Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Circulating Insulin-like Growth Factor-I in Pregnancy and Maternal Risk of Breast Cancer

Adetunji T. Toriola[1,2], Eva Lundin[4], Helena Schock[3], Kjell Grankvist[4], Eero Pukkala[5,6], Tianhui Chen[3], Anne Zeleniuch-Jacquotte[7,8], Paolo Toniolo[8,9,10], Matti Lehtinen[6], Helja-Marja Surcel[1], and Annekatrin Lukanova[3,9]

Abstract

Background: Elevated serum concentrations of insulin-like growth factor (IGF)-I have been associated with increased risk of developing breast cancer. Previously, we reported a similar association in samples obtained during pregnancy. This study was conducted to further characterize the association of IGF-I 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 younger than 40 years, who donated blood samples during early (median, 12 weeks) pregnancy and delivered a single child at term. Seven hundred nineteen women with invasive breast cancer were eligible. Two controls ($n = 1,434$) were matched with each case on age and date at blood donation. Serum IGF-I concentration was measured using an Immulite 2000 analyzer. Conditional logistic regression was used to estimate ORs and 95% CIs.

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

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

Impact: Serum IGF-I concentrations during early pregnancy may not be related to maternal risk of developing breast cancer. *Cancer Epidemiol Biomarkers Prev; 20(8); 1798–801. ©2011 AACR.*

Introduction

Previously, in a study nested within the Northern Sweden Maternity Cohort (NSMC), we observed that insulin-like growth factor (IGF)-I measured mostly during the first trimester of a primiparous pregnancy were positively associated with maternal risk of breast cancer (1), consistent with observations in nonpregnant 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 6th and 14th gestational weeks of a primiparous, singleton, full-term pregnancy, younger than 40 years of age, and with no history of *in situ* breast or any other cancer (except nonmelanoma of the skin) were eligible. Case subjects were 535 women with breast cancer identified through linkage with the Finnish Cancer Registry. Because 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, 2 controls were matched on age at sampling (±6 months) and date of sampling (±3 months), for a total of 1,434 controls. Ninety-two percent of the cases were younger than 50 years at the time of diagnosis; thus, the vast majority of cases were likely had a diagnosis during fertile.

Authors' Affiliations: [1]National Institute for Health and Welfare, Oulu, Finland; [2]Division of Preventive Oncology, National Center for Tumor Diseases, and [3]Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany; [4]Department of Medical Biosciences, University of Umeå, Umeå, Sweden; [5]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland; [6]Tampere School of Public Health, University of Tampere, Tampere, Finland; [7]New York University Cancer Institute; Departments of [8]Environmental Medicine and [9]Obstetrics and Gynecology, New York University School of Medicine, New York; and [10]Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

Corresponding Author: Annekatrin Lukanova, Division of Cancer Epidemiology, German Cancer Research Center, In Neuenheimer Feld 581, Heidelberg 69120, Germany. Phone: 0049-6221-42-2241; Fax: 0049-6221-42-2203; E-mail: a.lukanova@dkfz.de

doi: 10.1158/1055-9965.EPI-11-0441

Table 1. Selected characteristics of breast cancer cases and controls, median (10th, 90th), or number (percentage) from the FMC, 1983–2006

Characteristic	Cases ($n = 719$)	Controls ($n = 1,434$)	P[a]
Maternal age during index pregnancy, y	29.2 (22.9–37.0)	29.1 (22.8–37.0)	
Grouped age, y			
<25	189 (26%)	372 (26%)	
25–29	194 (27%)	396 (28%)	
30–34	176 (24%)	358 (25%)	
≥35	160 (22%)	308 (21%)	
Gestational age,[b] d	73 (57–89)	73 (57–90)	0.48
Gravidity	534 (79%)	1,088 (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, y	40.9 (32.1–49.3)		
Lag time, y	11.3 (4.4–17.9)		
Histology			
Ductal carcinoma	574 (80%)		
Lobular carcinoma	98 (14%)		
Medullary carcinoma	19 (3%)		
Others	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,[c] g	3,500 (2,970–4,100)	3,510 (2,930–4,140)	0.99
Child birth length,[d] cm	50 (48–53)	50 (48–53)	0.55
IGF-I,[e] ng/mL	133.7 (94.9–198.0)	134.7 (94.5–195.0)	0.53

[a]Comparison between cases and controls: conditional logistic regression models.
[b]Gestational age available for 535 cases and 1,044 controls.
[c]Data on child's birth weight are available for 537 cases and 1,077 controls.
[d]Data on child's birth length are available for 535 cases and 1,076 controls.
[e]Geometric mean and (10th, 90th) percentile of hormone.

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

Laboratory analyses

IGF-I assay was quantified by immunometric assays on an 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 81.5 and 229 ng/mL, respectively. The inter- and intrarun CVs for a blinded pool of controls (mean concentration of 177 ng/mL) were 3.9% and 8.3%, respectively.

Statistical analysis

Prior to analysis, IGF-I values were $\log_2$-transformed to normalize their distributions. The correlation of IGF-I with gestational age was assessed by Pearson's partial correlation ($r = -0.03$). Subjects were categorized into quintiles on the basis of IGF-I distribution among the controls. Conditional logistic regression was used to calculate the OR and corresponding 95% CI of breast cancer across quintiles of IGF-I. The associations were also explored by histologic subtypes, median ages at first full-term pregnancy (29 years), diagnosis (41 years), and lag time to cancer diagnosis (11 years), as well as 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 (gravidity, parity by index date, family history of breast cancer, smoking, and gestational day) sporadically

Table 2. ORs with 95% CIs of breast cancer associated with quintiles of IGF-I concentrations among women from the FMC, 1983–2006

	Quintiles						
	q1	q2	q3	q4	q5	P_{trend}	$P_{heterogeneity}$
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[a]	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 y	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 y	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 y	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 y	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 y	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 y	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	

[a]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), $P = 0.44$].

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 2-sided, and values of $P < 0.05$ were considered statistically significant.

Results

Selected characteristics of the study population and IGF-I 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-I 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 between breast cancer and IGF-I, 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-I during early pregnancy was not associated with maternal risk of developing breast cancer. Both studies had very similar design and were nested in population-based maternity cohorts in neighboring countries. The samples were stored at comparative temperature (−25°C), and the mean IGF-I concentrations in the FMC controls (134.7 ng/mL) were comparable with those from the NSMC (133.6 ng/mL). IGF-I 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 (92%) had a diagnosis before 50 years of age and thus were more likely to be ER negative (4). The analysis by the

Endogenous Hormones and Breast Cancer Collaborative Group suggested that the association of IGF-I 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-I concentrations during early pregnancy and maternal breast cancer risk was observed in the FMC.

Disclosure of Potential Conflicts of Interest

The funding source had no role in the study design, interpretation of data, and publication of results.

Acknowledgments

We appreciate the excellent technical assistance provided by Pirjo Kontiokari, Annika Uimonen, and Sara Kuusiniemi in the conduct of the study.

Grant Support

This work was supported by research grants from the U.S. National Cancer Institute (CA114329 and CA120061). A.T Toriola was supported by a European Association for Cancer Research (EACR) Travel Fellowship Award to visit the Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg.

Received May 13, 2011; revised May 27, 2011; accepted June 4, 2011; published OnlineFirst June 15, 2011.

References

1. Chen T, Lukanova A, Grankvist K, Zeleniuch-Jacquotte A, Wulff M, Johansson R, et al. IGF-I during primiparous pregnancy and maternal risk of breast cancer. Breast Cancer Res Treat 2010;121:169–75.
2. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010;11:530–42.
3. Lukanova A, Surcel HM, Lundin E, Kaasila M, Lakso HA, Schock H, et al. Circulating estrogens and progesterone during primiparous pregnancies and risk of maternal breast cancer. Int J Cancer 2011 Mar 16. doi: 10.1002/ijc.26070.
4. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 2007;9:R6.