Original Article

Atopy and Development of Cancer: A Population-Based Prospective Study

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What is already known about this topic? Previous epidemiologic studies that investigated the association of atopy and allergic diseases with cancer have shown inconsistent results.

What does this article add to our knowledge? In a large population-based study with longitudinal and complete registry-based follow-up on cancer incidence, we did not observe any statistically significant associations between atopy (specific IgE to inhalants) and risk of any cancer or specific types of cancer.

How does this study impact current management guidelines? The risk of cancer may not be a particular concern of persons with atopy.

BACKGROUND: Atopy is the familial or personal propensity to develop IgE antibodies against environmental allergens. Atopy, theoretically, could both prevent and promote the development of cancer. However, evidence from epidemiologic studies has been inconclusive.
OBJECTIVE: We investigated the longitudinal association between atopy and the incidence of total and specific types of cancers of 5 Danish population-based studies.
METHODS: Atopy was defined as serum specific IgE positivity against inhalant allergens. A total of 14,849 persons were followed up prospectively by linkage to the Danish Cancer Registry. We used Cox regression analysis, and risk was expressed as hazard ratios (HR) (95% CIs) for persons with atopy versus those without atopy.
RESULTS: There were 1919 incident cancers (median follow-up, 11.8 years). There were no statistically significant associations between atopy and risk of any cancer (HR 1.00 [95% CI, 0.89-1.12]), any cancer excluding nonmelanoma skin cancer (HR 0.93 [95% CI, 0.82-1.07]), head and neck cancer (HR 1.74 [95% CI, 0.98-3.09]), colorectal cancer (HR 0.92 [95% CI, 0.64-1.32]), cancer of the bronchus and lung (HR 0.78 [95% CI, 0.54-1.13]), breast cancer (HR 1.00 [95% CI, 0.73-1.37]), cancer of the uterus (HR 0.90 [95% CI, 0.43- 1.88]), prostate cancer (HR 0.79 [95% CI, 0.53-1.18]), urinary cancer (HR 1.08 [95% CI, 0.60-1.96]), malignant melanoma (HR 0.95 [95% CI, 0.54-1.66]), and nonmelanoma skin cancer (HR 1.20 [95% CI, 0.98-1.47]).
CONCLUSION: Our data did not support the hypothesis that atopy is associated with an altered risk of total cancer development, although effects of atopy on specific types of cancer cannot be excluded. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:779-85)**

Key words: *Atopy; Cancer; Breast cancer; Lung cancer; Colorectal cancer; Prostate cancer; Nonmelanoma skin cancer; Head and neck cancer; Serum specific IgE; Inhalant allergens*

Atopy is the familial or personal propensity to develop IgE antibodies against common environmental allergens.[1] The immunologic basis of atopy is often viewed as a deviation toward the Th2-cell—mediated immune response and a decreased Th1 response,[2] and Th2-related cytokines have a key role in the initiation, maintenance, and amplification of allergic inflammation.[2] Accordingly, it has been shown that persons without atopy usually recognize most allergens, but the response is mainly characterized by the Th1-polarizing cytokine, IFN-γ, rather than Th2-type cytokine production, and they have no allergic symptoms or inflammatory response to allergens.[2] Individuals with atopy are at high risk of developing atopic diseases, such as allergic rhinitis, allergic asthma, atopic dermatitis, and food allergies. Atopic diseases and atopy have increased markedly in Westernized, urbanized, and affluent populations.[3] In Denmark, a more than 2-fold increase in prevalence of atopy documented by measurements of serum specific IgE against inhalant allergens has occurred among adults ages 30 to 60 years over a 25-year period,[3] and this was accompanied by increases in symptoms and diagnoses of allergic respiratory disease.[4] The high and increasing

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Abbreviations used
BMI- body mass index
HR- Hazard ratio
ICD- International Classification of Diseases
ICD-7- International Classification of Diseases, Seventh Revision
ICD-10- International Classification of Diseases, Tenth Revision
NMSC- nonmelanoma skin cancer

prevalence of atopy warrant studies that investigate any possible health effects of atopy beyond atopic disease.

There has been a long-standing interest in determining whether individuals with atopic diseases have an altered risk of developing cancer. Atopy could theoretically both prevent and induce the development of cancer.[5] According to the hyperreactive state and/or immune surveillance theory, allergic disease may reduce the risk of cancer by increasing the ability of the immune system to recognize and destroy malignant cells. However, the chronic inflammation—antigenic stimulation theory suggests that allergy causes repeated inflammation, damage, and repair of the tissue, which, in turn, may increase the risk of cancer.

Several studies investigated the association between atopic diseases and specific cancers. Asthma, hay fever, and atopic dermatitis have been associated with the risk of several specific cancers, such as pancreatic cancer, lymphomas, brain tumors, and leukemia, although inconsistently.[6-9] Vojtechova and Martin[5] found no association between atopic disease and breast or colorectal cancer in a meta-analysis of 16 observational studies, most of which used self-reported atopic disease as a measure of atopy. In the same meta-analysis, atopy (skin prick test or serum specific IgE positivity against inhalant allergens) was associated with a higher risk of prostate cancer, but there was no association with a history of asthma, hay fever, or any allergy.[5] Another meta-analysis, by Wang and Diepgen,[10] suggested that atopic disease may be associated with a higher risk of lung cancer and a lower risk for pancreatic cancer, childhood leukemia, and brain tumors.

Because associations appear to be site-specific, the association between atopy and specific types of cancer needs clarification. The inconsistency of results from previous studies may be at least partly due to differences in defining atopy and atopic diseases, and few studies have used an objective marker of atopy. Determination of serum specific IgE against inhalant allergens is considered a valid objective marker of atopy. We, therefore, investigated the association between serum specific IgE positivity and the incidence of a registry-based diagnosis of any cancer and specific types of cancer according to the International Classification of Diseases (ICD) in 5 Danish cohort studies.

METHODS

Ethics statement

All the participants gave their informed written consent, and the studies were approved by the Danish Data Protection Agency and the ethics committee of Copenhagen. The recommendations of the Declaration of Helsinki were followed.

Study populations

We used the 5 population-based studies, Monica1, Inter99, Health2006, the 1936-cohort, and Allergy98, recruited from the Danish Central Personal Register as random samples of the population in the southern part of Copenhagen. An overview of studies performed in this area has previously been published.[11] The studies included questionnaires, physical examinations, and blood tests. In The Monica1 study (1982-1984), 4807 persons with Danish citizenship (ages, 30, 40, 50, and 60 years old) were invited. The participation rate was 79%, which yielded a total of 3785 participants.[12]

In the Inter99 study, from 1999 to 2001, 12,934 persons (ages, 30-60 years) were invited. A total of 6784 persons participated, which gave a participation rate of 52.5%.[13] The study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on cardiovascular disease.[13] In the Health2006 study, a sample of 7931 persons from 18 to 69 years old, was invited to a general health examination.[14] A total of 3471 persons (43.8%) were examined from 2006 to 2008. The Copenhagen Allergy study began in 1990 and included a group of persons randomly selected from the general population and a selected group of persons with allergic respiratory symptoms (recruited from a random sample of the general population by a screening questionnaire). We used data from the follow-up health examination in 1997 to 1998 (referred to as "Allergy98"), in which a total of 1966 persons ages 15 to 77 years with Danish nationality were invited, and 1216 (61.9%) participated.[15]

The 1936-cohort comprised a random sample, drawn from the Danish Civil Registration System, of persons living in 4 municipalities of Copenhagen County. In 1976, a total of 1200 randomly selected persons born in 1936 (age 40 years at the time of the study) were invited by a letter for a health examination that focused on cardiovascular disease risk factors. A questionnaire on medical history and of health and lifestyle was enclosed to be completed in advance. Between August 1976 and July 1977, a total of 1052 persons were examined (participation rate, 87.7%). The 1936-cohort has previously been described.[16,17]

From these 5 studies, a total of 15,098 individuals had measurements of atopy (Monica1, 3481; Inter99, 5999; Allergy98, 1186; 1936-cohort, 989; Health2006, 3443). Of these, a total of 249 persons participated in more than 1 of the studies, and these persons were included only as participants in the study in which they were first examined and excluded from the subsequent studies (see Figures E1-E5 in this article's Online Repository at www.jaci-inpractice.org). Thus, we included a total of 14,849 persons (Monica1, 3481; Inter99, 5961; Allergy98, 1172; 1936-cohort, 989; Health2006, 3246).

Assessment of atopy

In the 1936-cohort and the Monica1 studies, serum specific IgE positivity measurements were performed by using the ADVIA Centaur Allergy Screen assay (Bayer HealthCare Diagnostics Division, Tarrytown, NY),[18] which is a multiallergen assay for the qualitative detection of specific serum IgE antibodies to common inhalant allergens. The assay includes 19 common inhalant allergens, and atopy was defined as a positive result according to manufacturer's instructions. In both the Allergy98 and the Health2006 studies, the ADVIA Centaur Specific IgE assay (Bayer Corp, New York, NY) was used for measurements of serum specific IgE to mite (*Dermatophagoides pteronyssinus*), cat, grass, and birch (in the Allergy98 study, in addition, dog and mugwort).[19] In the Inter99 study, serum samples were analyzed for specific IgE to mite (*D pteronyssinus*), cat, grass, and birch by the IMMULITE 2000 Allergy Immunoassay System (Siemens Medical Solutions Diagnostics, Tarrytown, NY).[20] In the Allergy98, the Health2006, and the