# Chapter 6
# Epigenetic Regulation of Breast Cancer

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## ABSTRACT

*Breast cancer is a carcinoma of mammary glands, which starts off as abnormal proliferation of ductal cells. This could, then, become either benign tumours or metastatic carcinomas. It is one of the most common causes of deaths because of cancer, and is one of the most common types of cancer in women in the whole world. India along with the US and China accounts for one-third of the breast cancer burden. The breast cancer carcinogenesis is attributed to epigenetics, which is the study of the reversible changes in the phenotype without any change in the DNA sequence. Genes, which are concerned with proliferation, anti-apoptosis, invasion, and metastasis, have been seen undergoing epigenetic changes in breast cancer. Cancer can be caused either by global hypomethylation (causing activation of oncogenes and leading to chromosomal instability) or by locus-specific hypermethylation (causing repression of gene expression and genetic instability due to inactivation of DNA repair genes). Other epigenetic mechanisms involved in carcinogenesis are histone modification and nucleosomal remodeling.*

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## INTRODUCTION

Cancer has profound socio-economic consequences on people, which causes family impoverishment and social inequality. In 2012, 6,00,000–7,00,000 deaths were caused by cancer alone (Mallath. et. al., 2014). It is one of the most growing diseases in the world today, everyday more and more people are succumbing to cancer; therefore, it is the need of the hour to invent effective treatment strategies for the same. Cancer occurs when cells lose the ability of contact inhibition, which causes the cells to divide without any control. In normal cells, the timing of the cell division is under strict constraints, and many signals are involved which dictate when a cell can divide and how often a cell can divide. In cancer cells, this restraint is lost and hence cells grow uncontrollably. Cancer develops when any kind of cell in our body proliferates abnormally, and since we have hundreds of types of cells, there are a variety of types of cancer. The two main types of tumors that all the cancers are classified into are Benign Tumors and Malignant Tumors. Benign tumors are localized to a particular location, and neither do they invade surrounding tumors nor do they spread to distant organs. Skin tumors usually fall in this category. Malignant tumors on the other hand invade the underlying basement membrane and intravaste the blood vessels and spread to distant organs, this phenomenon is known as Metastasis. For instance, the usual metastatic sites for breast cancer cells are bone, lung, liver and brain. This process by which particular cancer cells metastasize from their primary location to the locations of their preference is called Tropism. The extent of severity of cancer is deduced by the extent of metastasis that had happened in a cancer patient.

The type of cancer which is behind highest death rate among females in the world is breast cancer. Breast cancer starts when a few cells in the breasts become abnormal and start dividing uncontrollably and ultimately form a tumour. Surprisingly, breast cancer can also develop in males, where it starts off in the lining of the ducts (ductal cancer). In women cancer can also develop in the milk producing glands (lobular cancer). Most inherited cases of breast cancer are due to BRCA1and BRCA2 genes whose function is to repair the DNA damage and keep the breast cells growing normally. The alterations in these genes is the cause of developing breast cancer. BRCA gene mutations account for only 10% of all the breast cancers, this low incidence of BRCA-mediated breast cancer is because these mutations are passed on from generation to generation. Women with BRCA gene mutations often have the family history of breast cancer (Genetics, Breastcancer.org). Other genes involved in development of breast cancer are HER2, EGFR and c-Myc genes. Aging is one of the biggest risk factor of breast cancer, the cases of breast cancer increase with increasing age. Family history of breast cancer also a risk factor. Endogenous and exogenous estrogen is a risk factor too. The main source of exogenous estrogen is oral contraceptives and hormone replacement therapy (HRT).

Among many strategies in place to treat cancer, one of the most promising one is the epigenetic therapy. Epigenetic changes are the changes in the gene activity/phenotype without the any alteration in DNA sequence. These changes can be transmitted to daughter cells, although experiments have shown that these changes can be reversed. These are the changes that can lead to development of cancers, and these changes are being exploited so that they can be reversed using natural and synthetic agents. Epigenetic changes are natural and essential at times, but if they occur improperly, they can be fatal. The major identified epigenetic changes are methylation, acetylation, deacetylation, phosphorylation, and ubiquitylation. Chromatin re-modeling and imprinting are other types of epigenetic changes that are identified. There are two kinds of genes involved in tumour development – Tumour Suppressor Genes (TSGs) and Oncogenes. TSGs are the ones that have anti-cancer effects and oncogenes have pro-cancer effects. Epigenetic changes in the tumour suppressor or oncogenes is the reason why cancer develops.