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# A tipping point in cancer epidemiology: embracing a life course exposomic framework

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**The pathogenesis of multifactorial malignant diseases, with variable onset, severity, and natural history, reflects development-specific exposures and individual responses to these exposures influenced by underlying genetic predisposition. Embedded in life course theory, exposomics provides a framework to more fully elucidate how environmental factors alter cancer risk, disease course, and response to treatment across the lifespan.**

## Introduction

For many cancers, environment has a larger role in susceptibility than does genetics [1]. This, combined with the lack of broadly applicable precision medicine approaches to cancer prevention and treatment, underscores the need to examine environmental exposures across the life course and their associated gene–environment interactions to fully elucidate the underpinnings of cancer initiation and progression. A multitude of environmental and microbial exposures (e.g., smoking, psychological stress, diet, indoor/outdoor pollutants, viral infections, and chemical toxins) are thought to have a role in cancer [2]. Yet, the role of the environment in risk, prognosis, and response to treatment is still largely uncharted in cancer studies. Additionally, studies examining the interaction between these exposures and sex-specific influences are rare [3]. Sex dimorphism strongly impacts tumor biology, disease expression, and treatment response, as well as vulnerability to environmental toxins. Social constructs shape the interaction between germline genetics and exogenous factors throughout the life course. Cancer outcomes are socially patterned, with greater burden among individuals of lower socioeconomic status (SES) or from minoritized groups who are disproportionately burdened by environmental toxins.

The exposome concept addresses these complexities by more comprehensively examining the effects of health-relevant environmental factors over the life course and our need to integrate biomarkers of exposure that allow for a more accurate assessment of risk and disease progression [4,5]. Embedded in life course theory, exposomics provides a framework to elucidate how environmental exposures have the potential to alter cancer risk, disease course, and response to treatment, which can vary within specific phases of the lifespan [6,7]. The underlying pathogenesis of multifactorial malignant diseases, with variable onset, severity, and natural history, reflects development-specific exposures and individual response to these exposures influenced by underlying genetic predisposition. Knowledge that early-life environmental factors (e.g., *in utero* and childhood) can be interactive and/or cumulative in programming disease expression over the life course, further highlights the need for a life course framework to guide cancer research (Figure 1). Figure 1 is a conceptual blueprint that illustrates how a life course lens informed by exposomics can be used to develop a multimodal approach for understanding neoplastic diseases.

At inception, the fetus is preprogrammed with a genetic risk profile for neoplastic disease. From this point on, this disease risk profile can be altered by exogenous factors. We refer to factors protecting cells from transforming to a neoplastic state as 'maintaining tissue balance' and factors increasing the probability of transformation to a neoplastic state as 'disrupting tissue balance'. Through this lens, an individual's cancer risk becomes transitory, continually shifting over time until the separation between normal and neoplastic tissue can be identified. In addition to linking environmental exposures to cancer incidence and mortality, we must understand how environmental factors influence comorbidities and response to treatment in patients with cancer. For example, breast cancer is tightly intertwined with cardiovascular and pulmonary disease through shared risk factors, including air pollution exposure and treatment-related cardiotoxicity [8]. Here, we highlight particular life-stage examples and new directions for expanding current understanding of the relationship between the environment and cancer outcomes. Within each example we describe promising advancements that will facilitate a life course exposomic framework and key challenges that need to be addressed before significant advances in the field can be made.

## Creating a life course exposomic framework

While environmental exposures have long been thought to have a role in pediatric malignancies, there are few well-established environmental risk factors. For malignancies presenting during mid to late life, more evidence exists. For example, while smoking is often cited as the main risk factor, a distinct set of patients develop lung and bladder cancer without a history of tobacco use. Other environmental exposures, such as air pollution, radon, aniline dyes, and arsenic exposure, have been linked to both lung and bladder cancer. The Surveillance Epidemiology and End Results (SEER) program estimates that radon gas exposure contributes to 21 000 lung cancer deaths per year in the USA. Exposure to arsenic and polycyclic aromatic hydrocarbons (PAHs) has been

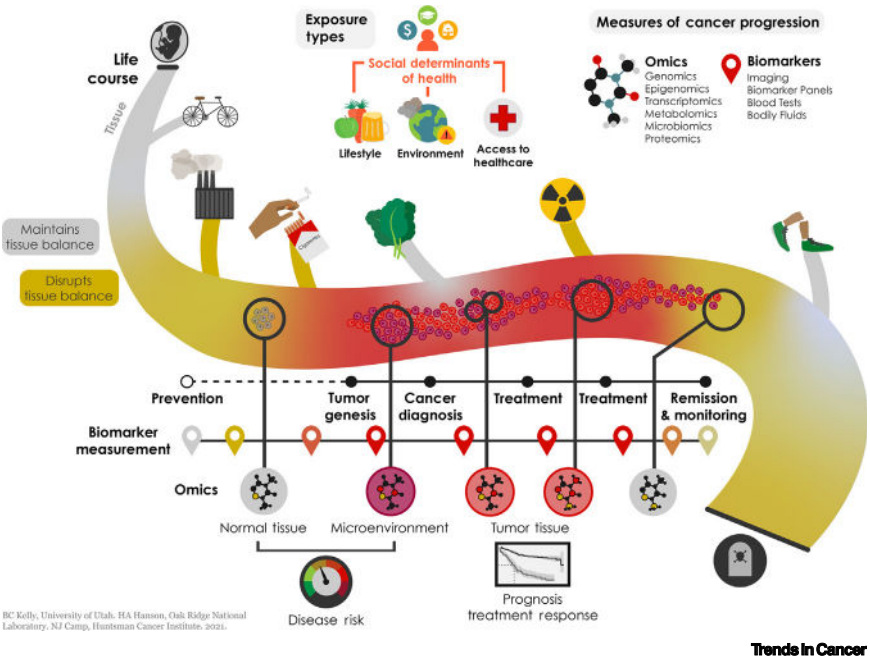


Figure 1. Conceptual framework of life course epidemiology in cancer. Research expanding our understanding of the multiple chemical, physical, and psychosocial factors contributing to programming cancer risk as well as influencing tumor biology, treatment response, and related toxicity over the course of the disease, calls for a life course approach. Moving toward an exposomic framework that more comprehensively considers high-dimensional measures of the external and internal environment reflecting biological response to environmental factors hold significant potential to move us closer to precision medicine in cancer.

linked to increased risk of both cancers. The association between ambient air pollutants ($PM_{2.5}$, $PM_{10}$, and $NO_2$) are strong for lung cancer and mixed for bladder malignancies [9].

For pediatric diseases, such as childhood leukemia, a short latency period points to *in utero* and early-life exposures as important risk factors. Complicating efforts to uncover the relationship between environmental exposures and cancer risk later in life is the long latency between carcinogen exposure and initiation of cancer and the need to consider the importance of the developmental period at time of exposure. Environmental factors that disrupt key processes and pathways (e.g., endocrine- and metabolism-disrupting chemicals, those impacting fidelity of the genetic code as well as epigenetic processes, and those influencing stress-response systems) contribute to cancer expression, even starting *in* utero, as do sexually dimorphic effects. The development of longitudinal biomarkers that continually monitor environmental exposures and individual trajectories of cancer development has been an elusive goal for decades. However, this goal is increasingly coming into reach as our ability to collect, store, and process increasingly complex biometric and environmental exposure data is rapidly improving.

Using biomonitoring data to assess environmental exposures at the population level integrated into large population-level health survey studies will be essential. For example, the Canadian Health Measures Survey (CHMS) successfully implemented a human biomonitoring component in their population level survey from 2007 to 2015. This survey provides population-level data for over 250 environmental chemicals in Canadians aged 3–79 years, demonstrating that such screening protocols are realistic at the population level. Similar long-term and longitudinal collection of biomonitoring data are needed to fully assess the risk of chemical exposures throughout the life course on later life cancer risk. Several non-invasive sample collection methods for identifying levels of environmental exposure and cancer risk in adults have been leveraged. For example, toenail clippings are easily collected and can provide valuable information about arsenic and other chemical exposures [10]. Collection of this information began during the late 1990s in studies cited in the aforementioned review and cover populations across 29 countries and ages. Additionally, urine and blood samples are easily collected biospecimens in adults that allow for monitoring exposure to chemicals as well as monitoring risk for cancer development over the life course [11]. Biomonitoring data in matrices including urine and blood can be used to assess current levels of exposure as well as longer term levels of exposure when repeated samples are collected longitudinally. Such information can also be used to interpolate population exposures in an area using physiologically based pharmacokinetic models [12].

Pediatric studies face unique challenges in collecting biological samples during critical developmental periods preceding diagnosis for direct measurements. Novel or readily available, underutilized biospecimens coupled with emerging molecular approaches for high-dimensional exposure assessment (epigenetics, metabolomics, and somatic mutational profiles) are being used to elucidate environmentally induced disease [13,14]. For example, with extensive bioarchiving programs in the USA and other countries, dried blood spots (DBS) have the potential to substantially aid childhood cancer research. Untargeted metabolomics of small molecules in archived

newborn DBS holds promise for discovering early-life exposures that contribute to risk [15]. Untargeted workflows can be used for the analysis of small molecules in archived DBS to discover novel biomarkers, to provide insights into the initiation and progression of diseases, and to provide guidance for disease prevention.

In addition to identifying new uses for archived biospecimens, high-dimensional analytics combining sophisticated histological and chemical analyses have been developed to reconstruct early-life exposome (e.g., metals, organic chemicals, nutrients, and infection) in teeth. For example, methods to measure chemical exposures in tooth layers corresponding to specific life stages have been used in epidemiological studies to link exposures over developmental periods, starting *in utero,* with health outcomes. This approach has significant potential for pediatric cancer research. Teeth naturally shed over childhood are easy to transport and store, being stable at room temperature. Even if shed after the initiation of therapy, primary teeth can be used to reconstruct exposures before a cancer diagnosis.

Humans are not exposed to one exposure at a time. Co-occurring exposures may result in additive, synergistic, antagonistic, or potentiating effects across the life course. Methods to examine complex mixture effects of multiple chemicals and co-varying exposures continue to emerge and will facilitate application of the exposome framework in cancer research [16]. Leveraging these and other emerging non-invasive and creative directions for biomarker collection and analyses across the life course could provide longitudinal metrics of exposure and lend additional information about transitory states of cancer development.

Lack of standardized data collection protocols, Big Data adoption and planning considerations, and regulatory hurdles related to health data privacy have hindered the broader integration of complex biomarker data for cancer research. For example, childhood cancer is rare, leading to samples sizes from a single institution that are too small for in-depth explorations into the relationship between environmental exposures and risk. Novel methods for combining information across multiple institutions while preserving patient privacy would allow for aggregation of data and increased sample sizes. Federated learning (FL) is one method that would allow multiple medical institutions to collaborate without sharing identifiable information. This is achieved by using edge computing to train shared models without disclosing or exchanging their respective data sets. These efforts could be expanded by developing standardized protocols and new ways to train models without requiring the sharing of identifying data.

## Concluding remarks

Integrating exposomic approaches and measures covering various periods of development, will allow for integrative approaches to generate and test hypotheses about the underlying mechanisms through which environmental exposures affect cancer risk, response to treatment, and risk for treatment-related toxicities and comorbidities. This work will greatly benefit from the adoption and continued development of the tools and infrastructure needed to facilitate the integration of environmental data into translational research.

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## Declaration of interests

None declared by authors.

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