Pathways to Cancer Prevention

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Resources allocated to cancer control are overwhelmingly dedicated to early detection and treatment. To be sure, they have resulted in significant improvements in survival and even cures when the outlook was previously grim. But this emphasis has diverted attention from opportunities to prevent many cancers from occurring in the first place, while the cancer burden and costs of treatment in the US and around the world continue to grow.

Cancer prevention lies upstream, toward the beginning of the cancer control continuum. Prevention programs mostly focus on well-established causes primarily under individual control. They emphasize what we can do to reduce our own cancer risk by adopting healthy lifestyles—avoiding tobacco smoking and excessive alcohol, maintaining healthy weight, exercising regularly, eating a healthy diet, and getting preventive medical care. These are important, although only partly effective, and more is needed.

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In June, the American Association for Cancer Research (AACR), the world’s largest scientific organization focused on cancer research, sponsored a conference called Environmental Carcinogenesis: Potential Pathway to Prevention. It was the organization’s first program on this topic in its history. The agenda included descriptions of recent findings of genetic “fingerprints” of environmental exposures, updated understanding of how environmental chemicals contribute to cancer risk, the ubiquity of exposures, disproportionately impacted communities, and calls for more prevention-oriented policies and research.
As reported previously in the Networker, in January a number of organizations came together to sponsor a conference on Cancer and the Environment in Pittsburgh. Here, too, speakers and panel discussions emphasized the need to act on what we already know to improve cancer prevention programs.

Also this year the International Agency for Research on Cancer (IARC) updated the Preamble to the IARC Monographs. While monographs systematically assess the carcinogenic potential of specific agents, the preamble describes the objective of the program and methods for scientific review. The revised preamble incorporates new insights into cancer biology as they apply to environmental agents. Scientists increasingly recognize the many ways by which environmental chemicals and contaminants can contribute to cancer risk—alone or in combination with other factors—and the implications for prevention.

**Models of Cancer Causation**

Although a few kinds of cancer are caused largely by single agents, most have multiple contributing causes. Tobacco smoking is surely the dominant cause of lung cancer, raising the risk more than ten-fold in smokers compared to non-smokers. Smoking also increases the risk of at least twelve other kinds of cancer. But lung cancer incidence is not entirely explained by personal smoking history. In fact, studies show that the proportion of never-smokers with some kinds of lung cancer has increased over the last 15 years, particularly among women. Exposures to other environmental agents known to increase lung cancer risk—including dozens of hazardous air pollutants, diesel exhaust, industrial chemicals, metals, asbestos, radon, and radiation—help to explain this. In an analysis of data from 18 counties in the US, epidemiologist David Kriebel estimates that about half of smoking-related cancer cases would still occur even if smoking were entirely eliminated.

The “web of causation” is among the most popular of models and metaphors describing the multifactorial origins of cancer. But as epidemiologist Nancy Krieger pointed out, the choice of factors incorporated in the “web” is often guided by “a hidden reliance upon the framework of biomedical individualism”. Community- and societal-level strands are frequently left out.

Years ago, epidemiologist Kenneth Rothman proposed a sufficient causal pie model for cancer primarily because of cancers’ multifactorial origins. In this model, a cause is not a single component, but a minimal set of conditions or events that produces the cancer in a person, although you could easily apply this thinking to a community. As illustrated below, different combinations of component causes A-J add up to sufficient causes I-III of a cancer. Each wedge is a component cause. The nature and number of component causes will differ among different kinds of cancer and even for the same kind of cancer in different people. Biologic interactions among component causes are common, making it difficult if not impossible to estimate the percentage of cases “caused” by a particular exposure.
A sufficient causal “pie” for a case of lung cancer might consist of a) an inherited defect in DNA repair, b) defective programmed cell death (apoptosis) from a tobacco carcinogen, c) a mutated anti-cancer gene from radon, d) a silenced tumor suppressor gene from a prenatal exposure and e) obesity with generalized inflammation. Another sufficient causal pie for a case of lung cancer might include component causes related to mutations from diesel exhaust.

Breast cancer is another multifactorial disease with more than a dozen well-established risk factors and others that are almost certainly related. Some, like peak height growth and early puberty, are established early in life. Prenatal exposure to diethylstilbestrol or DDT also increases breast cancer risk decades later. Among known risk factors, none increases the likelihood of developing breast cancer anywhere near the impact of smoking on lung cancer risk. Rather, combinations of exposures explain breast cancer patterns in populations although their relative importance varies among individuals. This is undoubtedly true for other common cancers as well.

Assembly of component causes can begin very early in life, but until the “pie” is completed, they are not sufficient to cause cancer. This suggests multiple opportunities for cancer prevention by avoiding exposures that together add up to a sufficient cause—even after some components are already in place.

**The exposome:**

In 2005 Christopher Wild, then the director of the International Agency for Research on Cancer (IARC), coined the term “exposome”, which he defined as the totality of exposures to all exogenous environmental agents, socioeconomic conditions, lifestyle, and diet along with markers of endogenous processes across the life-time of an organism or community of interest. (Table 1) Wild saw a need to balance the outsized emphasis on the genome with a comparable concept that encompassed the complexity of exposures that interact with the genome, tissues and organs influencing health and disease risk.

Table 1: Components of the exposome potentially directly or indirectly related to cancer risk

<table>
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<th>External environmental exposures</th>
<th>Internal chemical environment</th>
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<td>Radiation</td>
<td>Metabolites of food, chemicals, pollutants</td>
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<tr>
<td>Air and water pollution</td>
<td>Proteins resulting from gene expression</td>
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Each of the exposures in Table 1 traces to individual-, community- or societal-level activities or circumstances and is potentially associated with cancer risk directly or indirectly, although the mechanisms for some are better understood than others. Chronic stress alone, for example, may not be sufficient to cause cancer, but associated chronic inflammation can promote tumors in their early stages of development. Similarly, socioeconomic factors impact biomarkers related to cancer risk as well as influencing the likelihood of exposures to other well-established risk factors.

Juarez et al. propose a “public health exposome”, which they see as a framework that helps compare differential levels of exposure at critical life stages, personal health outcomes, and population health disparities. It includes mediating and moderating factors at both the individual and population levels. The public health exposome includes exposures in Table 1 and adds factors with strong influences on personal and public health, including poverty, education, employment, segregation, discrimination, racism, adverse childhood experiences, control in life and on the job, and the policy environment—Federal, state, and local—that directly influence personal and community-level exposures.

**Chemicals, pollutants, and cancer—key characteristics of carcinogens:**

Among each of the general categories of exposures in Table 1, the contribution of environmental chemicals and pollutants to cancer incidence has been among the most hotly debated over the past forty years with wide-ranging estimates. New understanding of cancer biology and the various ways that chemicals can contribute to cancer causation show that earlier estimates based on old assumptions are not valid. The 2010 President’s Cancer Panel agreed. They focused on industrial, occupational, and agricultural chemical exposures, indoor/outdoor air pollution, water contamination, nuclear fallout, radiation, and electromagnetic fields and said “The previous estimates [of environmental causes of cancer] are woefully out of date…and underestimate significantly the true toll of cancer related to these exposures.”

Environmental chemicals can contribute to tumor formation in a variety of ways. Genetic toxicants can cause mutations and other DNA damage that increase cancer risk. Some chemicals acting as “co-carcinogens” do not cause cancer by themselves but can enhance the potency of genetic toxicants, adding to the “causal pie”. Tumor promoters enhance tumor formation, once the process is initiated. Chemical exposures during fetal and childhood development can alter tissue architecture, for example in the breast and prostate, making them more prone to tumor development years later.
Early this year, IARC updated their methods for evaluating chemicals when considering whether or not to classify them as “carcinogens”. They have incorporated “key characteristics of carcinogens” in the process at an early stage. These key characteristics are based on empirical observations of chemical and biologic properties of substances already known to be human carcinogens and describe mechanisms by which they can contribute to cancer causation. The agency notes that many carcinogens act through multiple mechanisms causing biologic changes in the multistage process of carcinogenesis. Carcinogens virtually always show at least one and frequently more than one of the ten key characteristics in Table 2.

Table 2.

<table>
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<th>Ten key characteristics of carcinogens</th>
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<tr>
<td>1. Is electrophilic or can be metabolically activated to an electrophile</td>
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<tr>
<td>2. Is genotoxic</td>
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<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
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<tr>
<td>4. Induces epigenetic alterations</td>
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<tr>
<td>5. Induces oxidative stress</td>
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<tr>
<td>6. Induces chronic inflammation</td>
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<tr>
<td>7. Is immunosuppressive</td>
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<tr>
<td>8. Modulates receptor-mediated effects</td>
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<tr>
<td>9. Causes immortalization</td>
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<tr>
<td>10. Alters cell proliferation, cell death, or nutrient supply</td>
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The first three characteristics deal with DNA damage or genotoxicity long known to be associated with increased cancer hazards. The other seven address additional mechanisms by which known carcinogens can also support tumor formation. This does not mean that any unstudied chemical with one or more of these properties will necessarily turn out to be carcinogenic, but it does mean that known carcinogens exhibit some combination of these characteristics, and when we see them, we should be concerned and take a closer look.

**More comprehensive approaches to cancer prevention**

Comprehensive programs for cancer prevention should of course encourage people to reduce their own risks. But they need to go further and insist on reduction in exposures to occupational and environmental carcinogens beyond individual control. IARC has identified 120 agents as known carcinogens and 82 as probable carcinogens in humans. Yet, exposures to many of them continue because of failure to act by governments, businesses, and policy makers who often point to uncertainties in risk estimates, the cost of changes to material and energy production processes and call for more research. The “delay game” employed by businesses and their political supporters assures that added restrictions on carcinogens are hard-won. Meanwhile families and communities bear the health consequences.

Throughout the country communities lie in the shadow of petrochemical plants and other industries releasing carcinogens into the environment. Manufacturers make consumer products
containing carcinogens when safer alternatives are available. In response, advocacy and community groups have joined together with scientists demanding reductions in exposures, reformulation of products, and re-design of processes.

Here are a few examples of communities and organized efforts throughout the country demanding greater protection from carcinogens and other hazardous substances in their daily lives:

**Coming Clean**, founded in 2001 by environmental health and environmental justice organizations to unite their efforts to reform industrial chemical and fossil fuel industries so they are no longer a source of harm, aims to secure systemic changes that allow a safe chemical and clean energy economy to flourish. Staff of the Science and Environmental Health Network (SEHN) worked with Coming Clean helping to develop background papers for the [Louisville Charter for Safer Chemicals](#).

Communities in St. John the Baptist parish in southern Louisiana are among those along the Gulf Coast, many predominantly African-American and low-income, beleaguered by the extensive petrochemical industry. The parish includes neighborhoods most at risk of cancer due to air toxicity, according to the EPA’s National Air Toxics Assessments. A mixture of known and probable carcinogens are regularly emitted from nearby petrochemical plants at levels that far exceed health-based limits. For years, residents have insisted on exposure reduction but industry has responded with half measures and critiques of “government science”, arguing that the risks are overblown. Recently, the state finally agreed to assess cancer incidence in the parish after an informal survey concluded that cancer rates are elevated compared to other areas.

Sterigenics, a medical product sterilization facility in Willowbrook, IL was forced to close in February after years of releasing excessive amounts of ethylene oxide, a known carcinogen, into the surrounding neighborhood. Regulators failed to act until community pressure could no longer be resisted. A judge recently ruled that the facility may re-open with improved pollution prevention equipment. Lawsuits are pending.

Water Gremlin, a manufacturer of battery terminals and lead sinkers in White Bear Lake Township in MN has been emitting excessive levels of trichloroethylene, a known carcinogen, into the air for years. Community groups, assisted from time to time by SEHN staff, pressured the Minnesota Pollution Control Agency (MPCA) to take stronger action to protect public health and determine what harm may already have occurred. The company was fined millions and required to switch to a different but less well studied solvent in their degreasing operations. Pollution violations continued and some of their operations have now been completely shut down. A legislative investigation is underway to examine the role of the MPCA in allowing the pollution to continue for so long.

Market-based campaigns pressuring large companies to alter their supply chains and inventories are also having success. Coming Clean pushed Dollar Stores to begin removing products with harmful chemicals from their shelves and stock healthy local, fresh food for their customers. Mind the Store has successfully driven other major retailers to discontinue selling products containing carcinogens and other hazardous chemicals. Healthy Building Network has been a
major driver of reducing carcinogens in building materials. Health Care Without Harm’s and Practice Greenhealth’s Green Building and Safer Materials programs, with which SEHN has worked for over 20 years, support efforts to clean up the supply chain for products purchased by health care institutions so that they contain fewer carcinogens and other hazardous materials. Clean Production Action designs tools and programs to reduce the use of carcinogens and other hazardous chemicals in materials and products, working with businesses, non-profits, governments, and academic institutions. These efforts build momentum and economic incentives for development of safer alternatives that will appeal to larger markets.

But there is much more to be done. Occupational and community-wide exposures to carcinogens are too common and they remain in many building materials and an array of consumer products. SEHN participates in the growing Cancer Free Economy Network. Along with others, we believe the water we drink, the air we breathe, the food we eat, the places we live, work, and go to school, and the products we use every day should not make us sick. Together we are working to make that a reality.