


# Chapter 4

## Deciphering the Role of Environmental Exposures in Androgen- Resistant Prostate Cancer an Insights from Multi-Omics and Toxicogenomics

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### **ABSTRACT**

*Prostate cancer (PCa), especially androgen-resistant PCa (ARPC), poses a major global health burden shaped by both genetics and environmental exposures. This chapter examines how toxicants like endocrine disruptors, POPs, and xenobiotics contribute to PCa progression through exposomics, toxicogenomics, and multi-omics approaches. It highlights mechanisms such as AR signaling disruption, mitochondrial dysfunction, metabolic shifts, and epigenetic changes driving therapy resistance.*

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*Using cell models and spatial transcriptomics, it explores how exposures promote metastasis. The chapter also discusses tools like eDNA, epigenetic biomarkers, and predictive models for early detection and prevention, underscoring the importance of integrating environmental risk into precision oncology.*

## **1. INTRODUCTION**

Prostate cancer remains one of the most frequently diagnosed cancers and is a major contributor to cancer-related deaths in men worldwide. Although early-stage prostate cancer generally responds well to androgen deprivation therapy (ADT), many patients eventually progress to androgen-resistant or castration-resistant prostate cancer (ARPC/CRPC). This advanced form is characterized by continued tumor growth despite reduced circulating androgen levels and is notably more aggressive and difficult to treat. The transition to androgen resistance represents a critical shift in disease biology; however, the environmental factors driving this change remain insufficiently investigated.

Recent evidence suggests that prolonged exposure to environmental toxins—such as endocrine-disrupting chemicals (EDCs), industrial waste, heavy metals, and food contaminants—may significantly contribute to the onset and progression of prostate cancer, as well as to the development of treatment resistance (Rappaport, 2011; Wild, 2005). These toxicants can disrupt hormonal signaling, induce oxidative stress, alter immune and inflammatory responses, and influence epigenetic modifications. Furthermore, environmental exposures often interact with inherited genetic susceptibilities and acquired somatic mutations, potentially contributing to tumor heterogeneity and the emergence of resistance mechanisms.

Understanding these complex interactions requires comprehensive approaches that extend beyond conventional research methods. Advances in multi-omics technologies—including genomics, epigenomics, transcriptomics, proteomics, and metabolomics—enable detailed molecular profiling of prostate tumors. When integrated with toxicogenomics, which examines how gene expression and molecular pathways respond to environmental toxins, these tools offer unprecedented insights into the environmental contributions to prostate cancer biology. Together, they facilitate the identification of exposure-related biomarkers, altered signaling networks, and novel therapeutic vulnerabilities.

Recent multi-omics studies have revealed distinct molecular alterations in prostate tumors associated with environmental exposure histories, including disruptions in androgen receptor (AR) signaling, DNA repair pathways, and metabolic reprogramming. Databases such as the Comparative Toxicogenomics Database (CTD) and TG-GATEs provide supporting evidence that environmental toxicants affect

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