SUMMARY
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This comprehensive study has evaluated IGF axis molecules in breast cancer prognostication by their estimation at circulatory and transcript levels. Estimation of serum levels of six molecules (IGF-1, IGF-2, IGFBP-2, -3, -4, -6) from breast cancer patients and controls was compared to almost all known clinico-pathologic prognosticators. This is the first comprehensive study from Indian subcontinent where relatively less explored IGFBPs (IGFBP-4 and IGFBP-6) are being explored.

Circulatory levels of IGF-1 were higher in breast cancer patients while IGF-2 was higher in controls. Correlations of IGF-1 with other clinical and pathological prognosticators raise a possibility of its use in breast cancer prognostication. IGFBP-3 on the other hand was higher in controls and its propensity in good clinico-pathological criteria possibly connects to its protective role in breast tumorigenesis. Increased circulatory levels of IGFBP-2 and IGFBP-4 and their preponderance in worse clinico-pathologic variables juxtapose their possible use in patient monitoring and may be hypothesized to have a tumor promoting role. IGFBP-6 on the other hand was higher in controls and was more connected to less detrimental tumor characteristics envisage its possible role as of IGFBP-3 demands further exploration.

Gene expression of IGF axis molecules was studied as copy numbers with absolute quantitation using the most sensitive and specific Taqman chemistry with real time PCR on a comprehensive scale and were compared to hormone receptors and HER2. The gene copy number of ten molecules (IGF-1, IGF-2, IGFR1, IGFR2, IGFBP-3, ERα, ERβ, PR, HER2 and GAPDH; expressed as per μg total RNA) was juxtaposed to all possible known clinical and pathologic variables and survival.

Expression of IGF-1 was twofold higher in normal breast tissues than the tumors while IGF-2 in tumors was half of the normal tissues. Their tumoral expression was evaluated as prognosticator. Higher expression of IGF-1 in small, node negative tumors without lymphatic invasion along with an inverse relation to protein levels point to its possible use as a prognosticator. In contrast, higher tumoral IGF-2 expression was seen in node positive, infiltrating lobular carcinoma and tumors with lymphocytic infiltration with an inverse correlation to protein levels point to its different role than IGF-1 in breast tumorigenesis. Higher expression of tumoral IGFR1 and IGFR2 than normal tissues possibly announces increased signaling through receptors rather than growth factors in the breast tumorigenesis in the cohort under study.

A crosstalk of IGF pathway, hormone receptors and EGF pathway was very evident in the current comprehensive study. Moreover, higher expression of IGF-2 and IGFR1 in TNBC point towards the most likely subgroup to benefit from anti IGF strategies.
The highest expression of both the growth factors (IGF-1 and IGF-2) in the reduction mammoplasty specimens reflect their highest production at the transcript level in benign breast proliferative disorders with significantly reduced levels in ANT followed by the tumor tissue. Such inference resulting from a direct comparison is derived for the first time in the current study to the best of our knowledge. IGFBP-3 had slightly different pattern than IGFs; pointing towards their different action potentials in breast tumorigenesis. The highest expression of IGFR1 in tumors as compared to other tissue types also leads us to hypothesize its major role in breast tumorigenesis in at least the current experimental cohort. The variations in IGFs and IGFBPs during the follow-up both in relapsed and not relapsed patients were very high ranging from two fold reduction to two fold rise; therefore their role in early picking up of relapses continue to remain inconclusive.

Univariate analysis did not reveal any significant effect of any of the IGF axis molecule (either circulating or transcript level). On addition of nodal status and / or hormone receptors and HER2 resulted into subgroups with an impact on relapse free survival especially ER⁺PR⁺HER⁺ versus Triple negative tumors. Altered expression of IGF axis molecules in such molecular subtypes points towards addition of anti-IGF axis targeted therapy in the adjuvant setup.

**Key Findings**

- IGF-1 and IGFBP-3 are likely prognosticators of breast cancer an correlated to other clinical and pathological prognosticators
- Circulatory IGFBP-3 may have a protective role in breast tumorigenesis
- Tumoral gene expression of IGF axis molecules is in the following order: IGFR1>IGFBP-3>IGFR2>IGF-2>IGF-1
- Higher tumoral expression of the IGFR1 and IGFR2 as compared to ANT may announce a higher signaling through receptors rather than IGFs in breast tumorigenesis
- The crosstalk of IGF pathway with hormone receptors and EGF pathway was clearly evident in the current comprehensive study
- Higher expression of IGF-2 and IGFR1 in TNBC suggest the most likely subgroup of patients benefited from anti IGF strategies