Insulin-like Growth Factor and Mammographic Density in Postmenopausal Norwegian Women

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Abstract

Insulin-like growth factor-I (IGF-I) is associated with breast cancer risk among premenopausal women but rarely among postmenopausal women. Recent data from two European studies suggested an increased risk of breast cancer with increasing levels of IGF-I among women >50 years old or among postmenopausal hormone therapy users ≥55 years old. Mammographic density is one of the strongest risk factors, and possibly an intermediate marker, for breast cancer. We examined the relationship between IGF and mammographic density among postmenopausal women overall and according to hormone therapy use. Altogether, 977 postmenopausal participants in the Norwegian governmental mammographic screening program had IGF concentrations measured by ELISA. Mammograms were classified according to percent and absolute mammographic densities using a previously validated computer-assisted method. After adjustment for age, number of children, age at menopause, body mass index, and hormone therapy use, both plasma IGF-I concentration (P_{trend} = 0.02) and IGF-I/IGF binding protein 3 ratio (P_{trend} = 0.02) were positively associated with percent mammographic density. The magnitudes of differences in percent mammographic density between women in the lowest and highest quartiles of IGF-I concentrations were 1.5% absolute difference and 21% relative difference. These associations were similar with absolute mammographic density as the outcome variable. When the analyses were stratified according to hormone therapy use, the associations between IGF-I and mammographic density were significant among noncurrent users (P_{trend} = 0.03). In conclusion, we found a positive but weak association between plasma IGF-I concentrations and both percent and absolute mammographic densities among postmenopausal women. These associations were found among noncurrent hormone therapy users but not among current users. (Cancer Epidemiol Biomarkers Prev 2007;16(1):57–62)

Introduction

Mammographic density is one of the strongest independent risk factors for breast cancer and possibly an intermediate marker for breast cancer (1). Women with high mammographic density have a 5- to 6-fold increase in breast cancer risk (2, 3).

Insulin-like growth factor I (IGF-I) has almost consistently been shown to be associated with breast cancer risk in young women (4-10), but more rarely so in older women (11-14). Meta-analyses of IGF-I and breast cancer association have shown that the effect differs by menopausal status rather than age (4-7, 10). However, the mechanism for this effect modification is not understood. Recently, a European study found an increased risk of breast cancer with increasing levels of IGF-I among women >50 years old (13). Another European study found an association of IGF-I with breast cancer among women ≥55 years old, especially among postmenopausal hormone therapy users (15).

Among premenopausal women, the association between IGF-I and mammographic density seems to mirror that between IGF-I and breast cancer (16-21). All studies of IGF-I and mammographic density association among postmenopausal women have thus far been restricted to noncurrent users of hormone therapy from North America (16, 17, 19, 20, 22) and United Kingdom (21). The only statistically significant finding among postmenopausal women thus far has been an inverse relationship between IGF-I/IGF binding protein 3 (IGFBP-3) ratio and percent mammographic density among 43 overweight former hormone therapy users (22).

The objective of this cross-sectional study was to examine the relationship between circulating concentrations of IGF-I and IGFBP-3, or IGF-I/IGFBP-3 molar ratio, and quantitative mammographic density among Norwegian postmenopausal women overall and according to hormone therapy use.

Materials and Methods

Study Population. The Mammography and Breast Cancer Study was conducted among postmenopausal women, ages 55 to 71 years, residing in the municipality of Tromsø, Norway, and attending the population-based Norwegian Breast Cancer Screening Program at the University Hospital of North Norway. The women were recruited in the spring of 2001 and 2002. After the women had undergone their screening mammograms, they were interviewed by a trained research nurse about reproductive and menstrual factors, previous history of cancer, smoking status, and use of postmenopausal hormone therapy or other medications. The participants had their height measured to the nearest centimeter and their weight measured to the nearest half kilogram. The women had blood samples drawn and each was subsequently given a questionnaire to be completed at home, eliciting information

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on demographics, additional menstrual and reproductive factors, as well as lifestyle and dietary factors. All women signed an informed consent. The National Data Inspection Board and the Regional Committee for Medical Research Ethics approved the study. Altogether, 1,041 women were included in the study. This accounted for 70.1% of the women attending the Norwegian Breast Cancer Screening Program during the recruitment period.

We excluded 22 women because of a previously ($n = 16$) or newly ($n = 6$) diagnosed breast cancer and one woman because of an ongoing chemotherapy treatment. Among the remaining 1,018 women, we were unable to retrieve mammograms on 11 women. Thus, 1,007 women had mammograms classified according to percent and absolute mammographic densities. More details are described elsewhere (23). We further excluded three women because they were equivocal for menopausal status and 17 women because they had not donated blood samples. In addition, 10 women were excluded due to missing IGF-I measurements, leaving 977 women for the analyses.

Mammographic Classifications. The women's left craniocaudal mammogram was digitized using a Cobrascan CX-812 scanner (Radiographic Digital Imaging, Torrance, CA) at a resolution of 150 pixels/in. Percent and absolute mammographic densities were determined using the University of Southern California Madena computer-based threshold method, which has been described in detail and validated elsewhere (24). Briefly, the method works as follows: The digitized mammographic image is viewed on a computer screen. A reader defines the total breast area using a special outlining tool. Next, the region of interest, excluding the pectoralis muscle, prominent veins, and fibrous strands, is defined. The computer software program assigns a pixel value of 0 to the darkest (black) shade in the image and a value of 255 to the lightest (white) shade, with shades of gray assigned to intermediate values. The reader then uses a tinting tool to apply a yellow tint to dense pixels with gray levels at or above some threshold X and a pixel value of ≤ 255. The reader searches for the best threshold where all pixels $\geq X$ within the region of interest are considered to represent mammographic densities. The software estimates the total number of pixels and the number of tinted pixels within the region of interest. Absolute density represents the count of the tinted pixels within the region of interest. Percent density, or the fraction (%) of the breast with densities, is the ratio of absolute density to the total breast area multiplied by 100.

The reader of the mammograms was blinded to the characteristics of the study participants.

Peptide Assays. Nonfasting venous samples were obtained from study participants at the day of mammographic screening. After centrifugation, plasma samples were stored at $-70^{\circ}C$.

IGF-I and IGFBP-3 were measured by ELISA from Diagnostic Systems Laboratories, Inc. (Webster, TX). The IGF-I assays included an acid-ethanol precipitation to extract IGF-I from its binding proteins. Measurements were done on previously never-thawed plasma samples.

All IGF-I and IGFBP-3 assays were done at the laboratory for hormone analyses (Nutrition and Cancer Group, IARC, Lyon, France), under supervision by one of the authors (S.R.). The mean intrabatch coefficients of variation were 5.1% for IGF-I and 6.1% for IGFBP-3. The interbatch coefficients of variation were 10.6% for IGF-I and 9% for IGFBP-3.

The IGF-I/IGFBP-3 molar ratio was calculated as a possible indicator of IGF-I bioavailability.

Statistical Analysis. We used ANOVA for an unbalanced design to study the association between plasma levels of IGF-I and IGFBP-3, or IGF-I/IGFBP-3 molar ratio, and mammographic density (Proc GLM, SAS Institute Inc., Cary, NC). Percent and absolute mammographic densities were log-transformed to obtain an approximate normal distribution. The crude and adjusted mean mammographic density results were back-transformed and are presented with 95% confidence intervals (95% CI). Trend tests across the quartiles of IGF concentrations were done by treating the quartile categories (scored 1, 2, 3, and 4) as continuous variables in the analyses.

Each of the following factors was evaluated as a potential confounder of the relationship between IGF and mammographic density: age at screening (continuous), age at menarche (continuous), age at menopause (continuous), number of children (continuous), age at first birth (continuous), years of education (continuous), family history of breast cancer in first-degree relatives (yes, no), smoking (daily, sometimes, no), alcohol intake (g/d), hormone therapy use (ever, never, past, current; never and past hormone therapy users were also grouped as noncurrent users, whereas past and current hormone therapy users were grouped as ever users), and body mass index (BMI, weight in kilogram divided by height in meters squared; continuous).

We did univariate and multivariate analyses with models that included the above-listed variables as independent variables and mammographic density as the dependent variable. Because all the above factors were presumed to be associated with IGF concentrations, we used the following criteria to include them in the model as a confounder: The factor had to either have been previously associated with the outcome variable in this study population (23) or it changed the estimate by 10% or more when included in the multivariate model. This procedure left the following factors for inclusion in the final model as confounders: age at screening, number of children, age at menopause, BMI, and hormone therapy use.

We did stratified multivariate analyses to examine the association between IGF and mammographic density according to hormone therapy use.

Results were considered statistically significant if the two-sided P value was <0.05. We did data management and statistical analyses using the SAS statistical software package, version 9.1 (SAS Institute).

Results

Among the 977 postmenopausal women in the study population, the mean age was 61.4 years (SD, 4.6 years) and the mean age at menopause was 48.6 years (SD, 5.1 years). The median percent mammographic density was 9.6% (range, 0-69.2%), and the median mammographic absolute dense area was 14.8 cm^2 (range, 0-155.2 cm^2). Furthermore, mean plasma concentrations were 223.4 ng/mL (SD, 74.3 ng/mL) for IGF-I and 4,339 ng/mL (SD, 993 ng/mL) for IGFBP-3; the IGF-I/IGFBP-3 molar ratio was 0.19 (SD, 0.06). Among the women, 26% were current, 17% were past, and 57% were never hormone therapy users. Of the women, 18.4% reported a history of breast cancer in the family, whereas 9.2% reported a history of breast cancer in first-degree relatives.

Table 1 shows the crude relationship between selected variables and mean concentrations of IGF-I and IGFBP-3, or IGF-I/IGFBP-3 molar ratio, among the 977 women. The plasma concentration of IGF-I ($P_{trend} = 0.12$) and the IGF-I/IGFBP-3 molar ratio ($P_{trend} = 0.11$) decreased with increasing age, although not statistically significantly. The plasma concentration of IGF-I also decreased with increasing alcohol consumption ($P_{trend} < 0.03$). The IGF-I/IGFBP-3 ratio decreased significantly with increasing BMI ($P_{trend} < 0.002$). Plasma concentration of IGF-I and IGF-I/IGFBP-3 molar ratio showed a positive association with increasing age at menopause (both P_{trend} values <0.001). Plasma IGFBP-3 decreased ($P_{trend} < 0.002$), whereas IGF-I/IGFBP-3 ratio increased ($P_{trend} < 0.05$), with increasing frequency of smoking (Table 1). Plasma IGF-I

Table 1. Selected variables in relationship with mean plasma concentrations (SD) of IGF-I and IGFBP-3 and IGF-I/IGFBP3 molar ratio among postmenopausal Norwegian women (*N* = 977)

	n	IGF-I (ng/mL)	P_{trend}	*n*	IGFBP-3 (ng/mL)	P_{trend}	*n*	IGF-I/IGFBP-3 molar ratio	P_{trend}
Age (y)									
<60	403	226.7 (72.8)		403	4,340 (1,011)		403	0.20 (0.05)	
60-64	311	224.3 (81.0)		310	4,349 (996)		310	0.19 (0.06)	
65-71	263	217.1 (67.8)	0.12	262	4,324 (964)	0.86	262	0.19 (0.05)	0.11
No. children									
0	71	221.5 (74.7)		71	4,277 (870)		71	0.19 (0.06)	
1-2	389	223.7 (68.6)		388	4,372 (1,024)		388	0.19 (0.05)	
3	309	221.5 (83.0)		309	4,251 (969)		309	0.20 (0.06)	
≥4	208	226.1 (71.0)	0.73	207	4,428 (1,004)	0.57	207	0.19 (0.05)	0.99
BMI (kg/m^2), tertiles									
<25	323	216.8 (69.7)		323	4,141 (953)		323	0.20 (0.06)	
25-28	328	235.1 (82.0)		326	4,384 (996)		326	0.20 (0.06)	
≥29	326	218.1 (69.1)	0.83	326	4,489 (999)	<0.001	326	0.18 (0.05)	<0.002
Age at menopause* (y)									
<48	308	217.0 (68.0)		307	4,311 (971)		307	0.19 (0.05)	
48-50	317	214.3 (67.7)		316	4,306 (958)		316	0.19 (0.05)	
>50	327	238.5 (82.7)	<0.001	327	4,400 (1,043)	0.24	327	0.20 (0.06)	<0.001
Postmenopausal hormone therapy use									
Never	553	224.5 (69.1)		551	4,400 (958)		551	0.19 (0.05)	
Past	170	251.8 (84.5)		170	4,583 (892)		170	0.21 (0.06)	
Current	254	201.9 (71.4)	<0.003	254	4,043 (1,064)	<0.001	254	0.19 (0.06)	0.87
Smoking									
Nonsmokers	645	223.7 (74.9)		644	4,408 (988)		644	0.19 (0.06)	
Sometimes	62	223.8 (60.3)		61	4,269 (870)		61	0.20 (0.04)	
Daily smokers	270	222.3 (75.9)	0.80	270	4,188 (1,015)	<0.002	270	0.20 (0.06)	<0.05
Alcohol consumption †									
Teetotaler	123	236.5 (70.2)		123	4,664 (927)		123	0.19 (0.05)	
No consumption reported in the previous 12 mo	101	223.2 (78.8)		101	4,410 (1,009)		101	0.19 (0.05)	
<1.50 g/d	215	224.4 (86.1)		213	4,264 (960)		213	0.20 (0.07)	
1.50-3.79 g/d	219	220.1 (68.5)		219	4,285 (965)		219	0.19 (0.05)	
≥3.80 g/d	224	216.7 (63.3)	<0.03	224	4,233 (1,022)	<0.001	224	0.19 (0.05)	0.58

NOTE: IGFBP-3 concentration and IGF-I/IGFBP-3 molar ratio are missing for two women.
*Age at menopause is missing for 25 women.
†Alcohol consumption is missing for 95 women.

and IGFBP-3 concentrations were significantly lower among current users of hormone therapy compared with noncurrent users (both *P* values <0.001).

In multivariate analyses, both plasma IGF-I concentration (P_{trend} = 0.02) and IGF-I/IGFBP-3 ratio (P_{trend} = 0.02) were positively associated with percent mammographic density (Table 2). Women with IGF-I concentrations in the highest quartile had a higher percent mammographic density (1.5% absolute difference, 21% relative difference) compared with women with values in the lower quartiles. The corresponding differences were 1.4% absolute difference and 19% relative difference for the IGF-I/IGFBP-3 ratio. A similar association was found between IGF-I and absolute mammographic density (P_{trend} = 0.04), whereas the association with IGF-I/IGFBP-3 ratio weakened and was of borderline significance (P_{trend} = 0.06).

When we stratified the women according to current, noncurrent, and never hormone therapy use, we found that the association between IGF-I and percent or absolute mammographic density was statistically significant only among women not currently using hormone therapy (all P_{trend} values < 0.05; Table 3). The association between IGF-I/IGFBP-3 ratio and percent mammographic density was statistically significant among these women (P_{trend} = 0.03), whereas the corresponding association with absolute mammographic density was of borderline significance (P_{trend} = 0.05).

We also did analyses among current hormone therapy users stratified by the type of hormone therapy used; however, no associations between IGF-I and mammographic density were observed (data not shown).

We found similar associations between IGF-I and percent mammographic density overall and among noncurrent hormone therapy users when BMI was adjusted in the multivariate model as a continuous and categorized variable (tertile or quintile) and when we excluded the 5% most extreme BMI values (2.5% highest and 2.5% lowest; data not shown). The associations with IGF-I/IGFBP-3 ratio weakened when BMI was modeled excluding the women with the most extreme BMI values (data not shown).

Discussion

This population-based cross-sectional study shows a positive association between mean plasma IGF-I concentration and percent mammographic density among women not currently taking hormone therapy after adjustment for potential confounders. This association was also present when absolute mammographic density was used as the outcome variable. For both outcome variables, the absolute difference in mammographic density between women with IGF-I concentrations in the upper and lower tertiles was small. However, the relative differences were not negligible. No associations were found between IGFBP-3 and the two measures of mammographic density.

The strengths of our study are the large sample size and the fact that it was a part of a population-based screening project with a high attendance rate (25). The reader of the mammograms was experienced and blinded to the characteristics of the women. Further, the IGF-I and IGFBP-3 analyses were done in a blinded manner at a laboratory specializing on hormone measurements. It was recently argued that the association between IGF and percent mammographic density is strongly confounded by adiposity (26) and that this is

Table 2. Adjusted mean (95% CI) percent and absolute mammographic densities by quartiles of IGF-I and IGFBP-3 concentrations and IGF-I/IGFBP-3 molar ratio among 977 postmenopausal Norwegian women

	Adjusted mean* (95% CI) percent mammographic density (%)	Adjusted mean* (95% CI) absolute mammographic density (cm^2)
IGF-I (N = 977)		
Q1	7.50 (6.56-8.56)	10.71 (9.22-12.44)
Q2	8.09 (7.11-9.21)	11.58 (10.01-13.38)
Q3	8.94 (7.84-10.18)	12.80 (11.05-14.83)
Q4	9.07 (7.97-10.32)	13.08 (11.31-15.13)
P_{trend}	0.02	0.04
IGFBP-3 (n = 975)		
Q1	8.46 (7.42-9.65)	12.12 (10.45-14.06)
Q2	7.93 (6.96-9.02)	11.45 (9.89-13.25)
Q3	8.67 (7.60-9.89)	12.25 (10.56-14.21)
Q4	8.54 (7.50-9.73)	12.32 (10.64-14.26)
P_{trend}	0.69	0.73
IGF-I/IGFBP-3 molar ratio (n = 975)		
Q1	7.37 (6.47-8.41)	10.67 (9.21-12.38)
Q2	8.16 (7.17-9.29)	11.65 (10.06-13.48)
Q3	9.40 (8.25-10.72)	13.47 (11.62-15.61)
Q4	8.77 (7.72-9.96)	12.52 (10.84-14.45)
P_{trend}	0.02	0.06

NOTE: Analyses are adjusted for age at screening, number of children, age at menopause, BMI, and postmenopausal hormone therapy use (never, past, and current). IGFBP-3 concentration and IGF-I/IGFBP-3 ratio are missing for two women.
*Reported means are back-transformed from log-transformed estimated means.

only partially accounted for by adjustments for BMI, given that percent mammographic density is highly influenced by the size of the breast. Thus, another strength of our study is that we found similar associations for IGF-I and mammographic density relationship when we did the analyses using absolute mammographic density as the outcome variable.

Furthermore, the associations between IGF-I and percent mammographic density were similar when BMI was modeled as a categorized and continuous variable. We also found the expected nonlinear relationship between BMI and IGF-I previously shown in a large and several smaller studies (27-29).

One limitation is that our study was cross-sectional; therefore, we do not have information on the temporal relationship between the concentrations of IGF and mammographic density. Also, assessing mammographic density is partly based on a subjective component. However, the reader was blinded to all characteristics of the women, and we have previously shown that the reader of the mammograms had a good correlation (Pearson correlation coefficient = 0.86) for a second independent reading of percent mammographic density of 37 mammograms done for as long as 18 months after the first reading (23).

The six previous studies that had examined the relationship of IGF-I and percent mammographic density in postmenopausal women did not find any association between the two (16, 17, 19-22). These studies differed from our study as they all excluded women who were current hormone therapy users. Also, five of the six studies included <250 postmenopausal women (16, 17, 19, 21, 22) and would not have power to detect a small difference of the magnitude we found. The cross-sectional study by Diorio et al. (20) included 791 postmenopausal women who were not currently using hormone therapy from two mammography screening clinics. The study by Diorio et al. (20) is similar to our study in the following aspects: the mammographic density was assessed by a computer-assisted method (30), the mean BMI was similar, and the IGF analyses were measured by ELISA. Their study differs from ours in the aspect that almost 31% of the women in their study reported a history of breast cancer in first-degree relatives, whereas the corresponding number is 9% in our study. Otherwise, we have no explanation for why our results are discrepant from the results by Diorio et al. (20).

In our study, the IGF-I/IGFBP-3 molar ratio did not show any stronger associations with mammographic density than those associations between IGF-I and mammographic density. Thus, our findings support the recent opinion that the IGF-I/IGFBP-3 ratio is a poor surrogate for bioavailable IGF-I (5).

Table 3. Adjusted mean (95% CI) percent and absolute mammographic densities by quartiles of IGF-I and IGFBP-3 concentrations and IGF-I/IGFBP-3 molar ratio by postmenopausal hormone therapy use among 977 Norwegian women

	Adjusted mean* (95% CI) percent mammographic density (%)			Adjusted mean* (95% CI) absolute mammographic density (cm^2)	
	Current hormone therapy use	Noncurrent hormone therapy use	Never hormone therapy use	Noncurrent hormone therapy use	Never hormone therapy use
IGF-I	n = 254	n = 723	n = 553	n = 723	n = 553
Q1	10.80 (8.84-13.20)	6.17 (5.24-7.27)	5.98 (5.00-7.15)	11.71 (9.13-15.01)	8.36 (6.83-10.22)
Q2	11.96 (9.34-15.31)	6.65 (5.76-7.69)	6.18 (5.23-7.30)	12.71 (9.95-16.25)	8.80 (7.29-10.63)
Q3	13.17 (10.07-17.23)	7.27 (6.31-8.38)	7.35 (6.35-8.64)	14.37 (11.32-18.25)	10.26 (8.55-12.31)
Q4	11.97 (8.91-16.08)	7.74 (6.73-8.89)	7.53 (6.34-8.95)	14.97 (11.80-18.98)	10.77 (8.87-13.09)
P_{trend}	0.38	0.03	0.03	0.03	0.04
IGFBP-3	n = 254	n = 721	n = 551	n = 721	n = 551
Q1	11.13 (9.05-13.69)	7.26 (6.20-8.51)	7.23 (6.06-8.64)	14.15 (11.07-18.09)	10.41 (8.52-12.71)
Q2	10.59 (8.38-13.37)	6.77 (5.83-7.87)	6.65 (5.59-7.91)	13.04 (10.18-16.70)	9.34 (7.68-11.36)
Q3	13.76 (10.25-18.46)	7.02 (6.10-8.06)	6.53 (5.57-7.66)	13.01 (10.21-16.58)	9.25 (7.73-11.07)
Q4	12.94 (9.88-16.94)	7.02 (6.08-8.12)	6.72 (5.62-8.02)	13.52 (10.65-17.17)	9.32 (7.63-11.39)
P_{trend}	0.23	0.88	0.55	0.75	0.46
IGF-I/IGFBP-3 molar ratio	n = 254	n = 721	n = 551	n = 721	n = 551
Q1	9.94 (7.95-12.44)	6.25 (5.36-7.28)	6.14 (5.17-7.30)	12.09 (9.45-15.47)	8.70 (7.16-10.57)
Q2	13.05 (10.05-16.94)	6.58 (5.70-7.59)	6.20 (5.25-7.33)	12.62 (9.93-16.03)	8.59 (7.13-10.36)
Q3	13.42 (10.57-17.05)	7.73 (6.67-8.96)	7.49 (6.34-8.85)	14.44 (11.31-18.44)	10.61 (8.79-12.80)
Q4	11.37 (8.78-14.72)	7.54 (6.53-8.70)	7.37 (6.17-8.80)	14.89 (11.71-18.92)	10.56 (8.65-12.90)
P_{trend}	0.34	0.03	0.06	0.05	0.07

NOTE: Analyses are adjusted for age at screening, number of children, age at menopause, and BMI. IGFBP-3 concentration and IGF-I/IGFBP-3 ratio are missing for two women.
*Reported means are back-transformed from log-transformed estimated means.

We have previously shown, in this study population, that women using a continuous estrogen plus progestin hormone therapy for ≥5 years had a 7% higher percent mammographic density compared with never hormone therapy users (31). This difference was also of a small absolute value. However, because the women in our study overall have a very low percent mammographic density, the relative difference is not negligible. The mean percent mammographic density in our study is similar to that found among non–Hispanic White postmenopausal women in the placebo group of the Women's Health Initiative study (32).

We found no association between plasma IGF-I levels and mammographic density among current hormone therapy users overall or according to type of hormone therapy used. This may be related to our finding that current users of hormone therapy had lower mean plasma IGF-I concentrations compared with noncurrent users. Previous studies have indicated that current use of p.o. hormone therapy may decrease plasma IGF-I concentration (33-37) and that this influence seem to differ according to the type of hormone therapy used (34-37). The mechanisms for the influence by hormone therapy use on plasma IGF-I levels are unclear. Another possible explanation for the lack of association between IGF-I and mammographic density among current hormone therapy users may be that the effect of IGF-I is masked by the fact that current hormone therapy users have more dense breasts (31).

In contrast to the findings in older women, IGF-I has been almost consistently shown to be associated with breast cancer risk in young women (4-10). In the recent and largest prospective study on IGF and breast cancer risk comprising 1,081 European breast cancer cases and 2,098 matched controls within the European Prospective Investigation into Cancer and Nutrition cohort, an increase in breast cancer risk was observed among women >50 years of age with increasing levels of IGF-I. This finding was attenuated to borderline significance when the analyses were restricted to women who were postmenopausal at the time of blood donation (13). In a recent meta-analysis including the studies described above, it was concluded that there was still no apparent association between IGF-I and breast cancer among postmenopausal women (5).

If, nonetheless, further prospective studies among postmenopausal women confirm that IGF-I is associated with breast cancer risk, our study indicates that mammographic density could be evaluated as an intermediate marker in studies affecting the IGF-I–breast cancer pathway.

In conclusion, we found a positive but weak association between plasma IGF-I concentration and both percent and absolute mammographic densities among postmenopausal Norwegian women. These associations were only significant among women who were currently not using hormone therapy.

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