Insulin-Like Growth Factor-I, IGF-Binding Protein-3, and Mammographic Breast Density

Abstract

(Cancer Epidemiol Biomarkers Prev 2005;14(5):1065–73)

Introduction

Insulin-like growth factor (IGF)-I is a well-established mitogen for breast tissue (1). In the bloodstream, IGF-I is bound to one of several IGF-binding proteins (IGFBP). Among these, IGFBP-3 carries >95% of circulating IGF-I (2). In addition to prolonging IGF-I half-life and modulating IGF-I biological activities, IGFBP-3 can promote apoptosis independently of IGF-I (3, 4).

There is growing evidence that IGF-I may contribute to the progression of several human cancers (5, 6), including breast cancer (7), whereas IGFBP-3 has been proposed as an anticancer protein (8). Women with acromegaly have clinically higher levels of IGF-I (9) and have an increased incidence of breast cancer compared with the general population (10-12). Moreover, high circulating levels of IGF-I were consistently found to be positively associated with breast cancer risk in premenopausal women (13-21), with few exceptions (22-25). Among postmenopausal women, some studies observed an IGF-I to breast cancer association (18, 24, 26) but most did not (14-17, 19-21, 23, 25, 27-29). Relationship between levels of IGFBP-3 and breast cancer risk is less clear. In studies conducted in premenopausal women, some observed that higher circulating levels of IGFBP-3 were associated with low breast cancer risk (13, 14), whereas positive (16, 17, 19-21) or null associations (15, 22-24) were found by others. Only two (20, 21) of several studies (14-17, 19, 23, 24, 28, 29) showed a positive association of IGFBP-3 with breast cancer risk in postmenopausal women. Finally, Bohlke et al. (13) examined the joint effect of IGF-I and IGFBP-3 on incidence of ductal carcinoma . Their data suggest that premenopausal women with a combination of high levels of IGF-I and low levels of IGFBP-3 had an elevated risk of ductal carcinoma of the breast compared with those with a combination of low levels of IGF-I and high levels of IGFBP-3.

Mammographic breast density is one of the strongest risk factors for breast cancer (30). Data from three small cross-sectional studies suggest that the extent of mammographic breast density, among premenopausal women, may be associated with high levels of IGF-I and low levels of IGFBP-3 (31-33). No association has been observed among postmenopausal women (31, 32, 34). Thus, the growth factor-breast density associations seem to mirror the growth factor-breast cancer relations.

Streams of Excellence Program of the Canadian Breast Cancer Research Initiative grant 011428 and Canadian Institutes of Health Research and Fonds de la recherche en santé du Québec scholarships (C. Diorio).

This cross-sectional study was designed specifically to determine whether plasma levels of IGF-I, IGFBP-3, and the molar ratio IGF-I/IGFBP-3 (an indicator of bioavailability of IGF-I) were separately related to mammographic breast density among premenopausal and postmenopausal women. Data also allowed examination of the combined relation of IGF-I and IGFBP-3 with breast density.

Materials and Methods

e e e e. The study subjects were women who received a screening mammogram between February 2001 and March 2002 at two private radiology clinics. Women were considered to be having a screening mammogram if they were referred for ( ) a mammography within the Quebec organized breast cancer screening program (Programme québécois de dépistage du cancer du sein), ( ) a routine periodic mammography in the absence of any breast problem (such as family history of breast cancer) even if outside of the Programme québécois de dépistage du cancer du sein, or ( ) a routine periodic mammography for follow-up of a known and stable benign breast condition.

To be eligible for the present study, women were either premenopausal if they had at least one natural menstrual cycle within 12 months or were younger than 48 years (if a nonsmoker) or 46 years (if a smoker) after hysterectomy without bilateral oophorectomy or use of hormonal derivatives (35). They were considered postmenopausal if they reported complete cessation of menses for at least 12 months, radiation-induced menopause, or bilateral oophorectomy or were at least ages 56 years (if a nonsmoker) or 54 years (if a smoker) after hysterectomy without bilateral oophorectomy or use of hormonal derivatives (35). Finally, eligibility was restricted to women not taking hormone medication, including oral contraceptives or postmenopausal hormones, within 3 months of the mammography, never having used tamoxifen or raloxifene, not pregnant, without a history of cancer at any site, without breast reduction or implants, and without diabetes mellitus, dwarfism/acromegaly, or thyroid, adrenal, or hepatic disease. No restriction criteria on age were applied.

Eligible women who accepted to participate provided written consent, including authorization for blood sampling and banking of samples, to provide information on breast cancer risk factors, to borrow, digitize, evaluate, and keep a digitized copy of their mammogram, and to review medical records to obtain the results of the mammographic examination, including pathologic findings. Women with known cognitive deficit of any cause were excluded because of impaired ability to provide informed consent.

Of the 9,559 women who received a screening mammogram and were approached, 1,021 refused to participate in our study. In the remaining 8,538 women, 6,924 were ineligible because they were using hormonal derivatives (= 4,987) or did not meet other eligibility criteria (= 1,937). A total of 800 premenopausal and 814 postmenopausal women were identified as potentially eligible for the study and provided informed consent. Among these women, 7 women (= 1 premenopausal and = 6 postmenopausal) were found ineligible during the interview because they had had a breast reduction (= 1 postmenopausal), they used hormone replacement therapy within the last 3 months (= 1 premenopausal and = 3 postmenopausal), they used raloxifene (= 1 postmenopausal), or they had uncertain menopausal status (= 1 postmenopausal). After the review of the reports provided by the radiologists, 9 women (= 8 premenopausal and = 1 postmenopausal) were excluded because they did not meet our definition of screening mammogram and 7 women (= 4 premenopausal and = 3 postmenopausal) were excluded because the investigation recommended by the radiologists following their screening mammogram led to a diagnosis of breast cancer. In the remaining 787 premenopausal and 804 postmenopausal women, a blood sample could not be obtained for 3 postmenopausal women and film mammograms were not available for 3 women (= 2 premenopausal and = 1 postmenopausal). Finally, 10 women (= 2 premenopausal and = 8 postmenopausal) declined to be interviewed and 1 postmenopausal woman revoked her participation. Therefore, a total of 783 premenopausal and 791 postmenopausal women were eligible for the present analysis. Of those, 99.5% were recruited at the Clinique Radiologique Audet (= 1,566) and 8 were recruited at the Clinique de radiologie Saint-Pascal.

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A . d B d . Women wearing light clothing without shoes were weighed (kg), and height (cm) was measured by a trained research nurse. Waist circumference was measured using a soft tape midway between the lowest rib margin and the iliac crest in the standing position, and hip circumference was measured over the widest of the gluteal region. From these measurements, the body mass index (BMI; kg/m^2) and waist-to-hip ratio (WHR; an indicator of central body fat distribution) were obtained. For each woman, blood (20 mL) was drawn and fasting status was recorded as the number of hours since last meal. Anthropometric measures and blood sampling occurred at time of mammography for 95.4% of the subjects (= 1,501), with an average ± SD of 0.4 ± 1.9 day between the time of the mammogram and when the blood was drawn. For premenopausal women, the first day of the last menstrual cycle was documented. In addition, a calendar was distributed to indicate the first day of the menstrual cycle after their mammogram and to transmit this information during the phone interview. Age (years) at time of the mammogram was recorded for all women. Finally, each woman received a validated (36) and self-administered semiquantitative food frequency questionnaire (97GP copyrighted at Harvard University) and was requested to return it by mail once completed. Intake of foods obtained through the questionnaire was translated into nutrient intake, including energy intake (kcal/d), at the Channing Laboratory of Harvard University (Boston, MA). This semiquantitative questionnaire was answered by 99.3% of women (= 1,563).

d . ν . Data on potential breast cancer risk factors were collected by trained interviewers using a questionnaire designed for this study. Risk factors for breast cancer included reproductive history, family history of breast cancer, history of breast biopsies, past use of hormonal derivatives, smoking status, alcohol intake, education, and physical activity. For the latter, the level of physical activity in metabolic equivalents-hour/wk was assessed using the Nurses' Health Study II Activity and Inactivity Questionnaire (37) and the classification by Ainsworth et al. (38) for the metabolic equivalent. Phone interviews took place on average ± SD of 27 ± 13 days after the mammogram; 72.7% of the subjects had their interview within 1 month of their screening mammogram.

d A . All mammograms were digitized using a Kodak Lumiscan85 digitizer at 260 μm per pixel (0.067 mm^2 per pixel), which creates a 12-bit gray scale image that is linear in the absorbance range 0 to 4.0. Calibration of the scanner was verified before each utilization. All mammograms were reviewed by one of the authors (C.D.). This reviewer was trained in the assessment of breast density using a set of mammographic images (= 110) previously read by one of the authors (C.B.) who has experience in the assessment

of breast density by computer-assisted method (31, 39-41). After the training period, proficiency in assessment of breast density was evaluated comparing C.D.'s readings with those of C.B.'s based on an additional 220 mammograms. The intraclass correlation coefficients of the mammographic features, includ-

= 0.027) compared with the third tertile of IGFBP-3 ($_s$ = −0.039; = 0.530). Similarly, within the highest tertile of IGF-I, the adjusted mean breast density was lower with ascending levels of IGFBP-3 (53.8%, 41.4%, and 39.5%). From Table 3, multivariate-adjusted correlation of IGFBP-3 with breast density was stronger in the highest tertile of IGF-I ($_s$ = −0.150; = 0.016) compared with the lowest tertile of IGF-I ($_s$ = −0.008; = 0.904).

Among premenopausal women, multivariate-adjusted

density appeared stronger at low levels of IGFBP-3, whereas the strength of the association of IGFBP-3 with breast density

at low compared with high levels of IGFBP-3. Similarly, the association of IGFBP-3 with breast density was stronger at high compared with low IGF-I levels. Thus, the highest breast density was observed for women with the combination of high IGF-I and low IGFBP-3. To our knowledge, combined IGF-I and IGFBP-3 levels have not been investigated in relation with breast density. However, the combination of high IGF-I with low IGFBP-3 levels is related to an increased risk of ductal carcinoma of the breast among premenopausal women compared with those with a combination of low IGF-I and high IGFBP-3 (13). Prospective data from the Physicians' Health Study on advanced-stage prostate cancer risk (47) and colorectal cancer risk (48) also suggest that patients with a combination of high IGF-I and low IGFBP-3 levels incur the greatest risk.

The strength of association of growth factors with breast density may vary substantially according to some characteristics of women. Among premenopausal women, stronger association of IGF-I and IGFBP-3 levels with breast density was observed among tal78tion denw

density should be relatively small, most likely be random, and therefore should not have biased our results. Thirdly, circulating levels of IGF-I and IGFBP-3 were each measured within 1 month using the same type of reagents for all assays. The laboratory analyses were done without any information on women, and the reliability of these measures was also shown to be high. Thus, our findings are unlikely to be explained by random misclassification of the measurements of the analytes. Fourth, for 95.4% of women, the blood was drawn on the same day as the mammogram, eliminating the potential problem of timing of density and growth factor measurements. Fifth, several factors potentially related to breast density and/or growth factors were documented and their confounding effects were assessed and taken into account when necessary. Finally, the effective sample size is relatively large.

This study has some limitations. Women in the present study reported a family history of breast cancer more frequently than those in other studies on esentnw10.5(ofbiase)5.6(d)-694(our)-otheu(7(h)-1(our)-oan)-617(tu6t)-137(tu6t.1(rw)8(p44)-5
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