Plasma Insulin-like Growth Factor (IGF) I, IGF-binding Protein 3, and Mammographic Density[1]

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ABSTRACT

Insulin-like growth factors (IGFs) and insulin-like growth factor-binding proteins (IGFBPs) play a role in the normal development of breast tissue and possibly in the etiology of breast cancer. Breast density is one of the strongest predictors of breast cancer. In a cross-sectional analysis within the Nurses' Health Study, we compared the associations of plasma levels of endogenous IGF-I and IGFBP-3 with breast density in 65 premenopausal and 192 postmenopausal women. The digitized film screen mammograms were evaluated by the computer-assisted Toronto method, in which visually selected gray-scale cut points are used to assess breast density. Generalized linear models and Spearman's partial correlation coefficients described the associations between breast density and IGF-I, IGFBP-3, and the IGF-I:IGFBP-3 ratio. Premenopausal breast density was positively correlated with IGF-I and inversely correlated with IGFBP-3; the association was strongest for the IGF-I:IGFBP-3 ratio and breast density ($r = 0.39$; $P = 0.004$). In contrast, the correlation between breast density and the IGF-I:IGFBP-3 ratio among postmenopausal women was -0.02 ($P = 0.83$). The associations of IGF-I:IGFBP-3 ratio with breast density differed significantly between premenopausal and postmenopausal women ($P = 0.01$). Mammographic density is positively associated with plasma IGF-I levels and inversely associated with plasma IGFBP-3 levels among premenopausal women, but not among postmenopausal women. These results are consistent with previous studies that showed a positive association between a higher IGF-I:IGFBP-3 ratio and subsequent risk of breast cancer only among premenopausal women. The findings raise the possibility that premenopausal levels of IGF-I and IGFBP-3 could be in the etiological pathway that relates higher breast density with increased breast cancer risk.

INTRODUCTION

IGF-I[3] is involved in the development of normal breast tissue (1) and may also play a role in a woman's risk of developing breast cancer (2–5). Because the bioactivity of IGF in tissue is partially determined by IGFBPs, any evaluation of the role of IGF-I in breast development and breast carcinogenesis must consider the simultaneous effects of these factors. The only prospective case-control study was nested within the NHS cohort, where no association was seen between the IGF-I level and breast cancer risk among postmenopausal women. However in this study, higher IGF-I levels in premenopausal women were strongly and significantly associated with an increased risk of developing breast cancer over 4 years of follow-up [top to bottom tertile contrast in IGF-I, controlling for IGFBP-3: relative risk = 2.9; confidence interval = 1.2–6.9 (2)].

The percentage of the total breast area that appears mammographically dense (percentage of breast density) is another strong predictor

of breast cancer risk (6). Mammographic breast density reflects a combination of epithelial and/or stromal proliferation relative to fat within the breast (7). Women with >74% breast density have about a 5-fold greater risk of developing breast cancer than women with 0% breast density (6). In light of the possible role of IGF-I in breast stromal and epithelial proliferation and the associations—at least in premenopausal women—between IGF-I and breast cancer risk, we evaluated the association of circulating IGF-I and IGFBP-3 levels with the percentage of the breast that is mammographically dense among participants in the NHS.

MATERIALS AND METHODS

The NHS was established in 1976, when 121,700 female registered nurses (age, 30–55 years) returned a completed mailed questionnaire. Since that time, biennial mailed questionnaires have been sent to update exposure histories and ascertain changes in medical and health status. Information collected includes height, weight, reproductive history, history of benign breast disease, alcohol intake, levels of physical activity, first-degree family history of breast cancer, menopausal status, and postmenopausal hormone use as well as any diagnosis of cancer or another illness. In 1989–1990, blood samples were collected from 32,826 participants in the NHS. Blood collection and sample storage methods have been detailed in a previous publication (8).

In the study reported here, we compared the percentage of the total breast area appearing dense on mammography with the plasma concentrations of IGF-I and IGFBP-3 among selected NHS participants who had served as controls in the previous study of plasma IGF-I and IGFBP-3 with risk of breast cancer (2). These participants had no history of cancer and were either premenopausal or postmenopausal and were not using postmenopausal hormones at the time of blood sample collection. Women using postmenopausal hormones within the last 3 months or whose menstrual periods were induced by hormones during the last year also were not included in this study because use of postmenopausal hormones has been reported to lower circulating IGF-I levels (9, 10) and increase the percentage of breast density (11–13). For each eligible participant, we sought to assess breast density from a mammogram that had been taken as close as possible to the date of blood collection. Because mammographic density is associated with both menopausal status and use of postmenopausal hormones, we restricted our analyses to participants whose reported menopausal status and postmenopausal hormone use at the time of mammography was the same as that at the time of blood sampling. This study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital.

Of the 99 eligible women with known IGF-I levels who were premenopausal at the time of blood sampling, 87 (88%) indicated that they had a mammogram and provided written consent for our evaluation. We obtained mammograms of 80 of these women (92%), 65 (81%) of whom were premenopausal at mammography. Of the 307 eligible women who were postmenopausal and were not using postmenopausal hormones at the time of blood sampling 263 (86%) indicated that they had a mammogram and provided written consent for our evaluation. We obtained a usable film screen mammogram for 221 (84%) of these women, 192 (87%) of whom were postmenopausal and had not been using postmenopausal hormones at mammography.

IGF-I and IGFBP-3 were assayed by ELISA with reagents from Diagnostic Systems Laboratory (Webster, TX). The correlations between IGF-I values obtained by ELISA and those obtained by RIA after acid chromatography were high [Pearson $r = 0.97$ (2)]. Plasma concentrations of IGF-I and IGFBP-3 were not affected by the blood collection and storage procedures followed in

the NHS (2). Previous studies have indicated that a single IGF-I measurement accurately reflects longer-term circulating IGF-I concentrations; the correlation coefficient between samples drawn 6 weeks apart was 0.94 (14). Masked split specimens were included in every batch assayed for assessment of within- and between-batch coefficients of variation. For IGF-I and IGFBP-3, the within-batch coefficients of variation were 8.7% and 9.3%, respectively (2), and the between-batch coefficients of variation were 15.6% and 19.4%, respectively (2). Laboratory batch was controlled for in all analyses.

To assess mammographic density, the cranio-caudal views of both breasts were digitized at 261 microns/pixel with a Lumysis 85 laser film scanner, which covers a range of 0–4.0 optical density. The software for computer-assisted thresholding was developed at the University of Toronto [Toronto, Canada (15, 16)]. Details regarding the software used to determine the total breast area and the area of dense mammographic appearance, based on variations in gray scale, have been published previously (15–17). In brief, the film screen images are digitized and viewed on the computer screen. For each image, the observer sets the appropriate threshold level that defines the edge of the breast. Next, within this region of interest determined by the edge of the breast threshold, the observer sets a second threshold level delineating the dense area of the image viewed on the screen. The computer calculates the total number of pixels within the entire region of interest and that within the region identified as dense; from these values, the percentage of the breast area that appears dense is estimated. This measure of mammographic breast density has been shown to predict breast cancer risk (17) and was highly reproducible as measured within this study [within-person intraclass correlation coefficient = 0.93 (18)].

The average density for both breasts was evaluated as the measure of interest. Additional analyses evaluated the associations when either a random side was selected for breast density determination or the greater breast density (right or left side) was used; results were essentially the same. Due to the symmetry between breast density for the right and left sides (mean difference, 0.47%), similar conclusions would be drawn no matter which measure was selected.

Information on menopausal status and use of postmenopausal hormones was obtained from either the biennial NHS questionnaire or by a supplemental questionnaire at the time of blood collection. From the supplemental questionnaire, women were defined as premenopausal if they reported having a menstrual period that was not induced by hormone medication within the last 12 months before blood collection or having had a hysterectomy with at least one ovary retained and were <49 years of age (nonsmokers) or <47 years (smokers). Women were defined as postmenopausal if they reported no menstrual period within the last 12 months before blood collection with natural menopause, radiation-induced menopause, bilateral oophorectomy, or surgical menopause with one or more ovaries retained and were >54 years (smokers) and >56 years (nonsmokers). These are the ages at which 90% of the participants in NHS who had a natural menopause were premenopausal or postmenopausal, respectively. Menopause status at the time of the mammogram was based on responses from the biennial questionnaire before the date of the mammogram. Women were asked whether their menstrual periods had ceased permanently. If they reported that their periods had not ceased and did not report use of postmenopausal hormones in the last 24 months, they were considered premenopausal. If they reported that their periods had ceased permanently, then the information regarding the reason their periods ceased and their age and smoking status determined whether they were postmenopausal as described above. All other covariates were assessed on the basis of the questionnaire preceding blood collection and, if different, on the basis of the questionnaire preceding mammography.

Age at mammography, BMI (kg/m^2), history of benign breast disease (yes or no), amount of usual alcohol consumption (none, <5 g/day, 5–14.9 g/day, 15+ g/day), smoking status (never, past, or current), parity (continuous), age at first birth (continuous), family history of breast cancer (yes/no), type of menopause (natural, surgical with ovaries removed, surgical with retained ovaries, or surgical with unknown ovarian status), age at menopause (continuous), and history of use of postmenopausal hormones (never, past for <5 years, past for 5+ years) were all evaluated as potential confounding variables because of their known associations with breast density (6, 19) or with IGF-I and IGFBP-3 levels (14, 20, 21). Generalized linear models evaluated the impact of each covariate as a predictor of percentage of breast density (F test) and the test of heterogeneity (t test) of the mean percentage of breast density

across categories of each covariate adjusted for age and BMI. Partial Spearman correlation coefficients, adjusting for age and BMI, were calculated between the percentage of breast density and each covariate. A covariate was included as a potential confounder in the models if there was *a priori* evidence of an association between the covariate and both percentage of breast density and IGF levels, if there was evidence of a trend in mean percentage of breast density across categories of the covariate, if including the covariate in the models changed the measures of association by ≥10%, or if any of the *P*s for the tests (F test, t test, or correlation) were ≤0.10. Due to the small size of this study and the limited prevalence of some covariates in this population, the associations that could be evaluated were limited. For example, although smoking may be associated with reduced IGF-1 levels, only 14% (9) of premenopausal women and 13% (22) of postmenopausal women were current smokers in this population, and smoking was not measurably associated with percentage of breast density in this study.

Data were analyzed with SAS software (22). Because log transformations of IGF-I, IGFBP-3, and mean percentage of breast density produced a distribution more skewed than obtained from the natural scale and because the measure of interest was mean percentage of breast density across categories of IGF-I and IGFBP-3, all analyses were conducted with the natural scaled variables. Statistical differences in the associations between the IGF-I:IGFBP-3 ratio and mammographic density by menopausal status were evaluated with an interaction term in a linear regression model. Generalized linear model analyses of variance provided estimates of the mean percentage of breast density for each quartile of IGF-I, IGFBP-3, or IGF-I:IGFBP-3 ratio, adjusted for potential confounders. Spearman's partial correlation coefficients were estimated for comparisons of the continuous measure of percentage of breast density with the continuous values for IGF-I, IGFBP-3, and the IGF-I:IGFBP-3 ratio. Two-sided *P*s are reported for the Spearman's partial correlation coefficients.

RESULTS

At the time of their mammography, the mean ages of the participants in this study were 48.3 years for premenopausal women and 62.8 years for postmenopausal women; the mean interval between blood sampling and mammography was 13 months and 18 months, respectively. As expected, the median percentage of breast density was greater for premenopausal women than for postmenopausal women (37.1% and 21.1%, respectively). Postmenopausal women had slightly lower median IGF-I levels (166 *versus* 177 ng/ml) and slightly higher IGFBP-3 levels (4275 *versus* 4000 ng/ml) than premenopausal women. IGF-I and IGFBP-3 levels were correlated with each other in both postmenopausal ($r = 0.59$; $P = 0.0001$) and premenopausal women ($r = 0.43$; $P = 0.0004$). Premenopausal women reported a slightly lower intake of alcohol (38% *versus* 31% reporting <5 g/day) and were more likely to have had their first child before age 25 (53% *versus* 46%). Other participant characteristics were similar among premenopausal and postmenopausal women (Table 1).

In evaluating the relation between IGF-I levels and breast density, factors associated with breast density were included in the full multivariate models. The linear association between the IGF-I:IGFBP-3 ratio and breast density differed for premenopausal *versus* postmenopausal women ($P = 0.01$). Therefore, results are presented separately by menopausal status. For premenopausal women, the covariates associated with mammographic density included alcohol intake and BMI in addition to age, laboratory batch, and levels of IGF-I and IGFBP-3. For postmenopausal women, age at the birth of their first child was also associated with mammographic density and was therefore included along with the other covariates in the full multivariate models.

In premenopausal women, breast density was positively correlated with IGF-I and inversely correlated with IGFBP-3 (Table 2). Adjustment for IGFBP-3 in the models clarified the association between IGF-I and breast density; likewise, adjustment for IGF-I levels further

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Table 1 *Characteristics of the study population*

Characteristic	Premenopausal (n = 65)	Postmenopausal[a] (n = 192)
Age at mammogram (mean/SD)	48.3/2.8	62.8/4.8
Percentage of breast density[b] (median/range)	37.1/3–85	21.1/0–70
IGF-I (ng/ml; median/range)	177/85–305	166/54–464
IGFBP-3 (ng/ml; median/range)	4000/2090–6670	4275/1930–8240
BMI (kg/m², mean/SD)	24.9/4.1	25.5/4.0
History of benign breast disease (%)	33%	33%
Alcohol consumption (%)		
None	29%	33%
<5 g/day	38%	31%
5–14.9 g/day	20%	20%
15+ g/day	8%	10%
Nulliparous (%)	8%	9%
Age at first birth (% of parous women)		
<25 yrs	53%	46%
30+ yrs	8%	6%
Family history of breast cancer (%)	9%	10%
Natural menopause (%)		73%
Age at menopause[c] (yrs; mean/SD)		49.9/3.6
Past use of postmenopausal hormones (%)		38%

[a] Includes only postmenopausal who were not using postmenopausal hormones at the time of blood sampling and mammography.

[b] The percentage of breast density is the average of the percentage of the total areas of the left and right breasts that appear mammographically dense.

[c] Age at menopause only includes women who had natural menopause or bilateral oophorectomy.

strengthened the association between IGFBP-3 and breast density. The strongest associations between premenopausal IGF-I and breast density were seen with comparisons adjusted for age, IGFBP-3, alcohol intake, batch, and BMI. The mean breast density was 30% for women in the lowest quartile of IGF-I and 44% for women in the highest quartile of IGF-I. The multivariate-adjusted correlation for the continuous measures of IGF-I and percentage of breast density was 0.36 (P = 0.007). In contrast, the mean percentage of breast density was 43% for women in the lowest quartile of IGFBP-3 and 36% for those in the highest quartile of IGFBP-3. The multivariate-adjusted correlation for IGFBP-3 was −0.24 (P = 0.07). Models that evaluated breast density across quartiles of the molar ratio of IGF-I:IGFBP-3 among premenopausal women showed a strong positive association in all analyses. Adjustment for BMI further strengthened this association. The multivariate adjusted mean breast density values were 30%, 33%, 38%, and 48% for the ascending quartiles of the IGF-I:IGFBP-3

ratio. The partial Spearman correlation for the continuous measure of the IGF-I:IGFBP-3 ratio was 0.39 (P = 0.004).

In contrast, mean breast density did not vary with IGF-I levels in postmenopausal women; furthermore, the partial Spearman correlation coefficient was 0.01 (P = 0.92), and the inverse association between mean density and IGFBP-3 was diminished and was not statistically significant [r = −0.05; P = 0.52 (Table 3)]. Likewise, there was no indication of an association between the IGF-I:IGFBP-3 ratio and breast density in postmenopausal women. There was no association noted with breast density and IGF-I or IGFBP-3 in analyses that excluded women who had used postmenopausal hormones in the past.

DISCUSSION

Higher levels of circulating IGF-I were associated with higher mammographic density, and higher levels of IGFBP-3 were associated with lower mammographic density in premenopausal but not postmenopausal women. The IGF-I:IGFBP-3 ratio showed the strongest association with breast density in premenopausal women. These results are consistent with previous studies of breast cancer risk that suggested a strong association of risk with the IGF-I:IGFBP-3 ratio (3) and with the IGF-I level adjusted for the IGFBP-3 level in premenopausal women (2, 5).

Previous studies showed that breast cancer risk rose steadily with increased percentage of the breast area with a dense appearance on a prediagnostic mammogram, and this association was not explained by other breast cancer risk factors such as age, weight, age at first child's birth, family history of breast cancer, alcohol use, prior benign breast disease, age at menarche, and age at menopause (6, 23). The computer-assisted technique developed at the University of Toronto for the quantification of percentage of breast density based on gray scale thresholding is more highly reproducible than previous visual estimates of breast density and has been shown to be useful in identifying high-risk women (16–18). Although techniques such as those applied in this study now exist to assess breast density more uniformly than methods used in the past, and the high risk of breast cancer associated with a greater proportion of breast density has been recognized for some time, it is still not known by what mechanism breast density is related to risk.

Table 2 *Mean percentage of breast density, by IGF-I and IGFBP-3 quartiles (Q), among premenopausal women*

Model covariates	Mean percentage of breast density by IGF-I (ng/ml) quartiles				Spearman correlation coefficient[a] (P)
	Q1 (85–134)	Q2 (135–177)	Q3 (178–212)	Q4 (213–305)	
Age and batch	31	42	35	44	0.21 (0.11)
Age, IGFBP-3, and batch	29	42	38	44	0.27 (0.04)
Age, IGFBP-3, alcohol intake, batch, and BMI	30	35	40	44	0.36 (0.007)

	Mean percentage of breast density by IGFBP-3 (ng/ml) quartiles				
	Q1 (2090–3150)	Q2 (3151–4000)	Q3 (4001–4520)	Q4 (4521–6670)	
Age and batch	44	40	31	39	−0.10 (0.42)
Age, IGF-I, and batch	47	39	29	37	−0.20 (0.12)
Age, IGF-I, alcohol intake, batch, and BMI	43	44	30	36	−0.24 (0.07)

	Mean percentage of breast density by IGF-I: IGFBP-3 (molar ratio) quartiles				
	Q1 (0.084–0.128)	Q2 (0.129–0.162)	Q3 (0.163–0.207)	Q4 (0.208–0.367)	
Age and batch	30	36	35	52	0.34 (0.006)
Age, alcohol intake, batch, and BMI	30	33	38	48	0.39 (0.004)

[a] Spearman correlation between the continuous measure of percentage of breast density and the continuous level of IGF-I or IGFBP-3. Adjusted correlations are partial Spearman coefficients.

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Table 3 *Mean percentage of breast density, by IGF-I and IGFBP-3 quartiles (Q), among postmenopausal women*

| Model parameters | Mean percentage of breast density by IGF-I (ng/ml) quartiles | | | | Spearman correlation coefficient[a] (P) |
	Q1 (40–136)	Q2 (137–166)	Q3 (167–222)	Q4 (223–464)	
Age and batch	23	23	26	21	0.02 (0.84)
Age, IGFBP-3, and batch	21	23	26	22	0.09 (0.29)
Age, IGFBP-3, alcohol intake, batch, BMI, and age at first birth	21	24	22	20	0.01 (0.92)
	Mean percentage of breast density by IGFBP-3 (ng/ml) quartiles				
	Q1 (1930–3680)	Q2 (3681–4275)	Q3 (4276–4975)	Q4 (4976–8240)	
Age and batch	25	26	22	19	−0.10 (0.22)
Age, IGF-I, and batch	25	26	22	19	−0.13 (0.11)
Age, IGF-I, alcohol intake, batch, BMI, and age at first birth	21	26	22	19	−0.05 (0.52)
	Mean percentage of breast density by IGF-I: IGFBP-3 (molar ratio) quartiles				
	Q1 (0.070–0.120)	Q2 (0.121–0.147)	Q3 (0.148–0.182)	Q4 (0.183–0.401)	
Age and batch	20	26	25	20	0.06 (0.42)
Age, alcohol intake, batch, BMI, and age at first birth	22	22	24	19	−0.02 (0.83)

[a] Spearman correlation between the continuous measure of percentage of breast density and the continuous level of IGF-I or IGFBP-3. Adjusted correlations are partial Spearman coefficients.

Current breast density, reflecting the proportion of stromal and epithelial proliferation, may simply indicate the area of susceptible tissue (number of epithelial cells) or may represent the interaction between stromal and epithelial proliferation influenced by local growth factors, including epidermal growth factor, transforming growth factors, IGF-I, and IGF-II (24). Growing evidence indicates that breast development and involution are influenced by IGFs (which increase proliferation) and IGFBPs (which reduce proliferation; Ref. 25). IGFBPs inhibit proliferation of breast cancer cells *in vitro* (26) and are associated with postlactational involution of the mammary gland in animal models (27). Thus, greater breast density may be a consequence of higher IGF levels and an associated increase in proliferation and/or of decreased IGFBP levels with a resulting reduction in the involution process.

Paradoxically, breast density declines gradually with age, whereas breast cancer risk increases (6). Because circulating levels of IGF-I and IGFBP-3 also decrease with age (21), the relation between breast density and circulating IGF-I and IGFBP-3 is of great interest. The findings of this analysis are consistent with those of the previous NHS analysis of plasma IGF-I and breast cancer risk, which indicated a strong association of risk with premenopausal IGF-I levels adjusted for IGFBP-3 levels and no association of risk with postmenopausal levels (2). A higher proportion of breast density has been associated with a 3–4-fold increase in the risk of breast cancer among premenopausal women and a 5–6-fold increase in the risk of breast cancer among postmenopausal women (6). Although the lack of association between IGF-I and breast density in postmenopausal women seems inconsistent with the strong association observed between breast density and breast cancer risk in both premenopausal and postmenopausal women, it is possible that local expression of IGF-I and IGFBP-3 in breast tissue is the biologically relevant determinant of risk. Under this hypothesis, breast density may serve as a better proxy for local tissue IGF-I and IGFBP-3 levels than circulating plasma levels among postmenopausal women. Alternatively, high IGF-I and/or low IGFBP-3 levels that were correlated to breast density when premenopausal may determine both premenopausal and postmenopausal breast cancer risk. Under this hypothesis, risk of postmenopausal breast cancer would be largely determined before menopause, when circulating IGF-I was high, and IGFBP-3 was low. Postmenopausal breast density would continue to reflect breast cancer risk because low levels of IGFBP-3 would be associated with a reduced involution process. Interestingly, with the use of the antiestrogen tamoxifen, which has been shown to reduce IGF-1 levels (28), mammographic parenchymal patterns became more lucent in postmenopausal women (29). Further research is needed to test these hypotheses and evaluate the association between tissue levels and circulating levels of IGF-I and IGFBP-3 in both pre- and postmenopausal women. Studies are also needed to quantitate the intraindividual variation and changes in both IGF-1 and IGFBP-3 and percentage of breast density as a woman goes from being premenopausal to postmenopausal.

The blood collection in the NHS was not timed to the menstrual cycle among premenopausal women and is thus another potential source of variability in the assessment of an association of premenopausal plasma IGF-I and IGFBP-3 levels with breast density. However, in previous studies (30–33), little variation in IGF levels has been observed over the menstrual cycle. Another potential limitation of this study is the time elapsed between the mammogram and the blood draw. However, analyses restricted to mammograms obtained within 6 months of the blood draw showed patterns of association similar to those reported herein. Furthermore, mammographic breast density has been shown to predict risk for 10 or more years. Therefore, given that the mammogram used in this study does not exactly reflect levels at the time of the blood draw, one would expect that the true associations between plasma levels and breast density measured concurrently would be even stronger than those demonstrated in this analysis. Likewise, to the degree that menopause status was misclassified and postmenopausal women were included among premenopausal women, there is likely to be a stronger association between IGF level and percentage of breast density in premenopausal women and a greater difference in the true associations between pre- and postmenopausal women than detected in this study. Because IGF-I is partially regulated by the levels of other endogenous hormones such as estradiol (34), additional studies that incorporate information on other hormones as well as IGFs may more clearly elucidate the biology underlying the association between breast density and breast cancer risk.

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To our knowledge, this is the first report of a direct comparison of plasma IGF-I and IGFBP-3 levels with breast density. The strong positive correlation between the IGF-I:IGFBP-3 ratio and breast density among premenopausal women and the lack of such an association in postmenopausal women provide further support for earlier reports of an increased risk of breast cancer associated with premenopausal levels of IGF-I adjusted for IGFBP-3 (2, 3, 5).

Future studies will determine to what extent breast density and the IGF-I:IGFBP-3 ratio are independent breast cancer risk factors.

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