

Clinical Communications

IgE deficiency is associated with high rates of new malignancies: Results of a longitudinal cohort study

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Clinical Implications

- This longitudinal study found that IgE-deficient patients have higher rates of newly diagnosed malignancy compared with non-IgE-deficient individuals. If these findings are confirmed in larger studies, they would suggest that IgE-deficient patients should be monitored closely for malignancy.

TO THE EDITOR:

Over the past few years, mice and *in vitro* studies found that IgE has a role in antitumor immunity and surveillance, establishing the basis of the emerging field of Allergo-Oncology.¹⁻⁴ In clinical practice, it is not known whether IgE levels are related to the risk of malignancy and whether there is a specific IgE level that confers protection against malignancy. Previous cross-sectional retrospective studies found that the risk and rates of previous malignancy diagnosis were higher in IgE-deficient patients than in non-IgE-deficient individuals.⁵⁻⁷ However, the IgE levels were measured after the malignancy development; therefore, it is not known whether the malignancy itself led to very low IgE levels or vice versa. In an effort to address this question, we performed a longitudinal cohort study, seeking to determine the rate of newly diagnosed malignancy in IgE-deficient patients (IgE < 2.5 kU/L) compared with matched non-IgE-deficient individuals.

In total, 42 IgE-deficient patients with no malignancy diagnosis were identified between 2014 and 2015 at Montefiore Medical Center (Bronx, NY). These patients were randomly matched at the beginning of the study on the basis of age and sex, to 3 groups of patients who had their IgE levels checked during the same time period: normal IgE levels (2.5-100 kU/L), high IgE levels (100-1,000 kU/L), and very high IgE levels (≥ 1000 kU/L). Chart reviews were performed annually, on all patients, until December 2018. Patients with no notes from our medical system providers for the previous 18 months were enquired by telephone about their malignancy status. The final analysis was performed on patients with known information about their malignancy diagnosis either through chart review or by telephone contact: 34 patients with IgE deficiency, 35 patients with normal IgE levels, 38 patients with high IgE levels, and 33 patients with very high IgE levels.

We found that the IgE levels had been ordered mainly by Allergy-Immunology physicians, but other subspecialists were also among the ordering providers (Table 1). Female was the predominant sex in the IgE deficiency group (82.3%), with a median age of 50.5 years (interquartile range, 37.7-64 years),

which led to similar results in the rest of the study groups (Table 1).

The 140 patients were followed for a median of 43.5 months (interquartile range, 39-49 months) from the time of IgE level data collection. Overall, the incidence of malignancy was 7% (10 of 140). The high number of women who developed neoplasia (9 of 10) (Table 1) is probably due in part to the overall higher percentage of women included in the study. The rate of newly diagnosed malignancy was significantly higher in the IgE deficiency group (6 of 34 [17.65%]) than in non-IgE-deficient individuals (4 of 106 [3.8%]; $P = .01$; odds ratio = 5.4; 95% CI, 1.3-22.9) (Figure 1, A). On comparing different IgE levels, we found that the proportion of new cancer was significantly elevated in IgE-deficient patients (6 of 34 [17.65%]) than in those with high (1 of 38 [2.63%]; $P = .04$) and very high (0 of 33; $P = .02$) IgE levels (Figure 1, B). The rate of new malignancy diagnosis was also higher in the IgE deficiency group compared with that in patients with normal IgE levels (8.57% [3 of 35]); however, this difference was not statistically significant ($P = .3$). Likewise, the rates of new cancer diagnosis were not statistically different between patients with normal and high IgE levels and between those with normal and very high IgE levels (data not shown). The different types of neoplasia are presented in Table 1.

Given that common variable immunodeficiency (CVID) may be associated with a higher risk of malignancy⁸ and that patients with CVID have a high rate of very low IgE levels,⁹ we checked how many patients had CVID at the time of malignancy. We found that only 1 patient (1 of 10) had a diagnosis of CVID and also had IgE deficiency (Table 1).

Although the inverse association between atopy (implying high IgE levels) and risk of cancer has been evaluated in different epidemiological studies,¹⁰⁻¹² the focus on the relationship between very low IgE levels and future malignancies is a new approach with potential clinical relevance. To our knowledge, this is the first longitudinal cohort study examining this aspect and we found that IgE-deficient patients have higher rates of newly diagnosed malignancy compared with non-IgE-deficient individuals. An important question rising from our findings is whether serum IgE levels can predict the risk of developing malignancy. In this study, although the rate of new malignancy diagnosis was higher in IgE-deficient patients than in those with normal IgE levels, the difference was not statistically significant. This may be explained by the small sample size, or alternatively, although IgE-deficient patients might be at the highest risk for developing new malignancies, IgE levels considered low or normal might also predispose to cancer development. Another question is whether IgE levels should be checked routinely in all patients (checked mainly by allergists in this study) and whether those with very low IgE levels should be monitored closely for malignancy occurrence.

Although our results are intriguing, our study has several limitations. First, patients had their IgE levels checked for various medical reasons; therefore, these results might not be generalizable. However, a previous National Health and Nutrition Examination Survey study found higher rates of previous malignancy diagnosis in IgE-deficient individuals compared with non-IgE-deficient

TABLE I. Patients' characteristics

Characteristic	IgE < 2.5 (N = 34)	2.5 ≥ IgE < 100 (N = 35)	100 ≥ IgE < 1000 (N = 38)	IgE ≥ 1000 (N = 33)
IgE level, mean ± SD	0.85 ± 0.7	35 ± 30*	247.3 ± 187.4 *	2495 ± 1547*
Medical specialty that ordered IgE level (%)				
Allergy-Immunology	85	77	71	88
Pulmonology	12	11	5*	3*
Primary care	NA	6	8	NA
Oncology	NA	NA	NA	NA
Infectious disease	3	NA	NA	NA
Gastroenterology	NA	3	NA	NA
Inpatient	NA	NA	NA	3
Unknown	NA	3	16	6
Sex: female (%)	82.3	72	73.6	82
Age at the time of IgE collection (y), median (IQR)	50.5 (37.7-64)	54 (34-68)	54 (37.5-69.2)	49 (26.5-64.5)
Race (%)				
White	35	20	13*	15*
Black	21	17	37	33
Hispanic	9	11	16	6
Other/unknown	35	53	34	56
Smoking status (%)				
Ever smoker	21	23	15.7	12
CVID, n (%)	7 (20.5)	2 (6)	0*	1 (3)*
Median (IQR) follow-up time for new malignancy diagnosis† (mo)	44.5 (38.7-49.2)	44 (39-49)	42 (39-46.2)	44 (40.5-50)
Patients with new malignancy diagnosis, n (%)	6 (17.65)	3 (8.57)	1 (2.63)*	0*
IgE level, mean ± SD	0.83 ± 0.82	24 ± 15	157.8	NA
Sex: female, n (%)	5 (83.3)	3 (100)	1 (100)	NA
Age at malignancy diagnosis (y), mean ± SD	56.17 ± 14.54	64.3 ± 7.6	73	NA
Months between IgE collection and new malignancy diagnosis, mean ± SD	25 ± 17.2	35.3 ± 9.5	11	NA
CVID, n (%)	1 (16.7)	0	0	NA
Type of malignancy (n)	Cervical cancer (2)	Breast cancer (1)	Breast cancer (1)	NA
	Chronic lymphocytic leukemia (1)	Lung cancer (1)		
	Marginal zone lymphoma stage 4 (1)	Gastrointestinal stromal tumor (1)		
	Poorly differentiated systemic sarcoma (1)			
	Papillary urothelial carcinoma of renal calyx and renal pelvis (1)‡			

IQR, Interquartile range; NA, not applicable/available.

*P < .05 (in bold); comparisons were made between patients with IgE deficiency (IgE < 2.5 kU/L) and those with normal IgE levels (IgE, 2.5-100 kU/L); patients with IgE deficiency (IgE < 2.5 kU/L) and those with high IgE levels (IgE, 100-1000 kU/L); and patients with IgE deficiency (IgE < 2.5 kU/L) and those with very high IgE levels (IgE ≥ 1000 kU/L).

†Until December 2018.

‡Had associated CVID.

persons,⁶ similar to institution-associated IgE-deficient patients.^{5,7} Second, we do not know exactly when these patients became IgE-deficient and at which level in the IgE production the impairment occurs (eg, B cells, T cells, cytokine production, or receptor signaling). Alternatively, low serum IgE levels could be due to the sequestration of IgE molecules in the tissues affected by neoplasia. Finally, because all cancer information was based solely on chart

review, we do not know how many patients might have had an undiagnosed underlying malignancy.

In conclusion, within an approximate 43-month period, IgE-deficient individuals developed significantly higher rates of malignancy compared with patients with high and very high IgE levels. If these findings are confirmed in larger and longer prospective studies, they would suggest that IgE-deficient patients

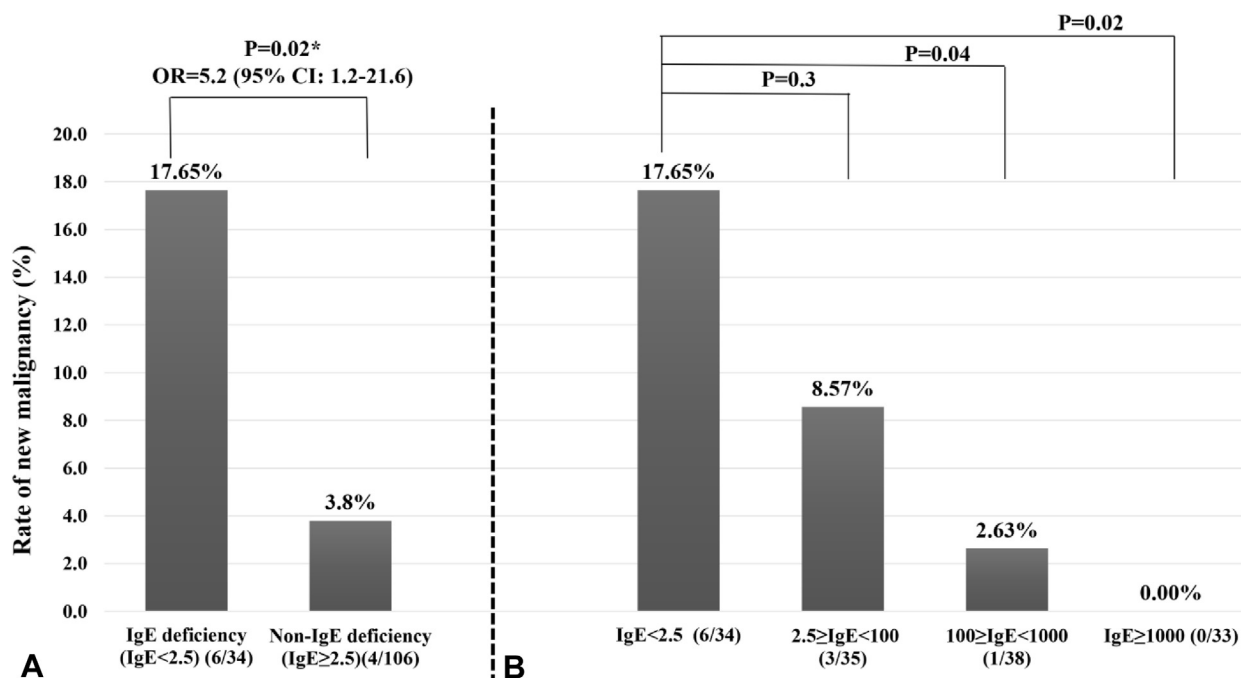


FIGURE 1. (A) The overall rate of new malignancy in IgE-deficient vs non-IgE-deficient individuals. (B) The rate of new malignancy in IgE-deficient patients compared with the other 3 groups with different IgE levels (Fisher exact test). OR, Odds ratio. *Adjusted for race, smoking status, and CVID diagnosis.

should be monitored closely for malignancy. Further research is needed to elucidate the exact pathophysiology underlying this phenomenon.

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