Environmental Tobacco Smoke and Lung Cancer: the Emerging Role of Carcinogen Biomarkers and Molecular Epidemiology

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In this issue of the Journal, Crawford et al. (/) report that children of mothers who smoke cigarettes have higher levels of polynuclear aromatic hydrocarbon (PAH)—serum albumin adducts than children of nonsmoking mothers. Certain PAHs, such as benzo[a]pyrene, are well-established respiratory carcinogens (2). Therefore, this study provides evidence that children exposed to environmental tobacco smoke (ETS) can take up and metabolically activate respiratory carcinogens. There are now data in the literature on the uptake and metabolism by nonsmokers exposed to ETS of all three major classes of carcinogens in tobacco smoke: PAH, nitrosamines, and aromatic amines (3,4). These have been obtained using analytical methods for the detection of carcinogen metabolites or their adducts to proteins. Carcinogen biomarkers such as these promise to be important in delineating the role of ETS as a possible cause of lung cancer in nonsmokers. The incorporation of biomarkers into epidemiologic studies potentially can provide greater specificity in linking exposure and disease than conventional techniques. This approach has become known as “molecular epidemiology.”

The potential role of carcinogen biomarkers in elucidating relationships between cigarette smoke exposure and cancer can perhaps best be seen by first considering their application in studies of active cigarette smoking and cancer. Cigarette smoking is firmly established as the major cause of lung cancer worldwide, with relative risks typically 10 times greater in smokers than in nonsmokers. This has been documented through case–control and prospective epidemiologic studies (5,6). The relative risk for cancer of the lung and other cancers is so great that the use of carcinogen biomarkers has not been necessary to establish it. Nevertheless, numerous carcinogen biomarker studies have been carried out with smokers. Examples include the quantitation of carcinojen hemoglobin adducts, carcinojen DNA adducts, and carcinojen metabolites in urine (7). These studies, which are generally small in scale and have been described as transitional epidemiologic studies (8), have bolstered the connection between smoking and cancer by providing a mechanistic framework for understanding it. At the same time, these studies have helped to validate carcinogen biomarkers through comparisons of their levels in smokers, who have documented exposure to carcinogens, with those of nonsmokers. The promise of larger molecular epidemiology studies of active smokers is to identify individuals who are particularly susceptible to tobacco smoke carcinogens because of the way in which they may respond to carcinogen exposure.

Three broad phases characterize the epidemiology of active smoking and cancer: phase I—cause and effect is established through conventional studies; phase II—carcinogen biomarkers are applied in transitional studies to provide mechanistic data and validate the biomarkers; and phase III—carcinogen biomarkers will be applied in larger molecular epidemiology studies to identify individuals at particularly high risk and provide further understanding of mechanisms.

Establishing cause and effect by conventional epidemiologic studies of ETS and lung cancer has been more difficult (9-12). The carcinogen dose received by a nonsmoker exposed to ETS may be only one one-hundredth of that received by an active smoker (3,6). Therefore, the risk for cancer will be less, although there may not be a direct relationship between carcinogen dose and risk due to differences in metabolic activation and other factors between active and passive smokers. Conventional epidemiologic studies of ETS and lung cancer have typically found relative risks between 1 and 2. Based on available epidemiologic data, several panels, including the National Research Council, the U.S. Surgeon General, and the Environmental Protection Agency, have concluded that ETS is a cause of lung cancer, with the strongest evidence coming from studies of nonsmoking women exposed to ETS; a recent study has provided further evidence supporting this conclusion (6,13-15). Cotinine has been used as a biomarker in some of these studies. Cotinine is not a carcinogen and its levels in blood or urine will not necessarily provide useful information about carcinogen uptake and metabolic activation. Cotinine levels can be used, however, to determine whether recent exposure to ETS has occurred and to prevent misclassification of active smokers as nonsmokers. Overall, conventional epidemiologic approaches (phase I

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A New Brochure to Increase Patient Awareness of the Importance of Treating Cancer Pain

- Patients have a right to pain control.
- Patients have a role in communicating their pain.
- Patients should talk to their doctors or nurses as soon as pain begins.
- Patients should not let fears keep them in pain.

Get Relief From Cancer Pain is written at a 5th grade reading level and is available through the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER or the American Cancer Society at 1-800-ACS-2345.