Chapter 2

Scope of Present Study
Breast cancer (BC) accounts for 25% of cancer burden in Eastern Indian population and it is showing a fast rising trend in major metropolitan cities of India (Ochayon et al., 2014). It has been associated with different susceptible genes (high, intermediate and low), molecular subtypes, early age of onset, menopausal status, nulliparity as discussed in Chapter 1, section 1.2.2.

BC is a highly heterogeneous tumor. This heterogeneity is one of the reasons behind its tolerance to therapy and relapse. The recent trend in therapy of BC is the administration of neoadjuvant chemotherapy (NACT) for better prognosis of the disease. But, in locally advanced tumors, only 4-31% showed pathological complete response even after NACT (Huober et al., 2010, Viswambharan et al., 2005, Khokher et al., 2011, Nakai et al., 2012). Apart from its heterogeneity, oxygen metabolism, epigenetic modulations in the BC cells also decide the drug tolerability of the tumors as discussed in Chapter 1 section 1.2.6.1. But the actual mechanism of chemo-tolerance of BC is not well understood.

Different molecular pathways play a potential role in breast tumorigenesis. Among them DNA damage response pathways are one of the most important pathways due to presence of several BC susceptible genes (Chapter 1 section 1.2.5). Chemo-sensitivity of the tumors is associated with competency of DNA damage response (DDR) activation. Among the different DDR pathways HRR and MMR are most important in BC (Chapter 1 section 1.2.5). Various studies reported the alterations (deletion/methylation/mutation/expression) of the key regulatory genes of HRR (BRCA1, BRCA2, FANCC and FANCD2) and MMR (MLH1, MSH2) pathway (Table 1.4). But their alterations in pretherapeutic BC were not studied in same set of samples to understand the importance of these pathways all together in development of BC. In addition, the alterations of HRR and MMR pathway genes in NACT treated BC are not well documented. The analysis of alterations of the key regulatory genes of these pathways in different subtypes of pretherapeutic and NACT treated primary BC samples as well as in BC cell lines all together may help in understanding the mechanism of chemo-tolerance and also prognosis of the disease.

Furthermore the drug tolerance properties of the NACT treated BC samples were not well studied particularly in relation with DDR pathways. The properties of the BC cells after
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treatment with common chemotherapeutic drugs like anthracycline antitumor antibiotics may put some light on the mechanism of chemo-tolerance in BC. Thus, characterization of the anthracycline tolerant BC cells and the analysis of the status of HRR and MMR pathway genes in them *in vitro* may mimic the NACT tolerant BC cells *in vivo*.

The objective of the study is to understand the alterations of DDR pathways, particularly HRR and MMR pathways in different BC subtypes of pretherapeutic and NACT treated BC. In addition, it is important to understand the role of these DDR pathways in chemo-tolerance of BC. Thus, our study has been focused on the following aspects:

1) **Analysis of alterations (deletion/methylation/expression) of some of the key regulatory genes of HRR pathway like BRCA1, BRCA2, FANCC, and FANCD2 in pretherapeutic and NACT treated BC patients.**

2) **Analysis of alterations (deletion/methylation/expression) of some of the key regulatory genes of MMR pathway like MLH1 and MSH2 in pretherapeutic and NACT treated BC patients.**

3) **Evaluation of the association of HRR and MMR pathways with chemo-tolerance in BC cell lines after treatment with the anthracycline antitumor antibiotics.**