Published in final edited form as:
Cancer Causes Control. 2012 August ; 23(8): 1241–1251. doi:10.1007/s10552-012-0002-2.

Components of Metabolic Syndrome and Risk of Breast Cancer by Prognostic Features in the Study of Osteoporotic Fractures Cohort

Katherine W. Reeves[1,*], **Vicki McLaughlin**[1], **Lisa Fredman**[2], **Kristine Ensrud**[3,4], and **Jane A. Cauley**[5]

[1]Division of Biostatistics and Epidemiology, University of Massachusetts Amherst, Amherst, MA

[2]Department of Epidemiology, Boston University, Boston, MA

[3]Department of Medicine, Section of General Internal Medicine, Veterans Affairs Medical Center, Minneapolis, MN

[4]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

[5]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

Abstract

Purpose—Metabolic syndrome (MetS) and most of its components have been previously associated with increased breast cancer risk. We hypothesized that increasing number of MetS components would be positively associated with breast cancer risk.

Methods—Data were obtained from the Study of Osteoporotic Fractures, a prospective cohort of women age ≥65 enrolled between 1986 and 1988 and still being followed prospectively (N=8,956). MetS components evaluated at baseline were: elevated waist circumference, hypertension, and diabetes. Data were not available on hyperlipidemia. Incident breast cancers were confirmed by pathology report. We compared women with 0, 1, and 2 or 3 MetS components. We used Cox proportional hazards regression to calculate associations for breast cancer overall and classified by prognostic features.

Results—At baseline 28.8% of participants had 2 or 3 MetS components. Over an average follow-up of 14.4 years, 551 breast cancer cases were identified. Compared to those with no components, women with 2 or 3 components had increased breast cancer risk (hazard ratio [HR] 1.30, 95% confidence interval [CI] 1.01–1.68) and increased risk of ER+ (HR 1.48, 95% CI 1.09–2.03) and PR+ (HR 1.56, 95% CI 1.10–2.20) cancer, adjusting for age, hormone use, and family history of breast cancer. These results became attenuated and not statistically significant when additionally adjusted for body mass index.

Conclusions—MetS is associated with increased postmenopausal breast cancer risk, especially for ER+ and PR+ cancers, though this effect may not be independent of the effect of body mass index. Managing the components of MetS could be efficacious for breast cancer risk reduction.

Keywords

Metabolic Syndrome; Breast Cancer; Postmenopausal; Body Mass Index

[*]To whom correspondence should be addressed: Katherine W. Reeves, PhD, MPH, 410 Arnold House, 715 North Pleasant Street, Amherst, MA 01003, Phone: (413) 577-4298, Fax: (413) 545-1645, kwreeves@schoolph.umass.edu.

Introduction

Breast cancer represents nearly one-third of all cancers diagnosed among women in the United States [1]. Metabolic syndrome (MetS) is the coincidence of several risk factors for cardiovascular disease and diabetes, including central adiposity, elevated fasting blood glucose, elevated blood pressure, elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C) [2]. Presence of MetS has been associated with increased risk of cardiovascular disease and diabetes [3] and all-cause mortality [4]. There is growing interest in MetS as a risk factor for breast cancer, especially given the positive associations between obesity and insulin resistance and postmenopausal breast cancer.

The few published reports of MetS as a single risk factor for breast cancer provide inconsistent results, though they suggest that MetS may be positively associated with risk [5–8]. A large case-control study [7] and two nested case-control studies [5,8] reported 60–75% increases in postmenopausal breast cancer risk associated with MetS. Two prospective cohort studies reported positive, yet non-significant, associations with breast cancer risk [6,9]. Upon further analysis, one prospective study reported an increased risk among women age ≥60 [9], and the other reported increased risk with repeated instances of MetS [6]. Studies among breast cancer patients have reported that those with MetS were more likely to have node positive or later stage disease [10], triple-negative breast cancer (estrogen receptor [ER] negative, progesterone receptor [PR] negative, and human epidermal growth factor 2 [HER2] negative) [11], and an increased risk of recurrence [12].

Clearly, further evaluation of the MetS as a risk factor for breast cancer is needed. We tested the hypothesis that greater number of MetS components was associated with increasing risk of breast cancer or with prognostic features of breast cancer within the Study of Osteoporotic Fractures (SOF), a large, prospective cohort of Caucasian women age ≥65 on whom up to 20 years of follow-up data are available.

Methods

Study Population

The Study of Osteoporotic Fractures (SOF) is a prospective cohort study primarily intended to identify risk factors for osteoporotic fractures. The initial SOF cohort included 9,704 primarily Caucasian women and has been described previously [13,14]. Briefly, SOF participants were recruited from population-based lists, such as voter registration lists, between 1986 and 1988 from four U.S. locations: Baltimore, MD, Minneapolis, MN, Monongahela Valley near Pittsburgh, PA, and Portland, OR. Eligible women were age ≥65 years, ambulatory, and had not received a bilateral hip replacement. We excluded from the present analysis SOF participants with a history of breast cancer at enrollment (N=496) or with missing information on breast cancer during follow-up (N=252); the final analytic sample was 8,956. All women provided written informed consent, and this study was approved by institutional review boards at each participating institution. Additional approval for this analysis was given by the institutional review board at the University of Massachusetts Amherst.

Data Ascertainment

SOF participants attended clinical examinations at baseline and at approximate 2-year intervals throughout follow-up. Telephone interviews and mailed questionnaires were used to collect data outside of clinic visits. Weight and height were measured at baseline using a balance-beam scale and fixed stadiometer in light indoor clothing. Waist circumference was measured at baseline to the nearest 0.1 cm using a steel tape and following a standard

protocol; the average of two measurements was reported as the participant's waist circumference. Blood pressure was measured in the supine position using a mercury sphygmomanometer after at least a 5-minute rest. Participants self-reported their history of and medication use for hypertension and diabetes. Additional data on demographics, medical history, and health behaviors (e.g. age, family history of breast cancer, alcohol use, physical activity) were collected using self-administered questionnaires. For the present analysis, data from the baseline visit were used for all MetS variables and covariates, except for age at menarche, ever had a live birth, and age at first birth, which were collected at the year 2 visit. Follow-up data were available through August 2009, with an average follow-up of 14.4 years (standard deviation 6.0).

Metabolic Syndrome Variables

We considered the following components of MetS: central adiposity (defined as waist circumference ≥88 cm), hypertension (defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, or takes medications for high blood pressure), and diabetes (defined as self-reported diabetes, or takes medications for diabetes). Data were not available on hyperlipidemia for the full study population. These definitions are similar to the criteria used by previous analyses of MetS in SOF [4,15] and are consistent with recent guidelines for the diagnosis of MetS [2].

Ten (0.1%) subjects were missing measured blood pressure, but were able to be classified as hypertensive or not based on self-reported use of medications used to treat hypertension. Data on waist circumference were missing for 83 (0.9%) subjects, and 23 subjects (0.2%) were missing data on diabetes status. Multiple imputation (a set of 5 imputations) was used to fill in missing data for waist circumference and diabetes, using an imputation model incorporating waist circumference, BMI, diabetes, hypertension, and age. The multiple imputation estimates of waist circumference and diabetes were incorporated into the MetS variable. MetS was analyzed as a score indicating the number of MetS components and was categorized as 0, 1, and 2 or 3.

Data on triglycerides and HDL-C were available on 716 participants who were included in either a randomly-selected sub-cohort for a prospective fracture study [16] or a stroke case-control study [17]. Analyses were repeated using these data, which allowed for complete determination of the five components of MetS in this subgroup.

Breast Cancer Ascertainment

Incident breast cancer cases were initially self-reported at each follow-up visit with subsequent confirmation using medical records, hospital discharge summaries, pathology reports, and death certificates as described previously [13]. Greater than 98% of self-reported cases were confirmed and counted as breast cancer outcomes. Data on prognostic features, including stage at diagnosis, ER status, and PR status were collected from these sources. Follow-up on the cohort was 99% complete [18]. A total of 551 incident breast cancer cases were diagnosed in our study population.

Statistical Analysis

We compared the distribution of demographic characteristics and other risk factors across participants having 0, 1, or 2 or 3 of the components for MetS using analysis of variance and chi square tests for continuous and categorical variables, respectively. For these analyses we classified each participant using the mode of her MetS score calculated under the imputation model.

SAS procedure PROC MI was used to generate the multiple imputation estimates for MetS components. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the effect of MetS on risk of breast cancer for each set of imputed data (m=5). The results of these analyses were combined using SAS procedure PROC MIANALZE. This process results in valid statistical inferences that reflect the uncertainty due to missing values [19].

Potential confounders were selected based on their known relationship with breast cancer and statistical significance in an unadjusted Cox proportional hazards models. All potential confounders (listed in Table 1) were entered as covariates in the initial multivariable models, then non-significant covariates were systematically removed from the models one at a time, leaving variables significant at the 0.05 level or if their inclusion in the adjusted model resulted in a >10% change in the estimated HR for the MetS. Dummy variables were used as appropriate. The time variable in all models was time from enrollment to breast cancer diagnosis. Respondents not diagnosed with breast cancer were censored at their date of death or last available follow-up visit. Tests of trend for number of MetS components also were performed. The proportional hazards assumption was checked for each covariate and globally using scaled and unscaled Schoenfeld residuals, respectively. Plots of Cox-Snell residuals were used to assess overall model fit.

We performed variations on these analyses, including repeating analyses by length of follow-up time (<5 yrs, 5–<10 years, ≥10 years) and stratified by ER status, PR status, stage, and BMI; we excluded in situ cases from analyses stratified by hormone receptor status. Analyses examining ER+ status as the outcome excluded ER- and unknown ER status cases from the sample; a similar method was applied for ER-, PR+, and PR- outcome models. Additionally, among breast cancer cases we compared the distribution of ER status, PR status, and stage between subjects with and without MetS.

Two-sided P values ≤0.05 were considered statistically significant. Stata version 10.0 (Stata Corporation, College Station, TX) or SAS version 9.2 (SAS Institute, Inc., Cary, NC) were used for the analyses.

Results

Of the 8,956 women included in this analysis, 2,037 (22.7%) had none of the MetS components at baseline, while 4,344 (48.5%) had one, 2,267 (25.3%) had two, and 308 (3.4%) had three components (Table 1). Presence of two or three components was considered as a single category in all analyses due to the small number of women with all three components. Women without any MetS components tended to be slightly younger (mean 70.2, SD 4.4) compared to those with one (mean 72.1, SD 5.4) and two or three components (mean 71.6, SD 5.0; p<0.001). Number of MetS components was significantly positively associated with greater body mass index and waist-to-hip ratio, number of live births, and history of breastfeeding. Number of MetS components was also inversely associated with education, smoking status, alcohol use, physical activity, and current hormone use. Women with two or three MetS components were more likely to report an age at menarche of <12 compared to women with fewer components. Among women with one MetS component, hypertension was the most common component (87.6%). Elevated waist circumference (92.2%) and hypertension (98.6%) were the most frequent components among women with two or three MetS components.

The majority of the 551 breast cancer cases were ER+ (86.3%) and PR+ (69.8%) (Table 2). Most cancers were diagnosed at an early stage (14.8% in situ, 58.2% stage I). No

statistically significant bivariate associations between number of MetS components and ER status (p=0.23), PR status (p=0.35), or stage (p=0.89) were observed.

Table 3 presents results of multivariable adjusted hazards ratios for all breast cancer cases and separately by disease characteristics. In a model adjusted for age, baseline hormone use, and family history of breast cancer (Model 1), a significant 30% increase in overall breast cancer risk was observed for women with two or three MetS components at baseline (95% CI 1.01–1.68) compared to those with none. In similar models we also observed statistically significant, positive associations for ER+ cases (HR 1.48, 95% CI 1.09–2.03) and PR+ cases (HR 1.56, 95% CI 1.10–2.20). Additional adjustment for BMI attenuated these associations and rendered them not statistically significant (Model 2). No statistically significant associations were observed for MetS with invasive, ER-, PR-, in situ, stage I, or stage II/III disease in any model. In Model 2 BMI was statistically significantly associated with overall (HR 1.04, 95% CI 1.01–1.07), invasive (HR 1.05, 95% CI 1.02–1.08), ER+ (HR 1.06, 95% CI 1.02–1.09), PR+ (HR 1.08, 95% CI 1.04–1.11), and stage I (HR 1.06, 95% CI 1.04–1.11) breast cancer, but not with ER- (HR 1.04, 95% CI 0.96–1.13), PR- (HR 0.99, 95% CI 0.94–1.05), in situ (HR 1.01, 95% CI 0.94–1.08), or stage II/II (HR 1.02, 95% CI 0.97–1.08) disease. Similar patterns were observed when stratified by age at baseline (<75 years, ≥75 years; data not shown).

We examined risk within 5 years, 5–10 years, or beyond 10 years of follow-up. Associations were strongest and statistically significant within 5 years of baseline, where presence of two or three MetS components was associated with an increase in overall risk (HR 1.63, 95% CI 1.01–2.63) and increases in risk of invasive (HR 1.76, 95% CI 1.03–2.99), ER+ (HR 2.63, 95% CI 1.33–5.21), and PR+ (HR 2.34, 95% CI 1.13–4.86) disease in models adjusted for age, current hormone use, and family history of breast cancer. Overall breast cancer risk 5–10 years after baseline was also increased with two or three MetS components, though of borderline statistical significance (HR 1.51, 95% CI 1.00–2.29), in this model. These significant associations were attenuated and non-significant upon additional adjustment for BMI, except in the case of ER+ disease (HR 2.39, 95% CI 1.08–5.28). We also observed elevated, though not statistically significant, risk of ER+ and PR+ disease 5–10 years after baseline. MetS components were unrelated to breast cancer risk 10 or more years after baseline (data not shown).

Among women with BMI <25.0 kg/m^2 or ≥25 kg/m^2, similar, though non-statistically significant, elevated overall breast cancer risk was observed with two or three MetS components in adjusted analyses (HR 1.29, 95% CI 0.64–2.59; HR 1.17, 95% CI 0.82–1.68, respectively). Further adjustment for BMI within each stratum did not substantively alter results among BMI <25.0 kg/m^2 (HR 1.31, 95% CI 0.65–2.66), but attenuated the association among BMI ≥25.0 kg/m^2 (HR 0.92, 95% CI 0.62–1.36). We further examined the joint distribution of BMI and MetS (Table 4). Compared to women with BMI <25.0 kg/m^2 and no MetS components, women with BMI ≥25.0 kg/m^2 and two or three MetS components had a 35% increase in overall breast cancer risk (95% CI 1.01–1.82). No elevation in risk was observed for BMI <25.0 kg/m^2 and one component or for BMI ≥25.0 kg/m^2 and no components. Elevated, but not statistically significant, overall breast cancer risk was observed for BMI <25.0 kg/m^2 and two or three components and for BMI ≥25.0 kg/m^2 and one component.

When each MetS component was examined separately, waist circumference ≥88 cm was associated with a borderline significant increased risk in overall breast cancer risk (HR 1.18, 95% CI 0.97–1.44) and statistically significant increased risk of ER+ (HR 1.30, 95% CI 1.03–1.66) and PR+ breast cancer (HR 1.51, 95% CI 1.16–1.97), adjusting for age, current hormone use, family history of breast cancer, diabetes, and hypertension (Table 5).

Similarly, diabetes was associated with a borderline significant increase in overall risk (HR 1.29, 95% CI 0.90–1.85), and a borderline significant increase in risk of ER+ (HR 1.47, 95% CI 0.98–2.21) and PR+ (1.50, 0.95–2.37) breast cancer. All of the aforementioned associations were slightly attenuated and of borderline significance after additional adjustment for BMI. Hypertension was not associated with breast cancer risk. No statistically significant associations were observed for waist circumference, diabetes, or hypertension with invasive disease, ER-, PR-, or stage (data not shown). We further examined associations between number of MetS components and breast cancer risk separately among groups of women without elevated waist circumference (N=6,105 with 356 cases), without diabetes (N=8,349 with 516 cases), or without hypertension (N=2,614 with 171 cases). Similar trends in positive associations with risk of overall, ER+, and PR+ disease were observed in these analyses, though many of the hazard ratios were not statistically significant, likely due to low power (data not shown).

Among the 716 participants on whom triglyceride and HDL-C data were available, 9.8% had zero, 25.8% had one, 24.9% had two, 21.1% had three, 14.9% had four, and 3.5% had five MetS components. Of participants originally classified as having three components, 92% had four or five components with the additional triglyceride and HDL-C data. A total of 47 breast cancers were diagnosed among this subgroup of participants with complete MetS data. In multivariable analyses (Model 1), HRs compared to women with no components were 1.83 (95% CI 0.5–6.15), for one or two components and 1.35 (95% CI 0.38–4.83) for three or more components. Additional adjustment for BMI yielded similar results (HR 1.97, 95% CI 0.58–6.65 and HR 1.87, 95% CI 0.497.14, respectively).

Discussion

In a large sample of older women followed for up to 20 years, we observed a statistically significant 30% increase in breast cancer risk among women with two or three components of MetS at baseline. In subgroup analyses this association was limited to risk of ER+ or PR+ disease, where risk was increased by approximately 50% compared to women with no MetS components at baseline. Presence of MetS components was not associated with stage of disease at diagnosis. Interestingly, these associations appeared to be driven by effects of elevated waist circumference and diabetes, but were unrelated to presence of hypertension. As the vast majority of women with only one component were hypertensive, the lack of association between hypertension and breast cancer risk may also explain the lack of association between having only one component of metabolic syndrome and breast cancer in our population.

The positive, statistically significant associations we observed were attenuated and rendered non-significant upon further adjustment for BMI, except in the case of ER+ disease diagnosed within 5 years after baseline. This may indicate that the effect of MetS on breast cancer risk is due to confounding by BMI. In analyses stratified on BMI, however, the number of MetS components remained a breast cancer risk factor, though not of statistical significance. The lack of statistical significance may be a reflection of limited statistical power. Further, the joint effect of elevated BMI and two or three MetS components was to increase risk 35% compared to normal BMI and no MetS components. These results may suggest that MetS confers an increased risk of breast cancer beyond that conferred by increased BMI, though these results should be interpreted with caution due to the small numbers of breast cancer cases in each group when stratified on BMI.

An alternate interpretation of our results is that MetS may be on the causal pathway linking elevated BMI to breast cancer risk, rather than a confounder. A true confounder bears a non-causal relationship to the exposure and/or disease under study; epidemiologic evidence

suggests that BMI may be causally related to both MetS and breast cancer. Additional research, with careful consideration of the impact of BMI, will be needed to determine whether or not MetS is an independent risk factor for postmenopausal breast cancer.

Few prospective studies have reported on the association between MetS and breast cancer risk. Our results are similar to those reported by Agnoli *et al.* in a nested case-control analysis [5]. In that study MetS increased breast cancer risk by approximately 60% in analyses not adjusted for BMI. Presence of three or more MetS components, as defined according to National Cholesterol Education Program guidelines, was associated with a non-significant 29% increased risk of postmenopausal breast cancer (95% CI 0.80–2.05) compared to less than three components, and presence of four or five components was associated with greater than a twofold increase in risk (HR 2.21, 95% CI 1.00–4.90) compared to no components. We were unable to assess the two components of MetS relating to triglyceride and HDL-C levels in the full study population, yet our results are consistent with their report of a 30% increase in risk for women with more than three components of MetS, though our association was statistically significant. Among the 716 participants in our population with complete MetS data, we observed a similar two-fold increase in risk, though our estimated hazard ratios were not statistically significant. These results should be interpreted with caution, however, due to the small number of participants and resulting breast cancer cases included. Capasso *et al.* [8] also reported a 31% increased risk of postmenopausal breast cancer associated with presence of three MetS components in a nested case-control study. Bjørge *et al.* [9] noted an increased risk associated with MetS only among women age ≥60, which is consistent with the characteristics of our study population. Their study included 287,320 women with 4,862 incident breast cancers. However, their definition of MetS was based on z-scores from the population distributions of each component, not on the 2009 harmonized definitions as in ours; thus, direct comparison of results is difficult. Overall, the existing literature and our study suggest an increased risk of breast cancer associated with MetS, which may be restricted to older women.

By contrast, an analysis of a sub-sample of Women's Health Initiative participants observed no association between MetS at baseline and later risk of breast cancer [6]. This sub-sample included a 6% random sample of Clinical Trial participants and a 1% sample of Observational Study participants who provided repeated fasting blood samples at specified intervals during follow-up. These analyses were adjusted for BMI, however, which may have obscured any relationship between MetS and breast cancer risk, as described above. Further, the WHI analyses were based on only 165 cases over a median 8 years of follow-up, thus lack of power is a possible explanation for the non-significant results. In analyses examining MetS as a time-dependent covariate, statistically significant, positive associations were observed for women having MetS three to five years prior to diagnosis and for those with repeated diagnoses of MetS during follow-up [6]. These findings agree with our report of MetS being most strongly related to breast cancer risk within the subsequent 5 years. It is unclear why MetS was not related to breast cancers diagnosed after 5 years. Given the tendency of women to gain weight and develop MetS with age, however, it is possible that baseline values of MetS components are not reflective of later values and thus the long-term association is attenuated as women without MetS at baseline likely developed at least one component of MetS during follow-up. Overall, the literature does provide support for an association between MetS and postmenopausal breast cancer risk, though the evidence is not overwhelmingly consistent.

Data relating MetS to breast cancer stage and subtypes are sparse. The aforementioned prospective studies did not examine risk of disease by hormone receptor status or stage. Other studies have reported a higher prevalence of MetS among breast cancer patients with

triple negative breast cancer compared to those without [11] and among those with later stage disease [10]. Our results are not consistent with these findings, which likely reflects a difference in examining risk of disease associated with MetS as opposed to prevalence of MetS among a group of women with breast cancer. However, we observed no association between ER status, PR status, or stage and number of MetS components among our breast cancer cases. In general, our observation of an increased risk of ER+ and PR+ disease associated with MetS is consistent with the literature on obesity and hormone receptor status, which notes an increased likelihood of ER+/PR+ disease among obese compared to non-obese women [20]. It is interesting to note that MetS remained a significant risk factor for ER+ disease within five years after baseline even after adjustment for BMI. Given the number of statistical comparisons made and the fact that all other associations were attenuated and rendered non-significant by adjustment for BMI, however, we cannot rule out the possibility that this finding is due to chance. We were unable to assess differences by HER2/neu status, as data were not available on this feature for the majority of cases.

Numerous biological mechanisms contribute to the association between obesity, MetS, and breast cancer risk; these have been reviewed in extensive detail by Vona-Davis *et al.* [21]. Effects of obesity and hyperinsulinemia on increasing circulating estrogen levels, decreasing sex hormone binding globulin levels, and altering levels of adiponectin and leptin appear to explain how MetS contributes to breast cancer development. Hypertension may affect breast cancer development through hormonal, inflammatory, and growth factor pathways [22], though epidemiologic data regarding hypertension and breast cancer risk are inconsistent [22–24]. Our analyses found no evidence of an independent effect of hypertension on breast cancer risk. Future research should strive to elucidate why the presence of multiple components of MetS appears to increase breast cancer risk beyond that conferred by presence of a single component of MetS, as well as to further investigate the very complex relationship between BMI, MetS, and breast cancer.

There are a number of limitations that must be considered when interpreting our results. We lacked data on triglyceride and HDL-C levels, and therefore we were only able to evaluate three of the five components of MetS recognized by the consensus panel. It is thus possible that some women classified as not having MetS in our analysis could have met criteria for one or two components of MetS had data on triglycerides and HDL-C been available. We estimated the extent of this misclassification by analyzing a subgroup of women with available triglyceride and HDL-C data. This analysis indicated that the number of MetS components increased for the majority of women. This misclassification of exposure would likely bias our results to the null. Also, the use of self-reported diabetes may have underestimated the prevalence of this condition, which also would have resulted in an underestimate of the true association between MetS and breast cancer risk. We also relied on only a single measurement of blood pressure to determine hypertension, which may have resulted in some misclassification. Additionally, the MetS components on which we did have data were measured only at baseline or year 2 on the entire cohort. Thus we were not able to account for changes in number of MetS components over time. Finally, though our study population included nearly 9,000 women, the vast majority (99%) was white and all women were age ≥65 at enrollment. Thus our results may not be generalizable to non-white or younger populations of women at risk for breast cancer.

Strengths of our study include the large, well-characterized study population on whom extensive follow-up data are available. The case ascertainment methodology and high rate of follow-up ensure that all true cases of breast cancer were captured. The prospective design of the study also prevents recall bias from affecting the results. Additionally, we were able to evaluate associations with subtypes of disease defined by ER and PR status and stage and to examine the associations at multiple lengths of follow-up.

Though our observational data cannot be considered conclusive, we do provide evidence of increased breast cancer risk, specifically for ER+ and PR+ breast cancer, associated with an increased number of MetS components, though the effect was not independent of BMI. Future prospective studies with data on all five components of MetS, and with careful consideration of the role of BMI, are needed to provide additional evidence for a relationship between MetS and breast cancer risk. Examining this association in younger and racially/ethnically diverse populations is also of substantial importance. MetS is a modifiable condition. Documenting its role as a risk factor for breast cancer could justify prevention and treatment of MetS as a means of breast cancer prevention and help to reduce the burden of breast cancer in the U.S. and globally.

Acknowledgments

Financial Support: The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: R01 AG005407, R01 AR35582, R01 AR35583, R01 AR35584, R01 AG005394, R01 AG027574, and R01 AG027576.

References

1. American Cancer S. Cancer Facts & Figures 2009. American Cancer Society, Inc; Atlanta: 2009.
2. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S, International Association for the Study of O . Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120 (16):1640–1645. [PubMed: 19805654]
3. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. International journal of obesity. 2008; 32(Suppl 2 Journal Article):S25–29. 2005. [PubMed: 18469839]
4. Hillier TA, Rizzo JH, Pedula KL, Cauley JA, Schwartz AV, Ensrud KE, Browner WS. Increased mortality associated with the metabolic syndrome in older women with diabetes. Diabetes care. 2005; 28 (9):2258–2260. [PubMed: 16123504]
5. 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(1):41–48. S0939-4753(09)00038-[pii]. 10.1016/j.numecd.2009.02.006 [PubMed: 19361966]
6. Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, Neuhouser 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(7):2046–2053. 1055-9965.EPI-09-0235 [pii]. 10.1158/1055-9965.EPI-09-0235 [PubMed: 19567502]
7. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, Negri E, La Vecchia C. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol. 201110.1093/annonc/mdr025
8. Capasso I, Esposito E, Pentimalli F, Crispo A, Montella M, Grimaldi M, De Marco M, Cavalcanti E, D'Aiuto M, Fucito A, Frasci G, Maurea N, Esposito G, Pedicini T, Vecchione A, D'Aiuto G, Giordano A. Metabolic syndrome affects breast cancer risk in postmenopausal women: National Cancer Institute of Naples experience. Cancer Biol Ther. 2011; 10 (12):1240–1243. [PubMed: 20935521]
9. Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, Haggstrom C, Stattin P, Engeland A. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev. 2010; 19(7):1737–1745.10.1158/1055-9965.epi-10-0230 [PubMed: 20615887]

10. 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(4):281–288. S0936-6555(10)00047-6 [pii]. 10.1016/j.clon.2010.02.001 [PubMed: 20189371]
11. Maiti B, Kundranda MN, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. Breast Cancer Res Treat. 2010; 121(2):479–483.10.1007/s10549-009-0591-y [PubMed: 19851862]
12. 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(1):236–238.10.1002/ijc.21812 [PubMed: 16450399]
13. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group.[see comment]. JAMA. 1996; 276 (17):1404–1408. [PubMed: 8892715]
14. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332 (12):767–773. [PubMed: 7862179]
15. Fredman L, Doros G, Cauley JA, Hillier TA, Hochberg MC. Caregiving, metabolic syndrome indicators, and 1-year decline in walking speed: results of Caregiver-SOF. The journals of gerontologySeries A, Biological sciences and medical sciences. 2010; 65 (5):565–572.
16. Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR. Hormonal predictors of bone loss in elderly women: a prospective study. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1998; 13(7):1167–1174.10.1359/jbmr.1998.13.7.1167 [PubMed: 9661081]
17. Browner WS, Lui LY, Cummings SR. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. J Clin Endocrinol Metab. 2001; 86 (2):631–637. [PubMed: 11158021]
18. Vogt MT, Cauley JA, Scott JC, Kuller LH, Browner WS. Smoking and mortality among older women: the study of osteoporotic fractures. Arch Intern Med. 1996; 156 (6):630–636. [PubMed: 8629874]
19. Rubin DB. Inference and Missing Data. Biometrika. 1976; 63:581–592.
20. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. Int J Cancer. 2009; 124(3):698–712.10.1002/ijc.23943 [PubMed: 18988226]
21. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev. 2007; 8(5):395–408. OBR396 [pii]. 10.1111/j.1467-789X.2007.00396.x [PubMed: 17716297]
22. Largent JA, Bernstein L, Horn-Ross PL, Marshall SF, Neuhausen S, Reynolds P, Ursin G, Zell JA, Ziogas A, Anton-Culver H. Hypertension, antihypertensive medication use, and breast cancer risk in the California Teachers Study cohort. Cancer Causes Control. 2010; 21(10):1615–1624.10.1007/s10552-010-9590-x [PubMed: 20526803]
23. Lindgren A, Pukkala E, Tuomilehto J, Nissinen A. Incidence of breast cancer among postmenopausal, hypertensive women. Int J Cancer. 2007; 121(3):641–644.10.1002/ijc.22689 [PubMed: 17372911]
24. Soler M, Chatenoud L, Negri E, Parazzini F, Franceschi S, la Vecchia C. Hypertension and hormone-related neoplasms in women. Hypertension. 1999; 34 (2):320–325. [PubMed: 10454461]

Table 1

Baseline characteristics of study population stratified by number of MetS components present, among 8956 participants from the Study of Osteoporotic Fractures [a]

Characteristic	Number of MetS Components			
	0 N=2037	1 N=4344	2 or 3 N=2575	P value [b]
Age, years; Mean (SD)	70.2 (4.4)	72.1 (5.4)	71.6 (5.0)	<0.001
Education				<0.001
< High school	113 (5.5)	426 (9.8)	321 (12.5)	
High school	971 (47.7)	2280 (52.6)	1452 (56.6)	
> High school	951 (46.7)	1625 (37.5)	791 (30.9)	
White race	2029 (99.6)	4331 (99.7)	2569 (99.8)	0.62
Body mass index, kg/m^2; Mean (SD)	23.9 (2.9)	25.2 (3.5)	30.5 (4.2)	<0.001
Waist-to-hip ratio; Mean (SD)	0.78 (0.05)	0.80 (0.06)	0.86 (0.06)	<0.001
Smoking Status				<0.001
Never	1198 (59.1)	2629 (60.7)	1562 (60.9)	
Past	612 (30.2)	1238 (28.6)	809 (31.5)	
Current	217 (10.7)	466 (10.7)	196 (7.6)	
Alcoholic drinks per week[c]				<0.001
0	760 (37.3)	1909 (44.0)	1384 (53.8)	
0.125 – 0.25	227 (11.2)	479 (11.0)	263 (10.2)	
0.3125 – 1.5	589 (28.9)	966 (22.2)	498 (19.3)	
1.5 – 39.25	461 (22.6)	990 (22.8)	430 (16.7)	
Physical activity per week, kcal[c]				<0.001
0 – 464.0	305 (15.1)	1008 (23.4)	865 (33.8)	
464.1 – 1092.8	488 (24.1)	1113 (25.8)	620 (24.3)	
1092.9 – 2172.0	573 (28.4)	1097 (25.4)	583 (22.8)	
2172.1 – 18282.0	655 (32.4)	1096 (25.4)	488 (19.1)	
Age at menopause, years				0.07
<30	15 (0.7)	36 (0.8)	27 (1.0)	
30 – 39	88 (4.3)	224 (5.2)	142 (5.5)	
40 – 49	732 (36.0)	1620 (37.3)	881 (34.3)	
50 – 59	837 (41.1)	1659 (38.2)	998 (38.8)	
≥60	9 (0.4)	25 (0.6)	15 (0.6)	
Don't know	355 (17.5)	778 (17.9)	510 (19.8)	
Number of live births				<0.001
0	401 (19.7)	859 (19.8)	418 (16.3)	
1	274 (13.4)	669 (15.4)	376 (14.6)	
2	553 (27.2)	1203 (27.7)	663 (25.8)	
3	405 (19.9)	829 (19.1)	548 (21.3)	
≥4	403 (19.8)	783 (18.0)	567 (22.0)	
Ever breastfed a child	1141 (56.1)	2459 (56.7)	1557 (60.6)	0.002

Characteristic	Number of MetS Components			
	0 N=2037	1 N=4344	2 or 3 N=2575	P value [b]
Age at menarche, years				<0.001
<12	217 (11.7)	421 (10.7)	345 (14.8)	
12	501 (27.0)	947 (24.1)	587 (25.3)	
13	537 (28.9)	1195 (30.5)	629 (27.1)	
14	326 (17.6)	787 (20.1)	452 (19.4)	
≥15	275 (14.8)	572 (14.6)	312 (13.4)	
Current hormone use	347 (17.6)	684 (16.3)	310 (12.6)	<0.001
Family history of breast cancer	275 (15.1)	555 (14.4)	324 (14.1)	0.58
MetS components				
Waist circumference ≥ 88 cm	0 (0.0)	480 (11.0)	2350 (92.2)	<0.001
Hypertension	0 (0.0)	3804 (87.6)	2538 (98.6)	<0.001
Diabetes	0 (0.0)	60 (1.4)	547 (21.3)	<0.001

[a] Numbers may not sum to 8956 due to missing data

[b] P values from analysis of variance for continuous variables and chi-square test for categorical variables

[c] Number of alcoholic drinks per week and physical activity were categorized as quartiles

Table 2

Description of breast cancer diagnosis and characteristics, among 551 cases diagnosed within the Study of Osteoporotic Fractures[a]

	Number of MetS Components				
	Total	**0**	**1**	**2 or 3**	**P value**
	N (%)	**N (%)**	**N (%)**	**N (%)**	
Breast cancer cases	551 (100.0)	134 (24.3)	242 (43.9)	175 (31.8)	0.10
ER status					0.23
Positive	385 (86.3)	89 (81.7)	167 (87.0)	129 (89.0)	
Negative	61 (13.7)	20 (18.3)	25 (13.0)	16 (11.0)	
PR status					0.35
Positive	303 (69.8)	71 (67.0)	125 (67.9)	107 (74.3)	
Negative	131 (30.2)	35 (33.0)	59 (32.1)	37 (25.7)	
Stage					0.89
In situ	76 (14.8)	19 (14.5)	36 (15.5)	21 (13.9)	
Stage I	299 (58.2)	73 (55.7)	139 (59.9)	87 (57.6)	
Stage II	120 (23.3)	33 (25.2)	51 (22.0)	36 (23.8)	
Stage III	19 (3.7)	6 (4.6)	6 (2.6)	7 (4.7)	

[a]Numbers may not sum to number of breast cancer cases due to unknown and missing data

Table 3

Estimated hazard ratios for the effects of MetS on breast cancer risk, among 8,956 participants from the Study of Osteoporotic Fractures

		Model 1[b]			Model 2[c]		
Number of MetS components	**Number of breast cancer cases [a]**	**Hazard Ratio**	**95% Confidence Interval**	**P value**	**Hazard Ratio**	**95% Confidence Interval**	**P value**
All breast cancers	551			0.14[d]			0.85 [d]
0	134	1.00	-	-	1.00	-	-
1	243	1.09	0.87, 1.38	0.45	1.03	0.81, 1.31	0.70
2 or 3	174	1.30	1.01, 1.68	0.04	0.99	0.72, 1.34	0.93
Invasive only	438			0.19[d]			0.22 [d]
0	112	1.00	-	-	1.00	-	-
1	197	1.04	0.81, 1.35	0.75	0.97	0.75, 1.26	0.83
2 or 3	129	1.17	0.88, 1.55	0.27	0.84	0.59, 1.18	0.31
ER Positive[e]	370			0.09 [d]			0.93 [d]
0	86	1.00	-	-	1.00	-	-
1	162	1.18	0.88, 1.58	0.27	1.08	0.81, 1.46	0.59
2 or 3	122	1.48	1.09, 2.03	0.01	0.99	0.68, 1.45	0.97
ER Negative[e]	55			0.46 [d]			0.30 [d]
0	19	1.00	-	-	1.00	-	-
1	20	0.56	0.29, 1.09	0.09	0.53	0.27, 1.04	0.06
2 or 3	16	0.65	0.30, 1.38	0.26	0.50	0.19, 1.29	0.15
PR Positive[e]	290			0.23 [d]			0.16 [d]
0	68	1.00	-	-	1.00	-	-
1	120	1.10	0.79, 1.53	0.57	0.97	0.70, 1.36	0.88
2 or 3	102	1.56	1.10, 2.20	0.01	0.89	0.58, 1.36	0.59
PR Negative[e]	123			0.43 [d]			0.82 [d]
0	34	1.00	-	-	1.00	-	-
1	54	0.94	0.59, 1.51	0.81	0.95	0.59, 1.54	0.85

		Model 1[b]			Model 2[c]		
Number of MetS components	**Number of breast cancer cases [a]**	**Hazard Ratio**	**95% Confidence Interval**	**P value**	**Hazard Ratio**	**95% Confidence Interval**	**P value**
2 or 3	35	0.95	0.56, 1.62	0.85	1.02	0.53, 1.95	0.95
In situ	76			0.23 [d]			0.35 [d]
0	19	1.00	-	-	1.00	-	-
1	36	1.28	0.68, 2.42	0.44	1.27	0.67, 2.41	0.47
2 or 3	21	1.34	0.66, 2.71	0.41	1.26	0.54, 2.94	0.60
Stage I	299			0.20 [d]			0.60 [d]
0	73	1.00	-	-	1.00	-	-
1	140	1.21	0.88, 1.65	0.24	1.11	0.80, 1.52	0.54
2 or 3	86	1.27	0.90, 1.80	0.18	0.84	0.55, 1.28	0.42
Stage II/Stage III	139			0.70 [d]			0.58 [d]
0	39	1.00	-	-	1.00	-	-
1	57	0.76	0.49, 1.19	0.23	0.74	0.47, 1.16	0.18
2 or 3	43	0.99	0.61, 1.61	0.98	0.84	0.46, 1.53	0.57

[a] Number of breast cancer cases by number of MetS components uses mode of multiply imputed data

[b] Model 1 adjusts for age, current hormone use, and family history of breast cancer

[c] Model 2 adjusts for BMI in addition to variables included in Model 1

[d] P value from a test of trend for increasing number of metabolic syndrome components

[e] Includes only invasive cases

Cancer Causes Control. Author manuscript; available in PMC 2013 August 01.

Table 4

Estimated hazard ratios for the joint effect of BMI and MetS components on overall breast cancer risk, N=8,956

	BMI<25.0 kg/m^2			BMI≥25.0 kg/m^2		
	Number of Subjects (Cases) [a,b]	Hazard Ratio[c]	95% Confidence Interval	Number of Subjects (Cases) [a,b]	Hazard Ratio[c]	95% Confidence Interval
Total	3,794 (206)			5.105 (342)		
0	1,356 (83)	1.00	-	671 (51)	1.14	0.77, 1.64
1	2,231 (114)	1.03	0.75, 1.41	2,088 (129)	1.26	0.94, 1.71
2 or 3	207 (9)	1.28	0.64, 2.57	2,346 (162)	1.35	1.01, 1.82

[a] Number of metabolic syndrome components uses mode of multiply imputed data

[b] Numbers do not sum to full dataset due to missing data on BMI at first visit (N=57; <1%)

[c] Hazard ratios are adjusted for age, current hormone use, and family history of breast cancer

Table 5

Estimated hazard ratios for the effects of each MetS component examined on breast cancer risk among 8,956 participants from the Study of Osteoporotic Fractures[a]

	Model 1[b]			Model 2[c]		
	Hazard Ratio	**95% Confidence Interval**	**P value**	**Hazard Ratio**	**95% Confidence Interval**	**P value**
All breast cancers						
Waist circumference ≥ 88 cm	1.18	0.97, 1,44	0.10	0.90	0.69, 1.18	0.44
Diabetes	1.29	0.90, 1.85	0.16	1.21	0.84, 1.76	0.30
Hypertension	1.05	0.86, 1.29	0.61	1.01	0.82, 1.24	0.93
Invasive only						
Waist circumference ≥ 88 cm	1.18	0.95, 1.48	0.14	0.89	0.66, 1.20	0.43
Diabetes	1.27	0.85, 1.91	0.24	1.18	0.77, 1.80	0.44
Hypertension	0.96	0.77, 1.21	0.74	0.92	0.73, 1.15	0.46
ER Positive[d]						
Waist circumference ≥ 88 cm	1.30	1.03, 1.66	0.03	0.91	0.66, 1.26	0.57
Diabetes	1.47	0.98, 2.21	0.07	1.35	0.88, 2.06	0.17
Hypertension	1.06	0.83, 1.37	0.63	1.00	0.78, 1.29	0.99
PR Positive[d]						
Waist circumference ≥ 88 cm	1.51	1.16, 1.97	<0.01	0.93	0.65, 1.34	0.70
Diabetes	1.50	0.95, 2.37	0.08	1.34	0.83, 2.17	0.22
Hypertension	0.96	0.73, 1.27	0.79	0.89	0.67, 1.18	0.42

[a] Hazard ratios are reported for waist circumference ≥88cm vs. waist circumference <88cm, diabetes vs. no diabetes, and hypertension vs. no hypertension

[b] Model 1 adjusts for age, current hormone use, family history of breast cancer, and other MetS criteria (e.g. waist circumference adjusted for diabetes and hypertension)

[c] Model 2 adjusts for BMI in addition to variables included in Model 1

[d] Includes invasive cases only