Editorial

Low immunoglobulin-E levels as potential biomarker to screen individuals susceptible to cancer in occupational settings

Ferastraoaru et al[1] reported an interesting observational study showing an enhanced risk of hematologic malignancies associated with low serum immunoglobulin (Ig)-E levels compared to subjects with non−low IgE levels in a cohort of emergency responders to the terrorist attack on the World Trade Centre (WTC). Most firefighters were of White ethnicity in their 40s, and risk estimates were adjusted for race (White vs non-White), age at blood draw smoking status, and time on arrival at the WTC. The study population was already known to be at risk of cancer in the 7 years after WTC disaster, especially prostate cancer, thyroid cancer, non-Hodgkin lymphoma, and melanoma.[1,2] Of 11,469 emergency responders, 1851 individuals had at least one IgE measurement any time after and within 6 months after the WTC attack. Patients with IgE levels in the lowest third percentile (IgE < 36.58 kU/L) were categorized as "Low IgE" levels and contrasted to patients with non−low IgE (defined as IgE ≥ 36.58 kU/L).[1] None of the study participants had IgE deficiency (IgE < 2.5 kU/L), with the lowest IgE level in the entire cohort being 4 kU/L.[1]

Discovered in 1968, IgEs are involved in type I hypersensitivity reactions and parasitosis, with research focused on elevated levels affecting immunologic disorders. Nevertheless, studies have also started to investigate the relationship between IgE levels and risk of cancer, with in vitro and in vivo evidence of higher risk of malignancy associated with low IgE levels, which is stronger than the relationship seen with IgG.[1,3] Immunoglobulin E appears capable of suppressing cancer cells by binding with high (FcεRI) and low (FcεRII, CD23) affinity IgE receptors, thereby triggering antibody dependent cytotoxicity or cell phagocytosis.[4] In addition, IgE/FcεRI-mediated cross-presentation maximizes the priming activity of dendritic cells on CD8+ T cell responses against free soluble antigens, enhancing cancer immunosurveillance.[5] Natural binding of IgE with CD23 receptors expressed by B lymphocytes prevented malignant degeneration and proliferation, thus potentially explaining the increased risk of hematologic tumors associated with low IgE levels in the WTC cohort.[1] Likewise, in a prospective study on 37,747 individuals from the general population, total serum IgE levels in the second and third tertiles were associated with lower risk of chronic lymphocytic leukemia than were IgE levels in the lowest tertile.[6] However, IgE in tumor surveillance also seems effective against solid malignancies, given mice deficient of IgE, interleukin-4 (cytokine essential for IgE production), or Fc RI were more likely to develop squamous cell cancers after exposure to 7,12 Dimethylbenz[a]anthracene (DMBA), a known risk factor for cancer in mice.[7] Furthermore, in a study assessing the impact of active and passive immunotherapy against tumor-associated antigen human epidermal growth factor receptor 2 in 3 murine models with different expression of the Epsilon-B-cell-receptor influencing IgE levels (wild type, low level, high level), high-IgE KN1 mice with 4- to 6-fold elevated serum IgE showed an innate survival benefit after challenge with mammary tumors overexpressing human epidermal growth factor receptor 2.[4]

Likewise, head and neck tumors reportedly had a higher concentration of IgE-expressing cells than normal mucosa,[8] and a case-control study contrasting 1169 incident lung cancer cases with 1486 controls found a decreased risk of lung cancer in patients affected by asthma, atopic eczema, and especially hay fever.[9] All this evidence suggested IgE as an anticancer therapy, and a phase I clinical trial is already in progress to test the efficacy of cancer-associated antigen-specific IgE against advanced solid tumors in humans (NCT02546921). However, the findings of Ferastraoaru et al[1] also open interesting prospects of using IgE as a surveillance biomarker for an early identification of individuals susceptible to cancer. Nevertheless, the adjusted risk estimate of hematologic malignancies associated with low IgE levels (odds ratio, 7.81; 1.77-29.35) found by Ferastraoaru et al[1] was rather wide, owing to the small numbers involved (4 cases in the low IgE levels vs 26 cases in the non−low IgE group) in the subset of responders with IgE levels measured any time after the WTC attack (N = 1851). Moreover, the risk of hematologic cancer in the WTC cohort was not confirmed in the subgroup of workers (N = 709) who underwent IgE measurement within the first 6 months after the attack.[1] The increased risk of cancer in relation to low IgE levels is still conflicting though, because a very recent case-control study contrasting 1236 cases vs 7416 controls reported an increased risk of Hodgkin lymphoma associated with allergic diseases, eczema, and immunosuppression, which could be only partially explained by steroid use.[10] The authors of the latter study concluded that allergic disorders or immunosuppression alter the human immune system function, thereby predisposing it to lymphoma development.[10] Moreover, albeit a distribution imbalance of cancers was found among patients treated with omalizumab in phase 1 to 3 clinical studies a recombinant humanized anti-IgE monoclonal antibody recommended for asthma or chronic urticaria, a pooled analysis on 32 randomized controlled trials did not find an increased risk of cancer (rate ratio, 0.93; 95% confidence interval, 0.39-2.27) in 4254 omalizumab vs 3178 placebo-treated patients.[11]

Ferastraoaru et al[1] did not find any association between IgE levels and risk of solid tumors, which was instead reported in several clinical studies.[4,7–9] It is also unclear whether a low IgE level is a risk factor or effect of cancer, in other words, whether low IgE could be used as a biomarker for early diagnosis of cancer or to screen susceptible individuals at higher risk of developing malignancies.[1]

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Therefore, confirmatory larger multicenter studies are needed, assessing the risk of cancer in different populations and by exposure to different environmental or occupational conditions.

Cancer is a complex disease involving multiple factors, making prevention complicated. The search for "markers" of cancer risk and susceptibility has a long-standing history, and in the last decade, many serologic molecules and genes have been proposed to detect cancer precociously. Public health approaches to fight common cancers (breast, colon, cervical, and prostate) have focused on screening for early diagnosis to improve patient survival, rather than disease prevention. Beyond some specific genetic markers as BRCA-1 and BRCA-2 for breast tumors, currently, there is no biomarker for individual immune susceptibility to cancer. If the evidence of the association between low IgE and cancer is confirmed, measuring IgE levels could be a cheap and easy approach to identifying individuals at higher risk of tumors. For instance, IgE could be employed not only to screen the general population against cancer risk, but also to identify individuals eligible for job tasks entailing occupational exposure to known risk factors for hematologic malignancies, eg, rubber manufacturing, benzene.

Luca Cegolon, MD, MSc, PhD[*,†,#]
Francesca Larese Filon, MD, PhD[*,‡]
Allan Prochazka, MD[§]
John H. Lange, MPH[‖]
[*] *Department of Medical, Surgical & Health Sciences*
University of Trieste
Trieste, Italy
[†] *Department of Public Health*
University Health Agency Giuliano-Isontina (ASUGI)
Trieste, Italy
[‡] *Occupational Medicine Unit*
University Health Agency Giuliano-Isontina (ASUGI)
Trieste, Italy
[§] *Department of Medicine*
University of Colorado Anschutz Medical Campus
Aurora, Colorado
[‖] *Envirosafe Training & Consultants*
Pittsburgh, Pennsylvania
l.cegolon@gmail.com

References

1. Ferastraoaru D, Zeig-Owens R, Goldfarb D, et al. Relationship between low serum IgE levels and malignancies in 9/11 World Trade Center responders.. *Ann Allergy Asthma Immunol*. 2022;129(6):769–775.
2. Zeig-Owens R, Webber MP, Hall CB, Schwartz T, Jaber N, Weakley J, et al. Early assessment of cancer outcomes in New York City firefighters after the 9/11 attacks: an observational cohort study. *Lancet*. 2011;378(9794):898–905.
3. Magen E, Schlesinger M, David M, Ben-Zion I, Vardy D. Selective IgE deficiency, immune dysregulation, and autoimmunity. *Allergy Asthma Proc*. 2014;35(2):e27–e33.
4. Singer J, Achatz-Straussberger G, Bentley-Lukschal A, Fazekas-Singer J, Achatz G, Karagiannis SN, et al. AllergoOncology: high innate IgE levels are decisive for the survival of cancer-bearing mice. *World Allergy Organ J*. 2019;12(7):100044.
5. Platzer B, Elpek KG, Cremasco V, Baker K, Stout MM, Schultz C, et al. IgE/FcεRI-mediated antigen cross-presentation by dendritic cells enhances anti-tumor immune responses. *Cell Rep*. 2015;10(9):1487–1495.
6. Helby J, Bojesen SE, Nielsen SF, Nordestgaard BG. IgE and risk of cancer in 37 747 individuals from the general population. *Ann Oncol*. 2015;26(8):1784–1790.
7. Crawford G, Hayes MD, Seoane RC, Ward S, Dalessandri T, Lai C, et al. Epithelial damage and tissue γδ T cells promote a unique tumor-protective IgE response. *Nat Immunol*. 2018;19(8):859–870.
8. Neuchrist C, Kornfehl J, Grasl M, Lassmann H, Kraft D, Ehrenberger K, et al. Distribution of immunoglobulins in squamous cell carcinoma of the head and neck. *Int Arch Allergy Immunol*. 1994;104(1):97–100.
9. El-Zein M, Parent ME, Siemiatycki J, Rousseau MC. History of allergic diseases and lung cancer risk. *Ann Allergy Asthma Immunol*. 2014;112(3):230–236.
10. Rafiq M, Hayward A, Warren-Gash C, Denaxas S, Gonzalez-Izquierdo A, Lyratzopoulos G, et al. Allergic disease, corticosteroid use, and risk of Hodgkin lymphoma: a United Kingdom nationwide case-control study. *J Allergy Clin Immunol*. 2020;145(3):868–876.
11. Busse W, Buhl R, Vidaurre CF, Blogg M, Zhu J, Eisner MD, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. *J Allergy Clin Immunol*. 2012;129(4):983–989. e6.