

CANCER AND ALLERGY

SAMUEL SHAPIRO, MB, MRCP, MRCPE, OLLI P. HEINONEN, MD,
AND VICTOR SISKIND, PhD

*The Boston Collaborative Drug Surveillance Program**

In a survey of three hospitals, a history of allergy was given by 7.1% of 605 cancer patients and by 6.6% of 3,310 controls. Such a history was recorded less commonly with increasing age and among men. The estimate of relative risk of cancer for those with a history of allergy, when controlling hospital, age, and sex, became 0.92, with 95% confidence limits of 0.63 and 1.33.

IN RECENT YEARS, ATTENTION HAS BEEN DRAWN to reports showing a negative correlation between cancer and allergy.^{4,7,8,10,14} However, there has been one study in which evidence of an association was not found,¹¹ and an earlier investigation produced contrary evidence to the effect that cancer and allergy are positively correlated.⁹ We have evaluated the relationship by reviewing a relatively large body of data collected for another purpose.

METHODS

The data were derived from the Boston Comprehensive Drug Surveillance Program in which trained nurse monitors use standardized forms to routinely record a wide variety of information on consecutive patients admitted to medical wards. Among other things, each patient is asked whether he has ever had hay fever, any allergic skin manifestation, a re-

action to an injection of serum or to blood transfusion, and/or asthma. If a history cannot be obtained, it is recorded as unknown. The system provides for recording up to four discharge diagnoses for any given patient in the same order as these are written by the attending physician. Coding of the diagnoses is compatible with the International Classification of Diseases.³ Details of the surveillance methods have been described elsewhere.^{2,6,12,13}

Of eight hospitals monitored, only those with appreciable numbers of patients with cancer were considered in the present study. Thus, three Boston hospitals, one of them a chronic disease hospital, one a general hospital, and one a veterans' hospital, were included. To further increase the homogeneity of the material, data from monitored admissions other than the first were not considered, and patients with any of the following characteristics were excluded from the analyses:

1. Discharge diagnosis of neoplasm of lymphatic and/or hemopoietic tissue (codes 200 through 209). Conditions such as Hodgkin's disease can be long-lasting and can suppress allergy. The inclusion of these diseases could thus have introduced a bias.
2. Discharge diagnosis of any illness designated as allergic. Hospitalization for such an illness would result in allocation to a control, non-cancer group. Since the history of previous allergy would tend to be positive, inclusion of patients with a discharge diagnosis of allergic illness could have given rise to problems related to confounding.
3. History of allergy unknown.
4. Age under 30 or over 79 years.
5. Race other than Caucasian.

From the Clinical Pharmacology Unit, Lemuel Shattuck Hospital, Boston, Mass., and the Department of Medicine, Tufts University School of Medicine.

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* Directors: Hershel Jick, MD, and Dennis Slone, MD.

Address for reprints: Dr. S. Shapiro, Clinical Pharmacology Unit, 400 Totten Pond Rd., Waltham, Mass. 02154.

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The cancer group was taken to consist of patients with any of the discharge diagnosis code numbers 140 through 199.1. All other patients constituted the control series. The history of allergy was taken to be positive whenever the patient had reported experiencing hay fever, any allergic skin manifestation, and/or a reaction to an injection of serum or blood transfusion. History of asthma was not considered because many patients in this category, in fact, suffer from a variety of respiratory or cardiac disorders.

An evaluation of frequencies of cancer and history of allergy by hospital, decade of age, and sex indicated a need for stratification by these factors, and this resulted in 30 subcategories. The assumption that the relative risk of cancer in the presence of allergic history was constant over the subcategories was examined⁵ and found to be tenable ($p \sim .60$). The overall relative risk was then estimated by combining the information from each subcategory.¹

RESULTS

The total series consisted of 605 patients with and 3,310 patients without cancer. The distributions by diagnosis are given in Table 1. In the cancer group, among males, lung cancer predominated (49%), and among females, cancer of the breast was the most common (46%). Cardiovascular disorders (17%),

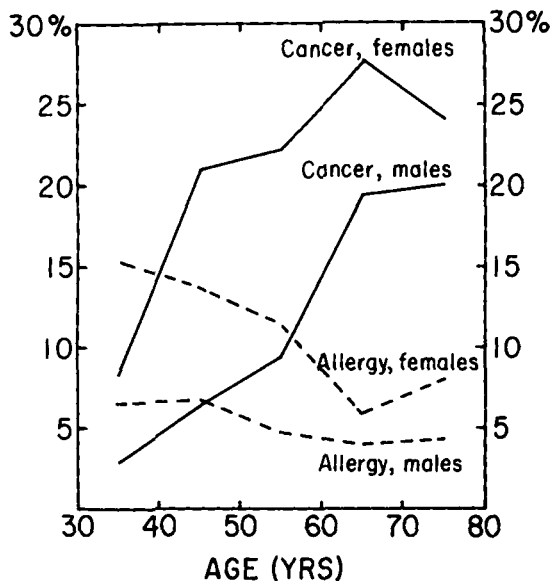


FIG. 1. Patients with cancer and patients giving a history of allergy are expressed as proportions of the total male and female monitored patients at each decade of age.

followed by liver disease (13%), headed the list among the controls.

As expected, cancer was more common with increasing age. Conversely, a history of allergy was recorded less commonly with increasing age. For each age category, and for each type of allergy, a positive history was more common among females. These trends also held

TABLE 1. Diagnoses among Cancer Controls and Patients*

A. Cancer Group	Male	Female	Total
Lung cancer	152 (48.9)	32 (10.9)	184 (30.4)
Breast cancer	5 (1.6)	136 (46.2)	141 (23.3)
Gynecological cancer	—	43 (14.6)	43 (7.1)
Prostatic cancer	31 (10.0)	—	31 (5.1)
Cancer of colon	15 (4.8)	18 (6.1)	33 (5.5)
Other	108 (34.7)	65 (22.1)	173 (28.5)
TOTAL	311 (100.0)	294 (100.0)	605 (100.0)
B. Control Group	Male	Female	Total
Cardiovascular disease	397 (17.5)	157 (15.1)	554 (16.7)
Cirrhosis	253 (11.1)	183 (17.6)	436 (13.2)
Chronic resp. disease	186 (8.2)	42 (4.0)	228 (6.9)
Joint disease	72 (3.1)	134 (12.9)	206 (6.2)
Diabetes mellitus	91 (4.0)	36 (3.5)	127 (3.8)
Other	1,276 (56.1)	483 (46.7)	1,759 (53.1)
TOTAL	2,275 (100.0)	1,035 (100.0)	3,310 (100.0)

* Percentages are given in parentheses.

TABLE 2. History of Allergy, Cancer Vs. Controls*

		Chronic disease hospital		General hospital		Veterans' hospital		All hospitals	
		Cancer	Control	Cancer	Control	Cancer	Control	Cancer	Control
Males	Allergic history	9 (4.5)	53 (6.6)	0	15 (3.8)	2 (2.7)	56 (5.2)	11 (3.5)	124 (5.5)
	Total	201	804	35	396	75	1,075	311	2,275
Females	Allergic history	32 (11.8)	74 (10.5)	0	26 (8.7)	0	5 (17.2)	32 (10.9)	105 (10.1)
	Total	271	708	20	298	3	29	294	1,035
All patients	Allergic history	41 (8.7)	127 (8.4)	0	41 (5.9)	2 (2.6)	61 (5.5)	43 (7.1)	229 (6.9)
	Total	472	1,512	55	694	78	1,104	605	3,310

* Percentages are given in parentheses.

good for each hospital, although there was variability in the frequencies of both cancer and allergic history between hospitals. Table 2 summarizes the data, and the accompanying graph illustrates the changing sex-specific proportions of cancer and allergic history with age (Fig. 1).

In the cancer group, 43 patients gave a history of allergy (7.1%), and among controls the corresponding figure was 229 (6.6%). The estimate of relative risk of cancer in the presence of history of allergy, when controlling for hospital, age, and sex, became 0.925 with 95% confidence limits of 0.632 and 1.330. Hay fever and allergic skin manifestation were the most common types of allergic history recorded, and relative risks for cancer in the presence of each of these two types of allergic history were estimated (Table 3). In each instance, the point estimates were close to unity. The 95% confidence limits for hay fever were 0.63 to 1.89, and for allergic skin manifestation, 0.43 to 2.59.

Finally, relative risks in the presence of a positive allergic history were estimated for the two particular types of cancer which were most common in the series, namely, lung cancer and breast cancer (Table 4). In the latter case, the analysis was confined to females. For lung cancer, the relative risk became 1.04 (95% confidence limits 0.52 to 1.93), and for breast cancer, 1.42 (95% confidence limits 0.77 to 2.54).

DISCUSSION

Evidence of a negative association between cancer and allergy has been reported for cancer patients in general,⁴ and specifically for women.^{10,14} Most striking of all has been a survey of a gynecologic population in which allergy was not noted among 40 patients with cancer compared with 28 instances of allergy among 110 control subjects (25%).¹⁴ On the other hand, earlier work suggested that there is an excess of allergy in patients with cancer.⁹ A number of factors could account for these contradictory findings. Among them, there is the possibility of biased history-taking due to awareness of the hypothesis, and of preferential publication of actual associations, either negative or positive, rather than of "negative studies." McKee et al.,¹¹ in a study in which evaluation of allergy was done by observers unaware of the diagnosis in 104 patients with cancer and in 299 controls, found no evidence of an association.

The present study is the largest reported thus far, and there was no hypothesis in mind at the time the data were collected. The findings are in agreement with those of McKee et al.¹¹: the point estimate of relative risk for cancer in the presence of allergic history is close to unity; however, the 95% confidence limits are rather wide. Given similar trends, a cancer group about four times as large as the present one, or some 2,500 patients, would be

TABLE 3. History of Hay Fever and History of Skin Allergy, Cancer Vs. Controls*

	Cancer	Control	Relative† risk	95% confidence† limits
History of hay fever	20 (3.3)	96 (2.9)	1.11	0.63-1.89
History of skin allergy	6	34	1.06	0.45-2.59
TOTAL	605	3,310	—	—

* Percentages are given in parentheses.

† Relative risks and 95% confidence limits estimated after controlling for hospital, age, and sex.

TABLE 4. History of Allergy

A. Lung cancer vs. controls

	Lung cancer	Control	Relative risk*	95% confidence limits*
Allergic history	12 (6.5)	229 (6.9)	1.04	0.52-1.93
TOTAL	184	3,310	—	—

B. Breast cancer vs. controls†

	Breast cancer‡	Control‡	Relative risk*	95% confidence limits*
Allergic history	18 (13.2)	105 (10.1)	1.42	0.77-2.54
TOTAL	136	1,035	—	—

* Relative risks and 95% confidence limits estimated after controlling for hospital, age, and sex in the case of lung cancer; hospital and age in the case of breast cancer.

† Percentages are given in parentheses.

‡ Female patients only.

needed to reduce the confidence limits around the relative risk to, say, ± 0.2 . This will become possible in due course. But even the present data suggest that if allergic diathesis indeed exercises a preventive influence against cancer, the connection is unlikely to be a strong one. Nor is there evidence to suggest that specific types of allergic history, such as hay fever or allergic skin manifestation, are connected to the risk of cancer.

For specific types of cancer, there is also no evidence to suggest that allergy confers a protective or potentiating effect. For lung cancer, the relative risk is again close to unity, although, because of wide confidence limits, the possibility of a positive or negative relation-

ship cannot be excluded. For breast cancer, this risk is 1.42, but interpretation of this estimate is rendered virtually meaningless by extremely wide 95% confidence limits. Since one report has furnished data on patients with gynecologic cancer,¹⁴ it is worth noting that of 43 patients with such cancer in the present series, three gave a history of allergy.

Finally, it is of interest that women appear to be more prone to allergic illnesses than men, and that a history of allergy is given less frequently with increasing age. This latter finding is probably accounted for partly by a progressive failure of recall, and partly by a greater general tendency to diagnose allergy in more recent years.

APPENDIX I.

Statistical Methods

The data were stratified by hospital, age, and sex to form 30 subtables; 5 of these (all with small total numbers) had at least one zero marginal total and were omitted from the analysis. Relative risk (i.e., odds-ratio) was assumed constant over the subcategories and estimated with the aid of a computer program which

1. Estimates relative risk by the method of Norton (1945; see Gart, 1962); this approach assumes only one pair of marginal totals in each subtable to be given; it provides estimates of expectations of cell frequencies, based on the computed relative risk, from which a goodness-of-fit statistic for homogeneity of the relative risk may be computed in the usual way

(see, e.g., Goodman 1969); this statistic is of course approximately a chi-square with 24 degrees of freedom, and in our case its value was 21.2;

2. Estimates relative risk on the assumption that both margins in each subtable are fixed, as discussed by Birch (1964). He shows that, given these margins, the total of the entries in cells in a given position is sufficient for the relative risk, and that the distribution of this total is the convolution of hypergeometric distributions with odds-ratio possibly differing from unity. Since only one unknown parameter is involved, it is easy to compute exact confidence limits by Newton-Raphson iteration, and the maximum likeli-

hood equation for the relative risk was also so solved. Double-precision arithmetic was used, and certain built-in checks showed the degree of accuracy to be adequate.

The estimates of relative risk and its standard error obtained by the two approaches were very similar, probably due to the fact that the estimated relative risk is close to unity. We mention only the second method in the paper, since in this case it clearly matters little what one assumes about the margins.

It may be shown that where the expected values of cell entries in a particular position in the tables are consistently much smaller

than those in the other positions, the (estimated) asymptotic variance of the estimate of relative risk depends almost entirely on the smallest total of the cell entries (see, e.g., Goodman, op. cit.) This implies that the width of the confidence limits cannot be substantially reduced by aggregation of subtables or equivalent methods.

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