Biomarkers of Exposure in Cancer Epidemiology

To the Editor:

Pearce *et al*[1] have written a thoughtful commentary on the limitations of the use of biological markers of exposure in cancer epidemiology. We would like to expand a bit on the integration of exposure biomarkers into cancer epidemiology, to provide readers with a somewhat broader view of the potential use of these tools.

We agree with many of the limitations described by Pearce *et al*[1] on the use of markers of internal dose as surrogates for cumulative exposure in case-control and prospective studies.[2,3] Exposure markers, however, do have several important applications in other study designs that were not mentioned. For example, internal dose markers can be used in cross-sectional studies to determine whether chemicals in the environment or diet are actually absorbed, helping to establish the biological plausibility of exposure-disease associations previously described. This use has played an important role in demonstrating that compounds present in cigarette smoke can be detected in people exposed to second-hand smoke.[4,5] Other examples come from intervention studies, which often use short-term internal dose markers to evaluate the efficacy of the intervention (for example, smoking cessation, dietary modulation).

Pearce *et al*[1] have noted that deoxyribonucleic acid (DNA) adduct levels may vary substantially among subjects who have similar levels of exposure to a particular agent, and as such may be limited in their ability to assess external exposure. This observed interindividual variation does, however, provide the opportunity to determine whether, among similarly exposed subjects, the subgroup with elevated adduct levels is at greater cancer risk. In this instance, the tendency to form DNA adducts functions as a marker of susceptibility, integrating absorbed dose, metabolic activation and detoxification, and DNA repair. This tendency can be evaluated in case-control studies for subjects still exposed to the agent of interest (for example, smoking[6]), particularly in early disease, when disease effects on cells are less likely, or in prospective cohort studies, if recent exposure to relevant compounds is assessed by questionnaire or environmental monitoring at the time of biological sample collection.

Furthermore, since DNA adduct formation is considered a critical step in the initiation of cancer for many compounds,[7] the observation that a suspected carcinogen has the capability to form macromolecular adducts in exposed humans has important public health policy implications in and of itself. The significance of this area of research was demonstrated in the recent evaluation of ethylene oxide by the International Agency for Research on Cancer. After considering available epidemiologic studies of cancer, it concluded that there is only *limited evidence* in humans for the carcinogenicity of ethylene oxide. Its overall evaluation, however, was that "Ethylene oxide is *carcinogenic to humans* (Group 1),"[8] which was based in part upon the observation that ethylene oxide is associated with a dose-related increase in hemoglobin adducts, chromosomal aberrations, and sister chromosome exchanges in peripheral lymphocytes, and micronuclei in bone marrow cells of exposed workers.

More broadly, Pearce *et al*[1] have noted that, in general, subdisciplines of epidemiology are not defined by the techniques used. We agree that molecular epidemiology is not a distinct branch of epidemiology and note that it is probably a transitory term.[2,9] As a heuristic device, however, it does describe the broad opportunities for inclusion of current and future generations of biomarkers in epidemiologic research, and it calls attention to the substantial logistical issues that must be taken into account to use biomarkers successfully. Regardless of what one chooses to call this area of research, or whether it even deserves its own appellation, it is likely to become increasingly important as epidemiologists seek out new opportunities to enhance understanding of cancer etiology.[10] We should be cautious about overselling these techniques, but not so cautious as to fail to take advantage of the breadth of their application.

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