Breast cancer ranks as commonest cancer in women in both developed and developing regions. In India, breast cancer is now the leading cause of cancer in females pushing cervical cancer to second. According to Globocan 2008 the estimated incidence of breast cancer in India is 22.2%. At Gujarat Cancer & Research Institute a regional cancer centre of Western India, according to the latest report of hospital based registry of the year 2010, 6942 total new female cancer cases had been registered of which 1460 (21%) were of breast cancer. The increasing incidence in India is because of changed lifestyle and work pattern of women which allows various risk factors such as late age at first childbirth, short duration of breast feeding, early age at menarche, late age at menopause, null parity, family history of breast cancer, to be the causative factors of breast cancer.

Besides, genetic factors too are considered as main risk factors for breast cancer development and progression, which involves complex interactions between hormone receptors and growth factors signaling pathways. One of the important interactions is the cross talk between members of Her family of receptor tyrosine kinases and intracellular signaling. Activated Her receptors can function to both stimulate and inhibit members of downstream signaling pathways.

Her-2/neu, the 185kDa oncoprotein located on chromosome 17q21 is found overexpressed in 10% to 35% of breast cancers and associated with poor prognosis, is controversial. Recent studies indicated the prognostic significance of Her-2/neu over expression may be due to associated expression of p95Her2, a truncated form of Her-2/neu lacking the extracellular domain. Deletion of Her-2/neu extracellular domain
increases the tyrosine kinase activity and transforming efficiency of the resulting truncated protein. p95 Her-2/neu is found to be associated with worse outcome in Her-2/neu positive breast cancer patients. Presence of a single nucleotide polymorphism (SNP) in the transmembrane coding region of the Her-2/neu gene at codon 655, encoding either isoleucine (Ile:ATC) or valine (Val:GTC) and changing the existing isoleucine to valine at 655 (Ile655Val), suggests an increased dimerisation, autophosphorylation of Her-2/neu and tyrosine kinase activity which may cause transformation of cells.

Further, overexpression of Her-2/neu leads to activation of PTEN/PI3K/AKT signaling that plays a central role in a variety of cellular processes including cell growth, proliferation, motility and survival both in normal and tumor cells.

PTEN gene leads to constitutive activation of PI3K-AKT pathway leading to tumorigenesis. Loss of function of PTEN gene could be due to microsatellite instability, mutation or hypermethylation. The fundamental role of PTEN therefore appears to be inhibition of PI3K dependent activation of AKT. AKT, which is also known as protein kinase B is a serine/threonine protein kinase. Besides PTEN, AKT is also activated by a variety of stimuli through growth factors receptors such as HER2 and EGFR. The disruption of normal AKT signaling occurs frequently in breast cancer.

AKT affects numerous downstream targets either directly or indirectly, many of which are involved in cell survival or protein translation. One of downstream target is mTOR, a mammalian target of rapamycin which activates in response to AKT phosphorylation resulting in the phosphorylation of p70S6 kinase and 4E-BPI, and consequently
increases the translation of mRNAs of protein involved in the regulation of the cell cycle.

Thus, Her-2/neu PI3K pathway play a critical role in growth and progression of breast cancer. It is important to understand the signaling pathway and its regulatory components which can be used as a drug target to better treatment efficacy.

Therefore, protein expression of Her-2/neu intracellular and extracellular domain, Her-2/neu Ile655Val single nucleotide polymorphism, molecules of PI3K-AKT pathway PTEN, AKT and mTOR were analysed to get better understanding of their role in breast cancer.