# Levels of C-Peptide and Mammographic Breast Density

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## Abstract

**Members of the insulin-like growth factor family have been associated with breast cancer risk and mammographic breast density, one of the strongest known breast cancer risk indicators. The aim of this cross-sectional study was to examine the association of levels of C-peptide (a marker of insulin secretion) with mammographic breast density among 1,499 healthy women recruited during screening mammography examinations. At time of mammography, blood samples and time since last meal were collected. Plasma C-peptide levels were measured by ELISA method, and mammographic breast density by a computer-assisted method. Spearman's partial correlation coefficients, adjusting for age and time since last meal (when necessary), were used to evaluate the associations. High body mass index and waist-to-hip ratio measurements were independently correlated with high levels of C-peptide ($r_s$ = 0.173 and $r_s$ = 0.252, respectively; $P < 0.0001$) or low breast density ($r_s$ = −0.389 and $r_s$ = −0.142, respectively; $P < 0.0001$). High levels of C-peptide were correlated with low breast density ($r_s$ = −0.210, $P < 0.0001$). However, the strength of the negative correlation was substantially reduced and was no longer significant after further adjustment for body mass index and waist-to-hip ratio ($r_s$ = −0.022, $P$ = 0.41). These results suggest that C-peptide levels are not associated with breast density after complete adjustment for adiposity. Thus, the insulin/C-peptide–breast density relation does not seem to mirror the insulin/C-peptide–breast cancer association.**

## Introduction

Hyperinsulinemia and insulin resistance, both characterized with increased levels of insulin and C-peptide, are conditions known to be associated with central adiposity, obesity, and several other diseases, including cancer (1, 2). Insulin and C-peptide are synthesized in the β cells of the islets of Langerhans by enzymatic cleavage of proinsulin and are both released into the circulation in equimolar amounts. In contrast to insulin, C-peptide physiologic function is not clearly known. However, C-peptide has a longer half-life in plasma than insulin and therefore can be used as a marker to reflect more accurately insulin secretion of a given individual (3).

Laboratory studies suggest that insulin, like its related growth factors, may exert a mitogenic effect on both normal and neoplastic breast epithelial cells (1, 2). Several epidemiologic studies (4-9), but not all (10-15), have shown that high circulating levels of insulin or C-peptide were associated with increased breast cancer risk in premenopausal and/or postmenopausal women. Lately, levels of C-peptide, among postmenopausal women, have been associated with risk of benign breast hyperplasia (15), a histologic change known to be related with breast cancer risk (16).

The extent of mammographic breast density has been repeatedly associated with benign breast diseases, including epithelial hyperplasia, in addition to being strongly associated with increased breast cancer risk (17). The breast is composed essentially of epithelial and stromal tissue and fat. By definition, mammographic breast density reflects the proportion of the breast occupied by epithelial and/or stromal tissue; in addition, factors such as hormones and insulin-like growth factors are believed to influence this proportion (18, 19). Recently, a negative association of fasting insulin levels with breast density was observed among premenopausal women with *CYP17 A1* allele (20). Moreover, high levels of insulin and diabetes were associated with low breast density in premenopausal women (21, 22). The purpose of this study was to examine the association of C-peptide levels with mammographic breast density among healthy women recruited during screening mammography examinations.

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## Materials and Methods

**Study Population and Recruitment Procedures.** Details of the study design and methods have been published elsewhere (19). Briefly, between February 2001 and March 2002, women who received a screening mammogram were recruited from two private radiology clinics in Quebec City (Quebec, Canada). To be eligible, women had first to be classified as premenopausal or postmenopausal (23). Thus, women were classified as 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. Women were classified as postmenopausal if they reported complete cessation of menses for at least 12 months, radiation-induced menopause, bilateral oophorectomy, or were ages at least 56 years (if a nonsmoker) or 54 years (if a smoker) after hysterectomy without bilateral oophorectomy or use of hormonal derivatives. Women were ineligible for the following reasons: diabetes mellitus, dwarfism/acromegaly, thyroid, adrenal or hepatic disease, pregnancy, use of hormonal derivatives in the last 3 months before mammography, ever use tamoxifen or raloxifene, history of cancer at any site, and breast reduction or implants. A total of 787 premenopausal and 804 postmenopausal women were found eligible. Among these women, 10 (premenopausal = 2 and postmenopausal = 8) declined to be interviewed, six (premenopausal = 2 and postmenopausal = 4) could not provide blood samples or film mammograms could not be retrieved for review, four (postmenopausal) had incomplete anthropometric measures, and one postmenopausal women revoked her participation. In the remaining 1,570 women, 71 accepted to participate in our initial study (19) but did not give authorization for blood banking of samples for further study. Therefore, a total of 1,499 (premenopausal = 746 and postmenopausal = 753) women were included in the present analysis.

**Data Collection.** At time of the mammography, women were measured wearing no shoes and in light clothing by a trained research nurse using standard procedures. Measurements included weight (kg), height (cm), and waist and hip circumferences (cm). From these measurements, the body mass index [BMI (kg/m$^2$); an indicator of body fat] and waist-to-hip ratio (WHR; an indicator of abdominal fat) were calculated. Blood samples were also taken (20 mL), and fasting status was recorded as the number of hours since last meal. Anthropometric measures and blood sampling occurred at time of the mammography for >95% of the subjects. Information on potential breast cancer risk factors was collected during a telephone interview and included menstrual and reproductive histories, family history of breast cancer, personal history of breast biopsies, past use of hormonal derivatives, smoking status, alcohol intake, and education. The Nurses' Health Study II Activity and Inactivity Questionnaire (24) and the semiquantitative food frequency questionnaire (97GP copyrighted at Harvard University) were used to estimate physical activity and dietary intake, respectively, during the year preceding the mammography.

All mammograms were scanned at 260 μm/pixel with a Kodak Lumiscan85 digitizer. Then, for each woman, mammographic breast density (%) and absolute area of dense tissue (absolute density, cm$^2$) were assessed by one trained author (C.D.) from the craniocaudal view of a randomly chosen breast. This assessment was done without any information on women using a computer-assisted method developed by one of us (M.Y.) and described elsewhere (25). In this study, the within-batch intraclass correlation coefficients were 0.98 and 0.98, the between-batch coefficients of variation were 4% and 5%, and the intraclass correlation coefficients between the right and left breasts were 0.95 and 0.93 for percent breast density and absolute density measurements, respectively.

Blood collection and sample storage conditions have been previously described (19). Time between blood donation and blood constituents' storage was <3 hours for almost all subjects. Under the supervision of one of us (M.P.), C-peptide was assayed without any information on women by ELISA method with reagents from Diagnostic Systems Laboratory (Webster, TX). The intrabatch and interbatch coefficients of variation from blinded split samples randomly included in the analytic runs were 7.7% and 4.6%, respectively.

**Table 1. Correlations of C-peptide levels and breast density with measures of adiposity ($n$ = 1,499)**

| Measures of adiposity | C-peptide (ng/mL) | Breast density (%) |
|---|---|---|
| BMI (kg/m$^2$), type of adjustment | | |
| Covariates 1* | 0.330 (<0.0001) | −0.497 (<0.0001) |
| Covariates 2† | 0.314 (<0.0001) | −0.488 (<0.0001) |
| Covariates 1 + WHR | 0.173 (<0.0001) | −0.389 (<0.0001) |
| Covariates 2 + WHR | 0.161 (<0.0001) | −0.383 (<0.0001) |
| WHR, type of adjustment | | |
| Covariates 1* | 0.374 (<0.0001) | −0.361 (<0.0001) |
| Covariates 2† | 0.362 (<0.0001) | −0.351 (<0.0001) |
| Covariates 1 + BMI (kg/m$^2$) | 0.252 (<0.0001) | −0.142 (<0.0001) |
| Covariates 2 + BMI (kg/m$^2$) | 0.246 (<0.0001) | −0.134 (<0.0001) |

NOTE: Spearman correlation between continuous variables ($P$). Adjusted correlations are partial Spearman coefficients.

*Adjusted for age (y). Associations with C-peptide levels are also adjusted for time since last meal (≤2, >2-3, >3-4, >4-5, >5 h).

†Adjusted for age (y), alcohol (drinks/wk) and total energy (kcal/d) intakes in the past year, menopausal status (premenopausal or postmenopausal), age at menarche (y), age at first full-term pregnancy (y), lactation (y), number of full-term pregnancies, number of personal breast biopsies, duration of past use of oral contraceptive and of hormone replacement therapy (y), family history of breast cancer in first-degree relative (yes/no), physical activity (METs h/wk), education (primary or less, secondary, college, or university diploma), and smoking status (never, former, or current smoker). Associations with C-peptide levels are also adjusted for time since last meal (≤2, >2-3, >3-4, >4-5, >5 h). Analysis are restricted to $n$ = 1,474 due to missing values for some breast cancer risk factors among participants.

**Statistical Methods.** Associations between continuous levels of C-peptide, continuous measures of breast density, and continuous measures of anthropometric factors were evaluated with the Spearman correlation coefficients ($r_s$). Breast density was square root transformed to normalize its skewed distribution. Then, multivariate-adjusted means breast density were assessed according to quartiles of C-peptide (≤1.324, 1.325-2.143, 2.144-3.497, >3.497 ng/mL) using generalized linear models. Results are presented as back-transformed values.

In the present analysis, factors included as confounders (covariates 1) or as potential confounders (covariates 2) in multivariate models are described in each table legend. Associations of BMI and WHR with C-peptide levels and breast density were investigated (Table 1) to show that these two measures of adiposity have independent effects; therefore, both should be considered as confounders in models evaluating the association between C-peptide levels and breast density. All continuous variables were examined in categories before they were included as continuous variables in final models. Levels of C-peptide were negatively associated with the number of hours since last meal if last meal was taken in ≤5 hours ($r_s = -0.375$, $P < 0.0001$) but not after 5 hours ($r_s = -0.034$, $P = 0.62$); therefore, hours since last meal was included as a categorical variable (≤2, >2 to 3, >3 to 4, >4 to 5, >5 hours) in the analysis. All statistical analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) software system. Statistical significance was based on two-sided $P$ values.

## Results

Characteristics of the study population are described elsewhere (19). Briefly, the 1,499 women included in the present study were on average (±SD) 54.1 ± 9.4 years old and had mean BMI and WHR of 26.2 ± 4.7 kg/m$^2$ and 0.80 ± 0.06, respectively. The average of the percentage of mammographic breast density was 30.3 ± 24.0, and levels of C-peptide were 2.76 ± 2.08 ng/mL.

Body fat (BMI) and abdominal fat (WHR) were independently associated with levels of C-peptide (Table 1). Age-adjusted and time since last meal–adjusted (covariates 1)

positive correlation between levels of C-peptide and BMI or WHR was statistically significant, even after adjustment for WHR or BMI ($r_s$ = 0.173 and $r_s$ = 0.252, respectively; $P$ < 0.0001). These measures of body and abdominal fat were also independently associated with mammographic breast density (Table 1). Breast density was negatively correlated with BMI or WHR, and these age-adjusted (covariates 1) negative correlations were also statistically significant when both variables were included in the model simultaneously ($r_s$ = −0.389 and $r_s$ = −0.142, for BMI and WHR, respectively; $P$ < 0.0001). Addition of several potential confounders (covariates 2) into these models did not substantially alter the results. Although BMI and WHR are correlated ($r_s$ = 0.554, $P$ < 0.0001), models including both factors revealed no multicolinearity problem.

Table 2 shows that correlation between C-peptide levels and breast density varied by type of adjustment. Age-adjusted and time since last meal–adjusted mean breast density was lower by ascending quartiles of C-peptide, and the multivariate-adjusted correlation was statistically significant ($r_s$ = −0.210, $P$ < 0.0001). This multivariate-adjusted correlation of C-peptide with breast density remained statistically significant after further adjustment were made for BMI ($r_s$ = −0.057, $P$ = 0.03) or WHR ($r_s$ = −0.086, $P$ = 0.0008) separately. However, after simultaneous adjustment for both BMI and WHR, C-peptide levels were no longer statistically correlated with breast density ($r_s$ = −0.022, $P$ = 0.41). Results were similar when several potential confounders (covariates 2) were inserted into these models.

We also evaluated the correlation of C-peptide levels with absolute area of dense tissue on the mammogram (absolute density) and, after full adjustment for covariates (covariates 2, BMI and WHR), found little or no correlation of C-peptide levels with absolute density ($r_s$ = −0.029, $P$ = 0.28 for $n$ = 1,474).

After adjustment for covariates 2, BMI and WHR, little or no correlation between C-peptide levels and percent breast density or absolute density was observed among premenopausal ($r_s$ = −0.034, $P$ = 0.37 and $r_s$ = −0.058, $P$ = 0.12 for $n$ = 736) or postmenopausal ($r_s$ = 0.003, $P$ = 0.94 and $r_s$ = 0.003, $P$ = 0.93 for $n$ = 738) women separately, or among women who had their last meal for >5 hours ago ($r_s$ = −0.049, $P$ = 0.51 and $r_s$ = −0.027, $P$ = 0.71 for $n$ = 208).

## Discussion

This cross-sectional study shows that C-peptide levels are not associated with mammographic breast density once adiposity is adequately taken into account in the analysis. Our findings suggest that adjustment for both BMI and WHR is important to evaluate this association and avoid residual confounding. For instance, a negative association between fasting insulin levels and breast density was found among premenopausal women with *CYP17 A1* allele (20). However, these negative associations were no longer observed after adjustment for BMI and WHR. In another study conducted among premenopausal women, fasting insulin levels were negatively associated with breast density (22). However, BMI and truncal fat were not taken into account in the analyses, although the authors found strong relations of these measures with breast density. Finally, in a southwestern Native American population in which nearly all diabetes cases are of type 2, a disease related to insulin resistance, diabetes was associated with lower premenopausal breast density in a model taking weight into account but no other measures of adiposity (21).

The major strengths of this study include the reliability of both mammographic breast density and C-peptide measurements, the assessment of several factors potentially related to breast density and/or C-peptide, and the relatively large sample size. Nonetheless, our findings have to be interpreted with caution because they are based on a single nonfasting plasma measurement of C-peptide, which might not reflect long-term circulating C-peptide concentrations particularly among diabetes (3). Insulin secretion and C-peptide levels increase after a meal. However, all models were adjusted for the number of hours since last meal. Moreover, our conclusions were unchanged when the analysis was restricted to women who had their last meal for >5 hours ago. In the present study, women with diabetes mellitus at time of the study entry were not eligible.

Our results are consistent with several studies that reported a strong correlation of high BMI and WHR with high levels of C-peptide (1-3). Hyperinsulinemia and insulin resistance have been proposed as a possible biological mechanism by which adiposity could affect breast cancer risk and prognosis (1, 2). However, high insulin or C-peptide levels have been associated with increase breast cancer risk independently of BMI (4, 6-9), WHR (4, 6) and weight (5). Moreover, in a prospective study of nondiabetic early-stage breast cancer patients, high fasting insulin levels were found to be associated with an increased risk of death after adjustment for BMI (26). Whether further adjustment for WHR (or other measures of adiposity) would affect some of these associations needs to be clarified. Insulin may affect breast cancer risk and prognosis through its mitogenic and

**Table 2. Means and correlations of C-peptide levels with breast density ($n$ = 1,499)**

| Type of adjustment | Means of breast density* (%) by quartiles of C-peptide (ng/mL) | | | | Spearman correlation coefficients† ($P$) |
|---|---|---|---|---|---|
| | Quartile 1 (≤1.324) | Quartile 2 (1.325-2.143) | Quartile 3 (2.144-3.497) | Quartile 4 (>3.497) | |
| Covariates 1‡ | 35.4 | 30.0 | 27.6 | 23.2 | −0.210 (<0.0001) |
| Covariates 2§ | 34.6 | 29.1 | 27.6 | 23.2 | −0.198 (<0.0001) |
| Covariates 1 + BMI (kg/m$^2$) | 28.7 | 28.1 | 27.6 | 27.0 | −0.057 (0.03) |
| Covariates 2 + BMI (kg/m$^2$) | 28.5 | 27.6 | 27.6 | 26.9 | −0.054 (0.04) |
| Covariates 1 + WHR | 30.9 | 28.7 | 28.2 | 26.0 | −0.086 (0.0008) |
| Covariates 2 + WHR | 30.6 | 28.0 | 28.2 | 25.9 | −0.081 (0.002) |
| Covariates 1 + BMI (kg/m$^2$) + WHR | 27.7 | 27.8 | 27.8 | 27.8 | −0.022 (0.41) |
| Covariates 2 + BMI (kg/m$^2$) + WHR | 27.6 | 27.3 | 27.9 | 27.6 | −0.022 (0.41) |

*Means of breast density are presented as back-transformed values.

†Spearman correlation between continuous variables. Adjusted correlations are partial Spearman coefficients.

‡Means and correlations are adjusted for age (y) and time since last meal (≤2, >2-3, >3-4, >4-5, >5 h).

§Means and correlations are adjusted for age (y) and time since last meal (≤2, >2-3, >3-4, >4-5, >5 h), alcohol (drinks/wk) and total energy (kcal/day) intakes in the past year, menopausal status (premenopausal or postmenopausal), age at menarche (y), age at first full-term pregnancy (y), lactation (y), number of full-term pregnancies, number of personal breast biopsies, duration of past use of oral contraceptive and of hormone replacement therapy (y), family history of breast cancer in first-degree relative (yes/no), physical activity (METs h/wk), education (primary or less, secondary, college, or university diploma), and smoking status (never, former, or current smoker). Analysis are restricted to $n$ = 1,474 due to missing values for some breast cancer risk factors among participants.

antiapoptotic effects on normal breast epithelial cells and its promoting effect on tumor growth and development suggested by animal models of carcinogenesis (1, 2).

In conclusion, increasing C-peptide may be related to an elevation of breast cancer risk but, if so, our study suggests that such a relation would not involve breast density because breast density seems unrelated to C-peptide independently from adiposity. Thus, C-peptide levels and breast density seem to be two independent risk factors for breast cancer.

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