic status [13;45;46]. Overall, the studies conducted to date provide no clear evidence that an allergic history is associated with overall cancer occurrence.

Lung Cancer

Several case-control studies which did not control for smoking found a significantly decreased risk for lung cancer associated with a history of allergy or asthma[47-51]. Since smoking is a major risk factor for lung cancer, adequate control for smoking is critical. All population-based case-control studies that evaluated the association between a history of asthma and lung cancer in non-smokers reported elevated odds ratios (OR)[52-54]. Increased risks of lung cancer in asthmatics were also reported in many cohort studies that controlled for smoking history [36;42;44;55;56] but not all [40;57].

Recently, a meta-analysis combining previous asthma and lung cancer studies was published [58]. A combined odds ratio of 1.8 (95% CI = 1.3-2.3) resulted from previous case-control studies that evaluated lung cancer risk in never smokers. A relative risk 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.

There are no consistent results for asthma associated with lung cancer subtypes. Wu et al. [59] found that the risk of adenocarcinoma was not associated with asthma in women (OR = 1.0, 95% CI = 0.5-2.1). Elevated odds ratios were reported for adenocarcinoma and other histological types of lung cancer in nonsmoking women with a history of asthma by both Alavanja et al. [52] and Wu et al. [54]. Osann et al. [60] reported an increased risk for small cell lung cancer in relation to a history of asthma (OR = 4.8, 95% CI = 1.0-22.8) in women. In a prospective study of 92 986 asthmatics in Sweden, a significant increase in risk 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)[61]. In a Finnish record linkage study, a significant increase in risk 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[39].

Age at diagnosis of asthma may affect the association between asthma and lung cancer. One study showed a significant increase in risk of lung cancer among those with an asthma diagnosis at or prior to 20 years of age (OR = 2.0, 95% CI = 1.1-3.6), and with a lapse of 11 to 20 years since first diagnosis of asthma (OR = 3.0, 95% CI = 1.1-8.3)[54]. Both Brenner et al. [62] and Kallen et al. [38] however, reported significantly increased risks for lung cancer within 1-5 years of an asthma diagnosis only.

Pancreatic Cancer

Population-based case-control studies have generally reported no association between a history of asthma and pancreatic cancer risk [12;63;64]. The results from cohort studies are less consistent. Kallen et al. [38] reported a significant decrease in the risk of pancreatic cancer among asthmatics (SMR = 64, 95% CI = 55-75). Vesterinen et al. [39] reported a reduced risk for men (SIR = 88, 95% CI = 67-113) but not women (SIR = 101, 95% CI = 80-124) with asthma. Mills et al. [65] reported no association between a history of asthma and pancreatic cancer mortality in the Seventh-Day Adventist cohort (RR = 0.9, 95% CI = 0.2-3.4). One cohort study examining risk in male smokers reported a two-fold increase in pancreatic cancer risk associated with a history of asthma [66]. Overall, there appears to be no strong evidence to suggest an association between a history of asthma and pancreatic cancer.

All four previous studies that evaluated hay fever in relation to pancreatic cancer risk reported a reduction in risk [12;64;65;67]. A large population-based case-control study reported a significant protective effect of hay fever on pancreatic cancer risk (OR = 0.6, 95% CI = 0.5-0.9) [64]. Mills et al. [65] reported a reduced risk of pancreatic cancer mortality in relation to a history of hay fever (RR = 0.7, 95% CI = 0.2-1.9). Dai et al. [12] reported an odds ratio of 0.3 (96% CI = 0.1-1.4) in a population-based case-control study in China, and Jain et al. [67] reported an odds ratio of 0.5 (95% CI = 0.2-1.3) in a Canadian case-control study. The most recent case-control study, which did not use any proxy data,

reported a significant 20% reduction in risk for pancreatic cancer among those with an allergy to plants [68]. This study also reported numerous other reduced risks for pancreatic cancer in relation to various allergic conditions, allergies to specific substances, and allergic symptoms [68]. A significant decreasing exposure-response relationship was also found with increasing number of allergies as well as increasing severity of symptoms. Overall, previous studies have indicated a protective effect of hay fever on pancreatic cancer. Although various other associations with pancreatic cancer have been tested, they are difficult to interpret due to variability in exposure measurement between studies.

Neoplasms of Lymphatic and Hematopoietic Tissue

A number of previous studies have evaluated the association between a history of allergy and the risk of non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, or multiple myeloma.

Non-Hodgkin's Lymphoma (NHL)

Briggs et al. [69] recently evaluated the association between a history of allergy and NHL. Inconsistent results were reported across studies examining specific allergies, such as allergies to food or insect stings[69]. Case-control studies have also provided conflicting results on the risk of NHL in association with eczema [70-75]. However, suggestions of an increased risk for NHL in relation to a history of hives have been reported in a number of studies [14;69;70;72;76], with relative risks ranging from 1.2 to 9.3.

Although case-control studies have generally reported reduced risk estimates for NHL in association with a history of asthma or hay fever [70-72;74-79], few prospective studies have addressed these associations. Unstable risk estimates were reported in three prospective studies with few cases[13;14;40]. Of the two remaining larger cohort studies, one reported no association with asthma in men (SIR = 94, 95% CI = 63-136) or women (SIR = 103, 95% CI = 72-141) [39], and the other reported a significantly reduced risk for NHL in asthmatics (SIR = 61, 95% CI = 51-74) [38]. Notably, one case-control study that evaluated the risk for NHL in HIV positive men found a significantly decreased risk for NHL among those with an allergy to grass, hay, leaves, plants, and pollen [77].

Hodgkin's Disease

There is no convincing evidence to support an association between a history of allergy and Hodgkin's disease. All cohort studies involve very small numbers of cases [13;33;37;38]. Virtually all case-control studies, with the exception of those conducted by Vineis et al. [75] and McKinney et al. [73], showed no significant association between Hodgkin's disease and history of allergy [79-83]. McKinney et al. [73] reported Hodgkin's disease 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. Vineis et al. [75] reported a significantly reduced risk for Hodgkin's disease with a history of hay fever (OR = 0.5, 95% CI = 0.3-0.8) but not eczema (OR = 0.7, 95% CI = 0.4-1.3) or allergies (OR = 0.9, 95% CI = 0.5-1.4).

Leukemia

In adults, in 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 results have not been consistent. As well, few cohort studies have evaluated leukemia as an outcome. Two cohort studies were based on very small numbers of cases and the results are not presented here [13;14]. Kallen et al. [38] reported a significantly decreased risk of leukemia in asthmatics (SMR = 55, 95% CI = 45.9-66.4). Vesterinen et al. [39] also reported reduced risks for leukemia in male (SIR = 76, 95% CI = 52-108) and female asthmatics (SIR = 86, 95% CI = 61-118). Upon stratification by type of leukemia, a significantly reduced risk for chronic lymphatic leukemia (CLL) was observed (SIR = 59, 95% CI = 35-93). In the study of Seventh-Day Adventists, Mills et al. [40] reported mixed non-significant results for leukemia in relation to a variety of indicators of allergic status.

Few consistent or significant findings have been reported in case-control studies of acute lymphatic leukemia (ALL)[73;84;85] or chronic myeloid leukemia (CML) in adults [73;85]. The risk of CLL was inversely associated with hay fever (OR = 0.5, 95% CI = 0.2-1.0), eczema (OR = 0.7, 95% CI = 0.3-1.5), hives (OR = 0.7, 95% CI = 0.3-1.6), drug allergy (OR = 0.6, 95% CI = 0.4-1.0), and allergy to insect stings (OR = 0.6, 95% CI = 0.3-1.4) but not with asthma (OR = 1.1, 95% CI = 0.5-2.6), in a large hospital-based study [86]. An inverse dose-response relationship was also reported between CLL and

number of allergic conditions [86]. McKinney et al. [73] reported an odds ratio of 0.7 (95% CI = 0.5-1.1) for CLL in relation to a history of allergies in a hospital-based study in England. No significant association between the risk of CLL and a history of hay fever, eczema, or asthma was reported in an American hospital-based study [71]. The only population-based study to examine such an association reported a significantly increased odds ratio of 3.9 for CLL in men in relation to a history of eczema [87]. Case-control studies by Severson et al. [88] and McKinney et al. [73] both reported a significantly reduced risk of acute myeloid leukemia (AML) in relation to a history of allergy. Severson et al. [88] also noted an inverse relationship between AML and number of allergies. The finding of a protective effect of allergy on risk for AML has not however, been replicated in subsequent case-control studies [71;89].

A protective effect of allergies has been reported in studies of childhood leukemia. Wen et al. [90] found reduced risks for ALL in children in relation to a variety of allergic conditions, as well as an inverse relationship between ALL and number of allergies. Nishi et al. [91] reported a significantly reduced risk 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 [92]. A large case-control study of childhood leukemia in Germany also reported significantly decreased risks for ALL in children associated with a history of allergies and atopic conditions [93].

Multiple Myeloma

Overall, little evidence exists for a relationship between allergy and multiple myeloma with the majority of studies reporting no association [38-40;71;75;94-105]. Williams et al. [105] restricted cases to light chain myeloma and found no association with a history of allergy. A large case-control study by Lewis et al. [102] evaluated the risk of multiple myeloma by immunoglobulin subtype. Although no overall association was found with a range of allergic conditions, significantly increased risks for IgG myeloma in whites were associated with a history of eczema (OR = 2.1, 95% CI = 1.1-4.2) and any 'allergic condition' (OR = 1.6, 95% CI = 1.1-2.3) [102]. Another study examining risk factors for multiple myeloma by immunoglobulin type reported no association with a history of allergy [100]. An increasing risk for multiple myeloma with increasing number of allergies was reported by Bourguet et al. [95]; the results however, were non-significant and based on a very small number of cases.

Other

A doubling in risk for Classical Kaposi's sarcoma was observed in asthmatic individuals infected with Kaposi's sarcoma-associated herpes virus (KSHV) [106]. An increased risk of Classical Kaposi's sarcoma was also observed amongst KSHV infected males with a history of allergy (OR = 2.6, 95% CI = 1.2-5.8), but not in females (OR = 0.1, 95% CI = 0.0-2.8) [106]. Inconsistent results have been reported between a history of allergy and mycosis fungoides [107;108].

Brain Cancer

Case-control studies have consistently reported a protective effect of allergy on the occurrence of glioma. An early study reported a 40% reduction in risk for glioblastoma among those who had ever received treatment for allergies or allergy shots[109]. Subsequently, a large international case-control study coordinated by the International Agency for Research on Cancer examined various potential risk factors for brain cancer in adults in eight centers [110]. Upon pooling of the data, inverse associations were found between risk of 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), eczema (OR = 0.6, 95% CI = 0.5-0.9), and other allergies (OR = 0.6, 95% CI = 0.5-0.7) [110]. Recently, two other large case-control studies reported similar results [111;112]. Brenner et al. [111] reported 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. [112] reported a 50% reduction in risk for glioma in relation to a history of any allergy. Significantly reduced risks were also noted with specific allergies and allergic symptoms. A significant trend in risk was also noted, with risk decreasing as the number of allergies increased. The only prospective study of the risk of glioma was based on the Swedish Twin Registry. A protective effect of allergies on glioma risk was reported in a cohort of same gender twins born between 1886 and 1925 (HR = 0.4, 95% CI = 0.2-1.1) [113]. 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 [113]. Although this is the only prospective study to date, it includes only a small number of brain cancer cases with a history of allergy. The cohort study by Kallen et al. [38] found a reduced risk of tumors of the 'eye and nervous system' among asthmatics (SMR = 75, 95% CI = 64-88).

No significant association has been reported between meningioma and a history of allergy in previous case-control studies [110;111;114]. The Swedish Twin Registry study reported a doubling in risk for meningioma among those with any allergic condition [113]. Significantly increased risks were noted in the study by Brenner et al. [111] for acoustic neuroma in association 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).

Reproductive Cancers

The association between a history of allergy and reproductive cancer has received less attention. Overall, no clear evidence exists for an association between a history of allergy and ovarian, cervical, breast, prostate or testicular cancer. However, there is relatively strong and consistent evidence of a protective effect of asthma on uterine cancer.

An early study noted an inverse relationship between allergies and gynecologic cancers in females [115]. Mills et al. [40] 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 number of allergies. No other significant associations were found between ovarian cancer and other allergy measures in this study. Kallen et al. [38] reported a reduction in the risk of ovarian cancer in asthmatics (SIR 52, 95% CI = 42-63). All other studies have reported no association between ovarian cancer and atopy, asthma, or hay fever [19;32;39].

Previous case-control studies have reported no association between a history of allergy, asthma, or hay fever and uterus cancer [30;32]. However, all previous cohort studies reported reduced risks of uterus cancer in relation to a history of asthma. Kallen et al. [38] reported a SMR of 36 (95% CI = 28-46) for cancer of the corpus uterus and 58 (32-104) for uterus, NOS (not otherwise specified) in those hospitalized for asthma. Mills et al. [40] reported hazard ratios for endometrial cancer of 0.7 (95% CI = 0.2-1.8) in asthmatics and 1.5 (95% CI = 0.9-2.5) in those with hay fever. Lastly, a SIR of 76 (61-92) was reported for corpus uterus cancer in asthmatics in a large record linkage study [39].

Kallen et al. [38] reported a significantly reduced risk of cervical cancer in asthmatics (SMR = 52, 95% CI = 39-69). Vesterinen et al. [39] reported a reduced (non-significant) risk for cervical cancer (SIR = 80, 95% CI = 58-108) in asthmatics. A case-control study reported a significantly reduced risk of cervical cancer in association with a history of hives (OR = 0.6), but not asthma or hay fever [32]. Recently, a tripling in risk for cervical cancer was reported in those with eczema, although this was considered to be likely of the non-atopic type and thus represented an immune deficiency [116]. The same study also reported no association between a history of hay fever and cervical cancer.

A reduction in the risk of breast cancer in asthmatics by nearly half was reported in a case-control study by Ghadirian et al. [117]. Kallen et al. [38] also reported a reduction in risk of a similar magnitude in individuals diagnosed with asthma in Swedish hospitals. However, Talbot-Smith et al. [57] reported no association between asthma (HR = 1.1, 95% CI = 0.5-2.6) or hay fever (HR = 0.9, 95% CI = 0.5-1.7) and breast cancer risk in the 1981 Busselton cohort. A clinic-based study reported a SIR of 250 (95% CI = 101-516) for atopic subjects [13]. The results of this study are, however, based on few cases in a select population, and are not adjusted for important covariates. Vena et al. [32] reported no association between breast cancer risk and a history of asthma or hay fever, but did report a significant reduction in risk in relation to a history of hives (OR = 0.7). Reductions in risk for breast cancer with a history of allergy were also reported in two other small case-control studies[19;30]. All remaining studies reported no association between a history of allergy and breast cancer risk [14;39;40].

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) [118]. The results were, however, 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 an increased risk for prostate cancer among those with asthma (HR = 1.9, 95% CI 1.0-3.6) and no association with hay fever (HR = 1.1, 95% CI 0.6-2.0) [57]. 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) [57]. The remaining cohort studies that evaluated the risk for prostate cancer in relation to a history of allergy reported no association, with the exception of the study by Kallen et al. [38] who reported a SMR of 72 (67-78) [14;32;39;40].

Kallen et al. [38] reported an inverse association between asthma and testicular cancer (SMR = 37, 95% CI = 16-85). Swerdlow et al. [119] 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 testicular cancer and allergy reported no association [37;120;121].

Other Cancers

Few other specific cancer sites have received much study. Overall, the association remains unclear for most of the remaining cancer sites. However, asthma has been frequently related with an increased risk of bladder cancer.

A large case-control study reported an odds ratio of 0.8 (95% CI = 0.6-1.0) for colorectal cancer in relation to a history of allergic conditions [122]. A prospective study by Talbot-Smith et al. [57] also recently reported reduced relative risk estimates for colorectal cancer in association with a history of asthma or hay fever, although none were significant. The remaining cohort studies evaluated colon and rectal cancer separately [38-40]. Although some significant findings were observed, these results were inconsistent.

Kallen et al. [38] reported a reduced risk for both colon (SMR = 72, 95% CI = 65-79) and rectal cancer (SMR = 59, 95% CI = 52-68) in asthmatics. Mills et al. [40] reported no association between a history of asthma or hay fever and colon cancer, but a reduced risk for rectal cancer in relation to a history of asthma (HR = 0.6, 95% CI = 0.1-2.3) and hay fever (HR = 0.8, 95% CI = 0.3-1.7). Vesterinen et al. [39] reported a significantly increased risk for rectal cancer in women with asthma (SIR = 142, 95% CI = 117-169) but not in men. No association was reported between asthma and colon cancer. All remaining case-control studies reported no significant associations, however some negative non-significant associations were observed [123-126].

Elevated risks were reported for esophageal and gastric cardia adenocarcinomas in asthma patients by Ye et al. [127]. Both Vena et al. [32] and Mills et al. [40] reported no association between asthma or hay fever and stomach cancer. In a larger prospective study, Vesterinen et al. [39] reported a SIR of 85 (95% CI = 71-100) for stomach cancer in men and 91 (95% CI = 77-107) in women with asthma. Kallen et al. [38] reported a 50% reduction in risk for stomach cancer in asthmatics. A small case-control study reported a 40% reduction in risk for esophageal cancer in those with a history of allergy[30]. Lastly, Dai et al. [128] also reported inverse associations between a history of various allergies and esophageal cancer.

The association between a history of allergies and medullary thyroid carcinoma was evaluated in a pooled analysis of 14 international case-control studies [129]. A doubling in risk was found for medullary thyroid carcinoma in those with a history of

allergies [129]. Other studies evaluating the relation between thyroid cancer and allergy have reported inconsistent results [130;131].

An early 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) [132]. 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) [133]. A significantly increased risk for bladder cancer in asthma patients has also been reported by Vesterinen et al. [39] in men (SIR = 125, 95% CI = 100-150) but not in women (SIR = 90, 95% CI = 60-128). Lastly, Kim et al. [134] reported an odds ratio of 4.2 (95% CI = 1.6-10.8) for bladder cancer among those with a history of asthma. An increased risk was seen 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.

Summary

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 due to insufficient evidence or a lack of consistency both within and among studies completed to date. It is clear, however, that the nature of the relationship depends on the cancer site studied. Protective effects of allergy have been reported for pancreatic cancer, glioma, and uterine cancer. Conversely, lung cancer and bladder cancer are

positively associated with asthma. No association was noted in our review between allergy and multiple myeloma or all cancers combined.

A number of important methodological issues are apparent in previous studies. A discussion of methodological considerations including exposure assessment, confounding, and bias, is now presented.

Measurement of Allergy

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 [54;135;136]. Similarly, the etiology of conditions such as asthma, eczema, or urticaria is variable, involving a number of immunological and non-immunological factors, including allergy [137;138]. For example, asthma development in childhood likely has an allergic mechanism; however, adult-onset asthma does not. The misclassification of allergic status could affect the direction of observed associations between allergy and cancer risk. The vast majority of previous studies use self-reported history of allergic conditions for measurement of allergy. Relatively few questionnaires that have attempted to measure a history of allergy have been validated. Validating asthma and eczema-related questionnaires is particularly difficult due to the absence of a universally accepted definition of these conditions.

In adults, physician-diagnosed asthma questions are preferable to symptom-based questions or questions asking if they have ever had the disease, as they demonstrate high reliability, specificity, and positive predictive values [136;139]. This is of importance in order to limit false positives in etiological studies in which the prevalence of asthma is fairly low [136]. 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 [140-144].

A questionnaire using "physician-diagnosed hay fever" has also been validated [139]. This physician-diagnosed hay fever question resulted in the most accurate diagnosis among different questions assessing a history of hay fever [139]. A score-based questionnaire to distinguish between allergic rhinitis and other similar conditions has also been validated, and found to demonstrate improved sensitivity but reduced specificity as compared to the "physician-diagnosed" questions discussed above [135].

A study validating a questionnaire for hand eczema reported that in a population-based sample, asking if the participant has/had eczema, resulted in a high specificity and sensitivity [145]. When inquiring about eczema-related symptoms, however, agreement between the participant and dermatologist was poor, leading to the conclusion that these types of questions were not appropriate for population-based studies [145].

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 four year period found that the concordance of reporting of current asthma was only 76.6%, likely due to variability in symptom presentation [146]. One study validating a questionnaire for atopic dermatitis reported that those most likely to be classified as false negatives were those with mild symptoms [147]. 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 [139]. 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[38;39].

Following a detailed symptom history, measurement of specific IgE antibodies through skin testing or a radioallergosorbent test (RAST) could be performed in order to confirm allergic status. In case-control studies, however, such information from cases may be affected by the developing cancer [68]. 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 [68;148-150]. Obtaining a history of other atopic conditions and assigning allergic status when a history of other atopic disorders exists has also been suggested in order to reduce misclassification [147]. For example, a list of criteria for use in epidemiological studies to improve discrimination between atopic dermatitis and other similar conditions that are

not allergic in nature was created [147]. Three of the five criteria must be present in order to classify an individual as having atopic dermatitis of which one is "a personal history of asthma or hay fever" [147]. Significant trends in cancer risk in relation to allergy and cancer have been reported, with the risk of cancer decreasing as the number of allergies increases [40;68;86;88;90;112]. A possible reason for this is that the accuracy of classification of individuals into allergic versus non-allergic 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 [151]. 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%) [152]. It has been suggested that a proxy effect is likely, however, in parents reporting allergic symptoms [153].

In adults, few studies have attempted to assess the accuracy of proxy respondents in reporting prior medical history. Linet et al. [154] measured agreement in reporting of medical history, including allergy, between interview data and medical records in self and proxy respondents[154]. 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 five years prior to the initial interview [155].

It was suggested that detailed information regarding medical history may need to be confirmed through medical records when using proxy respondents [155;156]. Obtaining a second source of medical information has also been suggested to improve accuracy of medical history [157]. Few studies have attempted to determine if an effect due to respondent type exists. Wiemels et al. [112] noted consistently stronger protective effects of a history of allergy and glioma risk with proxy respondents versus self-respondents. However, an opposite effect was seen in some pancreatic cancer studies [158;159]. Schwartzbaum et al. [113] 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 cases due to pre-clinical 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 would be particularly useful as these potential sources of bias would be minimized.

Other Issues

In addition to concerns about measurement of allergy, there are other important methodological issues in studies of allergy and cancer. 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. 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 [14;45;49]. 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. Socio-economic status is another important factor that has not often been taken into consideration. Socio-economic status has been associated both with allergy [160-163] and with cancer occurrence and survival [164;165], and may represent an important confounder. Other important site-specific cancer risk factors have only been considered by the most recent studies.

Symptoms of certain developing malignancies may be mistaken as being allergic in origin, and may result in misdiagnosis and misclassification of allergy. For example, symptoms similar to asthma have been expressed in those with tumors of the respiratory tract, leukemia, and NHL [166-173]. Similarly, eczema in adulthood has been reported as a presenting sign in those with lymphoproliferative malignancies, mycosis fungoides [174;175], and pancreatic carcinoma [176]. This could produce a positive bias because of the greater number of cancer cases reporting previously diagnosed allergic symptoms. 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 [38;62].

Another potential source of bias relates to screening. A screening bias may exist in those with frequent contact with the medical profession due to allergic symptoms

increasing the opportunity for cancer detection [40]. The increased likelihood of cancer detection may introduce a positive bias into the observed association in incidence-based studies, because of a greater proportion of allergic individuals being diagnosed. It could also lead to a negative bias if the diagnoses were occurring at an earlier time among people with allergies, hence improving survival due to earlier detection.

Several biases in the literature review process may have exerted an effect on the findings of this review. Study selection was restricted by language to papers written in English. Publication bias may exist as a consequence of null studies not appearing in the literature. The search strategy may have also failed to locate studies in which a history of allergy was obtained and examined as a risk factor for cancer, but which was not reported in the search fields. This is a real possibility, since a large number of studies were found through citations within the primary articles located. Finally, the impact of findings not indexed in the databases searched on conclusions drawn is unknown.

Overall, the findings of this literature review can be summarized into the following key points:

(1) It remains unclear if an allergic history is associated with overall cancer occurrence.

(2) A history of asthma may increase risk for lung cancer.

(3) A history of allergy may protect against glioma.

(4) Numerous other protective associations have been reported at other cancer sites, however additional studies are needed and limitations of previous studies need to be addressed in order to confirm these findings.

METHODS – DATA ANALYSIS

Study Design

The Cancer Prevention Study II is a longitudinal study designed and conducted by the American Cancer Society. The study design and population have been previously described[177]. A total of 508 334 men and 676 288 women were enrolled by 77 000 volunteers in 1982, with the goal of examining the role of environmental and lifestyle factors in cancer etiology. Participants were recruited from all 50 states as well as the District of Columbia and Puerto Rico, and were composed largely of individuals known to the volunteers such as friends or family. Study participants were required to be at least 30 years of age, as well as having one family member 45 years of age or older. Participants completed a four-page baseline self-administered questionnaire in 1982, which included questions about a range of lifestyle factors, demographic characteristics, medical history, family cancer history, and other characteristics (Appendix 2).

The determination of the vital status of study participants is conducted every two years, and is complete through to December 31, 2000. Two different methods were used to ascertain follow-up status. In September of 1984, 1986, and 1988, volunteers inquired as to the vital status of participants they had previously enrolled. This inquiry was confirmed by obtaining the corresponding death certificates. Computerized linkage to the National Death Index was used since 1989 to complete the follow-up[178]. As of December 31 2000, 176 140 (34.7%) men and 156 533 (23.2%) women had died, 331 360 (65.2%)

men and 517 659 (76.5%) women were alive, and 818 (0.2%) men and 2 078 (0.3%) women had follow-up terminated in September of 1988 due to inadequate information with which to link to the National Death Index. Over 98% of deaths have been assigned a cause.

Cancer deaths were classified by the underlying cause of death according to the International Classification of Disease (ICD). The ninth revision was used for follow-up through to 1998, and the tenth revision was used for follow-up from 1999 through to the end of 2000. The following ICD 9/10 codes respectively were used to define cancer deaths by site.

- All Cancer (140-195, 199-208 / C00-C76, C80-C97)
- Lung Cancer (162 / C33, C34)
- Colorectal Cancer (153, 154 / C18-C21)
- Breast Cancer (Women) (174 / C50)
- Prostate Cancer (185 / C61)
- Pancreas Cancer (157 / C25)
- Non-Hodgkin's Lymphoma (200, 202 / C82-C85)
- Leukemia (204-208 / C91-C95)
- Brain Cancer (191 / C71)
- Multiple Myeloma (203 / C88, C90)
- Stomach Cancer (151 / C16)
- Ovarian Cancer (183 / C56)
- Corpus and Uterus NOS Cancer (182, 179 / C54, C55)

Ascertainment of Asthma and Hay Fever Status

The baseline survey prompted the individual to "place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor". Included in the listing of 25 diseases or medical conditions were asthma and hay fever. Four categories of were constructed: asthma, hay fever, asthma and hay fever, asthma and/or hay fever. A reference category comprised of individuals with no asthma and no hay fever was also constructed. These categories allowed for the testing of the independent effects of asthma and hay fever. The combined category of asthma and hay fever allowed for the evaluation of a group of individuals more likely to be truly atopic.

Statistical Analysis

Following approval of the study protocol by the ACS, SAS data sets were provided which included 348 variables for men and 356 variables for women. In order to limit instability of risk estimates, cancer sites were selected for analysis if there were at least 10 deaths across all exposure categories in men and women. Men and women were analyzed separately due to the physiological differences between the sexes, thereby permitting an evaluation of effect modification by gender. For each cancer site evaluated, participants were excluded from analysis if they reported prevalent cancer at study entry (except non-melanoma skin cancer) or had missing information on asthma or hay fever status. Additional participants were excluded from analysis of uterine cancer

mortality if they reported a previous hysterectomy or an artificial as opposed to a natural menopause. This removed individuals who were not at risk for developing uterine cancer from the study population. Participants were excluded from analysis of ovarian cancer mortality if they reported a previous hysterectomy, artificial menopause, or ovarian surgery (because it was unknown if or how many ovaries were removed in these surgeries).

Death rates per 100 000 person-years were calculated according to asthma and/or hay fever status and were directly age-standardized to the sex-specific age distribution of the entire cohort. The following age categories were used for the standardization procedure: less than 45 years, 45 to 49 years, 50 to 54 years, 55 to 59 years, 60 to 64 years, 65 to 69 years, 70 to 74 years, and 75 years or greater. All covariates (except age) were also adjusted by this procedure upon presentation of the distribution of the variables by asthma and/or hay fever status. This age adjustment allowed for greater comparability of the death rates and covariates by asthma and/or hay fever status.

Cox proportional hazards regression models were used to determine the independent effects of asthma and/or hay fever on cancer mortality, while adjusting for other cancer site-specific covariates. This was performed using the SAS procedure PROC PHREG. Cox regression is a standard modelling technique used to analyze survival data[179-182], providing both hazard ratios and associated 95% confidence intervals for cancer mortality in relation to asthma and/or hay fever. Survival data are unique in that they contain information on both the occurrence and timing of events, with

individuals who do not experience the event of interest being censored. Cox regression is a robust technique as it does not require a specific probability distribution to be applied to the survival times. As discussed below, it also allows for a particular type of model stratification [183]. The use of Cox regression requires assumptions including the independence of observations, noninformative censoring, the proportionality of covariates over time, and a log-linear effect of the covariates on the hazard function.

In this analysis, follow-up time since baseline (1982) was used as the time axis. The survival times of those still alive were censored at the end of follow-up. Two separate main effects models were fit for each exposure category: an age-adjusted model and a multi-variable model which included additional variables to adjust for the effects of other site-specific cancer risk factors. Age adjustment was achieved by stratifying the baseline hazard of each proportional hazards regression model by one-year age categories. The allowance of separate baseline hazards for each age category avoids the proportional hazards assumption for this variable (this technique is often utilized in cancer epidemiology in order to adjust for different birth cohort effects). Once a stratified Cox proportional hazards regression model is specified, the product of the stratum specific partial likelihoods

$$l_{Sp}(\beta) = \prod_{s=1}^{S} l_{sp}(\beta),$$

is maximized in order to estimate the parameters ß, where the partial likelihood for a given stratum s is[184]:

$$l_{sp}(\beta) = \prod_{i=1}^{n_s} \left[\frac{e^{x'_{si}\beta}}{\sum_{j \in R(t_{si})} e^{x'_{sj}\beta}} \right]^{c_{si}}.$$

The exponent c_{si} is the value of the censoring variable (0 or 1) associated with each death time t_{si}. The total number of subjects in each stratum is represented by n_s, and $R(t_{si})$ is the total number of subjects in the risk set at a particular time t_{si}. Lastly, x_{si} represents the vector of p covariates. Testing of the ß coefficients remains appropriate in a stratified model as their associated variance remains a function of the total sample size contributed and total number of survival times[184]. Stratification by age is a robust method in the sense that it does not require a specific form for the interaction with time to be specified[183]. Stratification is also computationally efficient, which is advantageous when working with large datasets such as the CPS-II cohort[183].

Covariates included in the cancer site-specific multi-variable models were chosen based on associations previously reported in this or other study populations. These covariates were categorized according to the categories presented in Table 1 and Table 2 in the results section. Adjustment for smoking was achieved by the inclusion of categorical variables for smoking status (never, current cigarette smoker, former cigarette smoker, ever cigarette smoker – unknown if current or former, pipe/cigar smoker (men only), missing). A sensitivity analysis was also conducted through the addition of variables representing pack-years of smoking and intensity of smoking to the previously mentioned smoking status variables. Categorical variables indicating the number of pack years (less than 20, 20 to less than 40, 40 to less than 60, 60 or greater, missing) or

cigarettes smoked per day (0 to19, 20, greater than 20, missing) were employed for both current and former smokers.

A number of derived variables were constructed from the original survey data. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Following the World Health Organization, BMI was divided into categories of less than 18.5 kg/m^2, 18.5 to 24.9 kg/m^2, 25 to 29.9 kg/m^2, 30 kg/m^2 or greater, and missing[185]. The total number of siblings was the sum of the number of bothers and sisters (0 to 6). The total number of hours exposed to environmental tobacco smoke per day was constructed by summing the total number of hours exposed per day at home, work and other areas (0, greater than 0 to less than 3 hours, 3 hours to less than 6 hours, 6 or more hours, and missing).

Nutritional variables were constructed from responses indicating the numbers of days per week 32 particular foods were consumed. Participants reporting consumption of less than 5 foods were classified as missing. Otherwise, participants with blank responses were considered as nonconsumers. Quartiles for each nutritional variable were constructed with the SAS PROC RANK procedure. Fat intake (grams/week) was estimated by an age and sex-specific algorithm that multiplies the numbers of times per week 20 different foods were consumed by the estimated portion size and fat content. Weekly vegetable intake was constructed by the sum of the weekly frequency of consumption of green leafy vegetables, tomatoes, cabbage/broccoli/brussel sprouts, raw vegetables, carrots, potatoes, and squash/corn. Weekly fruit consumption was the

number of times per week participants reported consuming citrus fruits or juices. Weekly fiber intake was represented by the sum of the weekly frequency of consumption of brown rice/whole wheat/barley, bran/corn muffins, and oatmeal/shredded wheat/bran cereals. Weekly intake of vegetables, fiber and fruit was considered the sum of weekly vegetable intake, weekly fruit intake, and weekly fiber intake. Weekly fatty meat intake was the sum of the weekly consumption of beef, pork, liver, ham, smoked meats, frankfurters/sausage, fried hamburgers/beef, and fried bacon.

Other variables were tested for a significance in the final multi-variable models, but were not included since they had virtually no effect on estimates of cancer risk. Although detailed results are not presented here, the variables which were tested included the following.

- Lung cancer: age started smoking among current and former smokers.
- Colorectal cancer: fruit intake, diabetes, colon polyps, and rectal polyps.
- Breast cancer: breast lump within the past 12 months, breast cysts, fat intake, and diabetes.
- Pancreas cancer: parity.
- NHL: alcohol, physical activity, arthritis, tuberculosis, bronchitis, diabetes, and height.
- Leukemia: Occupational exposure (x-rays/radioactive materials and diesel engine exhaust). Occupation (farmer, miner, electrician, or oil field worker/refinery worker).

- Brain cancer: alcohol, parity, artificial menopause, occupational exposures (chemicals/acids/solvents, x-rays/radioactive materials, and pesticides/herbicides), occupation (electrician, oil field worker/refinery worker, health professional (doctor, ophthalmologist, physician, veterinarian, GP, dentist), farmer), diabetes, marital status, and arthritis.
- Multiple myeloma: family history of multiple myeloma, diabetes, tuberculosis, occupational exposures (x-rays/radioactive materials, pesticides/herbicides, chemicals/acids/solvents, and asbestos), occupation (farmer, or oil field worker/refinery worker).
- Stomach cancer: alcohol, exercise, occupational exposures (coal/stone dusts, wood dust, asbestos, and pesticides), occupation (farmer), Tagamet use, antiacid use, duodenal ulcer, stomach ulcer, chronic indigestion, age at menopause, age at menarche, parity, and estrogen replacement therapy use .
- Ovarian cancer: aspirin use.
- Corpus and uterus NOS cancer: fat/fiber/vegetable intake, family history of uterus cancer, and family history of breast/ovarian cancer.

Effect modification was assessed by cigarette smoking status and age at baseline in order to identify differences across cigarette smoking and age sub-groups. Separate risk estimates were calculated within each stratum and multiplicative interaction terms were constructed to evaluate heterogeneity across subgroups. The significance of these interaction terms was assessed using a likelihood ratio test at the $\alpha = 0.05$ level. For

cigarette smoking status, interaction terms were constructed between asthma and/or hay fever and either both current and former smoking status (excluding ever smokers, pipe/cigar smokers, and unknown smoking status) or ever smoking status, which combines current, former and ever smokers (excluding pipe/cigar smokers and unknown smoking status) according to the available sample size. As cigarette smoking status can be strongly influenced by asthma and/or hay fever status, the estimation of risk among the subgroup of non-smokers also allows for a determination of the effect of asthma and/or hay fever status on cancer survival that is largely free of possible residual confounding by smoking history. It also reduces possible asthma misclassification as other smoking related conditions. For age at baseline, an interaction term was constructed between asthma and/or hay fever and a dichotomous variable representing age below 55 years or age equal to or above 55 years. The potential for effect differences of asthma with age exists, as the potential for misclassification of asthmatic status increases with age.

The proportional hazards assumption was tested through the inclusion of a multiplicative interaction term between asthma and/or hay fever and follow-up time[183]. The significance of the interaction term was tested at the $\alpha = 0.05$ level. All analyses were conducted using SAS version 8.2. Two-sided statistical tests were used throughout the analysis.

RESULTS – ANALYSIS

From a total sample of 508 318 men, 483 079 were retained for analysis following exclusions for prevalent cancer at baseline except non-melanoma skin cancer (25 238) and missing asthma or hay fever status (1). From 676 270 women, a total of 618 668 were retained for analysis following exclusions for prevalent cancer at baseline except non-melanoma skin cancer (57 103) and missing asthma or hay fever status (499). Additional women were excluded if a hysterectomy or artificial menopause was reported (201 142) for the analysis of ovarian cancer and uterine cancer; 12 385 women were also excluded for prior ovarian surgery in the analysis of ovarian cancer. This resulted in 417 526 women remaining for analysis of uterine cancer, and 405 141 for the analysis of ovarian cancer.

The prevalence of self-reported asthma was 4.4% in men and 4.7% in women. Hay fever was reported by 10.3% of men and 12.8% of women. Both asthma and hay fever were reported in 2.2% of men and 2.7% of women.

Table 1 displays the distribution of risk factors for cancer mortality by history of asthma and/or hay fever in men; similar results for women are presented in Table 2. On average, individuals with asthma and/or hay fever tended to be younger and more likely to be non-smokers or former smokers. Those with a history of asthma and/or hay fever also tended to have achieved a higher level of education than those without. Those with asthma and/or hay fever tended to consume greater amounts of vegetables, fruit, and

fiber, and were more likely to take multivitamins. In women, those with asthma and/or hay fever were more likely to use oral contraceptives and estrogen replacement therapy. Previous lung diseases were more frequently reported by those with asthma and/or hay fever. In particular, asthmatics were much more likely to report a history of chronic bronchitis and emphysema than non-asthmatics.

Table 1. Distribution of Risk Factors for Cancer Mortality by History of Asthma and Hay Fever in Men *

Asthma and/or Hay Fever Status	Asthma (n = 21 101)	Hay Fever (n = 49 764)	Asthma and Hay Fever (n = 9 416)	Asthma and/or Hay Fever (n = 61 469)	No Asthma and no Hay Fever‡ (n = 421 610)
SOCIODEMOGRAPHIC VARIABLES					
Age (years)					
<40	5.3	5.3	5.9	5.2	3.7
40-49	20.3	22.5	23.0	21.7	17.8
50-59	37.4	38.8	38.9	38.3	37.7
60-69	26.2	24.4	23.8	25.1	28.6
70-79	9.3	8.0	7.4	8.5	10.6
80+	1.5	1.0	1.1	1.2	1.7
Race					
White	93.8	94.2	95.2	93.9	93.9
Black	3.7	3.2	2.7	3.4	3.8
Other†	2.5	2.6	2.0	2.6	2.3
Education					
Less than HS	14.8	9.9	10.1	11.6	16.2
HS graduate	16.2	14.0	13.4	14.8	20.6
Some college	26.2	26.1	25.6	26.1	26.9
College grad	41.5	48.9	49.7	46.2	34.8
Missing	1.3	1.1	1.2	1.2	1.5
BMI (kg/m^2)					
<18.5	1.2	0.8	1.0	0.9	0.9
18.5-24.9	40.7	42.1	42.3	41.6	37.5
25-29.9	46.3	46.8	46.3	46.7	48.9
30+	9.8	8.4	8.7	8.9	10.4
Missing	2.1	1.8	1.8	1.9	2.3
Marital Status					
Single	6.5	5.7	6.3	5.9	5.6
Married	93.0	93.8	93.3	93.6	93.8
Missing	0.5	0.4	0.4	0.5	0.6
No. of Siblings					
None	31.8	32.1	33.6	31.7	28.9
1 sibling	17.7	18.3	18.8	18.0	15.7
2 siblings	16.2	16.4	16.4	16.3	15.8
3 siblings	11.8	11.8	11.5	11.8	12.5
4 siblings	7.6	7.6	7.0	7.7	9.0
5 siblings	5.4	5.4	4.8	5.5	6.9
6 siblings	9.5	8.6	7.9	9.0	11.2
BEHAVIOURAL VARIABLES					
Smoking					
Non smoker	26.7	33.1	31.2	31.2	24.3
Current	16.8	13.3	13.5	14.5	21.8
Former	31.2	27.8	28.8	28.9	29.4
Ever	1.7	1.3	1.4	1.4	1.6
Pipe/cigar	20.9	21.7	22.8	21.3	19.7
Missing	2.7	2.7	2.3	2.8	3.2
Exercise					
None	2.8	1.9	2.2	2.2	2.2
Slight	25.5	23.5	25.6	23.9	21.5
Moderate	60.2	63.4	61.1	62.6	63.1
Heavy	10.4	10.4	10.1	10.4	12.1
Missing	1.1	0.9	1.0	1.0	1.2
Alcohol					
Non drinker	12.6	13.1	13.5	12.9	11.8
Occasional	13.5	14.2	14.4	14.0	13.0
1 drink/day	7.0	7.6	7.6	7.4	6.5
>1 drink/day	17.2	17.3	17.9	17.2	16.8
Former	3.0	2.5	3.1	2.6	2.2
Missing	46.6	45.3	43.5	46.0	49.6
Beer Consumption					
No	22.0	22.6	23.8	22.3	19.6

Yes	25.2	25.4	25.6	25.3	25.4
Missing	52.8	52.0	50.6	52.4	55.0
Wine Consumption					
No	24.2	23.7	25.0	23.6	22.8
Yes	17.8	20.3	20.8	19.3	15.0
Missing	58.0	56.0	54.2	57.0	62.2
Liquor Consumption					
No	23.2	23.3	24.1	23.2	21.4
Yes	24.7	25.7	27.2	25.1	22.7
Missing	52.1	51.0	48.7	51.8	56.0
MEDICATIONS AND VITAMINS					
Aspirin Use					
Non user	42.2	39.4	39.9	40.3	43.7
Occasional	29.5	30.3	29.1	30.2	30.6
<15 per month	17.7	19.1	19.3	18.6	16.3
15+ per month	9.3	9.9	10.3	9.6	8.3
Missing	1.4	1.3	1.4	1.3	1.1
Multivitamin Use					
Non user	67.0	65.4	64.1	66.2	71.3
Occasional	5.4	5.8	5.5	5.7	5.1
<15 per month	6.2	6.3	6.5	6.2	5.5
15+ per month	20.8	21.9	23.3	21.3	17.6
Missing	0.6	0.6	0.7	0.6	0.5
NUTRITIONAL VARIABLES					
Vegetable Consumption					
1st quartile	22.4	19.5	19.6	20.5	23.7
2nd quartile	22.2	21.8	22.0	21.9	22.4
3rd quartile	24.4	25.5	25.3	25.2	24.0
4th quartile	24.1	26.7	26.7	25.8	22.2
Fruit Consumption					
1st quartile	22.1	19.2	19.8	20.2	23.6
2nd quartile	25.5	25.4	25.8	25.3	25.4
3rd quartile	11.4	12.3	11.7	12.0	11.2
4th quartile	34.1	36.6	36.3	35.8	32.1
Fiber Consumption					
1st quartile	13.4	12.6	13.1	12.8	13.9
2nd quartile	30.6	28.2	28.3	29.0	33.0
3rd quartile	24.0	24.6	24.6	24.3	22.6
4th quartile	25.0	28.1	27.7	27.1	22.8
Vegetable, Fruit, Fiber Consumption					
1st quartile	22.0	18.7	19.2	19.8	23.9
2nd quartile	22.6	21.5	21.9	21.8	23.0
3rd quartile	23.4	24.4	24.2	24.1	22.6
4th quartile	25.0	28.9	28.4	27.6	22.8
Fat Consumption					
1st quartile	21.9	21.7	20.3	21.9	23.3
2nd quartile	23.2	24.0	24.3	23.7	23.0
3rd quartile	23.2	24.1	23.6	23.8	23.0
4th quartile	24.7	23.8	25.5	23.9	23.0
Red Meat Consumption					
1st quartile	22.1	23.6	22.4	23.2	22.7
2nd quartile	25.1	25.1	25.3	25.1	24.8
3rd quartile	23.3	23.0	23.1	23.1	22.8
4th quartile	22.5	21.8	22.8	21.9	21.8
Unclassifiable	7.0	6.5	6.3	6.7	7.8
OTHER MEDICAL CONDITIONS					
Diabetes					
Yes	6.3	5.0	6.5	5.3	5.8
No†	93.7	95.0	93.5	94.7	94.2
Gallstones					
Yes	6.2	5.2	6.9	5.3	4.8
No†	93.8	94.8	93.1	94.7	95.2
Chronic Bronchitis					

Yes	14.4	5.0	13.7	7.0	2.4
No†	85.6	95.0	86.3	93.0	97.6
Emphysema					
Yes	11.5	3.4	9.7	5.3	2.7
No†	88.5	96.6	90.3	94.7	97.3
Tuberculosis					
Yes	2.3	1.6	3.3	1.6	1.1
No†	97.7	98.4	96.7	98.4	98.9
OCCUPATIONAL / ENVIRONMENTAL EXPOSURES					
Asbestos					
Yes	7.1	6.7	6.8	6.8	6.5
No†	92.9	93.3	93.2	93.2	93.5
Chemicals/Acids/Solvents					
Yes	20.2	19.4	19.6	19.7	18.6
No†	79.8	80.6	80.4	80.3	81.4
Coal/Stone Dust					
Yes	8.0	6.6	6.8	7.0	7.0
No†	92.0	93.4	93.2	93.0	93.0
Coal Tar/Pitch/Asphalt					
Yes	3.7	3.4	3.5	3.5	3.4
No†	96.3	96.6	96.5	96.5	96.6
Diesel Engine Exhaust					
Yes	14.6	12.8	13.8	13.3	13.6
No†	85.4	87.2	86.2	86.7	86.4
Formaldehyde					
Yes	3.9	3.8	4.1	3.8	3.1
No†	96.1	96.2	95.9	96.2	96.9
Passive Tobacco Smoke					
0 hours	32.0	31.9	32.0	31.9	31.5
>0-<3 hours	33.2	35.4	35.3	34.6	30.7
3-<6 hours	9.4	9.7	9.5	9.6	9.4
6+ hours	24.5	22.3	22.4	23.0	27.4
Missing	0.9	0.8	0.9	0.8	1.0
FAMILY HISTORY OF CANCER					
Colorectal Cancer					
Yes	4.8	4.8	5.0	4.8	4.5
No†	95.2	95.2	95.0	95.2	95.5
Prostate Cancer					
Yes	3.2	3.4	3.5	3.3	2.9
No†	96.8	96.6	96.5	96.7	97.1
Pancreatic Cancer					
Yes	1.2	1.2	1.1	1.2	1.1
No†	98.8	98.8	98.9	98.8	98.9
NHL					
Yes	1.0	1.0	1.0	1.0	0.9
No†	99.0	99.0	99.0	99.0	99.1
Leukemia					
Yes	1.7	1.7	1.7	1.7	1.6
No†	98.3	98.3	98.3	98.3	98.4
Brain Cancer					
Yes	0.9	1.0	1.0	1.0	1.0
No†	99.1	99.0	99.0	99.0	99.0
Stomach Cancer					
Yes	3.5	3.3	3.2	3.4	3.6
No†	96.5	96.7	96.8	96.6	96.4

* Directly standardized to the sex-specific age distribution of the entire cohort

† Includes missing

‡ Reference category

Table 2. Distribution of Risk Factors for Cancer Mortality by History of Asthma and Hay Fever in Women*

Asthma and/or Hay Fever Status	Asthma (n = 28 898)	Hay Fever (n = 79 162)	Asthma and Hay Fever (n = 14 486)	Asthma and/ or Hay Fever (n = 93 574)	No Asthma and no Hay Fever‡ (n = 525 094)
SOCIODEMOGRAPHIC VARIABLES					
Age (years)					
<40	6.5	6.7	6.9	6.6	5.3
40-49	24.8	26.8	27.5	26.1	22.2
50-59	34.5	35.4	35.9	35.1	34.2
60-69	23.3	21.6	21.2	22.2	25.2
70-79	9.1	7.9	7.1	8.4	10.7
80+	1.8	1.4	1.4	1.6	2.4
Race					
White	91.1	91.8	92.6	91.4	92.6
Black	5.9	5.2	4.7	5.5	5.0
Other†	3.0	3.0	2.7	3.1	2.4
Education					
Less than HS	13.6	10.5	10.5	11.4	14.0
HS graduate	25.8	24.7	23.5	25.3	31.2
Some college	31.9	32.7	33.7	32.3	29.3
College grad	27.0	30.6	30.8	29.4	23.9
Missing	1.7	1.5	1.5	1.5	1.6
BMI (kg/m^2)					
<18.5	2.9	2.6	2.8	2.7	2.7
18.5-24.9	53.5	59.3	55.8	58.0	57.6
25-29.9	27.0	25.4	26.7	25.7	26.2
30+	14.2	10.5	12.5	11.3	11.2
Missing	2.4	2.2	2.2	2.2	2.3
Height					
<66 inches	67.8	67.1	67.0	67.3	67.3
66-68 inches	26.4	27.3	27.2	27.1	27.2
>68 inches	4.5	4.5	4.7	4.5	4.2
Missing	1.3	1.1	1.1	1.2	1.3
Marital Status					
Single	25.4	23.4	23.9	23.9	23.8
Married	73.9	75.9	75.3	75.4	75.5
Missing	0.7	0.7	0.8	0.7	0.7
No. of Siblings					
None	27.9	28.2	28.9	28.0	26.1
1 sibling	18.8	19.2	19.6	19.0	17.5
2 siblings	17.1	16.9	17.7	16.8	16.5
3 siblings	11.8	11.9	11.4	11.9	12.7
4 siblings	8.5	8.1	8.0	8.2	9.1
5 siblings	6.3	6.1	5.6	6.2	7.0
6 siblings	9.6	9.6	8.8	9.8	11.2
BEHAVIOURAL VARIABLES					
Smoking					
Non smoker	50.1	56.0	53.6	54.6	52.4
Current	18.0	15.5	15.1	16.3	20.8
Former	25.1	21.9	24.9	22.4	19.9
Ever	2.2	1.9	2.2	2.0	1.8
Missing	4.6	4.7	4.3	4.7	5.1
Exercise					
None	3.0	2.1	2.8	2.3	2.3
Slight	26.9	24.6	26.6	25.1	23.5
Moderate	62.4	65.7	63.1	65.1	66.1
Heavy	5.5	5.6	5.4	5.6	6.0
Missing	2.2	1.9	2.0	2.0	2.1
Alcohol					
Non drinker	16.8	16.6	17.0	16.6	16.4
Occasional	11.5	12.1	12.3	11.9	11.2

1 drink/day	4.2	4.8	4.6	4.6	4.2
>1 drink/day	7.8	7.8	8.1	7.7	7.1
Former	1.7	1.5	1.8	1.5	1.2
Missing	58.0	57.3	56.2	57.6	59.8
Beer Consumption					
No	28.1	28.3	29.6	28.0	26.4
Yes	7.1	6.8	7.1	6.8	6.7
Missing	64.8	65.0	63.4	65.2	66.9
Wine Consumption					
No	22.2	21.4	22.2	21.5	21.0
Yes	17.1	18.6	19.2	18.0	15.7
Missing	60.8	60.1	58.6	60.5	63.3
Liquor Consumption					
No	24.8	24.5	25.3	24.5	23.3
Yes	14.3	14.8	15.3	14.6	13.3
Missing	60.9	60.7	59.5	61.0	63.4
MEDICATIONS AND VITAMINS					
Aspirin					
Non user	42.2	37.1	39.5	38.3	38.6
Occasional	30.4	33.3	30.9	32.8	35.0
<15 per month	16.1	17.5	16.8	17.2	16.4
15+ per month	9.4	10.1	10.6	9.8	8.2
Missing	2.0	2.0	2.2	2.0	1.8
Multivitamin Use					
Non user	60.1	57.9	57.1	58.7	63.9
Occasional	7.4	8.1	7.7	8.0	7.5
<15 per month	6.3	6.5	6.8	6.4	5.6
15+ per month	24.8	26.1	27.0	25.5	21.8
Missing	1.4	1.4	1.5	1.4	1.1
OC Use[‡]					
Never	66.0	65.5	64.3	65.9	68.8
Ever	29.6	30.4	31.7	30.0	26.6
Missing	4.4	4.1	4.1	4.2	4.6
ERT Use[§]					
Never	52.1	50.6	49.9	51.2	57.3
Ever	37.6	40.1	41.1	39.1	31.3
Missing	10.2	9.4	9.0	9.7	11.4
NUTRITIONAL VARIABLES					
Vegetable Consumption					
1st quartile	21.5	19.1	18.8	19.9	22.4
2nd quartile	22.4	22.4	21.9	22.5	23.0
3rd quartile	22.5	23.4	23.5	23.1	22.0
4th quartile	22.4	24.2	24.9	23.5	21.2
Fruit Consumption					
1st quartile	24.8	22.4	22.7	23.1	24.6
2nd quartile	22.3	23.3	22.5	23.1	22.9
3rd quartile	3.3	3.7	3.5	3.6	3.5
4th quartile	38.4	39.9	40.3	39.4	37.5
Fiber Consumption					
1st quartile	13.5	12.1	13.0	12.4	13.6
2nd quartile	29.0	27.4	27.0	28.0	30.7
3rd quartile	23.7	24.5	24.1	24.3	23.1
4th quartile	22.7	25.2	25.0	24.4	21.2
Vegetable, Fruit, Fiber Consumption					
1st quartile	21.6	18.7	18.6	19.6	22.6
2nd quartile	21.3	21.3	20.8	21.4	22.1
3rd quartile	23.0	24.0	23.6	23.7	22.6
4th quartile	22.9	25.2	26.1	24.3	21.4
Fat Consumption					
1st quartile	21.6	20.2	20.5	20.6	22.4
2nd quartile	21.8	22.4	22.2	22.2	22.2
3rd quartile	22.4	22.9	22.5	22.8	22.0
4th quartile	23.2	23.6	23.8	23.5	21.9
Red Meat Consumption					
1st quartile	21.3	20.8	21.0	20.9	21.2
2nd quartile	20.0	20.4	20.6	20.2	20.2

3rd quartile	23.4	24.4	23.4	24.2	24.2
4th quartile	24.2	23.6	24.1	23.7	23.0
Unclassifiable	11.1	10.8	11.0	10.9	11.5
OTHER MEDICAL CONDITIONS					
Diabetes					
Yes	6.2	4.4	6.2	4.7	4.4
No[†]	93.8	95.6	93.8	95.3	95.6
Gallstones					
Yes	14.0	11.8	14.4	12.1	10.9
No[†]	86.0	88.2	85.6	87.9	89.1
Hypertension					
Yes	29.6	27.4	29.5	27.7	26.6
No[†]	70.4	72.6	70.5	72.3	73.4
Chronic Bronchitis					
Yes	19.6	7.5	18.8	9.6	3.2
No[2]	80.4	92.5	81.2	90.4	96.8
Emphysema					
Yes	5.6	1.5	5.2	2.3	0.8
No[†]	94.4	98.5	94.8	97.7	99.2
Tuberculosis					
Yes	2.3	1.6	3.0	1.6	1.0
No[†]	97.7	98.4	97.0	98.4	99.0
OCCUPATIONAL / ENVIRONMENTAL EXPOSURES					
Asbestos					
Yes	2.2	2.0	2.3	2.0	1.5
No[†]	97.8	98.0	97.7	98.0	98.5
Chemicals/Acids/Solvents					
Yes	7.8	6.7	8.2	6.9	5.3
No[†]	92.2	93.3	91.8	93.1	94.7
Coal/Stone Dust					
Yes	2.6	2.0	2.7	2.1	1.6
No[†]	97.4	98.0	97.3	97.9	98.4
Coal Tar/Pitch/Asphalt					
Yes	0.9	0.6	1.0	0.6	0.4
No[†]	99.1	99.4	99.0	99.4	99.6
Diesel Engine Exhaust					
Yes	3.0	2.8	3.3	2.8	2.0
No[†]	97.0	97.2	96.7	97.2	98.0
Formaldehyde					
Yes	3.2	2.9	3.6	2.9	2.1
No[†]	96.8	97.1	96.4	97.1	97.9
Passive Tobacco Smoke					
0 hours	41.9	43.1	42.2	42.9	43.0
>0-<3 hours	27.5	28.5	29.0	28.1	26.4
3-<6hours	8.0	7.9	7.9	7.9	7.9
6+ hours	21.7	19.6	20.0	20.2	21.8
Missing	1.0	0.8	0.9	0.9	0.9
FAMILY HISTORY OF CANCER					
Colorectal Cancer					
Yes	4.9	5.2	4.9	5.2	5.3
No[†]	95.1	94.8	95.1	94.8	94.7
Breast Cancer					
Yes	7.4	7.4	7.8	7.3	7.2
No[†]	92.6	92.6	92.2	92.7	92.8
Breast or Ovarian Cancer					
Yes	8.1	8.0	8.6	7.9	7.6
No[†]	91.9	92.0	91.4	92.1	92.4
Pancreatic Cancer					
Yes	1.4	1.3	1.5	1.4	1.4
No[†]	98.6	98.7	98.5	98.6	98.6
NHL					
Yes	1.0	1.0	1.0	1.0	1.0
No[†]	99.0	99.0	99.0	99.0	99.0

Leukemia					
Yes	1.7	1.6	1.6	1.7	1.7
No[†]	98.3	98.4	98.4	98.3	98.3
Brain Cancer					
Yes	1.1	1.0	1.1	1.0	1.1
No[†]	98.9	99.0	98.9	99.0	98.9
Stomach Cancer					
Yes	3.1	2.9	3.1	2.9	3.2
No[†]	96.9	97.1	96.9	97.1	96.8
REPRODUCTIVE VARIABLES					
Menopausal Status					
Pre/peri	25.7	26.0	25.6	26.0	26.7
Post	71.7	71.4	71.6	71.4	70.8
Missing	2.7	2.6	2.7	2.6	2.5
Parity					
Nulliparous	11.5	11.3	10.8	11.4	11.6
1 child	10.9	10.9	11.0	10.9	10.9
2 children	25.7	27.0	26.2	26.8	26.2
3 children	22.4	22.9	23.4	22.7	22.1
4+ children	25.6	24.2	25.0	24.5	24.9
Missing	3.8	3.8	3.5	3.8	4.3
Age at First Birth (years)					
<20	13.2	11.0	11.6	11.6	11.5
20-29	62.0	63.9	64.3	63.3	62.3
30+	8.4	9.0	8.8	8.8	9.0
No births	11.5	11.3	10.8	11.4	11.6
Missing	4.9	4.8	4.4	4.9	5.6
Age at Menarche (years)					
<12	19.5	18.8	19.7	18.9	17.1
12-13	51.1	51.9	52.0	51.6	52.0
14+	25.9	25.9	25.1	26.0	27.0
Missing	3.5	3.4	3.2	3.5	4.0
Age at Menopause (years)					
<45	18.5	17.7	18.7	17.8	15.9
45-54	35.8	36.2	35.9	36.1	37.5
55+	5.6	5.8	5.6	5.8	5.5
Pre/peri	25.7	26.0	25.6	26.0	26.7
Missing	14.4	14.3	14.1	14.3	14.4
Tubal ligation					
Yes	8.2	7.7	8.4	7.9	7.2
No	91.8	92.1	91.6	92.1	92.8

[*] Directly standardized to the sex-specific age distribution of the entire cohort
[†] Includes missing
[‡] Oral Contraceptive Use
[§] Estrogen Replacement Therapy Use
[¶] Reference Category

All Cancer

Following exclusions, a total of 44 524 all cancer deaths in men and 36 567 in women were observed. Table 3, Table 4, and Table 5 summarize the results for all cancer mortality in relation to asthma and/or hay fever in men; Table 6, Table 7, Table 8 provide the corresponding results for women. Overall risk estimates indicated no association between a history of asthma and all cancer mortality in men or women. However, significantly reduced risks for all cancer mortality ranging from 4 to 12% were found in men and women in relation to hay fever, asthma and hay fever, and asthma or hay fever. The greatest protective effect was observed among those with both asthma and hay fever.

Upon stratification by smoking status, the relationship between hay fever and all cancer mortality was found to vary significantly in both men and women. The hazard ratio for all cancer mortality in relation to hay fever was found to approach the null value of unity in never smokers, yet remained less than one in current and former smokers. Upon stratification by age at baseline, asthma was associated with a significantly reduced risk for all cancer mortality in females less than 55 years of age at baseline, but not among those aged 55 years or greater. No significant age effect was found in male asthmatics. Hazard ratios for hay fever were also reduced in those less than 55 years of age at baseline.

Table 3. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	1 652	325 840	547.24	0.91 (0.87, 0.96)	0.97 (0.92, 1.02)
No	40 002	6 552 116	603.12	1.00	1.00
Hay Fever					
Yes	3 496	810 109	479.75	0.79 (0.76, 0.81)	0.90 (0.87, 0.93)
No	40 002	6 552 116	603.12	1.00	1.00
Asthma and Hay Fever					
Yes	626	152 010	473.04	0.78 (0.72, 0.84)	0.88 (0.81, 0.95)
No	40 002	6 552 116	603.12	1.00	1.00
Asthma and/or Hay Fever					
Yes	4 522	983 939	503.33	0.83 (0.80, 0.86)	0.93 (0.90, 0.96)
No	40 002	6 552 116	603.12	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake

Table 4. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.96 (0.85, 1.08)	1.00 (0.92, 1.09)	1.08 (0.98, 1.18)	0.20
Hay Fever	0.98 (0.91, 1.05)	0.87 (0.81, 0.93)	0.94 (0.87, 1.01)	0.05
Asthma and Hay Fever	0.94 (0.80, 1.12)	0.87 (0.75, 1.01)	0.93 (0.79, 1.10)	0.69
Asthma and/or Hay Fever	0.98 (0.91, 1.04)	0.92 (0.87, 0.97)	0.99 (0.93, 1.05)	0.11

* Age stratified and adjusted for race, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake

Table 5. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.91 (0.82, 1.01)	0.96 (0.90, 1.01)	0.22
Hay Fever	0.85 (0.79, 0.91)	0.88 (0.85, 0.92)	0.09
Asthma and Hay Fever	0.86 (0.74, 1.01)	0.84 (0.77, 0.92)	1.00
Asthma and/or Hay Fever	0.87 (0.82, 0.93)	0.92 (0.88, 0.95)	0.03

* Adjusted for race, smoking, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake

Table 6. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	1 572	474 558	351.14	1.00 (0.96, 1.06)	1.01 (0.96, 1.06)
No	31 784	8 747 815	358.87	1.00	1.00
Hay Fever					
Yes	3 872	1 346 998	313.40	0.87 (0.84, 0.90)	0.93 (0.90, 0.96)
No	31 784	8 747 815	358.87	1.00	1.00
Asthma and Hay Fever					
Yes	661	244 655	300.30	0.84 (0.78, 0.91)	0.89 (0.83, 0.96)
No	31 784	8 747 815	358.87	1.00	1.00
Asthma and/or Hay Fever					
Yes	4 783	1 576 901	326.87	0.91 (0.88, 0.94)	0.96 (0.93, 0.99)
No	31 784	8 747 815	358.87	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake, menopausal status, parity, OC use, ERT use

Table 7. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.98 (0.90, 1.06)	1.00 (0.90, 1.11)	1.05 (0.95, 1.15)	0.64
Hay Fever	0.97 (0.92, 1.02)	0.88 (0.81, 0.95)	0.91 (0.85, 0.97)	0.04
Asthma and Hay Fever	0.91 (0.81, 1.02)	0.80 (0.68, 0.94)	0.95 (0.82, 1.11)	0.26
Asthma and/or Hay Fever	0.98 (0.94, 1.02)	0.93 (0.87, 1.00)	0.95 (0.90, 1.01)	0.32

* Age stratified and adjusted for race, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake, menopausal status, parity, OC use, ERT use

Table 8. Hazard Ratios (95% CI) for All Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.88 (0.80, 0.97)	1.03 (0.97, 1.10)	0.004
Hay Fever	0.87 (0.82, 0.93)	0.94 (0.90, 0.98)	0.03
Asthma and Hay Fever	0.82 (0.72, 0.95)	0.90 (0.82, 0.98)	0.24
Asthma and/or Hay Fever	0.88 (0.83, 0.94)	0.98 (0.94, 1.01)	0.002

* Adjusted for race, smoking, education, marital status, BMI, diabetes, exercise, alcohol, aspirin, vegetable intake, fat intake, menopausal status, parity, OC use, ERT use

Lung Cancer

There was a total of 13 296 lung cancer deaths in men and 7 859 in women. Table 9, Table 10, and Table 11 summarize the results for lung cancer mortality in relation to asthma and/or hay fever in men, with results for women given in Table 12, Table 13, and Table 14. There was no significant association between a history of asthma and lung cancer mortality in men or women overall or in male or female never smokers. A history of hay fever, as well as a history of both asthma and hay fever, was associated with a significantly reduced risk for lung cancer mortality in both men and women overall. Upon stratification by smoking status, the protective effect of hay fever and both asthma and hay fever in men were attenuated and approached null values in never smokers. In men, the protective effect of hay fever on lung cancer mortality was more pronounced in those less than 55 years of age at baseline. Age at baseline did not significantly affect risk estimates in women.

Table 9. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	521	325 840	172.34	0.98 (0.89, 1.06)	0.94 (0.85, 1.02)
No	12 085	6 552 116	182.44	1.00	1.00
Hay Fever					
Yes	840	810 109	115.17	0.62 (0.57, 0.66)	0.81 (0.76, 0.87)
No	12 085	6 552 116	182.44	1.00	1.00
Asthma and Hay Fever					
Yes	150	152 010	111.41	0.61 (0.52, 0.71)	0.70 (0.59, 0.82)
No	12 085	6 552 116	182.44	1.00	1.00
Asthma and/or Hay Fever					
Yes	1 211	983 939	134.82	0.73 (0.69, 0.77)	0.88 (0.83, 0.93)
No	12 085	6 552 116	182.44	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Table 10. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	1.08 (0.69, 1.68)	0.81 (0.68, 0.97)	1.08 (0.94, 1.22)	0.27
Hay Fever	0.98 (0.73, 1.30)	0.75 (0.66, 0.86)	0.87 (0.78, 0.97)	0.09
Asthma and Hay Fever	0.95 (0.50, 1.81)	0.43 (0.29, 0.62)	0.91 (0.72, 1.14)	0.003
Asthma and/or Hay Fever	1.01 (0.78, 1.32)	0.83 (0.74, 0.93)	0.95 (0.87, 1.04)	0.23

* Age stratified and adjusted for race, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Table 11. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.86 (0.71, 1.03)	0.92 (0.83, 1.02)	0.64
Hay Fever	0.69 (0.59, 0.80)	0.82 (0.76, 0.89)	0.02
Asthma and Hay Fever	0.72 (0.53, 0.97)	0.64 (0.53, 0.78)	0.45
Asthma and/or Hay Fever	0.75 (0.66, 0.85)	0.89 (0.83, 0.95)	0.01

* Adjusted for race, smoking, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Table 12. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	371	474 558	81.28	1.06 (0.95, 1.17)	0.98 (0.88, 1.10)
No	6 899	8 747 815	78.11	1.00	1.00
Hay Fever					
Yes	720	1 346 998	57.57	0.73 (0.68, 0.79)	0.85 (0.78, 0.92)
No	6 899	8 747 815	78.11	1.00	1.00
Asthma and Hay Fever					
Yes	131	244 655	57.21	0.74 (0.62, 0.88)	0.78 (0.66, 0.93)
No	6 899	8 747 815	78.11	1.00	1.00
Asthma and/or Hay Fever					
Yes	960	1 576 901	64.64	0.83 (0.77, 0.88)	0.91 (0.85, 0.97)
No	6 899	8 747 815	78.11	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Table 13. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.91 (0.66, 1.26)	0.92 (0.73, 1.17)	1.03 (0.90, 1.18)	0.39
Hay Fever	0.99 (0.82, 1.20)	0.81 (0.68, 0.96)	0.84 (0.76, 0.93)	0.31
Asthma and Hay Fever	0.76 (0.46, 1.25)	0.61 (0.40, 0.91)	0.88 (0.70, 1.09)	0.20
Asthma and/or Hay Fever	1.00 (0.84, 1.19)	0.89 (0.76, 1.04)	0.90 (0.82, 0.98)	0.74

* Age stratified and adjusted for race, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Table 14. Hazard Ratios (95% CI) for Lung Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.96 (0.79, 1.16)	0.97 (0.85, 1.10)	0.60
Hay Fever	0.78 (0.68, 0.90)	0.86 (0.78, 0.94)	0.12
Asthma and Hay Fever	0.71 (0.52, 0.98)	0.78 (0.63, 0.97)	0.45
Asthma and/or Hay Fever	0.85 (0.75, 0.96)	0.91 (0.84, 0.98)	0.17

* Adjusted for race, smoking, education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, vegetable/fruit/fiber intake, fat intake, and passive smoking

Pancreatic Cancer

A total of 2 691 pancreatic cancer deaths were observed in men, and 2 468 in women. Table 15, Table 16, and Table 17 summarize the results for pancreatic cancer mortality in relation to asthma and/or hay fever in men and Table 18, Table 19, and Table 20 summarize the results in women. A history of hay fever was associated with a significantly reduced overall risk of pancreatic cancer in men but not in women. Neither a history of asthma nor asthma and hay fever were associated with overall pancreatic cancer risk.

After stratification by smoking status, a significantly reduced risk for pancreatic cancer was observed in females with hay fever who were never smokers. In males, pancreatic cancer risk in relation to hay fever did not vary by smoking status. In men who reported a history of asthma or asthma and hay fever at entry into the study, the risk of pancreatic cancer was elevated among current smokers and reduced among never smokers and approached statistical significance. No significant effect modification by age at baseline was observed.

Table 15. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	109	325 840	35.50	0.99 (0.82, 1.20)	1.02 (0.84, 1.24)
No	2 416	6 552 116	36.43	1.00	1.00
Hay Fever					
Yes	218	810 109	29.41	0.81 (0.70, 0.93)	0.86 (0.74, 0.98)
No	2 416	6 552 116	36.43	1.00	1.00
Asthma and Hay Fever					
Yes	52	152 010	37.73	1.07 (0.81, 1.41)	1.12 (0.85, 1.47)
No	2 416	6 552 116	36.43	1.00	1.00
Asthma and/or Hay Fever					
Yes	275	983 939	30.15	0.83 (0.74, 0.94)	0.87 (0.77, 0.99)
No	2 416	6 552 116	36.43	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Table 16. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.86 (0.56, 1.34)	1.12 (0.80, 1.59)	1.40 (0.98, 2.01)	0.20
Hay Fever	0.91 (0.70, 1.18)	0.89 (0.68, 1.17)	0.91 (0.66, 1.26)	0.99
Asthma and Hay Fever	0.73 (0.38, 1.40)	1.23 (0.74, 2.06)	1.81 (1.08, 3.03)	0.08
Asthma and/or Hay Fever	0.92 (0.73, 1.18)	0.93 (0.73, 1.18)	0.97 (0.74, 1.28)	0.92

* Age stratified and adjusted for race, education, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Table 17. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	1.24 (0.87, 1.78)	0.92 (0.73, 1.16)	0.24
Hay Fever	0.99 (0.76, 1.30)	0.79 (0.67, 0.93)	0.32
Asthma and Hay Fever	1.45 (0.90, 2.32)	0.95 (0.68, 1.33)	0.23
Asthma and/or Hay Fever	1.00 (0.78, 1.28)	0.81 (0.70, 0.94)	0.29

* Adjusted for race, smoking, education, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Table 18. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	120	474 558	27.46	1.14 (0.95, 1.38)	1.14 (0.94, 1.37)
No	2 141	8 747 815	24.09	1.00	1.00
Hay Fever					
Yes	265	1 346 998	22.26	0.92 (0.81, 1.04)	0.95 (0.83, 1.08)
No	2 141	8 747 815	24.09	1.00	1.00
Asthma and Hay Fever					
Yes	58	244 655	27.59	1.14 (0.88, 1.48)	1.16 (0.89, 1.51)
No	2 141	8 747 815	24.09	1.00	1.00
Asthma and/or Hay Fever					
Yes	327	1 576 901	23.09	0.95 (0.85, 1.07)	0.98 (0.87, 1.10)
No	2 141	8 747 815	24.09	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Table 19. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	1.06 (0.80, 1.40)	1.21 (0.82, 1.77)	1.10 (0.74, 1.64)	0.88
Hay Fever	0.81 (0.67, 0.98)	1.04 (0.79, 1.38)	1.12 (0.87, 1.45)	0.08
Asthma and Hay Fever	0.92 (0.61, 1.39)	1.38 (0.82, 2.31)	1.48 (0.88, 2.48)	0.30
Asthma and/or Hay Fever	0.87 (0.73, 1.03)	1.04 (0.81, 1.35)	1.07 (0.84, 1.36)	0.25

* Age stratified and adjusted for race, education, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Table 20. Hazard Ratios (95% CI) for Pancreatic Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.88 (0.57, 1.37)	1.16 (0.95, 1.42)	0.26
Hay Fever	0.82 (0.61, 1.09)	0.94 (0.82, 1.09)	0.32
Asthma and Hay Fever	0.95 (0.54, 1.70)	1.15 (0.86, 1.55)	0.54
Asthma and/or Hay Fever	0.81 (0.62, 1.06)	0.98 (0.86, 1.12)	0.19

* Adjusted for race, education, smoking, BMI, alcohol, diabetes, gall stones, family history of pancreatic cancer, vegetable consumption, red meat consumption, fruit consumption

Non-Hodgkin's Lymphoma

A total of 2 049 deaths from NHL in men and 1 752 deaths in women were observed in the cohort. Table 21, Table 22, and Table 23 summarize the results for NHL mortality in relation to asthma and/or hay fever in men and Table 24, Table 25, and Table 26 summarize the results for women. In men, a history of allergy had no effect on the overall risk of NHL mortality, or on mortality according to smoking status or age at baseline. In women, histories of asthma or hay fever were each associated with a 10% reduction in risk. An even greater reduction in risk was seen in women who reported a history of asthma and hay fever, although none of these reductions were statistically significant. No significant modification of risk was seen in women according to smoking status. However, the protective effect of allergy on NHL mortality in women was greater in those less than 55 years of age and approached statistical significance.

Table 21. Hazard Ratios (95% CI) for NHL Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	88	325 840	29.33	1.08 (0.87, 1.33)	1.09 (0.88, 1.35)
No	1 799	6 552 116	27.15	1.00	1.00
Hay Fever					
Yes	200	810 109	26.86	0.99 (0.85, 1.14)	1.01 (0.87, 1.17)
No	1 799	6 552 116	27.15	1.00	1.00
Asthma and Hay Fever					
Yes	38	152 010	28.35	1.03 (0.75, 1.42)	1.05 (0.76, 1.45)
No	1 799	6 552 116	27.15	1.00	1.00
Asthma and/or Hay Fever					
Yes	250	983 939	27.52	1.01 (0.88, 1.15)	1.03 (0.90, 1.18)
No	1 799	6 552 116	27.15	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, BMI, education, family history of NHL

Table 22. Hazard Ratios (95% CI) for NHL Mortality in Men in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	1.12 (0.74, 1.69)	1.10 (0.81, 1.50)	0.94
Hay Fever	1.11 (0.86, 1.43)	0.97 (0.77, 1.22)	0.40
Asthma and Hay Fever	1.26 (0.74, 2.15)	0.97 (0.58, 1.61)	0.45
Asthma and/or Hay Fever	1.09 (0.86, 1.39)	1.02 (0.83, 1.24)	0.63

* Age stratified and adjusted for race, BMI, education, family history of NHL
† Combines current, former, and ever cigarette smokers

Table 23. Hazard Ratios (95% CI) for NHL Mortality in Men in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.85 (0.54, 1.35)	1.15 (0.90, 1.46)	0.21
Hay Fever	1.11 (0.85, 1.46)	0.93 (0.78, 1.11)	0.45
Asthma and Hay Fever	1.19 (0.68, 2.06)	0.95 (0.64, 1.42)	0.64
Asthma and/or Hay Fever	1.01 (0.78, 1.31)	1.00 (0.86, 1.17)	0.83

* Adjusted for race, smoking, BMI, education, family history of NHL

Table 24. Hazard Ratios (95% CI) for NHL Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	68	474 558	15.64	0.91 (0.71, 1.16)	0.90 (0.71, 1.15)
No	1 528	8 747 815	17.21	1.00	1.00
Hay Fever					
Yes	186	1 346 998	15.37	0.89 (0.76, 1.04)	0.90 (0.77, 1.05)
No	1 528	8 747 815	17.21	1.00	1.00
Asthma and Hay Fever					
Yes	30	244 655	13.99	0.82 (0.57, 1.17)	0.82 (0.57, 1.17)
No	1 528	8 747 815	17.21	1.00	1.00
Asthma and/or Hay Fever					
Yes	224	1 576 901	15.69	0.91 (0.79, 1.04)	0.91 (0.79, 1.05)
No	1 528	8 747 815	17.21	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified adjusted for race, smoking, BMI, education, family history of NHL

Table 25. Hazard Ratios (95% CI) for NHL Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	0.85 (0.60, 1.20)	0.82 (0.56, 1.22)	0.94
Hay Fever	0.88 (0.72, 1.09)	0.96 (0.75, 1.22)	0.58
Asthma and Hay Fever	0.60 (0.34, 1.06)	1.01 (0.60, 1.68)	0.16
Asthma and/or Hay Fever	0.92 (0.76, 1.11)	0.90 (0.72, 1.14)	0.97

* Age stratified and adjusted for race, BMI, education, family history of NHL
† Combines current, former, and ever smokers

Table 26. Hazard Ratios (95% CI) for NHL Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.52 (0.28, 0.98)	0.99 (0.76, 1.29)	0.05
Hay Fever	0.69 (0.49, 0.97)	0.93 (0.79, 1.11)	0.09
Asthma and Hay Fever	0.38 (0.14, 1.03)	0.93 (0.63, 1.37)	0.07
Asthma and/or Hay Fever	0.69 (0.50, 0.95)	0.95 (0.81, 1.11)	0.06

* Adjusted for race, smoking, BMI, education, family history of NHL

Leukemia

Deaths from leukemia occurred in 1 966 men and in 1 414 women. Table 27, Table 28, and Table 29 summarize the results for leukemia mortality in relation to asthma and/or hay fever in men and Table 30, Table 31, and Table 32 summarize the results in women. In men, asthma was associated with a significantly reduced risk of leukemia mortality. Hay fever did not affect risk for leukemia mortality in men. In women, neither a history of asthma or hay fever was associated with leukemia mortality. In both men and women, neither smoking status nor age at baseline had a significant effect on the association between asthma and/or hay fever and leukemia.

Table 27. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	47	325 840	15.56	0.60 (0.44, 0.80)	0.60 (0.45, 0.81)
No	1 755	6 552 116	26.44	1.00	1.00
Hay Fever					
Yes	187	810 109	25.23	0.96 (0.83, 1.12)	0.99 (0.85, 1.15)
No	1 755	6 552 116	26.44	1.00	1.00
Asthma and Hay Fever					
Yes	23	152 010	17.88	0.66 (0.44, 1.00)	0.68 (0.45, 1.02)
No	1 755	6 552 116	26.44	1.00	1.00
Asthma and/or Hay Fever					
Yes	211	983 939	23.15	0.88 (0.77, 1.02)	0.91 (0.78, 1.05)
No	1 755	6 552 116	26.44	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, family history

Table 28. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	0.46 (0.23, 0.93)	0.74 (0.51, 1.06)	0.22
Hay Fever	1.01 (0.76, 1.36)	1.08 (0.87, 1.34)	0.54
Asthma and Hay Fever	0.70 (0.31, 1.57)	0.86 (0.50, 1.45)	0.61
Asthma and/or Hay Fever	0.90 (0.67, 1.20)	0.99 (0.81, 1.20)	0.47

* Age stratified and adjusted for race, education, family history
† Includes current, former, and ever smokers

Table 29. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.70 (0.40, 1.22)	0.56 (0.40, 0.78)	0.52
Hay Fever	1.15 (0.86, 1.54)	0.91 (0.76, 1.08)	0.22
Asthma and Hay Fever	0.76 (0.36, 1.62)	0.61 (0.37, 1.00)	0.65
Asthma and/or Hay Fever	1.06 (0.80, 1.40)	0.83 (0.70, 0.98)	0.18

* Adjusted for race, smoking, education, family history

Table 30. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	61	474 558	13.90	1.02 (0.79, 1.32)	1.02 (0.79, 1.32)
No	1 223	8 747 815	13.75	1.00	1.00
Hay Fever					
Yes	159	1 346 998	13.23	0.96 (0.82, 1.14)	0.97 (0.82, 1.14)
No	1 223	8 747 815	13.75	1.00	1.00
Asthma and Hay Fever					
Yes	29	244 655	13.90	1.00 (0.69, 1.45)	1.00 (0.69, 1.45)
No	1 223	8 747 815	13.75	1.00	1.00
Asthma and/or Hay Fever					
Yes	191	1 576 901	13.36	0.98 (0.84, 1.14)	0.98 (0.84, 1.14)
No	1 223	8 747 815	13.75	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, family history

Table 31. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	1.02 (0.72, 1.46)	0.99 (0.66, 1.47)	0.91
Hay Fever	1.06 (0.85, 1.31)	0.87 (0.66, 1.15)	0.33
Asthma and Hay Fever	1.21 (0.76, 1.91)	0.66 (0.33, 1.34)	0.16
Asthma and/or Hay Fever	1.02 (0.84, 1.25)	0.94 (0.74, 1.21)	0.66

* Age stratified and adjusted for race, education, family history
† Includes current, former, and ever smokers

Table 32. Hazard Ratios (95% CI) for Leukemia Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.69 (0.37, 1.30)	1.07 (0.81, 1.42)	0.19
Hay Fever	0.89 (0.63, 1.25)	0.94 (0.78, 1.13)	0.76
Asthma and Hay Fever	0.75 (0.34, 1.70)	1.01 (0.67, 1.53)	0.50
Asthma and/or Hay Fever	0.85 (0.61, 1.18)	0.97 (0.81, 1.15)	0.48

* Adjusted for race, smoking, education, family history

Multiple Myeloma

The total number of deaths from multiple myeloma was 1 005 in men and 916 in women. Table 33, Table 34, and Table 35 summarize the results for mortality from multiple myeloma in relation to asthma and/or hay fever in men; results for women are presented in Table 36, Table 37, and Table 38. Although overall risk estimates showed no effect of asthma and/or hay fever on mortality from multiple myeloma, risk estimates were found to vary significantly by smoking status. In men who were never smokers, a two-fold significant increase in mortality from multiple myeloma was observed in asthmatics. An increased risk was also seen in males with asthma and hay fever. In women, the opposite was found. Significant protective effects of both asthma and hay fever were found in never smokers, while ever smokers were at increased risk for mortality from multiple myeloma. Age at baseline did not exert a significant effect on the association between asthma and/or hay fever and multiple myeloma.

Table 33. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	46	325 840	15.03	1.16 (0.86, 1.56)	1.18 (0.88, 1.59)
No	880	6 552 116	13.27	1.00	1.00
Hay Fever					
Yes	95	810 109	12.83	0.96 (0.78, 1.19)	1.00 (0.81, 1.24)
No	880	6 552 116	13.27	1.00	1.00
Asthma and Hay Fever					
Yes	16	152 010	11.25	0.90 (0.55, 1.47)	0.94 (0.58, 1.55)
No	880	6 552 116	13.27	1.00	1.00
Asthma and/or Hay Fever					
Yes	125	983 939	13.77	1.04 (0.86, 1.25)	1.07 (0.89, 1.29)
No	880	6 552 116	13.27	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education

Table 34. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Men in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	2.13 (1.39, 3.28)	0.84 (0.51, 1.38)	0.006
Hay Fever	1.10 (0.77, 1.57)	0.92 (0.65, 1.28)	0.53
Asthma and Hay Fever	1.68 (0.86, 3.28)	0.54 (0.20, 1.45)	0.06
Asthma and/or Hay Fever	1.32 (0.96, 1.80)	0.94 (0.70, 1.26)	0.15

* Age stratified and adjusted for race, education
† Combines current, former, and ever cigarette smokers

Table 35. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Men in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	1.04 (0.57, 1.92)	1.19 (0.84, 1.67)	0.75
Hay Fever	1.07 (0.72, 1.59)	0.94 (0.73, 1.21)	0.58
Asthma and Hay Fever	1.16 (0.52, 2.63)	0.80 (0.43, 1.50)	0.46
Asthma and/or Hay Fever	1.04 (0.72, 1.52)	1.04 (0.84, 1.30)	0.96

* Adjusted for race, smoking, education

Table 36. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	34	474 558	7.58	0.86 (0.61, 1.21)	0.85 (0.60, 1.20)
No	802	8 747 815	9.04	1.00	1.00
Hay Fever					
Yes	101	1 346 998	8.09	0.91 (0.74, 1.12)	0.91 (0.74, 1.12)
No	802	8 747 815	9.04	1.00	1.00
Asthma and Hay Fever					
Yes	21	244 655	9.46	1.08 (0.70, 1.66)	1.08 (0.70, 1.67)
No	802	8 747 815	9.04	1.00	1.00
Asthma and/or Hay Fever					
Yes	114	1 576 901	7.74	0.87 (0.72, 1.06)	0.86 (0.71, 1.05)
No	802	8 747 815	9.04	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified adjusted for race, smoking, education

Table 37. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	0.53 (0.30, 0.94)	1.27 (0.80, 2.03)	0.02
Hay Fever	0.68 (0.50, 0.92)	1.32 (0.97, 1.80)	0.006
Asthma and Hay Fever	0.61 (0.29, 1.29)	1.75 (0.98, 3.12)	0.03
Asthma and/or Hay Fever	0.65 (0.49, 0.86)	1.24 (0.93, 1.66)	0.004

* Age stratified and adjusted for race, education
† Combines current, former, and ever smokers

Table 38. Hazard Ratios (95% CI) for Multiple Myeloma Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.89 (0.45, 1.74)	0.81 (0.54, 1.20)	0.81
Hay Fever	0.97 (0.66, 1.45)	0.86 (0.67, 1.09)	0.60
Asthma and Hay Fever	1.30 (0.61, 2.77)	0.96 (0.56, 1.62)	0.56
Asthma and/or Hay Fever	0.90 (0.61, 1.32)	0.83 (0.66, 1.04)	0.71

* Adjusted for race, smoking, education

Brain Cancer

A total of 1 158 deaths from brain cancer occurred during the follow-up period in men, with 1 036 deaths in women. Table 39, Table 40, and Table 41 summarize the results for mortality from brain cancer in relation to asthma and/or hay fever in men, and Table 42, Table 43, and Table 44 summarize the results in women. Overall, a history of allergy did not exert a protective effect on brain cancer mortality in men, but did appear to exert a protective influence against brain cancer mortality in women. The greatest protective effect was seen in women with a history of asthma and hay fever, where a 30% reduction in risk was observed.

Examination of hazard ratios by smoking status did not reveal any significant findings, although the protective effect of asthma and hay fever in women was attenuated by approximately 15% when restricted to never smokers only. Age at baseline did not exert an effect on risk estimates in men. A significant protective effect of hay fever was seen only in women less than 55 years of age.

Table 39. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	51	325 840	16.15	1.06 (0.80, 1.41)	1.05 (0.79, 1.40)
No	1 014	6 552 116	15.38	1.00	1.00
Hay Fever					
Yes	121	810 109	15.50	1.02 (0.84, 1.23)	1.00 (0.82, 1.21)
No	1 014	6 552 116	15.38	1.00	1.00
Asthma and Hay Fever					
Yes	28	152 010	19.14	1.28 (0.88, 1.86)	1.24 (0.85, 1.81)
No	1 014	6 552 116	15.38	1.00	1.00
Asthma and/or Hay Fever					
Yes	144	983 939	15.15	0.99 (0.83, 1.18)	0.98 (0.82, 1.17)
No	1 014	6 552 116	15.38	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, BMI, education, vegetable intake, family history of brain cancer

Table 40. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	1.37 (0.86, 2.18)	0.89 (0.57, 1.40)	0.20
Hay Fever	1.10 (0.80, 1.50)	1.01 (0.75, 1.36)	0.74
Asthma and Hay Fever	1.34 (0.71, 2.53)	1.08 (0.58, 2.02)	0.65
Asthma and/or Hay Fever	1.13 (0.85, 1.52)	0.96 (0.73, 1.26)	0.42

* Age stratified and adjusted for race, BMI, education, vegetable intake, family history of brain cancer
† Combines current, former, and ever cigarette smokers

Table 41. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.98 (0.61, 1.57)	1.08 (0.76, 1.53)	0.74
Hay Fever	0.97 (0.71, 1.33)	1.00 (0.78, 1.27)	0.90
Asthma and Hay Fever	1.18 (0.64, 2.15)	1.26 (0.78, 2.03)	0.86
Asthma and/or Hay Fever	0.94 (0.70, 1.26)	0.98 (0.79, 1.23)	0.80

* Adjusted for race, smoking, BMI, education, vegetable intake, family history of brain cancer

Table 42. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	40	474 558	8.85	0.87 (0.63, 1.19)	0.87 (0.63, 1.19)
No	893	8 747 815	10.12	1.00	1.00
Hay Fever					
Yes	119	1 346 998	9.43	0.92 (0.76, 1.12)	0.92 (0.76, 1.11)
No	893	8 747 815	10.12	1.00	1.00
Asthma and Hay Fever					
Yes	16	244 655	7.08	0.69 (0.42, 1.13)	0.68 (0.42, 1.12)
No	893	8 747 815	10.12	1.00	1.00
Asthma and/or Hay Fever					
Yes	143	1 576 901	9.61	0.94 (0.79, 1.12)	0.94 (0.79, 1.12)
No	893	8 747 815	10.12	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified adjusted for race, smoking, BMI, education, vegetable intake, family history of brain cancer

Table 43. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	1.00 (0.67, 1.50)	0.73 (0.43, 1.25)	0.36
Hay Fever	0.92 (0.72, 1.19)	0.92 (0.67, 1.27)	0.92
Asthma and Hay Fever	0.83 (0.46, 1.50)	0.55 (0.23, 1.33)	0.42
Asthma and/or Hay Fever	0.96 (0.76, 1.21)	0.92 (0.68, 1.23)	0.77

* Age stratified and adjusted for race, BMI, education, vegetable intake, family history of brain cancer
† Combines current, former, and ever smokers

Table 44. Hazard Ratios (95% CI) for Brain Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.73 (0.41, 1.30)	0.94 (0.64, 1.37)	0.44
Hay Fever	0.70 (0.49, 1.00)	1.03 (0.82, 1.30)	0.05
Asthma and Hay Fever	0.55 (0.23, 1.34)	0.76 (0.42, 1.38)	0.50
Asthma and/or Hay Fever	0.73 (0.52, 1.01)	1.04 (0.84, 1.29)	0.05

* Adjusted for race, smoking, BMI, education, vegetable intake, family history of brain cancer

Colorectal Cancer

In men, a total of 4 822 colorectal cancer deaths were observed through to the end of follow-up, along with 4 518 deaths in women. Table 45, Table 46, and Table 47 summarize the results for colorectal cancer mortality in relation to asthma and/or hay fever in men, and Table 48, Table 49, and Table 50 summarize the results in women. A significant reduction in risk for colorectal cancer mortality was observed in men with a history of hay fever, asthma and hay fever, and asthma or hay fever. There was a similar protective effect in women, although none of these effects were significant. The greatest reduction in risk occurred among those with asthma and hay fever, where a 20-25% reduction in risk of colorectal cancer mortality was observed. No significant effect modification was observed according to smoking status or age at baseline.

Table 45. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	171	325 840	56.33	0.88 (0.75, 1.02)	0.90 (0.78, 1.05)
No	4 329	6 552 116	65.24	1.00	1.00
Hay Fever					
Yes	382	810 109	52.47	0.80 (0.72, 0.89)	0.87 (0.78, 0.96)
No	4 329	6 552 116	65.24	1.00	1.00
Asthma and Hay Fever					
Yes	60	152 010	45.39	0.69 (0.54, 0.90)	0.75 (0.58, 0.96)
No	4 329	6 552 116	65.24	1.00	1.00
Asthma and/or Hay Fever					
Yes	493	983 939	54.83	0.84 (0.77, 0.92)	0.90 (0.82, 0.99)
No	4 329	6 552 116	65.24	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, multivitamin use, family history

Table 46. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.76 (0.54, 1.07)	0.86 (0.65, 1.12)	1.22 (0.87, 1.73)	0.15
Hay Fever	0.81 (0.66, 1.00)	0.81 (0.67, 0.99)	0.86 (0.64, 1.15)	0.92
Asthma and Hay Fever	0.68 (0.40, 1.12)	0.71 (0.45, 1.14)	0.79 (0.40, 1.60)	0.94
Asthma and/or Hay Fever	0.82 (0.68, 0.99)	0.84 (0.71, 1.00)	1.01 (0.79, 1.28)	0.34

* Age stratified and adjusted for race, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, multivitamin use, family history

Table 47. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.97 (0.72, 1.30)	0.85 (0.71, 1.02)	0.48
Hay Fever	0.70 (0.56, 0.88)	0.88 (0.79, 1.00)	0.07
Asthma and Hay Fever	0.70 (0.42, 1.15)	0.73 (0.54, 0.98)	0.89
Asthma and/or Hay Fever	0.79 (0.65, 0.97)	0.90 (0.81, 1.00)	0.27

* Adjusted for race, smoking, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, multivitamin use, family history

Table 48. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	180	474 558	41.15	0.94 (0.81, 1.09)	0.95 (0.82, 1.10)
No	3 949	8 747 815	44.39	1.00	1.00
Hay Fever					
Yes	459	1 346 998	38.09	0.86 (0.78, 0.95)	0.92 (0.84, 1.02)
No	3 949	8 747 815	44.39	1.00	1.00
Asthma and Hay Fever					
Yes	70	244 655	34.09	0.76 (0.60, 0.96)	0.80 (0.63, 1.01)
No	3 949	8 747 815	44.39	1.00	1.00
Asthma and/or Hay Fever					
Yes	569	1 576 901	39.76	0.90 (0.83, 0.99)	0.95 (0.87, 1.04)
No	3 949	8 747 815	44.39	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, ERT use, multivitamin use, family history

Table 49. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	1.08 (0.89, 1.32)	0.86 (0.62, 1.18)	0.88 (0.60, 1.27)	0.35
Hay Fever	0.98 (0.86, 1.12)	0.97 (0.79, 1.20)	0.74 (0.57, 0.96)	0.16
Asthma and Hay Fever	0.86 (0.62, 1.18)	0.74 (0.45, 1.22)	0.86 (0.48, 1.52)	0.91
Asthma and/or Hay Fever	1.03 (0.92, 1.16)	0.97 (0.80, 1.17)	0.77 (0.61, 0.97)	0.08

* Age stratified and adjusted for race, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, ERT use, multivitamin use, family history

Table 50. Hazard Ratios (95% CI) for Colorectal Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.85 (0.61, 1.17)	0.94 (0.80, 1.12)	0.52
Hay Fever	0.92 (0.76, 1.12)	0.89 (0.79, 0.99)	0.84
Asthma and Hay Fever	0.71 (0.44, 1.14)	0.78 (0.60, 1.03)	0.65
Asthma and/or Hay Fever	0.93 (0.78, 1.12)	0.92 (0.83, 1.02)	1.00

* Adjusted for race, smoking, education, BMI, exercise, alcohol, aspirin, vegetable intake, red meat intake, fiber intake, ERT use, multivitamin use, family history

Stomach Cancer

A total of 1 309 stomach cancer deaths occurred in men and 722 occurred in women through to the end of follow-up. Table 51, Table 52, and Table 53 summarize the results for mortality from stomach cancer in relation to asthma and/or hay fever in men and Table 54, Table 55, and Table 56 summarize the results in women. Overall, a history of allergy was associated with a reduced risk of stomach cancer mortality in both men and women. Protective effects ranged from 6% to 24% although none of these reductions were statistically significant. Both smoking status and age at baseline did not significantly alter the hazard ratios in men or women.

Table 51. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever in Men

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	38	325 840	12.45	0.70 (0.51, 0.98)	0.75 (0.54, 1.04)
No	1 184	6 552 116	17.85	1.00	1.00
Hay Fever					
Yes	106	810 109	14.67	0.81 (0.66, 0.99)	0.93 (0.76, 1.14)
No	1 184	6 552 116	17.85	1.00	1.00
Asthma and Hay Fever					
Yes	19	152 010	14.36	0.80 (0.51, 1.26)	0.92 (0.59, 1.46)
No	1 184	6 552 116	17.85	1.00	1.00
Asthma and/or Hay Fever					
Yes	125	983 939	13.92	0.78 (0.65, 0.94)	0.87 (0.72, 1.04)
No	1 184	6 552 116	17.85	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history

Table 52. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Men

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	0.94 (0.48, 1.84)	0.69 (0.44, 1.07)	0.49
Hay Fever	0.92 (0.61, 1.40)	0.93 (0.70, 1.22)	0.87
Asthma and Hay Fever	0.85 (0.32, 2.29)	1.03 (0.57, 1.86)	0.71
Asthma and/or Hay Fever	0.94 (0.64, 1.39)	0.82 (0.63, 1.06)	0.68

* Age stratified and adjusted for race, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history
† Includes current, former, and ever cigarette smokers

Table 53. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Men

	<55 years*	>=55 years*	*p*
Asthma	0.79 (0.42, 1.49)	0.71 (0.49, 1.04)	0.79
Hay Fever	0.90 (0.61, 1.35)	0.90 (0.71, 1.13)	1.00
Asthma and Hay Fever	0.70 (0.26, 1.87)	0.96 (0.58, 1.60)	0.52
Asthma and/or Hay Fever	0.90 (0.62, 1.29)	0.82 (0.66, 1.02)	0.71

* Adjusted for race, smoking, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history

Table 54. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	28	474 558	6.41	0.90 (0.62, 1.32)	0.88 (0.60, 1.29)
No	635	8 747 815	7.13	1.00	1.00
Hay Fever					
Yes	72	1 346 998	6.03	0.84 (0.66, 1.08)	0.89 (0.70, 1.13)
No	635	8 747 815	7.13	1.00	1.00
Asthma and Hay Fever					
Yes	13	244 655	5.86	0.88 (0.50, 1.52)	0.91 (0.52, 1.58)
No	635	8 747 815	7.13	1.00	1.00
Asthma and/or Hay Fever					
Yes	87	1 576 901	6.15	0.86 (0.69, 1.08)	0.88 (0.71, 1.11)
No	635	8 747 815	7.13	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history

Table 55. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Ever Smoker*,†	*p*
Asthma	0.87 (0.51, 1.49)	0.84 (0.47, 1.50)	1.00
Hay Fever	0.95 (0.68, 1.30)	0.76 (0.50, 1.15)	0.48
Asthma and Hay Fever	0.80 (0.36, 1.80)	1.12 (0.53, 2.38)	0.50
Asthma and/or Hay Fever	0.94 (0.70, 1.27)	0.74 (0.50, 1.08)	0.37

* Age stratified and adjusted for race, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history
† Combines current, former, and ever cigarette smokers

Table 56. Hazard Ratios (95% CI) for Stomach Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.65 (0.27, 1.60)	0.92 (0.61, 1.40)	0.47
Hay Fever	0.91 (0.56, 1.48)	0.83 (0.63, 1.11)	0.85
Asthma and Hay Fever	1.29 (0.53, 3.16)	0.71 (0.36, 1.44)	0.34
Asthma and/or Hay Fever	0.77 (0.48, 1.25)	0.88 (0.68, 1.14)	0.57

* Adjusted for race, smoking, education, BMI, aspirin, vegetable intake, fruit intake, fiber intake, number of siblings, family history

Prostate Cancer

A total of 5 674 deaths from prostate cancer were observed in the 18 years of follow-up in this cohort. Table 57, Table 58, and Table 59 summarize the results for prostate cancer mortality in relation to asthma and/or hay fever. Overall, a history of allergy was not associated with prostate cancer mortality. (Although a modest reduction in risk of about 5% was observed in relation to a history of asthma and/or hay fever, these results were not significant). Null values were also reported in those who were never smokers. No significant interaction was observed between any allergy category and smoking status or age at baseline.

Table 57. Hazard Ratios (95% CI) for Prostate Cancer in Relation to Asthma and/or Hay Fever

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	200	325 840	68.44	0.92 (0.80, 1.06)	0.93 (0.81, 1.07)
No	5 068	6 552 116	75.95	1.00	1.00
Hay Fever					
Yes	492	810 109	71.45	0.93 (0.84, 1.02)	0.95 (0.86, 1.04)
No	5 068	6 552 116	75.95	1.00	1.00
Asthma and Hay Fever					
Yes	86	152 010	69.56	0.92 (0.74, 1.13)	0.94 (0.76, 1.17)
No	5 068	6 552 116	75.95	1.00	1.00
Asthma and/or Hay Fever					
Yes	606	983 939	70.60	0.93 (0.85, 1.01)	0.94 (0.86, 1.02)
No	5 068	6 552 116	75.95	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, exercise, alcohol, family history of prostate cancer, vegetable consumption, fat consumption, red meat consumption

Table 58. Hazard Ratios (95% CI) for Prostate Cancer in Relation to Asthma and/or Hay Fever Stratified by Smoking Status

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.96 (0.74, 1.26)	1.01 (0.79, 1.29)	0.96 (0.65, 1.43)	0.95
Hay Fever	1.05 (0.89, 1.23)	0.88 (0.73, 1.05)	1.05 (0.80, 1.37)	0.37
Asthma and Hay Fever	1.06 (0.74, 1.53)	0.97 (0.66, 1.43)	1.12 (0.62, 2.03)	0.95
Asthma and/or Hay Fever	1.02 (0.88, 1.18)	0.91 (0.78, 1.07)	1.00 (0.79, 1.28)	0.64

* Age stratified and adjusted for race, education, BMI, exercise, alcohol, family history of prostate cancer, vegetable consumption, fat consumption, red meat consumption

Table 59. Hazard Ratios (95% CI) for Prostate Cancer in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline

	<55 years*	>=55 years*	*p*
Asthma	0.72 (0.46, 1.14)	0.92 (0.79, 1.06)	0.25
Hay Fever	0.78 (0.58, 1.04)	0.92 (0.83, 1.01)	0.17
Asthma and Hay Fever	0.86 (0.47, 1.56)	0.88 (0.70, 1.11)	0.81
Asthma and/or Hay Fever	0.74 (0.57, 0.98)	0.92 (0.84, 1.00)	0.07

* Adjusted for race, smoking, education, BMI, exercise, alcohol, family history of prostate cancer, vegetable consumption, fat consumption, red meat consumption

Breast Cancer

A total of 5 246 deaths from breast cancer were observed in the cohort following exclusions. Table 60, Table 61, and Table 62 summarize the results for breast cancer mortality in relation to asthma and/or hay fever. A history of asthma or hay fever independently did not exert affect overall breast cancer mortality. However, a history of both asthma and hay fever was associated with a 14% reduction in risk. The effect of hay fever on breast cancer mortality was seen to vary significantly by smoking status; a significantly reduced risk was noted in former smokers, with null effects in never smokers and current smokers. No significant effect modification by age was observed.

Table 60. Hazard Ratios (95% CI) for Breast Cancer in Relation to Asthma and/or Hay Fever in Women

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	228	474 558	49.85	0.98 (0.86, 1.12)	0.98 (0.86, 1.12)
No	4 493	8 747 815	51.02	1.00	1.00
Hay Fever					
Yes	625	1 346 998	48.34	0.95 (0.87, 1.03)	0.97 (0.89, 1.06)
No	4 493	8 747 815	51.02	1.00	1.00
Asthma and Hay Fever					
Yes	100	244 655	42.88	0.85 (0.70, 1.04)	0.86 (0.71, 1.05)
No	4 493	8 747 815	51.02	1.00	1.00
Asthma and/or Hay Fever					
Yes	753	1 576 901	49.63	0.98 (0.90, 1.05)	0.99 (0.92, 1.07)
No	4 493	8 747 815	51.02	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, exercise, alcohol, OC use, ERT use, age at first birth, age at menarche, age at menopause, height, family history of breast cancer

Table 61. Hazard Ratios (95% CI) for Breast Cancer in Relation to Asthma and/or Hay Fever Stratified by Smoking Status in Women

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	1.01 (0.84, 1.22)	1.01 (0.77, 1.32)	0.93 (0.68, 1.28)	0.83
Hay Fever	1.02 (0.92, 1.14)	0.77 (0.63, 0.95)	1.03 (0.85, 1.26)	0.05
Asthma and Hay Fever	0.92 (0.70, 1.20)	0.80 (0.53, 1.21)	0.74 (0.44, 1.26)	0.63
Asthma and/or Hay Fever	1.04 (0.93, 1.15)	0.85 (0.71, 1.02)	1.04 (0.87, 1.25)	0.15

* Age stratified and adjusted for race, education, BMI, exercise, alcohol, OC use, ERT use, age at first birth, age at menarche, age at menopause, height, family history of breast cancer

Table 62. Hazard Ratios (95% CI) for Breast Cancer in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline in Women

	<55 years*	>=55 years*	*p*
Asthma	0.90 (0.72, 1.12)	1.03 (0.87, 1.22)	0.28
Hay Fever	0.99 (0.87, 1.12)	0.95 (0.85, 1.06)	0.65
Asthma and Hay Fever	0.86 (0.64, 1.16)	0.85 (0.65, 1.11)	1.00
Asthma and/or Hay Fever	0.98 (0.87, 1.11)	0.99 (0.90, 1.10)	0.89

* Adjusted for race, smoking, education, BMI, exercise, alcohol, OC use, ERT use, age at first birth, age at menarche, age at menopause, height, family history of breast cancer

Ovarian Cancer

A total of 1 989 ovarian cancer deaths were observed. Table 63, Table 64, and Table 65 summarize the results for ovarian cancer mortality in relation to asthma and/or hay fever. A history of asthma was associated with a nearly 20% reduction in risk for ovarian cancer mortality, and approached statistical significance. Hay fever was not associated with ovarian cancer mortality overall. Smoking status did not modify the association between a history of allergy and ovarian cancer mortality. Age at baseline was found to significantly modify the effect of a history of hay fever, with a reduction of approximately 20% in the risk for ovarian cancer mortality seen in those less than 55 years old at baseline.

Table 63. Hazard Ratios (95% CI) for Ovarian Cancer Mortality in Relation to Asthma and/or Hay Fever

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	67	296 291	25.22	0.82 (0.64, 1.05)	0.82 (0.64, 1.04)
No	1 727	5 791 214	30.76	1.00	1.00
Hay Fever					
Yes	229	842 254	31.24	1.00 (0.87, 1.14)	1.00 (0.87, 1.15)
No	1 727	5 791 214	30.76	1.00	1.00
Asthma and Hay Fever					
Yes	34	151 292	26.74	0.84 (0.60, 1.18)	0.84 (0.60, 1.18)
No	1 727	5 791 214	30.76	1.00	1.00
Asthma and/or Hay Fever					
Yes	262	987 652	30.11	0.97 (0.85, 1.10)	0.97 (0.85, 1.10)
No	1 727	5 791 214	30.76	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, exercise, parity, age at menarche, age at menopause, OC use, ERT use, tubal ligation, family history of breast or ovarian cancer

Table 64. Hazard Ratios (95% CI) for Ovarian Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Smoking Status

	Never Smokers*	Former Smoker*	Current Smoker*	*p*
Asthma	0.84 (0.60, 1.18)	0.86 (0.54, 1.36)	0.75 (0.40, 1.40)	0.94
Hay Fever	1.04 (0.87, 1.25)	1.02 (0.76, 1.36)	0.92 (0.64, 1.33)	0.86
Asthma and Hay Fever	0.93 (0.60, 1.44)	0.66 (0.31, 1.41)	0.84 (0.34, 2.02)	0.74
Asthma and/or Hay Fever	1.00 (0.84, 1.19)	1.02 (0.79, 1.33)	0.88 (0.62, 1.24)	0.79

* Age stratified and adjusted for race, education, BMI, exercise, alcohol, OC use, ERT use, age at first birth, age at menarche, age at menopause, height, family history of breast cancer

Table 65. Hazard Ratios (95% CI) for Ovarian Cancer Mortality in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline

	<55 years*	>=55 years*	*p*
Asthma	0.79 (0.53, 1.20)	0.81 (0.60, 1.10)	0.89
Hay Fever	0.81 (0.63, 1.04)	1.10 (0.93, 1.30)	0.03
Asthma and Hay Fever	0.80 (0.46, 1.39)	0.86 (0.56, 1.32)	0.82
Asthma and/or Hay Fever	0.81 (0.64, 1.02)	1.05 (0.90, 1.23)	0.05

* Adjusted for race, smoking, education, BMI, exercise, alcohol, OC use, ERT use, age at first birth, age at menarche, age at menopause, height, family history of breast cancer

Uterine Cancer

A total of 981 deaths from uterine cancer were observed in the cohort. Table 66, Table 67, and Table 68 summarize the results for mortality from uterus cancer in relation to asthma and/or hay fever. A significant reduction in risk for uterus cancer mortality was observed in asthmatics. A 40% reduction in risk was also observed in those reporting both a history of asthma and hay fever. No significant effect modification was noted by either smoking status or age at baseline.

Table 66. Hazard Ratios (95% CI) for Uterus Cancer in Relation to Asthma and/or Hay Fever

Asthma and/or Hay Fever Status	Number of Deaths	Person-Years	Death Rate*	Age-adjusted Hazard Ratio (95% CI)†	Fully-adjusted Hazard Ratio (95% CI)‡
Asthma					
Yes	28	306 965	10.42	0.71 (0.48, 1.03)	0.67 (0.46, 0.97)
No	856	5 967 988	14.86	1.00	1.00
Hay Fever					
Yes	109	871 048	14.69	0.98 (0.80, 1.20)	0.95 (0.78, 1.16)
No	856	5 967 988	14.86	1.00	1.00
Asthma and Hay Fever					
Yes	12	157 073	9.40	0.62 (0.35, 1.10)	0.59 (0.33, 1.04)
No	856	5 967 988	14.86	1.00	1.00
Asthma and/or Hay Fever					
Yes	125	1 020 940	14.15	0.95 (0.79, 1.15)	0.92 (0.76, 1.10)
No	856	5 967 988	14.86	1.00	1.00

* per 100 000 person-years, age-standardized to the sex-specific age distribution of the entire cohort
† Age stratified
‡ Age stratified and adjusted for race, smoking, education, BMI, parity, diabetes, ERT use, OC use, age at menarche, age at menopause, exercise, hypertension

Table 67. Hazard Ratios (95% CI) for Uterus Cancer in Relation to Asthma and/or Hay Fever Stratified by Smoking Status

	Never Smokers*	Ever Smokers*†	*p*
Asthma	0.82 (0.52, 1.28)	0.52 (0.26, 1.05)	0.27
Hay Fever	0.84 (0.64, 1.10)	1.10 (0.79, 1.53)	0.20
Asthma and Hay Fever	0.65 (0.32, 1.31)	0.56 (0.21, 1.51)	0.81
Asthma and/or Hay Fever	0.86 (0.68, 1.10)	0.99 (0.72, 1.35)	0.49

* Age stratified and adjusted for race, education, BMI, parity, diabetes, ERT use, OC use, age at menarche, age at menopause, exercise, hypertension
† Combines current, former, and ever smokers

Table 68. Hazard Ratios (95% CI) for Uterus Cancer in Relation to Asthma and/or Hay Fever Stratified by Age at Baseline

	<55 years*	>=55 years*	*p*
Asthma	0.57 (0.27, 1.21)	0.69 (0.44, 1.06)	0.72
Hay Fever	0.93 (0.64, 1.36)	0.94 (0.74, 1.19)	0.90
Asthma and Hay Fever	0.45 (0.14, 1.41)	0.63 (0.32, 1.21)	0.64
Asthma and/or Hay Fever	0.90 (0.63, 1.29)	0.91 (0.73, 1.13)	0.93

* Adjusted for race, smoking, education, BMI, parity, diabetes, ERT use, OC use, age at menarche, age at menopause, exercise, hypertension

Figure 1 to Figure 8 provide a summary of the results according to a history of asthma and/or hay fever. Overall hazard ratios are presented by cancer site in increasing order. For cancer sites where significant effect modification by smoking status was observed, the results for never smokers are given (indicated by asterisks). As well, results presented for lung cancer mortality are for never smokers only. The nature of the association between a history of asthma and/or hay fever and cancer mortality varied by cancer site and by sex. Reduced risk estimates in relation to asthma and/or hay fever were observed across a number of cancer sites, although few confidence limits excluded the null value. Few risk estimates above one were observed. Overall, the strongest protective effects on cancer mortality were observed in the asthma and hay fever category, particularly among females. Figures summarizing hazard ratios among never smokers are presented in Appendix 3.

The sensitivity analysis, which included two different methods for further control of smoking history, yielded results which were virtually identical to the results presented here where only smoking status at baseline (never, current, former, ever, pipe/cigar – men only, and missing) was utilized for adjustment, consequently, detailed results are omitted here. The proportional hazards assumption was also tested across all asthma and/or hay fever categories and cancer sites, with no evidence of non-proportionality of the hazard function.

Figure 1. Summary of Hazard Ratios for the Association between a History of Asthma and Cancer Mortality in Men

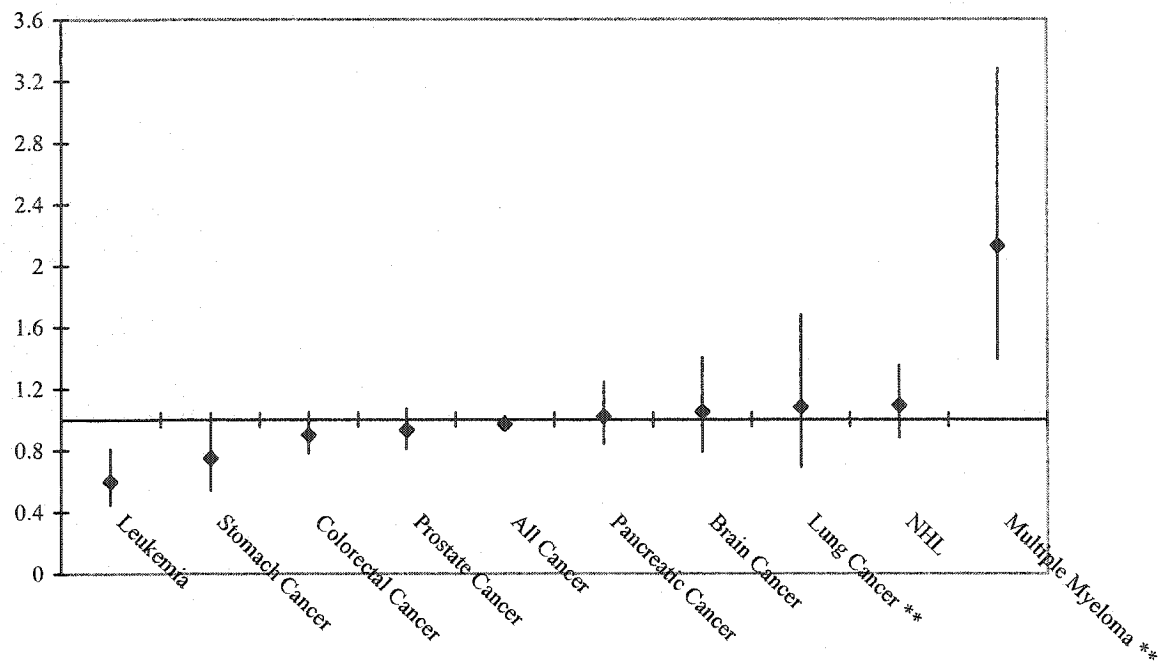


Figure 2. Summary of Hazard Ratios for the Association between a History of Asthma and Cancer Mortality in Women

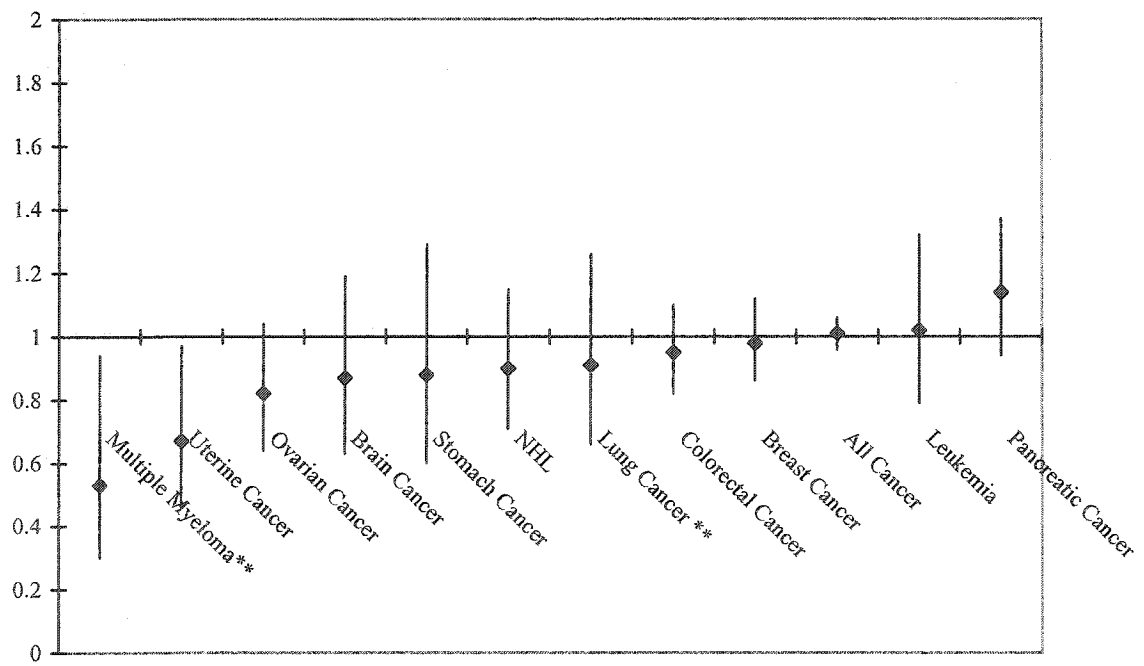


Figure 3. Summary of Hazard Ratios for the Association between a History of Hay Fever and Cancer Mortality in Men

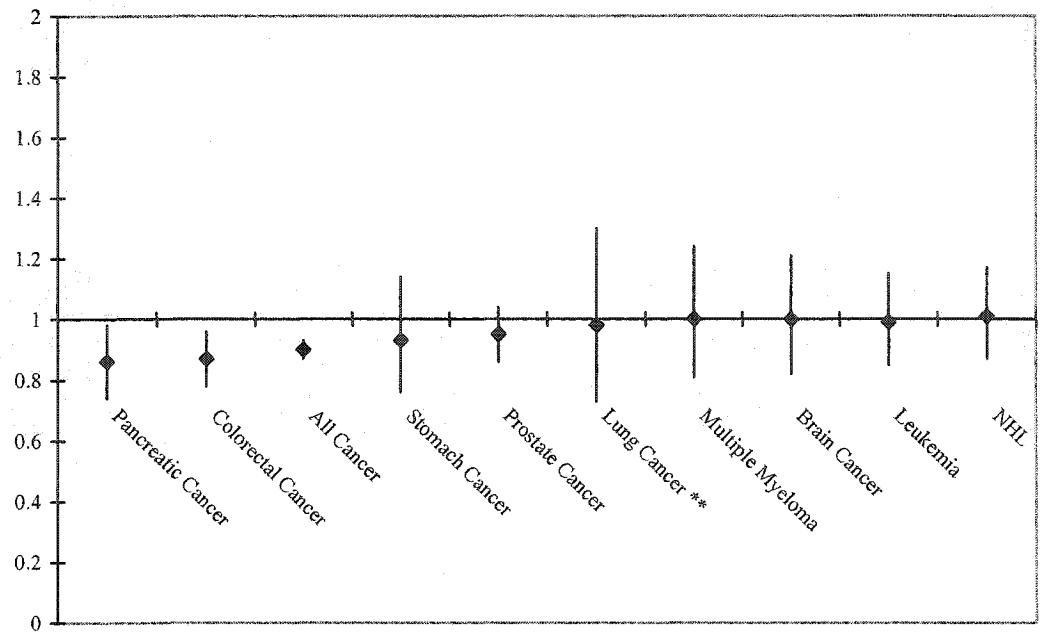


Figure 4. Summary of Hazard Ratios for the Association between a History of Hay Fever and Cancer Mortality in Women

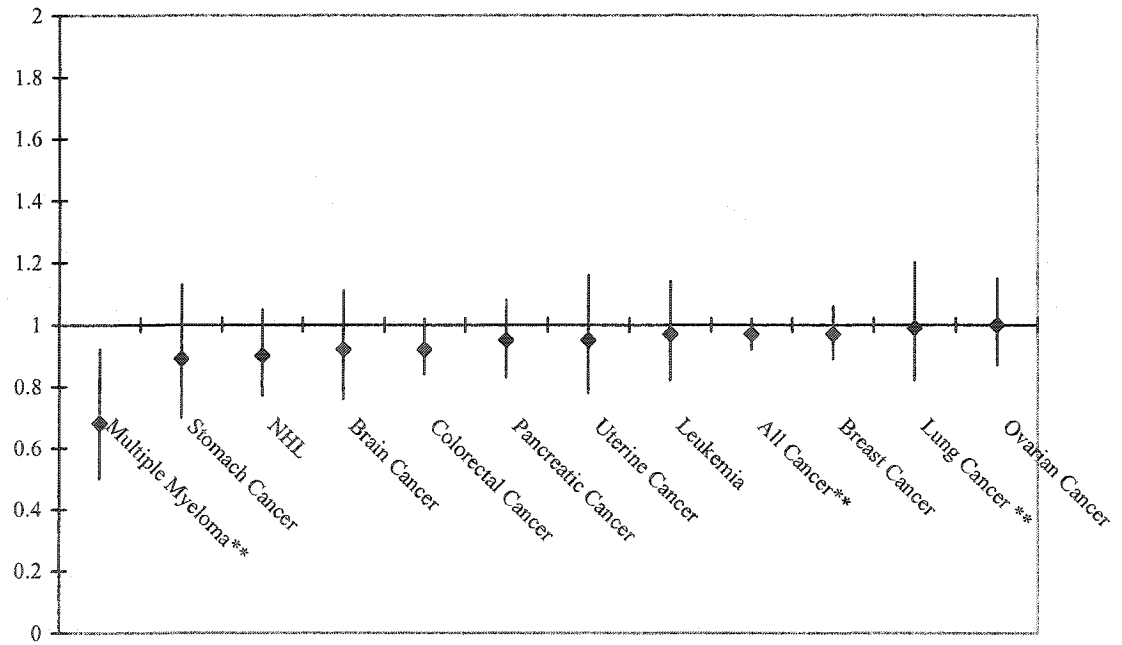


Figure 5. Summary of Hazard Ratios for the Association between a History of Asthma and Hay Fever and Cancer Mortality in Men

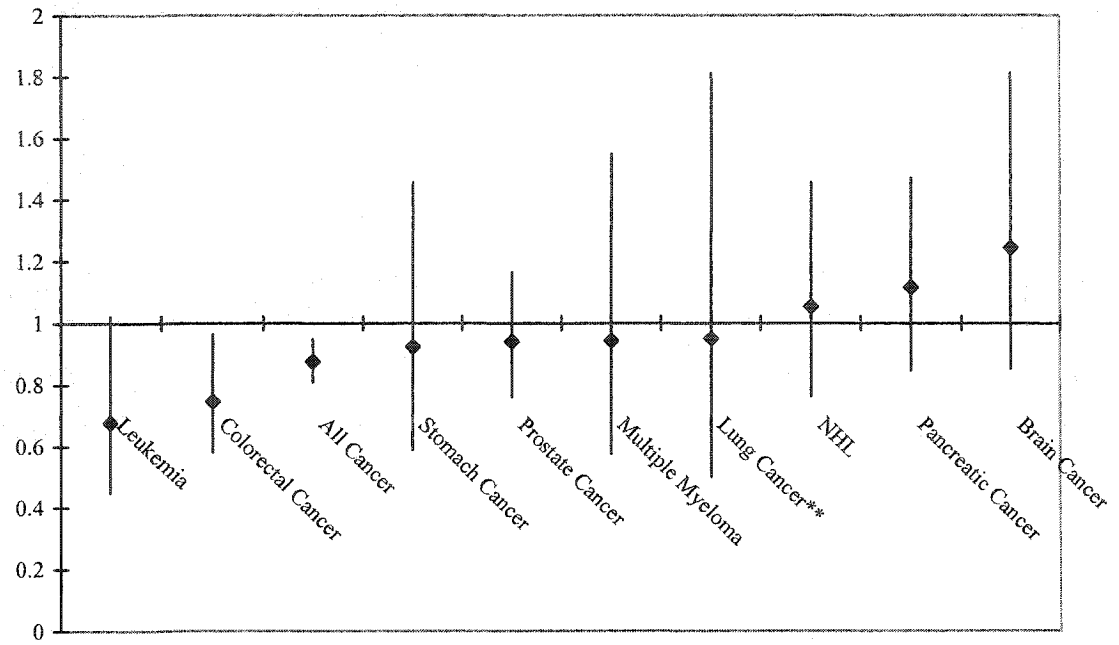


Figure 6. Summary of Hazard Ratios for the Association between a History of Asthma and Hay Fever and Cancer Mortality in Women

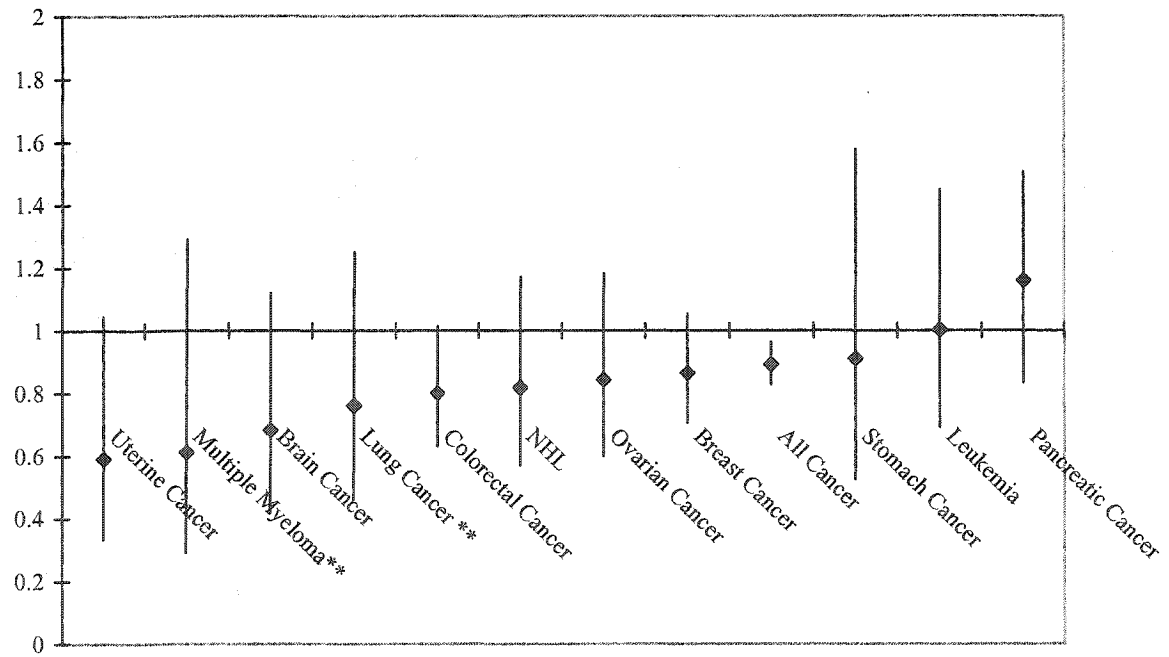


Figure 7. Summary of Hazard Ratios for the Association between a History of Asthma and/or Hay Fever and Cancer Mortality in Men

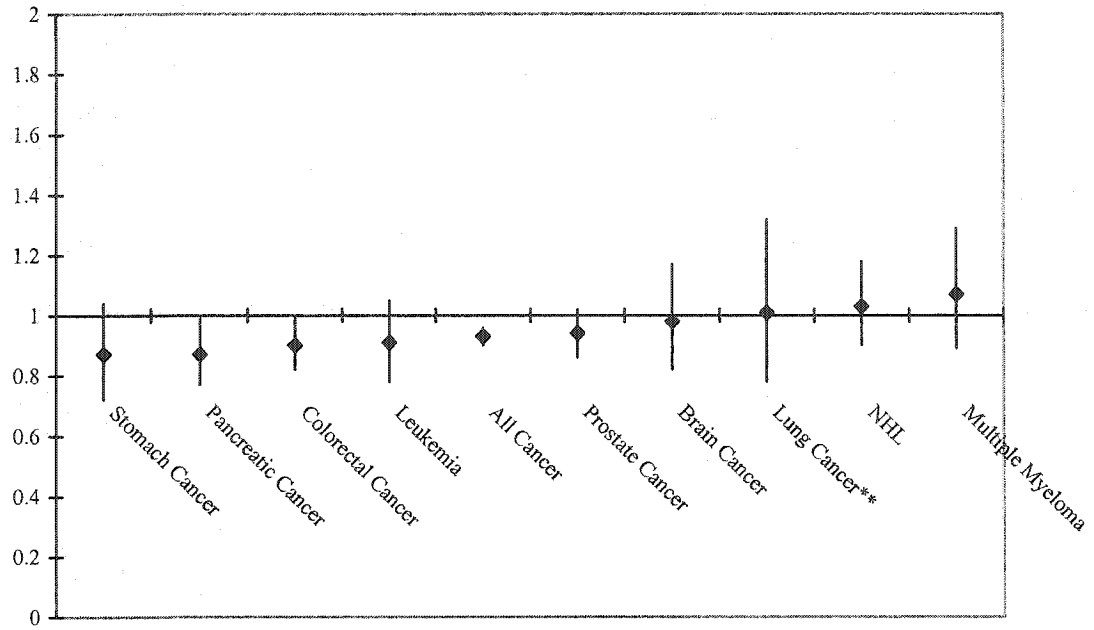
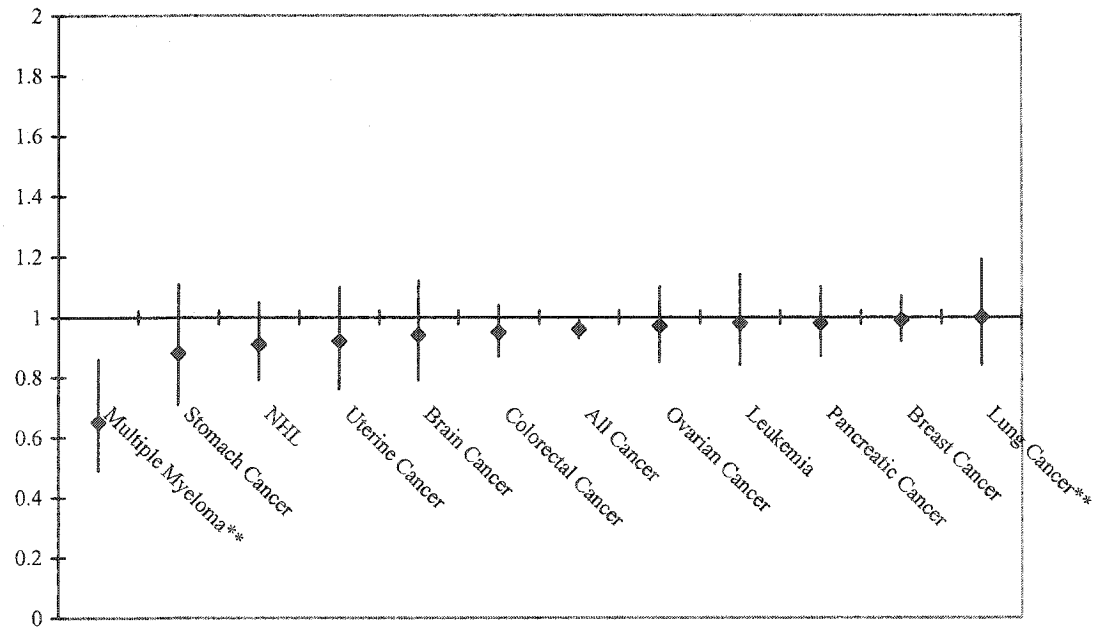


Figure 8. Summary of Hazard Ratios for the Association between a History of Asthma and/or Hay Fever and Cancer Mortality in Women



DISCUSSION

This thesis represents the largest prospective study to date that has evaluated the relation between a history of asthma and/or hay fever and cancer occurrence. Several strong protective relationships were noted between a history of asthma and/or hay fever and cancer mortality. However, the results can be seen to vary by cancer site, sex, and smoking status. In men, a history of asthma was associated with a reduced risk for leukemia mortality, but an increased risk for multiple myeloma mortality in never smokers. A history of hay fever was associated with a reduced risk for pancreatic and colorectal cancer mortality. A history of both asthma and hay fever was associated with a reduced risk for leukemia, colorectal, and all cancer mortality. In women, a history of asthma was associated with a reduced risk for uterine and ovarian cancer mortality as well as multiple myeloma mortality in never smokers. A history of hay fever was associated with a reduced risk for multiple myeloma in never smokers and pancreatic cancer mortality in never smokers. A history of both asthma and hay fever was associated with a reduced risk for uterine cancer, brain cancer, lung cancer, colorectal cancer, non-Hodgkin's lymphoma, ovarian cancer, breast cancer, multiple myeloma in never smokers, and all cancer mortality. A reduced risk for stomach cancer mortality was associated with a history of allergy in both men and women.

This thesis has a number of strengths. It is based on a large prospective study with over 18 years of follow-up. Large numbers of cancer deaths were observed in both men and women (approximately 40 000 each). The large sample size allowed a

meaningful examination of the association between asthma and/or hay fever and cancer mortality across thirteen different sites. The detailed information collected at baseline on each participant allowed for an assessment of the effects of covariates that may modify or confound the association between asthma and/or hay fever status and site-specific or overall cancer mortality. The prospective nature of this study and the exclusion of those with prevalent cancer at baseline avoids limitations in asthma and/or hay fever ascertainment and potential biases of previous studies. The large sample size allowed for the stratification of risk estimates by important variables, as well as the control for the effects of age in a robust manner. In addition, the large study population allowed for the creation of an exposure category comprised of those with both asthma and hay fever, which may be subject to less misclassification of allergic status.

Previous studies have failed to provide any clear evidence of an association between asthma or hay fever and all cancer occurrence. This study also found no association of all cancer mortality with asthma or with hay fever. A significantly reduced risk for all cancer mortality was found, however, in relation to a history of asthma and hay fever in both men and women. This study was the first study to create the combined asthma and hay fever category.

An increasing body of evidence has suggested that asthmatic patients experience an increased risk of lung cancer [58]. However, potential misclassification and differential recall bias in previous studies are still of concern and large prospective studies are needed to further address the issue [58]. Assessment of the effect of asthma on lung cancer

mortality in never smokers is believed to represent a valid method to reduce the possible misclassification of asthma as other chronic lung diseases [58]. This study found no increased risk for lung cancer mortality in asthmatics overall or in never smokers. In addition to the numerous advantages of this study population, this study is also the only study to date that controlled for various demographic and lifestyle variables as well as occupational exposures, passive smoking, and respiratory tract infections.

Previous studies evaluating asthma and hay fever in relation to pancreatic cancer risk have generally reported similar results. Large population-based studies have generally reported no association between a history of asthma and pancreatic cancer risk [12;63-65]with the exception of one study, which reported a significantly increased risk of pancreatic cancer in relation to a history of asthma in male smokers [66]. This study reports no association between a history of asthma and pancreatic cancer mortality overall. Although no significant effect modification by smoking status was observed, a 40% increase in risk was observed in asthmatic men who were current cigarette smokers at baseline. Men who reported both asthma and hay fever at baseline and who were current cigarette smokers experienced a significant 80% increase in risk for pancreatic cancer mortality. Stolzenberg-Solomon et al. [66] indicated that misclassification of asthma as an indicator of smoking status was not likely the explanation for this finding, since chronic bronchitis and emphysema were not related to pancreatic cancer risk in their study. The same was found in this study. In male smokers, no association was noted between chronic bronchitis (HR = 0.95, 95% CI = 0.64-1.4) or emphysema (HR = 0.96, 95% CI = 0.66-1.4) and pancreatic cancer mortality. All four previous studies evaluating hay fever

in relation to pancreatic cancer have reported reduced risks. A significant protective effect of hay fever on pancreatic cancer mortality was observed in this study in men overall, as well as in women who were never smokers (14% and 19% respectively). The results of this study therefore appear to be consistent with previous research, and are suggestive of a modifying effect of smoking status in men.

This study found a 20% reduction in risk for mortality from NHL in women but, not in men, in relation to a history of asthma and hay fever. The protective effect appeared to be most prominent in those aged less than 55 years at baseline. As has previously been described, the risk for NHL in association with a history of asthma or hay fever has not been subject to much prospective investigation. Case-control studies have, however, indicated a modest reduction in risk for NHL in relation to a history of asthma or hay fever. This is the first study to indicate a potential modifying effect of gender on the association between asthma and hay fever and NHL mortality.

Overall, the results from previous studies evaluating risk for leukemia in association with a history of asthma or hay fever remain unclear. Two cohort studies did report reductions in risk for leukemia associated with a history of asthma. They were, however, unable to control for potentially confounding variables in the analysis and differ from this study in that incident cases, not deaths, were studied [38;39]. The most recent cohort study reported an increased risk for leukemia in men and women in relation to a history of asthma or hay fever [57]. However, these results were based on very small numbers of observed and exposed cases and are highly unstable. This study found a 40%

reduction in risk for leukemia in men with asthma, but not in women. Previous studies have indicated that the effect of a history of asthma, hay fever, or other allergic conditions may vary by leukemia subtype. The comparison of results across studies is therefore complicated as the proportion of the different leukemia subtypes observed in the study population differs across different studies. The results from this study indicate that further investigation is warranted in order to further characterize a potential association between asthma and leukemia.

Previous studies have reported little convincing evidence for an association between a history of asthma or hay fever and multiple myeloma. This is the first study to evaluate risk for multiple myeloma mortality by sex and smoking status. In never smokers, asthma was associated with a doubling in risk for death from multiple myeloma in men, and a halving in risk for death from multiple myeloma in women. The only other study of multiple myeloma stratified by sex reported a significant protective effect of asthma in women (SIR = 53, 95% CI = 30-85), but no effect in men (SIR = 107, 95% CI = 67-162)[39].

A history of allergy, including both asthma and hay fever, has been associated with a reduced risk for glioma but not meningioma or acoustic neuroma in a number of previous studies. This study evaluated the more heterogeneous outcome represented by all brain cancer deaths, and found evidence of a protective association in women with asthma and hay fever. The results from this study are dependent on the proportion of deaths from the different brain cancer subtypes experienced by both sexes. This study is

unable to contribute to the evidence for an association of asthma or hay fever with specific brain cancer subtypes; further investigation to confirm such an association is necessary.

This study observed a reduction in risk for colorectal cancer mortality in men and women who reported a history of asthma and hay fever of approximately 20%. A large case-control study reported an odds ratio of 0.8 (95% CI = 0.6-1.0) for colorectal cancer in relation to a history of allergic conditions [122]. A prospective study by Talbot-Smith et al. [57] also recently reported that colorectal cancer was negatively associated with a history of asthma or hay fever, although none were significant. The remaining cohort studies evaluated colon and rectal cancer separately, with no consistent results [38-40]. Colon and rectal cancers were analyzed together in this study because of concerns about misclassification of cause of death on on death certificates between these two sites [186]. Unfortunately, this analytic decision precludes evaluation of site-specific associations for colon and rectal cancer.

A prospective study by Ye et al. [127] reported an increased risk for gastric cardia adenocarcinomas in asthma patients hospitalized for their respiratory condition. In that study, risk was estimated among those with severe asthma and was attributed to excess gastro-esophageal reflux in that population. In this study, modest reduced risks were observed across all exposure categories for stomach cancer mortality, although, none achieved significance. Both Vena et al. [32] and Mills et al. [40] reported no association between asthma or hay fever for stomach cancer. In a larger prospective study, SIRs of

85 (71-100) in men and 91 (77-107) in women with asthma were reported for stomach cancer [39]. Kallen et al. [38] reported a 50% reduction in the risk of stomach cancer in asthma patients.

Two small cohort studies previously observed an increased risk of prostate cancer in asthma patients [57;118]. The majority of the larger prospective studies, however, reported no association with a history of asthma or hay fever [32;39;40]. This study also found no association between either asthma or hay fever and prostate cancer mortality. Overall, there is no evidence for an association between a history of asthma or hay fever and prostate cancer occurrence.

Most studies examining the association between a history of asthma or hay fever and breast cancer reported no association [14;32;39;40;57]. In this study, histories of either asthma or hay fever were not associated with risk for breast cancer mortality. A history of asthma and hay fever was, however, associated with a 14% reduction in risk for breast cancer mortality in this cohort.

In this study, a history of asthma was associated with an 18% reduction in risk for ovarian cancer. Only one other study, the study by Kallen et al. [38], has reported a reduction in risk for ovarian cancer in asthmatics (SIR 52, 95% CI = 42-63). All other studies have reported no association between ovarian cancer and asthma as well as hay fever [32;39;40].

All previous cohort studies reported reduced risks of uterine cancer in relation to a history of asthma [38-40]. This study reported a significantly reduced risk for uterine cancer mortality of approximately 34% in asthma patients. The risk estimate in this study is very similar to that reported by Mills et al. [40], although they evaluated incident cancers not cancer deaths. Both of these studies were able to control for a number of potentially confounding variables, and both excluded those who reported a hysterectomy at baseline. In this study, a hysterectomy was reported in 33% of women at baseline, a value similar to national estimates for the United States[187]. Unfortunately, we were not able to assess hysterectomy rates since baseline. Given that the average age of hysterectomy in the United States is between 40 and 45 years, the advanced average age of this cohort (approximately 55 years), and the fact that no effect modification by age at baseline was observed, the potential for bias may be minimal [187].

Methodological Issues

There are a number of methodological issues, which may have an impact on the study results. While attempts were made to address the limitations of earlier studies, a number of important concerns remain.

Ascertainment of Asthma and Hay Fever Status

A major limitation of this thesis is the ascertainment of asthma and hay fever status. This thesis is based on self-reported history of physician-diagnosed asthma or hay

fever. Although these questions have not been validated in the ACS-CPS II cohort, it has been previously reported that asthma and hay fever questions of this type are highly specific and more reliable than symptom-based questions or questions asking if they have ever had the disease [136]. Questions asking about a previous physician-diagnosed condition, however, may exclude those with mild symptoms not seeking medical assistance. Physician-diagnosed questions of asthma and hay fever have been widely used in other population-based surveys in the United States, including the Behavioural Risk Factor Surveillance System (BRFSS), the National Health Interview Surveys (NHIS), and the National Health and Nutrition Examination Surveys (NHANES). The prevalence of asthma and hay fever in this study is very similar to that found from other surveys of adults in the United States. McWhorter et al. [14] reported a prevalence of asthma of 5.7% and a prevalence of hay fever of 10.8% among those 25-74 year of age in the NHANES I survey. In 1999, the NHIS reported a prevalence of asthma of 8.5% and a prevalence of hay fever of 8.9% in adults 18 years and over [188]. No information was collected on age at diagnosis or allergy medication.

Age at diagnosis is potentially an important factor for asthma classification as those diagnosed with asthma late in adulthood likely suffer from non-allergic as opposed to allergic asthma. To address this issue, we stratified risk estimates by age at baseline. Virtually all of the associations tested indicated no significant effect modification by age at baseline. This indicates that the potential for misclassification of allergic vs non-allergic asthma may be low. There is a possibility that asthma and allergy medications are related to cancer; however, the evidence to date has been scarce and results are not

consistent. An increased risk for esophageal cancer was reported among those using asthma drugs containing theophylline or ß agonists[189], whereas cortisone may have a protective effect on cancer development [117;130]. Most other studies have found no significant associations between allergy or asthma treatments and cancer [64;74;86;100-102;104;105;110;114;131;190-192].

We further evaluated cancer mortality among a sub-group of never smokers in order to reduce potential misclassification of asthma with other smoking related chronic respiratory conditions, and to obtain a relative risk estimate largely free of potential residual confounding by smoking status. As well, those with both asthma and hay fever are thought to represent a group with the potential for minimum misclassification. Overall, misclassifications of asthma or hay fever status would likely result in a bias of the association estimate towards the null. Misclassification of asthmatic status in smokers however, may be more complex and could be differential in nature. Associations between asthma and cancer mortality in smokers need to be interpreted with caution.

Outcome Assessment

In mortality-based studies, cancer incidence as well as factors affecting survival influence the observance of an outcome. Therefore, this mortality-based study is limited in its ability to make clear inferences regarding the development of cancer. However, mortality rates are considered to be the most significant indicator of the cancer burden in

humans [7]. 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 non-asthmatic lung cancer patients in one study was found not to differ [193]. Another study reported however, that asthma exerted a negative impact on survival from lung cancer[194]. Asthma was also associated with a two-fold increase in risk for breast cancer death 30 months post-diagnosis in postmenopausal women over age 55 years of age [195]. Lastly, Yancik et al. [196] concluded that asthma did not impact the survival experience of those with colorectal cancer[196]. 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.

This study has a high rate of follow-up, with over 98% of deaths assigned a cause. The reliance on death certificates for outcome assessment may, however, introduce bias due to outcome misclassification. The majority of cancer sites studied in this thesis have been reported to be recorded reliably over 80% of the time on death certificates [186]. Colon and rectal cancer deaths were studied as one outcome, however, due to previously reported over-reporting of colon cancer deaths and underreporting of rectal cancer deaths on death certificates [186]. This grouping is often performed [7;197], but does not permit the assessment of the nature of site-specific associations. The combination of corpus uterus cancer and cancer of the uterus NOS is also often performed in order to include cases of noncervical carcinoma of the uterus[198]. However, this may introduce misclassification of uterus cancer as cancer of the uterus NOS may represent a heterogeneous group of cancers with different etiologies [7;198]. The extent of misclassification may be minimal, as

it has been reported that the proportion of cervical cancers in the uterus NOS category has declined over the past three decades to approximately 2% or less[198].

Other Issues

Cigarette smoking status represents an important factor in the association between asthma and/or hay fever and cancer mortality for many sites as both a confounding and modifying factor. The sensitivity analysis related to cigarette smoking status indicated that more refined control for cigarette smoking history did not appreciably alter risk estimates beyond those with a crude adjustment for cigarette smoking. Unfortunately, all covariates, including smoking status, were measured only at baseline. Although it is unlikely that study participants who had never smoked would begin smoking cigarettes (with an average age at baseline in the mid-fifties) [44], those with a history of asthma and/or hay fever have been reported to be more likely to quit smoking. 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 [58]. Although a departure from the proportional hazards assumption was not observed, the potential for such a dependency of hazard ratios over time further supports the estimation of risk in the sub-group of never smokers for smoking related cancers [58]. Similarly, no subsequent information was collected on the asthma or hay fever status of study participants with which to confirm the baseline measurement.

Multiple testing is involved in this study as well as in previous studies as they have evaluated a number of indicators of allergic status, including a number of allergic conditions, allergy to specific substances, and specific allergic symptoms. One would expect a certain number of "statistically significant" associations to occur by chance with the numerous associations being tested based on the commonly used alpha level of 0.05 with no further adjustment. It is important that p-values should not be overly interpreted. The significance level is arbitrarily set while p-values are determined by a number of factors including effect size of an exposure, multiple testing, sample size and assumptions. To avoid misinterpretation, the estimates should be evaluated by not only statistical but also other criteria such as consistency across different studies.

It has been noted that CPS-II participants are generally more educated and more affluent than the general American population (likely due to the volunteer-based recruitment). Although this may potentially affect comparisons of this cohort to the general population, the internal validity of the study is unlikely affected by the enhanced socio-economic status of the cohort as a whole [182].

Another limitation is the inability to control for certain potentially important covariates. For example, there was no information on H. pylori infection which is important in stomach cancer mortality. In a recent community-based cross-sectional study, those with an active H. pylori infection were found to be 30% less likely to have an atopic disorder [199]. However, we were able to control for number of siblings as an indicator of H. pylori infection.

Despite these limitations, many strong protective associations have been reported for a number of cancer sites; those associations persist within the subgroup of never smokers. The nature of the association between allergy and cancer at a specific site may be the result of the different etiologies and the potential global or local effects that allergic disorders could exert.

Possible Biological Mechanisms

Global Effects

Higher numbers of NK cells have been observed in the peripheral blood of asthmatics [200]. Those with allergic asthma were found to possess significantly stronger NK cell activity against the K-562 leukaemic cell line [201] and U937 cell growth [202]. Children with atopic dermatitis were found to possess greater NK cell activity against Burkitt's lymphoma cells [203]. NK cell activity has been suggested to be related with total serum IgE levels [204]. A large cohort study with eleven years of follow-up has also demonstrated that low NK cell activity was associated with an enhanced risk of cancer at all sites [205].

Th2-type cytokines such as IL-10 and IL-4 have been found to demonstrate anti-tumor properties [206-208]. Successful tumor rejection has also been achieved with various Th2-type cytokines [209-211].

IgE driven immune reactions have been shown to be effective in inhibiting tumor growth in vivo [212;213]. Loading tumors with IgE has been shown to result in a strong inhibition of tumor growth or complete tumor rejection [214]. Immunizing with irradiated tumor cells loaded with IgE has shown to be protective against future tumor growth [214].

Histamine has demonstrated anti-cancer activity. Low blood and tissue levels of histamine have been found to be related to reduced anti-tumor activity and tumor occurrence [215]. Histamine has been suggested to be able to protect NK cells from reactive oxygen species inhibition by the monocytes and macrophages, as well as synergize with other cytokines to stimulate anti-tumor NK cell and T cell activity [216].

It has been suggested that eosinophils may play a role in the initiation of the anti-tumor response[214]. A moderate survival advantage has also been demonstrated in some cancer patients with tumor-associated tissue eosinophilia[217]. It has been speculated that eosinophil recruitment to the tumor may depend on the nature of the host anti-tumor response due to suggestions that a Th2 type response and IL-4 may be responsible for such activity [217-219].

Local Effects

Local mechanisms may also play an important role in the association between a history of allergy and the risk of cancer of different types. The positive association that

has previously been reported between asthma and lung cancer may be related to various mechanisms including: 1) elevated levels of free radicals and reduced levels of antioxidants in the respiratory tract [61;220], 2) continual stimulation of cell regeneration to repair inflammatory lung damage[53;220], and 3) an increased sensitivity to carcinogens[39]. In this study, lung cancer risk was not elevated among asthmatics.

The increased risk for bladder cancer in Korean subjects associated with a history of asthma with GSTM1 null genotypes has been suggested to be due to a deficiency in the detoxification of reactive asthma medication intermediates through a lack of these enzymes[134].

Mack et al. [159] have speculated that atopy could act in a protective manner towards exocrine pancreatic cancer through histamine. Histamine indirectly affects pancreatic function through its direct effect on gastric acid secretions which in turn stimulate pancreatic secretions [159].

In explaining the strong protective effect between a history of allergy and glioma, Wiemels et al. [112] noted that immune responses within the central nervous system appear to be primarily humoral-based rather than cell-mediated in order to restrict potential damage to adjacent central nervous system tissue. Since many factors are released by the growing tumor cells, which are suppressive towards cell-mediated immunity, those with an allergic history may be able to more effectively mount a successful humoral anti-glioma response[112].

Laboratory evidence has suggested a protective effect of atopy on lymphoma development[221]. Significantly decreased tumor (lymphomatous lesions) development rates were found in mice injected with peripheral blood mononuclear cells from atopic subjects compared to normal subjects. Significantly decreased lymphoma development also occurred in mice injected from atopic donors categorized with high IgE levels versus atopic donors with low IgE levels or normal subjects. Holly et al. [77] suggested that the negative association for NHL in those with plant allergies may be due to the continual capacity for differentiation of B-cells, resulting in a reduced accumulation of these cells.

Lastly, the chronic antigenic hypothesis has been suggested by some as a potential mechanism for a potential increase in risk for multiple myeloma associated with a history of allergy [101;102;108]. Gender differences have not been discussed in relation to any of these hypotheses.

Conclusions and Future Directions

Overall, this thesis has indicated that an association exists between allergy and cancer at a number of sites, which may be modified by sex and smoking status. Nonetheless, however, there exists considerable opportunity for further research in this area. For virtually all cancer sites, few large prospective studies exist with the ability to control for potential cancer site-specific confounders. The potentially modifying effects of sex and smoking status need to be confirmed in future studies, and additional studies in

never smokers would be particularly useful to confirm an association. Also of importance is the classification of allergic status. Further studies must carefully consider methodological difficulties in assessing a history of allergy. Further study is needed in the validation of indicators of allergic status for use in large epidemiological studies, including biological markers in order to reduce potential misclassification of allergic status and to confirm the results of previous studies based on self-reports. There is also a need for further laboratory research in order to clarify the biological mechanisms behind the associations observed. If a definitive link between allergies, the immune system, and cancer is established in the future, it is crucial that allergy treatments do not disrupt this protective mechanism [113].

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APPENDIX 1 – SUMMARIES OF PREVIOUS EPIDEMIOLOGICAL STUDIES

TABLE 1. Cohort Studies Evaluating Risk of Any Type of Cancer in Relation to a History of Allergy

Reference (Country)	Population (Number of cases)	Risk Factor	Relative Risk (95% Confidence Interval)
Alderson [33] (England)	1892 from asthma clinic (63 all cancer deaths, also studied 3 other cancer sites)	Asthma – Physician diagnosed	**71***
Polednak [35] (USA)	12098 *men* from Harvard (1074 all cancer deaths, also studied 9 other cancer sites)	Asthma	No association
Robinette et al. [37] (USA)	9550 *men* with asthma in army hospitals (328 all cancer deaths, also studied 23 other cancer sites)	Asthma – Physician diagnosed	**1.3**
Hughes et al. [46] (USA)	Clinic-based (26 incident cases)	Positive scratch test or intradermal skin test	No association
Markowe et al. [34] (England)	2547 asthmatic & non-asthmatic patients (34 all cancer deaths also studied cancer of trachea/bronchus/lung)	Asthma - Physician diagnosed	0.9 (0.5-1.5)
Reynolds et al. [36] (USA)	6848 in California (472 incident cases, 277 all cancer deaths, also studied lung cancer)	Asthma (incidence M,F)† (mortality)	**2.1**, 1.1 **2.4**, 0.5
McWhorter [14] (USA)	NHANES I ‡ cohort of 6913 given supplemental questionnaire (341 all cancer incidence and deaths, also studied 9 other sites)	Any allergy Hives Asthma Hay fever Food allergy Other allergy	**1.4 (1.1-1.8)** **1.5 (1.0-2.2)** 1.0 (0.6-1.6) 1.2 (0.8-1.7) 1.4 (0.9-2.2) **1.4 (1.0-1.9)**
Mills et al. [40] (USA)	34198 Seventh-day Adventists (1102 incident cases, also studied 16 other sites)	Any allergy (M,F)† Asthma Hay fever Reaction to medication Reaction to chemicals Reaction to bee sting Reaction to poisonous plants	1.1 (0.9-1.4), 1.0 (0.8-1.2) 0.8 (0.5-1.3), 1.0 (0.7-1.3) 1.1 (0.8-1.4), 1.2 (0.9-1.4) **1.3 (1.0-1.7), 0.8 (0.6-1.0)** 0.7 (0.3-1.4), 0.8 (0.5-1.2) 0.7 (0.4-1.1), 1.1 (0.8-1.5) 1.1 (0.9-1.4), 1.0 (0.8-1.2)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (4520 incident cases, also studied 30 other sites)	Asthma - Physician diagnosed	**66 (64-68)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (3842 incident cases, also studied 18 other sites)	Asthma (M,F)† - Physician diagnosed	**112 (107-117)***, 103 (98-107)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (87 incident cases, also studied 25 other sites)	Atopic – Skin test Intermediate atopic – Skin test Rhinitis Asthma Urticaria - Physician diagnosed	107 (63-173)* **167 (118-235)*** 111 (83-147)* 127 (92-174)* 170 (99-280)*
Lange et al. [42] (Denmark)	13540 from Copenhagen Heart Study (1338 all cancer deaths)	Asthma	1.0 (0.7-1.4)
Knuiman et al. [41] (Australia)	4277 in Busselton Health Study (372 all cancer deaths)	Asthma (M,F)†	1.3 (0.7-2.3), 0.9 (0.4-2.0)
Gergen et al. [45] (USA)	NHANES II§ – Mortality Study cohort of 9252 (998 all cancer deaths)	Skin test	0.9 (0.3-2.4) 30-44 year olds 0.8 (0.4-1.4) 45-59 year olds 1.1 (0.8-1.5) 60-75 year olds
Margolis et al. [43] (USA)	Medicaid database (13013 incident cases, also studied 3 other sites)	Severe eczema - Physician diagnosed	1.0 (0.8-1.3)
Vandentorren et al. [44] (France)	14267 in PAARC Study‖ (932 all cancer deaths)	Asthma	1.1 (0.8-1.4)

* Standardized incidence/mortality ratio
† M = males, F = females
‡ First National Health and Nutrition Examination Survey
§ Second National Health and Nutrition Examination Survey
‖ Air pollution and chronic respiratory diseases study

TABLE 2. Studies Evaluating Risk of Lung Cancer in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)
Cohort Studies			
Alderson [33] (England)	1892 from asthma clinic (16 lung cancer deaths)	Asthma – Physician diagnosed	80*
Robinette et al. [37] (USA)	9550 *men* with asthma in army hospitals (274 respiratory system cancer deaths)	Asthma – Physician diagnosed	**1.4**
Markowe et al. [34] (England)	2547 asthmatic non-asthmatic patients (25 lung cancer deaths)	Asthma - Physician diagnosed	0.8 (0.3-1.8)
Reynolds et al. [36] (USA)	6848 in California (66 incident cases, 56 deaths)	Asthma (incidence M,F)* (mortality)	**6.3**, 1.2 **5.4**, -
McWhorter [14] (USA)	NHANES I ‡ cohort of 6913 given supplemental questionnaire (73 incident cases and deaths)	Any allergy	1.2 (0.7-2.0)
Mills et al. [40] (USA)	34198 Seventh-day Adventists (62 incident cases)	Any allergy Asthma Hay fever Reaction to medication Reaction to bee sting Reaction to poisonous plants	1.0 (0.6-1.7) 1.2 (0.4-3.3) 1.2 (0.6-2.5) 0.6 (0.2-1.4) 0.9 (0.3-2.9) 0.9 (0.4-1.8)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (632 incident respiratory tract cancers)	Asthma - Physician diagnosed	105 (97-113)‡
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (783 incident cases)	Asthma (M,F)* - Physician diagnosed	**132 (122-142)‡, 166 (139-194)‡**
Lange et al. [42] (Denmark)	13540 from Copenhagen Heart Study (378 deaths)	Asthma	1.3 (0.7-2.3)
Huovinen et al. [56] (Finland)	31110 (mostly twins) (115 deaths)	Asthma (M)*	**3.2 (1.4-7.3)**
Hospers et al. [55] (Netherlands)	2008 in three communities (54 deaths)	Asthma Positive skin test	2.3 (0.5-10.0) 0.8 (0.3-2.2)
Boffetta et al. [61] (Sweden)	92986 hospitalized for asthma (713 incident cases)	Asthma - Physician diagnosed	**158 (147-170)‡**
Talbot-Smith et al.[57] (Australia)	3308 in 1981 Busselton Health Survey (28 incident cases)	Asthma (M,F)* Hay fever Any atopy	1.2 (0.2-9.1), 1.0 (0.1-7.5) 0.6 (0.1-4.9), 1.4 (0.4-5.3) 0.3 (0.0-2.5), 0.9 (0.1-9.9)
Vandentorren et al.[44] (2003) (France)	14267 in PAARC Study§ (178 deaths)	Asthma	1.4 (0.8-2.3)
Case-Control Studies			
Fisherman [19] (USA)	Clinic-based (48/294)	Atopy	0.1 (0.0, 1.1)‖
Van der Wal et al. [222] (Netherlands)	Hospital patients/Population controls/ Population controls matched for smoking (150/150/100)	Positive skin test (Population controls) (Matched controls)	 1.8 (0.8-3.8)‖ 1.6 (0.7-3.6)‖
Damon et al. [223] (USA)	Nested in cohort of 17 000 *men* at Harvard (130/130)	Asthma	1.0 (0.2-4.1)‖
Shapiro et al. [31] (USA)	Hospital-based (184/3310)	Allergy	1.0 (0.5-1.9)
Gabriel et al. [47] (England)	Hospital-based, *men* (150/150)	Allergy (asthma, hay fever, eczema, urticaria, food reaction)	**0.1(0.0-0.4)**‖

Hallgren et al. [48] (Sweden)	Hospital cases/Hospital controls/ Health survey controls (217/143/246)	Atopy (asthma, rhinitis, urticaria, eczema) (Hospital controls) (Health survey controls)	**0.3 (0.2-0.7)**‖ **0.2 (0.1-0.3)**‖
Vena et al. [32] (USA)	Hospital-based (1186/4039)	Asthma (M,F)* Hay fever Hives Other allergies	**1.5**, 0.8 0.8, 0.7 **0.5**, 1.2 **0.5**, 0.6
Samet et al. [224] (USA)	Population-based (518/769)	Asthma	**1.8 (1.2-2.6)**‡
Sanchez-Borges et al.[225] (Venezuela)	Hospital cases/Normal controls (48/50)	Atopy (eczema, rhinitis, asthma)	0.3 (0.1-1.2)§
McDuffie et al. [49] (Canada)	Population-based (137/137)	Positive skin prick test Asthma Hay fever Allergies	**0.4 (0.2-0.6)**‖ 0.6 (0.2-1.6)§ 0.5 (0.2-1.5)‖ **0.5 (0.3-0.8)**§
Wu et al. [59] (USA)	Population-based, *women* (336/336 - adenocarcinoma)	Asthma	1.0 (0.5-2.1)
McDuffie [50] (Canada)	Population-based (176/209 - squamous cell and adenocarcinoma)	Positive skin prick test	**0.6 (0.4-0.9)**
Osann [226] (USA)	Hospital-based, *women* (217/217)	Asthma or hay fever	0.5 (0.3-1.0)
Alavanja et al. [52] (USA)	Population-based, non-smoking *women* (618/1402)	Asthma	1.3 (0.8-2.1)
Michils et al. [227] (Belgium)	Hospital cases/Healthy controls (103/102)	Positive radioallergosorbent test	1.1 (0.5-2.2)
Pavlakou et al. [51] (Greece)	Hospital cases/Population controls (92/194)	Atopic disease - Questionnaire and skin test	**0.3 (0.2-0.6)**‖
Wu et al. [54] (USA)	Population-based, lifetime nonsmoking *women* (412/1253)	Asthma	**1.7 (1.1-2.5)**
Mayne et al. [53] (USA)	Population-based, nonsmokers (437/437)	Asthma (model 1)	**2.0 (1.0-4.1)**
Brownson et al. [228] (USA)	Population-based, *women* (676/700)	Asthma	1.1 (0.7-1.7)
Cocco et al. [229] (China)	Workers exposed to silica (316/1356)	Asthma	1.0 (0.6-2.0)
Osann et al. [60] (USA)	Hospital cases/Population controls, *women* (98/204 - small cell lung cancer)	Asthma Hay fever	4.8 (1.0-22.8) 1.3 (0.5-3.6)
Brenner et al. [62] (China)	Hospital cases/Population controls (886/1765)	Asthma	1.4 (0.9-2.1)

* M = males, F = females
† First National Health and Nutrition Examination Survey
‡ Standardized incidence/mortality ratio
§ Air pollution and chronic respiratory diseases study
‖ Original study presented frequency data only. Unadjusted odds ratio and 95% confidence interval calculated from original data.

TABLE 3. Studies Evaluating Risk of Pancreatic Cancer in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)
Cohort Studies			
McWhorter [14] (USA)	NHANES I* cohort of 6913 given supplemental questionnaire (11 incident cases and deaths)	Any allergy	1.7 (0.5-5.8)
Mills et al. [65] (USA)	34 198 Seventh-day Adventists (40 pancreatic cancer deaths)	Asthma Hay fever Reaction to plants Reaction to bee sting Reaction to medication Reaction to chemicals	0.9 (0.2-3.4) 0.7 (0.2-1.9) 1.0 (0.4-2.3) 0.4 (0.1-3.2) 0.7 (0.1-6.0) 1.5 (0.4-6.3)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (160 incident cases)	Asthma - Physician diagnosed	**64 (55-75)**†
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (142 incident cases)	Asthma (M,F)‡ - Physician diagnosed	88 (67-113)†, 101 (80-124)†
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (1 incident case)	Atopic – Skin test Intermediate atopic – Skin test	0 (0-1250)† 189 (5-1050)†
Stolzenberg-Solomen et al. [66] (Finland)	29 048 *male* smokers in ATBC study§ (172 pancreatic cancer deaths)	Asthma Allergic skin lesions	2.2 (1.2-4.0) 0.6 (0.3-1.2)
Case-Control Studies			
Lin et al. [230] (USA)	Hospital-based (109/109)	Allergy/eczema/dermatitis	**2.6 (1.3-4.9)**‖
Gold et al. [231] (USA)	Hospital cases/Hospital controls/ Population controls (201/201/201)	Allergic disorders (Hospital controls) (Population controls)	 **0.4 (0.2-0.7)** 1.0 (0.5-1.9)
Mack et al. [159] (USA)	Population-based (490/490)	Asthma Allergic skin reactions Allergy to natural antigens Allergy to commercial products Any allergic disease	0.7 (0.4-1.1) **0.2 (0.1-0.5)** **0.5 (0.3-0.9)** 0.9 (0.5-1.6) **0.6 (0.4-0.8)**
Farrow et al. [63] (USA)	Population-based, *men* (148/188)	Asthma Allergy to medication Food allergy Plant allergy Animal allergy	1.1 (0.4-3.2) 1.7 (1.0-3.0) 2.1 (0.8-5.5) 0.7 (0.3-1.8) 1.2 (0.4-3.4)
La Vecchia et al. [232] (Italy)	Hospital-based (247/1089)	Drug allergy	0.9 (0.6-1.6)
Jain et al. [67] (Canada)	Hospital cases/Population controls (249/505)	Hay fever Eczema Asthma Other allergies	0.5 (0.2-1.3) 0.7 (0.3-1.5) 0.5 (0.2-1.7) 1.3 (0.7-2.3)
Bueno de Mesquita et al. [158] (Netherlands)	Population-based (176/487 – exocrine cancer)	Any allergy Eczema Other allergies	**0.6 (0.4-0.9)** 0.8 (0.4-1.3) **0.4 (0.2-0.8)**
Kalapothaki et al. [233] (Greece) (181/362)	Hospital cases/Hospital and healthy hospital visitor controls	Asthma	0.33
Dai et al. [12] (China)	Population-based (108/275)	Any allergic condition Drug allergy Food allergy Contact dermatitis Urticaria Asthma Allergic rhinitis Moderate reaction to mosquito Strong reaction to mosquito	0.7 (0.4-1.1) 1.1 (0.5-2.4) 0.3 (0.0-2.6) 0.5 (0.1-1.7) 0.5 (0.2-1.3) 1.0 (0.3-3.2) 0.3 (0.1-1.4) 0.7 (0.1-1.1) 1.0 (0.3-3.1)

Silverman et al. [64] (USA)	Population-based (484/2099)	Any allergic condition	**0.7 (0.5-0.9)**
		Hay fever	**0.6 (0.5-0.9)**
		Asthma	1.0 (0.6-1.5)
		Eczema	1.1 (0.7-1.9)
		Animal allergy	0.5 (0.2-1.1)
		Insect bite/sting allergy	0.8 (0.6-1.2)
		Dust or mold allergy	0.6 (0.3-1.1)
		Drug allergy	**1.4 (1.1-1.9)**
		Household products allergy	1.5 (0.8-2.9)
Holly et al. [68] (USA)	Population-based (532/1701)	Any allergy	**0.8 (0.6-1.0)**
		House dust	**0.7 (0.5-0.9)**
		Plants	**0.8 (0.6-1.0)**
		Mold	**0.5 (0.3-0.8)**
		Any animals	**0.7 (0.5-0.9)**
		Insect bite/sting	0.7 (0.4-1.0)
		Any food	0.7 (0.5-1.1)
		Eczema	**0.7 (0.5-0.9)**
			Reduced risks also seen with the following allergic symptoms: runny nose, burning or watery eyes, sneezing or congestion, wheezing or asthma, hives, severe swelling, anaphylactic shock, and allergy shots. **Dose-response found** – decreasing risk with increasing number of allergies, increasing severity of symptoms, increasing age at first allergy, increasing duration of exposure to plants, molds and animals.

* First National Health and Nutrition Examination Survey
† Standardized incidence/mortality ratio
‡ M = males, F = females
§ Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
‖ Original study presented frequency data only. Unadjusted odds ratio and 95% confidence interval calculated from original data.

TABLE 4. Studies Evaluating Risk of Lymphatic and Hematopoietic Neoplasms in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)
HODGKIN'S DISEASE			
Cohort Studies			
Alderson [33] (England)	1892 from asthma clinic (2 Hodgkin's disease deaths)	Asthma – Physician diagnosed	256*
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (23 incident cases)	Asthma - Physician diagnosed	68 (46-102)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (3 incident cases)	Atopic – Skin test Intermediate atopic – Skin test Rhinitis Asthma Urticaria - Physician diagnosed	531 (64-1920)* 0 (0-1620)* 263 (32-9520)* 0 (0-1000)* 1730 (209-6240)*
Case-Control Studies			
Schier [83] (USA)	Hospital-based (33/64)	Allergy	1.1 (0.4-3.2)†
McCormick et al. [81] (USA)	Hospital-based (98/42)	Allergy	0.9 (0.4-2.2)†
Newell et al. [82] (USA)	Hospital-based (176/176)	Asthma Hay fever	0.8 0.9
Amlot et al. [80] (England)	Hospital cases/Hospital staff and patient controls (115/180)	Atopy	1.2 (0.6-2.4)†
McKinney et al. [73] (England)	Hospital-based (248/489)	Eczema Allergies – Interview and review of medical notes	**1.9 (1.2-3.0)** No association
Tavani et al. [79] (Italy)	Population-based (158/1157)	Asthma Food/drug allergy	1.1 (0.5-2.4) 1.1 (0.7-1.8)
Vineis et al. [75] (Italy)	Population-based (354/1718)	Eczema Allergies Hay fever	0.7 (0.4-1.3) 0.9 (0.5-1.4) **0.5 (0.3-0.8)**
LEUKEMIA			
Cohort Studies			
Alderson [33] (England)	1892 from asthma clinic (2 leukemia deaths)	Asthma – Physician diagnosed	109*
Robinette et al.[37] (USA)	9550 *men* with asthma in army hospitals (23 deaths)	Asthma – Physician diagnosed	1.4
Mills et al. [40] (USA)	34198 Seventh-day Adventists (46 incident cases)	Any allergy Asthma Hay fever Reaction to medication Reaction to chemicals Reaction to bee sting Reaction to poisonous plants	1.4 (0.8-2.5) 1.6 (0.6-4.5) 0.8 (0.3-2.0) 1.3 (0.6-2.8) 0.6 (0.1-4.8) 0.8 (0.2-3.3) 1.2 (0.6-2.5)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (110 incident cases)	Asthma - Physician diagnosed	**55 (46-66)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (70 incident cases)	Asthma (M,F)‡ - Physician diagnosed	76 (52-108)*, 86 (61-118)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (3 incident cases)		ALL / AML
		Atopic – Skin test	0 (0-6300)* / 0 (0-6300)*
		Intermediate atopic – Skin test	2500(63-13900)* / 0(0-2030)*

			CML
		Atopic – Skin test	0 (0-7710)*
		Intermediate atopic – Skin test	1620(41-9010)*
Talbot-Smith et al. [57] (Australia)	3308 in 1981 Busselton Health Survey (14 incident cases)	Asthma (M,F)‡	-, 2.1 (0.2-17.8)
		Hay fever	1.2 (0.1-10.6), 3.6 (0.8-16.5)
		Any atopy	1.3 (0.1-21.5), -
Case-Control Studies			
Manning et al. [234] (USA)	Hospital-based (168/50)	Allergy	2.4 (1.0-6.1)†
McCormick et al. [81] (USA)	Hospital-based (45/41)	Allergy	0.3 (0.1-1.8)†
Bross et al. [235] (USA)	Population-based (34/813 – childhood leukemia)	Asthma and hives	3.5
Viadana et al. [236] (USA)	Population-based (1345/1237)		LL ML
		Asthma (M,F)‡	**4.1**, 1.3 1.8, **5.0**
		Hay fever	**3.8**, 2.0 1.8, 4.8
		Hives	3.2, **4.4** 1.2, 0.3
		Eczema	**4.8**, 1.4 **7.1**, 1.3
Gibson et al. [87] (USA)	Population-based, *men* (605/668) (47/668 – ALL) (133/668 – AML) (234/668 – CLL) (106/668 – CML)		ALL CLL AML CML all
		Eczema	**2.3** **3.9** **3.8** 2.3 **2.0**
		Contact dermatitis	1.1
		Hives	0.8 **2.9** **3.0** 1.2
		Asthma	1.4
		Hay fever	1.0
		Other allergies	1.3
Linet et al. [86] (USA)	Hospital cases/Hospital and community controls (342/342 – CLL)	Hay fever	0.5 (0.2-1.0)
		Eczema	0.7 (0.3-1.5)
		Asthma	1.1 (0.5-2.6)
		Hives	0.7 (0.3-1.6)
		Drug allergy	0.6 (0.4-1.0)
		Allergy to insect sting	0.6 (0.3-1.4)
		Other allergic reaction	1.0 (0.4-2.3)
			Dose-response found – decreasing risk with increasing number of allergies
Nishi et al. [91] (Japan)	Hospital cases/Population controls (63/126 – childhood non-T cell ALL)	Atopic diathesis	**0.3 (0.1-0.8)**
Severson et al. [88] (USA)	Population-based (98/133 – AML)	Any allergy	**0.4 (0.2-0.6)**
		Asthma	**0.1 (0.1-0.4)**
		Eczema	0.4 (0.1-1.2)
		Hives	0.5 (0.2-1.0)
		Allergy to penicillin	0.4 (0.2-1.1)
		Allergy to sulfa drugs	0.4 (0.1-1.8)
		Allergy to other antibiotics	0.3 (0.1-1.1)
		Allergy to other drugs	**0.3 (0.1-0.8)**
		Allergy to dust	**0.2 (0.1-0.5)**
		Allergy to eggs/feathers	**0.2 (0.1-0.6)**
		Allergy to foods	**0.2 (0.1-0.4)**
		Allergy to pollen	**0.2 (0.1-0.5)**
		Allergy to bee/insect stings	**0.2 (0.1-0.6)**
		Allergy to dogs/cats	**0.1 (0.1-0.4)**
			Dose-response found – decreasing risk with increasing number of allergies
McKinney et al. [73] (England)	Hospital-based (85/139 - LL) (245/417 - CLL) (122/241 - CML) (64/119 - ALL) (161/310 - AML)	Allergies	**0.57 (0.36-0.90)** AML
		Eczema -	No association for other cancers
		Interview and review of medical notes	
Doody et al. [71] (USA)	Hospital-based (299/787)		CLL AML CML all
		Hay Fever	0.6 2.5 1.0 1.2
		Eczema	0.5 0.6 1.0 0.6
		Asthma - Medical records	No association
Zheng et al. [85] (China)	Population-based (236/502 - ANLL)§ (79/502 - CML)		ALL ANLL
		Asthma	0.5 (0.1-42) 0.5 (0.1-1.6)
		Eczema	1.7 (0.7-4.5) 0.6 (0.3-1.5)

	(81/502 - ALL) (21/502 – CLL) (7/502 – Other)	Asthma Eczema	CML 1.5 (0.4-5.5) 0.5 (0.1-2.2)	
Buckley et al. [237] (USA)	Hospital cases/Other cancer controls/ Population controls (1282/2002/679 - childhood ALL)	Allergy (Other cancer controls) (Community controls)	 1.2 **1.3**	
Cooper et al. [89] (USA)	Clinical trial participant cases/ Population controls (624/637 - AML) (124/637 - ALL) (63 - other leukemias)		AML	ALL
		Hay fever	1.0 (0.7-1.4)	1.0 (0.6-1.8)
		Bee or wasp allergy	1.0 (0.6-1.7)	0.8 (0.3-2.1)
		Allergy to penicillin	1.0 (0.6-1.7)	**2.2 (1.0-4.4)**
		Other allergies	1.2 (0.9-1.7)	0.6 (0.3-1.2)
		Asthma	0.7 (0.5-1.2)	0.9 (0.4-1.9)
		Eczema	1.1 (0.6-2.0)	1.7 (0.7-4.2)
		1 allergy	0.9 (0.7-1.2)	0.9 (0.6-1.5)
		2+ allergies	1.3 (0.9-2.0)	1.1 (0.6-2.2)
Petridou et al. [92] (Greece)	Hospital-based (153/306 - childhood acute leukemia)	Hospitalization for allergic disease	0.4 (0.1-1.4)	
Vineis et al. [75] (Italy)	Population-based (261/1718 - LL) (313/1718 - ML)		LL	ML
		Eczema	1.2 (0.7-2.7)	0.8 (0.4-1.4)
		Allergies	1.0 (0.6-1.6)	0.7 (0.4-1.2)
		Hay fever	1.1 (0.6-1.9)	**0.4 (0.2-0.9)**
Wen et al. [90] (USA)	Hospital cases/ Population controls (1842/1986 - childhood ALL)	Asthma	0.8 (0.6-1.0)	
		Hay fever	**0.6 (0.5-0.8)**	
		Food or drug allergies	**0.7 (0.6-0.8)**	
		Eczema	**0.7 (0.5-0.9)**	
		Hives	0.9 (0.7-1.2)	
		Any allergic condition	**0.7 (0.6-0.8)**	
			Dose-response found - risk decreasing with number of allergies increasing	
Schuz et al. [93] (Germany)	Population-based (1130/2957 – childhood ALL) (164/2957 – childhood AML)		ALL	AML
		Hay fever	**0.4 (0.3-0.7)**	1.0 (0.5-2.1)
		Neurodermatitis	**0.5 (0.3-0.7)**	0.8 (0.4-1.7)
		Asthma	0.6 (0.3-1.4)	
		Contact eczema	**0.6 (0.4-1.0)**	0.8 (0.3-2.1)
		Hives	1.3 (0.6-2.9)	
		Food allergy	0.8 (0.6-1.2)	0.6 (0.2-1.9)
		Other allergy	0.6 (0.3-1.1)	0.9 (0.2-3.3)
MULTIPLE MYELOMA				
Cohort Studies				
Mills et al. [40] (USA)	34198 Seventh-day Adventists (23 incident cases)	Any allergy	1.7 (0.7-4.0)	
		Asthma	0.8 (0.1-6.0)	
		Hay fever	1.5 (0.5-4.6)	
		Reaction to medication	1.2 (0.4-3.6)	
		Reaction to chemicals	1.3 (0.2-10.0)	
		Reaction to bee sting	1.8 (0.4-7.7)	
		Reaction to poisonous plants	1.1 (0.4-3.4)	
Bourguet et al. [95] (USA)	14407 in NHANES I[‡] survey (18 incident cases and deaths)	One allergy	1.7 (0.3-10.5)	
		Two or more allergies	3.4 (0.0-285.7)	
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (39 incident cases)	Asthma - Physician diagnosed	**38 (28-52)***	
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (38 incident cases)	Asthma (M,F)[‡] - Physician diagnosed	107 (67-162)*, **53 (30-85)***	
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (1 incident case)	Atopic – Skin test	0 (0-3120)*	
		Intermediate atopic – Skin test	456 (12-2360)*	
Case-Control Studies				
Gallagher et al. [98] (Canada)	Clinic-based (84/168)	Allergies	**3.1 (1.6-6.3)**	
Pearce et al. [104] (New Zealand)	Hospital cases/ Other cancer controls, *men* (76/315)	Eczema	0.9 (0.3-2.8)	
		Asthma	1.3 (0.6-2.9)	
		Hay fever	1.9 (0.1-3.5)	
		Food allergies	2.1 (0.5-8.5)	

		Drug allergies	0.8 (0.3-2.5)
Koepsell et al. [101] (USA)	Population-based (698/1683)	Allergies	0.9 (0.7-1.1)
Linet et al. [103] (USA)	Hospital-based (100/100)	Allergy related disorders	1.0 (0.5-2.3)
Cuzick et al. [96] (England)	Hospital-based (399/399)	Asthma	0.7 (0.4-1.3)†
		Eczema	0.9 (0.5-1.9)†
		Non-eczema skin allergy	1.2 (0.8-1.6)†
		Rhinitis	0.9 (0.5-1.9)†
		Other allergies	0.8 (0.4-1.4)†
		Any allergies	1.2 (0.9-1.6)†
Boffetta et al. [94] (USA)	Nested in ACS CPS II¶ cohort (282/1128)	Asthma	1.0 (0.3-2.7)
		Hay fever	1.6 (0.8-2.9)
Williams et al. [105] (USA)	Population-based (69/1683 - light chain myeloma)	Childhood eczema	2.1 (0.7-6.7)
		Allergy	0.7 (0.4-1.4)
		Asthma	0.2 (0.0-1.7)
Gramenzi et al. [99] (Italy)	Hospital-based (117/477)	Allergic conditions	0.6 (0.3-1.1)
Doody et al. [71] (USA)	Hospital-based (175/787)	Hay fever	1.3 (0.6-2.7)
		Eczema - Medical records	**2.0 (1.1-4.0)**
Eriksson [97] (Sweden)	Population-based (239/220)	Allergy	1.1 (0.5-2.3)
Herrinton et al. [100] (USA)	Population-based	Asthma	
	(86/1663 - IgA myeloma)	IgA myeloma	0.6 (0.2-1.8)
	(226/1663 - IgG myeloma)	IgG myeloma	0.8 (0.4-1.5)
Lewis et al. [102] (USA)	Population-based (573/2131 - IgA and IgG myeloma)	Asthma	1.2 (0.8-1.8)
		Allergy to drugs	1.2 (0.9-1.5)
		Allergy to dust	0.9 (0.5-1.4)
		Eczema	1.1 (0.7-1.8)
		Hay fever	1.0 (0.8-1.3)
		Allergy to household products	1.2 (0.6-2.3)
		Previous severe allergic reaction	1.1 (0.8-1.5)
Vineis et al. [75] (Italy)	Population-based (263/1718)	Eczema	0.6 (0.3-1.3)
		Allergies	1.1 (0.6-1.8)
		Hay fever	0.8 (0.4-1.5)
CLASSICAL KAPOSI'S SARCOMA			
Case-Control Studies			
Goedert et al. [106] (Italy)	Population-based, those infected with KSHV** (141/192)	Asthma	2.2 (1.0-5.0)
		Allergy (M, F)‡	**2.6 (1.2-5.8)**, 0.1 (0.0-2.8)
MYCOSIS FUNGOIDES			
Case-Control Studies			
Whittemore et al. [108] (USA)	Hospital and Population Cases/ Population controls (174/294)	Any allergic skin reaction	0.7 (0.5-1.0)
		Allergy to plants	0.7 (0.1-1.1)
		Allergy to metals	**0.3 (0.1-0.8)**
		Allergy to cosmetics	0.7 (0.4-1.2)
		Allergy to skin medication (M,F)‡	**5.9 (1.2-29.9)**, 0.5 (0.1-1.6)
		Allergy to other drugs	0.9 (0.5-1.6)
		Allergy to hair dyes (F)‡	1.2 (0.3-4.4)
		Food allergy (M,F)‡	1.5 (0.6-3.8), **0.3 (0.1-0.8)**
		Allergy to insect bites (M,F)‡	1.8 (0.6-5.6), 0.3 (0.1-1.1)
		Positive scratch/needle test	**0.2 (0.1-0.7)**
		Positive patch skin test	0.5 (0.2-1.4)
Morales et al. [107] (Multicentre)	Hospital and Population Cases/ Population controls (76/2904)	Asthma	1.6 (0.7-3.8)
		Atopic dermatitis	1.6 (0.8-3.0)
		Urticaria	1.4 (0.6-3.6)

* Standardized incidence/mortality ratio
† Original study presented frequency data only. Unadjusted odds ratio and 95% confidence interval calculated from original data.
‡ M = males, F = females
§ Acute non-lymphocytic leukemia
ʃ First National Health and Nutrition Examination Survey
¶ American Cancer Society Cancer Prevention Study
** Kaposi's sarcoma associated herpes virus

TABLE 5. Studies Evaluating Risk of Brain Cancer in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)	
Cohort Studies				
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (154 incident eye and nervous system cases)	Asthma - Physician diagnosed	**75 (64-88)***	
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (2 incident cases)	Atopic – Skin test Intermediate atopic – Skin test	94 (2-5230)* 0 (0-3860)*	
Schwartzbaum et al. [113] (Sweden)	Cohort I: 14535 in Swedish Twin Registry born between 1886-1925 (37 incident gliomas, 41 meningiomas) Cohort II: 29573 in Swedish Twin Registry born between 1926-1958 (42 incident gliomas, 26 meningiomas)		Glioma	Meningioma
		Cohort I Hay fever Eczema Allergic conditions Cohort II Allergic conditions	0.7 (0.3-2.1) 0.5 (0.2-1.5) 0.4 (0.2-1.1) 1.1 (0.5-2.5)	0.8 (0.3-2.2) 0.7 (0.3-1.7) 0.8 (0.4-1.7) **2.4 (1.1-5.5)**
Case-Control Studies				
Giuffre et al. [238] (Italy)	Hospital-based (200/100)	Asthma	**0.3 (0.1-0.7)**†	
Hochberg et al.[109] (USA)	Hospital-based (160/128 – glioblastoma)	Treated for allergies Allergy shots	0.6 (0.4-1.0) 0.6 (0.3-1.3)	
Ryan et al. [114] (Australia)‡	Hospital and Population cases/ Population controls (110/417 – glioma) (60/417 – meningioma)		Glioma	Meningioma
		Eczema Any allergy Asthma Other allergies	**0.2 (0.1-0.9)** **0.5 (0.3-0.9)** 0.4 (0.1-1.2) 0.7 (0.4-1.2)	0.6 (0.2-1.7) 1.1 (0.6-2.0) 1.1 (0.4-2.8) 1.5 (0.8-2.6)
Schlehofer et al. [239] (Germany)‡	Hospital cases/Population controls (226/418)	At least one allergy	0.7 (0.5-1.0)	
Cicuttini et al. [240] (Australia)‡	Hospital and Population cases/ Population controls (416/422 – glioma)	Asthma Eczema	0.8 (0.5-1.2) 0.9 (0.5-1.4)	
Schlehofer el al.[110] (International)	Hospital and Population cases/ Population controls (1178/1987 – glioma) (331/1123 – meningioma)		Glioma	Meningioma
		Any allergy Asthma Eczema Other allergies	**0.6 (0.5-0.7)** 0.8 (0.6-1.0) **0.6 (0.5-0.9)** **0.6 (0.5-0.7)**	0.9 (0.6-1.2) 0.8 (0.5-1.4) 0.7 (0.4-1.1) 1.0 (0.7-1.4)
Brenner et al.[111] (USA)	Hospital-based (489/799 – glioma) (197/799 – meningioma) (96/799 – acoustic neuroma)		Glioma	Meningioma
		Any allergy Asthma Eczema Hay fever Allergy to medicine Allergy to insects Allergy to food Chemical allergy Other allergy	**0.7 (0.5-0.9)** **0.6 (0.4-0.9)** 0.8 (0.4-1.3) 1.0 (0.7-1.4) 0.8 (0.5-1.3) 0.6 (0.4-1.0) 0.7 (0.2-1.7) **0.2 (0.1-0.8)** 0.8 (0.3-2.0)	0.9 (0.5-1.4) 0.8 (0.4-1.5) 0.8 (0.4-1.5) 0.9 (0.6-1.5) 0.8 (0.4-1.5) 1.3 (0.7-2.4) 1.2 (0.4-3.5) 0.3 (0.1-1.2) 1.2 (0.4-3.4)
			Acoustic neuroma	
		Any allergy Asthma Eczema Hay Fever Allergy to medicine Allergy to insects Allergy to food Chemical allergy Other allergy	1.0 (0.6-1.6) 1.3 (0.7-2.5) 0.9 (0.3-2.5) **2.4 (1.4-4.0)** 0.5 (0.2-1.4) 1.1 (0.5-2.5) **3.0 (1.1-8.5)** 0.8 (0.2-2.8) **3.8 (1.4-10.0)**	
Wiemels et al.[112] (USA)	Population-based (405/402 – glioma)	Any allergy	**0.5 (0.3-0.7)** Reduced risks also seen with allergy to: pollens, dairy, wheat, nuts, poison oak, cosmetics, other; and with the following allergic symptoms: runny nose, watery eyes, sneezing, wheezing, itching, swelling, headaches, anaphylactic shock, other.	

Dose-response found – decreasing risk with increasing number of allergies

* Standardized incidence/mortality ratio
† Original study presented frequency data only. Unadjusted odds ratio and 95% confidence interval calculated from original data.
‡ Studies by Ryan et al. (1992), Schlehofer et al. (1992), and Cicuttini et al. (1997) present preliminary findings from international IARC study. Other participating centres did not publish preliminary findings.

TABLE 6. Studies Evaluating Risk of Reproductive Cancers in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)
OVARIAN CANCER			
Cohort Studies			
Mills et al. [40] (USA)	34198 Seventh-day Adventists (38 incident cases)	Any allergy Asthma Hay fever Reaction to medication Reaction to bee sting Reaction to poisonous plants	0.8 (0.4-1.5) 1.0 (0.2-4.2) 0.9 (0.4-2.4) 0.7 (0.3-1.8) 1.8 (0.5-5.8) **0.1 (0.02-1.0)** **Dose-response found** - risk decreasing with number of allergies increasing
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (91 incident cases)	Asthma - Physician diagnosed	**52 (42-63)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (114 incident cases)	Asthma - Physician diagnosed	107 (88-126)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (5 incident cases)	Atopic – Skin test Intermediate atopic – Skin test Rhinitis Asthma Urticaria - Physician diagnosed	0 (0-544)* 103 (3-573)* 195 (53-500)* 137 (17-496)* 0 (0-819)*
Case-Control Studies			
Fisherman [19] (USA)	Clinic-based (38/294)	Atopy	1.0 (0.4, 2.8)‡
Vena et al. [32] (USA)	Hospital-based (317/2477)	Asthma Hay fever Hives Other allergies	1.1 0.7 0.9 0.8
UTERINE CANCER			
Cohort Studies			
Mills et al. [40] (USA)	34198 Seventh-day Adventists (122 incident cases - endometrium)	Any allergy Asthma Hay fever Reaction to medication Reaction to bee sting Reaction to poisonous plants	1.0 (0.7-1.6) 0.7 (0.2-1.8) 1.5 (0.9-2.5) 1.0 (0.6-1.6) 2.0 (0.9-4.1) 0.8 (0.5-1.4) **Dose-response found** - risk decreasing with number of allergies increasing
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (60 incident cases – uterine body) (11 incident cases – uterine unspecified)	Asthma - Physician diagnosed	Uterine body: **36 (28-46)*** Uterine Unspecified: 58 (32-104)*
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (93 incident cases – uterine body)	Asthma - Physician diagnosed	**76 (61-92)***
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (1 incident case – uterine body) (1 incident case – uterine unspecified)	Atopic – Skin test Intermediate atopic – Skin test	Uterine body: 0 (0-774)* 126 (3-700)* Uterine Unspecified: 1960 (50-10900)* 0 (0-4570)*
Case-Control Studies			
Vena et al. [32] (USA)	Hospital-based (471/2477 – uterine body)	Asthma Hay fever Hives Other allergies	1.2 1.3 1.2 1.1
Petroianu et al. [30] (Brazil)	Hospital cases/Population controls (36/400)	Allergy	0.9 (0.5-1.9)‡

CERVICAL CANCER

Cohort Studies

Mills et al. [40] (USA)	34198 Seventh-day Adventists (28 incident cases)	Any allergy	0.8 (0.5-2.8)
		Asthma	2.6 (0.9-7.7)
		Hay fever	0.5 (0.2-1.7)
		Reaction to medication	0.8 (0.3-2.3)
		Reaction to bee sting	0.7 (0.1-5.4)
		Reaction to poisonous plants	1.1 (0.4-2.9)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (45 incident cases)	Asthma - Physician diagnosed	**52 (39-61)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (42 incident cases)	Asthma - Physician diagnosed	80 (58-108)*
Montgomery et al.[116] (Sweden)	7595 from two British longitudinal birth cohort studies (87 incident cases)	Hay Fever	1.0 (0.5-2.2)
		Eczema	**3.3 (2.0-5.5)**

Case-Control Studies

Vena et al. [32] (USA)	Hospital-based (1430/2477)	Asthma	0.6
		Hay fever	0.9
		Hives	**0.6**
		Other allergies	**0.6**

BREAST CANCER

Cohort Studies

McWhorter [14] (USA)	NHANES I † cohort of 6913 given supplemental questionnaire (34 incident cases and deaths)	Any allergy	1.2 (0.6-2.4)
Mills et al. [40] (USA)	34198 Seventh-day Adventists (215 incident cases)	Any allergy	1.2 (0.9-1.6)
		Asthma	1.2 (0.7-2.0)
		Hay fever	1.3 (1.0-1.9)
		Reaction to medication	1.0 (0.7-1.3)
		Reaction to chemicals	1.2 (0.6-2.2)
		Reaction to bee sting	1.2 (0.7-2.1)
		Reaction to poisonous plants	1.2 (0.9-1.6)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (385 incident cases)	Asthma - Physician diagnosed	**53 (47-58)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (429 incident cases)	Asthma - Physician diagnosed	96 (87-105)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (18 incident cases)	Atopic – Skin test	**250 (101-516)***
		Intermediate atopic – Skin test	128 (42-299)*
		Rhinitis	152 (81-259)*
		Asthma	139 (60-274)*
		Urticaria - Physician diagnosed	215 (59-551)*
Talbot-Smith et al.[57] (Australia)	3308 in 1981 Busselton Health Survey (65 incident cases)	Asthma	1.1 (0.5-2.6)
		Hay fever	0.9 (0.5-1.7)
		Any atopy	1.4 (0.6-3.4)

Case-Control Studies

Fisherman [19] (USA)	Clinic-based (192/294)	Atopy	0.2 (0.1, 0.5)‡
Shapiro et al. [31] (USA)	Hospital-based (136/1035)	Allergy	1.4 (0.8-2.5)
Vena et al. [32] (USA)	Hospital-based (1835/2477)	Asthma	1.0
		Hay fever	0.9
		Hives	**0.7**
		Other allergies	0.8
Petroianu et al. [30] (Brazil)	Hospital cases/Population controls (49/400)	Allergy	0.7 (0.4-1.4)‡

Ghadirian et al. [117] (Canada)	Hospital cases/Population controls (414/429)	Asthma	0.5 (0.2-1.0)
PROSTATE CANCER			
Cohort Studies			
McWhorter [14] (USA)	NHANES I † cohort of 6913 given supplemental questionnaire (34 incident cases and deaths)	Any allergy	1.3 (0.6-2.8)
Mills et al. [40] (USA)	34198 Seventh-day Adventists (180 incident cases)	Any allergy Asthma Hay fever Reaction to medication Reaction to chemicals Reaction to bee sting Reaction to poisonous plants	1.2 (0.9-1.7) 1.0 (0.5-1.9) 1.2 (0.8-1.8) 1.3 (0.9-2.0) 0.5 (0.1-1.9) 0.6 (0.3-1.4) 1.3 (0.9-1.8)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (671 incident cases)	Asthma - Physician diagnosed	**72 (67-78)***
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (256 incident cases)	Asthma - Physician diagnosed	110 (97-124)*
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (1 incident case)	Atopic – Skin test Intermediate atopic – Skin test	0 (0-855)* 88 (2-490)*
Ohrui et al. [118] (Japan)	483 male asthmatics and 1201 non-asthmatics from a university hospital (10 incident prostate cancer cases)	Asthma	22.8 (5.5-94.7)
Talbot-Smith et al.[57] (Australia)	3308 in 1981 Busselton Health Survey (86 incident cases)	Asthma Hay fever Any atopy	1.9 (1.0-3.6) 1.1 (0.6-2.0) 2.5 (1.0-5.9)
Case-Control Studies			
Vena et al. [32] (USA)	Hospital-based (263/1562)	Asthma Hay fever Hives Other allergies	0.4 0.9 1.4 0.8
Petroianu et al. [30] (Brazil)	Hospital cases/Population controls (22/400)	Allergy	0.1 (0.0-0.5)‡
TESTICULAR CANCER			
Cohort Studies			
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (5 incident cases)	Asthma - Physician diagnosed	**37 (16-85)***
Case-Control Studies			
Henderson et al. [120] (USA)	Population-based (131/131 - testicular cancer)	Asthma Hay fever Other allergies	0.9 1.0 0.8
Vena et al. [32] (USA)	Hospital-based (77/1562)	Asthma Hay fever Hives Other allergies	1.6 1.6 1.7 0.7
Morris Brown et al.[121] (USA)	Hospital cases/Other cancer controls (271/259 - testicular cancer)	Allergy	0.9 (0.6-1.4)
Swerdlow et al. [119] (England)	Hospital cases/Other cancer controls and other hospital patients controls (259/489 - testicular cancer)	Atopy Hay fever Eczema Asthma - Interview and hospital case notes	**1.8 (1.1-3.1)** **2.6 (1.2-5.6)** 3.1 (1.0-10.0) 1.7 (0.8-3.6)

* Standardized incidence/mortality ratio
† First National Health and Nutrition Examination Survey
‡ Original study presented frequency data only. Unadjusted odds ratio and 95% confidence interval calculated from original data.

TABLE 7. Studies Evaluating Risk of Other Cancers in Relation to a History of Allergy

Reference (Country)	Population (Number of cases or cases/controls)	Risk Factor	Relative Risk (95% Confidence Interval)	
COLORECTAL CANCER				
Cohort Studies				
McWhorter [14] (USA)	NHANES I * cohort of 6913 given supplemental questionnaire (45 incident colorectal cases and deaths)	Any allergy	1.7 (0.9-3.1)	
Mills et al. [40] (USA)	34198 Seventh-day Adventists (138 incident colon cancer cases 58 incident rectal cancer cases)		Colon Cancer	Rectal Cancer
		Any allergy	1.0 (0.7-1.3)	0.9 (0.5-1.4)
		Asthma	1.0 (0.5-2.0)	0.6 (0.1-2.3)
		Hay fever	1.1 (0.7-1.7)	0.8 (0.3-1.7)
		Reaction to medication	0.7 (0.4-1.2)	1.3 (0.7-2.4)
		Reaction to chemicals	0.4 (0.1-1.6)	1.4 (0.4-4.5)
		Reaction to bee sting	0.7 (0.3-1.6)	0.3 (0.0-2.1)
		Reaction to poisonous plants	0.8 (0.5-1.2)	0.7 (0.3-1.4)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (389 incident colon cancer cases) (188 incident rectal cancer cases)	Asthma - Physician diagnosed (colon cancer) (rectal cancer)	**72 (65-79)**† **59 (52-68)**†	
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (220 incident colon cancer cases) (187 incident rectal cancer cases)		Colon Cancer	Rectal Cancer
		Asthma - Physician diagnosed (M)‡	116 (92-144)†	110 (86-138)†
		(F)‡	118 (99-138)†	**142 (117-169)**†
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (6 incident colon cancer cases) (6 incident rectal cancer cases)		Colon Cancer	Rectal Cancer
		Atopic – Skin test	111 (3-619)†	0 (0-688)†
		Intermediate atopic – Skin test	138 (17-500)†	**469 (128-1200)**†
		Rhinitis	108 (22-315)†	238 (65-610)†
		Asthma	139 (29-407)†	75 (2-419)†
		Urticaria - Physician diagnosed	0 (0-588)†	**1070 (291-2730)**†
Talbot-Smith et al.[57] (Australia)	3308 in 1981 Busselton Health Survey (67 incident colorectal cases)	Asthma (M,F)‡	0.4 (0.1-3.2), 0.4 (0.0-2.8)	
		Hay fever	0.8 (0.2-2.7), 1.1 (0.5-2.5)	
		Any atopy	0.3 (0.0-2.8), 1.4 (0.4-5.0)	
Case-Control Studies				
Vobecky et al. [126] (Canada)	Population-based (207/207)	Allergy	No association	
Vena et al. [32] (USA)	Hospital-based (579/4039 - colon) (352/4039 – rectal)		Colon Cancer	Rectal Cancer
		Asthma (M,F)‡	1.3, 0.6	0.6, 0.8
		Hay fever	1.3, 1.0	1.2, 0.6
		Hives	0.8, 0.6	0.5, 0.8
		Other allergies	0.5, 0.8	0.5, 0.6
Kune et al. [124] (Australia)	Population-based (715/727)	Asthma	0.9 (0.6-1.3)	
		Allergies or hay fever	0.8 (0.7-1.0)	
La Vecchia et al. [125] (Italy)	Hospital-based (673/1501 - colon) (405/1501 - rectal)		Colon Cancer	Rectal Cancer
		Drug allergy	0.7 (0.5-1.0)	0.7 (0.4-1.1)
Ghadirian et al. [123] (Canada)	Hospital cases/Population controls (402/668 - colon)	Asthma	0.8 (0.4-1.4)	
		Eczema	0.7 (0.3-1.3)	
		Hay fever	1.8 (1.0-3.3)	
		Other allergy	0.8 (0.5-1.4)	
Negri et al. [122] (Italy)	Hospital-based (1225/4154 - colon) (728/4154 - rectal)	Allergy	Colon Cancer	Rectal Cancer
			0.9 (0.7-1.1)	0.6 (0.4-0.9)
ESOPHAGEAL CANCER				
Cohort Studies				
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (44 incident cases)	Asthma - Physician diagnosed	**67 (50-90)**†	
Ye et al. [127]	92 986 hospitalized for asthma	Asthma - Physician diagnosed	150 (90-250)†	

(Sweden)	(17 incident adenocarcinoma, 46 squamous-cell carcinoma)	(adenocarcinoma) (squamous-cell carcinoma)	110 (80-140)†
Case-Control Studies			
Petroianu et al. [30] (Brazil)	Hospital cases/Population controls (48/400)	Allergy	0.6 (0.3-1.1)‡
Dai et al. [128] (China)	Population-based (163/275)	Any allergy Drug allergy Food allergy Contact dermatitis Urticaria Asthma Allergic rhinitis Moderate reaction to mosquito bite Strong reaction to mosquito bite	**0.6 (0.4-0.9)** 0.8 (0.4-1.6) 0.7 (0.2-2.3) **0.2 (0.0-0.9)** **0.4 (0.2-0.9)** 1.3 (0.5-3.1) 0.8 (0.3-1.9) **0.6 (0.4-0.9)** 0.7 (0.2-1.9)
THYROID CANCER			
Cohort Studies			
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (25 incident cases)	Asthma - Physician diagnosed	**47 (32-68)†**
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (4 incident cases)	Atopic – Skin test Intermediate atopic – Skin test Rhinitis Asthma Urticaria - Physician diagnosed	320 (8-1780)† 389 (10-2170)† 434 (89-1270)† 254 (6-1420)† 0 (0-2770)†
Case-Control Studies			
Ron et al. [131] (USA)	Population-based (159/285)	Asthma Hay fever	No association No association
Hallquist et al. [130] (Sweden)	Population-based (180/360)	Asthma or allergy (all thyroid cancer) (papillary cancer)	 **0.4 (0.2-0.9)** 0.4 (0.2-1.0)
Negri et al. [129] (International)	Pooled analysis of 14 studies (67/335 - medullary thyroid carcinoma)	Allergies	2.2 (1.0-4.7)
BLADDER CANCER			
Cohort Studies			
Mills et al. [40] (USA)	34198 Seventh-day Adventists (54 incident cases)	Any allergy (M,F)‡ Asthma Hay fever Reaction to medication Reaction to chemicals Reaction to bee sting Reaction to poisonous plants	0.9 (0.5-1.6) 0.4 (0.0-2.8) 1.3 (0.6-2.8) 0.7 (0.3-1.7) 0.7 (0.1-5.1) 0.4 (0.0-2.5) 0.8 (0.4-1.9)
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (139 incident cases)	Asthma (M,F)‡ - Physician diagnosed	**125 (103-149)†**, 90 (60-128)†
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (5 incident cases)	Atopic – Skin test Intermediate atopic – Skin test Rhinitis Asthma Urticaria - Physician diagnosed	0 (0-669)† **473 (129-1210)†** 119 (14-429)† 216 (45-631)† 0 (0-1030)†
Case-Control Studies			
Miller et al. [132] (Canada)	Hospital-based (265/530)	Allergies (M,F)‡	1.7, 0.3
Steineck et al. [133] (Sweden)	Hospital cases/Population controls (325/393 - urothelial cancer-transitional cell carcinoma)	Allergic asthma Allergic dermatitis Allergic rhinitis	**3.1 (1.4-6.8)** 0.8 (0.4-1.6) 0.9 (0.5-1.6)
Kim et al. [134] (Korea)	Hospital-based (113/221)	Asthma (with GSTM1 null genotype) (with GSTT1 null genotype)	**4.2 (1.6-10.8)** **9.2 (2.3-37.8)** **19.2 (2.3-160.1)**

STOMACH CANCER

Cohort Studies

Mills et al. [40] (USA)	34198 Seventh-day Adventists (18 incident cases)	Any allergy	0.7 (0.2-1.8)
		Hay fever	1.1 (0.2-4.7)
		Reaction to medication	1.4 (0.4-4.8)
		Reaction to chemicals	2.0 (0.3-15.4)
		Reaction to poisonous plants	0.3 (0.0-2.4)
Kallen et al. [38] (Sweden)	64346 discharged from hospital with asthma (188 incident cases)	Asthma - Physician diagnosed	**50 (43-57)**†
Vesterinen et al. [39] (Finland)	77952 asthmatics on Social Insurance Register (268 incident cases)	Asthma (M,F)‡ - Physician diagnosed	85 (71-100)†, 91 (77-107)†
Eriksson et al. [13] (Sweden)	6593 patients from allergy clinic (1 incident case)	Atopic – Skin test	0 (0-1040)†
		Intermediate atopic – Skin test	0 (0-609)†
Ye et al. [127] (Sweden)	92 986 hospitalized for asthma (43 adenocarcinoma of gastric cardia, 219 other stomach cancer)	Asthma - Physician diagnosed	
		(gastric cardia)	140 (100-190)†
		(other stomach cancer)	90 (80-110)†

Case-Control Studies

Vena et al. [32] (USA)	Hospital-based (311/4039)	Asthma (M,F)‡	1.0, 0.0
		Hay fever	0.4, 1.7
		Hives	0.7, 0.3
		Other allergies	0.4, 0.6

* First National Health and Nutrition Examination Survey
† Standardized incidence/mortality ratio
‡ M = males, F = females

APPENDIX 2 – QUESTIONNAIRES

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR MEN	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes," a) What type? _____ b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Prostate Trouble
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No If "yes," specify type and date(s) of operation(s): _____
4. How many x-ray or fluoroscopic examinations (GI series, barium enema, etc.) have you ever had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Arms/Legs	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been treated with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night?_____
3. On the average, how many times a month do you have insomnia?_____ ☐ None
4. Within the last month, have you noticed:
   a) Painful or frequent urination? ☐ Yes ☐ No
   b) An unusual discharge from your penis? ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains?_____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition?_____

HABITS:

1. **Whether or not you smoke,** on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____.
2. Do you now or have you ever smoked cigarettes, cigars or pipes, at least one a day for one year's time? ☐ Yes ☐ No
   If never smoked, skip to question 8.
3. If you **currently** smoke cigarettes, cigars or pipes, fill in the information below:

Current Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
INHALATION:			
Do not inhale			
Inhale slightly			
Inhale moderately			
Inhale deeply			
Total years of smoking			
Years smoked **filtered** cigarettes			
Years smoked **non-filtered** cigarettes			

4. Current brand of cigarette:_____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand:_____

5. If you have quit smoking cigarettes, cigars or pipes, fill in the information below:

Ex-Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
Age quit			
INHALATION:			
Did not inhale			
Inhaled slightly			
Inhaled moderately			
Inhaled deeply			
Total years smoked			
Years smoked **filtered** cigarettes			
Years smoked **non-filtered** cigarettes			

6. Last brand of cigarette smoked:_____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand:_____

7. Current **and** ex-cigarette smokers, fill in the following information for:
   1) The **first** brand smoked regularly; and
   2) The brand of cigarette smoked for the **longest** period of time.

Brand Name	Size	Filter		Menthol		Number Per Day	Years
		Yes	No	Yes	No		
1.							
2.							

8. Have you ever chewed tobacco at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to question 9.
   a) Age began chewing tobacco:_____
   b) How many times a week?_____
   c) For how many years?_____
   d) Do you still chew tobacco? ☐ Yes ☐ No

9. Have you ever used snuff at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to "Diet."
   a) Age began using snuff:_____
   b) How many times a week?_____
   c) For how many years?_____
   d) Do you still use snuff? ☐ Yes ☐ No

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef	Raw vegetables
Pork	Carrots
Chicken	Squash/Corn
Liver	Citrus fruits/Juices
Ham	Spaghetti/Macaroni/ White rice
Fish	
Smoked meats	White bread/Rolls/ Biscuits
Frankfurters/ Sausage	Brown rice/Whole wheat/Barley
Butter	Bran/Corn muffins
Margarine	Potatoes
Cheese	Oatmeal/Shredded wheat/Bran cereals
Eggs	
Green leafy vegetables	Cold (Dry) cereals
Tomatoes	Ice cream
Cabbage/Broccoli/ Brussels sprouts	Chocolate

2. How many days a week do you eat the following **fried** foods?

Fried eggs	Fried hamburgers or beef
Fried bacon	Other fried foods
Fried chicken/fish	
French fries	

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
If "yes," what type and for how many years?

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
If "yes," what was the change?

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
☐ Yes, currently ☐ Formerly ☐ Never
b) If **ever** used artificial sweeteners, indicate amount per day and for how long.
Packets: No. per day____ Years____
Drops: No. per day____ Years____
Tablets: No. per day____ Years____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify)____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2.)

Beverages	Currently		Previously	
	Amount	Years	Amount	Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other:		

OCCUPATIONS:

1. What is your current occupation and what are your duties?_____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____, volunteer work _____,
   housework _____.
6. In your work or daily life, are (were) you **regularly** exposed to any of the following? If "yes," indicate the number of years exposed.

Exposure to:	Check One: Yes	No	Number of Years
Asbestos			
Chemicals/Acids/Solvents			
Coal or Stone Dusts			
Coal Tar/Pitch/Asphalt			
Diesel Engine Exhaust			
Dyes			
Formaldehyde			
Gasoline Exhaust			
Pesticides/Herbicides			
Textile Fibers/Dusts			
Wood Dust			
X-rays/Radioactive Materials			

REMARKS:

MISCELLANEOUS:

1. Where were you born? _____ (city) (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish
   ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. Were you in the U.S. Armed Services? ☐ Yes ☐ No
   If "yes,"
   a) What branch of the service were you in? _____
      _____
   b) What were your dates of service?
      _____ to _____,
      _____ to _____.
   c) Where did you serve? _____
      _____
9. What is the most upsetting event that happened to you in about the last five years? _____
   _____
   _____ ☐ None
10. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR WOMEN	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes,"
   a) What type? _____
   b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Breast Cysts
   - ☐ Gynecological Problems
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No
   If "yes," specify type and date(s) of operation(s):
4. How **many** x-ray or fluoroscopic **examinations** (GI series, barium enema, etc.) have you **ever** had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Breast	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been **treated** with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night?_____
3. On the average, how many times a month do you have insomnia?_____ ☐ None
4. Within the last twelve months, have you noticed:
   a) A lump or thickening in your breast?
   ☐ Yes ☐ No
   b) An unusual discharge from your breast?
   ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains?_____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition?_____

MENSTRUAL AND REPRODUCTIVE HISTORY:

1. How old were you when menstruation began?_____
2. What is your current menopausal status?
   ☐ Still regularly menstruating
   ☐ In menopause ☐ Past menopause
3. During your menstrual history:
   a) Are (were) your periods: ☐ Regular ☐ Irregular
   b) What is (was) the usual number of days of flow?_____
4. **If past menopause:**
   a) Was your menopause: ☐ Natural ☐ Artificial
   b) Age when periods stopped completely?_____
   c) Did you have excessive bleeding during menopause? ☐ Yes ☐ No
5. Have you ever had or tried to have children?
   ☐ Yes ☐ No
   If "no," skip to question 9.
6. Have you ever had difficulty becoming pregnant?
   ☐ Yes ☐ No
   If "yes," what was the reason?_____
7. How many times have you been pregnant?_____
   a) Your age at your first pregnancy?_____
   b) Your age at your first live birth?_____
   c) Number of children born alive?_____
   d) Number of stillbirths (carried 5 months or more)?_____
   e) Number of miscarriages (carried less than 5 months)?_____
8. Were you ever given DES (Diethylstilbestrol) to prevent miscarriage? ☐ Yes ☐ No
   If "yes,"
   a) At what age did you take it?_____
   b) For how many months did you take it?_____
9. Birth control methods: Indicate your age when **first used** and number of years of use.

Method Used	Age	Years
Rhythm		
Diaphragm		
Cream/Foam/Jelly		
Tubal Ligation		
Intrauterine Device (IUD)		
Condom (partner)		
Vasectomy (partner)		
NONE OF THE ABOVE ☐		

10. Have you **ever** taken oral contraceptives (birth control pills)? ☐ Yes ☐ No
    If "no," skip to question 11.
    a) Age when you first took them?_____
    b) How many years did you take them?_____
    c) What brand(s) do (did) you take?_____
    d) If you stopped taking them, what was the reason?_____
    e) Did you have irregular or painful periods when you stopped? ☐ Yes ☐ No
11. Have you **ever** used female hormones (estrogens) other than oral contraceptives? ☐ Yes ☐ No
    a) Why do (did) you take estrogens?
    ☐ Menopausal symptoms ☐ Hysterectomy
    ☐ Bone problems ☐ Cancer
    ☐ Other (specify)_____
    b) Age first took estrogens?_____
    c) For how many years did you take them?_____
    d) How did you take them? ☐ Injection ☐ Cream ☐ Pill (brand)_____

HABITS:

1. **Whether or not you smoke**, on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____
2. Do you now or have you ever smoked cigarettes, at least one a day for one year's time? ☐ Yes ☐ No

Smoking History	Current Smokers	Ex-Smokers
Number smoked a day		
Age began smoking		
Age quit smoking		
Most recent (last) brand		
Years smoked this brand		
Total years smoked **filtered** cigarettes		
Total years smoked **non-filtered** cigarettes		
Total years of smoking (filtered + non-filtered)		

3. Current and ex-smokers:
   a) Do (did) you inhale? ☐ No, never
   ☐ Slightly ☐ Moderately ☐ Deeply
   b) Fill in the following information for:
   1) The first brand smoked regularly; and
   2) The brand of cigarette smoked for the longest period of time.

Brand Name	Size	Filter		Menthol		Number Per Day	Years
		Yes	No	Yes	No		
1.							
2.							

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef	Raw vegetables
Pork	Carrots
Chicken	Squash/Corn
Liver	Citrus fruits/Juices
Ham	Spaghetti/Macaroni/ White rice
Fish	
Smoked meats	White bread/Rolls/ Biscuits
Frankfurters/ Sausage	Brown rice/Whole wheat/Barley
Butter	Bran/Corn muffins
Margarine	Potatoes
Cheese	Oatmeal/Shredded wheat/Bran cereals
Eggs	
Green leafy vegetables	Cold (Dry) cereals
Tomatoes	Ice cream
Cabbage/Broccoli/ Brussels sprouts	Chocolate

2. How many days a week do you eat the following fried foods?

Fried eggs	Fried hamburgers or beef
Fried bacon	Other fried foods
Fried chicken/fish	
French fries	

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years?

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change?

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If ever used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day____ Years____
   Drops: No. per day____ Years____
   Tablets: No. per day____ Years____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify)____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2).

Beverages	Currently		Previously	
	Amount	Years	Amount	Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other:		

OCCUPATIONS:

1. What is your current occupation and what are your duties? _____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____, volunteer work _____,
   housework _____.
6. In your work or daily life, are (were) you **regularly** exposed to any of the following? If "yes," indicate the number of years exposed.

Exposure to:	Check One: Yes	No	Number of Years
Asbestos			
Chemicals/Acids/Solvents			
Coal or Stone Dusts			
Coal Tar/Pitch/Asphalt			
Diesel Engine Exhaust			
Dyes			
Formaldehyde			
Gasoline Exhaust			
Pesticides/Herbicides			
Textile Fibers/Dusts			
Wood Dust			
X-rays/Radioactive Materials			

REMARKS:

MISCELLANEOUS:

1. Where were you born? _____ (city) _____ (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish
   ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. What is the most upsetting event that happened to you in about the last five years? _____
   _____
   _____ ☐ None
9. How many people do you take care of in your household? (Include yourself) _____
10. Do you now or have you ever used a **permanent** hair dye? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) What color? _____
    c) How often applied? _____
    d) How many years have you used it? _____
11. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

APPENDIX 3 – SUMMARY OF RESULTS IN NEVER SMOKERS

Figure 9. Summary of Hazard Ratios for the Association between a History of Asthma and Cancer Mortality in Never Smoking Men

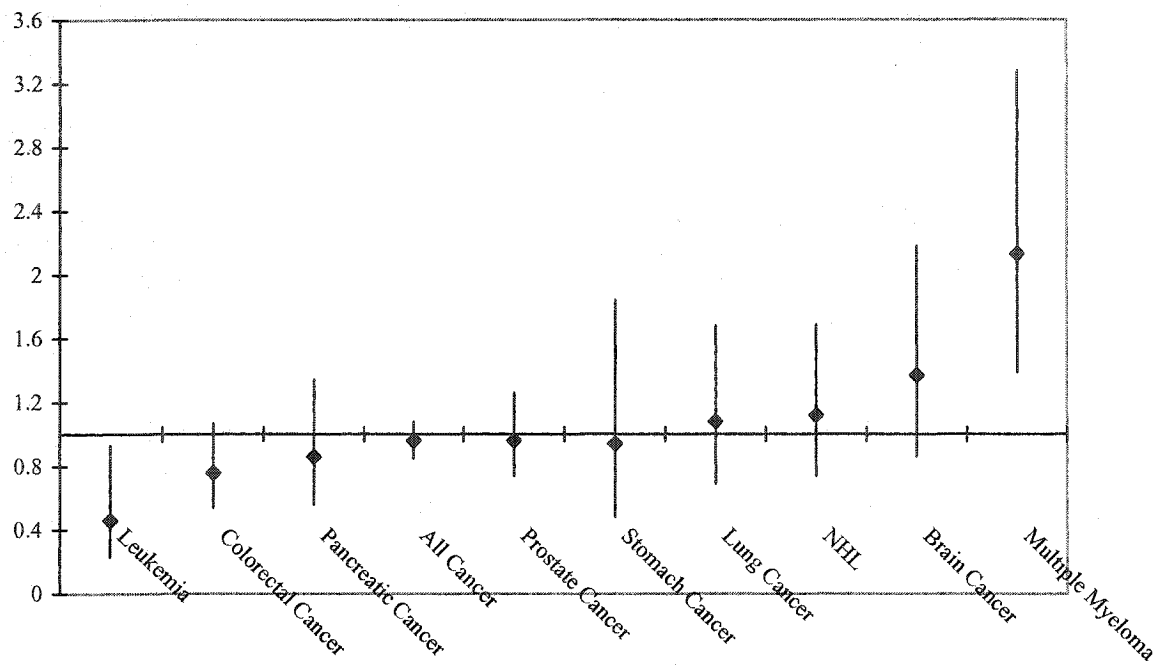

Figure 10. Summary of Hazard Ratios for the Association between a History of Asthma and Cancer Mortality in Never Smoking Women

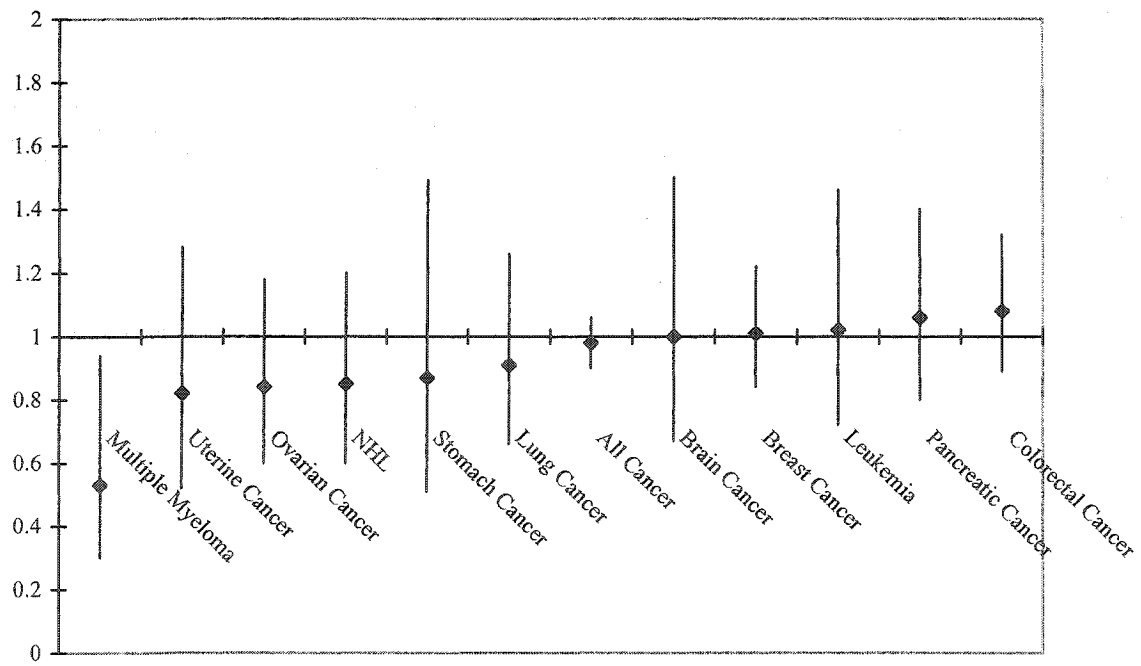

Figure 11. Summary of Hazard Ratios for the Association between a History of Hay Fever and Cancer Mortality in Never Smoking Men

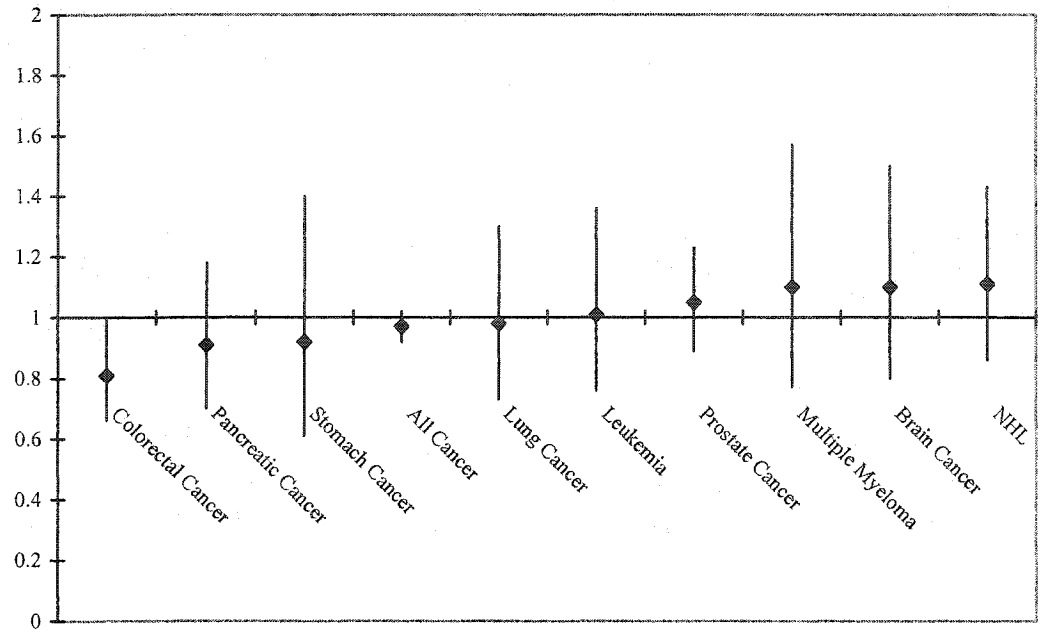

Figure 12. Summary of Hazard Ratios for the Association between a History of Hay Fever and Cancer Mortality in Never Smoking Women

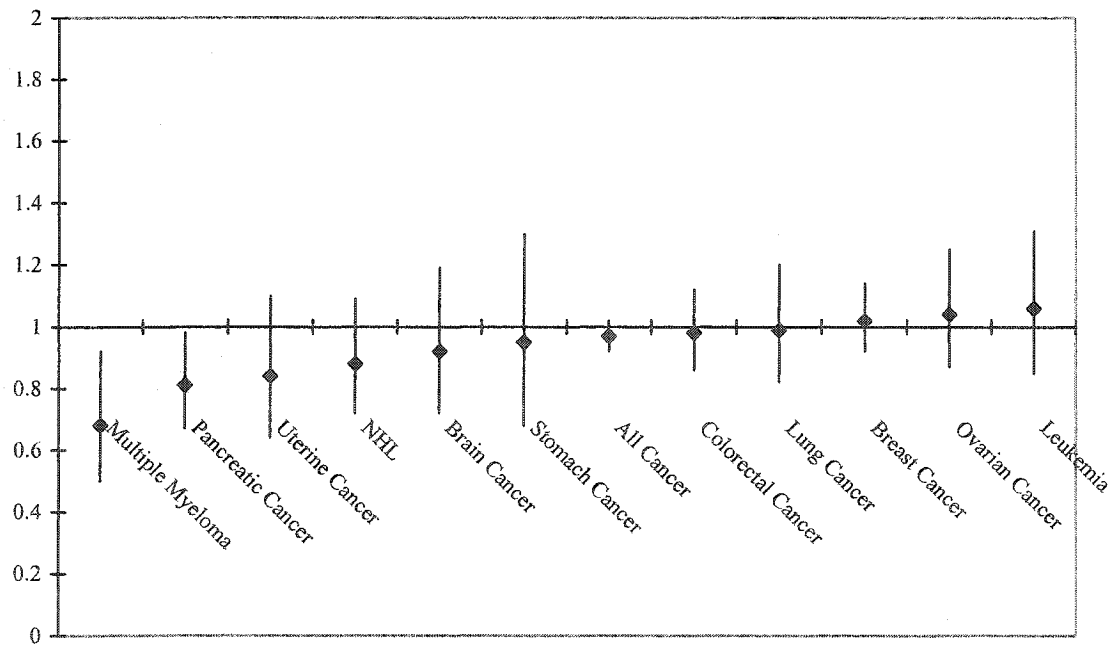

Figure 13. Summary of Hazard Ratios for the Association between a History of Asthma and Hay Fever and Cancer Mortality in Never Smoking Men

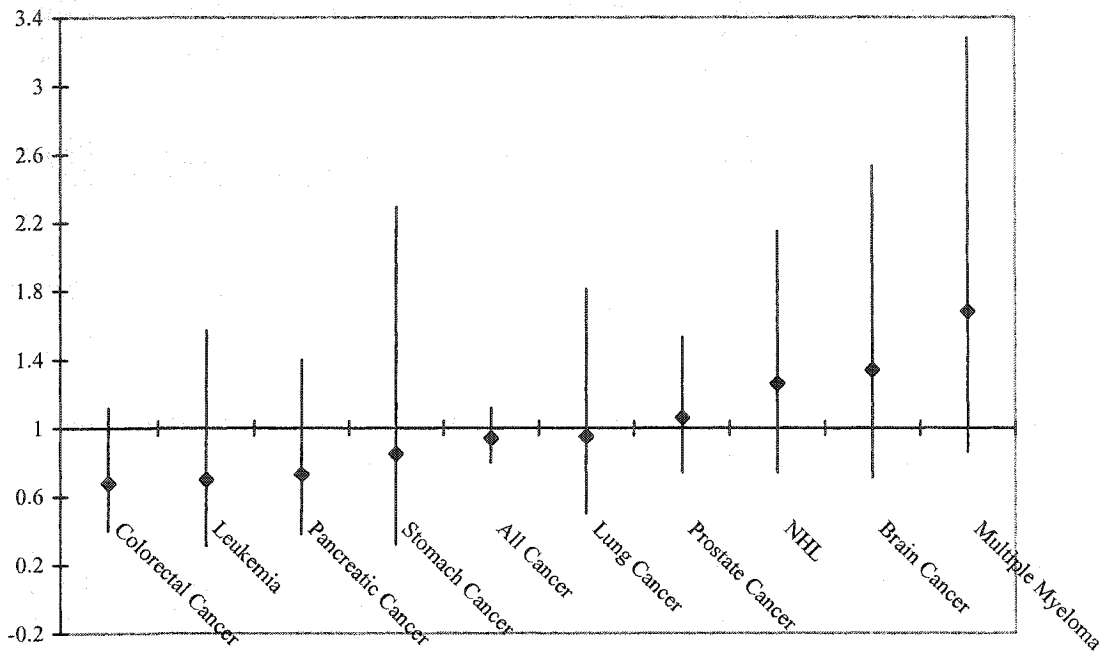

Figure 14. Summary of Hazard Ratios for the Association between a History of Asthma and Hay Fever and Cancer Mortality in Never Smoking Women

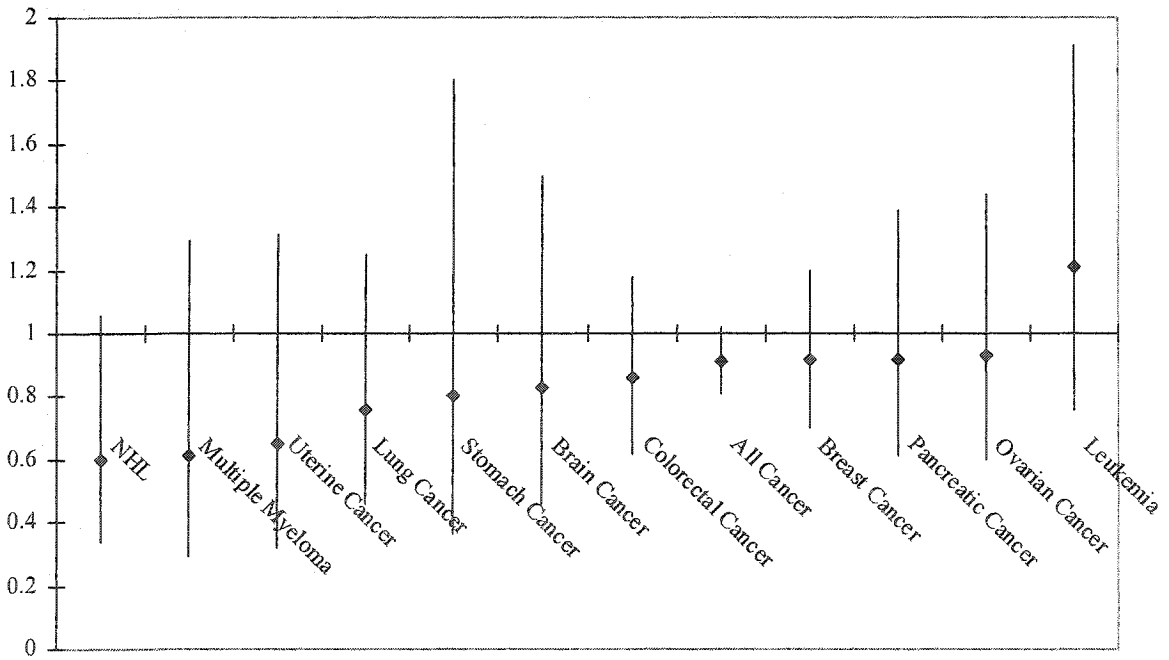

Figure 15. Summary of Hazard Ratios for the Association between a History of Asthma and/or Hay Fever and Cancer Mortality in Never Smoking Men

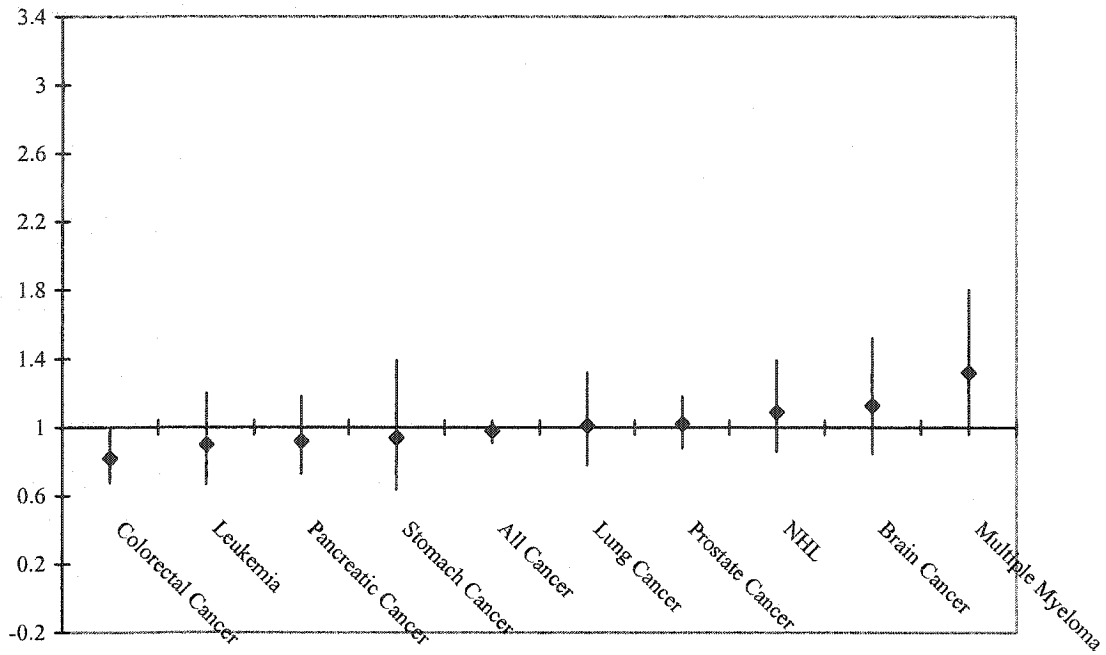

Figure 16. Summary of Hazard Ratios for the Association between a History of Asthma and/or Hay Fever and Cancer Mortality in Never Smoking Women