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Relationship between low serum immunoglobulin E levels and malignancies in 9/11 World Trade Center responders

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ABSTRACT

Background: Individuals with very low immunoglobulin E (IgE) levels have a high risk of developing malignancy. Previous studies have revealed that World Trade Center (WTC) responders exposed to carcinogens have an elevated risk of some cancers.
Objective: To evaluate the association between low-serum IgE levels and cancer development in WTC-exposed responders.
Methods: IgE levels were measured in 1851 WTC responders after September 11, 2001. This is the first pilot study in humans comparing the odds of developing cancer in this high-risk population, between the "low-IgE" (IgE in the lowest third percentile) vs "non–low-IgE" participants.
Results: A significantly higher proportion of hematologic malignancies was found in low-IgE (4/55, 7.3%) compared with non–low-IgE (26/1796, 1.5%, $P < .01$) responders. The proportion of solid tumors were similar in both groups (5.5% vs 11.4%, $P > .05$). After adjustment for relevant confounders (race, sex, age at blood draw, WTC arrival time, smoking status), the low-IgE participants had 7.81 times greater odds (95% confidence interval, 1.77-29.35) of developing hematologic cancer when compared with non–low-IgE participants. The hematologic cancers found in this cohort were leukemia (n = 1), multiple myeloma (n = 1), and lymphoma (n = 2). No statistical significance was found when estimating the odds ratio for solid tumors in relation to IgE levels.
Conclusion: WTC responders with low serum IgE levels had the highest odds of developing hematologic malignancies. This hypothesis-generating study suggests that low serum IgE levels might be associated with the development of specific malignancies in at-risk individuals exposed to carcinogens. Larger, multicenter studies with adequate follow-up of individuals with different IgE levels are needed to better evaluate this relationship.

Introduction

In addition to its involvement in type I hypersensitivity reactions[1] and antiparasite response,[2] immunoglobulin E (IgE) plays an important, but less well-known role in antitumor immunity. Clinical studies conducted on different populations describing an inverse association between elevated IgE levels, malignancy risk,[3-7] and survival from cancer[8,9] suggest that IgE may be involved in antitumor surveillance. For instance, among a large cohort of 37,747 individuals from the general population followed prospectively for up to 30 years, those with total serum IgE levels in the highest (second and third) tertiles had a lower risk of developing chronic lymphocytic leukemia when compared with individuals with IgE in the lowest tertile.[5] Conversely, individuals with IgE deficiency (IgE < 2.5 kU/L) who have very low or absent total serum IgE levels have a considerably higher risk of developing malignancy compared with those who have normal or elevated levels of serum IgE,[10-14] further supporting the role of IgE in tumor

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surveillance. Studies have revealed several potential mechanisms underlying IgE antitumor immunity. After binding to high (FcεRI)- and low (FcεRII)-affinity IgE receptors, IgE can promote death of malignant cells through both antibody-dependent, cell-mediated cytotoxicity and antibody-dependent, cell-mediated phagocytosis.[15-18] In addition, IgE-FcεRI-mediated cross-presentation by dendritic cells results in priming of $CD8^+$ T cells against tumor cells, further enhancing cancer immune surveillance.[19] Antitumor IgE can also activate human macrophages and engage these cells to mediate antitumor functions ex vivo.[20]

World Trade Center (WTC)-exposed responders are a unique cohort of individuals, who after the terrorist attack on September 11, 2001 (9/11), were suddenly exposed to large amounts of carcinogenic compounds, such as asbestos, silica, benzene, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, volatile organic compounds, and numerous metals.[21] In the subsequent 10-month recovery effort, these responders were also exposed to toxic fumes from diesel fuel from heavy equipment.[22] In the 7 years after 9/11, there was a 19% excess incidence for all types of malignancies among WTC-exposed Fire Department of the City of New York (FDNY) firefighters, compared with unexposed firefighters.[22] Most of this excess incidence was owing to prostate cancer, thyroid cancer, non-Hodgkin's lymphoma, and melanoma. As part of the long-term WTC Health Program, many of these individuals had serum IgE levels measured shortly after 9/11 allowing an opportunity to prospectively measure the role of IgE in the development of malignancy in an at-risk population of previously healthy adults. We therefore evaluated the association between serum IgE levels and the development of malignancy after September 11, 2001, in this group of WTC-exposed responders. This pilot study is the first in humans assessing the relationship between low- and non–low-IgE levels and cancer occurrence in at high risk for cancer population.

Methods

Study Population

Overall, 11,469 firefighters and emergency medical service providers with no previous diagnosis of cancer self-reported having worked at the WTC disaster site between September 11, 2001, and July 24, 2002 (ie, the date when the site closed). A total of 1851 individuals had at least one IgE measurement after the event (Fig 1): 709 participants had total serum IgE levels measured as part of their first medical monitoring examination within 6 months after the WTC attacks (between September 26, 2001, and March 28, 2002), whereas 1142 WTC responders had IgE levels measured at times more than 6 months after the 9/11 attacks (1099 individuals had IgE levels measured between November 20, 2013, and June 18, 2015, as part of another WTC study[23] and 43 responders had an IgE measurement as part of medical testing at any other time during the study period).

Demographic data were obtained from the FDNY employee database. Participants' race, sex, date of birth, and self-reported smoking status (current, former, or never smoker) and time of initial arrival at the WTC site were assessed during routine medical monitoring examinations at FDNY (both active-duty workers and retirees are scheduled to have a monitoring examination once every 12 to 18 months). Individuals were further classified based on the day they first worked at the WTC site: either on September 11, 2001 or on September 12, 2001, and after.

Total Serum Immunoglobulin E Levels as Exposure Data

Serum was stored at −80°C until processed, and serum samples were analyzed for total IgE levels using MILLIPLEX MAP Human Immunoglobulin IgE Single Plex Magnetic Bead Kit—Isotyping Assay. IgE levels were measured in nanogram per milliliter which were then converted to kilounit per liter (1 kU/L is equal to 2.4 ng/mL[24]). The lowest detectable IgE level using this technology was 4.8 ng/mL, equivalent to 2 kU/L.

None of the study participants were found to have IgE deficiency (IgE < 2.5 kU/L). The lowest IgE in the entire cohort was 4 kU/L. Given that the prevalence of IgE deficiency is approximately 3% in the general population,[12,25] and because this was the group with the highest risk of malignancy in previous studies,[11,12,14] all responders with IgE levels in the lowest third percentile (IgE < 36.58 kU/L) were categorized as having "low IgE" levels. Remaining patients with IgE more than or equal to 36.58 kU/L (non-low IgE) were further categorized into cohorts of patients with "normal IgE" (36.58 kU/L ≤ IgE < 100 kU/L), "high IgE" (100 kU/L ≤ IgE < 1000 kU/L), and "very high IgE" (IgE ≥ 1000 kU/L) levels.[10]

Cancer Outcome Data

The methods used to obtain information on cancer diagnoses are described elsewhere.[22,26] Briefly, cancer diagnoses were ascertained by the following 2 methods: (1) by linkage to state cancer registries[27] and (2) medical record confirmation of cases reported to the Fire Department Bureau of Health Services. Specifically, confirmation was completed by a trained clinician who contacted participants reporting a cancer not already identified through state cancer registry matches and requested documentation. Only confirmed cancers, either by medical records or as obtained from any state cancer registry match, diagnosed between September 12, 2001, and December 6, 2020, were included in this study. The study was approved by the institutional review board.

Statistical Analyses

Although analyzing the responders who had IgE levels measured within 6 months after the WTC event separately reduces the potential bias of having a malignancy diagnosis before the IgE level was tested, the cohort size was too small to allow us to perform only this type of analysis. Therefore, we present the results of malignancy occurrence in the entire population of WTC responders who had their IgE levels measured after 9/11 and in the subgroup of participants who had their IgE levels tested within the first 6 months after WTC attacks.

Demographics and other characteristics of the source population and of those individuals with total serum IgE levels were assessed as proportions and median (interquartile range [IQR]), with Kruskal-Wallis and χ^2 tests used to evaluate differences, as appropriate. Time from IgE measurement to cancer diagnosis was calculated using the diagnosis closest to the blood collection date. For participants with multiple IgE measurements (n = 143), we used the lowest IgE value for the primary analyses, and the earliest value in sensitivity analyses.

The Cochran-Mantel-Haenszel method was used to evaluate the association between the exposure (IgE levels) and outcome (cancer), stratifying by a priori confounders. Confounders were selected based on theory by the common cause criterion in lieu of traditional statistical selection methods[28] to reduce the potential for bias in estimating the causal relationship between IgE level and incidence of a malignancy. The confounders were selected based on existing knowledge of the relationship between IgE levels and cancer. The stratification variables were race (White vs non-White), sex, age at blood draw (in 5-year groupings), time of arrival at WTC site (on September 11, 2001, vs arrived later), and smoking status (ever smoking vs never smoking). Each exposure-confounder-outcome combination was assigned a unique stratum. Data were aggregated and common odds ratios (ORs) were calculated across all strata. Exact 95% confidence intervals (CIs) were then computed. Database management and statistics were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

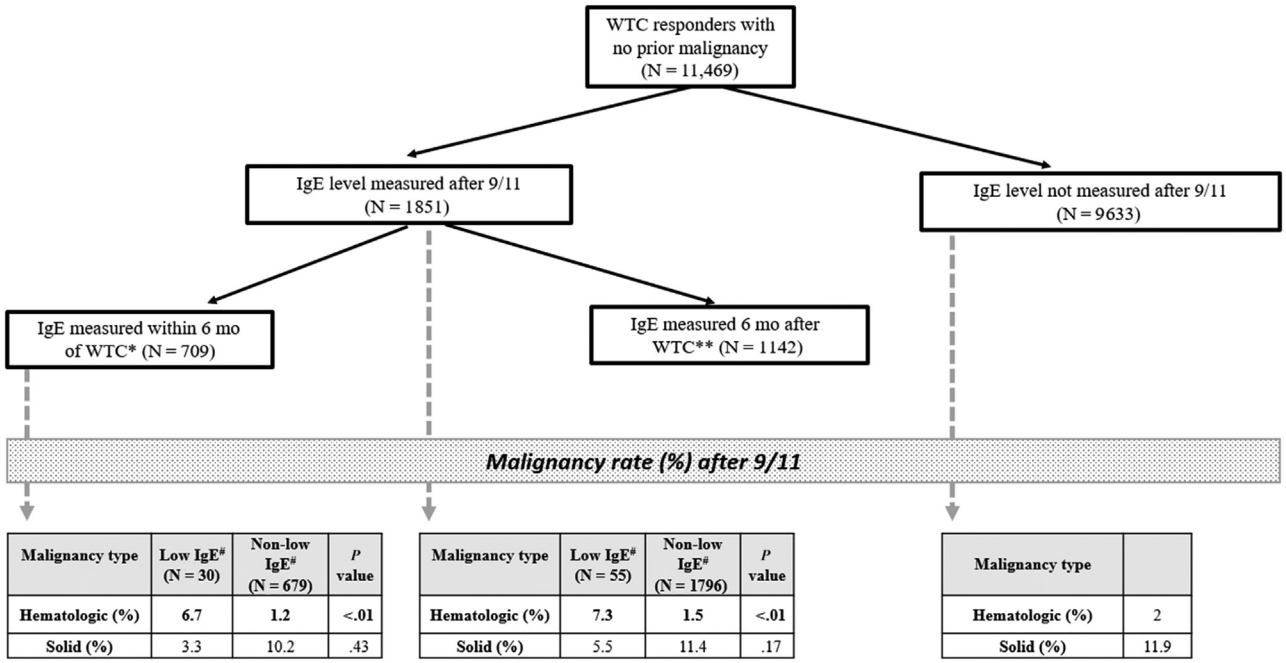

Figure 1. Study patients and malignancy (%) in WTC responders based on IgE levels. Asterisk denotes IgE levels measured between September 26, 2001, and March 28, 2002. Double asterisks denote 1099 individuals who had IgE levels measured between November 20, 2013, and June 18, 2015, as part of another WTC study and those who had IgE measurement as part of medical testing at another time after March 28, 2002 (n = 43). Hashtag denotes responders with IgE in the lowest third percentile who were categorized as having "low-IgE" levels. Remaining patients formed the "non–low-IgE" group. IgE, immunoglobulin E; WTC, World Trade Center.

Results

Demographic and Clinical Characteristics of World Trade Center Responders With and Without Immunoglobulin E Measurements

Table 1 reveals the demographic and clinical characteristics of WTC responders. Most were male firefighters of White race, in their 40s. Participants in whom IgE levels were measured (N = 1851) had a higher proportion of responders in the morning of September 11, 2001 (69.3%), compared with those who did not have IgE measured (N = 9633) (57.4%, $P < .01$). Both cohorts with and without IgE levels available had a similar proportion of a hematologic cancer (1.6% vs 2%, $P = .29$) or a solid tumor (11% vs 11.9%, $P = .26$) diagnosis after 9/11. On average, a diagnosis of malignancy was made 12.1 years (IQR, 7.2-15.9) after 9/11 in those who had IgE level measured and 11.6 years (IQR, 7.7-15.6; $P = .75$) in those without an IgE level measured.

Characteristics of World Trade Center Responders Who Had Immunoglobulin E Levels Measured

Demographic Characteristics

Among the 1851 participants who had IgE levels measured after 9/11, 55 individuals had IgE levels in the lowest third percentile and comprised the group with low IgE level (IgE < 36.58 kU/L; median

Table 1
Characteristics of All WTC Responders

Characteristics	Cohort with IgE level available (n = 1851)	Cohort with no IgE level available (n = 9633)	*P* value
Male sex, n (%)	1818 (98.2)	9320 (96.8)	**<.01**
White race, n (%)	1642 (88.7)	8375 (86.9)	**.03**
Firefighters, n (%)[a]	1670 (90.2)	8200 (85.1)	**<.01**
Age on September 11, 2001, median (IQR)	41.7 (35.1-46.8)	39.9 (33.3-46.4)	**<.01**
Arrival at WTC site on September 11, 2001, n (%)	1282 (69.3)	5531 (57.4)	**<.01**
Malignancy diagnosis, n (%)			
Hematologic malignancy	30 (1.6)	192 (2.0)	.29
Solid malignancy	203 (11.0)	1142 (11.9)	.26
Number of overall malignancies per person, n (%)			
1	202 (10.9)	1152 (12.0)	.32
≥ 2	31 (1.7)	182 (1.9)	
Time elapsing between September 11, 2001 and first cancer diagnosis, y, median (IQR)	12.1 (7.3-15.9)	11.6 (7.7-15.6)	.72
Age at first cancer diagnosis, n (% of total cancers)			
< 30	0 (0.0)	5 (0.4)	.23
30-39	3 (1.3)	35 (2.6)	
40-49	28 (12.0)	186 (13.9)	
50-59	83 (35.6)	481 (36.1)	
60-69	85 (36.5)	411 (30.8)	
70-79	32 (13.7)	177 (13.3)	
> 80	2 (0.9)	39 (2.9)	

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; WTC, World Trade Center.
Note: Bold values indicate P < 0.05.
[a]The source population included firefighters and emergency medical service workers.

Table 2
Characteristics of Responders With Low- and Non-Low IgE Levels

Characteristics	Entire cohort with IgE level checked after the WTC attack (N = 1851)		Cohort with IgE level checked within the first 6 mo after the WTC attack (N = 709)	
	Low IgE level (IgE < 36.58 kU/L) (N = 55)	Non-low IgE level (IgE ≥ 36.58 kU/L) (N = 1796)	Low IgE level (IgE < 36.58 kU/L) (N = 30)	Non-low IgE level (IgE ≥ 36.58 kU/L) (N = 679) *P* value
Age at time of IgE collection, median (IQR)	47.5 (40.6-57.3)	48.7 (42.1-57.0)	42.1 (39.0-47.5)	42.2 (36.2-46.7)
IgE level, median (IQR)	26.0 (19.0-33.4)	188.6 (110.5-351.7)[a]	27.1 (21.0-34.4)	154.5 (87.1-281.4)[a]
Male, n (%)	53 (96.4)	1765 (98.3)	30 (100.0)	679 (100.0)
White race, n (%)	54 (98.2)	1588 (88.4)[b]	30 (100.0)	645 (95.0)
Firefighters, n (%)[c]	51 (92.7)	1619 (90.1)	30 (100.0)	679 (100.0)
Arrival at WTC site on September 11, 2001, n (%)	38 (69.1)	1244 (69.3)	14 (66.7)	508 (73.8)
Ever smoker, n (%)	15 (27.3)	579 (32.2)	8 (26.7)	105 (15.5)
Malignancy diagnosis, n (%)				
Hematologic malignancy	4 (7.3)	26 (1.5)[a]	2 (6.7)	8 (1.2)[b]
Solid malignancy	3 (5.5)	204 (11.4)	1 (3.3)	69 (10.2)
More than 1 malignancy, n (%)	2 (3.6)	29 (1.6)	1 (3.3)	11 (1.6)
Cancer characteristics				
Hematologic malignancies	N = 4	N = 26	N = 2	N = 8
Age at cancer diagnosis, y, median (IQR)	54.6 (50.2-56.8)	61.4 (55.2-64.5)	52.5 (46.2-58.8)	54.3 (46.5-59.3)
IgE level, median (IQR)	29.5 (24.2-31.5)	179.2 (95.5-339.8)[a]	24.3 (19.0-29.7)	125.7 (97.9-362.0)
Arrival at WTC site on September 11, 2001, n (%)	2 (50)	17 (65.4)	1 (50.0)	7 (87.5)
IgE done before cancer diagnosis, n (%)	2 (50)	19 (73.1)	2 (100.0)	8 (100.0)
Years between malignancy and IgE collection, median (IQR)	10.4 (4.1-16.6)	4.4 (2.7-6.4)	10.4 (4.1-16.6)	8.1 (3.4-13.2)
IgE done after cancer diagnosis, n (% total)	2 (50)	7 (26.9)	0 (0.0)	0 (0.0)
Years between malignancy and IgE collection, median (IQR)	2.9 (2.0-3.8)	5.8 (0.7-8.4)	n/a	n/a
Type of hematologic malignancies, n				
Leukemia	1	9	0	3[a]
Multiple myeloma	1	5	1	1
Non-Hodgkin's lymphoma	2	9	1	5
Other hematologic malignancies[d]	1	4	1	0
Solid malignancies	N = 3	N = 204	N = 1	N = 69
Age at cancer diagnosis, y, median (IQR)	68.9 (51.5-74.2)	59.2 (52.6-63.4)	68.9 (68.9-68.9)	56.1 (50.3-61.5)
IgE level, median (IQR)	19.9 (13.5-22.0)	211.4 (107.7-375.9)[a]	19.9 (19.9-19.9)	170.4 (91.0-268.1)
Arrival at WTC site on September 11, 2001, n (%)	2 (66.7)	132 (64.7)	1 (100.0)	49 (71.0)
IgE done before cancer diagnosis, n (% total)	2 (66.7)	146 (71.5)	1 (100.0)	69 (100.0)
Years between malignancy and IgE collection, median (IQR)	5.2 (1.3-9.1)	4.8 (2.4-10.0)	9.1 (9.1-9.1)	10.4 (5.6-15.2)
IgE done after cancer diagnosis n (% total)	1 (33.3)	58 (28.4)	0 (0.0)	0 (0.0)
Years between malignancy and IgE collection, median (IQR)	6.4 (6.4-6.4)	5.0 (1.9-7.7)	n/a	n/a
Type of solid tumors, n				
Prostate	3	104	1	34
Melanoma	0	32	0	13
Bladder	0	12	0	2
Colon	0	11	0	6
Kidney	0	9	0	1
Lung	0	9	0	2
Thyroid	0	9	0	3
Pancreatic	0	7	0	4
Rectal	0	7	0	5
Nasopharyngeal	0	6	0	2
Eye	0	4	0	1
Connective tissue	1[d]	2	0	0
Other solid tumors[d]	0	23	0	3

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; n/a, not available; WTC, World Trade Center.
[a] *P* value < .01.
[b] = .01 ≤ *P* value < .05.
[c] The source population included firefighters and Emergency Medical Service (EMS) workers.
[d] 1 patient had more than 2 cancers.

IgE level: 25.95 kU/L [range, 4-36.47 kU/L]), whereas the rest of the 1796 participants had non–low-IgE levels (IgE ≥ 36.58 kU/L, median IgE level: 188.62 [range, 36.58-9021.13 kU/L]). The characteristics of individuals with low- and non–low-IgE levels are presented in Table 2. The 2 groups had similar proportions of men (96.4% vs 98.3%; *P* = .29) and comparable median ages at blood collection (47.5 years [IQR, 40.6-57.3] vs 48.7 years [IQR, 42.1-57.0]; *P* = .51). A higher proportion of White participants was found in those with low-IgE levels (98.2%) compared with those with non–low-IgE levels (88.4%, *P* = .02).

In the subcohort of responders who had their IgE levels measured within the first 6 months of the WTC attack, 30 individuals had IgE levels in the third percentile and comprised the group with low IgE level (IgE < 36.58 kU/L). All such responders were White males.

Higher Proportion and Risk of Hematologic Malignancies in World Trade Center Responders With Low Immunoglobulin E Levels

Among all WTC responders who had their IgE levels measured after 9/11, a significantly higher proportion of hematologic malignancies was found in the low-IgE level group (4/55, 7.3%) compared with those with non–low-IgE levels (26/1796; 1.5%; *P* < .01), whereas the proportion of solid tumors were similar in both groups (5.5% in the low-IgE group vs 11.4% in the non–low-IgE group; *P* > .05) (Table 2).

Analysis of the risk of malignancy in the subcohort that had IgE levels measured in the first 6 months after WTC revealed similar results. A significantly higher proportion of hematologic malignancies was found in low-IgE level responders (2/30, 6.7%) compared with those with non–low-IgE levels (8/679; 1.2%; $P < .01$), whereas the proportion of solid tumors were similar in both groups (3.3% in the low-IgE group vs 10.2% in the non–low-IgE group; $P > .05$) (Table 2).

Logistic regression models (Table 3) reveal that after adjustment for confounders, the responders with low-IgE levels had 7.81 times greater odds (95% CI, 1.77-29.35) of developing a hematologic cancer when compared with non–low-IgE responders. In the smaller cohort of responders who had the IgE levels measured in the first 6 months after the WTC attacks, participants with low-IgE levels had 7.66 times greater odds (95% CI, 0.59-41.04) of having a hematologic cancer when compared with non–low-IgE participants.

Proportion of Hematologic Malignancies in Groups With Different Levels of Immunoglobulin E

The proportion of hematologic malignancy of the 4 different IgE groups are found in Figure 2. Responders with low IgE levels seemed to have higher odds of developing a hematologic cancer (4/55, 7.3%) compared with those in each of the other IgE groups. However, this difference was relevant only for the comparison to the high IgE level group (16/1321, 1.2%; OR, 12.96; 95% CI, 2.47-56.12) (Fig 2). The association between IgE and solid tumors was not statistically significant in either cohort ($P > 0.05$; data not shown).

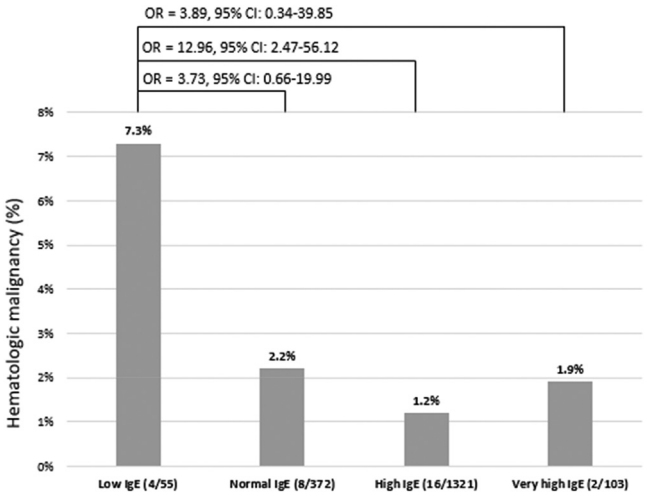

Figure 2. Odds ratio of developing hematologic malignancy in responders who had IgE levels measured after WTC, based on different IgE levels. Confounders included in the calculation of odds ratio included race (White vs non-White), sex, age at blood draw, World Trade Center exposure (arrived on September 11, 2001, vs arrived later), and smoking status (ever smoking vs never smoking). CI, confidence interval; IgE, immunoglobulin E; OR, odds ratio; WTC, World Trade Center.

Characteristics of World Trade Center Responders Who Developed Cancer After 9/11 and Had Immunoglobulin E Levels Measured

Among participants who had IgE levels measured after 9/11 and who also developed a hematologic malignancy, IgE was tested before the occurrence of malignancy in 50% (2/4) of responders with low-IgE levels and in 73.1% (19/26) of those with non–low-IgE levels. Leukemia (n = 1), multiple myeloma (n = 1), and non-Hodgkin's lymphoma (n = 2) comprised the hematologic neoplasms in those participants with immunoglobulin E less than 36.58 kU/L (Table 2).

Among responders who developed solid tumors, IgE levels were measured before the cancer diagnosis in 66.7% (2/3) in those with low-IgE levels and in 71.5% (146/204) of participants with non–low-IgE levels. Prostate cancer was the most common diagnosed solid tumor in the study cohort (104/207, 50.2%). All responders in the low-IgE level group who developed solid tumors had prostate cancer (n = 3).

Discussion

Previous studies have revealed that after 9/11, there was an elevated incidence of some types of cancer among WTC-exposed firefighters, compared with the general population.[22,29] This may have been caused by exposure to high amounts of carcinogenic compounds at the disaster site. In this regard, recent data reveal that mice treated with WTC particulate matter developed an increased burden of mutations in hematopoietic stem and progenitor cell compartments, and WTC-exposed responders developed a significantly higher rate of clonal hematologic abnormalities (10%) compared with non–WTC-exposed firefighters (6.7%; 95% CI, 1.64-6.03; $P < .01$).[30]

Because most WTC-exposed responders did not develop a malignancy, we were interested in exploring whether differences in

Table 3
The Odds Ratio of Malignancy Diagnosis in WTC Responders With Low-IgE Levels, Compared With Those With Non–Low-IgE

Outcome	Unadjusted analysis				Adjusted analysis[a]			
	IgE category	Cases/total	OR	95% CI	IgE category	Cases/total	OR	95% CI
Entire cohort with IgE level checked after the WTC attack (N = 1851)								
Any type of malignancy	Low IgE	7/55	1.01	0.38-2.29	Low IgE	7/55	1.19	0.43-2.82
	Non-low IgE	226/1796	n/a		Non-low IgE	226/1796	n/a	
Hematologic malignancy	Low IgE	**4/55**	**5.34**	**1.31-16.19**	Low IgE	**4/55**	**7.81**	**1.77-29.35**
	Non-low IgE	26/1796	n/a		Non-low IgE	26/1796	n/a	
Solid malignancy	Low IgE	3/55	0.45	0.09-1.41	Low IgE	3/55	0.47	0.09-1.59
	Non-low IgE	204/1796	n/a		Non-low IgE	204/1796	n/a	
Cohort with IgE level measured within 6 mo from the WTC attack (N = 709)								
Any type of malignancy	Low IgE	3/30	0.88	0.17-2.97	Low IgE	3/30	0.94	0.17-3.44
	Non-low IgE	76/1679	n/a		Non-low IgE	76/1679	n/a	
Hematologic malignancy	Low IgE	2/30	5.99	0.59-31.84	Low IgE	2/30	7.66	0.59-41.04
	Non-low IgE	8/679	n/a		Non-low IgE	8/679	n/a	
Solid malignancy	Low IgE	1/30	0.31	0.01-1.90	Low IgE	1/30	0.24	0.01-2.03
	Non-low IgE	69/679	n/a		Non-low IgE	69/679	n/a	

Abbreviations: CI, confidence interval; IgE, immunoglobulin E; n/a, not available; OR, odds ratio; WTC, World Trade Center.
NOTE. Bold values indicate statistically significant.
[a]Reported estimates are Mantel-Haenszel common ORs with exact 95% CIs to account for small cell sizes.

biological processes with a role in antitumor surveillance might play a role in malignancy development in conjunction with these environmental exposures. Numerous studies have revealed that IgE promotes death of malignant cells, having antitumor surveillance capabilities.[16,18-20] Therefore, in this study, we investigated the association between serum IgE levels and the development of malignancy after September 11, 2001, in this group of WTC-exposed responders. We found that the WTC responders with IgE measurements in the lowest third percentile had a substantially higher proportion and odds of developing a hematologic malignancy after the 9/11 attacks, compared with responders with non–low-IgE levels. This study is the first in humans to reveal that being exposed to carcinogens (resulting from the WTC exposure[21]) while having a low-serum IgE level is associated with malignancy development. Experimental murine findings support the fact that the combination of these 2 factors is associated with tumor development. Mice deficient in IgE or cytokine interleukin 4 (IL-4, which is required for IgE production), or in the high-affinity IgE receptor (Fc RI), had a higher rate of developing squamous cell cancers after exposure to DMBA (7,12-dimethylbenz[a]anthracene), a known mouse carcinogen.[31] These results are consistent with the idea that IgE plays a role in tumor surveillance and that a low IgE level represents a risk factor for malignancy development.[5-7,11-13,32]

Previous studies have also revealed that among individuals with different IgE levels, IgE-deficient participants have the highest odds for developing a malignancy.[11,12] Because none of the WTC responders in this study were found to be IgE-deficient, our results raise the possibility that individuals with IgE levels within the lower level of the normal range (IgE < 100 kU/L is considered "normal" in adults[33]) may also have increased odds for developing cancer under certain conditions, such as exposure to carcinogens. If so, identifying such individuals may be important for further clinical follow-up and management. In this regard, the unique cohort of WTC responders used in this study has been informative.

We found that study participants with low IgE levels had higher odds for developing a hematologic malignancy, whereas the odds for developing a solid tumor was similar in low- and non–low-IgE participants. Although these results might be explained by the small cohort size, other factors may contribute to these results as well. We previously revealed that IgE-deficient individuals with no tissue-bound IgE (as evidenced by negative skin prick test result to environmental allergens in IgE-deficient individuals with chronic rhinitis) had considerably higher rates of malignancy compared with those with at least 1 positive skin test result (suggesting the presence of tissue-bound IgE).[32] Most of the cancers reported in the latter cohort of IgE-deficient individuals with no cell-bound IgE were solid tumors. It is possible that although decreased levels of serum IgE might contribute to the development of hematologic malignancies, it might be that only the complete absence of tissue-bound IgE will cause reduced local tumor surveillance of solid tumors. The fact that IgE is the most abundant immunoglobulin isotype found in head and neck cancer tissues,[34] and that there are IgE transcripts at the site of squamous skin cancers in mice that promote a unique tumor-protective IgE response,[31] support the hypothesis that tissue-bound IgE is involved in local antitumor immunity. In the current study, none of the WTC responders were IgE-deficient, suggesting both low- and non–low-IgE groups had cell-bound IgE, which may explain the similar proportion of solid tumors in both groups. Another possible explanation is that combination between exposure to this type of carcinogens and low IgE levels might be an important trigger only for certain hematologic malignancies, whereas solid tumors require a different carcinogenic pathway which needs yet to be defined.

The relative efficacy of serum IgE in protecting against hematologic malignancies compared with solid tumors might also be explained by the fact that IgE is a natural ligand for the low-affinity IgE receptor (CD23) expressed by B cells and it has been found that binding of IgE to CD23 prevents the proliferation and differentiation of malignant B lymphocytes.[35] It is therefore possible that in our cohort, the low levels of serum IgE were insufficient to allow this natural antilymphoid tumor mechanism to occur, facilitating the observed increased development of hematologic malignancies.

Our results reveal that in the low-IgE group, hematologic malignancies were diagnosed at a median age in the early 50 years (Table 2), which is younger than the national median age of 67 to 69 years for the development of leukemia, lymphoma, or multiple myeloma.[36] Although the cohort is small with relatively few total cancer events, our results suggest that in combination with carcinogen exposure, lower IgE levels might be associated with greater risk of developing a hematologic malignancy. Replication of these findings would have broad implications. At this time, there is no biomarker reflecting deficient antitumor immunity that could be used in clinical practice to predict malignancy susceptibility. The data so far suggest that in certain conditions, very low IgE levels might emerge as a potential biomarker for cancer susceptibility. Although the exact IgE threshold which poses a higher risk for cancer occurrence has yet to be established, its utility as a screening instrument might have broad implications as a useful tool to predict cancer susceptibility.

There are several limitations of our study. First, the sample size of responders who had IgE levels measured after 9/11 was small, specifically in those who had their IgE levels tested soon after WTC attacks. Moreover, the IgE levels were not measured at multiple points in time, and there are no available pre-WTC measured IgE levels. We plan to expand this pilot study and measure IgE levels in the remaining stored samples from the WTC responders to better assess the relationship between malignancy occurrence and IgE levels. Furthermore, IgE levels were not measured in all subjects before the malignancy diagnosis, so we do not know how malignancy or the cancer treatment might have influenced the IgE levels. To minimize this bias and reduce the potential for reverse causality, we performed a sensitivity analysis of malignancy occurrence in the group of responders who had their IgE levels measured in the first 6 months after 9/11 and found that there was a similar magnitude of association. In addition, longitudinal data in other studies of IgE-deficient individuals indicate that very low IgE levels often precede the cancer diagnoses.[13] Another limitation is that potentially other factors such as genetic background or other exposures could have contributed to development of hematologic cancers as well (among these, smoking status was included as a covariate in the adjusted analysis). It is impossible, however, to measure and assess for these factors. Nevertheless, based on the available data we have so far, very low IgE levels might develop into a prediction tool for malignancy in certain individuals.[10] The lack of generalizability to other demographic groups is another limitation of this pilot study. Our cohort is restricted to primarily middle-aged, White men, a select group of individuals who might have high rates of leukemia and lymphomas, compared with females or men of other ethnic backgrounds.[37] However, the finding of a higher risk of hematologic malignancy only in those responders with low IgE levels suggests that having a low level of serum IgE is an important contributor to malignancy susceptibility. We were not able to evaluate whether IgE was the only molecule from the T_H2 pathway that is involved in the association with malignancy occurrence. There may be other molecules, cells, interleukins, or signaling pathways involved in this process which may also be dysfunctional in these individuals. Last, we observed a higher than usual IgE level cutoff for the third percentile in this study when compared with other works.[12] Pre-WTC IgE levels are not available, and it is not known whether exposure to high-level particulate matter, metals, and carcinogenic compounds might have resulted in higher IgE levels than expected.[38] Although IgE-deficient individuals seem to have the highest risk of cancer,[11-13] there are data revealing a decreased risk of developing chronic lymphocytic leukemia in individuals with higher IgE levels compared with those with IgE level in the first

tertile.[5] Nevertheless, it is not clear whether the use of MILLIPLEX MAP assay for IgE measurement may have contributed to this observation; however, the assay detected IgE levels as low as 4 kU/L.

In conclusion, WTC responders with low serum IgE levels had a greater likelihood of developing a hematologic malignancy, compared with those with higher IgE levels. Experimental studies have revealed that IgE is involved in antitumor immunity, and several epidemiologic studies have found that IgE-deficient individuals have the highest risk of developing malignancy. Although the cohort size is small, the results of this hypothesis-generating study also suggest that when exposed to carcinogens or other exogenous factors, those patients with ostensibly normal but low IgE levels have higher odds of developing a malignancy. Larger, multicenter studies with adequate follow-up of patients with different IgE cutoff levels are needed to better evaluate different aspects in this question, including the relationship between IgE levels and malignancy susceptibility prediction, whether normal but low-IgE levels might be associated with malignancy occurrence in other environmental conditions, and exactly how this information can be used in clinical practice.

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