Biomarkers of Tobacco Carcinogenesis in Diverse Populations: Challenges and Opportunities

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ABSTRACT

Biomarkers can provide distinct information about cancer risk factors in populations from diverse ancestries and with different exposure patterns by measuring the internal dose of carcinogens. While similar environmental exposures can lead to different cancer risks across racial or ethnic groups, seemingly different exposures can cause the same cancers because they produce the same biomarkers in the body. Smoke-related biomarkers are among the most commonly studied biomarkers in relation to cancer, and they include tobacco-specific biomarkers (nicotine metabolites and tobacco-specific nitrosamines) and biomarkers which can result from exposure to tobacco and non-tobacco pollutants (polycyclic aromatic hydrocarbon and volatile organic compounds). Biomonitoring is superior to self-reported exposure assessment because it is less prone to information and recall biases. However, biomarkers generally reflect recent exposure determined by their metabolism and half-life and how they are stored in and excreted from the body. Many biomarkers are correlated because the sources of exposure usually contain several carcinogens at the same time, making it difficult to identify specific chemicals which lead to cancer. Despite these challenges, biomarkers will continue to be essential to cancer research. Prospective studies, with detailed exposure assessment and large sample sizes from diverse backgrounds, along with studies designed to enrich the methodology of biomarker research are the necessary steps in that direction.

See related article by Cigan et al., p. 306

Smoking causes an estimated 80%–90% of lung cancer in the United States (1). Yet, most smokers do not develop lung cancer. Instead, lung cancer risk varies substantially by self-reported duration, frequency, and intensity of tobacco use. In addition, lung cancer risk may also vary by individual carcinogen exposure and metabolism. Studies using biomarkers to assess smoking-associated compounds are important complements to studies using self-reported smoking information. Smoke-related biomarkers are among the most commonly studied biomarkers in relation to cancer, and they include tobacco-specific biomarkers [nicotine metabolites and tobacco-specific nitrosamines (TSNA)] and biomarkers which can result from exposure to tobacco and non-tobacco pollutants [polycyclic aromatic hydrocarbon (PAH), and volatile organic compounds]. Many of these biomarkers are the result of exposure to chemicals identified by the FDA list of "harmful and potentially harmful chemicals in tobacco smoke" as carcinogenic (2).

Biomarkers can be used to explore the variations in exposure-cancer associations in different settings and diverse populations by measuring the internal dose of exposure. For example, the association between smoking and lung cancer is modified by race/ethnicity; African Americans and Native Hawaiians having significantly greater risks of lung cancer than other groups (3), and these differences cannot be fully explained by differences in smoking patterns (4). Biomarker studies have been instrumental in understanding the underlying mechanism for this difference by documenting a higher take-up of nicotine in African Americans, as well as the accumulation of carcinogens such as TSNAs in African Americans smoking the same number of cigarettes (5). In addition to contributing toward etiologic understanding, studies examining associations between biomarkers of specific carcinogens, such as TSNAs, with cancer may also be important for the regulation of tobacco products (6). In addition, biomarkers can potentially be used to illuminate mechanistic similarities between disparate environmental exposures. For example, opium consumption in the Middle East and Asia, a recognized Group 1 carcinogen (7), is associated with a similar list of cancers as those caused by tobacco smoking (8), and measuring biomarkers of exposure in opium users suggests that some of the same carcinogens in tobacco are also present in opium (9).

The study by Cigan and colleagues (10) provides an important contribution to the literature because it examines associations between tobacco-associated biomarkers and incident lung cancer across multiple racial and ethnic groups in the Multiethnic Cohort (MEC; ref. 11). The authors reported that age-standardized incidence rates of lung cancer were highest in Native Hawaiians and African Americans, followed by Whites, Japanese Americans, and Latinos. In the combined analysis of all these five groups, three biomarkers, 3-HCOT (trans-3′-hydroxycotinine)/cotinine, 3-HPMA, and cadmium were each associated with increased lung cancer risk after adjusting for major confounders, including tobacco smoking intensity and race/ethnicity. Total 3-HCOT/cotinine ratio is a phenotypic measure of CYP2A6 enzymatic activity, the primary enzyme involved in nicotine metabolism (12). 3-HPMA is a metabolite of acrolein, designated as probably carcinogenic to humans (Group 2A) by International Agency for Research on Cancer (13), and previously shown to be associated with lung cancer risk (14). Finally, cadmium which was mainly associated with lung adenocarcinoma in this study, is a known human carcinogen with exposure in the general population driven by cigarette smoke (15). Interestingly, the results observed for the acrolein metabolite was primarily driven by the associations observed in Japanese Americans and Latinos who also smoked less intensely, while those of cadmium were predominantly seen in the whites and those who were

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Cancer Epidemiol Biomarkers Prev 2023;32:289–91

doi: 10.1158/1055-9965.EPI-22-1289

heavier smokers. However, the study did not replicate some of the previous biomarkers reported to be associated with lung cancer risk, including those of PAHs and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is a biomarker of a highly carcinogenic TSNA, nicotine-derived nitrosamine ketone (16). At least one previous study also showed a null association between NNAL and lung cancer (14), and the authors attributed these seemingly conflicting results to variations in smoking behaviors, other characteristics of the study populations, and sample sizes across studies.

Biomarkers can provide distinct information about lung cancer risk factors in populations from diverse ancestries and with different exposure patterns. Even the absence of anticipated associations, such as what was seen for NNAL, can lead to important hypotheses regarding tobacco carcinogenicity. Biomarkers measured in individuals are generally considered to be more objective measures of exposure compared with the self-report and/or environmental assessment (17). Self-reported exposure is prone to information and recall biases and may prove challenging to compare across populations. For a given self-reported smoking intensity in different populations, individuals may be exposed to different amounts of carcinogens. This may be due to the composition of the cigarettes; for example, levels of TSNAs in Chinese cigarettes have been shown to be lower than U.S. brand cigarettes (18). Variations in smoking behaviors across populations, cultural and language differences affecting the definition of active or regular smoking, or the validity of the questionnaire used to collect the exposure data are other potential sources of error in self-reported data. Biomonitoring provides a more direct measure of internal dose of the carcinogenic exposure, regardless of variations in reporting and exposure characteristics (19).

Using exposure biomarkers to study cancer risk has its own limitations and challenges. Biomarkers generally reflect the exposure limited to a time period determined by the metabolism and half-life of the specific biomarker and how it is stored in and excreted from the body. There are a few instances where existence of a long-term reservoir means that the biomarker level reflects an equilibrium between recent and chronic exposure. For example, blood lead level, reflects a balance between long-term storage in the bone and short-term intake (20). However, most biomarkers do not have similar reservoirs and are more reflective of short-term exposure. As such, recent changes in exposure pattern may lead to misclassification of the overall level of exposure. Biomarkers which are metabolized more slowly, like NNAL, have a longer half-life and are less prone to this error (21). Nevertheless, studies with repeated sample collections over time provide important information about the utility of specific biomarkers in assessing long-term exposure. There are not many reports of this type in the literature, and the study by Cigan and colleagues is not unique in relying on a single sample collected at baseline. However, a previous study of two samples collected 5 years apart showed that most smoke-related biomarkers are appropriate for exposure assessment in longitudinal studies, especially in tobacco smokers (22).

The design of biomarker-cancer association studies should optimally include appropriate biospecimens collected before cancer diagnosis in a prospective study. Samples collected in case–control or cross-sectional studies, are not generally useful for biomarker studies, because the development of cancer would change the individuals' behavior and exposure patterns and lead to reverse causation. The logistic complexities of prospective cohort studies and the cost and infrastructure needed to create them have limited the availability of such data in diverse populations, particularly in limited-resource settings and low-and-middle-income countries. Compared with blood and breath, urinary metabolites of exposure to smoke have longer physiologic half-lives and are better suited for these assays (23). However, not many large prospective cohort studies, like MEC, have collected the urine samples necessary to perform such analyses.

Although biomarker studies can be used to evaluate associations of specific chemicals in tobacco products with cancer, such specific associations may be difficult to establish in practice because individuals are generally exposed to multiple correlated carcinogens at the same time. Tobacco smokers are exposed to a mixture of many different toxicants and can be challenging to single out a few of these as causative agents. One strategy used by many researchers, including the current study, is to adjust tobacco-related biomarkers for nicotine metabolites such as cotinine or total nicotine equivalent. Nicotine itself is not carcinogenic, but it is a direct quantitative indicator of recent tobacco consumption. Adjusting for nicotine metabolites serves two major goals: (i) To adjust for the overall exposure to tobacco, which allows estimating a specific biomarker-cancer association beyond what is expected for other tobacco constituents, and (ii) to adjust for the short-term changes in biomarkers resulting from the most recent smoking behavior. However, because most of the tobacco-related biomarkers (including nicotine) are correlated (22), mutual adjustments may lead to overadjustment and a reduced power to detect a carcinogenic association. Unfortunately, there are no other known alternatives for epidemiologic studies in humans, where single-agent exposures are impossible and/or unethical.

Despite these challenges, biomarkers will continue to serve as an essential tool to study and "translate" risk across populations and exposure patterns. To do so more effectively, we will need more prospective studies like that of Cigan and colleagues (10), with detailed exposure assessment and large sample sizes from diverse backgrounds. Other future efforts should focus studies that can enrich the methodology of biomarker research such as (i) identifying biomarkers which reflect longer duration of exposure, including those in potentially longer-lasting media such as hair and nail, (ii) studying the pharmacodynamics of exposure-biomarker relationship in longitudinal studies over several months and years, and (iii) linking biomarkers to other mechanistic evidence including genomic and epigenetic studies.

Authors' Disclosures

No disclosures were reported.

Received December 23, 2022; revised January 10, 2023; accepted January 11, 2023; published online March 6, 2023.

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