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On the Relationship between Type I Hypersensitivity and Cancer: A Review

Shih Jui[1] and Zhang You-hui[2]

The relationship between allergy, and cancer has received much attention [1-9] since the 1950's. Most people think that there is, indeed, a correlation between the two, but a few have reached different conclusions. Clarification of these conflicting results may be useful in developing new approaches in cancer prophylaxis and treatment.

Clinical observations

Many investigators suggest that an anaphylactic condition may play a possible preventive role in cancer prevention. Almot and Brown [10] showed atopy was a favourable prognostic factor for survival in Hodgkin's disease (HD). One hundred and forty-eight patients with HD were stratified into 4 groups according to atopic status. Group 1 (n = 29) had personal history of atopy and Group 2 (n = 26) had family history of atopy. In Group 3 (n = 31) and 4 (n = 62) there was no history of atopy but high serum IgE level (Group 3) and normal IgE level (Group 4). Comparison of the survival of these groups showed a significant trend (P = < 0.0001) where the number of survival was: Group 1 > Group 2 > Group 3 > Group 4. Adjustment to allow for the variation in each of the other prognostic factors and for a combination of age, symptoms and histology still showed a significant trend of survival on the basis of atopic status. Cockcroft *et al* [11] analyzed 218 patients with malignancy of endodermal origin (lung, gut,bladder, prostate), 104 patients with mesodermal malignancy (tumors of the hematopoietic system and genitourinary system), 70 patients with ectodermal malignancy (skin and breast) and 303 age-and sex-matched controls. There was a significantly lower frequency of respiratory allergy in patients with endodermal malignancy when compared with their matched controls (6.4% versus 13.2%, P < 0.005). There were no significant differences among any of the other groups. Six thousand and twenty-one chronic asthma sufferers over 40 years old were analyzed by Ford [12] with regard to the development of primary lung cancer and their smoking habits. Over 20 years, only two developed lung cancer (0.032%), while 1,100 (0.314%) lung cancer patients arose from the general population (350,000). The number of people in the general population who developed lung cancer was about 10 times higher than with chronic asthmatics. A fact worth mentioning, was that about 15 percent of the asthma patients in this survey had received at one time or another during the 20-year period long-term immunosuppressive therapy with corticosteroids and/or desensitization therapy but none of them developed lung cancer or neoplasia of any kind. It is possible that asthmatic patients have a protective immune mechanism against cancer. However, a few authors have obtained different results. Hughes and Raitz [13] found that in the allergic population of 500 persons in their cancer prone age, there were 12 malignancies, while the nonallergic group of 421 individuals had 14 malignancies. There was no significant difference in the incidence of malignancy between the allergic and nonallergic groups ($X^2 = 0.75$).

The role of IgE in immune response to cancer

Total serum IgE levels have been found to be elevated, normal, or decreased in patients with different tumors. Only in Hodgkin's disease

From the [1]Department of Immunology and [2]Cancer Institute, CAMS Beijing, China

Correspondence : Dr. Shih Jui

does an increase of serum IgE seem to be a constant finding.

With a conventional double-antibody sandwich technique, total IgE levels in 35 serum samples from malignant lymphoma patients and 35 matched normal controls was measured by ELISA. It was found that there was a statistically higher total IgE levels in patients than in the control ($p < 0.005$), indicating an obvious correlation between an elevated IgE and malignant lymphoma (Table 1).[14] Total IgE level in 46 serum samples from esophagus cancer patients, 42 near carcinoma, 47 severe dyplasia and 46 normal controls were also measured.[15] No differences were found in IgE levels among these four groups ($P > 0.05$) but an obvious trend was accompanied with the elevated IgE concentration in the processing of esophagus cancer (Table 1).

Elevated levels of IgE have also been reported in bronchogenic carcinoma. Total IgE and specific IgE antibodies against six common allergens were measured in the sera of 217 unselected patients with bronchogenic carcinoma by Hällgren *et al*[16] Their median total IgE level was significantly increased as compared to that in two control populations consisting of 246 individuals in the general population and 143 patients with benign pulmonary disorder. The titer of specific IgE antibodies was also significantly increased in the cancer patients. Patients with adenocarcinoma had the best prognosis and also had non-elevated IgE levels in contrast to patients with squamous-cell carcinoma and small- or large-cell carcinoma. The favorable prognosis with non-elevated IgE levels also was demonstrated in patients with squamous-cell carcinoma. Hällgren held that high IgE-related poor prognosis in cancer patients could be due to suppressed cellular immunity leading to weak immune defense against the growing neoplasm.

Blőndal and Nou[17] found that serum IgE in 107 patients with bronchogenic carcinoma was significantly elevated. This elevation appeared to occur early in the course of disease, or possibly before the development of carcinoma. T cell dysfunction or a fall in T cell levels has been assumed to give rise to high IgE concentrations. Immune status in general and T cell count in particular have been reported to be reduced in bronchogenic carcinoma. There are results which would support the concept of a link between T cells and serum IgE, one being the fact that the highest IgE values are seen in the most aggressive form of carcinoma (small cell carcinoma).

Ownby *et al*[18] investigated the relationship between Ig levels and length of survival in breast carcinoma patients. IgG, IgA, IgM and IgE levels in 400 breast carcinoma patients were determined before operation. They were followed up for 55 months and 65 cases died. The allergic status of patients were tested with multi-antigens (RAST). The survival time of patients with levels above and below the means for each class of Ig was compared. Only IgE and IgM were related to survival. Patients with IgE below the mean

Table 1. Tendency of serum total IgE levels of patients with esophageal cancer in Lin–xian, Henan Province, China

	normal (52) : severe dyplasia (48)	normal (52) : near carcinoma (45)	normal (52) : carcinoma (53)
mean	97.2212 : 107.6458	97.2212 : 133.3111	97.2212 : 144.566
T=	0.4025	1.1031	1.7991
P	> 0.6882	> 0.05	> 0.05

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	near carcinoma : carcinoma	near carcinoma : severe dyplasia	carcinoma : severe dyplasia
mean	133.31 : 144.566	133.31 : 107.64	144.566 : 107.64
T=	0.3261	0.733	1.2639
P	> 0.7451	> 0.05	> 0.292

Carcinoma (53) 144.566 > near carcinoma (45) 133.3111 > severe dyplasia (48) 107.648 > normal (52) 97.2212
(The number of subjects are in parenthesis)

level survived longer than those with IgE above the mean ($P = 0.02$). Patients with IgM below the mean level survived longer ($P = 0.01$). The patients were divided into three groups according to their IgE, IgM, RAST with antigens and tumor estrogen receptor. The five-year survival rate was 94 percent in low-risk group, 85 percent in median-risk group and 67 percent in high-risk group. The serum IgE and IgM levels are significant prognostic indicators in primary breast carcinoma, especially when multi-RAST and estrogen receptor status are put under consideration. Radioimmunoassay of the CEA, gastrin and IgE was performed in the blood serum of more than 300 esophageal and gastric cancer patients by Mapxomehko *et al.*[19] They considered an increase in the IgE level a risk factor. But Augustin[20] and Winters *et al*[21] showed no significant difference in the geometric mean serum IgE level between cancer subjects (sarcoma, melanoma, breast carcinoma, colon and lung cancer, etc) and the control. This conflicting result may be related to the difference in the types of malignancy investigated and to the technique of IgE quantitation used. Currently, only the double-antibody method and the direct sandwich method are regarded reliable for quantitative measurement of low serum IgE levels.

Evidence from animal experiments

Early in 1970, animal experiments not only revealed the relationship between allergy and cancer, but also succeeded in rejecting neoplasm by the induction of a local immediate anaphylactic reaction at the site of tumor growth. The possible preventive role of anaphylaxis on tumor development was further evaluated by Correnti *et al.*[22] Mice sensitized with egg albumin (EA) adsorbed to $Al(OH)_3$ were treated with 3-Methylcholanthrene. The sensitized mice had significantly lower incidence of sarcoma in comparison to the unsensitized controls. In contrast, hyperimmunized animals, which received repetitive doses of antigen and were therefore tolerized for anti-EA IgE production, did not differ from controls in their tumor frequency. Lower tumor incidence (70%) was restricted to the sensitized mice having high IgE titers ($> 1{:}640$). Sensitization and hyperimmunization did not have any significant effect on the latency period. However, sensitized, but not hyperimmune mice, showed significantly longer survival time, which correlated with the secondary anti-EA IgE titer. Animals with low titers ($< 1{:}640$) exhibited a shorter survival period, whereas those with higher IgE responses ($> 1{:}640$) survived longer. Correlation index between both parameters was 0.79 ($p < 0.01$). Maximal tumor size at the end of the experiment was not different between control and the two experimental groups of mice, and did not correlate with their anti-EA IgE levels. The tumor growth rates for 3 experimental groups were 0.090 mm/week (control group), 0.080 mm/week (hyperimmunized) and 0.073 mm/week (high IgE group), respectively. Therefore, the rate of growth appeared to be faster for control than for immunized mice. This results are consistent with those from Lynch and Salomon[23] who found an accelerated rate of tumor rejection in mice when an anaphylactic reaction was induced locally in the tumor.

The informations alluded to above suggest that systemic IgE-mediated hypersensitivity can inhibit tumor development, since a specific, not tumor-related, IgE production is accompanied by a significant decrease in tumor occurrence, an increase in survival time and a decrease in tumor growth rate in sensitized animals. The mechanisms involved have still to be clarified, but at the present time it could be speculated that the release of chemical mediators with vasoactive properties, such as histamine and serotonin, could account for an increase in vascular permeability which would, in turn, enhance the access of humoral and cellular cytotoxic effectors into the tumor tissues. Interestingly, Burtin *et al*[24] treated C57BL/6 and C3H mice carrying methyl-cholanthrene-induced fibrosarcoma with histamine and found that in all treated mice the tumor growth significantly slowed down. In histamine-responsive C3H mice, histological studies showed numerous and large loci of acute hemorrhagic necrosis in the tumors. Then Burtin *et al*[25] studied the effect of histamine and related substance, including histamine, metiamide (anti-histamine type-2 receptor), histamine plus methamide, mepyramine (anti-histamine type-1 receptor), serotonin and methysergide (anti-serotonin). Inhibition of tumor growth with prolonged survival time was observed with histamine and histamine plus metiamide. The best results (both on tumor growth and survival) were obtained with serotonin. Survival was increased by metiamide and decreased by mepyramine and methysergide. In histamine-treated and in serotonin-treated mice the above-mentioned histological findings was observed. Stimulation of histamine type-1 or serotonin receptors and inhibition of histamine type-2 receptors play a beneficial role in the host's defence against tumors.

Burtin *et al*[26] found in patients with solid malignant tumors that the blood histamine level was low in patients with progressive primary tumors or metastasis. He suggested constant monitoring of blood histamine levels for the clinical evaluation of the progression of diseases.

In summary, the effect of type I hypersensitivity on tumor growth is yet a controversial issue. Much needs to be studied and clarified before valuable clues can be obtained for new approaches to cancer prevention and treatment.

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