

# A double-blind study of the comparative incidence of malignancy and allergy

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*Four hundred and three preoperative patients were questioned as to past or present allergic symptoms. One hundred and four patients in this group were subsequently shown to have malignancy. There was no significant difference in the incidence of seasonal or possible allergic symptoms in those patients with cancer as compared with those with no cancer. In the allergic group, no significant difference was found in the intensity of allergic symptoms in cancer patients and the intensity of allergic symptoms in noncancer patients. The incidence of allergic symptoms was similar in patients with localized cancer when compared to those with invasive malignancy. The incidence of reported allergy was less in the older age patients, but this did not affect the present study as there was a similar incidence of allergy in cancer patients compared to noncancer patients at each age level.*

**R**enewed interest has developed in recent years in immunological factors which play a role in the development and progression of malignancy. It has been shown that tumors may be rejected in a manner similar to homotransplantation reactions<sup>1, 2</sup> and that tumors may have cancer-specific antigens.<sup>2-6</sup> In the host's response to malignancy, the ability to detect and respond immunologically in an adequate fashion is important. Failure to respond adequately may account for the enhanced tendency to develop malignancy in certain animal strains and human families. This may also be true of individuals with multiple tumors. The reverse situation may be postulated to take place in animals or individuals who are resistant to the development of malignancy. If so, is there a method for detecting cancer prone and resistant individuals? Atopic individuals represent a group which has an enhanced capacity to form reaginic antibody to environmental antigens, and they may also respond immunologically in a different

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manner to tumors.<sup>7</sup> The incidence of malignancy in allergic patients compared to that in nonallergic patients is the subject of this paper.

## **METHOD OF STUDY**

Over the period of one year, 403 preoperative surgical patients of the Palo Alto Medical Clinic were questioned as to any past or present symptoms which might be considered allergic. The questioning was done by the same research-oriented medical student in the hospital on the evening prior to operation. Patients having emergency and outpatient surgery were excluded as well as patients having operative procedures in which malignancy was rarely found, as demonstrated by review of the previous year's pathology reports. Excluded in the latter group were cholecystectomies, appendectomies, and hysterectomies. By this approach many factors which might have affected the questionnaire results were standardized. These included: interview of patients during similar periods of stress, use of a standard questionnaire asked by the same person, and most importantly, neither the patient nor the medical student knew if the subsequent operative procedure would reveal cancer. The patient's tissue diagnosis was obtained approximately one month later from the pathology report. Those patients having cancer were then divided into those with localized malignancy and those in whom cancer showed tissue invasion or metastasis.

The allergy questionnaire indicated those patients with past or present seasonal hay fever or asthma and the degree of symptoms. It also indicated those patients with symptoms which may or may not be due to allergic factors. This group includes chronic rhinitis and asthma, urticaria, eczema, and possible food allergy. The remaining questionnaires indicated those patients with no complaints considered allergic. Only those patients with seasonal rhinitis or asthma were considered as proven atopic.

## **RESULTS**

A tabulation of the 403 patients in this study showed that 104 patients had cancer and 299 had no evidence of malignancy (Table IA). Fifty-nine patients gave a history of seasonal allergy and 213 patients gave no evidence of allergy by history. There was a total of 131 patients with symptoms which were considered possibly allergic.

Of the 59 patients with seasonal allergy, 23.7 per cent had cancer at operation as compared with a finding of 25.4 per cent cancer in the group with no history of allergy (Table IA). Of the 104 proven cancer patients, 13.4 per cent gave a history of seasonal allergy as compared to 15.0 per cent of the noncancer group (Table IB).

The degree of seasonal allergic symptoms and the decrease or loss of these symptoms in the last 10 years is shown in Table II. Twenty-one per cent (14 per cent plus 7 per cent) of the cancer patients had a decrease or loss of seasonal symptoms in the past 10 years. This is similar to 18 per cent (9 per cent plus 9 per cent) in the noncancer group. Severe to moderately severe seasonal symptoms were noted in the questionnaire of 14 per cent of the cancer patients and 29 per cent of the noncancer patients.

**Table IA**

|                                | <i>No. with cancer</i> | <i>No. without cancer</i> | <i>Total</i> |
|--------------------------------|------------------------|---------------------------|--------------|
| Patients with seasonal allergy | 14 (23.7%)             | 45 (76.3%)                | 59 (100%)    |
| Patients with possible allergy | 36 (27.4%)             | 95 (72.6%)                | 131 (100%)   |
| Patients with no allergy       | 54 (25.4%)             | 159 (74.6%)               | 213 (100%)   |
| Total                          | 104                    | 299                       | 403          |

**Table IB**

|                         | <i>No. with seasonal allergy</i> | <i>No. with possible allergy</i> | <i>No. with no allergy</i> | <i>Total</i> |
|-------------------------|----------------------------------|----------------------------------|----------------------------|--------------|
| Patients with cancer    | 14 (13.4%)                       | 36 (34.6%)                       | 54 (52.0%)                 | 104          |
| Patients without cancer | 45 (15.0%)                       | 95 (31.7%)                       | 159 (53.3%)                | 299          |

**Table II.** *Change or degree of allergic symptoms in cancer and noncancer patients*

|                                                             | <i>No. with cancer</i> | <i>No. without cancer</i> | <i>Total</i> |
|-------------------------------------------------------------|------------------------|---------------------------|--------------|
| Seasonal allergy disappeared last 10 years                  | 1 (7%)                 | 4 (9%)                    | 5 (9%)       |
| Seasonal allergy decreased last 10 years                    | 2 (14%)                | 4 (9%)                    | 6 (10%)      |
| Seasonal allergy minimal but not decreased in last 10 years | 9 (65%)                | 24 (53%)                  | 33 (56%)     |
| Seasonal allergy moderate to severe last 10 years           | 2 (14%)                | 13 (29%)                  | 15 (25%)     |
| Total                                                       | 14 (100%)              | 45 (100%)                 | 59 (100%)    |

**Table III.** *Extent of cancer in seasonally allergic and nonallergic patients*

| <i>Cancer patients</i>            | <i>Cancer with metastasis</i> | <i>Localized cancer</i> | <i>Total</i> |
|-----------------------------------|-------------------------------|-------------------------|--------------|
| Those with seasonal allergy       | 8 (57%)                       | 6 (43%)                 | 14 (100%)    |
| Possible allergy                  | 20 (56%)                      | 16 (44%)                | 36 (100%)    |
| Those with no evidence of allergy | 32 (59%)                      | 22 (41%)                | 54 (100%)    |

**Table IV.** *Location of malignancy in the cancer group*

| <i>Location of cancers</i> | <i>No. with seasonal allergy</i> | <i>No. without allergy</i> | <i>Total</i> |
|----------------------------|----------------------------------|----------------------------|--------------|
| Respiratory                | 1                                | 3                          | 4            |
| Breast                     | 6                                | 25                         | 31           |
| Digestive                  | 2                                | 32                         | 34           |
| Urinary                    | 2                                | 16                         | 18           |
| Lymphoma                   |                                  | 5                          | 5            |
| Genital                    |                                  | 4                          | 4            |
| Other                      | 3                                | 5                          | 8            |
| Total                      | 14                               | 90                         | 104          |

The extent of malignancy in seasonal allergic and nonallergic patients is indicated in Table III. Fifty-seven per cent of seasonally allergic patients had invasive cancer or cancer with metastasis as compared to 59 per cent of those with no allergy. Forty-three per cent of seasonally allergic patients had localized malignancy as compared to 41 per cent of the nonallergic group.

Table IV shows the area of malignant involvement in patients with seasonal allergy and those with no seasonal symptoms, but the numbers are too small to be of much value for comparative studies. Most of the operations involved the breast, digestive, or urinary systems.

Patients were also grouped by age, and in each age group comparisons of those with and without cancer and allergic symptoms were tabulated (Fig. 1). An increasing percentage of patients in the older age groups had cancer, but the proportion of those in each age group with seasonal allergy did not vary significantly between the cancer and noncancer patients. The older age group (71 to 100 years) did not report as much seasonal or possible allergic symptoms as did the younger age groups.

STATISTICAL EVALUATION

Statistical analyses were performed on the data appearing in Tables IA, II, and III, and in each of the four age groups of Fig. 1. In each case the data take the form of a two-way contingency table. It was not appropriate, however, to carry out the standard chi square test for independence of the two classifications. Instead, a modification of the Wilcoxon 2 sample test was used. (See Goldstein,<sup>8</sup> pp. 114, 115. The formula for  $\chi^*$  on page 115 is incorrect, due to the presence of ties. For the correct formula, see Armitage,<sup>9</sup> p. 382.) To explain this choice consider, for example, Table IA. Here the 403 patients studied were grouped according to two classifications—the presence or absence of cancer, and

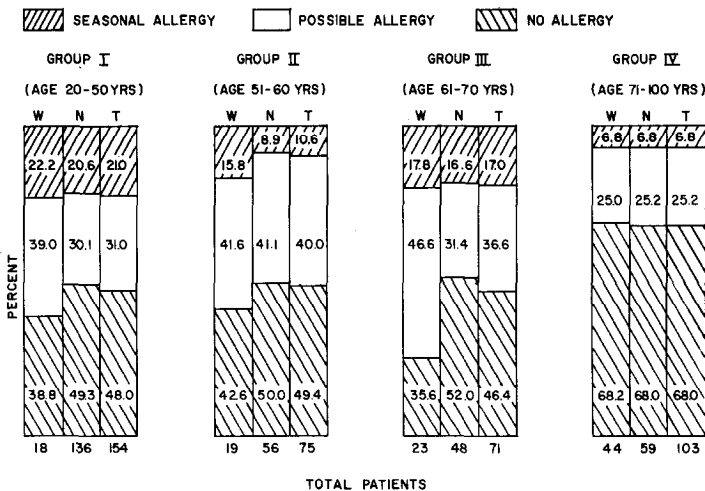


Fig. 1  
Allergic symptoms in cancer and noncancer patients in different age groups. W, patients with cancer; N, patients with no cancer; T, total patients.

the presence, absence, or possibility of allergy. We wish to determine whether or not the two classifications may be regarded as independent. If they are independent, then the probability  $P_1$  that a seasonally allergic patient has cancer, the probability  $P_2$  that a "possible allergic" patient has cancer, and the probability  $P_3$  that a nonallergic patient has cancer, are equal. If the two classifications are dependent, then  $P_1$ ,  $P_2$ , and  $P_3$  are not equal, but we can conclude more than this because there is a natural ordering associated with the three allergy categories. That is, since the members of the "possible allergic" group exhibit border-line or questionable allergic symptoms, it is natural to consider this category as intermediate, lying "between" the allergic and nonallergic groups. Therefore, if the two classifications are dependent, not only are  $P_1$ ,  $P_2$ , and  $P_3$  unequal, but also we in fact expect one of the following two orderings to hold:  $P_1 < P_2 < P_3$  or  $P_1 > P_2 > P_3$ . The standard chi square test is designed to detect any lack of inequality among  $P_1$ ,  $P_2$ , and  $P_3$ , while the modified Wilcoxon test is specifically designed to detect inequality taking the form of one of the two orderings given above. Thus in this example of "ordered alternatives," the Wilcoxon test is substantially more powerful than the chi square test in detecting dependence between the two classifications. An important implication of this fact is that to attain the same power (i.e., the same probability of detecting dependence) one can use a smaller sample size with the modified Wilcoxon test than with the chi square test.

The main results of the study are summarized in Table IA. Particular attention was given to the detection of alternatives of the form  $P_1 < P_2 < P_3$ , because it has been suggested in another paper<sup>7</sup> that the incidence of cancer is lower in allergic patients than in nonallergic patients. Analysis of the data by the method described above revealed no significant relationship between cancer and allergy in the population studied. A one-sided significance level of 0.52 was obtained. Approximate power calculations showed that this study possessed a 71 per cent chance of detecting a deviation from independence such as that reported by Fisherman,<sup>7</sup> if such a deviation actually existed. In order for the study to have had a 95 per cent chance of detecting such a deviation if it existed, approximately 1,000 patients would have been needed, or  $2\frac{1}{2}$  times the 403 actually examined.

Each of the four age groups appearing in Fig. 1 was also analyzed by this method. None of the age groups exhibited a statistically significant deviation from independence. Groups I, II, III, and IV yielded two-sided significance levels of 0.50, 0.68, 0.28, and 0.84, respectively. Only Group IV, the oldest group of patients, showed a deviation in direction consistent with Fisherman's<sup>7</sup> hypothesis, and this deviation was quite insignificant.

Finally, Tables II and III were analyzed in the same manner and also showed no significant effects, yielding two-sided significance levels of 0.38 and 0.94, respectively.

## DISCUSSION

The increased incidence of malignancy in certain animal strains and human families has been well documented.<sup>10-12</sup> It is generally believed that most ma-

lignancy has cancer-specific antigens which may be recognized as "nonself" by the host. If these antigens stimulate sufficient cellular or lytic antibodies, regression or disappearance of the tumor may occur. However, if nonlytic antibodies are produced, they may bind tumor antigen and block the other antibodies' action. The result is enhancement of tumor growth.<sup>13</sup>

One mechanism for the increased incidence of malignancy in certain animals and humans could be the failure of the host's immunological mechanism to reject cancer at the onset. This failure could occur at several locations in the immunological response: (1) the failure of the host to recognize the tumor as foreign and make an antibody response. (2) If the tumor had weak antigens and rapid growth, a state of immunological paralysis could result. (3) The host's antibody response was weak, again resulting in immunological paralysis. (4) The antibody response to the tumor is of the type to produce enhancement. Therefore, either diminished or excessive antibody response of certain types could account for this phenomenon.

Atopic individuals are unusual in their ability to produce reaginic antibody. This capacity may be the result of the handling of antigen by the mucous membrane rather than different immunological capacity to make reaginic antibody.<sup>14, 15</sup> Most individuals are capable of developing this type of antibody if a potent antigen is given intracutaneously a sufficient number of times.<sup>16, 17</sup> However, there are conflicting reports as to whether allergic individuals respond to intradermal injections at the same rate or faster than nonallergic individuals.<sup>14, 18</sup> Increased organ-specific autoantibody production<sup>19</sup> and increased antibody response to orally ingested antigens<sup>20</sup> in reaginic individuals has been documented. It has also been written that persons with malignancy have a lesser history of previous atopy than normal individuals.<sup>7</sup> The inference was made that atopic individuals have an increased immunological protection from malignancy. However, the present study fails to substantiate a significant difference in the incidence of malignancy between atopic and nonatopic individuals.

There appeared to be no significant difference in the percentage of patients having a decrease or loss of allergic symptoms between the cancer and noncancer group. Therefore, a change in intensity of allergic symptoms does not appear to alter the patient's future chance of developing malignancy.

There was also no significant difference in the per cent of patients with or without allergy when comparing the localized cancer group with the group with invasive cancer. Thus, this study did not supply evidence to support the idea that cancer is less extensive in patients with allergic symptoms.

The fact that most of the malignancy involved breast, digestive, and urinary systems was of value in a double-blind study of this type. The is true, because it is difficult to predict malignant involvement of these areas prior to surgery.

The high percentage of patients with cancer in the older age groups as found in this study is to be expected. A higher percentage of allergic symptoms would be expected in the older age groups because of the cumulative effect of past and present symptoms. The finding that the group of patients over age 70 had relatively fewer individuals with past or present seasonal allergy or possible allergic symptoms was unexpected. Two possible explanations for this finding

may be given. This age group may have had symptoms years ago, but did not know the diagnosis, as general knowledge of allergic diseases at that time was limited. It is also possible that this group had less memory of past symptoms compared to younger age groups. This decrease in reported allergy in the elderly may account for much of the low incidence of allergy in cancer patients reported in another paper.<sup>7</sup> That paper used orthopedic patients as a control group, which may well have been a younger population group than the cancer group. Another possible cause for difference was that that study was done in a retrospective manner rather than the prospective, double-blind fashion of our study.

The incidence of allergy in this study was less than that reported in a survey of 1,000 patients in this area.<sup>21</sup> Again the difference in allergy reported may be that we are dealing with different age groups. In addition, studies of college students<sup>22, 23</sup> in other regions show a higher incidence of allergy than in this study, perhaps due to the fact that they represent younger, more alert, and more knowledgeable population groups.

## SUMMARY

This double-blind study failed to demonstrate a significant difference in the incidence of malignancy in atopic and nonatopic individuals. This information may be valuable for two reasons. First, the risk of cancer in allergic patients is not sufficiently lower to influence the clinical evaluation of suspicious symptoms. Second, the chance of discovering any fundamental information on tumor rejection in laboratory experiments now seems remote (relative to the atopic state).

In the allergic group, we found no significant difference in the intensity of allergic symptoms in cancer patients and the intensity of allergic symptoms in noncancer patients.

The per cent of patients with allergy was no different in the group with invasive cancer than in the group with localized malignancy.

Patients past the age of 70 years reported less past and present allergic symptoms than younger age groups. Nevertheless, there was no significant difference in the incidence of malignancy in atopic and nonatopic individuals at any age level.

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