ABSTRACT

Breast cancer is a complex and miscellaneous disease. Many factors are involved in the pathogenesis of breast cancer. In addition to high penetrance genes, low penetrance genes like ESR1 and DNA repair genes (XRCC1, NEIL1 and XRCC4) also confer genetic predisposition to cancer and affects the prognosis. Susceptibility to breast cell tumorigenesis is influenced by genetic variants of these genes.

The present study was conducted to determine the susceptibility of these genes to breast cancer using computational approach and to evaluate the association of variants in these genes in women of West India diagnosed with breast cancer. This study was undertaken in two groups of participants: breast cancer patients i.e., cases (120) and controls (130). ESR1, XRCC1, NEIL1 and XRCC4 genes polymorphisms were analysed using PCR-RFLP method. Screening of exonic and 3’UTR regions of ESR1 gene for variants was carried out using direct sequencing method. Computational analysis of XRCC1, NEIL1 and XRCC4 genes was conducted using various software tools like SIFT, PolyPhen, I-mutant etc. to explore the effects of variants on structure, function and stability of proteins.

Computational analysis revealed many genetic variants of these genes to be associated with diseases which have not been studied yet but are potential candidates that determine susceptibility to breast cancer and needs to be validated using case-control study. SNPs rs2307166 of XRCC1, rs5745906 of NEIL1 and rs79561451 of XRCC4 were found to be most damaging by computational analysis. Molecular genetic analysis found significant associations of SNPs rs25487 of XRCC1, rs4462560 and rs7182283 of NEIL1, rs3734091 of XRCC4 and rs9340799 and rs2234693 of ESR1 genes with breast cancer risk. The results suggest that polymorphisms of these genes may be associated with progression of breast cancer and may confer genetic susceptibility to this diseases in West Indian population. We obtained two earlier reported SNPs (rs3798577 and rs2747648) and one new SNP in 3’UTR region of ESR1 gene which may influence the expression of ESR1 by affecting the binding of miRNAs.

This study supports a significant correlation of polymorphisms of DNA repair and ESR1 genes with breast cancer which may help to detect patients that are highly susceptible to breast cancer.