

Elevated serum immunoglobulin E in bronchial carcinoma: its relation to the histology and prognosis of the cancer

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Total IgE and specific IgE antibodies against six common allergens were measured in the sera of 217 unselected patients with bronchial carcinoma. Their median total IgE level was significantly increased as compared to the median levels found in two control populations consisting of 246 individuals representing the adult general population and 143 patients with benign pulmonary disorders. The frequency of serological atopy, i.e., the presence of specific IgE antibodies, was also significantly increased in the cancer population as compared to the controls. In contrast, the incidence of possible clinical atopy was about five times higher in the general population than in the cancer group. Patients with bronchial carcinoma typed as adenocarcinoma had the best prognosis and also had nonelevated IgE levels in contrast to patients with bronchial carcinoma typed as squamous cell carcinoma, small or large cell carcinoma. The favorable prognosis with nonelevated IgE levels also was demonstrated in patients with squamous cell carcinoma. It is suggested that the elevated IgE levels in bronchial carcinoma reflect impaired cellular immunity.

The coexistence of different atopic disorders with one or more types of malignancies has been studied by a number of investigators,¹⁻⁷ but the results have been conflicting. In atopic patients high concentrations of circulating total IgE are often observed.⁸ Raised levels of IgE have also been reported in bronchial carcinoma,^{9, 10} findings that have not been confirmed by others.¹¹⁻¹³ The reasons for these equivocal results concerning the possible relationship between malignant neoplasms and clinical symptoms and laboratory signs associated with atopy are not immediately clear. This study supports both the earlier reports on elevated total IgE in bronchial carcinoma and the findings of a negative correlation between clinical atopy and malignancy of endodermal origin.⁵⁻⁷ We have measured the serum levels of IgE using the direct sandwich type of radioimmunoassay (PRIST) in an unselected population of patients with

bronchial carcinoma and compared the levels with two reference populations: subjects attending a health survey and patients admitted to hospital with suspected bronchial carcinoma, a diagnosis later dismissed. We have related our IgE data to possible clinical atopy and to serological atopy defined as presence of specific IgE antibodies against common allergens. Finally we have evaluated the prognostic value of raised IgE levels in bronchial carcinoma.

MATERIAL AND METHODS

Subjects

Two hundred and seventeen patients with bronchial carcinoma were included in the study. There were 168 males and 49 females. The mean age was 67 years, range 36 to 93. The patients were admitted to the Department of Lung Medicine, University Hospital, Uppsala, Sweden, from the whole county of Uppsala during the period 1972 to 1976 and were included in an epidemiologically unselected and prospectively collected 5-yr material.¹⁴ The "early" character of this material was underlined by the fact that 40% of the patients were detected either by chest X-ray because of suspicion of organic disease or by mass miniature chest X-ray at a general health survey. The patients were classified according to the WHO histological classification.¹⁵ The histological diagnoses were confirmed by autopsy performed on 95% of the deceased patients.

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Received for publication Nov. 10, 1980.

Accepted for publication Feb. 3, 1981.

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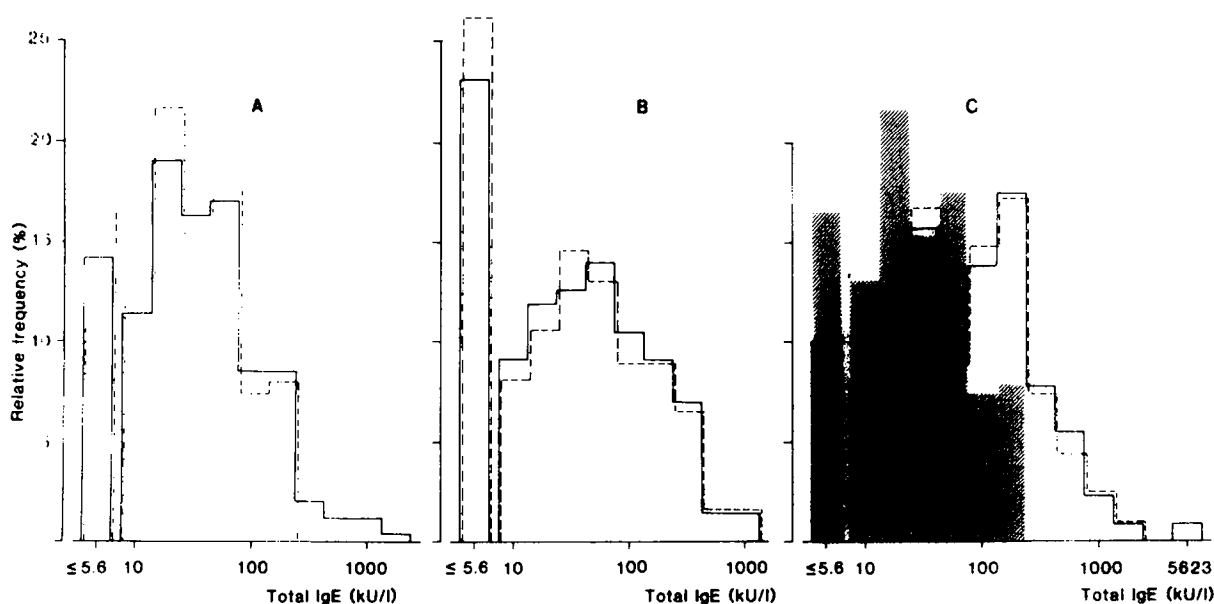


FIG. 1. Distribution of total serum IgE in (A) controls collected at a general health survey control ($n = 246$), in (B) patients with nonmalignant pulmonary disorders ($n = 143$) and in (C) patients with bronchial carcinoma ($n = 217$). Broken lines: distribution obtained when individuals with possible clinical atopy were excluded; striped area in C: total IgE levels in the general population.

Patients admitted to the Department of Lung Medicine mainly because of suspected lung cancer but proven to be free of any type of malignancy were chosen as patient controls. The mean age of the group was 59 years, range 17 to 85. There were 106 males and 37 females. The diagnoses included pulmonary infiltrations of proven nonmalignant origin and unspecified bronchopneumonias, cases of observation only, postbronchopneumonic status, pleurisy and postpleurisy status, tuberculosis in the lungs and non-active tuberculosis, chronic bronchitis, hemoptysis, sarcoidosis, benign tumours, bronchiectasis, and pulmonary abscessus.

Two hundred and forty-six adults from the county of Uppsala consecutively attending a general health survey in 1974 served as another reference group. There were 104 males and 142 females in this group. They had a mean age of 45 years, range 17 to 80.

Those individuals who had previous or current symptoms suggesting allergy, i.e., asthma, rhinitis, urticaria, or eczema, were considered as having a possible clinical atopy. None of the patients or controls had signs or symptoms suggesting parasitic infection.

Total and specific IgE antibodies

Total IgE levels in serum were measured with a paper radioimmunoassay technique according to the manufacturer's instructions (Phadebas IgE PRIST; Pharmacia Diagnostics AB, Uppsala, Sweden). All samples were examined in duplicate. Specific IgE antibodies were determined for all subjects having a total IgE >20 kU/L (the same as >20 IU/ml) against common allergens found in the Uppsala area, including common silver birch, cocksfoot, timothy

grass, dandelion, mites, and cat epithelium. The radioallergosorbent test (RAST) (Phadebas RAST; Pharmacia) grades the reactivity to an allergen in five classes: class 0, no detectable level of specific IgE antibodies; classes 1 to 4, increasing levels of specific IgE antibodies with increasing numbers. Serological atopy was defined according to two different principles. The more restrictive definition—named type A—included a total IgE >40 kU/L combined with detectable levels of specific IgE antibodies (graded as $\geq$ class 2) against two or more allergens or, alternatively, a total IgE >120 kU/L combined with detectable levels of specific IgE antibodies (graded as $\geq$ class 1) against one or more allergens. The broader definition of serological atopy—named type B—included the criteria of a total IgE >40 kU/L combined with detectable levels of specific IgE antibodies (graded as $\geq$ class 1) against one or more allergens.

All serum samples were kept frozen until analyzed in sequence, in order to minimize the coefficient of variation. The intra-assay and day-to-day variation of the IgE measurements was 12%. The coefficient of variation of specific IgE measurements varied between 4.1% and 10.8%, depending on the allergens tested.

Statistical analyses

The chi-square test was used to study the differences in median total IgE level between the various populations. To test for differences in observed frequencies of serological atopy, Fisher's exact test was used. The actuarial probabilities were calculated, and the significance between the survival curves was tested by the Wilcoxon and the log-rank test.

TABLE I. Total serum IgE levels and prevalence of clinical atopy in health survey controls, patient controls, and patients with bronchial carcinoma

	Total number	Number atopic	Percent atopic	Median total IgE (kU/L) (actual ranges)	
				Nonselected populations	Nonatopic populations
Health survey controls	246	71	28.8*	21.0‡ (≤5-1,200)	17.0‡ (≤5-163)
Patient controls	143	24	16.8†	24.8§ (≤5-920)	23.2§ (≤5-920)
Bronchial carcinoma population	217	14	6.5	48.3 (≤5-4,600)	43.8 (≤5-1,745)

p value vs bronchial carcinoma population (Fisher's exact test): *p < 0.001; †p < 0.05.

p values vs bronchial carcinoma population (χ^2 of medians): ‡p < 0.001; §p < 0.025.

TABLE II. Frequency of serological atopy in health survey controls, patient controls, and patients with bronchial carcinoma

	Total number of patients	Percent serological atopy of type A*	p value†	Percent serological atopy of type B‡	p value†
<i>Nonselected</i>					
Health survey controls	246	8.1	n.s.	21.1	<0.001
Patient controls	143	10.5	n.s.	25.2	<0.05
Bronchial carcinoma population	217	11.1	—	35.4	—
<i>Nonatopic</i>					
Health survey controls	175	2.3	<0.01	16.0	<0.001
Patient controls	123	9.8	<0.01	22.7	<0.05
Bronchial carcinoma population	203	9.4	—	34.5	—

*Total IgE >40 kU/L + positive RAST (≥ class 2) against 2 allergens; or total IgE >120 kU/L + positive RAST (≥ class 1) against ≥ 1 allergen.

†Compared to the bronchial carcinoma population (Fisher's exact test, two-sided test).

‡Total IgE >40 kU/L + positive RAST (≥ class 1) against ≥ 1 allergen.

RESULTS

Total serum IgE levels in health survey controls, in patients with nonmalignant pulmonary disorders, and in patients with bronchial carcinoma

The distribution of total serum-IgE levels in 246 controls collected at a general health survey is presented in Fig. 1. The median IgE level was 21.0 kU/L. When those individuals who had possible clinical atopy (29%) were excluded, the median IgE level was 17.0 kU/L. The distribution of total IgE levels in the nonatopic population is also illustrated in Fig. 1. The two distributions are largely log normal. No significant sex or age dependency of total IgE levels was found.

The patient control group, consisting of 143 patients with nonmalignant pulmonary disorders, had a

median total IgE level of 24.8 kU/L, which was not significantly raised as compared to the health survey controls (Table I). Seventeen percent of the patients suffered from possible clinical atopy. The nonatopic patients had a median total IgE level of 23.2 kU/L. The distribution of total IgE in the patient controls was similar to the distribution of total IgE in the health survey controls (Fig. 1). No significant sex or age dependency of total IgE levels was found (data not shown).

The median total IgE level in the group of 217 bronchial carcinoma patients was 48.3 kU/L, and with cases with possible clinical atopy (6.5%) excluded, it was 43.8 kU/L; both frequencies are significantly elevated as compared to the health survey controls (Table I) or patient controls. In contrast to the near log normal distribution of total IgE levels ob-

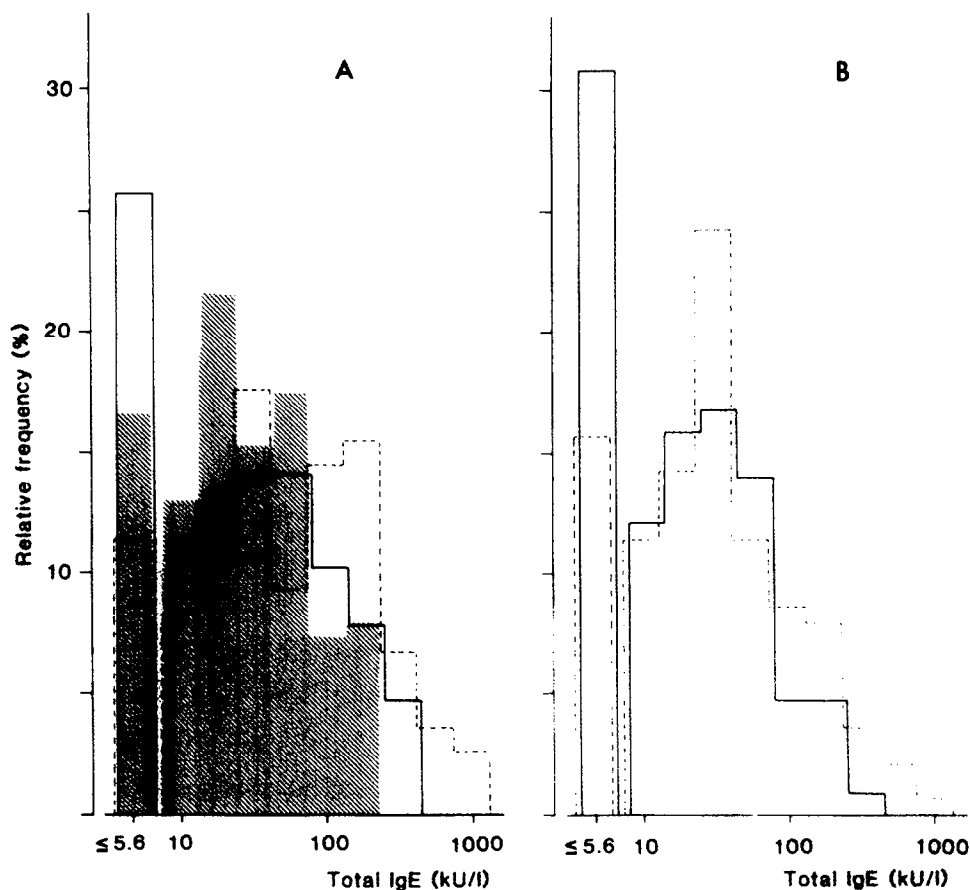


FIG. 2. Distribution of total serum IgE in (A) the cancer patients and in (B) the patient controls after exclusion of individuals seropositive according to criterion A (broken line) or criterion B (solid line). For definition of criteria A and B see Table III. Striped area: distribution of total serum IgE in the general population.

served in the controls, the distribution of total IgE in patients with bronchial carcinoma showed two distinct peaks (Fig. 1). Thus this group of patients seemed to be subdivided into two populations, one with an IgE antibody distribution comparable to the control groups and one with elevated total IgE levels. Data on total serum IgE levels and prevalence of possible clinical atopy in the groups studied are summarized in Table I.

Allergen-specific IgE antibodies in health survey controls, in patients with nonmalignant pulmonary disorders, and in patients with bronchial carcinoma

The frequency of serological atopy according to the more restricted definition (type A; see Material and Methods) was 11.1% in the patients with bronchial carcinoma. This figure did not differ significantly as compared to the patient controls or the healthy controls (Table II). When the cancer patients with possi-

ble clinical atopy were excluded, the frequency of serological atopy was significantly raised over that of the nonatopic controls ($p < 0.001$). With the broader definition of serological atopy (type B) 35.4% of the nonselected and 34.5% of the nonatopic cancer patients were positive. These frequencies were significantly higher than those found in the controls (Table II).

The distributions of total IgE levels after exclusion of the individuals with type A serological atopy was near log normal in the two control groups, whereas the cancer population showed two peaks (Fig. 2). After exclusion of type B serological atopy the distribution curve of the cancer population also became near log normal.

Quantitation of specific IgE reactivity against the various allergens revealed a similar interallergen distribution of positive RAST results in the groups studied (Fig. 3). The highest frequency of positive RAST results was observed against cocksfoot, dandelion,

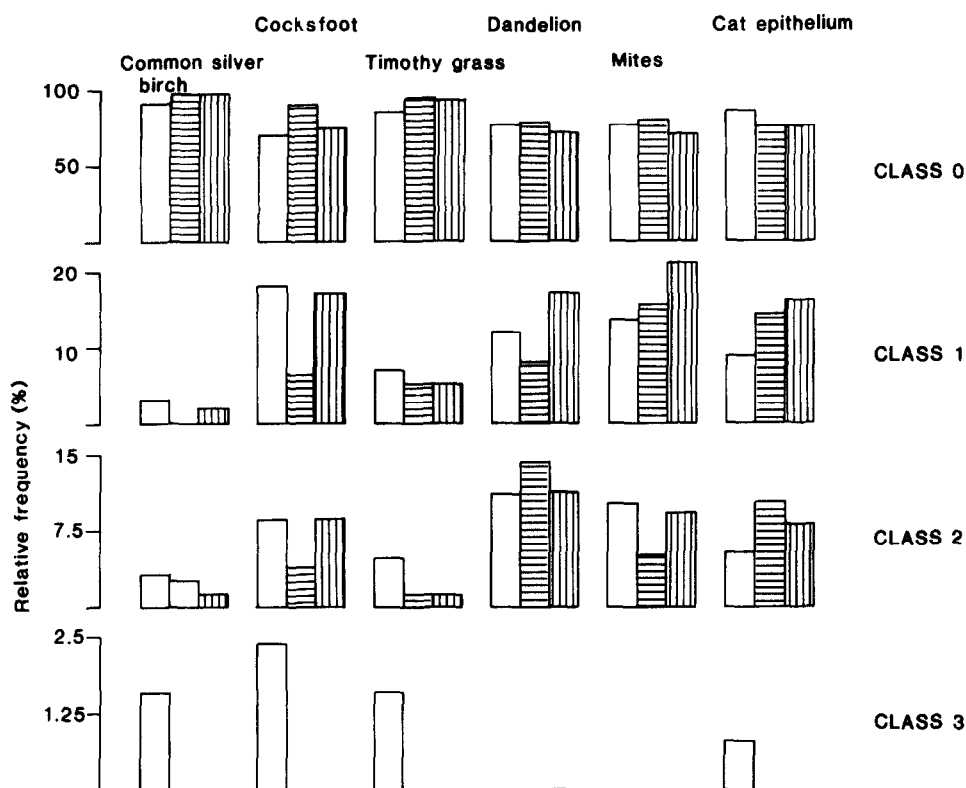


FIG. 3. Specific IgE antibodies to six allergens (common silver birch, cocksfoot, timothy grass, dandelion, mites, and cat epithelium) in health survey controls (□), patient controls (▨) and patients with bronchial carcinoma (▩). The relative frequencies of individuals within each population with no (class 0) and with detectable levels of specific IgE antibodies (classes 1 to 3) are presented.

mites, and cat epithelium. The scoring of RAST revealed that classes 1 and 2 were predominant in all populations.

Total and specific serum IgE levels in the WHO histological groups of bronchial carcinoma

The distributions of total IgE levels in the patients with bronchial carcinoma subgrouped in the WHO histological groups I to IV are shown in Fig. 4. Although groups I (squamous cell carcinoma), II (small cell carcinoma), and IV (large cell carcinoma) had a distribution similar to that for the total cancer population, group III (adenocarcinoma) had an IgE distribution similar to that of the controls. The median total IgE level in WHO III was 28 kU/L, which was not significantly different from the IgE levels of the control populations but significantly reduced from the IgE levels in WHO groups I and II (Table III).

The frequencies of serological atopy did not differ significantly between the WHO groups, although tendencies were noted for the highest frequency to be in

individuals in WHO groups I and II (Fig. 5). The relative interallergen distribution of positive RAST results revealed no apparent differences between the WHO groups (data not shown).

Survival in patients with bronchial carcinoma in relation to serum IgE levels

When the patients were subgrouped in WHO histological groups, the best prognosis was evident among patients of WHO group III, with 19.0% surviving more than 3 yr. Corresponding figures for WHO groups I, II, and IV were 5.8%, 0, and 4.8%, respectively. Patients in WHO group III also had, as pointed out above, the lowest total IgE levels at time of diagnosis. As seen in Table IV, no differences in IgE levels related to prognosis was found in WHO group III. In contrast, significantly lower IgE levels were noted in patients of WHO group I with a survival of more than 2 yr than in WHO group I patients who died within 12 mo from diagnosis (Table IV). The actuarial survival rates of patients of WHO group I subgrouped into RAST-positives and RAST-nega-

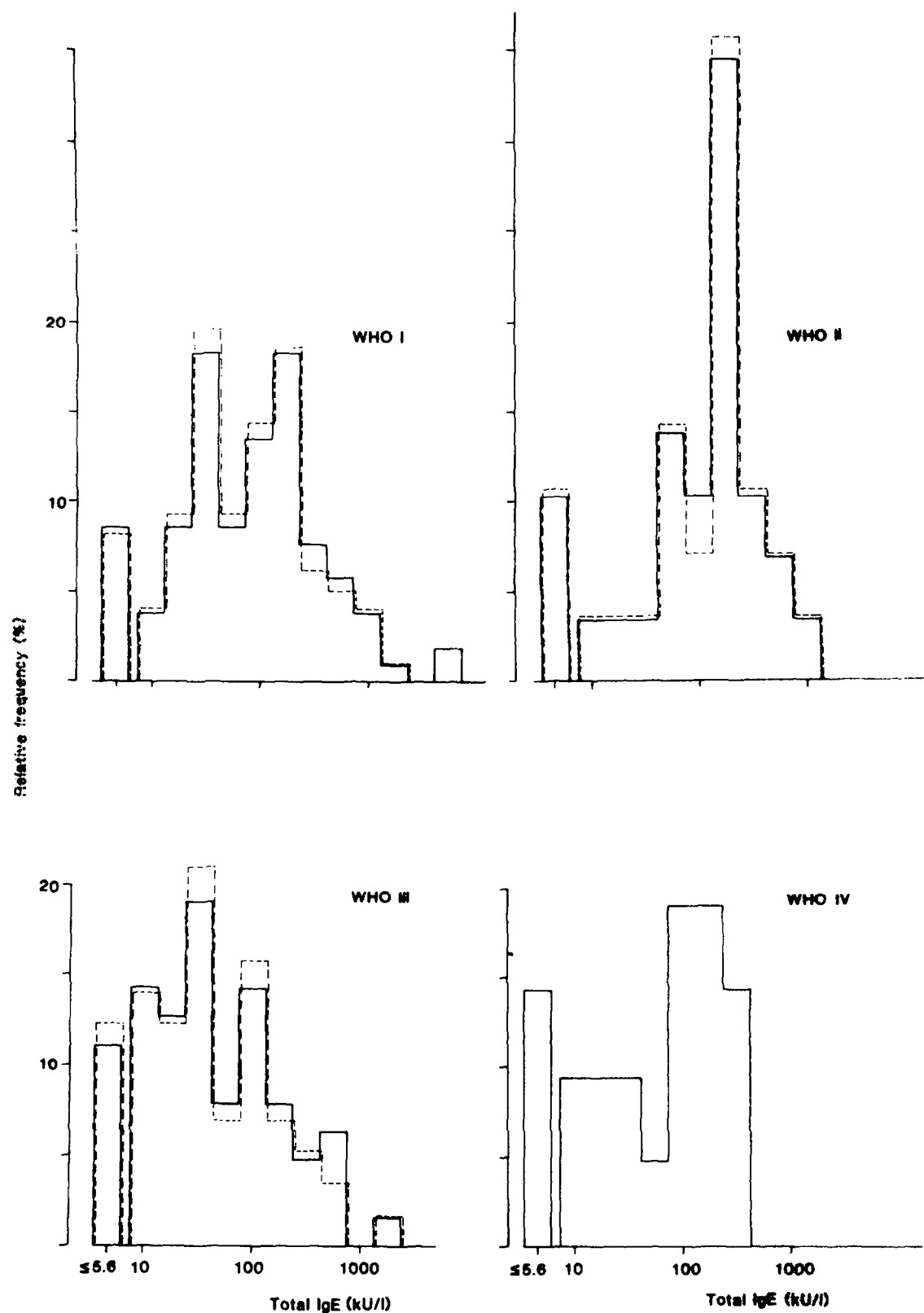


FIG. 4. Distribution of total IgE levels in patients with bronchial carcinoma with the WHO histological types I to IV. Broken lines: distributions obtained when individuals with possible clinical atopy were excluded.

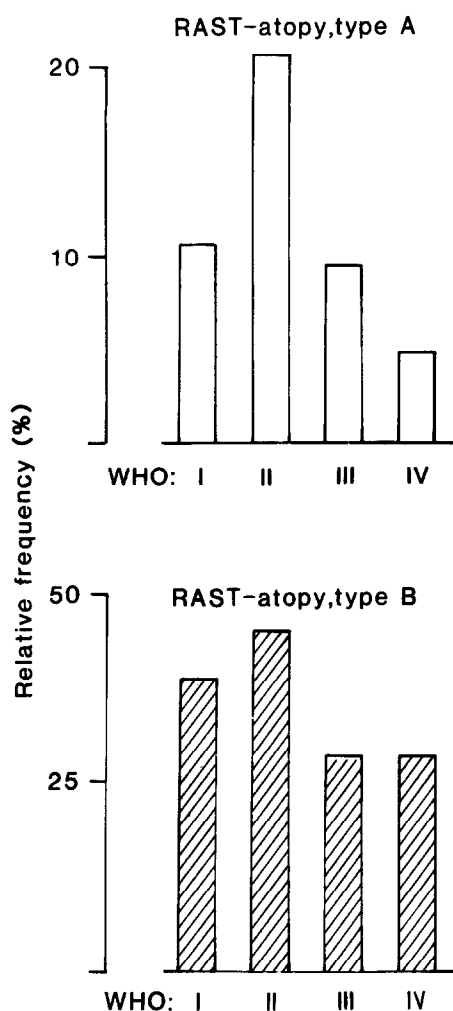


FIG. 5. Frequency of serological atopy types A and B in WHO histological groups I to IV.

tives described different curves, suggesting that RAST-positive patients had a worse prognosis (Fig. 6). Those operated patients of WHO I who had a total IgE <40 kU/L ($n = 13$) had significantly longer survival ($p < 0.025$) than those operated patients of WHO I who had a total IgE >100 kU/L ($n = 10$).

DISCUSSION

It has been suggested that atopic diseases are less common in patients with malignant diseases but other studies have shown no such correlation.¹⁻⁷ Observations on total serum IgE levels in serum of cancer patients have also been conflicting; increased, normal, or even reduced levels have been reported.⁹⁻¹³ In the present study, patients with bronchial carcinoma were less likely than the general population to have a positive history of clinical atopy in spite of significantly elevated serum IgE levels in the cancer patients. The reasons for these conflicting results are not

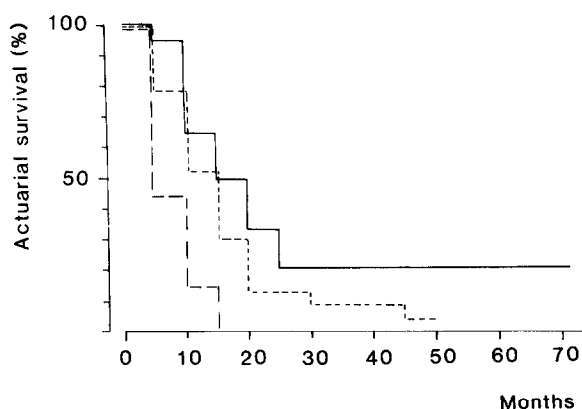


FIG. 6. Actuarial survival rate of patients with bronchial carcinoma of WHO histological type I, stages 1 and 2, related to serological atopy. Solid line: patients without serological atopy ($n = 40$); small-dashed line: patients with serological atopy type B ($n = 23$); large-dashed line: patients with serological atopy type A ($n = 7$). The small-dashed and large-dashed curves were significantly ($p < 0.05$ and $p < 0.001$, respectively) different from the solid curve as tested by the log-rank test.

immediately clear. However, the recent finding that only malignancy of endodermal origin, but not of mesodermal or ectodermal origin, was negatively correlated to respiratory atopy⁷ suggests that the discrepancies in results might relate to differences among the various investigators with regard to type of allergy and malignancy considered. The conflicting IgE data reported in cancer patients might also relate to type of malignancy investigated and to type of IgE quantitation technique used. Only the double-antibody method and the direct sandwich method used in the present study are reliable for the quantitative measurement of low serum IgE levels.^{16, 17}

Our observation of the low frequency of clinical atopy among bronchial carcinoma patients has support in a recent prospective study on the development of primary lung cancer in chronic asthma sufferers.⁶ According to this study, 0.032% of the subjects developed bronchial carcinoma, i.e., some 10% of the incidence in the general population. In our study we found about a five times higher frequency of various types of atopic diseases in the general population than in the cancer population. Admittedly, the frequency of asthmatic disorders may have been underestimated in our cancer patients, since their asthmatic symptoms, particularly mild ones, might have been missed in domination of chronic bronchitis symptoms induced by smoking. In the present report as many as 85% of the cancer patients were smokers as compared to approximately 40% of the general population.

The total IgE level is generally higher in atopic than

in nonatopic individuals, but elevated IgE levels are not invariably associated with clinical atopy, as illustrated by the present findings in bronchial carcinoma patients. IgE increases are also observed in most individuals infected with helminths.¹⁸ However, it seems unlikely that parasitic infections have had influence on our reported IgE levels in patients or controls due to the extremely low prevalence of such infections among adults in the county of Uppsala. For estimation of the concentration of IgE antibodies against various allergens, the RAST has been used. Significant correlations have been found between the results of RAST and those of skin tests and provocation tests.^{19, 20} In the present study we found that elevated IgE and positive RAST were associated with a history suggesting clinical atopy in the control population. Since the total IgE level can be regarded as the sum of specific antibodies against various antigens, elevated total IgE levels in bronchial carcinoma patients without clinical atopy may reflect IgE antibodies not directed against common allergens but against a bronchial carcinoma-associated antigen. This idea, however, seems less likely because a higher frequency of serological atopy was found in the cancer population than in the general population and because the most common positive RAST reactions were observed against the same allergens in all populations. Moreover, when patients with serological atopy were excluded from the cancer population, the remaining IgE levels were no longer significantly raised as compared to those of the control populations.

Based on the RAST data, the low incidence of clinical atopy in the cancer patients seems even more difficult to understand. However, it must be remembered that our knowledge of mechanisms behind manifest clinical atopy is imperfect. The presence of circulating specific IgE antibodies is certainly not the only prerequisite for the appearance of allergic symptoms. At present it is believed that one mechanism behind an atopic predisposition relates to an increased local production of IgE due to increased immune response on normal exposure to common allergens. However, it is also clear that the incidence of atopy increases by increased dose and time exposure of allergens. One may then speculate that smoking, frequently observed in bronchial carcinoma patients, may induce defects at the epithelium or basement membrane in lung tissue permitting an easier penetration of soluble antigens across the epithelium and thereby enhancing sensitization. Another explanation of raised total IgE levels in bronchial carcinoma is based on experimental findings on rats, which when depressed in suppressor T-cell activity, are more apt to react with enhanced formation of reaginic an-

TABLE III. Total IgE in the WHO histological groups of bronchial carcinoma

Histological group	n	Median total IgE kU/L	p value*
WHO I	104	64.2	<0.05
WHO II	29	133	<0.01
WHO III	63	28	--
WHO IV	21	78.5	n.s.

*Compared to WHO type III (χ^2 of medians).

TABLE IV. Median IgE levels (kU/L) and different survival in patients with bronchial carcinoma

Survival (months)	Histological group							
	WHO I		WHO II		WHO III		WHO IV	
	n	IgE	n	IgE	n	IgE	n	IgE
<1 ≤ 12	49	99.0*	12	66.1	28	28.2	14	81.2
>24	13	23.0*	0	—	17	29.3	2	—

*p < 0.05 by χ^2 test of medians.

tibodies.^{21, 22} By analogy, patients with carcinoma may have a suppressed cellular immunity and, in consequence, may react with specific IgE antibody formation against allergens in the environment. The idea that patients with bronchial carcinoma may have a depressed cellular immune reactivity is supported by the demonstration of decreased levels of circulating thymus-dependent lymphocytes and an impaired in vitro reactivity of the lymphocytes to phytohemagglutinin.²³

The observation that raised IgE levels in cancer patients were related to a bad prognosis could also be explained in terms of suppressed cellular immunity leading to weak immune defense against the growing neoplasm. Patients with bronchial carcinoma classified as adenocarcinoma (WHO histological group III) had a better prognosis than did patients with squamous cell carcinoma, small cell carcinoma, and large cell carcinoma (WHO histological groups I, II, and IV). The WHO group III was the only cancer group which had a median total IgE level not different from the general population, suggesting that patients with adenocarcinoma in general may have an unimpaired cellular immunity controlling the cancer growth. Previous data also indicate that the cellular immunity is less often affected in patients with adenocarcinoma than in patients with squamous cell carcinoma.^{24, 25} In the present report the favorable prognosis with nonelevated IgE levels was also demonstrated in patients with squamous cell carcinoma.

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