Exploring a Cancer Biomarker: The Example of C-Reactive Protein

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An elevated plasma level of C-reactive protein (CRP) is an established biomarker of increased risk of cardiovascular diseases and diabetes (1,2). An association has also been suggested between plasma CRP level and the risk of cancer, particularly lung and colon cancers; however, the evidence is inconclusive because of the lack of large-scale prospective studies in which CRP levels were measured in healthy individuals before the onset of the disease (3). One explanation for why CRP may identify individuals at increased risk of disease lies in its association with chronic—mostly subclinical—disease. There is also some evidence that CRP may act as an active contributor to inflammation, and this activity may depend on the conformation of the protein (4). Whether CRP is only a biomarker or an active player in inflammation might have important clinical implications.

The study by Allin et al. (5) in this issue of the Journal addresses precisely the role of CRP as a biomarker vs as a contributor to carcinogenesis. The study is an elegant example of how genetic variants that have a functional impact can be used to explore associations between environmental factors and disease, and specifically to identify and control for confounding factors, based on the approach that has become known as Mendelian randomization, a term first used by Gray and Wheatley in 1991 in the context of treatment of childhood leukemia (6).

The basic principle of Mendelian randomization is that if a genetic variant influences a nongenetic (i.e., environmental) factor that is relevant to disease risk, and if the same variant has no other associations with the same disease, then the variant predicts disease risk through its influence on the risk factor. Therefore, genetic variants with well-characterized functions (or that are in linkage disequilibrium with other variants with a well-characterized function) can be used to characterize associations between environmental factors and disease risk (7). Furthermore, using genetic variants instead of their environmental counterparts ensures protection from confounding and reverse causality and—at least in some cases—allows one to assess the effect of long-term exposures.

The requirements for Mendelian randomization to be useful (strong functional significance of the variant and the absence of an effect on other pathways) are demanding and are not often fulfilled. There are examples, however, in which the analysis of genetic variants has helped to elucidate the role of environmental exposures, such as polymorphisms in genes encoding alcohol-metabolizing enzymes that explain the possible protective role of alcohol intake in cardiovascular disease as well as its detrimental role in pregnancy outcomes (8,9). The Mendelian randomization approach would be particularly valuable in the case of environmental factors that are not easily measurable.

Allin et al. (5) found that variants in the CRP gene were associated with altered plasma levels of the protein but not with cancer risk. The interpretation of their results would benefit from a parallel examination of recent results on other conditions associated with CRP. Also, in the case of cardiovascular diseases and diabetes, it has been observed that the increased risk associated with increased CRP level is not attributable to genetic variants (10–12). Experimental data showing that reducing the plasma CRP level would decrease disease risk would provide strong evidence that CRP is causally implicated in the inflammation that leads to endothelial damage, but such data are currently not available (13).

Although the results of the study by Allin et al. argue against a direct role of CRP in carcinogenesis, they do not detract from the potential value of CRP as biomarker of cancer risk. A biomarker is an indicator of a biologically relevant status or event (altered cancer risk in this particular case), and the only prerequisite for its usefulness is a strong and valid (i.e., unbiased) association with the relevant underlying phenomenon. The etiognostic, diagnostic, or prognostic value of a biomarker is not diminished by a lack of involvement in the underlying biological events. In the specific case of CRP, further characterization of its value as cancer biomarker is certainly warranted. One aspect that is important to clarify is its ability to predict the risk of specific types of cancers: Cancers that are strongly associated with chronic inflammation, such as stomach and colorectal cancers, would be the prime candidates for such studies. In addition, it would be useful to investigate the temporal relevance of an elevated plasma level of CRP, specifically, when before the onset of symptoms and diagnosis, a plasma CRP is able to predict cancer. The elucidation of these two aspects requires prospective studies with a large number of events to allow for stratified analyses. Most studies available to date, including the one by Allin et al., are limited by the small number of cases, resulting in low statistical power for analyses other than those that include all cancers occurring during the entire follow-up (3). Therefore, an important lesson of this study is, not unexpectedly, that validation of etiologic cancer biomarkers, in view of their possible application in the population, requires large carefully conducted prospective studies.

References


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