A Meta-Analysis of Cancer Risk and Asthma Status Fails to Demonstrate an Association

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Abstract

Background: Some investigators have hypothesized that the enhanced immune system activity in atopic individuals (e.g., elevated IgE) may play a protective role against the development of neoplasms.

Objectives: To assess whether there is an association between asthma and incidence of all cancers or between allergies and all cancers.

Methods: We conducted a literature search and identified studies to be included in a meta-analysis based on predefined inclusion criteria. Included studies clearly specified how asthma status and cancer were ascertained, assessed asthma status prior to cancer incidence, provided data on relative risk estimates and precision, and controlled for age and sex in analyses. Across-study estimates for the relative incidence of all cancers among asthmatic versus non-asthmatic populations, or allergic versus non-allergic populations, were generated using a random-effects approach (Cochrane Reviewers' Handbook, 2000). The random-effects approach is preferred when results are heterogeneous. Chi-square tests of heterogeneity and forest plots were generated by gender or gender combined, depending on the data reported from each study. This analysis did not evaluate any association between asthma and incidence of specific cancers.

Results: Six cohort studies and one case-control study of asthma and cancer met the inclusion criteria, in addition to three studies of asthma and cancer mortality, and three studies of allergy and cancer. The overall pooled incidence ratio from the cohort studies was 0.95 (0.69, 1.30) with statistically significant heterogeneity across the study results. A single large study demonstrated a protective effect of asthma, whereas the remaining studies, when pooled, demonstrated a slightly elevated risk of cancer associated with asthma. For studies of cancer mortality, the pooled relative risk estimate was 1.03 (0.81, 1.3). The incidence ratio of cancers among patients who were allergic versus those who were not was also not statistically significant (IR=1.2, 95% CI: 0.9, 1.4).

Conclusions: This meta-analysis did not demonstrate a statistically significant association between asthma and cancer incidence. This result suggests that background risk of all cancer in asthma populations is not different from the general population.

Objectives

- Summarize and evaluate the strength of the epidemiologic evidence for the relationship between IgE and cancer.
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- Examine patient characteristics that may impact the relationship between asthma and cancer.

Methods

In the National Library of Medicine Gateway we identified all relevant published papers in English through October 2003. Search terms included *asthma* combined with the following: *human, epidemiology, cancer, neoplasia, neoplasm, case-control study, cohort study*.

Methodological Criteria for Inclusion of Studies

Inclusion Criteria	
Case-Control Studies	**Cohort Studies**
Controlled for age through stratification, matching, and/or analysis	Controlled for age through stratification, matching, and/or analysis
Controlled for sex through stratification, matching, and/or analysis	Controlled for sex through stratification, matching, and/or analysis
Asthma definition reflects exposure prior to diagnosis of cancer	Incidence denominator based on person-years of follow-up
Case ascertainment method identical for cases and controls	Case ascertainment method identical for exposed and unexposed

Method Used For Each Study

- Published results were used to derive sex-adjusted relative risk and variance estimates for cancer in asthma patients, or
- Gender-specific estimates were used to derive and impute an overall study estimate.

Across-Study Estimates of Relative Risk

- We used a fixed-effects and a random-effects approach (Cochrane Reviewers' Handbook, 2000).
- Tests of heterogeneity and forest plots were generated.

Statistical Software

- STATA software version 7.0 and 8.1 (Stata Corporation, 2002, 2003)

Results

Case-Control Studies

No case-control study of IgE and cancer incidence met the inclusion criteria. We identified only one eligible case-control study of cancer in asthma (Vena et al., 1985):

- Age- and smoking-adjusted odds ratios were 0.96 and 0.92 (confidence intervals not reported).
- Rate of asthma in males and females, respectively, were not statistically different from one another at a significance level of p=0.1.

Asthma and Cancer Incidence. Six cohort studies met methodologic inclusion criteria and five provided data for meta-analysis.

Study	Time Period and Location	# Cancers in Asthma Patients/ # Asthma Patients	Association Measure	Covariates Matched or Otherwise Controlled
INCIDENCE				
McWhorter, 1988	1976-1989 Allergy clinic in Sweden	Not specified/348	OR=1.02 (0.63, 1.65)	Age group, sex, race, and smoking status
Reynolds, 1987*	1976-1982 Seventh-Day Adventists in California	11/102 males 8/115 females	Males RR = 2.1 (ns) Females = 1.1 (ns)	Age, smoking, and gender
Vesterinen, 1993	1969-1987 Sweden	3,842 all/ 35,126 males 42,826 females	All: SIR = 1.37 (p< 0.001) Males: SIR=1.12 (1.07, 1.17) Females: SIR=1.03 (0.98, 1.07)	Age, sex, period (1970-1975, 1976-1981, 1982-1987), 5-year age group, and follow-up period
Eriksson, 1995	1976-1989 Allergy clinic in Sweden	41/2,512	SIR=1.27 (0.92, 1.74)	Age group, calendar period, atopy, and gender
Mills, 1992	1976-1982 Seventh-Day Adventists in California	Not specified/ 2,189	Males: RR=0.78 (0.48, 1.27) Females: RR=0.96 (0.69, 1.34)	Age, sex, smoking history, time since last physician contact, number of allergies
Kallen, 1993	1969-1987 Sweden	4,275/64,346	SMR=0.66 (0.64,0.68) Males: SMR=0.69 (0.66, 0.71) Females: SMR=0.62 (0.59, 0.65)	Age, sex, period of cancer development (first 5 years vs. last 5 years)

*Excluded from meta-analysis due to lack of variance estimate.

Asthma and Cancer Mortality. Four studies met methodologic inclusion criteria. Two studies—Markowe, 1987 and Vandentorren, 2003—that provided adequate data for analysis were combined to give a pooled estimate of RR=1.026 (0.807, 1.303).

Study	Time Period and Location	# Cancers in Asthma Patients/ # Asthma Patients	Association Measure	Covariates Matched or Otherwise Controlled
MORTALITY				
Robinette, 1978	1944-1974 U.S. Army	Not specified/9,550	Males: RR=1.28 (p< 0.05)	Age at admission to hospital and calendar year of death
Alderson, 1974	1936-1970 Asthma clinic at Manchester Royal Infirmary (England)	63/1,892	O/E=0.71 (p< 0.05)	Age, sex, geographical area, year of entry into study (asthma diagnosis)
Markowe, 1987	1970-1985 60 general practices in Great Britain	34/2,158	All: RR=0.90 (0.5, 1.5) Males: RR=0.7 (0.3, 1.4) Females: RR=1.2 (0.6, 2.5)	Age, sex, and general practice
Vandentorren, 2003	Households in France, 1974-1998	76/940	RR=1.064 (0.812, 1.395)	Age, sex, educational level, smoking habit, occupational exposure, forced expiratory volume in one second (FEV1)

Allergy and Cancer Incidence. Three cohort studies met inclusion criteria. The combined analysis resulted in an incidence ratio = 1.2, 95% CI: 0.9, 1.4.

Author	# Cancers in Allergy Patients/ # Allergy Patients	Association Measure	Covariates Matched or Otherwise Controlled
McWhorter	118/1,840	ROR=1.40 (1.10-1.77)	Race, sex, smoking, age
Eriksson et al.	17/2,397	SIR=1.07 (0.63-1.73)	Sex and calendar year
Mills et al.	Not specified/ Not specified	Males: RR=1.13 (0.92-1.39) Females: RR=1.00 (0.85-1.17)	Age, sex, smoking history, time since last physician contact, number of allergies

References

Alderson M. *Lancet* 1974; **2**(7895):1475-1477.

Cochrane Reviewers' Handbook 4.1. Oxford, England: The Cochrane Collaboration, 2000.

Eriksson NE, Holmen A, Hogstedt B, Mikoczy Z, Hagmar L. *Allergy* 1995; **50**(9):718-722.

Kallen B, Gunnarskog J, Conradson TB. *Eur Respir J* 1993; **6**(5):694-697.

Markowe HL, Bulpitt CJ, Shipley MJ, Rose G, Crombie DL, Fleming DM. *Br Med J (Clin Res Ed)* 1987; **295**(6604):949-952.

McWhorter WP. *Cancer* 1988; **62**(2):451-455.

Mills PK, Beeson WL, Fraser GE, Phillips RL. *Am J Epidemiol* 1992; **136**(3):287-295.

Reynolds P, Kaplan GA. *Am J Epidemiol* 1987;**125**(3):539-540.

Robinette CD, Fraumeni JF, Jr. *J Chronic Dis* 1978; **31**(9-10):619-624.

Vandentorren S, Bladi I, Maesano IA, Charpin D, Neukirch F, Filleul L, et al. *Eur Respir J* 2003; **21**: 462-467.

Vena JE, Bona JR, Byers TE, Middleton E Jr, Swanson MK, Graham S. *Am J Epidemiol* 1985; **122**(1):66-74.

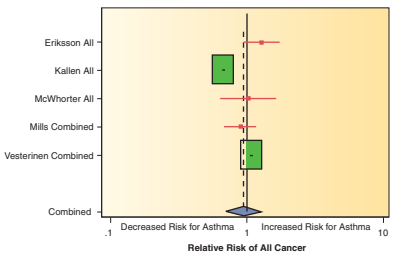
Vesterinen E, Pukkala E, Timonen T, Aromaa A. *Int J Epidemiol* 1993; **22**(6):976-982.

Results (continued)

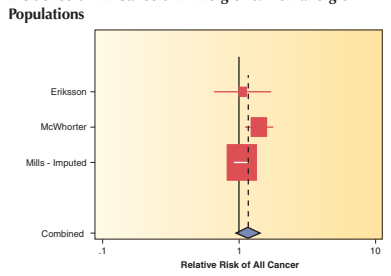
Forest Plot of Measures of Association for All Cancer Among Individuals with Asthma and Those Without Asthma (All Studies)

Inclusion of all eligible studies (N=5) resulted in RR=0.95 (95% CI=0.69-1.3).

Exclusion of the Kallen study (N=4), resulted in RR=1.07 (95% CI=1.04-1.10).



Forest Plot of Measures of Association Comparing Incidence of All Cancers in Allergic vs. Non-allergic Populations



Discussion

- Meta-analysis failed to provide evidence of a negative association between cancer incidence and conditions with heightened immune system activity, i.e. asthma or allergies
- Study design characteristics (e.g. clinic-based vs population-based and knowledge of smoking status) were 100% correlated, and meta-regression could not be conducted
- Asthma status at baseline may not represent immune status over long time.
- Between-study variation in countries and in calendar time could be influenced by asthma treatments and other factors.
- These studies (and this meta-analysis) did not address risk of individual cancers.

Disclosure

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