

Cancer: The Big Questions to Address in Coming Years

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Molecular epidemiology was introduced in the study of cancer in the early 1980s, with the expectation that it would help overcome some important limitations of epidemiology and facilitate cancer prevention (1, 2). Since then, it has become clear that the great majority of cancers are in theory preventable because the factors that determine their incidence are largely exogenous or "environmental" (3–5) including exposures related to lifestyle (diet and smoking), occupation, and pollutants in the air, water, and food supply. This awareness has lent greater urgency to the search for more powerful early-warning systems to identify causal environmental agents and flag risks well before the malignant process is entrenched. The first generation of biomarkers has contributed important understanding of mechanisms, risk, and susceptibility as they relate largely to genotoxic carcinogens. The newer generation of biomarkers, including epigenomics, genomics, and proteomics, can vastly strengthen efforts to identify carcinogenic risks, design interventions, and reshape public health policy to be more preventative. However, the systematic validation of these newer "omic" biomarkers is urgently needed, as is the development of automated high-

throughput methods capable of measuring the so-called "exposome"—the diversity of exposures acting on the individual through lifestyle, occupation, or the ambient environment—with the same detail and precision as genomics (6). Another important future direction in molecular epidemiology is longitudinal, life-course, and multigenerational research on the role of early-life (prenatal and early postnatal) environmental exposures in childhood and adult cancer. Since its founding in 1991, *Cancer Epidemiology, Biomarkers & Prevention* has been at the forefront of the field, publishing key papers on biomarker validation and their application to molecular epidemiologic studies on the causes, early detection, and prevention of cancer.

Key Questions for the Future

What is the role of environmental exposures in cancer and who are susceptible?

Molecular epidemiologic studies using biomarkers have already provided evidence of causality and have successfully identified at-risk populations. For example, we now know that lung carcinogens in tobacco smoke, including polycyclic aromatic hydrocarbons (PAH) and other aromatic carcinogens, act both through genotoxic (DNA adducts; refs. 7 and 8) and epigenetic mechanisms (e.g., altered methylation; ref. 9), opening new avenues for early detection of this often fatal disease. Biomarkers have demonstrated that the foodborne mutagen aflatoxin B₁ (AFB₁) is a human hepatocarcinogen acting synergistically with the hepatitis B virus (HBV), teaching that both reduction in dietary levels of AFB₁ and wide-scale HBV vaccination are needed for prevention (10, 11). Biomarkers have also forged causal links between the leukemogen benzene and leukemia, indicating that in "healthy" workers benzene exposure is linked to chromosome

Note: This commentary has been drawn in part from Vineis and Perera (29).

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aberrations, altered protein expression, and decreased white blood cell counts in genetically susceptible individuals (12). All three examples provide direct policy-relevant evidence that reduction or elimination of carcinogenic exposures below current levels will have direct benefits in prevention of cancer.

Molecular epidemiologic studies have further shown that certain subgroups and individuals have heightened susceptibility to environmental exposures due to single-nucleotide polymorphisms (13–15), but most observed associations between cancer and low-penetrant gene variants have been weak (with 20% to 50% increases in cancer risk). Genome-wide association studies using platforms such as Illumina or the Affymetrix microchips offer the possibility of analyzing up to 550,000 or even 1 million gene variants in one run. While this revolution is giving rise to an unprecedented wave of new potentially significant discoveries, genome-wide scans are vulnerable to false-positive findings due to multiple comparisons. Very importantly, the interaction between genes and environmental exposures is usually ignored. Molecular epidemiology has also shown that ethnicity, sex, and nutritional factors contribute to differential susceptibility, providing mechanistic support for the observed higher rates of various smoking-related cancers in blacks (16), evidence that women may be inherently more susceptible than are men to certain lung carcinogens (17), and illustrating that nutritional deficits, such as low levels of antioxidants, can heighten susceptibility to lung and other carcinogens (18). To be effective, prevention strategies must target the most sensitive subgroups. By harnessing new technologies, the pace and scope of research in this critical area can be greatly expanded.

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What are the lifetime cancer risks associated with early (especially prenatal) exposures, and how can these be prevented?

Compared with exposures occurring in adult life, exposures *in utero* and in the early years can disproportionately increase the risks of childhood cancer and many types of cancer later in life (19–21). Fetuses and newborns are particularly susceptible to diverse carcinogens, including PAH, nitrosamines, pesticides, tobacco smoke, air pollution, and radiation. Although the epidemiologic evidence is still inconclusive on the role of transplacental exposure to PAH in air pollution and childhood cancer (22), airborne PAH measured by personal air monitoring during pregnancy has been significantly associated with stable aberration frequencies (a validated risk marker) in cord blood (23). Prenatal or postnatal exposure to tobacco smoke or its constituents has been associated with increased frequencies of DNA and hemoglobin adducts, as well as chromosomal aberrations in newborns or children (24, 25). Direct chromosomal evidence (*MLL-AF4* and *TEL-AML1* gene fusion in cord blood) also suggests a link between *in utero* exposures and cancer in infancy and childhood (26, 27). These studies can now be expanded using new technologies and "systems epidemiology" (28, 29). By addressing these key questions, future research will provide new tools for early detection of cancer and quantification of the lifetime cancer risks posed by specific environmental factors, resulting in more effective clinical and policy interventions.

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No potential conflicts of interest were disclosed.

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