Research Article

Cancer Prevention Research

Adiposity, Inflammation, and Breast Cancer Pathogenesis in Asian Women

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Abstract

Obesity is associated with white adipose tissue (WAT) inflammation in the breast, elevated levels of the estrogen biosynthetic enzyme, aromatase, and systemic changes that predispose to breast cancer development. We examined whether WAT inflammation and its associated systemic effects correlate with body fat levels in an Asian population where body mass index (BMI) is not an accurate assessment of obesity and cancer risk. We also investigated whether biologic differences could account for the greater proportion of premenopausal estrogen receptor (ER)–positive breast cancer in Asian versus Western countries. Breast WAT and fasting blood were prospectively collected from Taiwanese women undergoing mastectomy for breast cancer treatment. Body composition was measured in a subgroup using bioelectrical impedance analysis. WAT inflammation was defined by the presence of crown-like structures of the breast, which are composed of dead or dying adipocytes surrounded by macrophages. Findings were compared with U.S. Caucasian women. In the Taiwanese cohort ($n = 72$), breast WAT inflammation was present in 31 (43%) women and was associated with elevated BMI ($P < 0.01$) and increased levels of body fat ($P < 0.01$), C-reactive protein ($P = 0.02$), triglycerides ($P < 0.01$), insulin resistance scores ($P = 0.04$), and lower HDL cholesterol ($P < 0.01$). ER^+ tumors were associated with greater body fat versus other subtypes ($P = 0.03$). Compared with U.S. Caucasians ($n = 267$), Taiwanese women had larger breast adipocytes despite lower BMI after adjusting for BMI and menopausal status ($P = 0.01$). A subclinical inflammatory state associated with increased adiposity and metabolic dysfunction could contribute to breast cancer pathogenesis in Asian women. *Cancer Prev Res; 11(4); 227–36. ©2017 AACR.*

Introduction

Anthropometric indices, such as body mass index (BMI), are widely utilized to assess population-level cardiometabolic health and risk of several types of malignancies including breast cancer (1, 2). The predictive utility of BMI for breast cancer risk varies by race/ethnicity, menopausal status, and tumor subtype (2–4). In Western populations, elevated BMI is an established risk factor for postmenopausal estrogen receptor (ER)–positive breast cancer, which is the most common phenotype (2, 5). Among East Asian populations, ER^+ tumors are also the most common breast cancer subtype (6–11). However, the incidence is highest in premenopausal women, and elevated BMI has not been associated with increased risk in this population (6, 7, 12). Higher levels of body fat per unit BMI in Asians compared with other ethnic groups and differences in adipose distribution may lead to underestimation of breast cancer risk by BMI (13, 14). For example, greater central adiposity measured by hip circumference is predictive of premenopausal breast cancer risk in Asian populations (15, 16). The incidence of invasive breast cancer is increasing in premenopausal Taiwanese women for unclear reasons and the use of BMI to assess whether adiposity is a contributing factor has not been informative for this population (7, 17). A better understanding of the relationships among adiposity, breast cancer, and underlying mechanisms in Asian

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women could lead to more effective population-specific screening and prevention programs.

Elevated BMI is associated with adipose tissue expansion characterized by adipocyte hypertrophy and the development of white adipose tissue (WAT) inflammation (18). Inflammation is histologically defined by the detection of crown-like structures (CLS), which are comprised of dead or dying adipocytes enveloped by macrophages (19–22). In a predominantly Caucasian population, we reported that 90% of women with BMI of 30 kg/m^2 or greater have WAT inflammation in the breast (21). Women with WAT inflammation have increased breast tissue levels of aromatase, the rate-limiting enzyme for estrogen biosynthesis, which could locally drive the growth of ER$^+$ tumors (20, 23). In addition to enhanced local production of estrogen, WAT inflammation may also promote breast tumor growth through systemic effects. Specifically, women with breast WAT inflammation have altered circulating levels of metabolic and inflammatory factors such as increased insulin and C-reactive protein (CRP; ref. 22), both of which are associated with greater breast cancer risk including in normal BMI women (24, 25). For women with established breast tumors, WAT inflammation is associated with shortened distant recurrence-free and overall survival independent of BMI (22, 26). The presence of breast WAT inflammation in cancer-free women could contribute to the development of tumors via similar mechanisms (27). Whether breast WAT inflammation is present and contributes to breast cancer pathogenesis in Asian populations has not been previously reported.

Some normal BMI women have breast WAT inflammation and its associated pathophysiology, including increased aromatase levels in the breast and systemic metabolic dysfunction (28). These women with WAT inflammation also have enlarged adipocytes in the breast, suggestive of a hyperadipose state despite normal BMI (28). In premenopausal European women, truncal adiposity is more predictive of breast WAT inflammation than BMI (29). These findings are particularly relevant to Asian populations in which BMI is an imprecise proxy of adiposity. Therefore, we investigated the relationships among adiposity, breast WAT inflammation, and markers of systemic metabolic health, in a cross-sectional cohort of Taiwanese women. To better understand population-specific patterns, we also compared breast WAT inflammation and associated findings among Taiwanese versus U.S. Caucasian women.

Materials and Methods

Study design

Taiwanese and U.S. Caucasian women enrolled in two independent cross-sectional cohorts were examined. In the Taiwanese cohort, women who underwent mastectomy for breast cancer treatment at National Taiwan University Hospital (NTUH, Taipei, Taiwan) were included. Patients with metastatic or unresectable breast cancer were excluded. Weight and height to calculate BMI, body composition measurements, and fasting blood samples were collected prior to surgery. During surgery, breast adipose tissue from a quadrant uninvolved by tumor was collected. The U.S. Caucasian cohort included women who underwent mastectomy for breast cancer treatment or prevention at Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY). Enrollment details for this cohort have been reported previously (21). This study was approved by the Institutional Review Boards of NTUH, MSKCC, and Weill Cornell Medical College (New York, NY).

Clinicopathologic data and biospecimen collection

Clinical data, including breast cancer features, menopausal status, and presence of comorbidities, were abstracted from the electronic medical record (EMR). Menopausal status was categorized as premenopausal or postmenopausal by National Comprehensive Cancer Network criteria (30). Comorbidities including diabetes, hypertension, and dyslipidemia were recorded if documented in the EMR by the treating clinician. Tumor phenotype was classified as hormone receptor (HR) positive if ER staining was >1% by IHC with negative or positive staining for the progesterone receptor. HER2 was categorized as positive or negative if IHC 3+ or FISH amplification $\geq$2.0 (31).

On the day prior to surgery, fasting blood was obtained and separated into serum and plasma by centrifugation within 3 hours of collection. Serum and plasma were stored at −80°C. On the day of mastectomy, breast WAT a minimum of 3 cm away from tumor was collected and was formalin fixed and paraffin embedded.

Anthropometric and body composition measurements

Preoperative weight and height were used to calculate BMI as weight (kg)/height (m)^2. World Health Organization (WHO) categorizations were used to classify BMI as under- or normal weight (<25 kg/m^2), overweight (25–<30 kg/m^2), or obese ($\geq$30 kg/m^2). In addition, suggested categorizations from the WHO expert consultation on BMI in Asian populations were also used to classify BMI in the Taiwanese cohort as under- or normal weight (<23 kg/m^2), overweight (23 to 27.5 kg/m^2), or obese ($\geq$27.5 kg/m^2; ref. 32). In a subgroup of women in the Taiwan cohort, fasting whole body and segmental body composition were determined by bioelectrical impedance analysis (InBody720, Biospace) one day prior to surgery. After 10 minutes of inactivity, body composition was measured in the standing position using eight metal electrodes (two for each hand and foot). Total fat mass (kg) and total body fat percentage were recorded. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) mass (kg) were also recorded.

Breast WAT assessments

The presence or absence of breast WAT inflammation was determined by established histologic methods (20–22). Breast WAT inflammation was defined by the presence of CLS in the breast (CLS-B). To determine whether CLS-B were present, 5 tissue sections were obtained at 50-μm intervals (5-μm thick and approximately 2 cm in diameter). All 5 sections were immunostained for CD68, a macrophage marker (mouse monoclonal KP1 antibody, Dako; dilution 1:4,000). The immunostained sections were examined by the study pathologist (D.D. Giri) using light microscopy to determine the number of CLS-B present on each slide. The severity of WAT inflammation was recorded as number of CLS-B per square centimeter of WAT (CLS-B/cm^2). ImageJ Software (NIH, Bethesda, MD) was used to measure total WAT area, exclusive of epithelial and/or fibrous areas, from digital photographs of each slide.

Breast adipocyte size was determined as described previously (20, 21). Two H&E sections were generated from breast WAT and photographed at 20× using an Olympus BX50 microscope and MicroFire digital camera (Optronics). A minimum of 30 individual adipocyte diameters were measured to determine mean adipocyte diameter using the calibrated linear dimensional tool in the Canvas 11 Software (ACD Systems International, Inc.).

Blood assessments

Serum glucose, high-sensitivity CRP (hsCRP), insulin, and lipid profiles, including total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were quantified in the Department of Laboratory Medicine at NTUH. Plasma levels of leptin, adiponectin, and IL6 were measured by ProCartaPlex multiplex immunoassay (eBioscience).

Biostatistical analyses

The differences between patients with versus without breast WAT inflammation were examined using logistic regression and the Fisher exact test where appropriate for categorical variables, and the nonparametric Wilcoxon rank-sum test for continuous variables. Interquartile range (IQR) was reported to summarize variability in continuous variables. Correlations between two continuous variables were examined using Spearman method. Differences in a continuous variable across multiple categories were examined using the nonparametric Kruskal–Wallis test. Associations between mean adipocyte size and categorical variables were evaluated using ANOVA and/or t test where appropriate. Fisher exact test and t test were used to compare variables in the Taiwanese versus U.S. Caucasian cohorts where appropriate. Adipocyte size was compared between the two cohorts by multiple linear regression analysis, and the model was adjusted for BMI and menopausal status. For all analyses, statistical significance was set at two-tailed $P < 0.05$. All statistical analyses were conducted using R software (R Foundation for Statistical Computing).

Results

Study population

From December 2011 to December 2016, 98 subjects who underwent mastectomy for breast cancer treatment at NTUH were enrolled. Breast WAT was available from 73 patients and one patient was excluded due to the presence of metastatic disease. Accordingly, a total of 72 women were included in the Taiwanese cohort (Fig. 1). After a protocol amendment in 2014, 50 of the 72 enrolled subjects had bioimpedance analysis to determine body composition. Overall, median age was 51 (IQR, 42–60) years, median BMI was 23.2 (IQR, 20.9–27.0) kg/m^2, and 38 women (53%) were premenopausal.

Patient characteristics in the U.S. cohort have previously been reported (21). A total of 267 Caucasian women who underwent mastectomy for breast cancer treatment or prevention at MSKCC between January 2011 and August 2013 were included in the U.S. Caucasian cohort. Overall, median age was 48 (IQR, 41–54) years, median BMI was 25.4 (IQR, 22.4–29.2) kg/m^2, and 159 women (60%) were premenopausal.

WAT inflammation in Taiwanese women

Breast WAT inflammation, detected by the presence of CLS-B (Fig. 2A), was found in 31 (43%) women. Patient characteristics stratified by the presence or absence of WAT inflammation are presented in Table 1. Median BMI was higher in women with breast WAT inflammation versus those without inflammation ($P < 0.01$) and the incidence of breast WAT inflammation in obese subjects was 76% and 73% when Asian and standard BMI categorizations were used, respectively (Fig. 2B).

The relationships among breast WAT inflammation and circulating factors in fasting blood are presented in Table 2. Breast WAT inflammation was associated with elevated levels of hsCRP ($P = 0.02$) and triglycerides ($P < 0.01$), and lower levels of HDL cholesterol ($P < 0.01$). Of note, only 3 women were diagnosed with dyslipidemia and all 3 had breast WAT inflammation (Table 1). Breast WAT inflammation was also associated with insulin resistance as evidenced by the homeostasis model assessment (HOMA2-IR, $P = 0.04$; Table 2), although WAT inflammation was not associated with a clinical diagnosis of diabetes mellitus (Table 1).

Adiposity and WAT inflammation in Taiwanese women

Of the 50 subjects who had body composition measured by BIA, 23 (46%) had breast WAT inflammation. Total body fat, VAT, and SAT stratified by BMI and WAT inflammation are presented in Table 3. Elevated BMI and breast WAT inflammation were both associated with increased amounts of total body fat, VAT, and SAT (Table 3). A positive correlation between age and body fat percentage ($\rho = 0.38$, $P < 0.01$) was also observed. Median body fat percentage was higher in women who were postmenopausal (31.5%; IQR, 27.5%–38.8%) versus premenopausal (27.8%; IQR,

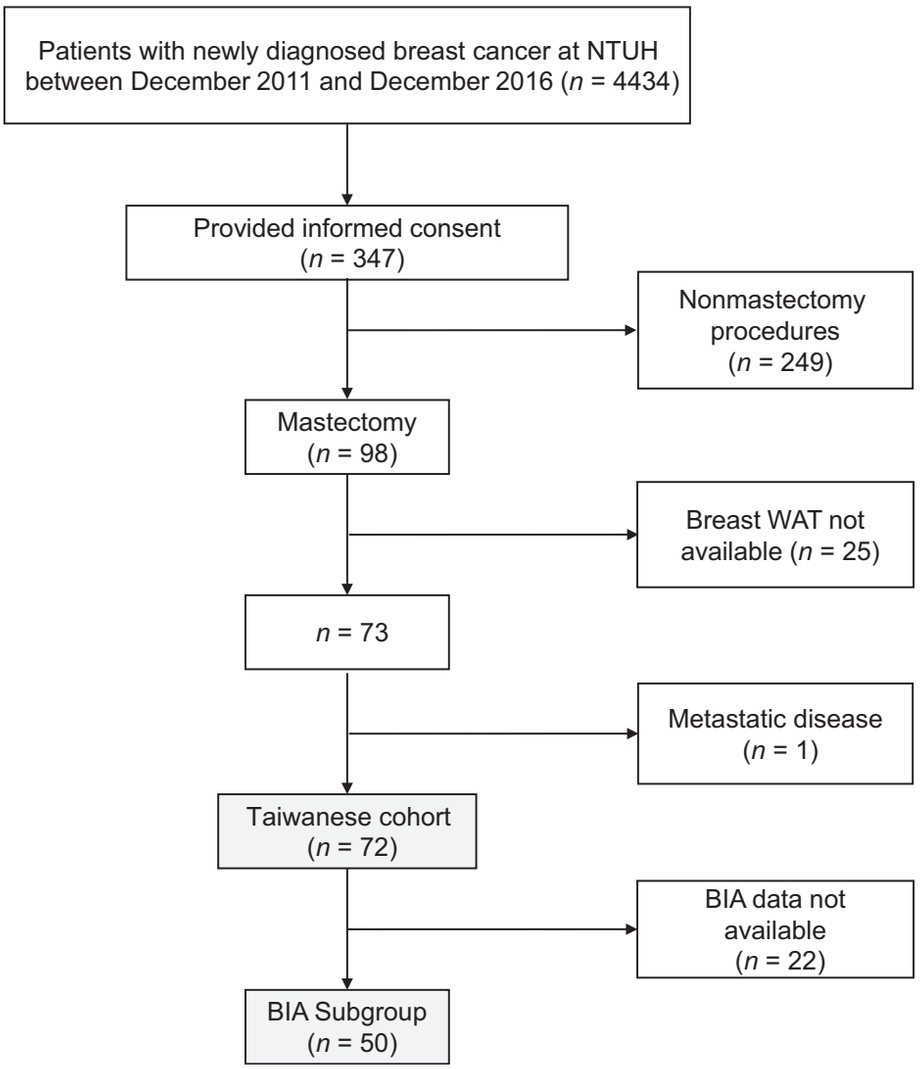

Figure 1.
Study flow diagram. BIA, bioelectrical impedance analysis.

23.2%–31.4%; $P = 0.02$). Among pre- and postmenopausal patients with invasive breast cancer, body fat percentage was highest in those with HR^+, $HER2^-$ tumors versus women with other tumor subtypes ($P = 0.03$; Fig. 2C).

At the cellular level, breast adipocyte size positively correlated with BMI ($\rho = 0.43$, $P = 0.01$; Fig. 2D) and total body fat percentage ($\rho = 0.52$, $P < 0.01$; Fig. 2E). Postmenopausal women had larger adipocytes (median diameter, 110.5; IQR, 102.8–116.7 μ) than premenopausal women (median diameter, 102.7; IQR, 94.1–106.3 μ; $P < 0.01$). Larger breast adipocyte size was associated with breast WAT inflammation ($P < 0.01$; Fig. 2F) and higher circulating levels of hsCRP ($\rho = 0.50$, $P < 0.01$).

Adiposity and WAT inflammation in Taiwanese versus U. S. Caucasian Women

Clinicopathologic characteristics among Taiwanese and U.S. Caucasian women are compared in Table 4. Age and menopausal status were similar between cohorts. The proportion of $HR^+/HER2^-$ tumors was higher in Taiwanese women compared with U.S. Caucasians. Median BMI was higher in U.S. Caucasians than in Taiwanese women ($P < 0.01$; Fig. 2G). In univariate comparison, a trend of larger breast adipocytes was observed among Taiwanese women versus U.S. Caucasians (Table 4). When adjusted for BMI and menopausal status, the observation that breast adipocyte size is larger in Taiwanese women versus U.S. Caucasians was statistically significant ($P = 0.01$; Fig. 2H). The prevalence of breast WAT inflammation was 55% in U.S. Caucasians and 43% in Taiwanese women, although this difference was not statistically significant (Table 4). However, among those with breast WAT inflammation, the severity of inflammation was slightly higher in U.S. Caucasians versus Taiwanese women as shown in Table 4.

Discussion

In this study, we demonstrate for the first time that breast WAT inflammation, defined by the presence of CLS-B,

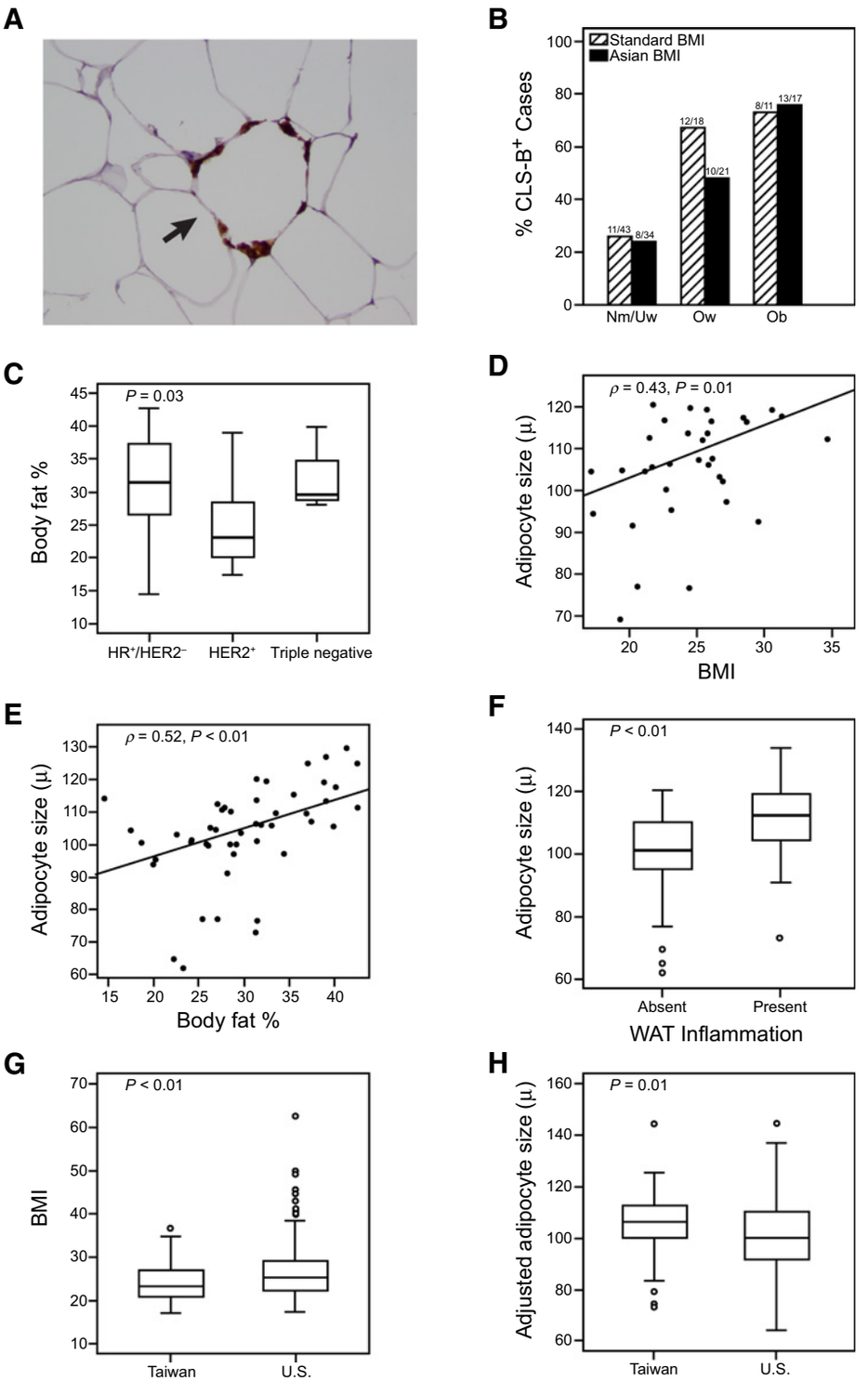

Figure 2.

Obesity, adiposity, and inflammation in Taiwanese women with breast cancer. **A,** Anti-CD68 immunostaining showing CLS-B (arrow; 200×). **B,** Prevalence of WAT inflammation (CLS-B) by BMI category using standard and Asian BMI cutoffs. **C,** Body fat percentage is highest in Taiwanese women with $HR^+/HER2^-$ breast cancer ($n = 31$) versus women with $HER2^+$ ($n = 10$) and triple-negative ($n = 3$) tumors ($P = 0.03$). **D,** Higher BMI correlates with larger breast adipocyte size ($\rho = 0.43$, $P = 0.01$). **E,** Higher body fat percentage correlates with larger breast adipocyte size ($\rho = 0.52$, $P < 0.01$). **F,** Taiwanese women with WAT inflammation have larger breast adipocytes than those without inflammation ($P < 0.01$). **G,** Median BMI was lower in the Taiwanese cohort versus U.S. Caucasian cohort ($P < 0.01$). **H,** Median breast adipocyte size was larger in the Taiwanese cohort versus U.S. Caucasian cohort after adjustment for BMI and menopausal status ($P = 0.01$). Nm/Uw, normal/underweight; Ow, overweight; Ob, obese.

occurs in an Asian population and is associated with elevated BMI, increased body fat, and alterations in circulating metabolic and inflammatory factors. When compared with U.S. Caucasian women, Taiwanese women had larger breast adipocytes despite lower BMI. Breast adipocyte size correlated with total body fat, and Taiwanese women with HR^+ breast cancers had the highest levels of body fat compared with women with other tumor

Table 1. Clinical characteristics of patients by breast WAT inflammation

Variables	Breast WAT inflammation		P
	Absent ($n = 41$)	Present ($n = 31$)	
Age, years			
Median (IQR)	51 (42–60)	49 (43–59)	0.80
BMI, kg/m^2			
Median (IQR)	22.6 (20.3–24.3)	25.9 (23.0–30.2)	<0.01
Menopausal status, *n* (%)			
Pre	22 (54%)	16 (52%)	
Post	19 (46%)	15 (48%)	1.00
Tumor subtype, *n* (%)[a]			
HR$^+$/HER2$^-$	25 (61%)	20 (67%)	
HER2$^+$	9 (22%)	6 (20%)	
Triple negative	2 (5%)	3 (10%)	
Not applicable (noninvasive)	5 (12%)	1 (3%)	0.55
Hypertension, *n* (%)	7 (17%)	8 (26%)	0.39
Diabetes mellitus, *n* (%)	3 (7%)	3 (10%)	1.00
Dyslipidemia, *n* (%)	0 (0%)	3 (10%)	0.07

[a]Data unavailable for 1 (1.4%) patient.

Table 2. Blood markers by breast WAT inflammation

Variables (median, IQR)	Breast WAT Inflammation		P
	Absent ($n = 41$)	Present ($n = 31$)	
hsCRP, ng/mL[a]	0.02 (0.01–0.06)	0.13 (0.03–0.31)	0.02
IL6, pg/mL[a]	1.92 (0.00–9.03)	3.42 (0.00–9.67)	0.49
Triglycerides, mg/dL	81 (64–106)	112 (92–180)	<0.01
Total cholesterol, mg/dL	178 (159–204)	180 (152–197)	0.36
LDL cholesterol, mg/dL	108 (91–123)	107 (88–126)	0.87
HDL cholesterol, mg/dL	56 (46–64)	47 (41–52)	<0.01
Glucose, mg/dL[a]	100 (89–115)	99 (88–119)	0.85
HbA1c, %[a]	5.5 (5.4–5.8)	5.7 (5.5–5.8)	0.15
Insulin, mU/L	7.2 (4.8–10.3)	9.7 (4.3–16.2)	0.09
HOMA2-IR[a]	0.87 (0.56–1.22)	1.19 (0.68–1.95)	0.04
Leptin[a]	3.67 (2.45–5.99)	5.59 (2.67–10.95)	0.12
Adiponectin[a]	8.1 (6.0–10.3)	6.2 (4.3–9.3)	0.08
Leptin to adiponectin ratio[a]	0.49 (0.25–0.97)	0.71 (0.38–1.54)	0.06

Abbreviations: HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; HOMA2-IR, homeostasis model assessment-2 of insulin resistance; LDL, low-density lipoprotein.

[a]Blood measurements unavailable for (*n*, %): glucose (1, 1.39%); HbA1c (25, 34.72%); HOMA2-IR (1, 1.39%); leptin (2, 2.78%); adiponectin (2, 2.78%); IL6 (2, 2.78%); hsCRP (1, 1.39%).

subtypes. Collectively, these findings identify excess adipose tissue as a potential breast cancer risk factor in Asian women, and WAT inflammation may be a contributing mechanism.

Our findings support the role of adipose tissue dysfunction prompted by fat mass expansion as a novel etiologic factor in breast cancer development for Taiwanese women. We previously reported that mammary WAT inflammation in mouse models of obesity is associated with adipocyte hypertrophy and local production of inflammatory cytokines that induce aromatase expression (33). In subsequent translational studies, we reported that approximately 90% of U.S. women with BMI $\geq$30 kg/m^2 have breast WAT inflammation and that increased levels of aromatase occur in association with both obesity and breast WAT inflammation (20, 21, 34). Women with breast WAT inflammation have increased circulating levels of hsCRP and evidence of metabolic dysfunction, such as insulin resistance and dyslipidemia (22). Taken together, WAT expansion and inflammation in the breast are associated with both local and systemic effects that could predispose to the development of breast cancer (35). We have also reported these findings in approximately one third of women with normal BMI (28). In these inflamed normal BMI women, the presence of breast adipocyte hypertrophy suggested a hyperadipose and metabolically obese state despite a normal BMI. This inference is now confirmed in the current study in which Taiwanese women with enlarged breast adipocytes had increased levels of body fat. A key finding from this study is the association between elevated total body fat and breast WAT inflammation. Collectively, these findings indicate that women with excess body fat have distinct alterations within the breast microenvironment, including adipocyte hypertrophy and WAT inflammation, which are likely to predispose to carcinogenesis.

Findings from this study are particularly relevant to Asian countries where breast cancer incidence is on the rise and the relationship with obesity is not yet fully elucidated. Breast cancer incidence rates in recent generations from Asian countries are surpassing rates in the United States, which has been attributed to the adoption of westernized lifestyles (36). However, breast cancer in Asian countries is distinct from Western populations (6, 7, 9, 10). Over 50% of breast cancers in Asian countries are diagnosed in premenopausal women, whereas the majority of breast cancers in the United States are found in postmenopausal women (7–11). Unlike premenopausal breast cancer in the United States, luminal A breast cancer characterized by positive ER expression is the most prevalent subtype in premenopausal Taiwanese women (6). Despite the predominance of ER$^+$ tumors, Asian women have lower serum estradiol levels than U.S. Caucasian women, which is not entirely attributable to differences in body weight (37). We found that the prevalence of WAT inflammation was similar between pre- and postmenopausal Taiwanese women, unlike U.S. Caucasian women in whom WAT inflammation is associated with the postmenopausal state (21). Furthermore, Taiwanese women

Table 3. Body composition parameters

Variables (median, IQR)	BMI category (Asian)			P	Breast WAT inflammation		P
	Underweight/normal ($n = 34$)	Overweight ($n = 21$)	Obese ($n = 17$)		Absent ($n = 27$)	Present ($n = 23$)	
Body fat, kg	14.3 (11.0–15.9)	19.0 (17.3–23.2)	32.7 (28.7–34.4)	<0.01	15.6 (11.4–17.0)	23.5 (16.0–29.8)	<0.01
Body fat (%)	26.5 (22.4–28.4)	32.0 (31.4–33.4)	39.1 (38.5–40.5)	<0.01	27.5 (23.7–31.4)	33 (28.9–39.0)	<0.01
VAT, kg	1.4 (0.9–1.7)	2.2 (2.1–2.7)	4.8 (4.1–5.2)	<0.01	1.5 (1.0–1.9)	2.7 (1.7–4.3)	<0.01
SAT, kg	12.9 (10.1–14.2)	16.8 (15.2–20.3)	27.9 (24.6–29.1)	<0.01	14 (10.4–15.0)	20.1 (14.3–25.5)	<0.01

Table 4. Comparison of Taiwanese and U.S. Caucasian cohorts

Variables	Taiwanese ($n = 72$)	U.S. Caucasian ($n = 267$)	P
Age (years)			
Median (IQR)	51 (42–60)	48 (41 to 54)	0.08
BMI			
Median (IQR)	23.2 (20.9–27.0)	25.4 (22.4–29.2)	<0.01
Menopausal status, *n* (%)			
Pre	38 (53%)	159 (60%)	
Post	34 (47%)	108 (40%)	0.35
Tumor subtype, *n* (%)[a]			
$HR^+/HER2^-$	45 (63%)	124 (47%)	
$HER2^+$	15 (21%)	26 (10%)	
Triple negative	5 (7%)	30 (11%)	
Not applicable (noninvasive)	6 (8%)	86 (32%)	<0.01
Breast WAT Inflammation, *n* (%)			
Absent (CLS-B negative)	41 (57%)	119 (45%)	
Present (CLS-B positive)	31 (43%)	148 (55%)	0.06
Severity of breast WAT inflammation among $CLS\text{-}B^+$ subjects[b]			
CLS-B/cm^2, median (IQR)	0 (0.00–0.19)	0.1 (0.00–0.41)	<0.01
Average breast adipocyte size (μ)[c]			
Median (IQR)	105.6 (100.1–113.6)	102.1 (91.6–111.2)	0.06
Hypertension, *n* (%)			
No	57 (79%)	232 (87%)	
Yes	15 (21%)	35 (13%)	0.13
Diabetes mellitus, *n* (%)			
No	66 (92%)	258 (97%)	
Yes	6 (8%)	9 (3%)	0.10
Dyslipidemia, *n* (%)[d]			
No	68 (96%)	230 (86%)	
Yes	3 (4%)	37 (14%)	0.02

NOTE: Data unavailable for *n*, (%): [a]1 (1.4%) Taiwanese and 1 (0.4%) U.S.; [b]3 (4.2%) Taiwanese and 3 (1.1%) U.S.; [c]62 (23.2%) U.S.; [d]1 (1.4%) Taiwanese.

with the highest body fat percentages were more likely to have ER^+ tumors than other subtypes. Our findings raise the possibility that the higher prevalence of ER^+ tumors in premenopausal Asian women could be attributable, in part, to the increased local production of estrogen within inflamed breast tissue of hyperadipose individuals.

The observation that Taiwanese women have larger breast adipocytes and lower BMI on average than U.S. Caucasian women underscores the need for improved assessments of obesity, particularly in the context of predicting cancer risk. Several groups have previously reported that Asian populations have higher body fat percentage despite lower BMI than Caucasians (38–41). On the basis of these observations, lower BMI cutoffs for obesity have been suggested for Asia-Pacific countries (32, 38). However, interpopulation differences in the relationship between BMI and body composition have been reported among Asian countries, and cardiometabolic dysfunction can be found in normal BMI individuals even when adjusted for race (41, 42). In this study, breast WAT inflammation was found in nearly a quarter of Taiwanese women with normal BMI by Asian criteria. This finding could help to explain the epidemiologic observation that central adiposity, and not BMI, is associated with breast cancer risk in premenopausal Asian women (12, 15, 16, 43). For example, in a prospective observational study of over 11,000 women in Taiwan, elevated hip circumference was a significant predictor of breast cancer incidence (16). In a case–control study of Chinese women in Shanghai, Shu and colleagues reported that high waist-to-hip ratio (WHR) was associated with an increased risk of premenopausal but not postmenopausal breast cancer (15). Notably, Wang and colleagues recently reported that associations among WHR, BMI, and breast cancer risk in Chinese women vary by tumor subtype (44). In contrast to other studies of Asian-Pacific women, higher BMI predicted increased risk of HR^+ breast cancer, whereas WHR correlated with risk of HR^- breast cancer in premenopausal women. Inconsistencies among studies examining the relationship between adiposity and breast cancer risk may be attributable to the imprecision of anthropometric indices, particularly in Asian populations. Measurement of body composition provides direct assessment of adiposity as well as fat mass distribution. In our study, breast WAT inflammation was associated with increased total, visceral, and subcutaneous adiposity. Thus, direct measurement of body composition is likely to be a more accurate cancer screening modality than indirect surrogates of adiposity, such as BMI or other anthropometric approaches.

The alterations among inflammatory and metabolic blood factors in Taiwanese women with WAT inflammation were consistent with our prior findings in Caucasian women (22). Taiwanese women with WAT inflammation had circulating changes associated with the metabolic syndrome including elevated triglyceride levels, decreased HDL cholesterol, and insulin resistance. Furthermore, women with breast WAT inflammation had higher levels of hsCRP, a proinflammatory biomarker and cardiovascular risk factor. Several proinflammatory mediators are known inducers of aromatase, which may contribute to the development of ER^+ tumors (45, 46). Elevated circulating levels of hsCRP and insulin have been associated with increased breast cancer risk in a large, multicenter American cohort (24, 25). Thus, in addition to local effects in the breast, the systemic impact of WAT inflammation may also contribute to breast cancer development in an estrogen-independent manner. Specifically, insulin can stimulate the synthesis of insulin-like growth factor 1 and both can activate the PI3K/Akt/mTOR and Ras/Raf/MAPK pathways, which are linked to breast tumor development (47, 48). Consistently, diabetes and dyslipidemia have been associated with increased breast cancer risk in Taiwan (49). The prevalence of glucose intolerance in Asians is equivalent or higher than Western populations despite lower BMI and similar to our finding of larger breast adipocytes in Taiwanese women despite lower BMI than U.S. Caucasian women (50).

The design of this study is strengthened by prospective collection of paired breast tissue and fasting blood from two independent cohorts with overlapping timing of enrollment and data collection. All breast specimens were centrally analyzed for WAT inflammation, allowing

for comparison between the two globally distinct cohorts. Further studies are needed to determine whether direct measurement of body composition is an effective method to predict cancer risk, particularly in Asian countries where BMI is of limited utility in assessing the degree and effects of adiposity.

In summary, this study demonstrates that WAT inflammation is prevalent in Asian women with increased levels of body fat. The local and systemic effects of WAT inflammation provide a plausible biologic mechanism for the increasing prevalence of ER^+ breast cancers among premenopausal Asian women. On the basis of these findings, future studies are warranted to determine whether reducing adiposity and WAT inflammation via interventions, such as structured diet modification and/or exercise programs, can attenuate breast cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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