

**Perspective**

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**Laboratory to Community: Chemoprevention Is the Answer**

Kenneth Olden and Suryanarayana V. Vulimiri

**Abstract**

In the current issue, Johnson and colleagues present exciting results, using biomarkers involved in aflatoxin B<sub>1</sub> (AFB<sub>1</sub>)-induced hepatocarcinogenesis, as an example of a conceptual framework to target mechanisms of action in developing chemopreventive agents. Their innovative approach offers considerable promise for a field that has long been neglected. Proof-of-principle was demonstrated using a synthetic triterpenoid (CDDO-Im), which activates Nrf2 signal transduction pathway, inhibits formation of AFB<sub>1</sub>-induced DNA adducts and neoplastic hepatic foci, and alters the expression of genes associated with aflatoxin-mediated toxicity. *Cancer Prev Res*; 7(7); 648–52. ©2014 AACR.

It is a special pleasure to write a commentary on the elegant studies of Johnson and colleagues (1) presented in this issue of *Cancer Prevention Research*. One of us (Ken Olden) has followed the excellent work of these investigators for more than 20 years and considered this research to be at the leading edge of cancer prevention related to environmental exposure. It is gratifying to see that their efforts led to the experimental demonstration that aflatoxin B<sub>1</sub> (AFB<sub>1</sub>)-induced liver cancer can be prevented using a chemical intervention approach that is practical to implement in developing countries.

The search for cancer prevention agents to reduce morbidity and mortality from cancer should be a national priority. Beta-carotene was the focus of one of the most intense chemoprevention research efforts more than two decades ago (2, 3). It was selected on the basis of epidemiologic evidence that it had the potential to reduce lung cancer. Although observational studies are important to consider in assessing possible study agents, they must be supported by *in vivo* and *in vitro* studies designed to elucidate mechanisms of action, identify intermediate or surrogate endpoints, and molecular interactions based on gene and protein expression. Johnson and colleagues (1) apparently have not lost sight of the lessons learned from the failed beta-carotene and other trials with similar design.

Now that it is known that genetic variation accounts for only a small fraction of disease phenotype, it is time to follow the lead of Johnson and colleagues. They were among the first to realize that for the promise of genetics to be realized, research efforts must move beyond discovery

of disease-associated genetic variants to understanding of mechanisms by which the environment can modulate gene expression and therefore disease risk. The rigorous, methodical approach used by Johnson and colleagues (1) to elucidate mechanisms involved in AFB<sub>1</sub>-induced hepatocarcinogenesis can serve as a model for developing strategies to prevent other cancers and diseases.

From conception to death, humans are exposed to numerous environmental chemicals and nonchemical stressors. Such stressors include food and nutrients, physiologic agents, such as heat and ionizing and nonionizing radiation, social, economic, and behavioral factors, and natural and synthetic chemicals. Exposure to these environmental stressors can cause disease by damaging DNA, disrupting hormone actions, inhibiting protein synthesis, blocking metabolic pathways, or by reprogramming gene transcription. Of all the cancer-causing agents, exposure to chemicals is a major contributor, and one of the primary sources of human exposure to chemicals occurs through the diet. In developing countries, one of the diet-related exposures to carcinogens is by ingestion of the natural toxin produced by the fungus *Aspergillus flavus*, called AFB<sub>1</sub>. AFB<sub>1</sub> has been shown to be carcinogenic; in particular, it induces hepatocellular carcinoma (HCC) in animals or humans (4). Most of the HCC cancers occur in parts of Southeast Asia and Africa due to chronic infection with hepatitis B and C (HBV and HCV) viruses and ingestion of aflatoxin through moldy grains (5).

For most of human history, we have been concerned about the acute effects of toxic chemicals. More recently, we have become concerned about the adverse effects of low-dose chronic exposures. Over the past 50 years, governments have increased efforts to protect people from exposure to hazardous environmental agents by investing in research and developing regulatory policies (6). Because of our success in reducing the levels of hazardous environmental and occupational exposures, coupled with increase in life expectancy, the relationship between low-dose chronic exposure and the epidemic of noncommunicable diseases (e.g., AFB<sub>1</sub> exposure and HCC) is now a high priority.

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Much of 20th century medicine focused on managing symptoms of end-stage disease, rather than preventing them at the outset. Yet, prevention is possibly the most innovative, cost effective, and quality-of-life-enhancing means to protect human health at every life stage. In the past, the environmental health sciences lacked the necessary tools to identify important disease triggers and pathways. Now that the nation's long-term investment in the basic sciences has put us in the position to fill knowledge gaps, we are poised to more efficiently and more precisely identify the environmental components that set the stage for disease initiation and progression.

Johnson and colleagues (1) report three important observations. First, that one can design an effective cancer chemoprevention strategy based on knowledge of mechanism of action. Second, toxicogenomic RNA expression profile (signature) is valid for assessment of AFB<sub>1</sub>-induced hepatotoxicity. Third, the dose-response characteristic of AFB<sub>1</sub> induction of liver cancer is consistent with a threshold model. Furthermore, their study illustrates the use of the powerful new tools in molecular biology, analytical chemistry, and informational science to (i) identify and validate quantifiable biomarkers linking AFB<sub>1</sub> exposure and development of hepatocellular carcinoma, and (ii) to develop a low-cost, context-appropriate strategy to prevent a devastating disease. In addition to reduction in human morbidity and mortality associated with AFB<sub>1</sub>-induced acute toxicity and liver cancer, these findings will have a huge impact on environmental health risk assessment.

Aflatoxins have been studied for more than 50 years (4). Most of this effort has been directed to understanding better the relationship between carcinogen exposures, the formation of AFB<sub>1</sub> metabolites, DNA adducts, mutations, and liver cancer. Mechanistic studies have demonstrated the importance of metabolism, DNA damage, and hepatotoxicity in aflatoxin-induced hepatocarcinogenesis. For example, chemicals that alter the rate of activation or detoxification of AFB<sub>1</sub> can modulate DNA adduct levels and liver carcinogenesis. Ingested AFB<sub>1</sub> undergoes metabolic activation to form adducts, such as AFB<sub>1</sub>-N7 guanine, which is rapidly excised from DNA. Of course, these studies could not have been done without methodologies for identifying and quantifying DNA adducts and aflatoxin metabolites. Such methodologies have increased in sensitivity and specificity such that molecular dosimetry studies can now approximate exposures experienced in the ambient environment.

Liver cancer is the second leading cause of cancer-related deaths worldwide (7). Because of coexposure to AFB<sub>1</sub> and hepatitis B virus, about 70% of cancer-related deaths in parts of Africa and Asia result from liver cancer, and an estimated 4.5 million individuals live in regions at risk of dietary contamination with aflatoxin (7). In addition to acute liver failure and liver cancer, aflatoxin exacerbates impaired growth in children (8). A World Health Organization priority is to make Africa "aflatoxin safe." However, climate change makes this effort more challenging as aflatoxin-producing fungi are becoming more prevalent, even

in high-income countries such as the United States. So, the potential public health impact of the Johnson and colleagues' (1) study cannot be overstated.

The magnitude of the cancer problem and our inability to develop curative therapies for the common malignancies indicate that new approaches to control the disease are needed. There has not been a decrease in overall cancer mortality since passage of legislation creating the National Cancer Act and the so-called "War on Cancer" in 1971 (9). Whether failure to reduce overall cancer mortality over the past 43 years is related to the program's emphasis on treatment of end-stage disease rather than prevention is widely debated. Even when investments were made in prevention, the agents were selected on the basis of observational studies without significant understanding of mechanism of action, based on studies conducted in animal models, or other critical information such as pharmacokinetic analysis to determine target tissue levels of carcinogens or their metabolites.

Given the long latency between exposure and overt disease, using disease development as the primary endpoint presents a daunting challenge, as management of end-stage disease has been unproductive and costly. Thus, to achieve a better outcome, one needs to use intermediate endpoints or biomarkers that occur earlier and can be linked to both exposure and end-stage disease. Hopefully, the study by Johnson and colleagues (1) will serve as a model for future efforts to develop chemoprevention.

In sharp contrast with the National Cancer Program's obsession with treatment, cardiovascular researchers devoted more attention to prevention. They identified biomarkers associated with increased risk for heart attack and stroke, such as high blood cholesterol levels and hypertension, then developed drugs, and identified and promoted behavioral practices to reduce the risks. A decline in mortality from cardiovascular disease over the past 50 years has been well documented (10, 11). To replicate this success, the cancer program must make prevention research a higher priority and must base their selection of chemoprotective agents on the use of better scientific knowledge and tools.

Although proof-of-principle of cancer chemoprevention has been demonstrated using agents that block enzymes involved in biotransformation, receptor-mediated or signal transduction mechanisms, none of these intervention strategies are ideal with respect to efficacy, potency, or toxic side effects. Whereas, recent efforts using therapies based on targeting of genes or gene products may circumvent limitations associated with earlier prevention efforts, these new gene-based approaches are likely to be too costly and technology-dependent to have practical application in low-income countries or neighborhoods within the United States. Furthermore, these gene-based approaches do not take into account intricate disease networks involving multiple genes and proteins operating in concert, so efficacy or side effects may still be a limitation. To date, the most significant impact on cancer prevention has come from public health policies and practices that reduced environmental and occupational exposures to carcinogens.

Examples include reduction in lung and head-and-neck cancers associated with change in tobacco use.

This publication by Johnson and colleagues (1) has significant implications for cancer risk assessment. Human health risk assessment process was developed to estimate the probability of adverse health effects in humans who are exposed to environmental stressors such as chemicals and radiation. The outcomes of such assessments are used by policy makers to put in place exposure limits to prevent the adverse health outcomes. Few issues in health policy are more contentious than the choice of the appropriate dose-response model for use in estimating risk of cancer associated with exposure to carcinogens. Dose-response models are mathematical expressions fitted to scientific data to characterize the relationship between dose and response. In most cases, dose-response data are not available for levels of exposure experienced by humans in the ambient environments. Therefore, extrapolation is used to estimate risk outside the observable range or from conditions where there is scientific support to situations where scientific support is not available.

Extrapolation is the most contentious issue in cancer risk assessment. Two basic approaches are used in the extrapolation of observational data from high-dose animal experiments to low-dose human exposure. One of these assumes that there is a threshold dose below which no effect is observed. The other approach assumes that there is no safe dose and that a single molecule is sufficient to increase risk for developing cancer. Our understanding of toxicologic mechanisms has advanced considerably since the linear-no-threshold model was adapted for cancer risk assessment. Knowledge of mechanism of action is critical for informing dose-response relationship below the experimental observable range. Johnson and colleagues (1) have used new technologies in analytical chemistry and molecular biology to characterize downstream biologic events in the exposure disease continuum. They showed that AFB<sub>1</sub> is a classic genotoxic substance in that it binds covalently to DNA and induces mutations. In fact, DNA adduct formation exhibits a characteristic linear dose-response curve over a wide range. But, further analysis demonstrated a threshold mode of action, with respect to internal dose of active metabolite and hepatocarcinogenesis. That is, there was substantial adduct formation and DNA damage without having any affect on development of hepatocellular carcinoma. AFB<sub>1</sub> is apparently promoting carcinogenesis via a second mode of action downstream to adduct formation related to expression of signature genes involved in hepatocellular carcinogenesis (12) and signaling pathways mediated by nuclear factor erythroid 2-related factor 2 (Nrf2; ref. 13).

Biomarkers can have a huge impact on the prevention of chronic diseases, provided researchers follow the example of Johnson and colleagues (1), who expended considerable effort to translate laboratory curiosity into useful tools that can now be used by physicians and public health practitioners. After completing basic studies in laboratory animals, their studies were extended to exposed human populations in Africa and China (14, 15). They demonstrated

that liver AFB<sub>1</sub>-N7 guanine DNA adducts and urinary AFB<sub>1</sub>-N7 guanine were biomarkers for aflatoxin-induced risk for liver cancer (16).

The primary need for biomarkers in public health is to identify at-risk or highly exposed populations so that strategies can be initiated to prevent adverse health outcomes. Biomarkers are increasingly being used to establish links between exposure and effect to determine causality. Given the specificity of biomarkers, they can be used to sort out confounding issues associated with population health studies under real-life exposure conditions. Furthermore, they can be used to integrate multiple portals of exposure or cumulative risk from exposure to multiple chemical and nonchemical stressors. And, given the large volume of chemicals in need of toxicity testing and human health risk assessment, the use of biomarkers as surrogate endpoints can reduce the time, cost, and animal use so that the backlogs can be reduced. Moreover, screening for biomarkers has the potential to be automated and put on a high-throughput platform.

Johnson and colleagues (1) realized that the relevance, reliability and overall value of any biomarker are crucially dependent on the quality of the data used in their development and validation. Therefore, they designed and executed rigorous studies to certify aflatoxin-DNA adducts as dynamic tools or surrogate endpoints for hepatocellular carcinoma (17, 18).

On the basis of the above discussion, it is apparent that the systematic development and application of biomarkers, for use in environmental health risk assessment, is a major area of interest. To date, the contribution of biomarkers to the process of risk assessment has remained disappointingly insignificant. However, we predict that their use will become more common and effective as tools, as mode and mechanism of action become more prominent in risk assessment. Also, as health promotion and disease prevention become more significant features of our healthcare system, use of surrogate markers will increase because efficacy can be demonstrated by trials that are smaller, shorter, and cheaper. This is especially true for chronic diseases because of the long latency between exposure and development of overt disease. Biomarkers can also be applied to investigate differences in metabolism and susceptibility to carcinogens in human populations due to genetic polymorphisms.

Johnson and colleagues (1) demonstrated the utility of toxicogenomics in elucidating mechanisms involved in chemical-induced toxicity, which represents yet another important advance in environmental health risk assessment. They took advantage of toxicogenomic microarray technology to examine the effect of a triterpenoid imidazole derivative, 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im) on the expression of genes known to be turned "-on or -off" by exposure to aflatoxin B<sub>1</sub> (12). Using the relatively inexpensive, high-throughput platform developed by the National Institute of Environmental Health Sciences (19, 20), they evaluated transcript profiles or gene signatures previously shown to be predictive

of aflatoxin B<sub>1</sub>-induced hepatocellular toxicity (21). First, they confirmed the gene expression pattern reported by others for aflatoxin-induced hepatocarcinogenesis; then, they showed that the expression pattern characteristic of this exposure-disease outcome disappeared in the context of risk-ablation intervention with CDDO-Im, accurately reflecting the underlying biology involved in hepatocellular carcinogenesis.

Toxicogenomics was initiated for the expressed purpose of addressing the paucity of mechanistic data for use in environmental health risk assessment (19, 20). Unlike traditional toxicity assays, the sensitivity of gene expression technology allows for derivation of information from low-dose challenges and for monitoring of multiple molecular events, pathways, and interactive networks simultaneously. The concept of gene expression profiling is based on the assumption that environmental toxicants will exert their effects directly or indirectly by perturbing normal cell signaling processes, consistent with the findings of Johnson and colleagues (1). It was predicted that by perturbing normal cell signaling processes, a cascade of events would be elicited that culminate in gene or protein expression patterns unique for specific toxicants (12, 19, 20).

As the adage "an ounce of prevention is worth a pound of cure" goes, this article on protection against AFB<sub>1</sub>-induced liver cancer will lead to intervention efforts to reduce morbidity and mortality and healthcare costs associated with this devastating disease. Whereas, prevention can take many forms; chemoprevention (chemical intervention to prevent) is one such strategy. Several chemopreventive agents have been selected on the basis of their efficacy in test systems and mechanism of action, such as cyclooxygenase-2 inhibitors, modulators of estrogen or retinoid receptors, etc. (22). One class of chemopreventive agents that are used in cancer prevention are the triterpenoids, a class of pentacyclic isoprene compounds derived from triterpenes (e.g., oleanolic acid), which naturally occur in flowering plants (23). However, synthetic triterpenoid analogs (e.g., CDDO-Im) have been shown to be more potent than their parent compounds with promising antioxidant, anticancerous, anti-inflammatory, apoptotic, and cytoprotective properties (24, 25). The mechanism of action of these synthetic triterpenoids is partly mediated through the Nrf2 signaling pathway (25).

Some of the earlier chemoprevention studies used oltipraz, a bifunctional agent involved in the activation of both phase I and phase II enzymes (26). Oltipraz has also been used to prevent AFB<sub>1</sub>-induced HCC in both animal models and clinical trials (27). An earlier study by Yates and colleagues (13) has shown that CDDO-Im inhibits gluta-

thione S-transferase placental form (GST-P) positive foci in rat liver model and also observed that the triterpenoid analog is 100-times more potent than oltipraz in cancer prevention. Synthetic oleanane triterpenoids, which were developed initially as anti-inflammatory agents in Dr. Sporn's laboratory, have been shown to be extremely potent inducers of Nrf2 signaling pathway *in vivo* (28), preventing aflatoxin-induced HCC in rats. Hepatocarcinogenesis induced by AFB<sub>1</sub> in rats is inhibited by CDDO-Im through the induction of Nrf2 gene that is involved in the regulation of hepatic detoxification and cytoprotective genes by reducing the AFB<sub>1</sub>-N7 guanine adduct formation (13). Besides being cancer chemopreventive agents, triterpenoids also have shown to protect against cigarette smoke-induced emphysema and cardiac dysfunction through Nrf2-mediated activation (29). Thus, the oleanane triterpenoids represent a very powerful class of chemopreventive agents owing to their broad tissue distribution and potential Nrf2 induction leading to cytoprotective responses.

It is gratifying that progress in environmental health sciences has reached the stage where knowledge of mechanisms is now being used to develop effective agents to prevent chronic diseases. Biomarkers can be used in clinical and epidemiologic studies to measure human impact of environmental exposures directly, circumventing the uncertainties in risk assessment associated with interspecies extrapolation. Monitoring of biomarkers is especially useful in dosimetric analysis, as they define the "internal dose" or "biologically effective dose" necessary to induce a specific biologic response, irrespective of the manner as routes of exposure.

In summary, the article by Johnson and colleagues (1) is a high-impact publication for the following reasons: first, it provides strong evidence that AFB<sub>1</sub>-induced liver cancer can be prevented; second, it provides a model for the development of effective chemopreventive agents for cancer and other diseases; and third, it makes a compelling case for the development, validation, and use of biomarkers as surrogates for overt disease and the need for mechanistic information in risk assessment.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views of the U.S. Environmental Protection Agency.

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# Cancer Prevention Research

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