Chapter 4
The Cancer Exposome: Gene–Environment Interactions (GxE) in Carcinogenesis

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ABSTRACT

Gene-environment interactions play a crucial role in tumor initiation by influencing cellular and tissue plasticity. Environmental and internal factors influence carcinogenesis by acting on specific sensing genes and pathways, leading to epigenetic, genetic, and metabolic changes that shape the TME. Understanding the exposome can inform gene expression, epigenetic changes, and immune responses, particularly for the reproductive health and cancer prevention. The authors discuss the latest methodologies in exposome assessment, challenges in defining and measuring harmful environmental impacts. Exposome applications in public health policy face challenges and also opportunities in translating exposome research into actionable measures. Gene-environment interactions are shown by analyzing case studies, emerging debates in research, and clinical practice. This work highlights the transformative potential of exposome informed policies in addressing global

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health challenges and reducing health disparities.

INTRODUCTION

Exposomics studies environmental, nongenetic determinants of human health. Exposome analysis is met with the complexity of exposures and interconnected etiological determinants of disease (Safarlou et al., 2024). Cancer, a global health challenge, emphasizes the need for a discovery-driven analysis of environmental risk factors. Cancers with multifactorial origin, show varying risk factors for population subgroups on incidence and mortality rates.

Environmental, social, chemical and biological factors shape the tumor microenvironment (TME) that drives carcinogenesis. The TME undergoes Epithelial-mesenchymal transition (EMT), and ECM remodeling (tissue morphogenesis) with abnormal cell growth and metabolism. Exposomics shows how environmental influences affect cellular and non-cellular components, including cancer-associated fibroblasts, extracellular matrix, endothelial and immune cells. These TME components are influenced by both internal (genetic, metabolic) and external (environmental, lifestyle) factors, towards immune escape, and resistance to treatment. However, some cancers show stronger associations with environmental factors, while others are more strongly linked to genetic predispositions (Biradar, Suresh, et al., 2025).

Gene-environment interactions (GxE) play a crucial role in tumor initiation by influencing cellular and tissue plasticity. Tumor-initiating plasticity is conceptualized as intrinsic responses of mutant epithelial cells to environmental changes, the reprogramming of non-neoplastic host cells. Exposomics enhances cancer biology by improving the understanding of how environmental exposures affect cellular and molecular processes. GxE can lead to pro-tumorigenic states in response to multiple environmental factors collectively known as the exposome. Epigenetic and metabolic changes in response to environment-sensing gene pathways. Phthalate exposure is linked to prostate cancer aggressiveness through the induction of microRNA-5010 and the Nrf2-EGR1-GDF15 signaling pathway (Tsai et al., 2025). Environmental carcinogens (e.g., benzo[a]pyrene, heavy metals, pesticides) induce DNA methylation changes, histone modifications, and alter sperm expression (Akhatova et al., 2025).

Epigenetic and metabolic changes can be transmitted across generations, priming offsprings for increased cancer susceptibility. Environment sensing genes involve cell surface receptors that bind to environmental cues (growth factors, cytokines), intracellular sensors for oxygen levels, DNA damage signaling pathways activated by environmental changes. Here we have some of the biomarkers of environment relevant to cancer biology (Table 1).

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