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Adipocytokines, Inflammation, and Breast Cancer Risk in Postmenopausal Women: A prospective study

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Abstract

Obesity is a known risk factor for postmenopausal breast cancer; it has been postulated that adipocytokines may mediate this association. We explored the relationship between three markers altered by obesity: leptin, adiponectin, and soluble tumor necrosis factor receptor 2 (sTNF-R2), an inflammatory marker, with breast cancer risk in postmenopausal women. A nested case-control study of postmenopausal women was conducted within CLUE II, a prospective population-based cohort. Baseline plasma levels of leptin, adiponectin, and sTNF-R2 were assayed in 272 female breast cancer cases and 272 controls matched on age, date and hour of blood draw. Conditional logistic regression was used to estimate matched odds ratios (OR) and 95% confidence intervals. sTNF-R2 and leptin were independently positively associated with breast cancer risk in adjusted models. The OR for breast cancer comparing the highest to lowest tertile was 2.44 (95% CI = 1.30–4.58) for sTNF-R2 and 1.98 (95% CI = 1.20–3.29) for leptin. While higher levels of adiponectin were protective (OR for the lowest tertile = 1.63, 95% CI = 1.02–2.60), there was no dose response. A 20% reduction in the breast cancer risk associated with overweight/obesity was observed when sTNF-R2 alone was included in multivariable models. Including both sTNF-R2 and adiponectin in the models resulted in a 29% reduction in the OR. Adipocytokines and sTNF-R2 are important factors in the etiology of postmenopausal breast cancer due to adiposity. This study informs our understanding of the relationship between obesity, inflammation and postmenopausal breast cancer and identifies potential biomarkers.

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Keywords

Adipocytokines; adiponectin; leptin; soluble tumor necrosis factor receptor 2 (sTNF-R2); breast cancer

Introduction

Obesity is a well-established risk factor for breast cancer in postmenopausal women, exerting its effect through multiple biological pathways (1–3). Alterations in adipocytokines such as leptin, adiponectin, and tumor necrosis factor (TNF) are believed to play a major role. These proteins are manufactured and secreted by cells within fat tissues (4). In postmenopausal women plasma levels of leptin have been shown to increase in conjunction with body mass index (BMI), and decrease in response to weight loss (5, 6), whereas levels of adiponectin have been shown to be decreased in obese individuals (7). Studies examining the association between leptin levels and breast cancer risk have been mixed but only include two prospective studies (8–12). In addition three case-control studies (13–15) and one prospective study (16) reported a protective effect of circulating adiponectin levels on the development of postmenopausal breast cancer. Plasma levels of TNF, a pro-inflammatory marker, have also been shown to increase with increasing BMI (17) and to decrease in association with weight loss in overweight breast cancer survivors (18). Soluble TNF-R2 (sTNF-R2), a receptor that binds TNF and other cytokines, appears to be a more stable biomarker than TNF in circulation (19). Serum levels of sTNF-R2 have also been found to highly correlate with those of TNF (20, 21). The association between circulating TNF and/or sTNF-R2 and breast cancer has been examined in a few small studies and the results have been inconclusive (21, 22).

Based on experimental data we hypothesized that elevated circulating levels of sTNF-R2 and leptin would be associated with increased risk for breast cancer, while adiponectin would be inversely related; further, that these three proteins would, in combination, contribute to increased risk for breast cancer conferred by obesity in postmenopausal women. We conducted a case-control study of postmenopausal women nested within the CLUE II Cohort to examine our hypotheses.

Materials and Methods

Study Population

CLUE II is a prospective population based cohort study on cancer and heart disease based in Washington County, MD that began in 1989. At baseline, participants were asked to donate a blood sample and to complete a brief questionnaire on demographic characteristics, and lifestyle factors including BMI (23) after signing an informed consent. Blood samples collected at baseline were processed within 12 hours and frozen at -70°C .

A 1996 follow-up questionnaire collected information on reproductive risk factors for breast cancer. Incident breast cancer was ascertained by linkage to the Washington County and Maryland Cancer Registries as well as through medical record review and death certificates. Cause of death has been confirmed in 94% of deceased cases.

Study Design

Postmenopausal women living in Washington County at enrollment in 1989, who had complete data for age and BMI, were eligible. Women with known breast cancer, or history of other cancers (except non-melanoma skin cancer and cervical carcinoma in situ) at baseline were excluded. Cases were women diagnosed with incident breast cancer during follow-up (n = 272), from 1990 through 2005. Controls were matched one to one to cases on age at blood draw, date and hour of blood draw (+/- 2 hours), and time since last menstrual period, and were required to be cancer free and alive at the time the case was diagnosed with breast cancer. The analytic cohort was restricted to Caucasian women due to the small number African-American women (n = 2).

Laboratory Methods

Samples, collected in heparinized tubes, were sent to the Rifai laboratory. Lab investigators were blinded to case control status or other information on the samples. Five percent of all samples assayed were randomly placed quality controls from pooled plasma of postmenopausal women to generate coefficients of variation (CV). The ELISA method from ALPCO Diagnostics Inc. (Salem, NH) was used to measure total adiponectin, using a 5151-dilution. After pretreatment to reduce multimeric adiponectin, samples were assayed using a quantitative “two-step” sandwich enzyme immunoassay technique. The CV for total adiponectin was 3.1%. Leptin was measured by an ultra-sensitive ELISA assay, an enzymatically amplified two-step sandwich-type immunoassay (R&D Systems, Minneapolis, MN), with a 100-fold dilution (24). The assay sensitivity was 7.8 pg/mL and the CV for leptin was 2.1%. sTNF-R2 was measured by a quantitative sandwich ELISA assay technique (R&D Systems), using a 20-fold dilution. The assay sensitivity was 0.6 pg/mL and the CV for sTNF-R2 was 2.8%. No samples were below the limit of detection.

Statistical Analysis

Baseline characteristics of cases and controls were first compared using paired t-tests for normally distributed continuous variables and Wilcoxon matched pairs sign-rank test for continuous variables without a normal distribution. Categorical variables were compared using the Chi-squared or Fisher's exact tests. Next, the age-adjusted associations of log-transformed values of the three plasma markers with each other were examined among the controls using partial correlation coefficients. Conditional logistic regression models were then used in both univariable and multivariable analyses to estimate the association of each marker and breast cancer risk. All three markers were categorized into tertiles, based on cut-points generated from their distribution among the controls. Confounders, including the matching variables, BMI, and reproductive and other breast cancer risk factors were added to age adjusted models. Multivariable conditional logistic regression models were also used to estimate the association between BMI and breast cancer risk. Comparison of odds ratios (OR) obtained in these models both with and without each of the markers, individually and combined, was used to estimate the extent to which these markers mediated the association between overweight, obesity and breast cancer risk.

Results

Baseline characteristics of the study population are shown in Table 1. Compared to controls, cases had significantly higher BMI, were more likely to have reported a family history of breast cancer, and reported former hormone use less frequently. Cases had significantly higher mean levels of sTNF-R2 and leptin, and a significantly lower mean adiponectin level than controls. Age-adjusted partial correlation coefficients among controls of leptin, sTNF-R2 and adiponectin (log transformed) and BMI were performed. Increasing BMI was more strongly correlated with leptin, ($r = 0.74$) compared to adiponectin ($r = -0.29$) and sTNF-R2 ($r = 0.26$). Correlations between sTNF-R2 and leptin ($r = 0.35$) and leptin and adiponectin ($r = 0.25$) were not strong.

The multivariable associations between sTNF-R2, leptin and adiponectin and breast cancer risk are shown in Table 2. In models adjusted for all covariates except BMI, women with sTNF-R2 levels in the 2nd and 3rd tertile were at significantly increased risk of breast cancer (OR comparing third to first tertile = 2.44; 95% CI = 1.30–4.58; OR comparing second to first tertile = 2.12; 95% CI = 1.24–3.65). Further, there was a significant dose response between sTNF-R2 levels and breast cancer risk (p -trend = 0.008). Leptin levels in the 2nd and 3rd tertile were also significantly associated with increased breast cancer risk; however this association was non-linear. On the other hand adiponectin levels only in the lowest tertile were significantly associated with increased risk.

When BMI was added to these models to assess independence of the markers apart from adiposity, the resulting ORs for all marker categories were attenuated towards the null, with the exception of the 2nd tertile of sTNF-R2. In sensitivity analyses, excluding pairs containing at least one woman who had reported hormone use ($n = 159$ pairs analyzed) the estimated associations between markers and breast cancer risk was not appreciably altered (data not shown). Similarly, restricting the analysis to pairs in which the case was diagnosed at least 2 years post blood draw ($n = 238$ pairs), resulted in comparable estimates.

Next, the extent to which sTNF-R2, leptin, and adiponectin might be acting as mediators of the relationship between adiposity and postmenopausal breast cancer was explored, and is shown in Table 3. An adjusted model containing no markers confirmed a significantly increased risk of breast cancer for women who were overweight/obese (OR = 2.34, 95% CI = 1.52–3.59). Adding sTNF-R2 to the model resulted in an attenuated but still statistically significant association between overweight/obesity and breast cancer risk, with a 20% reduction in the OR. The addition of leptin and adiponectin, separately and then jointly, reduced the OR by approximately 10%. The greatest reduction in the estimated association of overweight/obesity with breast cancer risk was seen in the model including both adiponectin and sTNF-R2, which reduced the OR by 29%. The addition of all three markers to the model resulted in a 27% reduction in the OR.

Discussion

In our nested case-control study, the strongest association was observed for increasing levels of sTNF-R2 and breast cancer risk, in a dose-response manner. High levels of leptin and low

levels of adiponectin were also associated with increased breast cancer risk, but a dose response was not observed. As we hypothesized, the combined effect of the markers was stronger than each of the markers alone, and appears to explain a substantial percentage of the association between overweight and postmenopausal breast cancer risk. Interestingly, the most substantial proportion of the increase in breast cancer risk associated with overweight/obesity could be explained by sTNF-R2, with comparatively lesser contributions coming from leptin and adiponectin.

TNF is a strongly pro-inflammatory cytokine that appears to directly stimulate the carcinogenic process by promoting tumor invasiveness, progression, angiogenesis and metastasis (4). More specifically linked to breast cancer, evidence also suggests TNF, derived largely from adipose-infiltrating macrophages in adipose tissue (25), can stimulate aromatase expression, thus increasing estrogen synthesis (26). The effects of TNF are mediated through its two receptors, TNF-R1 and TNF-R2. sTNF-R2, the soluble fragment of TNF-R2, is shed from the cell surface in response to stimulation by TNF itself as well as other cytokines (19). Therefore, an increase in sTNF-R2, as we observed in our study, is unlikely due solely to an increase in TNF expression. The sTNF-R2 is expressed by many cell types including neutrophils, monocytes and activated T cells (19). The function of this soluble receptor appears to be complex, as it may diminish the activity of TNF, and may also act as a slow-release reservoir for TNF, regulating its bioavailability (27).

A previous nested case-control study found no association between serum levels of TNF, sTNF-R1 and sTNF-R2 and breast cancer incidence (21); however, this study was small with only 52 pairs having available serum for sTNF-R2 measurement. In a prospective cohort study examining the association of circulating inflammatory markers and all cancers in older adults no association was observed between baseline TNF levels and incident breast cancer (22). However, this study contained 296 total cancers, only 11% of which were breast cancer, limiting precision. Our results are consistent with a previous prospective study finding a protective association between adiponectin and postmenopausal breast cancer. Previous studies of the relationship between leptin and breast cancer risk have been mixed. One prospective study of premenopausal women found an inverse association for leptin with breast cancer risk (12); another earlier prospective study of postmenopausal women failed to find an association (10). One case-control study found no association among postmenopausal women and inverse association for premenopausal women (9) and no association was found in another case-control study of premenopausal women with ductal carcinoma in situ (8). Our findings in postmenopausal women with invasive breast cancer are consistent with *in vitro* studies providing evidence for biological plausibility of leptin and adiponectin with cancer risk.

The major limitation of our study is the measurement of inflammatory markers at one time point. We make the assumption that these measures reflect chronic metabolic and inflammatory changes. However, any misclassification based on these measures would most likely be non-differential and therefore would lead to an underestimation of the true associations. In addition, our results may not be generalizable to a racially diverse population. Strengths of our study include the prospective nature of the study design, the ability to adjust for confounders, and the high reliability of our biomarkers.

In conclusion, our study suggests that inflammation, a sequela of obesity, is a stronger risk factor for postmenopausal breast cancer than leptin and adiponectin, and substantially mediates the risk of breast cancer attributed to obesity in these women.

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Table 1

Baseline characteristics of a case-control study nested within the CLUE II Cohort (1989–2005)

	Cases (n=272)	Controls (n=272)	p-value
Age at blood-draw, years, mean (SD)	62.6 (9.4)	62.5 (9.2)	0.9
BMI* at baseline, kg/m ² , mean (SD)	27.1 (0.3)	25.7 (0.3)	0.002
BMI category, n(%)			0.001
Normal (<25kg/m ²)	100 (36.8)	143 (52.6)	
Overweight (25 – <30 kg/m ²)	102 (37.5)	79 (29.0)	
Obese (>=30 kg/m ²)	70 (25.7)	50 (18.4)	
Education, n(%)			0.7
<12 years	84 (30.9)	88 (32.4)	
12 years	106 (39.0)	111 (40.8)	
>12 years	82 (30.2)	74 (26.8)	
Married at baseline, n (%)	192 (70.6)	176 (64.7)	0.36
Cigarette smoking, n (%)			0.46
Never	166 (61.0)	173 (63.6)	
Former	73 (26.8)	61 (22.4)	
Current	33 (12.1)	38 (14.0)	
Alcohol use, n (%)			0.77
Never	206 (75.7)	203 (74.6)	
Ever	66 (24.3)	69 (25.4)	
Gravidity, n (%)			0.60
Ever pregnant	201 (73.9)	194 (71.3)	
Never pregnant	27 (9.9)	25 (9.2)	
Missing	44 (16.2)	53 (19.5)	
Age at first birth of those reporting pregnancy (n=395), n (%)			0.33
<20 years	54 (26.9)	45 (23.2)	
20–24 years	98 (48.8)	92 (47.4)	
25–29 years	37 (18.4)	34 (17.5)	
30 years	10 (5.0)	20 (10.3)	
Missing	2 (1.0)	3 (1.6)	
Ever breastfed, n (%)	72 (26.5)	84 (30.9)	0.33
Age at menarche, n (%)			0.40
<12 years	33 (12.1)	40 (14.7)	
12–13 years	128 (47.1)	109 (40.1)	
>13 years	54 (19.9)	63 (23.2)	
Missing	57 (21.0)	60 (22.1)	
Ever oral contraceptive use, n (%)	39 (14.3)	35 (12.9)	0.54
Hormone therapy use**, n (%)			0.04
Never	204 (75.0)	196 (72.1)	
Former	31 (11.4)	49 (18.0)	
Current	35 (12.9)	22 (8.1)	

	Cases (n=272)	Controls (n=272)	p-value
Missing	2 (0.7)	5 (1.8)	
Family history of breast cancer ^{***} , n (%)			0.003
None	169 (62.1)	195 (71.7)	
Yes	55 (20.2)	27 (9.9)	
Missing	48 (17.7)	50 (18.4)	
sTNF-R2, ng/ml ^{****} , mean (SD)	3.2 (1.2)	2.8 (0.9)	0.005
Leptin, ng/ml, mean (SD)	32.9 (36.1)	27.4 (27.4)	0.007
Adiponectin, ng/ml, mean (SD)	7990.0 (3830.8)	8703.7 (4042.0)	0.02

* BMI, body mass index, weight in kilograms divided by height in meters squared.

** Hormone therapy use defined as ever use of hormone therapies other than oral contraceptives, including estrogen, progesterone, or a combination.

*** Family history defined as breast cancer in first-degree relatives and maternal and paternal grandparents.

**** sTNF-R2, leptin and adiponectin measured in plasma.

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Table 2

Adjusted odds ratios and confidence intervals for the relationship between sTNF-R2, leptin and total adiponectin and breast cancer risk.

	Tertile 1	Tertile 2	Tertile 3	p-trend
sTNF-R2				
cutpoint (ng/mL)	<2.38	2.38–3.19	>3.19	
No. cases/controls	67/91	99/91	106/90	
OR and 95% CI adjusted for				
Age and other covariates*	Ref	2.12 (1.24–3.65)	2.44 (1.30–4.58)	0.008
Age, BMI, and other covariates*	Ref	1.84 (1.04–3.23)	1.90 (0.97–3.70)	0.08
Leptin				
cutpoint (ng/mL)	<11.56	11.56–29.74	>29.74	
No. cases/controls	56/91	115/91	101/90	
OR and 95% CI adjusted for				
Age and other covariates*	Ref	2.10 (1.30–3.41)	1.98 (1.20–3.29)	0.05
Age, BMI, and other covariates*	Ref	1.69 (1.00–2.83)	1.16 (0.59–2.30)	0.75
Total adiponectin				
cutpoint (ng/mL)	<6498	6499–9350	>9350	
No. cases/controls	117/91	77/91	78/90	
OR and 95% CI adjusted for				
Age and other covariates*	1.63 (1.02–2.60)	0.95 (0.60–1.52)	Ref	0.08
Age, BMI, and covariates*	1.36 (0.84–2.22)	0.88 (0.54–1.41)	Ref	0.34

OR = odds ratio, CI= confidence interval

* adjusted for date and hour of blood draw, family history, alcohol use, gravidity, age at first birth, breastfeeding, oral contraceptives use, and hormone therapy use.

Table 3

Adjusted odds ratios and the percent of the association between overweight/obesity and breast cancer risk explained by sTNF-R2, leptin and adiponectin.

	Normal weight	Overweight/Obese O.R. 95% CI	Effect explained %
No markers	Ref	2.34 (1.52–3.59)	-
sTNF-R2	Ref	2.07 (1.32–3.24)	20
Leptin	Ref	2.21 (1.28–3.80)	10
Adiponectin	Ref	2.22 (1.44–3.44)	9
sTNF-R2 and Leptin	Ref	2.02 (1.16–3.53)	24
sTNF-R2 and Adiponectin	Ref	1.95 (1.23–3.08)	29
Leptin and Adiponectin	Ref	2.19 (1.26–3.79)	11
sTNF-R2, Leptin and Adiponectin	Ref	1.98 (1.13–3.49)	27

All models adjusted for age, date/hour of blood draw, family history, alcohol use, ever pregnant, age first birth, breast feeding, age at menopause, oral contraceptives and hormone therapy use