Nested Case-Control Study of the Association of Circulating Levels of Serum Insulin-like Growth Factor I and Insulin-like Growth Factor Binding Protein 3 with Breast Cancer in Young Women in Norway

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Abstract

Background: High circulating levels of insulin-like growth factor (IGF-I) may elevate the risk of breast cancer in premenopausal women, possibly by increasing cell proliferation and reducing apoptosis.

Methods: We conducted a nested case-control study among 35,105 Norwegian women who participated in a health screening survey, ages 40 to 42 years, and who were subsequently followed for a mean period of 4.3 years. During this period, 325 women were diagnosed with breast cancer; 647 women without breast cancer, matched on age and time of blood sampling, were selected as controls. Serum concentrations of IGF-I and its main binding protein (IGFBP-3) were measured with radioimmunoassay, and logistic regression analysis was used to adjust for relevant covariates.

Results: The mean age at blood collection was 41.1 years in both groups, and the mean age at diagnosis for the cases was 45.4 years (range, 40-51 years). The median IGF-I level did not differ between cases (205 ng/mL) and controls (202 ng/mL). When analyzed by categories of serum IGF-I, the relative risk for women in the highest versus the lowest quintile was 1.46 (95% confidence interval, 0.93-2.32; \( P_{\text{trend}} = 0.15 \)) after adjusting for serum IGFBP-3, age, and year of blood collection. The exclusion of cases that were diagnosed within 2 years after blood collection did not materially affect the results.

Conclusion: We found only a modest positive association between serum IGF-I levels and risk of breast cancer in women younger than 50 years of age.

Introduction

Because a nested case-control study based on the Nurses’ Health Study cohort showed that plasma insulin-like growth factor-I (IGF-I) levels were positively associated with breast cancer risk in premenopausal women (1), many studies have assessed the association of IGFs and functional polymorphisms in genes coding for components of the growth hormone-IGF axis with breast cancer (2-4). Although the results have not been consistent, recent meta-analyses and reviews conclude that the evidence points to a positive association with IGF-I among premenopausal women (2-4).

IGF-I promotes the proliferation, survival, and renewal of normal cells (5-8) and amplifies the local action of trophic hormones such as gonatropins. These effects may lead to the accumulation of genetic mutations over time. It has also been suggested that the main binding protein, IGFBP-3, is involved in apoptosis (8). Therefore, circulating levels of IGF-I and its binding proteins may be important for the risk of multiple cancers (2, 8), as supported by the positive associations of plasma IGF-I levels with prostate cancer risk (9), as well as for colorectal (10) and lung cancer (11).

There is some evidence that preclinical or prevalent breast cancer may influence IGF-I levels, and this may influence associations with risk during the first few years following baseline measurement (12). Therefore, it could be useful to conduct separate analyses exploring different follow-up times. Progression of early cancers may also be stimulated by IGF-I, and advanced cancers may influence circulating levels of IGF-I. Therefore, studies with a prospective design are necessary to examine the relation of IGFs with cancer risk.

In this analysis, we examined the relation between serum IGF-I and breast cancer risk in a nested case-control study among young Norwegian women.

Subjects and Methods

Men and women in Norway who were between the ages of 40 and 42 y were previously offered a health examination by the National Health Screening Service (13, 14). Participants were invited by mail and asked to fill in a health-related questionnaire that was included with the invitation. At the examination, measurements were made of blood pressure, height, and weight. Blood was drawn for lipid determination, and the remaining blood was centrifuged and stored as part of the Janus serum bank (15) at −25°C for future studies. The Janus
bio-bank is jointly administered by the Norwegian Cancer Registry and an appointed steering committee. By using the unique 11-digit identity number of every Norwegian citizen, individual information collected by the National Health Screening Service can be readily linked with data on cancer incidence registered at the Cancer Registry. Thus, one may identify breast cancer diagnosis subsequent to blood collection. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

In this study, 35,105 women who provided blood specimens between 1986 and 1997, when they were 40 to 42 y of age, were followed for a mean period of 4.3 y (range, 0.5-11 y). During follow-up, 325 women developed breast cancer, and blood was available for 323. For each case of breast cancer, women who were examined and had provided blood within 6 mo of the case were eligible as controls. Among these women, 647 were randomly selected and served as controls. IGF-I and IGFBP-3 could be measured in 641 of the control women, leaving 323 cases and 641 controls for analysis. Only 3 of the 323 cases were older than 50 y at diagnosis, and the oldest was 51 y. Thus, nearly all the women in this study were likely to be premenopausal when blood was drawn (40-42 y), and a great majority of the cases were likely to be premenopausal at diagnosis.

Serum IGF-I and IGFBP-3 levels were measured using in-house double-antibody radioimmunoassay as previously described (16). Measurements were done without knowledge of case or control status. The average coefficients of variation for intra-assay variability were 8% for IGF-I and 5% for IGFBP-3, and for interassay the variations were 10% and 8% for IGF-I and IGFBP-3, respectively. IGF-I was categorized into quintiles based on the values among control women.

The association with IGF-I was assessed with and without IGFBP-3 as a covariate in the analysis because there is evidence to indicate that IGFBP-3 may reduce the bioactivity of IGF-I (17). Other risk factors relevant to breast cancer (e.g., parity and age at first birth) were not available in this study but did not materially influence the association with IGF-I in multivariable analysis in previous analyses (1, 18, 19). We used Mann-Whitney tests to compare medians between cases and controls, and unconditional logistic regression analysis adjusted for age and year of blood collection was used to estimate the strength of association between IGFs and breast cancer. The precision of the odds ratios (OR) is given by 95% confidence intervals (95% CI).

### Results

The mean age at the time of blood collection (Table 1) was 41.1 years in both groups, and mean age at diagnosis for the cases was 45.4 years (range, 40-51 years). Among all participants, the concentration of IGF-I was only slightly higher in cases compared with controls (205 versus 202 ng/mL; \( P = 0.27 \)). After restricting the analysis to women 50 years and younger at diagnosis of breast cancer, there was still no difference in IGF-I.

We analyzed the association according to quintiles of IGF-I using the distribution of IGF-I among controls (Table 2). After adjustment for level of IGFBP-3, age, and year of blood collection, we found a weak, positive association between quintiles of IGF-I and breast cancer risk (\( P_{\text{trend}} = 0.15 \)). Comparing women in the highest to the lowest quintile of IGF-I the OR was 1.46 (95% CI, 0.93-2.32). In a separate analysis, we excluded 51 cases diagnosed 2 years subsequent to blood sampling, but this did not substantially change the results (data not shown).

In Table 3, the association of quintile levels of IGFBP-3 with breast cancer risk is displayed, with adjustment for IGF-I, age, and year of blood collection. The results show a weak inverse association (\( P = 0.12 \)). We further examined whether the association of IGF-I with breast cancer differed across different levels of IGFBP-3 (Table 4). The highest risks of breast cancer were seen among women in the highest tertile of IGF-I and the lowest tertile of IGFBP-3 (OR 2.00; 95% CI, 1.01-3.96).

### Table 1. Characteristics of breast cancer cases and control women

<table>
<thead>
<tr>
<th></th>
<th>Case patients</th>
<th>Control women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at measurement (SD), y</strong></td>
<td>n = 325</td>
<td>n = 647</td>
</tr>
<tr>
<td>Range</td>
<td>41.1 (0.65)</td>
<td>41.1 (0.71)</td>
</tr>
<tr>
<td><strong>Mean age at diagnosis (SD), y</strong></td>
<td>45.4 (2.56)</td>
<td>40-43</td>
</tr>
<tr>
<td>Range</td>
<td>41.1 (0.71)</td>
<td>40-43</td>
</tr>
<tr>
<td><strong>Median IGF-I, ng/mL</strong></td>
<td>205</td>
<td>202</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>38-541</td>
<td>53-419</td>
</tr>
</tbody>
</table>

*Mann-Whitney test for difference between groups, \( P = 0.27 \).

### Table 2. Relative risk (OR) of breast cancer, according to quintile values of serum IGF-I (ng/mL), adjusted for age and year of blood collection

<table>
<thead>
<tr>
<th>IGF-I quintiles(^a)</th>
<th>Cases/controls</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;164</td>
<td>54/130</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>164-190</td>
<td>78/130</td>
<td>1.44 (0.94-2.21)</td>
<td>1.45 (0.95-2.22)</td>
</tr>
<tr>
<td>191-214</td>
<td>45/126</td>
<td>0.86 (0.54-1.38)</td>
<td>0.86 (0.53-1.38)</td>
</tr>
<tr>
<td>215-255</td>
<td>75/128</td>
<td>1.42 (0.92-2.18)</td>
<td>1.49 (0.96-2.31)</td>
</tr>
<tr>
<td>&gt;255</td>
<td>71/127</td>
<td>1.36 (0.88-2.10)</td>
<td>1.46 (0.93-2.32)</td>
</tr>
</tbody>
</table>

\( P_{\text{trend}} = 0.26 \) \( P_{\text{trend}} = 0.15 \)

\(^a\)With additional adjustment for IGFBP-3.

\(^b\) Quintiles on basis of control group IGF-I.
Discussion

In this prospective study of breast cancer risk in young women, we found limited evidence of a positive association between IGF-I and breast cancer risk. Our finding is consistent with that reported in a recent meta-analysis of the association of IGF-I with breast cancer: that analysis reported a pooled OR of 2.13 (95% CI, 1.25-3.64) comparing the highest versus lowest IGF-I category for breast cancer diagnosed among women younger than 50 years of age (3). The results are also very similar to those originally reported in this field (20).

A weakness of our study may be the lack of information on established risk factors for breast cancer that could have potentially confounded our results. However, there is little knowledge available to indicate that such confounding is likely, and adjustment for known risk factors did not alter the results of previous studies that investigated this topic (1, 18, 19). It is also possible that current use of oral contraceptives could have influenced IGF-I levels. However, a study of a random sample of Norwegian women ages 40 to 44 years reported that only 1.5% confirmed current use of oral contraceptives (21). This makes it unlikely that our results could be substantially confounded by this factor. It is also possible that past long-term use of oral contraceptives could have influenced IGF levels and that a single measure of IGF, as in our study, may not reflect their long-term levels (presumably the most relevant exposure). Repeated measurements of IGF-I indicate substantial intraindividual measurement error, suggesting that the association with breast cancer risk is likely to be underestimated in this study. However, we could adjust for the binding protein IGFBP-3 in the analysis.

This adjustment slightly increased the positive association, which nevertheless remained weak.

On the other hand, many features strengthen the validity of our results. These include the general population base of the study, the narrow age range of the participants, the large number of cases, and the standardized procedures including those of case ascertainment from the Norwegian Cancer Registry.

We attempted to minimize a possible preclinical effect of prevalent but undiagnosed cancers by excluding from analysis the 51 women who were diagnosed within 2 years subsequent to blood collection. However, the results remained essentially unchanged. In a separate analysis, we assessed whether low IGFBP-3 would strengthen the positive association between IGF-I and breast cancer risk. The consistent increase in risk that we observed with decreasing levels of IGFBP-3 seems to be biologically plausible, but the statistical evidence for this association was weak ($P = 0.12$). Nonetheless, our results seem to be compatible with a permissive role of IGF-I, as previously suggested (22). In this large study among young women, only a modest positive association between IGF-I and breast cancer risk was observed. The findings suggest that any association between circulating levels of IGF-I and breast cancer risk may not be as strong as reported in the early studies. This is consistent with the weakening of risk in more recent studies, as reported in Renehan’s meta-analysis (3). However, because of the lack of data on known breast cancer risk factors, including oral contraceptive use, and because the confidence intervals for women in the highest category of IGF-I readily include a 2-fold increase, further evaluation of IGF-I as a predictor of breast cancer incidence is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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Lars Vatten and Steinar Tretli coordinated the study, analyzed and interpreted the data, and wrote the paper. Jeff Holly initiated the study of IGs, directed the laboratory analysis, interpreted the data, and wrote the paper. David Gunnell interpreted the data and wrote the paper.

Table 3. Relative risk (OR) of breast cancer, according to quintile values of serum IGFBP-3, adjusted for age and year of blood collection

<table>
<thead>
<tr>
<th>IGFBP-3</th>
<th>OR (95% CI)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-1</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Q-2</td>
<td>1.14 (0.75-1.72)</td>
<td>1.10 (0.73-1.66)</td>
</tr>
<tr>
<td>Q-3</td>
<td>1.00 (0.66-1.52)</td>
<td>0.94 (0.22-1.44)</td>
</tr>
<tr>
<td>Q-4</td>
<td>0.91 (0.59-1.39)</td>
<td>0.80 (0.52,1.25)</td>
</tr>
<tr>
<td>Q-5</td>
<td>0.87 (0.57-1.34)</td>
<td>0.78 (0.49,1.23)</td>
</tr>
</tbody>
</table>

$P_{\text{trend}} = 0.31$ P$_{\text{interaction}} = 0.12$

*Additionally adjusted for IGF-I levels.

But patterns of association were inconsistent, and there was no evidence that associations of IGF-I with breast cancer risk differed at differing levels of IGFBP-3 ($P_{\text{interaction}} = 0.12$).

Table 4. Relative risk (OR) of breast cancer according to tertile values of IGF-I and IGFBP-3

<table>
<thead>
<tr>
<th>IGFBP-3 (tertiles)</th>
<th>IGF-I (tertiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>III (reference)</td>
<td>1.0(7.4-0)</td>
</tr>
<tr>
<td>II</td>
<td>1.16 (0.60-2.27)</td>
</tr>
<tr>
<td>I</td>
<td>1.43 (0.79-2.58)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
References

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