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

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Abstract

Background: **The role of insulin-like growth factor (IGF)-I in breast cancer remains controversial, despite numerous reports on the association of the hormone with breast cancer or high-risk mammographic densities. We hypothesized that exposure to elevated IGF-I during early pregnancy, a period characterized by intense cell proliferation in the breasts and in the presence of high concentrations of sex steroids, will be associated with increased maternal risk to develop a breast malignancy.**

Methods: **The Northern Sweden Maternity Cohort is an ongoing prospective study, collecting blood samples from first-trimester-pregnant women since 1975 as part of screening for infectious diseases. A case-control study (212 cases and 369 controls) was nested among Northern Sweden Maternity Cohort members who delivered singleton babies. RIA was used to measure IGF-I and IGF-II levels. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI).**

Results: **Breast cancer risk increased with increasing IGF-I (top tertile OR, 1.7; 95% CI, 1.1-2.7). The association was stronger among the primiparous (OR, 2.2; 95% CI, 1.1-4.4) than in the nonprimiparous women (OR, 1.4; 95% CI, 0.7-2.8). Upper-tertile risks seemed to decrease within the <28-, 28 to 33, and >33-year groups of age at sampling, from 2.5 (0.9-7.6) to 2.1 (0.9-5.0) and 1.2 (0.5-2.5), respectively. There was no association of breast cancer with first-trimester-pregnancy IGF-II.**

Conclusions: **The study offers further evidence that IGF-I is important in breast cancer. Our findings suggest that the adverse effect of IGF-I on the breast may be stronger before the remodeling of the gland induced by a first pregnancy.**
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Introduction

The association of circulating insulin-like growth factor (IGF)-I with breast cancer or high-risk mammographic density has been extensively investigated in >10 large and well-designed epidemiologic studies (1-6). Most studies with IGF-I measurements in samples collected during fertile life have shown a positive association with risk, whereas the association was predominantly unremarkable when hormone measurements were done in blood specimens drawn after menopause (1-4). The reasons for the observed effect modification by menopausal status at sampling are unknown, but two main, not mutually exclusive theories were put forward (7).

The first hypothesis states that the influence of the growth hormone/IGF-I during breast growth and development in adolescence and early adulthood are etiologically important because of increased vulnerability of the gland during its development, as shown in studies relating radiation to breast cancer (8-10) and animal experiments (11-13). However, because of the progressive decline in IGF-I starting soon after puberty and continuing until very old age (14), circulating levels of the hormone may reflect such influences less and less accurately with increasing age (7). A strong indirect argument in support for this theory is the well-established association of breast cancer with height, considered a proxy for IGF-I exposure during puberty, but only very weakly correlated with IGF-I during adult life (15, 16). The second hypothesis stipulates that the effect of IGF-I is enhanced by the high estrogen concentrations during fertile life (7, 17-19).

During the early part of pregnancy, on a background of increasing sex steroid concentrations, intense cell proliferation in the breasts marks the onset of the maturation and differentiation processes that will prepare the glands for lactation. We hypothesized that during this period of gland development, exposure to elevated IGF-I is associated with increased maternal risk of subsequent breast cancer. To test this hypothesis, we used the resources of the Northern Sweden Maternity Cohort, a prospective cohort of >83,000 women who gave blood during the early months of pregnancy. In addition to IGF-I, we explored the association of breast cancer with IGF-II, a member of the large IGF family that plays an important role in fetal development (20) and possibly in mammary gland development (21). This study is part of a larger research program focused on elucidating the role of pregnancy in breast carcinogenesis.

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Materials and Methods

Study subjects were part of the Northern Sweden Maternity Cohort based at the University Hospital in Umeå (Umeå, Sweden). The cohort was established in November 1975 with the purpose of preserving for research purposes serum samples from pregnant women tested for systemic infections. Cohort subjects are residents of the four northernmost counties of Sweden (total population ~800,000) attending any one of the maternity health care clinics in the region. Blood samples

are drawn mostly during the final weeks of the first trimester of pregnancy, or the early weeks of the second (weeks 7-18), and periodically shipped frozen to a central repository at Umeå University Hospital, where they are analyzed for systemic infections and stored at −20°C. As of 2002, the biorepository included ~110,000 serum specimens from >83,000 women.

We conducted a case-control study nested within the cohort. Cohort members whose pregnancy resulted in the delivery of one live or stillborn infant were eligible. Miscarriages, abortions, and twin pregnancies were reasons for exclusion. Women whose blood had been drawn after the 20th week of gestation, had used hormonal medications before or during pregnancy, or had previously been treated for any cancer (except nonmelanoma skin cancers) were also excluded. Potential cases were women diagnosed for the first time with invasive breast cancer after their entry into the cohort. Potential controls were cohort members alive and free of any cancer at the time of diagnosis of a case and individually matching the case (2:1 ratio) on parity at the time of blood sampling (primiparous, nonprimiparous), age at sampling (±2.5 years), and date of blood sampling (±3 months).

Cases were identified through record linkages with the nationwide Swedish Cancer Registry using the unique 10-digit personal identity number assigned to every person born in, or legally resident of, Sweden. Linkages done in 2000 and 2001 led to the identification of 426 potential case subjects. Because information on subjects in the cohort is limited to the personal identity number, name, consecutive serial number of sampling, and place of sampling, the identification of appropriately matched controls required a multistep approach. First, lists of up to eight potential controls were drawn for each case based on approximate dates of blood draw and birth (part of the personal identity number). Potential cases and controls were subsequently contacted individually by letter (up to two) and, if necessary, by phone, to describe the project and elicit permission to participate in the study. Women willing to participate were asked to return the signed informed consent along with a brief one-page reproductive history questionnaire to facilitate matching for parity before requesting medical records. Subjects were also asked to consent to the release of their pregnancy medical records. For those consenting, a full copy of the maternity and delivery records was requested from the 10 hospitals in the region. Records were first abstracted on matching information (parity and age at blood drawing; date of blood drawing) and eligibility (gestational age). Among those eligible who met the matching criteria for a given case, the remainder of the information was abstracted for two controls, chosen randomly, and for each potential case.

Of the potential study subjects initially identified (426 cases and 3,408 controls), 1,279 controls were never contacted. Among the subjects contacted, 2,378 (415 cases and 1,963 controls; 93%) returned the baseline information and 177 (11 cases and 166 controls; 7%) were nonrespondents. Among the respondents, 547 (58 cases and 489 controls) did not meet the eligibility criteria for various reasons (late week of gestation, twin pregnancy, abortion/miscarriage, not pregnant, and other reasons). Inadequate matching (596 controls) and matched sets lacking either the case or both controls (6 cases and 28 controls) further reduced the number of subjects available for study to 1,201 (351 cases and 850 controls). Finally, insufficient funding at the end of the study period forced us to cease retrieval of information and selection of study subjects and exclude from laboratory analyses an unselected subset of otherwise eligible study subjects (139 cases and 481 controls in total), so that 212 cases and 369 controls were included in the final statistical analyses.

Laboratory analyses were done in the laboratory of Clinical Chemistry, University Hospital of Umeå, by technicians who were unaware of the case-control status of the specimens. Individually matched case and control samples were always included in the same batch. IGF-I was quantified with IGF-I immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA). The intrabatch and interbatch coefficients of variation at 12.2 nmol/L were 6.3% and 7.6%, respectively. IGF-II was quantified by IGF-II immunoradiometric assay (Diagnostic System Laboratories, Webster, TX), with intrabatch and interbatch coefficients of variation at 108 nmol/L of 9.0% and 11.0%, respectively. All samples were run in duplicate. If measurements between duplicates deviated by >5%, then all samples in a batch were rerun. Bio-Rad control samples (Lyphochek, Bio-Rad, Irvine, CA) at two levels of the analyte were included in duplicate in each run as quality controls.

Statistical analyses were done after log transformation of the original hormone levels; no adjustment for gestational age was carried out because IGF-I and IGF-II were virtually unaffected by gestational age (Figs. 1 and 2). Paired t test was used to compare mean hormone concentrations of cases and controls (case value versus mean of the matched controls). The conditional logistic regression model, which is appropriate for matched data, was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) associated with increasing hormone concentrations. Subjects were classified in tertiles using the frequency distribution of the cases and controls combined. Tests for trend were computed by treating the hormone variables as ordered categorical variables. Likelihood ratio tests were used to assess statistical significance.

Additionally, hormone-disease associations were examined within strata of parity (primiparous versus nonprimiparous) and three strata of age at index pregnancy (<28, 28-33, and >33 years). The cut points for the latter strata were chosen to ensure a balanced number of cases in each group and a reasonably young age in the youngest group. Interaction was assessed by including interaction term in the logistic regression models.

The study, including its consent form and access to human subjects, was approved annually by the Ethics Committees of the University of Umeå and New York University School of Medicine.

Results

Median age at blood sampling was 32.3 years (range, 19.3-43.9 years) for the cases and 31.6 years (range, 18.8-44.4 years) for the controls. Forty-nine percent of study subjects were primiparous at blood donation, with median age at blood

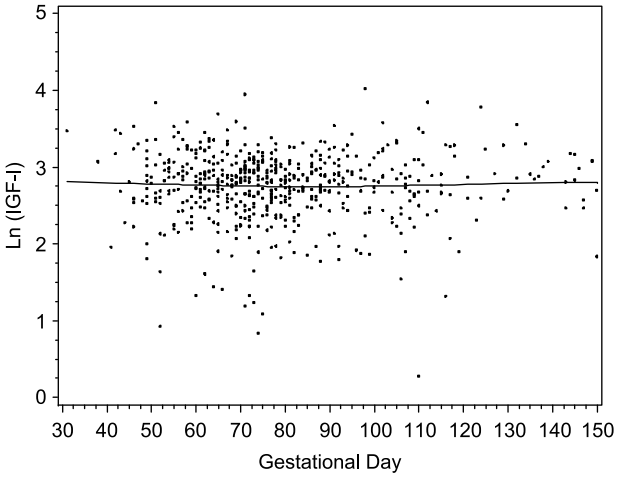

Figure 1. Variation of IGF-I levels with gestational age during early pregnancy.

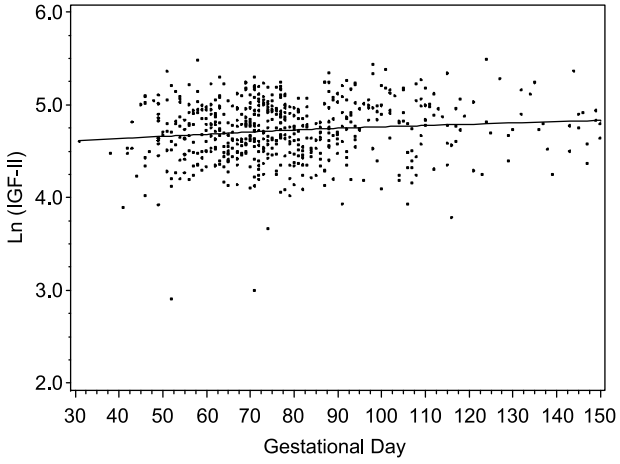

Figure 2. Variation of IGF-II levels with gestational age during early pregnancy.

donation of 28.3 years. The median age of multiparous women at blood donation was 33.8 years. For the majority of study subjects (75%), blood samples were drawn between the 8th and the 14th gestational week, 11% were drawn before the 8th gestational week, and 14% were drawn after 14th gestational week. Median day of gestation was 74 for cases and 77 for controls. Among the cases, median lag time between blood drawing and date of diagnosis was 12.1 years (range, 1.3-22.6 years); 85.8% of the cases had a lag time $\geq$6 years and 65.1% of the cases had a lag time of >10 years. Mean (median) age at diagnosis was 42.8 years (43.0 years), ranging from 25 to 59 years. Only 16 cases (7.5%) were diagnosed after age 51 years, which is the mean age at menopause in Swedish women. Thus, most of the tumors have been diagnosed in women who were either premenopausal or in the transition to menopause.

Concentrations of both IGF-I and IGF-II were stable with increasing gestational age (Figs. 1 and 2). Among the cases and the controls combined, median IGF-I and IGF-II were 17.2 and 111 nmol/L before the 9th week of gestation, 16.6 and 114 nmol/L between the 9th and 14th week, and 16.8 and 121 nmol/L between the 15th and 20th week, respectively. The two hormones were positively correlated, with Spearman coefficients of 0.45 ($P < 0.0001$) among the cases and 0.47 ($P < 0.0001$) among the controls. Mean and median concentrations of IGF-I and IGF-II among cases and controls are presented in Table 1. There were no significant differences in hormone concentrations between the two groups in all subjects and within subgroups defined by parity (data not shown).

Table 2 reports the results of conditional logistic regression analyses. In the whole study population, there was a significant increase in the risk of maternal breast cancer with increasing IGF-I. The top tertile OR was 1.7 (95% CI, 1.1-2.7). The association of breast cancer with IGF-I was substantially stronger in primiparous (OR, 2.2; 1.1-4.4) than in nonprimiparous women (OR, 1.4; 0.7-2.8), although the test for interaction was not significant ($P = 0.38$). Within the <28-, 28 to 33, and >33-year age groups at sampling, ORs decreased from 2.5 (0.9-7.6) to 2.1 (0.9-5.0) and 1.2 (0.5-2.5), respectively. Risk estimates did not differ according to the median lag time to cancer diagnosis (data not shown), but the association seemed stronger in subjects with age at diagnosis above the median: OR for the top tertile is 2.0 (95% CI, 1.1-4.0) for women diagnosed after age 43 years versus an OR of 1.3 (95% CI, 0.7-2.5) for those diagnosed before age 43 years. None of the potential confounders considered (smoking, placental weight, baby length, and weight) had appreciable effects on the risk estimates (>10%).

There was no evidence that risk of breast cancer was associated with IGF-II, either in analyses that included all subjects or in subgroups defined by age at sampling, parity, and age at cancer diagnosis (Table 2).

Discussion

To our knowledge, this is the first epidemiologic study that addresses the association of breast cancer risk with circulating concentrations of IGF-I in a population of pregnant women. In the nested case-control study as a whole, risk of long-term breast cancer increased with increasing circulating concentrations of IGF-I, but not with IGF-II. The 70% increase in risk in the upper tertile of IGF-I is consistent with previous observations in nonpregnant women during fertile life (1, 3, 22).

Several biological mechanisms may contribute to the observed association. First, similar to nonpregnant women, increased IGF-I signaling during a period of intense cell proliferation in the breast may affect cancer risk by increasing the pool of damaged cells that have undergone early genetic ''hits'' and/or by affecting the early progression of already established neoplasms (23-25). Second, during the first trimester of pregnancy, pituitary growth hormone still has the leading role in the control of circulating IGF-I, but it is subject to feedback down-regulation by the stimulus to IGF-I synthesis induced by placental growth hormone (26-30), and there is an inverse correlation between pituitary growth hormone and circulating IGF-I (31, 32). Consequently, high circulating IGFI during early pregnancy may indicate less-efficient suppression of pituitary growth hormone by negative feedback mechanisms, which may serve as an indicator of an underlying susceptibility of some women to high circulating IGF-I in other phases of fertile life. Last, first-trimester IGF-I could be a proxy for nonpregnant exposure to IGF-I at a given age. Circulating IGF-I during the first half of the pregnancy is fairly constant and similar to the concentrations measured before the index pregnancy or in age-matched nonpregnant women (30, 32-35), although some recent longitudinal studies suggested that a decline in maternal IGF-I around 8 to 16 weeks of pregnancy may occur (33, 34, 36). However, the data from the largest and well-designed longitudinal study published thus far indicate that despite the drop in mean IGF-I during early pregnancy, there is still an important degree of correlation between preconception and 8-week-gestation IGF-I ($r^2 = 0.32$, corresponding to $r = 0.57$; ref. 36). In comparison, correlations between repeated measurements of IGF-I in nonpregnant women and men range from 0.5 to 0.9 over various periods of time (3, 37-40).

Analyses in subgroups by parity and age at index pregnancy showed that the association of breast cancer risk with circulating IGF-I was stronger in primiparous women and in younger subjects at the time of blood collection (Table 2). Albeit intriguing, these observations should be interpreted with caution given that the study was not designed to specifically address the effects of parity or age on the association of IGF-I with breast cancer. There was no sufficient

Table 1. Means (SD) and medians (10th-90th percentiles) of circulating concentrations of IGF-I and IGF-II in cases and controls

Hormone (nmol/L)	Cases (n = 212)	Controls (n = 369)	P*
IGF-I	17.6 (7.0) 17.5 (8.9-25.9)	17.0 (7.0) 16.0 (9.3-25.6)	0.46
IGF-II	117 (37) 114 (70-165)	119 (36) 115 (77-168)	0.38

*Paired t test for the case versus the mean of the two controls.

Table 2. Maternal breast cancer ORs (95% CIs) associated with circulating concentrations of IGF-I and IGF-II in pregnancy

	Tertile			P_{trend}
	1	2	3	
IGF-I				
OR (95% CI) [cases/controls]	1.0 [60/135]	1.4 (0.9-2.1) [74/120]	1.7 (1.1-2.7) [78/114]	0.02
Parity*				
Primiparous	1.00	1.2 (0.6-2.4)	2.2 (1.1-4.4)	0.02
Multiparous	1.00	1.6 (0.9-2.8)	1.4 (0.7-2.8)	0.26
Age at sampling (y) †				
<28	1.00	1.9 (0.6-5.8)	2.5 (0.9-7.6)	0.10
28-33	1.00	2.2 (1.0-4.9)	2.1 (0.9-5.0)	0.08
>33	1.00	0.9 (0.4-1.9)	1.2 (0.5-2.5)	0.67
IGF-II				
OR (95% CI) [cases/controls]	1.00 [74/120]	0.9 (0.6-1.4) [72/121]	0.9 (0.5-1.4) [66/128]	0.54

*Number of cases out of controls in parity subgroups are 103 of 180 (primiparous) and 109 of 189 (multiparous).
†Number of cases out of controls in age groups <28, 28-33 and >33 years are 51 of 82, 58 of 86, and 80 of 126, respectively; 23 case-control sets were excluded from these analyses because the index case was not in the same age group as at least one of her controls.

statistical power to test for interaction, and the overlap between the subgroups did not allow discrimination between independent effects of parity and age.

Nevertheless, the stronger adverse effect of IGF-I in primiparous women, compared with women sampled during a subsequent full-term pregnancy, is in line with observations from animal experiments showing that parous rodents are far less likely to develop mammary tumors after carcinogen exposure than age-matched virgin control animals (13). IGF-I concentrations during the early months of the first full-term pregnancy captures exposure immediately preceding the full maturation and differentiation of the breasts associated with a pregnancy completed to term, which would render the glands more resistant to the influence of mitogenic and antiapoptotic stimuli in the future and possibly mitigate the observed effect of IGF-I on disease risk. Furthermore, a full-term pregnancy may induce long-lasting changes in the secretion and circulating levels of endogenous hormones (41-43), including growth hormone, the major stimulus for IGF-I synthesis (31). Although, in our study, there were no indications that mean IGF-I concentrations changed with increasing parity, the large Nurse's Health Study had previously reported that parous women had lower IGF-I than nulliparous women, suggesting that parity could permanently alter the circulating concentrations of the hormone (44). Further animal data indicate that parous rats have lower circulating growth hormone than age-matched virgin animals (45) and that plasma concentration of IGF-I during pregnancy are higher in primiparous than in multiparous cows (46). A strong effect modification by parity may account for some of the conflicting results about the effect of IGF-I on breast cancer risk.

A number of epidemiologic studies have studied the effect of premenopausal levels of IGF-I on risk of breast cancer (2), but most of these included women recruited after age 35 years. Thus far, only one prospective study directly addressed the role of age as an effect modifier, but its results lacked stability (3). However, the stronger adverse effect of exposure to the mitogenic and antiapoptotic IGF-I signaling at an earlier age is supported by epidemiologic evidence suggesting increased vulnerability of the human breast before age 20 years and experimental evidence showing that the incidence of chemically induced mammary tumors diminishes with age (11, 12).

Some limitations of the study warrant discussion. We could not finalize recruitment of study subjects as initially intended because the data collection processes far exceeded the available financial resources. Thus, sample size was too small to allow us to conduct meaningful analyses for interaction, and the results suggesting effect modifications must be taken cautiously as merely indicative and preliminary. Another concern is the possible effect of long-term sample storage at −20°C on the quality of the peptide measurements. However, we are confident about the quality of the analyses as (*a*) there was no consistent or significant effect of storage time on both IGF-I and IGF-II concentrations; (*b*) the mean IGF-I concentrations observed in our study were very similar to those reported by other groups, where IGF-I was measured in first-trimester-pregnancy samples stored for a much shorter period of time and at −70°C or −60°C by the same laboratory assay kit (immunoradiometric assay by the Nichols Institute; refs. 33, 34); (*c*) we observed the expected association of IGF-I with breast cancer risk.

In summary, this case-control study nested in the large Northern Sweden Maternity Cohort offers further evidence that IGF-I plays an important role in breast cancer. The study provides preliminary evidence that the association is best reflected by measurements taken before the completion of full-term pregnancy and possibly early during a woman's reproductive life. These observations are consistent with the hypothesis that growth hormone/IGF-I may influence breast cancer risk when these hormones are at their peak during postpubertal breast development. However, because of our small sample size, confirmation of our results by other studies is essential. Currently, we are in the planning phase of a much larger study, restricted to women who donated blood during their first full-term pregnancy, which will have adequate statistical power to address the effect of age on the association of breast cancer with circulating IGF-I.

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