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## Metabolic syndrome and mammographic density: The Study of Women's Health Across the Nation (SWAN)

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### Abstract

The metabolic syndrome (MetS) is associated with an increase in breast cancer risk. In this study, we evaluated whether the MetS was associated with an increase in percent mammographic density (MD), a breast cancer risk factor. We used linear regression and mixed models to examine the cross-sectional and longitudinal associations of the MetS and components of the MetS to percent MD in 790 pre- and early perimenopausal women enrolled in the Study of Women's Health Across the Nation (SWAN). In cross-sectional analyses adjusted for body mass index (BMI), modest inverse associations were observed between percent MD and the MetS ( $\beta = -2.5$ , SE = 1.9,  $p = 0.19$ ), abdominal adiposity ( $\beta = -4.8$ , SE = 1.9,  $p = 0.01$ ) and raised glucose ( $\beta = -3.7$ , SE = 2.4,  $p = 0.12$ ). In longitudinal models adjusted for covariates including age and BMI, abdominal adiposity ( $\beta = 0.34$ , SE = 0.17,  $p = 0.05$ ) was significantly positively associated with slower annual decline in percent MD with time. In conclusion, our results do not support the hypothesis that the MetS increases breast cancer risk via a mechanism reflected by an increase in percent MD.

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## Keywords

adiposity; body mass index; breast cancer risk factor; mammographic density; metabolic syndrome

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The metabolic syndrome (MetS) is a cluster of metabolic abnormalities. It is clinically defined as having at least three of the following disorders: abdominal adiposity, raised blood pressure, raised fasting plasma glucose, raised triglycerides and reduced high-density lipoprotein (HDL) cholesterol.<sup>1</sup> Women with the MetS have an estimated 58% higher risk for postmenopausal breast cancer, compared to women without the MetS.<sup>2</sup> The MetS is positively associated with triple-negative breast cancer,<sup>3</sup> aggressive tumor phenotype,<sup>4</sup> and breast cancer recurrence<sup>5</sup> and mortality.<sup>6</sup> Approximately one-third of U.S. women between 40 and 59 years of age are estimated to meet the criteria for the MetS.<sup>7</sup> Characterizing metabolic markers of breast cancer risk among these at risk women is of major public health relevance.

Several possible biologic mechanisms exist by which the MetS may adversely influence breast carcinogenesis. The components of the MetS may cooperatively contribute to cancer initiation and progression via mechanisms involving hyperinsulinaemia, adipokine production, glucose utilization, chronic low-grade inflammation and oxidative stress.<sup>8</sup> For example, the effects of abdominal adiposity on breast cancer risk may be mediated via insulin, insulin-like growth factors and leptin; all of these factors act as mitogens in breast epithelial cells<sup>9–11</sup> and are pro-angiogenic in breast cancer animal models and human breast cell lines.<sup>12–13</sup> Neoplastic breast cells have elevated glucose metabolism,<sup>14</sup> suggesting that a glucose rich environment is associated with breast cancer development. Additionally, glucose levels and hypertension have been positively correlated with markers for systemic inflammation<sup>15</sup> and oxidative stress,<sup>16–17</sup> both of which may increase breast cancer risk.

Epidemiologic studies have reported moderate positive associations for breast cancer risk with individual components of the MetS.<sup>2, 18–20</sup> For postmenopausal breast cancer, the presence of raised triglycerides or reduced HDL-cholesterol was associated with 60% higher risk,<sup>2</sup> and abdominal adiposity was associated with 34% higher risk.<sup>18</sup> Raised fasting glucose was associated with a 2-fold higher risk for premenopausal breast cancer.<sup>19</sup> Only a few studies have been conducted of breast cancer and the MetS as a single entity, and results have been inconsistent; with one study reporting a positive association with postmenopausal breast cancer<sup>2</sup> and two reporting no association.<sup>21–22</sup>

The proportion of the breast occupied by radiologically dense breast tissue, or percent mammographic density (MD), may be on the causal pathway between metabolic abnormalities and breast cancer development.<sup>23</sup> Percent MD is associated with a four to six-fold increase in breast cancer risk, comparing high (> 60%) versus low (< 10%) density.<sup>24</sup> The elevated breast cancer risk may persist for an estimated 10 years after breast density assessment regardless of menopausal status or age.<sup>25</sup> Percent MD may be a biological marker of cumulative exposure to hormones and other growth factors.<sup>23</sup> Abdominal adiposity influences MD and breast cancer risk in opposite directions, with abdominal adiposity associated with low percent MD.<sup>26</sup> Data on the effect of other metabolic abnormalities on MD requires further study; for example, limited available data support a modest positive association with HDL-cholesterol<sup>27–28</sup> and a modest inverse association with triglycerides.<sup>28</sup> No epidemiologic studies have been conducted to date that have evaluated the association between the MetS and percent MD.

We examined the cross-sectional and longitudinal associations of the MetS and components of the MetS to percent MD in a subset of women in the Study of Women's Health Across the Nation (SWAN), a community-based cohort of African American, Chinese, Japanese, and Caucasian women. Specifically, we hypothesized that the MetS would be positively associated with percent MD and inversely associated with annual decline in percent MD.

## Materials and Methods

### Study population

SWAN, a multi-ethnic, community-based, longitudinal study of the menopausal transition, enrolled 3,302 women in 1996–1997 from seven clinical sites.<sup>29</sup> The SWAN MD ancillary study included SWAN participants enrolled in three of the seven study sites: University of California Davis-Kaiser (Oakland), University of California Los Angeles (Los Angeles) and University of Pittsburgh (Pittsburgh). To identify community-based women, two sites (Los Angeles, Pittsburgh,) used random digit dialing-sampling and one site selected randomly from a healthcare organization membership listing (Oakland). Eligible women were aged between 42 and 52 years, reported having had a menstrual period and no use of exogenous hormones within the three months prior to recruitment and identified their primary race as African-American (Pittsburgh), Chinese (Oakland), Japanese (Los Angeles), or Caucasian (all sites). Of the 1,248 women in follow-up at these three sites at the time of enrollment into the ancillary MD study (i.e. at visit 5 or 6), 1,005 (81%) agreed to participate and had at least one eligible mammogram for MD assessment.

For analyses presented here, women were excluded if they were not pre- or early perimenopausal (defined below) at their index mammogram (N = 205), were missing MD measures (N = 4) or were missing MetS information (N = 6). The remaining 790 women were included in these analyses. The study protocol for both the core SWAN study and the ancillary study were approved by the institutional review boards of the participating institutions, and all women provided signed, written informed consent for participation in the studies.

### Mammographic density

Eligible mammograms were those taken as part of routine medical care from two years prior to the baseline SWAN visit through two years after the 6<sup>th</sup> visit and were restricted to those done on breasts without prior surgery. We defined the “index” mammogram as the earliest available mammogram within two years of a SWAN visit when the MetS was assessed. The SWAN visit closest in time to the index mammogram date was the baseline or visit 1 for the majority of women (84%). The average lag between the date of the index mammogram and the date of the closest SWAN visit was 0.6 years (SD = 0.4, range 0–2 years).

Film-screen mammograms were sent periodically in batches for assessment by Martine Salane, an established expert in the techniques of measuring MD.<sup>30–32</sup> Unknown to Ms. Salane, 10% of the films for this study were sent for her re-review. The initial and repeat readings had excellent concordance (the intraclass correlation coefficient was 0.96 for percent MD and 0.98 for area of dense breast). Quantitative assessment was obtained by measuring the total area of the breast and the area of dense breast tissue with a compensating polar planimeter (LASICO, Los Angeles, CA) on the craniocaudal view of the right breast. Mammograms from the left breast were used for density assessments when a woman reported surgery in the right breast (e.g., biopsy, breast augmentation, reduction or reconstruction) or when films from the right breast were unavailable.

## Metabolic syndrome

At baseline and annual follow-up visits, all participants completed a standard protocol that included self- and interviewer administered questionnaires, phlebotomy and anthropometry, and this information was used to determine MetS status. Phlebotomy was performed in the morning following an overnight fast. Participants were scheduled for venipuncture on days 2 to 5 of a spontaneous menstrual cycle within 60 days of their previous annual visit or if this timed blood draw was not possible within 2 months of the anticipated annual visit and then whenever was convenient. Blood pressure measurements were taken using a standard mercury sphygmomanometer when seated and after a minimum of 5 minutes of rest, and two sequential measurements were averaged. Waist circumference was measured with the respondents in nonrestrictive undergarments. Biochemical assays for triglycerides,<sup>33</sup> HDL-cholesterol,<sup>34</sup> glucose<sup>35</sup> and insulin<sup>35</sup> were performed on the serum samples obtained at baseline and at visits 1, 3–7.

The MetS was defined in accordance with the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII)<sup>36</sup> with racial/ethnic-specific cut points for waist circumference.<sup>1</sup> Any participant with at least three of the following components were considered to have the MetS: (a) waist circumference (  $\geq$  88 cm for African Americans and Caucasians and  $\geq$  80 cm for Chinese and Japanese); (b) triglycerides level  $\geq$  150 mg/dL; (c) HDL-cholesterol levels  $<$  50 mg/dL; (d) systolic blood pressure (SBP)  $\geq$  130 mm Hg, diastolic blood pressure (DBP)  $\geq$  85 mm Hg, or self-reported use of antihypertensive medications; and (e) fasting glucose levels  $\geq$  110 mg/dL or self-reported use of antidiabetic medication (insulin or oral agents).

## Covariates

Self-reported race/ethnicity, education, age at menarche, parity, age when first child was born, family history of breast cancer, prior oral contraceptive use and prior exogenous hormone use (e.g. fertility drugs, estrogens or progestins, hormone patches or creams, hormone injections or post-menopausal hormones) were obtained at the baseline examination. Age was calculated based on the date of the index mammogram. Time-dependent covariate data, such as body mass index (BMI, in kg/m<sup>2</sup>), menopausal status, diabetes status, insulin resistance, physical activity, alcohol consumption, smoking status and annual household income, were obtained from the SWAN visit closest in time to the mammogram date.

BMI was calculated from measurements of weight and height that were obtained with a calibrated scale and a stadiometer at each visit. Menopausal status was based on response to questions on date of last menstrual bleeding, changes in regularity of bleeding, menopausal hormone therapy (MHT) use and hysterectomy and oophorectomy at each visit as follows: 1) premenopause: a menstrual period within the past three months with no change in regularity; 2) early perimenopause: a menstrual period within the past three months but with a change in cycle lengths; 3) late perimenopause: no menstrual bleeding for three to 11 months; 4) postmenopause: no menstrual bleeding for at least 12 months; 5) surgical menopause: hysterectomy and/or bilateral oophorectomy; and 6) undetermined: use of MHT prior to 12 months of amenorrhea.

Diabetes status and insulin resistance were based on fasting serum samples obtained at baseline and at visits 1, 3–7. Diabetes status was determined by glucose levels  $\geq$  126 mg/dL or self-reported use of antidiabetic medication (insulin or oral agents). Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR).<sup>37</sup>

Physical activity was assessed using the Kaiser Physical Activity Survey<sup>38</sup> at baseline and at visits 3, 5 and 6. Physical activity information associated with sports/exercise activities was

used in this study because it more strongly correlated with the MetS than other activity domains (e.g., routine activities and household/child care) and moderate-to-vigorous activity had been shown to prevent the MetS.<sup>39</sup> The sports/exercise activity index was based on participant responses about frequency, duration, perceived physical exertion, and an activity-specific intensity code. The values ranged from 1 (lowest) to 5 (highest) and represented relative ranking of individuals.

Active smoke exposure was annually assessed using a self-administered questionnaire adapted from the American Thoracic Society.<sup>40</sup> Secondhand smoke (SHS) exposure for never smokers, defined as more than 1 hour of cumulative tobacco smoke exposure while at home, work, or other places within the past 7 days,<sup>41</sup> was assessed at baseline and at visit 3.

## Statistical analyses

The characteristics of the study population by metabolic status were compared using  $\chi^2$  tests for categorical variables and Student's t-test for continuous variables. General linear models were used to estimate the association between metabolic abnormalities and percent MD (index mammogram). Our primary analyses focused on percent MD because previous studies reported stronger associations for breast cancer risk with percent MD than area of dense breast tissue, after adjusting for body size.<sup>42</sup> We built two models with different primary independent variables: the first used presence or absence of the MetS and the second used each of the five components of the MetS. We included the following covariates in all adjusted models because these factors have been associated with MD in previous analyses<sup>43</sup> of this subcohort: age (continuous), BMI (continuous), race/ethnicity-study site (Caucasian-Oakland, Chinese-Oakland, Caucasian-Los Angeles, Japanese-Los Angeles, Caucasian-Pittsburgh, African American-Pittsburgh), parity (0, 1–2, 3), menopausal status (premenopausal, early perimenopausal), past use of oral contraceptive hormones (never, ever), smoking (never active/without SHS, never active/with SHS, former active, current active) and physical activity (continuous). Other covariates were then added to the MetS models individually, including annual household income (< \$50 K, \$50 K – \$75 K, \$75 K), age at menarche (<12, 12, 13, 14 years), prior use of exogenous hormones not including oral contraceptive use (never, ever) and alcohol consumption (abstainer, 1 drink/week). The addition of these covariates did not change the beta coefficient value for the MetS in minimally adjusted models by at least 10% and, therefore, were not included in the final adjusted model.

We performed a number of additional analyses. First, we examined interactions, e.g., whether the association between percent MD and the MetS varied by race/ethnicity (Caucasian, other), menopausal status (pre-, early peri-) or BMI (< 27.5, 27.5 kg/m<sup>2</sup>) using stratified analyses and the inclusion of interaction terms. Second, we performed two sensitivity analyses. One excluded women with diabetes at baseline, and the other used the American Heart Association (AHA)'s revised version of the NCEP-ATPIII definition of the MetS that included a lower threshold for raised fasting glucose of 100 mg/dL,<sup>1</sup> compared to 110 mg/dL.<sup>36</sup> Third, we modeled area of dense breast tissue and area of non-dense breast tissue as the outcome of interest; the variables were log transformed to normalize their distributions.

Longitudinal analyses were performed among a subset of women who had at least two mammograms (N = 728). We used mixed-effects linear models to estimate the annual change in percent MD and how the MetS or components of the MetS assessed at the index mammogram modified that change; time was modeled as years since the index mammogram. The average number of mammograms per woman was 5.3 (SD = 1.8, range 2–10 mammograms). The average follow-up from the index to last mammogram was 5.7 years (SD = 1.7; range = 0.9–9.3 years). In addition to the covariates included in the cross-



sectional models above, within-woman changes for BMI and menopausal status were calculated as the difference between the value at a subsequent assessment and the index value collected at the SWAN visit closest to the index mammogram and modeled as interactions with time. The change variable for menopausal status was defined as 1) no change in menopausal status, 2) premenopausal to early perimenopausal, 3) premenopausal to late perimenopausal, 4) early perimenopausal to late perimenopausal, 5) perimenopausal to naturally postmenopausal, 6) early perimenopausal to naturally postmenopausal and 7) became postmenopausal due to hysterectomy and/or bilateral oophorectomy or became undetermined due to use of MHT prior to 12 months of amenorrhea. The change by time interaction variables were evaluated only in the longitudinal models.

Statistically significant interactions in the final adjusted models were determined by  $p$ -values  $< 0.05$ . Statistical computing was conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, U.S.).

## Results

In the cohort of 790 women, approximately 50% were Caucasian, the average age was 46.4 years (SD = 3.0) and the median BMI was 24.1 kg/m<sup>2</sup> (IQR = 6.4) at the time of the index mammogram. A majority of the women were parous (82%), had used oral contraceptives (75%), abstained from alcohol (71%) and never smoked (68%) (Table I). Women with the MetS were more likely to be overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup>), have an earlier age at menarche, abstain from alcohol, be less physically active, be diabetic and have insulin resistance, compared to women without the MetS (Table I).

Lower mean percent MD was observed for women with the MetS and each component of the MetS, compared to those without the metabolic abnormality (Table II). Abdominal adiposity and reduced HDL-cholesterol were the most prevalent metabolic abnormalities among women with the MetS (Table II). Lower mean percent MD was observed among women with abdominal adiposity, regardless of their MetS status (Table II). For women with raised glucose, lower mean percent MD was only observed among those who had the MetS, although the interaction between raised glucose and the MetS was not statistically significant (Table II).

In multivariable cross-sectional analyses, lower percent MD was associated with the MetS, abdominal adiposity and raised glucose (\*\*\*\*\*Table III, Model 1). All associations were attenuated after adjustment for BMI (Table III, Model 2). Only the association with abdominal adiposity remained statistically significant. Similar results for all metabolic abnormalities were obtained with percent MD after excluding women with type 2 diabetes (N = 25) (Data not shown). An additional 13 women were classified with the MetS when we used a lower threshold of  $\geq 100$  mg/dL for determining raised glucose, in accordance with the AHA's revised NCEP-ATPIII definition.<sup>1</sup> The association between MetS and percent MD did not change with the less conservative definition ( $\beta = -2.4$ , SE = 1.8,  $P = 0.19$ ). No statistically significant interactions were observed between the MetS and race/ethnicity ( $P = 0.18$ ), menopausal status ( $P = 0.98$ ) or BMI ( $P = 0.36$ ) in its relation with percent MD.

We evaluated associations for non-dense and dense breast tissue area separately in multivariable models adjusted for BMI. Abdominal adiposity was positively associated with non-dense breast tissue area [ $\beta = 0.24$ , SE = 0.06,  $P < 0.001$ ], but not with dense breast tissue area [ $\beta = -0.01$ , SE = 0.08,  $P = 0.93$ ]. Raised glucose was not associated with non-dense [ $\beta = 0.08$ , SE = 0.08,  $P = 0.31$ ] or dense breast area [ $\beta = -0.13$ , SE = 0.10,  $P = 0.19$ ].

Our longitudinal analyses revealed an unadjusted mean annual decline of 1.1 (SD = 0.1) in percent MD. In analyses unadjusted for BMI, the MetS, abdominal adiposity and raised

glucose were associated with annual decline in percent MD (Table IV, Model 1). These associations were attenuated and lost statistical significance after adjusting for BMI (Table IV, Model 2). Abdominal adiposity was associated with a 0.34 point slower annual decline in percent MD, although the association had borderline statistical significance.

## Discussion

Using data from a multi-ethnic cohort of pre- and early perimenopausal women, we found a moderate inverse association between the MetS and percent MD; however, after adjusting for BMI, the strength of this association was greatly attenuated and it was no longer statistically significant. Examination of the relations between percent MD and each of the five components of the MetS revealed a statistically significant inverse association between percent MD and raised glucose, and abdominal adiposity. The inverse association between abdominal adiposity and lower percent MD remained statistically significant after controlling for BMI, although the effect size was roughly halved with the adjustment. In longitudinal models adjusted for BMI, abdominal adiposity lessened the annual decline in percent MD.

The inverse association between abdominal adiposity and percent MD after adjustment for BMI is consistent with findings from other studies.<sup>26, 44</sup> This inverse association is paradoxical to the positive association between abdominal adiposity and breast cancer, independent of BMI.<sup>18, 45</sup> One explanation for the paradox is that the effects of abdominal adiposity on breast cancer risk are not mediated by MD but via alternative pathways that are not represented by MD.<sup>46</sup> This notion is supported by our observation, as well as others,<sup>44</sup> that abdominal adiposity was positively associated with nondense breast area.

We found a modest inverse association between percent MD and raised glucose that did not reach statistical significance. There is evidence that metabolic conditions are associated with an increase in MD. Diabetic fibrous mastopathy is a rare complication of women with longstanding and often poorly controlled type I diabetes, and characterized by stromal fibrosis and, therefore increased MD.<sup>47</sup> To our knowledge no previous study examined high plasma glucose and mammographic density; however, our inverse association is consistent with some<sup>48</sup> but not all studies of MD in relation to diabetes.<sup>49</sup> Almost half (46%) of the women in our study with high glucose ( $\geq 110$  mg/dL) were also classified as diabetic. A cross-sectional study found diabetes to be associated with lower MD patterns (BIRADS, Breast Imaging Reporting and Data System) in pre- but not postmenopausal Native American women.<sup>48</sup> In contrast, a cross-sectional analysis using data from the large Minnesota Breast Cancer Family Study did not reveal a difference in percent MD by diabetes status in BMI-adjusted models in pre- or postmenopausal Caucasian women.<sup>49</sup> Findings from these studies, as well as our study, suggest that although raised glucose may be positively related to breast cancer risk,<sup>19</sup> the effects of glucose on breast cancer risk are not mediated by an increase in percent MD.

The lack of association between percent MD and raised triglycerides or low HDL-cholesterol observed in our study is consistent with a study in postmenopausal Caucasian women that adjusted for abdominal adiposity,<sup>50</sup> but conflicts with studies in premenopausal women.<sup>27–28</sup> In a small sample of premenopausal Caucasian women ( $N = 273$ ), Boyd *et al.* found an inverse association between triglyceride levels and percent MD after adjustment for age and BMI.<sup>28</sup> Boyd *et al.* also found a positive association for percent MD with HDL-cholesterol levels<sup>28</sup> that was consistent with another study in premenopausal Caucasian women conducted by Furberg *et al.*<sup>27</sup> Reasons for the discrepant findings across these studies may include residual confounding by abdominal adiposity, due to inadequate adjustment by using BMI as a measure of overall body size.

Our study was conducted among a multi-ethnic, community-based cohort of midlife women, and therefore, is likely to be more generalizable to the U.S. population than previous studies of primarily Caucasian women or among clinic-based populations. The strengths of our study included the longitudinal measurement of the MetS, MD and covariates by a specified protocol.<sup>29</sup> The interviewers and MD assessor were blind to MetS status of the women, thereby limiting differential misclassification of exposure, outcome and important confounders, such as weight and height for the calculation of BMI. Fasting measurements were based on plasma samples taken on days 2 to 5 of a spontaneous menstrual cycle among 82% of our cohort, thus reducing variability in measurements of reproductive hormones and glucose.<sup>27</sup> In addition, MD measurements were made using a planimeter assessment by a single expert with high reproducibility and accuracy.<sup>30-31</sup> She has been considered the standard expert against which computer-based methods have been evaluated.<sup>30-31</sup>

Our study also had limitations. Only a small percentage (15%) of our study population had the MetS, limiting our power to detect a small effect of the MetS or its components on MD, if an effect truly existed. For instance, we only had 54 women with high plasma glucose levels, which may account for the lack of statistical significance of our observed modest association on percent MD. Also, only a few women (N = 9) with normal BMI (BMI < 25 kg/m<sup>2</sup>) had the MetS, raising the question of whether results would be different in women with normal BMI. The later however, is less of a concern given that our findings for the MetS did not change when analyses were limited to women with BMI < 27.5 kg/m<sup>2</sup> (Data not shown).

It is possible that we were unable to observe the hypothesized positive association between the MetS or components of the MetS and percent MD because we did not evaluate the most relevant etiologic time period. There is more consistent epidemiologic evidence for the positive association between the MetS and postmenopausal breast cancer than with premenopausal breast cancer.<sup>2, 6</sup> Although we did not observe an association between the MetS and postmenopausal MD (Data not shown), we only had these data among 271 women. Thus, it remains a possibility that the MetS is related to an increase in breast cancer risk through a mechanism involving MD, but that we did not have enough statistical power to observe the positive association, if in fact it exists.

Contrary to our hypotheses, we did not observe a positive association between the MetS nor any of the components of the MetS and percent MD. In conclusion, our results do not support the hypotheses that metabolic abnormalities affect breast cancer risk through a mechanism that involves an increase in percent MD or amount of dense breast tissue among pre-and early peri-menopausal women.

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## Abbreviations

<b>AHA</b>	American Heart Association
<b>BMI</b>	body mass index



<b>HDL</b>	high-density lipoprotein
<b>HOMA-IR</b>	homeostasis model assessment of insulin resistance
<b>MHT</b>	menopausal hormone therapy
<b>MD</b>	mammographic density
<b>MetS</b>	metabolic syndrome
<b>NCEP-ATPIII</b>	National Cholesterol Education Program - Adult Treatment Panel III
<b>SD</b>	standard deviation
<b>SHS</b>	secondhand smoke
<b>SWAN</b>	Study of Women's Health Across the Nation

## References

1. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112:2735–52. [PubMed: 16157765]
2. Agnoli C, Berrino F, Abagnato CA, Muti P, Panico S, Crosignani P, Krogh V. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. *Nutr Metab Cardiovasc Dis*. 2010; 20:41–8. [PubMed: 19361966]
3. Maiti B, Kundranda MN, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. *Breast Cancer Res Treat*. 2010; 121:479–83. [PubMed: 19851862]
4. Healy LA, Ryan AM, Carroll P, Ennis D, Crowley V, Boyle T, Kennedy MJ, Connolly E, Reynolds JV. Metabolic Syndrome, Central Obesity and Insulin Resistance are Associated with Adverse Pathological Features in Postmenopausal Breast Cancer. *Clin Oncol (R Coll Radiol)*. 2010; 22:281–8. [PubMed: 20189371]
5. Pasanisi P, Berrino F, De Petris M, Venturelli E, Mastroianni A, Panico S. Metabolic syndrome as a prognostic factor for breast cancer recurrences. *Int J Cancer*. 2006; 119:236–8. [PubMed: 16450399]
6. Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, et al. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev*. 2010; 19:1737–45. [PubMed: 20615887]
7. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report*. 2009;1–7. [PubMed: 19634296]
8. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? *Am J Pathol*. 2006; 169:1505–22. [PubMed: 17071576]
9. Shukla A, Grisouard J, Ehemann V, Hermani A, Enzmann H, Mayer D. Analysis of signaling pathways related to cell proliferation stimulated by insulin analogs in human mammary epithelial cell lines. *Endocr Relat Cancer*. 2009; 16:429–41. [PubMed: 19153208]
10. Strange KS, Wilkinson D, Emerman JT. Mitogenic properties of insulin-like growth factors I and II, insulin-like growth factor binding protein-3 and epidermal growth factor on human breast epithelial cells in primary culture. *Breast Cancer Res Treat*. 2002; 75:203–12. [PubMed: 12353809]
11. Hu X, Juneja SC, Maihle NJ, Cleary MP. Leptin--a growth factor in normal and malignant breast cells and for normal mammary gland development. *J Natl Cancer Inst*. 2002; 94:1704–11. [PubMed: 12441326]

12. Tang X, Zhang Q, Shi S, Yen Y, Li X, Zhang Y, Zhou K, Le AD. Bisphosphonates suppress insulin-like growth factor 1-induced angiogenesis via the HIF-1 $\alpha$ /VEGF signaling pathways in human breast cancer cells. *Int J Cancer*. 2010; 126:90–103. [PubMed: 19569175]
13. Cao R, Brakenhielm E, Wahlestedt C, Thyberg J, Cao Y. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. *Proc Natl Acad Sci U S A*. 2001; 98:6390–5. [PubMed: 11344271]
14. Brown RS, Wahl RL. Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. *Cancer*. 1993; 72:2979–85. [PubMed: 8221565]
15. Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor- $\alpha$ , and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. *Am J Cardiol*. 2005; 96:92–7. [PubMed: 15979442]
16. Abdilla N, Tormo MC, Fabia MJ, Chaves FJ, Saez G, Redon J. Impact of the components of metabolic syndrome on oxidative stress and enzymatic antioxidant activity in essential hypertension. *J Hum Hypertens*. 2007; 21:68–75. [PubMed: 17066087]
17. Menon V, Ram M, Dorn J, Armstrong D, Muti P, Freudenheim JL, Browne R, Schunemann H, Trevisan M. Oxidative stress and glucose levels in a population-based sample. *Diabet Med*. 2004; 21:1346–52. [PubMed: 15569139]
18. Huang Z, Willett WC, Colditz GA, Hunter DJ, Manson JE, Rosner B, Speizer FE, Hankinson SE. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol*. 1999; 150:1316–24. [PubMed: 10604774]
19. Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schunemann HJ, Ram M, Freudenheim JL, Sieri S, Trevisan M, Berrino F. Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*. 2002; 11:1361–8. [PubMed: 12433712]
20. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst*. 2004; 96:1152–60. [PubMed: 15292387]
21. Russo A, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. *Eur J Cancer*. 2008; 44:293–7. [PubMed: 18055193]
22. Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, Neuhauser ML, Parker DR, Shikany JM, Stefanick ML, Thomson CA, Rohan TE. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:2046–53. [PubMed: 19567502]
23. Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, Hammond G, Minkin S. The association of breast mitogens with mammographic densities. *Br J Cancer*. 2002; 87:876–82. [PubMed: 12373602]
24. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 1998; 7:1133–44. [PubMed: 9865433]
25. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst*. 1995; 87:1622–9. [PubMed: 7563205]
26. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000; 11:653–62. [PubMed: 10977110]
27. Furberg AS, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, Ellison PT, Thune I. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:33–40. [PubMed: 15668473]
28. Boyd NF, Connelly P, Byng J, Yaffe M, Draper H, Little L, Jones D, Martin LJ, Lockwood G, Tritchler D. Plasma lipids, lipoproteins, and mammographic densities. *Cancer Epidemiol Biomarkers Prev*. 1995; 4:727–33. [PubMed: 8672989]
29. Sowers, MF.; Crawford, S.; Sternfeld, B.; Morgenstein, D.; Gold, EB.; Greendale, G.; Evans, DB.; Neer, R.; Matthews, K.; Sherman, S.; Lo, A.; Weiss, G., et al. *Menopause: Biology and Pathobiology*. 1. New York, NY: Academic Press, Inc; 2000. SWAN: a multi-center, multi-ethnic,

- community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus R, eds; p. 175-88.
30. Haiman CA, Bernstein L, Berg D, Ingles SA, Salane M, Ursin G. Genetic determinants of mammographic density. *Breast Cancer Res.* 2002; 4:R5. [PubMed: 12052257]
  31. Ursin G, Astrahan MA, Salane M, Parisky YR, Pearce JG, Daniels JR, Pike MC, Spicer DV. The detection of changes in mammographic densities. *Cancer Epidemiol Biomarkers Prev.* 1998; 7:43–7. [PubMed: 9456242]
  32. Wellings SR, Wolfe JN. Correlative studies of the histological and radiographic appearance of the breast parenchyma. *Radiology.* 1978; 129:299–306. [PubMed: 704841]
  33. Steiner PM, Friedel J, Bremner WF, Stein EA. Standardization of Micro-Methods for Plasma-Cholesterol, Triglyceride and Hdl-Cholesterol with the Lipid Research Clinics Methodology. *J Clin Chem Clin Bio.* 1981; 19:850.
  34. Warnick GR, Albers JJ. A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res.* 1978; 19:65–76. [PubMed: 202660]
  35. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, Korenman S, Lasley WL, Luborsky JL, McConnell D, Sowers MF, Weiss G. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. *J Clin Endocrinol Metab.* 2005; 90:4836–45. [PubMed: 15840738]
  36. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002; 106:3143–421. [PubMed: 12485966]
  37. Haffner SM. Progress in population analyses of the insulin resistance syndrome. *Ann N Y Acad Sci.* 1997; 827:1–12. [PubMed: 9329738]
  38. Sternfeld B, Ainsworth BE, Quesenberry CP. Physical activity patterns in a diverse population of women. *Prev Med.* 1999; 28:313–23. [PubMed: 10072751]
  39. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome. *Sports Med.* 2004; 34:371–418. [PubMed: 15157122]
  40. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis.* 1978; 118:1–120. [PubMed: 742764]
  41. Coghlin J, Hammond SK, Gann PH. Development of epidemiologic tools for measuring environmental tobacco smoke exposure. *Am J Epidemiol.* 1989; 130:696–704. [PubMed: 2773917]
  42. Vachon CM, Brandt KR, Ghosh K, Scott CG, Maloney SD, Carston MJ, Pankratz VS, Sellers TA. Mammographic breast density as a general marker of breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:43–9. [PubMed: 17220330]
  43. Habel LA, Capra AM, Oestreicher N, Greendale GA, Cauley JA, Bromberger J, Crandall CJ, Gold EB, Modugno F, Salane M, Quesenberry C, Sternfeld B. Mammographic density in a multiethnic cohort. *Menopause.* 2007; 14:891–9. [PubMed: 17414171]
  44. Tseng M, Byrne C. Adiposity, adult weight gain, and mammographic breast density in US chinese women. *Int J Cancer.* 2010 (published online: 22 March 2010). 10.1002/ijc.25338
  45. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. *Obes Rev.* 2003; 4:157–73. [PubMed: 12916817]
  46. Boyd NF, Martin LJ, Sun L, Guo H, Chiarelli A, Hislop G, Yaffe M, Minkin S. Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:2086–92. [PubMed: 17119032]
  47. Soler NG, Khardori R. Fibrous disease of the breast, thyroiditis, and cheiroarthropathy in type I diabetes mellitus. *Lancet.* 1984; 1:193–5. [PubMed: 6141337]
  48. Roubidoux MA, Kaur JS, Griffith KA, Sloan J, Wilson C, Novotny P, Lobell M. Correlates of mammogram density in southwestern Native-American women. *Cancer Epidemiol Biomarkers Prev.* 2003; 12:552–8. [PubMed: 12815002]
  49. Sellers TA, Jensen LE, Vierkant RA, Fredericksen ZS, Brandt KR, Giuliano AR, Pankratz VS, Cerhan JR, Vachon CM. Association of diabetes with mammographic breast density and breast

- cancer in the Minnesota breast cancer family study. *Cancer Causes Control*. 2007; 18:505–15. [PubMed: 17437179]
50. Tamburrini AL, Woolcott CG, Boyd NF, Yaffe MJ, Terry T, Yasui Y, Jones CA, Patten SB, Courneya KS, Friedenreich CM. Associations between mammographic density and serum and dietary cholesterol. *Breast Cancer Res Treat*. 2010 (published online: 13 May 2010). 10.1007/s10549-010-0927-7

**Novelty and impact**

The metabolic syndrome is unlikely to affect breast cancer risk via a mechanism reflected by an increase in percent mammographic density. The findings contribute to the available data elucidating the biological mechanisms through which mammographic breast density affects breast cancer risk.



Table 1

Study population characteristics by metabolic syndrome status, Study of Women's Health Across the Nation, 1996–2004, N = 790

Characteristics <sup>1</sup>	Total Cohort <sup>2</sup>	Without Metabolic Syndrome <sup>2</sup>	With Metabolic Syndrome <sup>2</sup>	p value <sup>3</sup>
N (%)	790 (100)	675 (85)	115 (15)	
Mean age, years (SD)	46.4 (3.0)	46.4 (3.0)	46.8 (3.0)	0.14
Race/Ethnicity, %				<0.001
Caucasian	49	50	43	
African American	7	6	17	
Chinese	22	23	18	
Japanese	22	22	22	
Body mass index, kg/m, %				<0.001
< 25.0	59	67	8	
25.0–29.9	24	22	33	
30	18	11	59	
Annual household income \$75,000, %	45	46	37	0.16
Early perimenopausal, %	54	53	57	0.40
Ever use oral contraceptive, %	75	74	82	0.08
Ever use exogenous hormones, <sup>4</sup> %	13	14	11	0.38
Parity, %				0.06
Nulliparous	18	18	18	
1–2	59	60	50	
3	23	22	31	
Menarche at age < 12 years, %	21	20	29	0.03
Consume alcohol 1 drinks/week, %	29	32	16	<0.001
Smoking Status, <sup>5</sup> %				0.01
Never/no SHS	43	45	30	
Never/with SHS	25	24	32	
Former smoker	23	22	26	
Current smoker	9	8	12	
Mean sports/exercise activity (SD)	2.9 (1.0)	2.9 (1.1)	2.6 (0.9)	0.02
Diabetic, <sup>6</sup> %	3	1	18	<0.001
Insulin resistance, <sup>7</sup> %	25	16	78	<0.001

Abbreviations: BMI: body mass index; SD, standard deviation; SHS, secondhand smoke.

<sup>1</sup>Metabolic syndrome status, pre- or early perimenopausal status, BMI and smoking were based on data from the SWAN visit closest to index mammogram. Age was based on date of index mammogram.

<sup>2</sup>Percentages may not add to 100 due to rounding. Missing values for: parity (N = 1), income (N = 2), exogenous hormones (N = 4), alcohol (N = 1), smoking status (N = 2), insulin resistance (N = 2).

<sup>3</sup>p from  $\chi^2$  test (for categorical variables) or Students *t* test (for continuous variables) comparing with and without the metabolic syndrome

<sup>4</sup>Exogenous hormones other than birth control pills included fertility drugs, estrogens or progestins, hormone patches or creams, hormone injections or post-menopausal hormones.

<sup>5</sup>SHS exposure for never smokers defined as more than one hour of cumulative tobacco smoke exposure.

<sup>6</sup>Diabetes defined as fasting glucose level  $\geq 126$  mg/dl or taking insulin medication.

<sup>7</sup>Insulin resistance defined as the upper quartile of the homeostasis model assessment of insulin resistance ( $\geq 2.35$ ) index for non-diabetics in the study population.

Table 2  
 Mean percent mammographic density by prevalence of metabolic abnormalities, Study of Women's Health Across the Nation, 1996–2004, N = 790

Characteristics	Total									
	Without Metabolic Syndrome					With Metabolic Syndrome				
	N (%)	Mean (SD)	p value	N (%)	Percent MD	N (%)	Mean (SD)	p value	N (%)	Percent MD
Metabolic syndrome										
No	675 (85)	47.4 (19.3)		---	-----	---	-----		---	-----
Yes	115 (15)	27.4 (17.2)	<0.001	---	-----	---	-----		---	-----
Metabolic syndrome components										
Abdominal adiposity, ethnicity-specific waist circumference ( < 80 cm or > 88 cm) <sup>2</sup>										
No	530 (67)	51.2 (17.4)		526 (78)	51.2 (17.4)	4 (3)	47.0 (17.2)		4 (3)	47.0 (17.2)
Yes	260 (33)	30.7 (18.8)	<0.001	149 (22)	33.7 (19.6)	111 (97)	26.7 (16.9)	0.02	111 (97)	26.7 (16.9)
Raised blood pressure (SBP > 130 mm Hg, DBP > 85mm Hg or taking blood pressure medication)										
No	636 (81)	46.7 (19.7)		591 (88)	47.9 (19.4)	45 (39)	30.2 (16.9)		45 (39)	30.2 (16.9)
Yes	154 (19)	35.3 (20.0)	<0.001	84 (12)	43.4 (18.4)	70 (61)	25.6 (17.3)	0.16	70 (61)	25.6 (17.3)
Raised fasting plasma glucose ( > 110 mg/dL or taking insulin medication)										
No	736 (93)	45.6 (19.9)		655 (97)	47.4 (19.4)	81 (70)	30.5 (17.1)		81 (70)	30.5 (17.1)
Yes	54 (7)	29.1 (19.6)	<0.001	20 (3)	44.6 (16.1)	34 (30)	19.9 (15.3)	<0.01	34 (30)	19.9 (15.3)
Raised triglycerides ( > 150 mg/dL)										
No	649 (82)	46.5 (20.1)		616 (91)	47.7 (19.6)	33 (29)	23.9 (13.8)		33 (29)	23.9 (13.8)
Yes	141 (18)	35.1 (18.6)	<0.001	59 (9)	43.9 (15.3)	82 (71)	28.8 (18.3)	0.17	82 (71)	28.8 (18.3)
Reduced HDL-cholesterol (< 50 mg/dL)										
No	570 (72)	47.0 (19.5)		552 (82)	47.6 (19.2)	18 (16)	26.9 (15.6)		18 (16)	26.9 (15.6)
Yes	220 (28)	38.0 (20.9)	<0.001	123 (18)	46.2 (19.7)	97 (84)	27.5 (17.6)	0.90	97 (84)	27.5 (17.6)

<sup>1</sup> P-value for interaction by metabolic syndrome status.

<sup>2</sup> Waist circumference cut point < 88 cm was used for Caucasian and African American women and > 80 cm was used for Chinese and Japanese women.

Multivariable cross-sectional analyses of percent mammographic density<sup>1</sup> by metabolic abnormalities, regression coefficients and standard errors, Study of Women's Health Across the Nation, 1996–2004, N = 790

**Table 3**

Characteristics	Model 1 <sup>2</sup> (without BMI adjustment)		Model 2 <sup>3</sup> (with BMI adjustment)	
	$\beta$	(SE)	$\beta$	(SE)
Metabolic syndrome	-17.9	(1.9)	-2.5	(1.9)
Metabolic syndrome components				
Abdominal adiposity, ethnicity-specific waist circumference ( 80 cm or 88 cm) <sup>4</sup>	-17.4	(1.5)	-4.8	(1.9)
Raised blood pressure (SBP 130 mmHg or DBP 85 mmHg)	-3.05	(1.7)	-1.8	(1.6)
Raised fasting plasma glucose ( 110 mg/dL or taking insulin medication)	-8.08	(2.5)	-3.7	(2.4)
Raised triglycerides ( 150 mg/dL)	-2.11	(1.8)	-0.0	(1.7)
Reduced HDL-cholesterol (< 50 mg/dL)	-0.86	(1.5)	0.5	(1.4)
			<i>p</i> value	<i>p</i> value
			<0.001	0.19

<sup>1</sup>Values are maximum likelihood estimates of coefficients, standard error and *p* values for two separate models: one with the metabolic syndrome and a second model that included each of the metabolic syndrome components.

<sup>2</sup>Model 1 represents the adjusted model including age, menopausal status, race/ethnicity, study site, parity, oral contraceptive use, sports/exercise activity and smoking.

<sup>3</sup>Model 2 represents Model 1 with an additional adjustment for BMI (kg/m<sup>2</sup>).

<sup>4</sup>Waist circumference cut point 88 cm was used for Caucasian and African American women and 80 cm was used for Chinese and Japanese women.

Multivariable longitudinal analyses of percent mammographic density<sup>1</sup> by metabolic abnormalities, regression coefficients and standard errors, Study of Women's Health Across the Nation, 1996–2004, N = 726

**Table 4**

Characteristics	Model 1 <sup>2</sup> (without BMI adjustment)		Model 2 <sup>3</sup> (with BMI adjustment)	
	$\beta$	(SE)	$\beta$	(SE)
Metabolic syndrome	0.56	(0.16)	0.16	(0.18)
Metabolic syndrome components				
Abdominal adiposity, ethnicity-specific waist circumference ( 80 cm or 88 cm) <sup>4</sup>	0.60	(0.13)	0.34	(0.17)
Raised blood pressure (SBP 130 mmHg or DBP 85 mmHg)	-0.19	(0.14)	-0.22	(0.14)
Raised fasting plasma glucose ( 110 mg/dL or taking insulin medication)	0.46	(0.24)	0.35	(0.24)
Raised triglycerides ( 150 mg/dL)	0.21	(0.16)	0.14	(0.16)
Reduced HDL-cholesterol (< 50 mg/dL)	-0.11	(0.13)	-0.11	(0.13)

<sup>1</sup>Values are maximum likelihood estimates of coefficients for each variable's interaction with time, standard error and *p* values for two separate models: one with the metabolic syndrome and a second model that included each of the metabolic syndrome components.

<sup>2</sup>Model 1 represents the adjusted model for age, menopausal status, race/ethnicity, study site, parity, oral contraceptive use, sports/exercise activity, smoking and change in menopause status.

<sup>3</sup>Model 2 represents Model 1 with an additional adjustment for BMI (kg/m<sup>2</sup>) and change in BMI.

<sup>4</sup>Waist circumference cut point 88 cm was used for Caucasian and African American women and 80 cm was used for Chinese and Japanese women.