



Expression of Insulin-Like Growth Factor-I Receptor (IGF-IR) in Normal Breast Tissue and Breast Cancer Risk: Results from the Nurses' Health Study

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Background

- IGF-IR is a transmembrane tyrosine kinase receptor activated by binding with insulin-like growth factor-I (IGF-I)
- Prior studies support a role for the IGF-I/IGF-IR pathway in breast cancer development and progression, and elevated serum IGF-I has been associated with an increased breast cancer risk
- However, a possible association between IGF-IR expression in normal breast tissue and risk of subsequent breast cancer has not been previously evaluated

Objective & Design

- We conducted a case-control study of benign breast disease (BBD) and breast cancer risk nested within the Nurses' Health Study
- Tissue microarrays (TMAs) containing normal terminal duct lobular units (TDLUs) were constructed from 240 benign breast biopsies with available tissue blocks (59 cases; 181 controls)
- TMA sections were immunostained for IGF-IR and assessed blinded to case/control status for membrane and cytoplasmic expression in normal TDLU epithelial cells
- Odds ratios (OR) and 95% confidence intervals (CI) were calculated for the association between IGF-IR expression and subsequent breast cancer risk adjusting for age and BBD category

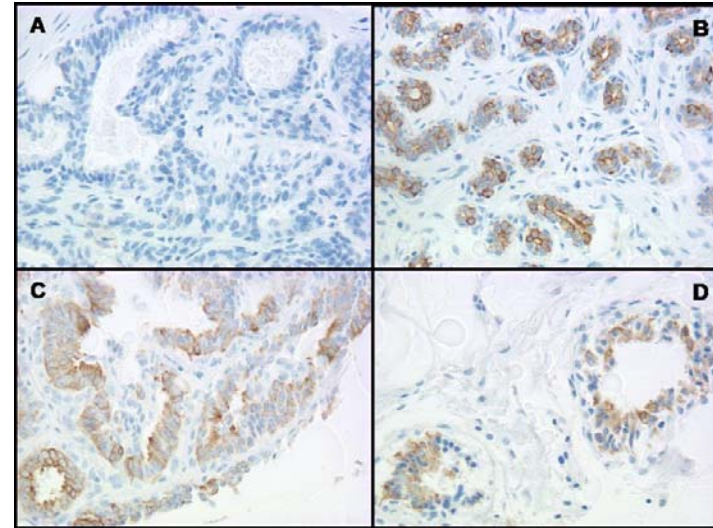


Figure 1. IGF-IR immunostain patterns in normal TDLUs
A. negative; B membranous staining;
C. membranous/cytoplasmic staining; D. cytoplasmic staining

Results

- There was no relationship between membranous expression of IGF-IR in normal TDLU epithelial cells and subsequent breast cancer risk (OR 0.84; 95% CI 0.51-1.38)
- In contrast, cytoplasmic IGF-IR expression was associated with an almost 2-fold increase in risk for subsequent breast cancer (OR 1.89; 95% CI 1.19-3.01) independent of BBD categories
- Among the small subset of women in whom the normal epithelium showed cytoplasmic staining for IGF-IR in the absence of membrane staining, the OR for subsequent breast cancer was 4.26, but the 95% confidence interval was broad (1.41-12.81)

Table 1. Risk of breast cancer in relation to membrane staining for IGF-IR in normal breast tissue

MEMBRANE IGF-IR	CASES	CONTROLS	OR* (95% CI)
Negative (<10%)	47 (32.0%)	122 (27.6%)	1.0 (REF)
Positive (>10%)	100 (68.0%)	319 (72.4%)	0.84 (0.51-1.38)

*Adjusted for age and category of benign breast disease
P-value = 0.12

Table 2. Risk of breast cancer in relation to cytoplasmic staining for IGF-IR in normal breast tissue

CYTOPLASMIC IGF-IR	CASES	CONTROLS	OR* (95% CI)
Negative (<10%)	102 (69.4%)	334 (76.1%)	1.0 (REF)
Positive (≥10%)	45 (30.6%)	105 (23.9%)	1.89 (1.19-3.01)

*Adjusted for age and category of benign breast disease
P-value = 0.04

Table 3. Cross classification of membrane and cytoplasmic IGF-IR staining in normal tissue and risk of breast cancer

Mem-brane	Cyto-plasmic	Cases	Controls	OR* (95% CI)	P-value
-	-	37	115	1.0 (REF)	0.78
+	+	34	98	0.99 (0.56-1.76)	
-	-	37	115	1.0 (REF)	0.003
-	+	10	7	4.26 (1.41-12.81)	
-	-	37	115	1.0 (REF)	0.73
+	-	65	219	0.92 (0.57-1.49)	

*Adjusted for age and category of benign breast disease

Conclusions

- Among women with biopsy-proven benign breast disease, cytoplasmic expression of IGF-IR in normal breast epithelial cells was associated with an almost 2-fold increase in breast cancer risk, independent of BBD category
- This finding raises the possibility that blocking IGF-I/IGF-IR signaling may represent a new breast cancer prevention strategy