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## Circulating insulin-like growth factor-1 in pregnancy and maternal risk of breast cancer

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### Abstract

**Background**—Elevated serum concentrations of insulin-like growth factor (IGF)-1 have been associated with increased risk of breast cancer. Previously, we reported a similar association in samples obtained during pregnancy. The current study was conducted to further characterize the association of IGF-1 during pregnancy with maternal breast cancer risk.

**Methods**—A case-control study was nested within the Finnish Maternity Cohort. The study was limited to primiparous women less than 40 years of age, who donated blood samples during early (median, 12 weeks) pregnancy and delivered a single child at term. Seven hundred and nineteen women with invasive breast cancer were eligible. Two controls (n = 1,434) were matched to each case on age and date at blood donation. Serum IGF-1 concentration was measured using an Immulite 2000 analyzer. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

**Results**—No significant associations were observed between serum IGF-1 concentrations and breast cancer risk in both the overall analysis (OR 1.08 (95% CI 0.80–1.47) and in analyses stratified by histological subtype, lag-time to cancer diagnosis, age at pregnancy or age at diagnosis.

**Conclusion**—There was no association between IGF-1 and maternal breast cancer risk during early pregnancy in this large nested case-control study.

**Impact**—Serum IGF-1 concentrations during early pregnancy may not be related to maternal risk of breast cancer.

### Keywords

insulin-like growth factor-1 (IGF-1); pregnancy; breast cancer; nested case-control study

## Introduction

Previously, in a study nested within the Northern Sweden Maternity Cohort (NSMC) we observed that insulin-like growth factor (IGF)-1 measured mostly during the first trimester of a primiparous pregnancy were positively associated with maternal risk of breast cancer [1], consistent with observations in non-pregnant women [2]. To confirm our initial findings and explore the association in greater detail we conducted a study with a very similar design, nested in the Finnish Maternity Cohort (FMC), the world's largest biorepository of serum samples from pregnant women.

## Materials and Methods

### Selection of cases and controls

Study design has been described in detail previously [3]. In brief, FMC members who donated serum samples between the 6<sup>th</sup> and 14<sup>th</sup> gestational weeks of a primiparous, singleton full-term pregnancy, younger than age 40 and with no history of in-situ breast or any other cancer (except non-melanoma of the skin) were eligible. Case subjects were 535 women with breast cancer identified through linkage with the Finnish Cancer Registry. As IGF-I concentration does not vary with gestational age during early pregnancy 184 cases with no data on exact gestational age were also included. For each case, two controls were matched on age at sampling ( $\pm 6$  months) and date of sampling ( $\pm 3$  months), for a total of 1,434 controls. Ninety two percent of the cases were less than 50 years at the time of diagnosis, thus the vast majority were likely diagnosed during fertile.

The study was approved by the ethical committee of the National Institute for Health and Welfare, Finland.

### Laboratory analyses

IGF-1 assay was quantified by immunometric assays on the Immulite 2000 Siemens analyzer. The inter-run coefficients of variation (CV) of the laboratory quality controls were 9.3% and 3.2% at concentrations of 81.5ng/mL and 229ng/mL respectively. The inter-run and intra-run CVs for a blinded pool of controls (mean concentration of 177ng/mL) were 3.9% and 8.3% respectively.

### Statistical analysis

Prior to analysis, IGF-1 values were log<sub>2</sub>-transformed to normalize their distributions. The correlation of IGF-1 with gestational age was assessed by Pearson's partial correlation ( $r = -0.03$ ). Subjects were categorized into quintiles based on IGF-1 distribution among the controls. Conditional logistic regression was used to calculate the odds ratio and corresponding 95% confidence interval (OR, 95% CI) of breast cancer across quintiles of IGF-1. The associations were also explored by histological subtypes, median ages at first full term pregnancy (29 years) and diagnosis (41 years) and lag-time to cancer diagnosis (11 years) and also in finer subgroups of the latter 3 variables. Analyses limited to women with information on gestational age and by tertiles of time in storage were also conducted. Adjustment for potential confounders (gravity, parity by index date, family history of breast cancer, smoking and gestational day) sporadically changed risk estimates but with less than 5% and were not retained in the final model. Similarly, adjustment for estradiol (available for 534 case-control sets) had negligible effect on risk estimates. All statistical tests were two-sided and p-values  $< 0.05$  were considered statistically significant.

## Results

Selected characteristics of the study population and IGF-1 concentrations are presented in Table 1. Cases and controls were comparable in all characteristics except for family history of breast cancer.

There was no association of breast cancer with IGF-1 concentrations overall and in all the subgroup analyses (by histology, age at sampling, age at diagnosis, lag-time to diagnosis, storage time) (Table 2). Similarly, in analysis limited to case-control sets with information on gestational age (n=535), there was no association of breast cancer with IGF-1 and adjustment for gestational age did not alter the risk estimates.

## Discussion

In contrast to our previous findings in the NSMC (1), in the FMC, IGF-1 during early pregnancy was not associated with maternal risk of breast cancer. The two studies had very similar design and were nested in population-based maternity cohorts in neighboring countries. The samples are stored at comparative temperature ( $-25^{\circ}\text{C}$ ) and the mean IGF-1 concentrations in the FMC controls (134.7 ng/mL) were comparable to those from the NSMC (133.6 ng/mL). IGF-1 was analyzed in the same laboratory with the same assay kits. The current study is 3 times larger and had 87% statistical power to detect an OR of 1.50. Nevertheless, we cannot exclude the possibility that some analyte degradation has occurred and reduced our ability to find an existing association.

Another limitation of our study is the lack of information on estrogen-receptor (ER) status of the tumors, as this is not collected centrally in Finland. Most of the cases were diagnosed before age 50 (92%) and thus more likely to be ER negative (4). The analysis by the Endogenous Hormones and Breast Cancer Collaborative Group suggested that the association of IGF-1 with breast cancer is confined to hormone-receptor positive tumors (2). Thus a relatively large proportion of receptor negative tumors in our data could have obscured an association with hormone-receptor positive disease.

In summary, no association between IGF-1 concentrations during early pregnancy and maternal breast cancer risk was observed in the FMC.

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**Table 1**

Selected characteristics of breast cancer cases and controls, median (10<sup>th</sup>, 90<sup>th</sup>) or n (percentage) from the Finnish Maternity Cohort, 1983–2006.

Characteristic	Cases (719)	Controls (1,434)	p-Value <sup>a</sup>
Maternal age during index pregnancy (years)	29.2 (22.9 – 37.0)	29.1 (22.8 – 37.0)	
Grouped Age			
< 25 years	189 (26%)	372 (26%)	
25 – 29 years	194 (27%)	396 (28%)	
30 – 34 years	176 (24%)	358 (25%)	
≥ 35 years	160 (22%)	308 (21%)	
Gestational age (days) <sup>b</sup>	73 (57 – 89)	73 (57 – 90)	0.48
Gravidity	534 (79%)	1088 (81%)	0.33
Parity by index date			0.10
1	257 (36%)	463 (32%)	
2	312 (43%)	652 (45%)	
≥ 3	150 (21%)	319 (22%)	
Age at diagnosis (years)	40.9 (32.1 – 49.3)		
Lag time (years)	11.3 (4.4 – 17.9)		
Histology			
ductal carcinoma	574 (80%)		
lobular carcinoma	98 (14%)		
medullary carcinoma	19 (3%)		
other	28 (4%)		
Family history of breast cancer	74 (11%)	62 (5%)	<0.0001
Family history of ovarian cancer	4 (1%)	13 (1%)	0.40
Smoking			0.23
no	443 (84%)	910 (86%)	
yes	87 (16%)	149 (14%)	
Child sex			0.74
male	360 (50%)	729 (51%)	
female	359 (50%)	705 (49%)	
Child birth weight (g) <sup>c</sup>	3,500 (2,970 – 4,100)	3,510 (2,930 – 4,140)	0.99
Child birth length (cm) <sup>d</sup>	50 (48 – 53)	50 (48 – 53)	0.55
IGF I (ng/mL) <sup>e</sup>	133.7 (94.9 – 198.0)	134.7 (94.5 – 195.0)	0.53

<sup>a</sup>Comparison between cases and controls: Conditional logistic regression models;

<sup>b</sup>Gestational age available for 535 cases and 1,044 controls

<sup>c</sup>Data on child's birth weight is available for 537 cases and 1,077 controls

<sup>d</sup>Data on child's birth length is available for 535 cases and 1,076 controls.

<sup>e</sup>Geometric mean and (10th, 90th) percentile of hormone

Table 2

Odds ratios with 95% confidence interval (OR, 95% CI) of breast cancer associated with quintiles of IGF-1 concentrations among women from the Finnish Maternity Cohort, 1983–2006.

	Quintiles					pTrend	pHeterogeneity
	q1	q2	q3	q4	q5		
All women	ref. 140/294	1.20 (0.91–1.59) 170/295	1.05 (0.78–1.42) 142/283	0.92 (0.68–1.23) 123/283	1.08 (0.80–1.47) 144/279	0.68	
Women with information on gestational age <sup>†</sup>	ref. 116/214	1.04 (0.75–1.44) 118/207	0.88 (0.62–1.23) 107/221	0.73 (0.51–1.05) 79/197	1.01 (0.71–1.42) 115/205	0.46	
Ductal carcinoma	ref. 106/235	1.31 (0.96–1.78) 142/240	1.18 (0.84–1.64) 119/225	0.96 (0.68–1.35) 96/223	1.10 (0.78–1.56) 111/223	0.70	
Lobular carcinoma	ref. 24/39	0.89 (0.43–1.82) 22/41	0.63 (0.28–1.40) 15/39	0.70 (0.33–1.49) 17/40	0.88 (0.39–2.01) 20/35	0.59	
Age at pregnancy							
< 29.2 years	ref. 63/116	0.99 (0.65–1.51) 71/132	1.03 (0.67–1.57) 75/133	0.77 (0.50–1.19) 63/148	0.83 (0.54–1.27) 84/182	0.19	0.07
≥ 29.2 years	ref. 77/178	1.40 (0.97–2.02) 99/163	1.06 (0.70–1.60) 67/150	1.05 (0.69–1.59) 60/135	1.46 (0.94–2.28) 60/97	0.46	
Age at diagnosis							
< 40.9 years	ref. 56/104	1.01 (0.65–1.56) 72/133	1.03 (0.66–1.62) 80/142	0.81 (0.52–1.27) 66/151	0.84 (0.53–1.31) 84/183	0.21	0.09
≥ 40.9 years	ref. 84/190	1.36 (0.95–1.94) 98/162	1.01 (0.67–1.51) 62/141	0.99 (0.65–1.49) 57/132	1.44 (0.93–2.22) 60/96	0.50	
Lag-time							
< 11.3 years	ref. 55/116	1.24 (0.81–1.91) 89/152	1.15 (0.73–1.81) 77/141	0.83 (0.53–1.31) 59/153	1.10 (0.69–1.74) 77/149	0.51	0.96
≥ 11.3 years	ref. 85/178	1.17 (0.81–1.69) 81/143	0.96 (0.65–1.43) 65/142	1.03 (0.69–1.54) 64/130	1.08 (0.71–1.64) 67/130	0.96	

<sup>†</sup> Adjustment for gestational age resulted in identical risk estimates with the exception of a minor change in the top quintile risk (1.00 (0.71–1.41), p = 0.44)