Chapter 5
The Interplay Between CES1 Gene Polymorphisms and Environmental Exposures in Chemotherapy Toxicity in Breast Cancer:
CES1 Variants and Environment in Chemo Toxicity

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ABSTRACT

Breast cancer remains one of the most prevalent malignancies worldwide, with chemotherapy serving as a cornerstone of treatment despite its substantial toxicity risks. Carboxylesterase 1 (CES1), a critical drug-metabolizing enzyme, plays a central role in the activation and clearance of various chemotherapeutic agents, including capecitabine. Genetic polymorphisms in CES1, together with environmental expo-

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sures such as pollutants, diet, and lifestyle factors, contribute to the interindividual variability in chemotherapy metabolism and toxicity profiles. This chapter examines the complex gene–environment interplay influencing treatment outcomes in breast cancer and highlights emerging strategies for integrating genetic and environmental assessments. A deeper understanding of these interactions paves the way for precision oncology approaches that personalize therapy, improve tolerability, and ultimately enhance patient outcomes in breast cancer care.

INTRODUCTION

As one of the most frequently occurring cancers worldwide, breast cancer continues to account for a substantial proportion of cancer mortality in the female population (Yüksel et al., 2019). Standard treatment often includes chemotherapy, which has significantly improved survival rates and reduced recurrence for patients with breast cancer . However, chemotherapy is a double-edged sword: while it targets rapidly dividing tumor cells, it also causes systemic toxicity that can vary widely among individuals. This variability in chemotherapy-induced toxicity is a major clinical challenge, as some patients experience severe adverse effects that necessitate dose reductions or even treatment discontinuation. Understanding the factors that underlie differences in toxicity profiles is therefore critical for optimizing breast cancer care and improving patient outcomes.

Chemotherapy toxicity is influenced by a combination of genetic factors (such as inherited polymorphisms in drug metabolism genes) and environmental factors (such as exposure to pollutants, lifestyle, and concurrent medications). The field of pharmacogenetics has demonstrated that patients' genetic makeup can substantially affect how they metabolize and respond to chemotherapeutic drugs (Wu & Xiong, 2024). In parallel, environmental exposures throughout a patient's life can modulate biological pathways through epigenetic changes or enzyme induction/inhibition, thereby altering drug efficacy and toxicity (Panahi et al., 2016; Kim et al., 2012; Alam et al., 2021; Swagatika & Tomar, 2016; Hu & Yu, 2019). Among the genetic factors, increasing attention has been given to polymorphisms in genes encoding drug-metabolizing enzymes. One such enzyme is Carboxylesterase 1 (*CES1*), a liver enzyme involved in the metabolism of various chemotherapeutic agents and prodrugs (Qian & Markowitz, 2020). Variations in the *CES1* gene may lead to altered enzyme activity, influencing the breakdown of chemotherapy drugs and consequently the intensity of side effects (Yüksel et al., 2019).

The interplay between *CES1* gene polymorphisms and environmental exposures represents a rapidly expanding area of research with significant implications for breast cancer therapy. *CES1* exhibits considerable genetic variability and is also