

Editorial

Allergy and cancer: a biological and epidemiological rebus

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The debate on the relation between allergy and cancer is not recent (1, 2). The increased burden of allergic diseases in the last decades (3–6) and the new discoveries about the immunology of cancer (7–9), enhanced the interest on such relationship. Theoretically, two general hypotheses may be advanced: either tumor immunosurveillance may operate more efficiently in those individuals who have allergies or the alterations of the immunologic system can enhance inflammatory response and favor the tumor onset.

Under the epidemiological point of view, the examination of the relation between allergic-related disorders and cancer development is still needed. To know the direction of a possible association between the two phenomena might contribute to cancer prevention. However, any epidemiological conclusion can't leave out the complex results of basic science and it must follow the rule of biological plausibility.

The concept of multi-stage carcinogenesis implies that cancer prevention is feasible, at each stage, with different strategies. Defense mechanisms existing in different stages of carcinogenesis (e.g. detoxification of metabolites coming from environmental carcinogens, trapping or decomposition of reactive oxygen species, DNA repair enzymes, natural inhibitors of proliferating initiated cells, etc.) have been recently emphasized (10). The immune system may be the last line of defense against cancer development. According to the most recent point of view about cancer immunology (8), the key issue is whether recognition of tumor antigens by the immune system leads to activation (i.e. surveillance) or tolerance. These apparently disparate views can be reconciled into a unified hypothesis in which tumors must develop specific mechanisms for locally inhibiting the activation of innate and adaptive immunity in order to progress successfully through invasive and

metastatic stages (8). At this regard, observations in human populations have been limited; thus, epidemiological approaches may be the most suitable way to assess the relation between host immunological status and future development of cancer in humans (10).

The papers from Wang and Diepgen (11) and from Lindelof et al. (12) represent a consistent basis for this open discussion. The former is a comprehensive review of the epidemiological studies after 1985. Sixty-six studies have been analyzed for more than eight different sites of tumor. The general conclusion is that 'Despite the mixed results...allergy is associated with a reduced risk for cancer'. It stands especially for colon cancer, pancreatic cancer, childhood leukemia and brain tumors. Conversely, the only tumor positively associated with allergy is lung cancer. As a consequence, if cancer is also an organ-specific diseases with a specific natural history, the role of immunity may be different for different cancer sites. In the case of lung cancer, for which particularly asthmatic subjects show an elevated risk, mechanisms related to the interaction between environmental and host factors, on one site, and the airways, on the other site (airway obstruction, remodeling, wall damages, etc.), might explain the epidemiological findings. For cancers in other sites, especially if related to microbiological agents, for which a reduced or a non-significant risk has been reported, a 'protective' effect of enhanced immunity system in allergic subjects might be taken into consideration. However, as the two Authors point out, many methodological problems or possible sources of bias have to be considered: study designs (many case-control instead of cohort-prospective studies), recall bias, small number of subjects, variability in the definition of allergy, lack of an objective measure of allergy, impossibility to analyze the role of confounders or effect modifiers.

The paper of Lindelof et al. (12) would appear able to provide sound results, at least under the epidemiological point of view. In fact, it overcomes many methodological sources of bias: it is a prospective study involving a very large population (although the study is not community based, but comprised of consecutive allergic patients tested in a hospital laboratory, thus limiting the generalizability of results) and it uses objective markers of allergy (IgE levels). A limit of the study is the consideration of only the underlying cause of death, although the information bias can be considered very limited when dealing with cancers. A more important source of information bias may be related to the decisions of counting only first cancer after the test performance and of disregarding multiple cancers and cancers detected incidentally at autopsy, possibly favoring conservative results. However, there is some gender and age unbalance in the cohort with fewer men and elderly subjects. Furthermore, while 23.8% of subjects had increased total IgE, up to 33.2% had a positive Phadiatop test (specific IgE). The major problem is the lack of the possibility of taking into account other risk factors, potentially related to both the determinant and the outcome. In fact, both IgE levels and cancer are related, for instance, to active and passive smoking or to occupational exposures (13–14). Neither the observed cases of total cancers nor specific cancers such as lung, cervix, pancreas, lymphoma and non-melanoma skin cancer were associated with IgE in either direction. An elevated standardized incidence ratio was found for cancer cases in childhood, especially brain cancer, in those with elevated IgE. Such findings, as the Authors comment, are to be interpreted with caution due to the small number of cases and the possible surveillance bias leading to earlier diagnoses in childhood with positive allergy test. Anyhow, the conclusion of the Authors is that the association between allergy and cancer has not been epidemiologically demonstrated, either as protective or as a risk factor.

The main question – is allergy a ‘risk’ or a ‘protective’ factor for cancer? – appears now well outlined, but far to be solved. Results from the literature still appear inconsistent or contradictory. Cancer immuno-epidemiology will hopefully clarify the role of immunity in protecting the host from nascent transformed cells and in regulating inflammatory response to pathogens (10), and it will provide reliable estimation of cancer risk for individuals with different immunological competences. A necessary development of the analyses on existing data, is the

implementation of a meta-analytic approach. The paper of Wang and Diepgen (11) represents a good starting point for researchers interested in performing such statistical approach in order to increase the limited power of individual studies and to achieve a more robust estimate of the magnitude of the association. On the other hand, only prospective cohort studies will be conclusive.

At this regard, the follow up of the large population samples enrolled in prospective studies started in the 70s in which biomarkers of atopy (such as IgE, skin prick test) were measured, would be a ‘within reach’ source of knowledge. A pooled analysis of cancer incidence in these cohorts of subjects, after controlling for many possible confounders, would complement information from mortality data of a US national cohort (15). Few specifically designed cohort studies, using immunological biomarkers, are available at present (16–18). The mentioned possible increase of longitudinal data would expand the knowledge on the role of immune cells in cancer surveillance and inflammation, on the effects of environment and lifestyle factors upon the immune system, and on the interaction between aging and immunity in the occurrence of cancer, as well as on the possibility to identify surrogate biomarkers for cancer prevention (10). Furthermore, the cohort studies have an added value in so far as they can provide new information on other aspects involved in the relationship ‘allergic disorders – cancer’, such as cancer onset in immunodepressed subjects and cancer immunotherapy.

In conclusion, the readers of this Allergy issue would probably recognize that the epidemiological knowledge about the relationships between allergy and cancer is still incomplete and does not point to a clear-cut direction. Certainly, new important findings on the issue of the more comprehensive question about immune system and cancer may be provided by immuno-epidemiology: also in this case the key way is the possibility to investigate the relation between host and environmental factors, using both epidemiological methods and the tools coming from basic science.

On the other hand, there seems to be a clear association of lung cancer with asthma. Lung cancer is the most frequent cancer in developed countries in males (and very soon also in females). Asthmatic subjects have to be considered subjects ‘at risk’ for lung cancer. Thus, preventive measures, smoking cessation and educational campaign in young people, have to be reinforced in these patients.

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