Published in final edited form as:

Breast Cancer Res Treat. 2014 November ; 148(2): 363–377. doi:10.1007/s10549-014-3157-6.

Metabolic syndrome and outcomes following early stage breast cancer

Gregory S. Calip, PharmD, MPH, PhD^{1,2,3}, Kathleen E. Malone, PhD, MPH^{2,3}, Julie R. Gralow, MD⁴, Andy Stergachis, PhD^{2,5}, Rebecca A. Hubbard, PhD^{6,7}, and Denise M. Boudreau, PhD, RPh^{2,7,8}

¹University of Illinois at Chicago, Center for Pharmacoepidemiology and Pharmacoeconomic Research, Chicago, IL, USA

²University of Washington Department of Epidemiology, Seattle, WA, USA

³Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, WA, USA

⁴Seattle Cancer Care Alliance, Seattle, WA, USA

⁵University of Washington, Department of Global Health, Seattle, WA, USA

⁶University of Washington, Department of Biostatistics, Seattle, WA, USA

⁷Group Health Research Institute, Seattle, WA, USA

⁸University of Washington, School of Pharmacy, Seattle, WA, USA

Abstract

Purpose—The prevalence of risk factors contributing to metabolic syndrome (MetS) is increasing, and numerous components of MetS are associated with increased primary breast cancer (BC) risk. However, less is known about the relationship of metabolic syndrome to BC outcomes. The aim of this study was to evaluate whether MetS, characterized by increased weight, hypertension, low HDL-cholesterol, high triglycerides and diabetes or impaired glucose tolerance, is associated with risk of second breast cancer events (SBCE) and BC-specific mortality.

Methods—Retrospective cohort study of women diagnosed with incident early stage (I–II) BC between 1990–2008, enrolled in an integrated health plan. Outcomes of interest were SBCE, defined as recurrence or second primary BC, and BC-specific mortality. We used multivariable Cox proportional hazards models to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for time-varying exposure to MetS components while accounting for potential confounders and competing risks.

Results—Among 4,216 women in the cohort, 26% had ≥ 3 MetS components and 13% developed SBCE during median follow-up of 6.3 years. Compared to women with no MetS components, presence of MetS (≥ 3 components) was associated with increased risk of SBCE (HR=1.50, 95%

Correspondence to: Dr. Gregory S. Calip, Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, 833 S. Wood St. M/C 871, Room 287, Chicago, IL 60612, USA. Tel: +1-312-355-5318, Fax: +1-312-996-2954; gcalip@fhcr.org.

Conflict of interest

The authors declare that they have no conflict of interest.

CI 1.08–2.07) and BC-specific mortality (HR=1.65, 95% CI 1.02–2.69). Of the individual components, only increased weight was associated with increased risk of SBCE (HR=1.26, 95% CI 1.06–1.49).

Conclusions—MetS is associated with modestly increased risk of SBCE and BC-specific mortality. Given the growing population of BC survivors, further research in larger and more diverse populations is warranted.

Keywords

Breast cancer; metabolic syndrome; recurrence; second primary breast cancer; mortality

Introduction

There are an estimated 2.8 million breast cancer (BC) survivors in the United States [1], among whom those with early stage BC have five-year survival rates of >90% [2]. These women are at ongoing risk for recurrences, second primary breast tumors and long-term sequelae related to their initial cancer and its treatment [2]. Accordingly, the recently updated American Society of Clinical Oncology guidelines on post-BC follow-up and management [3] describe a need for further evidence on subsets of patients that may benefit from BC survivorship care models, such as women with comorbid conditions [4].

A large fraction of breast cancers arise in older women, many of whom are also burdened with comorbidities such as obesity, diabetes mellitus (DM) and cardiovascular disease (CVD) [4]. Co-occurrence of risk factors for both DM and CVD, such as abdominal obesity, high blood pressure, dyslipidemias, and hyperglycemia, describes the clinical profile of risk for metabolic syndrome (MetS) [5,6]. The American Heart Association clinical definition of MetS is the presence of 3 of the following criteria: elevated waist circumference (≥ 88 cm in women), elevated blood pressure (BP $\geq 130/85$ mm Hg), reduced HDL-cholesterol (HDL <50 mg/dl), elevated triglycerides (TG ≥ 150 mg/dl), and elevated fasting glucose (FPG ≥ 100 mg/dl) [5,6].

MetS includes several comorbidities linked to BC etiology, particularly obesity and diabetes [7,8], although associations with these conditions in combination remain to be further substantiated by additional research [9]. Increased visceral and intra-abdominal fat often present with MetS is rich in aromatase [10], the converter enzyme of testosterone to estrogens that stimulate ductal cell proliferation, and is also a source of free fatty acids, antiapoptotic factors and reduced adiponectin [11]. Hyperinsulinemia and insulin resistance are hallmarks of MetS and reduce levels of insulin-like growth factor (IGF) binding proteins and raise bioavailability of IGF-1, a growth factor and gonadotrophic factor in BC that also inhibits hepatic synthesis of sex hormone binding globulin (SHBG) [12–14]. So, overweight, hyperinsulinemia and insulin resistance, and hormonal changes in postmenopausal women may contribute jointly to both MetS and breast carcinogenesis.

Comorbid conditions contributing to MetS, particularly DM and obesity, are not only risk factors for BC development but also appear to be risk factors for adverse outcomes after BC [15,16]. However, results from studies on MetS and BC outcomes have been inconsistent

and most studies have focused primarily on the evaluation of individual MetS components rather than the constellation of risk factors [17–19,9,20,16,15,21–25]. The objective of this study was to evaluate MetS constituents individually and in combination in relation to risk of second breast cancer events (SBCE) (i.e., recurrence and second primary BC) and BC-specific mortality.

Methods

Study population and setting

We conducted the study using an established cohort, the Commonly Used Medications and Breast Cancer Outcomes (COMBO) study, within Group Health (GH), a nonprofit integrated delivery system that provides comprehensive health care to approximately 600,000 individuals throughout Washington State and parts of Idaho. GH is located within the reporting region of the western Washington Cancer Surveillance System, a population-based cancer registry and member of the Surveillance, Epidemiology and End Results (SEER) program [26,27].

Eligibility, selection, and data collection for women in the COMBO study at GH have been described previously and are summarized in Figure 1 [28–30]. Briefly, the final cohort consisted of 4,216 women that were alive and recurrence-free for 120 days after completion of definitive surgery for incident BC and were (i) ages 18 years; (ii) residing within the 13 Washington State counties covered by SEER (iii) diagnosed with American Joint Committee on Cancer (AJCC) stage I or II BC; (iv) had no bilateral disease; and (v) continuously enrolled (<90 day lapse) in GH's integrated group practice for at least 1 year before and 1 year after incident BC diagnosis (unless they died).

Data were collected from one year before incident breast cancer diagnosis through the earliest of death, disenrollment from GH, or end of study (August 2011). Data collection was through health plan administrative databases including GH's Breast Cancer Screening Recruitment and Reminder (BSRR) survey on breast cancer risk factors at the time of each mammography [31], SEER, and medical record review (paper and electronic). SEER was the primary source of information for incident BC characteristics including diagnosis year, stage, lymph node status, hormone receptor status and tumor size. GH's administrative data files include demographics, enrollment, inpatient and outpatient diagnoses and procedures, breast services and results, pharmacy dispensing, laboratory results, vital signs, and death [32]. The pharmacy database includes all medications dispensed at GH's outpatient pharmacies as well as reimbursement claims from contracting pharmacies. Pharmacy data are estimated to be 97% complete [32–34]. Automated death data is from an ongoing link to Washington State death tapes [35]. The GH Institutional Review Board approved this study.

Exposure classification

Presence of MetS components, weight risk (proxy for elevated waist circumference) [36], hypertension, low HDL, high triglycerides, and DM or impaired glucose tolerance, were our main exposures of interest as described in Table 1. Exposure was further classified by number of MetS components to compare presence of 0 (reference), 1, 2, or 3 components.

All exposures were time-varying and allowed unidirectional transition only (e.g., number of MetS components present can increase but not decrease over time).

Outcomes

Main outcomes of interest were SBCE, defined as first of recurrence in any regional or distant sites or second primary ductal carcinoma in situ (DCIS) or invasive cancer of the ipsilateral or contralateral breast [37], and BC-specific mortality. Recurrence and second primary BC was determined by medical record review. Secondary outcomes included overall (all-cause) mortality.

Statistical analysis

We estimated hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards models to assess whether MetS components individually or in combination were associated with SBCE and BC-specific mortality while accounting for competing risks (i.e., death due to other causes) [38]. We modeled time from incident BC with left truncation at 120 days post-surgery to SBCE or death as a function of exposure to individual MetS components and number of MetS components present while adjusting for potential confounders. Individual events that comprise SBCE (i.e., recurrence and second primary BC) were modeled separately with the other outcome treated as a competing event [38]. Women were followed until first of SBCE, death, disenrollment or end of study. Overall mortality was modeled in a similar fashion but with no competing risks.

Estimates for individual MetS components were adjusted for presence of other MetS components. Women in the cohort with zero MetS components present were the reference category for comparison to 1, 2, and 3 MetS components present. All multivariable models were adjusted for confounders selected a priori, including incident BC diagnosis year, age, stage, hormone receptor status, primary BC treatment, chemotherapy, endocrine therapy (time-varying), race, smoking status, menopausal status and receipt of surveillance mammography [39] in prior 12 months (time-varying).

Proportional hazards assumptions were evaluated by testing the interaction between MetS components and the logarithm of follow-up time. There was no evidence suggesting violation of proportional hazards assumptions. All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC).

Sensitivity analyses

Our approach included use of data elements as surrogates for direct clinical measurement of MetS components (e.g., documented diagnosis in the medical chart) [40]. Therefore, we performed sensitivity analyses to describe the patterns of missing data among the covariates used to define exposure to MetS components. We evaluated our assumptions regarding reasons for missing data by applying multiple imputation under a missing at random assumption which yielded results similar to our main analysis for SBCE and BC-specific mortality, suggesting our data were robust to assumptions made with respect to exposure classification. As such, we present results from the main analyses only.

Results

The majority were postmenopausal (median diagnosis age: 63 years), Caucasian, non-Hispanic, never smokers, and had some college education or more and Charlson comorbidity score of zero (Table 2). A majority of the incident BC were AJCC stage I, node-negative, ER-positive/PR-positive, ≤ 2 cm in size, HER2-negative (if tested), treated with breast-conserving surgery $\pm$ radiation, not treated with chemotherapy, and treated with endocrine therapy. At baseline, 9% of women had ≥ 3 MetS conditions present (Online Resource 1) with 26% having ≥ 3 MetS conditions present throughout follow-up (Table 3). In women with ≥ 1 conditions during follow-up, the most prevalent conditions were weight risk (52%), hypertension (68%) and DM or impaired glucose tolerance (26%). The majority of women with ≥ 3 MetS conditions had the following three conditions: weight risk + hypertension + DM or impaired glucose tolerance (67%).

Median follow-up was 6.3 years (interquartile range, 3.7–9.7 years), which varied by diagnosis date with women diagnosed in earlier study years having longest follow-up.

Among the 4,216 eligible women, 13% experienced SBCE (first of $n=415$ recurrences and $n=143$ second primary BC) (Online Resource 2). Among recurrences, 67% were distant, 32% local or regional, and 1% DCIS. Among second primary BC, 21% were DCIS, 49% stage I, 21% stage II, 4% stages III or IV, and 5% unknown stage. Compared to women with no SBCE during follow-up, women experiencing a SBCE were more likely to have been diagnosed with AJCC stage II BC, be peri- or premenopausal, lymph node positive, ER and/or PR negative, tumor size >2 cm, HER2-positive, treated by mastectomy, treated with chemotherapy, not treated with endocrine therapy and have incident BC detected by diagnostic versus surveillance mammography. Overall, 6% of women experienced BC-specific death and 16% died due to other (non-BC-related) causes.

In multivariable models, we observed a dose-response relationship between number of MetS components and risk of SBCE, with risk for those with ≥ 3 MetS components significantly elevated compared to women with 0 MetS components (HR=1.50, 95% CI 1.08–2.07) (Figure 2). Weight risk (BMI ≥ 27.7 kg/m²), adjusted for other MetS conditions, was also independently associated with increased risk of SBCE (HR=1.37, 95% CI 1.14–1.64) (Figure 3). Associations with risk of recurrence were stronger for both ≥ 3 MetS conditions present (HR=1.65, 95% CI 1.15–2.38) and weight risk (HR=1.49, 95% CI 1.21–1.83). No statistically significant association was observed for second primary BC risk with ≥ 3 MetS conditions (HR=1.16, 95% CI 0.59–2.27) or weight risk (HR=1.25, 95% CI 0.88–1.77) but point estimates suggested potential increased risk. There were no significant associations between other MetS components and either SBCE or recurrence but point estimates suggested a possible increase in risk of second primary BC associated with high triglycerides.

The presence of ≥ 3 MetS components was associated with increased risk of BC-specific death (HR=1.65, 95% CI 1.02–2.69) compared to women with 0 MetS components (Figure 2). Weight risk was also associated with increased risk of BC-specific mortality (HR=1.36, 95% CI 1.04–1.78), whereas no other individual MetS components were significantly

associated with BC-specific mortality. Compared to women with 0 MetS components, presence of one (HR=1.17, 95% CI 1.00–1.38), two (HR=1.36, 95% CI 1.12–1.65) or 3 MetS components (HR=1.81, 95% CI 1.44–2.29) were associated with increased risk of overall mortality (Figure 2). Hypertension (HR=1.33, 95% CI 1.13–1.55) and DM or impaired glucose tolerance (HR=1.53, 95% CI 1.26–1.71) were also independently associated with a higher risk of death.

Discussion

In this population-based, retrospective cohort study, presence of 3 MetS components was associated with risk of recurrence and BC-specific mortality but not second primary BC. Of individual components, only weight risk was associated with increased risk of recurrence and BC-specific mortality; hypertension and DM or impaired glucose tolerance were associated with increased risk of overall mortality; and estimates suggested a possible increased risk of second primary BC with high triglycerides.

Few studies have examined combined MetS risk factors in relation to SBCE. Our observed association between 3 MetS components and recurrence is consistent with increased risk of recurrence reported by Pasanisi et al. [41] (HR=3.0, 95% CI 1.2–7.1) in a dietary intervention trial including 110 postmenopausal BC patients, although we observed a more modest increase in recurrence risk. Our findings of increased risk of SBCE with weight risk in MetS concur with other studies [22,23,21,16] reporting a relation between increased BMI and prognosis following BC but not others [20,24]. In a study of 18,967 women in a population-based Danish cohort, Ewertz et al. [16] reported no association between increased BMI and locoregional recurrence, but increased risk of distant metastases with BMI 25–29 kg/m² (HR=1.42, 95% CI 1.17–1.73) and BMI ≥30 kg/m² (HR=1.46, 95% CI 1.11–1.92) compared with BMI <25 kg/m². Our observed increased risk of BC-specific mortality with 3 MetS components and weight risk further supports our findings on increased risk of SBCE. Women in the Danish cohort [16] were also at increased risk of BC-specific mortality with BMI 25–29 kg/m² (HR=1.26, 95% CI 1.09–1.46) and BMI ≥30 kg/m² (HR=1.38, 95% CI 1.11–1.71) compared with BMI <25 kg/m².

DM along with obesity epitomizes MetS and the etiologic processes underlying the possible link with cancer [42,43]. Presence of DM can impact BC prognosis through the hypothesized role of insulin resistance and hyperinsulinemia in breast carcinogenesis, as well as through possible differences in treatment decisions and intensity of chemotherapy side effects and complications [44]. While our results were not statistically significant for DM, they suggest that DM but not impaired glucose tolerance may increase risk of recurrence and second primary BC. However, results from a retrospective cohort study of 3,124 women with stages I–III BC by Kiderlen et al. [45] suggest a decreased risk of recurrence in women with diabetes compared to women without diabetes (HR=0.77, 95% CI 0.59–1.01), particularly in ages ≥75 years (HR=0.67, 95% CI 0.45–0.98). One possible explanation for results indicating no association or possibly an inverse relationship is that adverse influences of DM or impaired glucose tolerance on BC prognosis could be counterbalanced by potential protective effects of some DM medications, such as metformin [46]. Kiderlen et al., suggested that the majority of women with DM in their study used

metformin. At GH, DM management largely includes metformin use, particularly in more recent years; throughout follow-up, 45% of women with DM had 1 pharmacy dispensings for metformin. However, these differences in our results in the context of these commonly used medications illustrate the need for larger epidemiological studies that examine the impact of treatment and control of MetS conditions as well as randomized trials of these medications in the adjuvant treatment setting [47] to help further substantiate their potential role in BC prognosis. Evaluating medications was out of scope for this study.

Studies evaluating MetS risk factors in relation to second primary BC risk are also limited. In our study, no statistically significant association was observed between number of MetS components and risk of second primary BC, although results were suggestive of an increased risk of second primary BC with weight risk and DM. The low number of second primary BC ($n=143$) that occurred in this cohort limited our ability to establish such a relation and future studies with greater power are needed to confirm potential associations between MetS components and second primary BC. Some studies describe increased risk of second primary BC with increased weight [48,24,49–51], but others report no association with increased BMI or obesity [52–54]. We observed a possibly increased risk of second primary BC with DM but not with impaired glucose tolerance only. In kind, a population-based case-control study [55] of women ages 40–79 years diagnosed with ER-positive, stages I–III, incident primary BC found that women with DM had an increased risk (OR=2.2, 95% CI 1.3–3.6) of second primary contralateral BC compared to women with no history of DM.

No other published studies have examined the role of hypertriglyceridemia (TG >150 mg/dl) specifically with risk of second primary BC. In our study, we observed an increased risk of second primary BC with elevated triglycerides (HR=8.38, 95% CI 1.04–67.69), although the estimate was unstable due to small sample sizes and should be interpreted cautiously. The role of serum triglycerides in BC is not clear, and studies examining primary BC incidence related to elevated triglycerides are inconsistent, showing no association in some prospective cohort studies [56,57], but a positive association in other cohort [58] and case-control studies [59,60]. There is suggestion that lipoprotein lipase may regulate clearance of triglycerides from blood to tissue and its activity in adipose tissue decreases in cancer patients, contributing to hypertriglyceridemia [61]. While tamoxifen is associated with reduced risk of second primary BC [62], tamoxifen and estrogen also have a known role in increasing serum triglyceride levels and sometimes inducing severe hypertriglyceridemia [63]. In light of the extremely elevated risk of second primaries that we observed with high triglycerides and elevated point estimates for SBCE and recurrence, additional studies are warranted in larger populations.

Risk of overall mortality in the general population is increased with MetS, and we observed increased risk of overall mortality with increasing number of MetS components and with DM and hypertension individually. In a large cohort study of 9,677 women ages 65 years [64], MetS defined by co-prevalence of DM, obesity and hypertension was associated with a 2.5-fold increased risk (95% CI 2.2–2.9) of overall mortality, as well as with presence of DM (HR=1.7 95% CI 1.4–1.9), obesity (HR=1.2 95% CI 1.1–1.4) and hypertension (HR=1.3 95% CI 1.2–1.4) individually. Also similar to our findings, a meta-analysis by

Peairs et al. [15] reported pre-existing diabetes in women with BC was associated with a 49% increased risk (95% CI 1.35–1.65) of all-cause mortality.

Strengths of this study include use of a well-characterized population-based cohort of BC survivors with comprehensive and high quality data on incident BC characteristics and treatment from both a validated registry and medical charts, health care utilization including medication use details and breast services, BC outcomes and death. Complete information on death, other cancers and disenrollment allows the application of robust analytic methods to address potential competing risks.

Our study is not without limitations. COMBO uses data from a single health plan and an insured and primarily Caucasian population. This may limit generalizability to some populations in the U.S., such as African American and Mexican American women where prevalence of MetS is estimated to be greater than in White women [65]. Loss to follow-up is a possible source of bias with 18% of women in the study censored due to disenrollment from the health plan. Also, residual confounding is possible in any observational study. We ascertained and considered the majority of potential confounders but lacked information on certain modifiable lifestyle factors such as diet and physical activity. We did not include adjustment for annual Charlson comorbidity scores in our main analysis because of the contribution of MetS components to their calculation. However, in sensitivity analyses, there was little change in risk estimates for SBCE and BC-specific mortality with adjustment for time-varying Charlson scores.

Our ability to detect associations between MetS components and SBCE is also limited by low occurrence of some events (i.e., second primary BC, 3.4%) and low prevalence of some MetS components (i.e., hypertriglyceridemia, 1.6%). We did not have information on duration of diseases at BC diagnosis because only one year of enrollment prior to BC diagnosis was required.

Conclusion

Our study examining MetS risk factors suggests that MetS is associated with a modestly increased risk of SBCE and BC-specific mortality that is concerning due to the growing population of BC survivors and prevalence of MetS risk factors. Understanding the role of MetS in relation to BC outcomes may be useful for prioritizing clinical care and management of these conditions following diagnosis and treatment of early stage BC with potential long-term survival. These findings highlight the considerable prevalence of comorbidities contributing to MetS among BC survivors and their potential impact on cancer-related outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (R01 CA120562 to D.M.B.) at Group Health Research Institute and the Cancer Prevention Training Grant in Nutrition, Exercise and Genetics (R25

CA094880) at the University of Washington and Fred Hutchinson Cancer Research Center. The authors are thankful to Ms. Onchee Yu and Dr. Heidi S. Wirtz for their help with statistical analyses.

References

1. American Cancer Society. Breast Cancer Facts & Figures 2013–2014. Atlanta: American Cancer Society, Inc; 2013.
2. American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2012–2013. Atlanta: American Cancer Society, Inc; 2012.
3. Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, Hantel A, Henry NL, Muss HB, Smith TJ, Vogel VG, Wolff AC, Somerfield MR, Davidson NE. American Society of Clinical O. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013; 31 (7):961–965.10.1200/JCO.2012.45.9859 [PubMed: 23129741]
4. Ritchie CS, Kvale E, Fisch MJ. Multimorbidity: an issue of growing importance for oncologists. *J Oncol Pract*. 2011; 7 (6):371–374.10.1200/JOP.2011.000460 [PubMed: 22379419]
5. 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. American Heart A, National Heart L Blood I. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005; 112 (17):2735–2752.10.1161/CIRCULATIONAHA.105.169404 [PubMed: 16157765]
6. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2010; 375 (9710):181–183.10.1016/S0140-6736(09)61794-3 [PubMed: 20109902]
7. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008; 371 (9612):569–578.10.1016/S0140-6736(08)60269-X [PubMed: 18280327]
8. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, Hartwick W, Hoffman B, Hood N. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002; 20 (1):42–51. [PubMed: 11773152]
9. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Giugliano D. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. *Menopause*. 2013; 20 (12):1301–1309.10.1097/GME.0b013e31828ce95d [PubMed: 23571527]
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. *Clinical oncology*. 2010; 22 (4):281–288.10.1016/j.clon.2010.02.001 [PubMed: 20189371]
11. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, Chou YC, Hsu GC, Yu CP, Yu JC, Sun CA. Anthropometric measures, plasma adiponectin, and breast cancer risk. *Endocrine-related cancer*. 2007; 14 (3):669–677.10.1677/ERC-06-0089 [PubMed: 17914097]
12. Baglietto L, Severi G, English DR, Krishnan K, Hopper JL, McLean C, Morris HA, Tilley WD, Giles GG. Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010; 19 (2):492–502.10.1158/1055-9965.EPI-09-0532 [PubMed: 20086116]
13. Kaaks R. Plasma insulin, IGF-I and breast cancer. *Gynecologie, obstetrique & fertilité*. 2001; 29 (3):185–191.
14. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*. 1998; 351 (9113):1393–1396.10.1016/S0140-6736(97)10384-1 [PubMed: 9593409]
15. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, Brancati FL, Wolff AC. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol*. 2011; 29 (1):40–46.10.1200/JCO.2009.27.3011 [PubMed: 21115865]
16. Ewertz M, Jensen MB, Gunnarsdottir KA, Hojris I, Jakobsen EH, Nielsen D, Stenbygaard LE, Tange UB, Cold S. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol*. 2011; 29 (1):25–31.10.1200/JCO.2010.29.7614 [PubMed: 21115856]

17. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *The American journal of clinical nutrition*. 2007; 86 (3):s823–835. [PubMed: 18265476]
18. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*. 2008; 300 (23):2754–2764.10.1001/jama.2008.824 [PubMed: 19088353]
19. Dignam JJ, Mamounas EP. Obesity and breast cancer prognosis: an expanding body of evidence. *Ann Oncol*. 2004; 15 (6):850–851. [PubMed: 15151938]
20. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, Holmberg SB, Lindtner J, Erien D, Collins J, Snyder R, Thurlimann B, Fey MF, Mendiola C, Werner ID, Simoncini E, Crivellari D, Gelber RD, Goldhirsch A. International Breast Cancer Study G. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Ann Oncol*. 2004; 15 (6):875–884. [PubMed: 15151943]
21. Chen X, Lu W, Zheng W, Gu K, Chen Z, Zheng Y, Shu XO. Obesity and weight change in relation to breast cancer survival. *Breast cancer research and treatment*. 2010; 122 (3):823–833.10.1007/s10549-009-0708-3 [PubMed: 20058068]
22. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? *Breast cancer research and treatment*. 2008; 111 (2): 329–342.10.1007/s10549-007-9785-3 [PubMed: 17939036]
23. de Azambuja E, McCaskill-Stevens W, Francis P, Quinaux E, Crown JP, Vicente M, Giuliani R, Nordenskjöld B, Gutierrez J, Andersson M, Vila MM, Jakesz R, Demol J, Dewar J, Santoro A, Lluch A, Olsen S, Gelber RD, Di Leo A, Piccart-Gebhart M. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. *Breast cancer research and treatment*. 2010; 119 (1):145–153.10.1007/s10549-009-0512-0 [PubMed: 19731015]
24. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst*. 2003; 95 (19):1467–1476. [PubMed: 14519753]
25. Jiralerspong S, Kim ES, Dong W, Feng L, Hortobagyi GN, Giordano SH. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. *Ann Oncol*. 2013; 24 (10):2506–2514.10.1093/annonc/mdt224 [PubMed: 23793035]
26. Cancer Surveillance System. <http://www.fhcrc.org/en/labs/phs/projects/cancer-surveillance-system.html>
27. Surveillance Epidemiology and End Results (SEER) Program Overview of the SEER Program. <http://seer.cancer.gov/about/overview.html>
28. Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJ, Fujii M, Buist DS. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. *Breast cancer research and treatment*. 2014; 144 (2):405–416.10.1007/s10549-014-2870-5 [PubMed: 24557337]
29. Wirtz HS, Buist DS, Gralow JR, Barlow WE, Gray S, Chubak J, Yu O, Bowles EJ, Fujii M, Boudreau DM. Frequent antibiotic use and second breast cancer events. *Cancer Epidemiol Biomarkers Prev*. 2013; 22 (9):1588–1599.10.1158/1055-9965.EPI-13-0454 [PubMed: 23833124]
30. Buist DS, Abraham LA, Barlow WE, Krishnaraj A, Holdridge RC, Sickles EA, Carney PA, Kerlikowske K, Geller BM. Breast Cancer Surveillance C. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer. *Breast cancer research and treatment*. 2010; 124 (3):863–873.10.1007/s10549-010-1106-6 [PubMed: 20700648]
31. Group Health Breast Cancer Surveillance Registry. [Accessed June 15, 2011] <http://www.grouphealthresearch.org/surveillanceproject>
32. Saunders, KW.; Davis, RL.; Stergachis, A. Group Health Cooperative. In: Strom, BL., editor. *Pharmacoepidemiology*. 4. J. Wiley; Chichester; Hoboken, NJ: 2005. p. 223-239.
33. Boudreau DM, Doescher MP, Jackson JE, Fishman PA, Saver BG. Impact of healthcare delivery system on where HMO-enrolled seniors purchase medications. *Ann Pharmacother*. 2004; 38 (7–8): 1317–1318.10.1345/aph.1D569 [PubMed: 15150379]

34. Buist DS, LaCroix AZ, Brenneman SK, Abbott T 3rd . A population-based osteoporosis screening program: who does not participate, and what are the consequences? *J Am Geriatr Soc.* 2004; 52 (7):1130–1137.10.1111/j.1532-5415.2004.52311.x [PubMed: 15209651]
35. Washington State Department of Health, Center for Health Statistics. [Accessed June 15, 2011] Death Data. <http://www.doh.wa.gov/ehsphl/CHS/chs-data/death/deatmain.htm>
36. Arterburn D, Ichikawa L, Ludman EJ, Operskalski B, Linde JA, Anderson E, Rohde P, Jeffery RW, Simon GE. Validity of Clinical Body Weight Measures as Substitutes for Missing Data in a Randomized Trial. *Obesity research & clinical practice.* 2008; 2 (4):277–281.10.1016/j.orcp.2008.09.002 [PubMed: 19956347]
37. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, Sparano JA, Hunsberger S, Enos RA, Gelber RD, Zujewski JA. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol.* 2007; 25 (15):2127–2132.10.1200/JCO.2006.10.3523 [PubMed: 17513820]
38. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care.* 2010; 48 (6 Suppl):S96–105.10.1097/MLR.0b013e3181d99107 [PubMed: 20473207]
39. Wirtz HS, Boudreau DM, Gralow JR, Barlow WE, Gray S, Bowles EJ, Buist DS. Factors associated with long-term adherence to annual surveillance mammography among breast cancer survivors. *Breast cancer research and treatment.* 2014; 143 (3):541–550.10.1007/s10549-013-2816-3 [PubMed: 24407530]
40. Bayley KB, Belnap T, Savitz L, Masica AL, Shah N, Fleming NS. Challenges in using electronic health record data for CER: experience of 4 learning organizations and solutions applied. *Med Care.* 2013; 51 (8 Suppl 3):S80–86.10.1097/MLR.0b013e31829b1d48 [PubMed: 23774512]
41. 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]
42. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab.* 2007; 92 (2):399–404.10.1210/jc.2006-0513 [PubMed: 17284640]
43. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care.* 2012; 35 (11):2402–2411.10.2337/dc12-0336 [PubMed: 23093685]
44. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. *Lancet Oncol.* 2005; 6 (2):103–111.10.1016/S1470-2045(05)01736-5 [PubMed: 15683819]
45. Kiderlen M, de Glas NA, Bastiaannet E, Engels CC, van de Water W, de Craen AJ, Portielje JE, van de Velde CJ, Liefers GJ. Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis. *Ann Oncol.* 2013; 24 (12):3011–3016.10.1093/annonc/mdt367 [PubMed: 24026538]
46. Peeters PJ, Bazelier MT, Vestergaard P, Leufkens HG, Schmidt MK, de Vries F, De Bruin ML. Use of metformin and survival of diabetic women with breast cancer. *Current drug safety.* 2013; 8 (5):357–363. [PubMed: 24215316]
47. Goodwin, PJ. ClinicalTrials.gov - A phase III randomized trial of metformin versus placebo on recurrence and survival in early stage breast cancer NCT01101438. [Accessed Feb 18, 2014]
48. Li CI, Daling JR, Porter PL, Tang MT, Malone KE. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. *J Clin Oncol.* 2009; 27 (32):5312–5318.10.1200/JCO.2009.23.1597 [PubMed: 19738113]
49. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, Somkin C, Wickerham DL. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. *Breast cancer research and treatment.* 2006; 97 (3):245–254.10.1007/s10549-005-9118-3 [PubMed: 16331345]
50. Li CI, Malone KE, Porter PL, Daling JR. Epidemiologic and molecular risk factors for contralateral breast cancer among young women. *Br J Cancer.* 2003; 89 (3):513–518.10.1038/sj.bjc.6601042 [PubMed: 12888823]

51. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. *Breast cancer research and treatment*. 2007; 105 (2):195–207.10.1007/s10549-006-9446-y [PubMed: 17186360]
52. Brooks JD, John EM, Mellemkjaer L, Reiner AS, Malone KE, Lynch CF, Figueiredo JC, Haile RW, Shore RE, Group WSC, Bernstein JL, Bernstein L. Body mass index and risk of second primary breast cancer: the WECARE Study. *Breast cancer research and treatment*. 2012; 131 (2): 571–580.10.1007/s10549-011-1743-4 [PubMed: 21892703]
53. Brooks JD, Bernstein L, Teraoka SN, Knight JA, Mellemkjaer L, John EM, Malone KE, Reiner AS, Lynch CF, Concannon P, Haile RW, Bernstein JL, Group WSC. Variation in genes related to obesity, weight, and weight change and risk of contralateral breast cancer in the WECARE Study population. *Cancer Epidemiol Biomarkers Prev*. 2012; 21 (12):2261–2267.10.1158/1055-9965.EPI-12-1036 [PubMed: 23033454]
54. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. *Am J Epidemiol*. 1992; 136 (8):925–936. [PubMed: 1456269]
55. Li CI, Daling JR, Tang MT, Malone KE. Relationship between diabetes and risk of second primary contralateral breast cancer. *Breast cancer research and treatment*. 2011; 125 (2):545–551.10.1007/s10549-010-1035-4 [PubMed: 20625814]
56. Gaard M, Tretli S, Urdal P. Risk of breast cancer in relation to blood lipids: a prospective study of 31,209 Norwegian women. *Cancer Causes Control*. 1994; 5 (6):501–509. [PubMed: 7827236]
57. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation*. 2001; 10 (1):33–42.
58. Hoyer AP, Engholm G. Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. *Cancer Causes Control*. 1992; 3 (5):403–408. [PubMed: 1525320]
59. Agurs-Collins T, Kim KS, Dunston GM, Adams-Campbell LL. Plasma lipid alterations in African-American women with breast cancer. *Journal of cancer research and clinical oncology*. 1998; 124 (3–4):186–190. [PubMed: 9619745]
60. Michalaki V, Koutroulis G, Syrigos K, Piperi C, Kalofoutis A. Evaluation of serum lipids and high-density lipoprotein subfractions (HDL2, HDL3) in postmenopausal patients with breast cancer. *Molecular and cellular biochemistry*. 2005; 268 (1–2):19–24. [PubMed: 15724433]
61. Ray G, Husain SA. Role of lipids, lipoproteins and vitamins in women with breast cancer. *Clinical biochemistry*. 2001; 34 (1):71–76. [PubMed: 11239519]
62. Bertelsen L, Bernstein L, Olsen JH, Mellemkjaer L, Haile RW, Lynch CF, Malone KE, Anton-Culver H, Christensen J, Langholz B, Thomas DC, Begg CB, Capanu M, Ejlersen B, Stovall M, Boice JD Jr, Shore RE, Bernstein JL. Women's Environment C, Radiation Epidemiology Study Collaborative G. Effect of systemic adjuvant treatment on risk for contralateral breast cancer in the Women's Environment, Cancer and Radiation Epidemiology Study. *J Natl Cancer Inst*. 2008; 100 (1):32–40.10.1093/jnci/djm267 [PubMed: 18159070]
63. Liu CL, Yang TL. Sequential changes in serum triglyceride levels during adjuvant tamoxifen therapy in breast cancer patients and the effect of dose reduction. *Breast cancer research and treatment*. 2003; 79 (1):11–16. [PubMed: 12779077]
64. 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]
65. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002; 287 (3):356–359. [PubMed: 11790215]

Figure 1.

Patient flow diagram showing Group Health Cooperative (GH) selection of women with stage I or II breast cancer diagnosed between 1990 and 2008 to the Commonly Used Medications and Breast Cancer Outcomes (COMBO) study cohort

Figure 2. Adjusted hazard ratios and 95% confidence intervals for the relation between number of metabolic syndrome components with risk of SBCE, breast cancer-specific mortality and overall mortality

Note: Reference group for all estimates is 0 MetS components. Hazard ratios are adjusted for age (18–39, 40–49, 50–59, 60–69, 70–79, 80+ years), incident breast cancer diagnosis year, AJCC stage (I, IIA, IIB), hormone receptor status (ER–/PR–, ER+/PR–, ER–/PR+, ER+/PR+), primary treatment for the initial breast cancer (mastectomy +/- radiation, BCS + radiation, BCS), chemotherapy (yes/no), endocrine therapy (yes/no, time-varying), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal), receipt of surveillance mammography (yes/no in prior 12 months, time-varying) as categorical variables; accounting for competing risks in multivariate-adjusted models. Tables of risk estimates with number of events and person-years in Online Resource 3 and 4.

A. Weight risk

B. Hypertension

C. Low HDL

D. High triglycerides

E. Diabetes or impaired glucose tolerance

F. Diabetes

G. Impaired glucose tolerance

Figure 3. Adjusted hazard ratios and 95% confidence intervals for the relation between individual metabolic syndrome components and risk of SBCE, breast cancer-specific mortality and overall mortality

Note: Hazard ratios are adjusted for age (18–39, 40–49, 50–59, 60–69, 70–79, 80+ years), incident breast cancer diagnosis year, AJCC stage (I, IIA, IIB), hormone receptor status (ER–/PR–, ER+/PR–, ER–/PR+, ER+/PR+), primary treatment for the initial breast cancer (mastectomy +/- radiation, BCS + radiation, BCS), chemotherapy (yes/no), endocrine therapy (yes/no, time-varying), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal), receipt of surveillance mammography (yes/no in prior 12 months, time-varying) as categorical variables; accounting for competing risks in multivariate-adjusted models. Tables of risk estimates with number of events and person-years in Online Resource 3 and 4.

Table 1

Classification of metabolic syndrome components

Weight risk	BMI ≥ 27.7 kg/m ² as a proxy for waist circumference ≥ 88 cm
Hypertension	2 blood pressure measurements $\geq 130/85$ mm Hg Hypertension diagnosis (2 ICD-9: 401.9 codes) in medical record Pharmacy dispensing of antihypertensive medication
Low HDL cholesterol	HDL laboratory value <50 mg/dl
Hypertriglyceridemia	TG laboratory value ≥ 150 mg/dl Hypertriglyceridemia diagnosis (2 ICD-9: 272.1 codes) in medical record Pharmacy dispensing of fibrates
Diabetes or impaired glucose tolerance	2 laboratory values FPG ≥ 100 mg/dl or HbA _{1C} $\geq 5.7\%$ Diabetes diagnosis (2 ICD-9: 250.00–93 codes) in medical record Pharmacy dispensing of medication to treat diabetes

Note: Women were classified as having specific MetS components as of the first date they met one of the following criteria for each component and were time-varying with unidirectional transition only.

Table 2

Descriptive characteristics of women in the COMBO cohort by SBCE status

	SBCE (N = 4,216)	
	No (n=3,658)	Yes (n=558)
Characteristics at diagnosis of initial breast cancer		
Year of diagnosis		
1990–1994	755 (20.6)	195 (34.9)
1995–1999	1,020 (27.9)	171 (30.6)
2000–2004	1,073 (29.3)	128 (22.9)
2005–2008	810 (22.1)	64 (11.5)
Years of follow-up		
Median (IQR)	6.7 (4.2–10.2)	6.4 (3.9–10.9)
Age at diagnosis, years		
Median (IQR)	63 (52–73)	62 (50–72)
18–39	112 (3.1)	27 (4.8)
40–49	544 (14.9)	102 (18.3)
50–59	866 (23.7)	129 (23.1)
60–69	889 (24.3)	129 (23.1)
70–79	824 (22.5)	116 (20.8)
80+	423 (11.6)	55 (9.9)
Menopausal status at diagnosis		
Peri- or premenopausal	956 (26.1)	189 (33.9)
Postmenopausal	2,702 (73.9)	369 (66.1)
Race		
White	3,232 (88.7)	487 (87.3)
African American	104 (2.9)	32 (5.7)
American Indian/Alaska Native	104 (2.9)	9 (1.6)
Asian/Pacific Islander	203 (5.6)	30 (5.4)
Unknown	15	0
Ethnicity		
Hispanic	209 (5.7)	20 (3.6)
Non-Hispanic	3,348 (94.3)	538 (96.4)
Unknown	11	0
Education		
High school or less	393 (23.5)	25 (21.4)
At least some college	1,279 (76.5)	92 (78.6)
Unknown	1,986	441
Body mass index (kg/m²)		
<18.5	55 (1.5)	14 (2.5)
18.5–24.9	1,269 (34.8)	184 (33.3)
25.0–29.9	1,186 (32.6)	176 (31.8)
30.0–34.9	666 (18.3)	100 (18.1)

	SBCE (N = 4,216)	
	No (n=3,658)	Yes (n=558)
35+	467 (12.8)	79 (14.3)
Unknown	15	5
Smoking status at diagnosis		
Current	230 (6.3)	23 (4.1)
Past	318 (8.7)	34 (6.1)
Never	3,110 (85.0)	501 (89.8)
Charlson score at diagnosis		
0	2,784 (76.1)	445 (79.7)
1	625 (17.1)	79 (14.2)
2+	249 (6.8)	34 (6.1)
AJCC stage		
I	2,384 (65.2)	264 (47.3)
IIA	906 (24.8)	172 (30.8)
IIB	368 (10.1)	122 (21.9)
Lymph node status		
Negative	2,525 (77.3)	322 (64.3)
Positive	739 (22.7)	179 (35.7)
Unknown	394	57
ER/PR status		
ER-/PR-	531 (14.5)	136 (24.4)
ER+/PR-	319 (8.7)	64 (11.5)
ER-/PR+	47 (1.3)	14 (2.5)
ER+/PR+	2,572 (70.3)	316 (56.6)
ER and/or PR unknown	189 (5.2)	28 (5.0)
Tumor size		
2 cm	2,785 (76.1)	325 (58.5)
>2 cm	873 (23.9)	231 (41.5)
Unknown	0	2
HER-2 test result		
Test done	1,874 (51.2)	200 (35.8)
Positive/Borderline	311 (16.6)	42 (21.0)
Negative	1,556 (83.0)	158 (79.0)
No result	7 (0.4)	0 (0.0)
Surgical procedure		
Mastectomy +/- radiation	1,289 (35.2)	232 (41.6)
BCS + radiation	1,927 (52.7)	245 (43.9)
BCS	442 (12.1)	81 (14.5)
Other treatment		
Chemotherapy	1,142 (31.2)	234 (41.9)
Completed course	1,003 (87.8)	209 (89.3)
Endocrine therapy	2,101 (57.4)	262 (47.0)

	SBCE (N = 4,216)	
	No (n=3,658)	Yes (n=558)
Characteristics throughout study period		
% of follow-up years with yearly surveillance mammogram		
<50%	793 (21.7)	146 (26.2)
50%–80%	1,284 (35.1)	155 (27.8)
>80%	1,581 (43.2)	257 (46.1)
# of MetS components		
0 present	635 (17.4)	122 (21.9)
1 only	1,173 (32.1)	163 (29.2)
2 only	937 (25.6)	136 (24.4)
3	913 (25.0)	137 (24.6)
Presence of MetS components ^a		
Weight risk ^b	1,901 (52.0)	309 (55.4)
Hypertension (HTN)	2,553 (69.8)	324 (58.1)
Low HDL cholesterol	901 (24.6)	138 (24.7)
High triglycerides	55 (1.5)	12 (2.2)
Diabetes (DM) or impaired glucose tolerance	966 (26.4)	141 (25.3)
DM diagnosed	539 (55.8)	90 (63.8)
Impaired glucose tolerance only	427 (44.2)	51 (36.2)
Weight risk + HTN	1,479 (40.4)	204 (36.6)
Weight risk + DM or impaired glucose tolerance	706 (19.3)	112 (20.1)
HTN + DM or impaired glucose tolerance	860 (23.5)	124 (22.2)
Weight risk + HTN + DM or impaired glucose tolerance	633 (17.3)	99 (17.7)

Note: Values are presented as *n* (%) unless otherwise noted; number of MetS components is presented as highest ever total throughout follow-up; presence of MetS components is presented as ever presence of single component or combination throughout follow-up.

Abbreviations: *SBCE*, second breast cancer events; *IQR*, interquartile range; *AJCC*, American Joint Committee on Cancer; *ER/PR*, estrogen and progesterone receptors; *BCS*, breast conserving surgery; *MetS*, metabolic syndrome; *HTN*, hypertension; *HDL*, high-density lipoprotein cholesterol; *DM*, diabetes mellitus; *HbA_{1C}*, glycosylated hemoglobin; *FPG*, fasting plasma glucose

^aMetabolic syndrome components defined as Weight risk: BMI ≥ 27.7 kg/m² as proxy for waist circumference ≥ 88 cm; Hypertension: ≥ 2 blood pressure measurements $\geq 130/85$, hypertension diagnosis and/or antihypertensive medications dispensed; Low HDL cholesterol: HDL <50 mg/dl; High triglycerides: TG ≥ 150 mg/dl, hypertriglyceridemia diagnosis or fibrates dispensed; DM or impaired glucose tolerance: ≥ 2 FPG ≥ 100 mg/dl and/or HbA_{1C} $\geq 5.7\%$, DM diagnosis or DM medications dispensed

^bArterburn D, Ichikawa L, Ludman EJ, et al: Validity of Clinical Body Weight Measures as Substitutes for Missing Data in a Randomized Trial. *Obes Res Clin Pract* 2:277–281, 2008

Table 3

Descriptive characteristics of women in the COMBO cohort by presence of metabolic syndrome components throughout follow-up

	0 MetS components (n=687)	1 MetS component (n=1,255)	2 MetS components (n=1,173)	3 MetS components (n=1,101)
Characteristics at diagnosis of initial breast cancer				
Year of diagnosis				
1990–1994	268 (39.0)	310 (24.7)	216 (18.4)	150 (13.6)
1995–1999	242 (35.2)	344 (27.4)	307 (26.2)	298 (27.1)
2000–2004	149 (21.7)	353 (28.1)	354 (30.2)	347 (31.5)
2005–2008	28 (4.1)	247 (19.7)	296 (25.2)	303 (27.5)
Years of follow-up				
Median (IQR)	8.3 (4.9– 12.5)	6.7 (3.9– 10.3)	6.4 (4.2– 9.8)	6.4 (4.0– 9.5)
Age at diagnosis, years				
Median (IQR)	52 (45–64)	63 (52–75)	65 (54–74)	65 (57–73)
18–39	59 (8.6)	48 (3.8)	22 (1.9)	10 (0.9)
40–49	233 (33.9)	184 (14.7)	141 (12.0)	88 (8.0)
50–59	172 (25.0)	290 (23.1)	267 (22.8)	266 (24.2)
60–69	108 (15.7)	255 (20.3)	303 (25.8)	352 (32.0)
70–79	79 (11.5)	284 (22.6)	306 (26.1)	271 (24.6)
80+	36 (5.2)	194 (15.5)	134 (11.4)	114 (10.4)
Menopausal status at diagnosis				
Peri- or premenopausal	363 (52.8)	330 (26.3)	261 (22.3)	191 (17.3)
Postmenopausal	324 (47.2)	925 (73.7)	912 (77.7)	910 (82.7)
Race				
White	606 (88.2)	1,135 (90.4)	1,035 (88.2)	943 (85.6)
African American	12 (1.7)	33 (2.6)	43 (3.7)	48 (4.4)
American Indian/Alaska Native	19 (2.8)	16 (1.3)	31 (2.6)	47 (4.3)
Asian/ Pacific Islander	47 (6.8)	67 (5.3)	63 (5.4)	56 (5.1)
Unknown	3	4	1	7
Ethnicity				
Hispanic	32 (4.7)	68 (5.4)	56 (4.8)	73 (6.6)
Non-Hispanic	650 (94.6)	1,182 (94.2)	1,116 (95.1)	1,028 (93.4)
Unknown	5	5	1	
Education				
High school or less	22 (13.1)	96 (19.5)	129 (23.1)	171 (30.0)
At least some college	146 (86.9)	396 (80.5)	430 (76.9)	399 (70.0)
Unknown	519	763	614	531
Body mass index (kg/m²)				
<18.5	31 (4.5)	27 (2.2)	9 (0.8)	2 (0.2)
18.5–24.9	530 (77.1)	681 (54.6)	190 (16.3)	52 (4.7)

	0 MetS components (n=687)	1 MetS component (n=1,255)	2 MetS components (n=1,173)	3 MetS components (n=1,101)
25.0–29.9	126 (18.3)	400 (32.1)	510 (43.8)	326 (29.7)
30.0–34.9	0 (0.0)	94 (7.5)	297 (25.5)	375 (34.2)
35+	0 (0.0)	45 (3.6)	158 (13.6)	343 (31.2)
Unknown	0	8	9	3
Smoking status at diagnosis				
Current	36 (5.2)	79 (6.3)	60 (5.1)	78 (7.1)
Past	22 (3.2)	81 (6.5)	118 (10.1)	131 (11.9)
Never	629 (91.6)	1,095 (87.3)	995 (84.8)	892 (81.0)
Charlson score at diagnosis				
0	626 (91.1)	1,053 (83.9)	922 (78.6)	628 (57.0)
1	55 (8.0)	164 (13.1)	179 (15.3)	306 (27.8)
2+	6 (0.9)	38 (3.0)	72 (6.1)	167 (15.2)
AJCC stage				
I	432 (62.9)	784 (62.5)	727 (62.0)	705 (64.0)
IIA	179 (26.1)	325 (25.9)	304 (25.9)	270 (24.5)
IIB	76 (11.1)	146 (11.6)	142 (12.1)	126 (11.4)
Lymph node status				
Negative	476 (75.1)	821 (74.8)	807 (76.7)	743 (75.7)
Positive	158 (24.9)	276 (25.2)	245 (23.3)	239 (24.3)
Unknown	53	158	121	119
ER/PR status				
ER–/PR–	122 (17.8)	187 (14.9)	187 (15.9)	171 (15.5)
ER+/PR–	76 (11.1)	142 (11.3)	90 (7.7)	75 (6.8)
ER–/PR+	18 (2.6)	19 (1.5)	12 (1.0)	12 (1.1)
ER+/PR+	423 (61.6)	842 (67.1)	826 (70.4)	797 (72.4)
ER and/or PR unknown	48 (7.0)	65 (5.2)	58 (4.9)	46 (4.2)
Tumor size				
2 cm	516 (75.1)	928 (73.9)	838 (71.4)	828 (75.2)
>2 cm	170 (24.7)	326 (26.0)	335 (28.6)	273 (24.8)
HER-2 test result				
Test done	181 (26.3)	605 (48.2)	646 (55.1)	642 (58.3)
Positive/Borderline	40 (22.1)	111 (18.3)	91 (14.1)	111 (17.3)
Negative	139 (76.8)	491 (81.1)	553 (85.6)	531 (82.7)
No result	506 (73.7)	650 (51.8)	527 (44.9)	459 (41.7)
Surgical procedure				
Mastectomy +/- radiation	258 (37.6)	459 (36.6)	423 (36.1)	381 (34.6)
BCS + radiation	343 (49.9)	633 (50.4)	606 (51.7)	590 (53.6)
BCS	86 (12.5)	163 (13.0)	144 (12.3)	130 (11.8)
Other treatment				
Chemotherapy	291 (42.4)	378 (30.1)	376 (32.1)	331 (30.1)
Completed course	254 (37.0)	337 (26.9)	342 (29.2)	279 (25.3)

	0 MetS components (n=687)	1 MetS component (n=1,255)	2 MetS components (n=1,173)	3 MetS components (n=1,101)
Endocrine therapy	342 (49.8)	708 (56.4)	666 (56.8)	647 (58.8)
Characteristics throughout study period				
% of follow-up years with yearly surveillance mammogram				
<50%	172 (25.0)	292 (23.3)	251 (21.4)	263 (23.9)
50%–80%	213(31.0)	463 (36.9)	423 (36.1)	426 (38.7)
>80%	302(44.0)	500 (39.8)	499 (42.5)	412 (37.4)
Presence of MetS components^a				
Weight risk ^b		321 (25.6)	876 (74.7)	1,013 (92.0)
Hypertension (HTN)		822 (65.5)	994 (84.7)	1,061 (96.4)
Low HDL cholesterol		85 (6.8)	242 (20.6)	712 (64.7)
High triglycerides		2 (0.2)	4 (0.3)	61 (5.5)
Diabetes (DM) or impaired glucose tolerance		25 (2.0)	230 (19.6)	852 (77.4)
DM diagnosed		10 (40.0)	87 (37.8)	532 (62.4)
Impaired glucose tolerance only		15 (60.0)	143 (62.2)	320 (37.6)
Weight risk + HTN			710 (60.5)	973 (88.4)
Weight risk + DM or impaired glucose tolerance			50 (4.3)	768 (69.8)
HTN + DM or impaired glucose tolerance			168 (14.3)	816 (74.1)
Weight risk + HTN + DM or impaired glucose tolerance				732 (66.5)

Note: Values are presented as *n* (%) unless otherwise noted; number of MetS components is presented as highest ever total throughout follow-up; presence of MetS components is presented as ever presence of single component or combination throughout follow-up.

Abbreviations: *SBCE*, second breast cancer events; *IQR*, interquartile range; *AJCC*, American Joint Committee on Cancer; *ER/PR*, estrogen and progesterone receptors; *BCS*, breast conserving surgery; *MetS*, metabolic syndrome; *HTN*, hypertension; *HDL*, high-density lipoprotein cholesterol; *DM*, diabetes mellitus; *HbA_{1C}*, glycosylated hemoglobin; *FPG*, fasting plasma glucose

^aMetabolic syndrome components defined as Weight risk: BMI ≥ 27.7 kg/m² as proxy for waist circumference ≥ 88 cm; Hypertension: ≥ 2 blood pressure measurements $\geq 130/85$, hypertension diagnosis and/or antihypertensive medications dispensed; Low HDL cholesterol: HDL <50 mg/dl; High triglycerides: TG ≥ 150 mg/dl, hypertriglyceridemia diagnosis or fibrates dispensed; DM or impaired glucose tolerance: ≥ 2 FPG ≥ 100 mg/dl and/or HbA_{1C} $\geq 5.7\%$, DM diagnosis or DM medications dispensed

^bArterburn D, Ichikawa L, Ludman EJ, et al: Validity of Clinical Body Weight Measures as Substitutes for Missing Data in a Randomized Trial. *Obes Res Clin Pract* 2:277–281, 2008