2. *Rationale of the study*

Breast cancer incidence is rapidly rising around the globe with a proportionate increase in cancer related mortality. A disturbing trend is seen in India, where breast cancer has overtaken cancer of the cervix in the urban areas. The morbidity coupled with breast cancer is largely due to the high rate of metastasis associated with it. The metastatic cascade is a sequence of events, with each step being regulated by a number of positive and negative modulators. This interplay of a plethora of molecules makes the process much intricate.

A number of studies are going on in various research laboratories, trying to find out the alteration affecting one or other of the molecules of the metastatic cascade. To the best of our knowledge, no such effort analysing alterations in each key step of the metastatic sequence has been attempted. Hence we thought it would be sensible to study the significant molecules of each step of the cascade and find out the important alterations in breast cancer. Given that nodal metastasis and metastasis to distant organs are equally but independently rampant in breast cancer, identification of important genomic insults in each of these pathways is also imperative.

Identification of persons at risk for developing metastasis is as important as treating the cancer patients. To serve this objective, we need more prognostic markers having the potential to predict the chances of developing recurrence or metastasis.

For biologists studying cancer, a major challenge is to identify the underlying molecular changes that switch cells to a metastatic state, with the ultimate aim being to devise treatments that inhibit metastasis. Previous research has focussed on the contribution of individual or group of genes to the process of metastasis. Bridging over this lacuna, we scanned the whole sequence of the metastatic process, studying the vital proteins of each step in order to identify the molecular switches to metastasis.
Thus, the primary objectives of the study were:

(1) To study the expression of vital proteins of the metastatic cascade in breast cancer by immunohistochemistry.

(2) To assess alterations of expression of these proteins in malignancy, nodal metastasis and distant metastasis.

(3) To identify molecular switches in nodal and distant metastasis in breast cancer.

(4) To spot out new prognostic markers in breast cancer, with the potential to predict nodal positivity and survival in breast cancer.
List of abbreviations

IDC- infiltrating ductal carcinoma
β-catenin- Beta catenin
FAK-Focal adhesion kinase
EGFR- Epidermal growth factor receptor
Memb-Membranous expression
Cyto-cytoplasmic expression
PDGF- Platelet derived growth factor
PTK-Protein tyrosine kinase
ECM- Extracellular matrix
HGF-Hepatocyte growth factor
NH2-terminus-Aminoterminus
C-terminus- Carboxyterminus
PI3K-Phosphatidylinositol-3-kinase
Cas-caspase
IHC-Immunohistochemistry
CAMs-Cell adhesion molecules
uPA-Urokinase plasminogen activator
PA-Plasminogen activator
PAI-plasminogen activator inhibitor
VEGF-Vascular endothelial growth factor
VCAM-1- vascular cell adhesion molecule-1
ICAM-1-Intercellular adhesion molecule-1
MMP-Matrix metalloproteinase
TIMP-Tissue inhibitor of metalloproteinase
μl- microlitres
E-cad-E-cadherin
P-cad-P-cadherin