Insulin-like growth factors and mammographic density

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There is growing evidence that insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs) play a role in the normal development of breast tissue and possibly in the aetiology of breast cancer. IGFs are known to have mitogenic and anti-apoptotic effects on normal and transformed breast epithelial cells¹. However, these effects of IGFs are regulated, at least in part, by IGFBPs, which can act directly on tissue² or indirectly through the binding of IGFs³. It has therefore been suggested that high levels of IGFs coupled with low levels of IGFBPs may increase the risk of breast cancer⁴.

Many other risk factors for breast cancer exist, one of the strongest of these being percent breast density⁵. In view of this, we were interested in assessing the correlations between breast density and serum IGF-I and IGFBP-3 levels. In a cross-sectional analysis within the Nurses' Health Study, we compared the associations between endogenous IGF-I and IGFBP-3 levels and the measured percent breast density among 65 pre-menopausal and 192 post-menopausal women. Generalized linear models were used to determine the mean percent breast density across quartiles of IGF-I and IGFBP-3 levels, and the ratio of IGF-I:IGFBP-3. Spearman's partial correlation coefficients and corresponding *P* values described the associations between the continuous measures of IGF-I and IGFBP-3, and IGF-I:IGFBP-3 and percent breast density.

The results showed a strong positive correlation between percent breast density and serum IGF-I levels in pre-menopausal women, whereas an inverse association existed between breast density and IGFBP-3. The strongest correlation was between breast density and IGF-I:IGFBP-3, with a partial Spearman's coefficient

among pre-menopausal women of 0.39 ($P = 0.004$). In contrast, the correlation between percent breast density and IGF-I:IGFBP-3 among post-menopausal women was -0.02 ($P = 0.83$).

In summary, among pre-menopausal women, increased levels of IGF-I were associated with increased mammographic density, and IGFBP-3 was associated with decreased mammographic density. Furthermore, the combined effect of IGF-I and IGFBP-3 levels had the strongest association with percent breast density in these women. Interestingly, however, we found no strong correlation between IGF-I and IGFBP-3 levels and breast density in post-menopausal women. These results are consistent with a previous study that showed that an increase in IGF-I:IGFBP-3 was associated with an increased risk of breast cancer in pre-menopausal women only⁶. Our findings suggest a potential mechanism for the effect of pre-menopausal IGF-I levels on subsequent breast cancer risk.

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