The Association between Cardiometabolic Risk Factors and Breast Cancer Outcomes

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ABSTRACT

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BACKGROUND: Prevalence of cardiometabolic risk factors contributing to metabolic syndrome is common, and numerous metabolic syndrome components are associated with increased primary breast cancer risk. However, less is known about their relation to breast cancer outcomes. In addition, adherence to chronic medications for metabolic syndrome risk factors such as diabetes is generally low and associated with adverse health outcomes. The growing population of breast cancer survivors and increasingly high prevalence of comorbidity warrants better understanding of medication adherence and clinical management. We sought to evaluate whether metabolic syndrome risk factors increase risk of second breast cancer events (SBCE) and breast cancer-specific mortality and describe whether adherence to oral diabetes medications and clinical control of diabetes vary prior to and following breast cancer treatment.

METHODS: We conducted a retrospective cohort study among female health plan enrollees ages ≥18 years diagnosed with stage I or II breast cancer between 1990-2008 via the Surveillance, Epidemiology, and End Results registry. Data sources included automated health plan data and medical records. We used Cox regression models to estimate the relation between metabolic syndrome components and SBCE (first of recurrence or second primary) and breast cancer-specific mortality while adjusting for potential confounders. We measured adherence and discontinuation of oral diabetes medications, biguanides (i.e., metformin) and sulfonylureas using medication possession ratios (MPR) and discontinuation rates (DR) in the year prior to incident cancer diagnosis, during treatment and the subsequent three years. We evaluated medication adherence (MPR ≥0.80), persistence (1–DR) and glycemic control (HbA_{1C} ≤7.0%) in corresponding periods.

RESULTS: Among the 4,216 women in the cohort, 26% had ≥3 metabolic syndrome components and 13% developed SBCE during follow-up. Presence of metabolic syndrome (≥3 components) was associated with increased risk of SBCE (HR 1.50, 95% CI 1.08-2.07) and increased risk of breast cancer-specific mortality (HR 1.65, 95% CI 1.02-2.69). Among the 509 oral diabetes medication users, the proportion of adherent users declined during breast cancer treatment (75.3% versus 24.6%, P<0.001), whereas the proportion of high HbA_{1C} (>7.0%) was increased in the year following treatment (34.9% versus 51.1%, P<0.001) compared with baseline.

CONCLUSION: Risk of SBCE and breast cancer-specific mortality may be altered by cardiometabolic risk factors contributing to metabolic syndrome. Adherence to oral medications for diabetes and glycemic control declines during and following breast cancer diagnosis. Further research in larger more diverse populations as well as other site-specific cancers and comorbidities is warranted.

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DEDICATION

For my parents, Manolita and Gil Calip, for their unconditional love and support.

INTRODUCTION

The Association between Cardiometabolic Risk Factors and Breast Cancer Outcomes

Breast cancer is the most frequently diagnosed cancer in women and the second most common cause of cancer mortality in the United States (U.S.).[1] Incidence of breast cancer increases with age,[1] as does the incidence and prevalence of chronic comorbid conditions including diabetes mellitus (DM) and cardiovascular disease (CVD).[2] The co-occurrence of risk factors contributing to these conditions, including obesity, hyperglycemia, dyslipidemias and high blood pressure, describes the clinical profile of metabolic syndrome (MetS).[3, 4] According to the International Diabetes Federation and American Heart Association, MetS is defined as ≥3 of the following risk factors: elevated waist circumference (≥88 cm in women), diagnosis of hypertension or elevated blood pressure (BP ≥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) or diagnosis of diabetes mellitus.[3, 4]

Previous studies, including meta-analyses, established associations between both individual MetS risk factors and MetS overall and increased risk of breast cancer incidence.[5] These factors, particularly DM and obesity, are not only risk factors for breast cancer development but also appear to be risk factors for adverse outcomes after breast cancer.[5-10] Hence, the effects of the individual and combined metabolic syndrome risk factors on breast cancer outcomes, including second breast cancer events (SBCE) and breast cancer-specific mortality, stand to be further substantiated and explained by additional research. The relative lack of documentation of some of these relationships is of concern given the estimated 2.8 million breast cancer survivors living in the U.S.,[11] and an aging population with multiple comorbidities.[12]

Poor clinical control of conditions included in the definition of MetS, such as hypertension and diabetes, and nonadherence to medications for these comorbidities all have a role in increasing

healthcare utilization, costs and all-cause mortality.[13, 14] The number and severity of comorbid conditions at the time of cancer diagnosis strongly influences the probability of dying from non-cancer causes and possibly cancer-specific survival.[2, 15-19] Also, stressful life events such as cancer diagnosis and the challenges related to transfer of care from oncology providers back to primary care providers can affect preventive care and chronic disease management.[20, 21] Older breast cancer survivors, for instance, are less likely to receive influenza vaccination, cholesterol screening, colorectal cancer screening, and bone densitometry.[22] Missing in studies of quality of care for comorbid conditions in breast cancer survivors is specific knowledge on trends in medication adherence and achieving treatment goals for conditions contributing to MetS, such as glycemic control in DM. Thus, questions remain whether prevention or improved control and pharmacotherapy for comorbid conditions will lead to improved cancer prognoses. Estimates of adherence to DM medications in the general population are considerably low, about 50-75% on average.[14, 23, 24] A better understanding of the influence of cancer on management of comorbidities and already poor adherence to chronic medication therapies is important to the growing population of breast cancer survivors and older women with comorbidities.

The overall objective of this dissertation is to (1) understand the relation between MetS risk factors and outcomes of early stage breast cancer and (2) how pharmacotherapeutic management of DM varies during and following breast cancer treatment. Results from studies of MetS risk factors related to breast cancer outcomes have been inconsistent and most studies have focused primarily on the evaluation of individual, specific components. To date, only a few studies have examined the role of multiple MetS risk factors or the full “syndrome” with regard to breast cancer prognosis.[25]

The specific aims of this research, as outlined below, underscore our overall goals to understand the etiology of cancer, improve breast cancer outcomes and improve the treatment of comorbidities among breast cancer survivors.

Aim I: To evaluate whether the risk factors that contribute to metabolic syndrome (MetS) individually or in combination increase risk of SBCE and breast cancer-specific mortality.

Aim II: To describe whether and how adherence to commonly prescribed DM medications and clinical control of DM vary during and following treatment of breast cancer.

Using data collected from Group Health Cooperative in a retrospective cohort study of 4,216 women diagnosed with incident early stage (I, II) invasive breast cancer between 1990 and 2008, we evaluated whether the risk factors that contribute to metabolic syndrome individually or in combination increase risk of SBCE, defined as the first of recurrence or second primary ductal carcinoma in situ or invasive cancer of the ipsilateral or contralateral breast,[26] and breast cancer-specific mortality. Additionally, comprehensively assessed clinical management of DM using automated pharmacy records and laboratory data to measure medication adherence and evaluate glycemic control among breast cancer survivors taking oral DM medications. As such, our study is one of the first of its kind to report longitudinal measures of adherence to oral DM medications and glycemic control during and following treatment of breast cancer.

Along with data on medication adherence and glycemic control in diabetes, knowledge about MetS and SBCE risk is potentially relevant to clinical practice. The medical community is familiar with the individual components of MetS, and motivations to improve breast cancer prognosis make the results of our study pertinent to oncology and primary care providers. If our findings are borne out and confirmed in other settings, then this knowledge could be used to raise awareness of the need for surveillance of comorbid conditions contributing to MetS and improve management of risk factors important to prevention of both cardiovascular and cancer-related outcomes in breast cancer survivors.

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CHAPTER 1

The Association between Metabolic Syndrome Risk Factors and Outcomes in Early Stage Breast Cancer

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ABSTRACT

BACKGROUND: Prevalence of cardiometabolic risk factors contributing to metabolic syndrome is increasing, and numerous components of metabolic syndrome are associated with increased primary breast cancer risk. However, less is known about their relation to breast cancer outcomes. The aim of this study was to evaluate whether metabolic syndrome, 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 breast cancer-specific mortality.

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

RESULTS: Among the 4,216 women in the cohort, 1,101 (26%) had ≥3 metabolic syndrome components and 558 (13%) developed SBCE during median follow-up of 6.3 years. Compared to women with no metabolic syndrome components, presence of metabolic syndrome (≥3 components) was associated with increased risk of SBCE (HR=1.50, 95% CI 1.08-2.07) and also breast cancer-specific mortality (HR=1.65, 95% CI 1.02-2.69). Of the individual components, only increased weight was associated with a significant increased risk of SBCE (HR=1.26, 95% CI 1.06-1.49).

CONCLUSIONS: Metabolic syndrome is associated with a modestly increased risk of SBCE and breast cancer-specific mortality. Given the growing population of breast cancer survivors, further research in larger and more diverse populations is warranted.

INTRODUCTION

There are an estimated 2.8 million breast cancer survivors in the United States,[1] among whom those with early stage breast cancer 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]

Breast cancer tends to arise in older women, many of whom are also burdened with comorbidities such as obesity, diabetes mellitus (DM) and cardiovascular disease (CVD).[3] The co-occurrence of risk factors for both DM and CVD (abdominal obesity, high blood pressure, dyslipidemias and hyperglycemia) describes the clinical profile of risk for metabolic syndrome (MetS).[4, 5] Clinical diagnosis of MetS according to the International Diabetes Federation and American Heart Association is made when ≥3 of the following criteria are present: elevated waist circumference (≥88 cm in women), elevated blood pressure (BP ≥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).[4, 5]

MetS includes several comorbidities linked to breast cancer etiology, particularly obesity and diabetes,[6, 7] although associations with the entire “syndrome” per se remain inconsistent.[8] Increased visceral and intra-abdominal fat often present with MetS is rich in aromatase,[9] 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.[10] Chronic 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 breast cancer that also inhibits hepatic synthesis of sex hormone binding globulin (SHBG).[11-13] So, overweight, hyperinsulinemia and insulin resistance, and hormonal changes in postmenopausal women may contribute jointly to both MetS and breast carcinogenesis. Relationships between breast cancer and the MetS components, hypertension, low HDL-cholesterol and hypertriglyceridemia, remain unclear.[14-18] However, the shared common pathophysiologic pathways in these three conditions and MetS overall in hormone synthesis, metabolism and growth factor signaling form a basis for their biologic role in breast cancer.[16] The role of TG in breast cancer could originate from altered lipid metabolism in malignant breast tissue or possibly through lowered concentrations of SHBG associated with hypertriglyceridemia, leading to an increased amount of

free estradiol.[15] In vitro studies have shown that low- and high-density lipoproteins stimulate the growth of human breast cancer cells, especially hormone-independent cells.[18] Alternatively, androgens have been found to lower HDL-cholesterol levels in women, and androgens have also been positively associated with breast cancer risk.[17]

Associations between some individual MetS risk factors and breast cancer risk are well documented. Obesity, usually defined by BMI, has been shown repeatedly to exert a modifying influence on breast cancer risk. Obesity has been consistently associated with an increased risk of postmenopausal breast cancer in population-based studies and has been inversely associated with premenopausal breast cancer risk.[6] The association between DM and increased risk of breast cancer is well documented with meta-analyses describing about a 20% increased risk of breast cancer in women with DM versus women without DM.[19] For markers of impaired glucose tolerance, typically measured by fasting plasma glucose (FPG) in epidemiological studies, higher FPG has been related to increased risk of breast cancer.[20-22] Epidemiological studies examining hyperinsulinemia, perhaps a mediating factor between impaired glucose tolerance and breast cancer, have shown that increased insulin levels are associated with risks of incident breast cancer, distant recurrence and death.[7]

Associations between other MetS risk factors and breast cancer risk are not as well established. Only a few studies[14, 23, 24] have examined the association between hypertension and breast cancer, some describing a possible increased risk of breast cancer in postmenopausal women[14] and others finding increased risk of breast cancer in peri- and premenopausal women only.[23] The roles of TG and HDL-cholesterol in breast cancer are still being debated. Prospective cohort studies have indicated either no association between higher TG levels and breast cancer[25, 26] or a positive association;[27] case-control studies showed higher triglyceride levels in women with breast cancer than in control women.[28, 29] Three studies have prospectively addressed the association between HDL and breast cancer incidence, with divergent results: one study[25] found no association, whereas the other two studies[16, 27] found a protective effect of higher HDL level on cancer risk. With the exception of one study[30], several case-control studies reported lower levels of HDL in women with breast cancer than in control women.[31-33] Together, these studies on individual components and a limited number of studies on the full “syndrome” support the

hypothesis of increased breast cancer risk associated with MetS. However, whether or not MetS is associated with SBCE and breast cancer-specific mortality remains uncertain.

Comorbid conditions contributing to MetS, particularly DM and obesity, are not only risk factors for breast cancer development but also appear to be risk factors for adverse outcomes after breast cancer.[34, 35] However, results from studies on MetS and breast cancer outcomes have been inconsistent and most studies have focused primarily on the evaluation of individual, specific components rather than the "syndrome" per se.[8, 34-44] The objective of this study was to evaluate the risk factors contributing to MetS individually and in combination in relation to second breast cancer events (SBCE) (i.e., recurrence and second primary breast cancer) and breast cancer-specific mortality.

METHODS

Study population

We conducted the study from a previously established cohort, the Commonly Used Medications and Breast Cancer Outcomes (COMBO) study,[45, 46] within Group Health (GH), a nonprofit integrated delivery system that provides comprehensive health care to approximately 620,000 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.[47] Women were included if they were: (i) ages ≥18 years; (ii) diagnosed with incident, histologically confirmed stage I or II breast cancer between January 1, 1990 and December 31, 2008 per the SEER registry; (iii) had no evidence of bilateral disease at the time of their first primary BC diagnosis per the SEER registry; and (iv) enrolled in GH's integrated group practice for at least 1 year before and 1 year after incident breast cancer diagnosis (unless they died). A total of 4,426 subjects were identified and underwent medical chart review, of which a subset (1,268 women diagnosed 1990-1999) was already partially abstracted as part of 2 previous studies.[48] Eligibility was evaluated per chart review, through which women were excluded for no medical record (n=72), synchronous breast cancer (n=6), breast cancer diagnoses that were not first primaries (n=79) and no definitive surgery (n=44). The final cohort included 4,216 women that were alive and recurrence-free for 120 days after completion of definitive surgery for the incident breast cancer, upon excluding 5 deaths

and 4 metastases occurring before 120 days post-surgery. The GH Institutional Review Board approved this study.

Data collection

Data were collected from one year prior to incident breast cancer diagnosis through the earliest of death, disenrollment from GH (>90 day lapse) or end of study (date of chart abstraction). Information on patient and tumor characteristics, breast cancer treatment, outcomes (i.e., recurrence and second primary breast cancer), comorbid conditions of interest and breast cancer surveillance were obtained from GH automated databases, review of medical records by trained abstractors and SEER. GH automated databases include patient demographics, enrollment, inpatient and outpatient diagnoses and procedures, breast imaging procedures and results, pharmacy dispensings, laboratory results, vital signs and death.[49] Charlson comorbidity index scores[50] were calculated annually from data in medical charts and automated databases. Deaths are determined through GH's link to the Washington State death tapes.[51] SEER was the primary source of information for incident breast cancer characteristics including year of diagnosis, American Joint Committee on Cancer (AJCC) stage,[52] lymph node status, hormone receptor status and tumor size. Education and menopausal status were collected from a self-administered questionnaire on breast cancer risk factors completed at each screening mammogram.[53]

Chart abstraction began in 2009 and continued through August 2011. Data from the medical record were abstracted by 5 trained abstractors and entered into an Access database. Three inter- and intra-rater reliability tests revealed good agreement (overall kappa) for key variables including recurrence (0.93), second primary breast cancer (0.95) and death (0.94).[54]

Exposure classification

Time-varying presence of MetS components were our exposures of interest (Table 1.1). Women were classified as having specific MetS components as of the first date they met the following criteria for each component: Weight risk – BMI ≥27.7 kg/m^2 as a proxy[55] for waist circumference ≥88 cm; Hypertension (HTN) – ≥2 consecutive measurements of BP ≥130/85 mm Hg, pharmacy dispensing of an antihypertensive medication, or HTN diagnosis (≥2 ICD-9 code: 401.9) in the medical record; Low HDL – laboratory measurement of HDL <50 mg/dl; High triglycerides – laboratory measurement of TG ≥150 mg/dl, pharmacy dispensing of fibrates, or hypertriglyceridemia diagnosis (≥2 ICD-9 code: 272.1) in the

medical record; and DM or impaired glucose tolerance – ≥2 consecutive measurements of FPG ≥100 mg/dl or glycosylated hemoglobin HbA_{1C} ≥5.7%, pharmacy dispensing of DM medications, or DM diagnosis (≥2 ICD-9 code: 250.00-93) in the medical record. Exposure was further classified by the time-varying number of MetS components present to compare person-time with 0 (reference), 1, 2, or ≥3 components present.

Outcomes

Women were included and became eligible (at risk) for outcomes in the analysis at 120 days post-surgery for their incident primary breast cancer. The main outcomes of interest were SBCE, defined as the first of recurrence in any regional or distant sites or second primary ductal carcinoma in situ or invasive cancer of the ipsilateral or contralateral breast,[56] and breast cancer-specific mortality. Classification of events as recurrence or second primary breast cancer was determined by medical record documentation of an event as recurrence and second primary breast cancer and also SEER-documented date of second primary breast cancer. Secondary outcomes included overall (all-cause) mortality.

Statistical analysis

We estimated unadjusted (controlling for age and AJCC stage only) and multivariate-adjusted hazard ratios (HR) and 95% confidence intervals using Cox proportional hazards models to assess whether metabolic syndrome components individually or in combination were associated with SBCE and breast cancer-specific mortality while accounting for competing risks (i.e., death due to other causes).[57] The potential competing risks situation in this analysis arises from the primary event in our study (i.e., SBCE) being precluded by other-cause death. By evaluating cause-specific hazards, we account for presence of these different types of events affecting the risk set of women surviving until a given event time. We modeled time from incident breast cancer with a delayed entry at 120 days post-surgery (at-risk date) to SBCE or death as a function of exposure to the individual MetS components and number of MetS components present while adjusting for potential confounders. Individual events that comprise the composite outcome SBCE (i.e., recurrence and second primary BC) were also modeled separately to obtain a comprehensive assessment of MetS effects. Women were followed until the first of SBCE, death, disenrollment or end of study. In analyses of individual events (e.g., recurrence), women were censored

at the earliest of disenrollment, end of follow-up (August 31, 2011) or other competing events (e.g., death or second primary BC).

Estimates for individual MetS components were mutually adjusted for presence of the other MetS components. Women in the cohort with zero MetS conditions present were the reference category for comparison to 1, 2, and ≥3 MetS conditions present. All multivariate models were adjusted for confounders selected a priori, including incident BC diagnosis year, age (18-39, 40-49, 50-59, 60-69, 70-79, ≥80 years), AJCC stage (I, IIA, IIB), hormone receptor status (ER-/PR-, ER+/PR-, ER-/PR+, ER+/PR+), primary treatment (mastectomy ± radiation, BCS + radiation, BCS), chemotherapy (yes/no), endocrine therapy (yes/no), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never) and menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables. Receipt of surveillance mammography (yes/no in prior 12 months) was adjusted for as a time-varying covariate to account for potential detection bias with differences in frequency of post-diagnosis screening.[58]

Proportional hazards assumptions were evaluated by testing the interaction between MetS components (ever versus never presence) 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

We assessed the influence of assumptions made on exposure covariates to determine presence of metabolic syndrome components. We evaluated the definition of metabolic syndrome based on laboratory values, clinical measurements, documented diagnosis in medical record or ICD-9 code and dispensing of medications used for treatment. Specifically, we examined how prevalence of these conditions and their effects on SBCE could possibly change with inclusion/exclusion of specific criteria determining exposure. We also assessed missing data for MetS exposure (i.e., tests not performed and/or no laboratory values and clinical measurements available) and explored multiple imputation under a missing at random (MAR) assumption. Neither varying the definition of metabolic syndrome components nor multiple imputation of missing data substantially changed prevalence of exposures or subsequent risk estimates. So, we report results here only on our main analysis.

RESULTS

The median age of the cohort at initial breast cancer diagnosis was 63 years. The majority were postmenopausal, Caucasian, non-Hispanic, never smokers, had at least some college education or more and a Charlson comorbidity score of zero (Table 1.2). A majority of incident breast cancers were AJCC stage I, lymph node negative, estrogen receptor-(+)/progesterone receptor-(+), ≤2 cm in size, HER-2 negative (if tested), treated with breast conserving surgery with or without radiation, not treated with chemotherapy, and treated with endocrine therapy. At baseline, 63% of women overall had ≥1 MetS component present; 35% had 1 MetS component present; 19% had 2 MetS components present; and 9% had ≥3 MetS conditions present (Figure 1.1). Throughout follow-up, prevalence was increased with 84% of women overall having ≥1 MetS component present; 30% had 1 MetS component present, 28% having 2 MetS components present and 26% having ≥3 MetS conditions present (Table 1.3). The most prevalent conditions throughout follow-up 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 the longest follow-up. The median follow-up was 12.7 years for women diagnosed between 1990-1994, 8.8 years for 1995-1999, 6.7 years for 2000-2004 and 4.1 years for 2005-2008.

Among the 4,216 eligible women, 13% experienced SBCE (first of *n*=415 recurrences and *n*=143 second primary breast cancers) (Figure 1.2). The median time to the first SBCE was 3.3 years. Among recurrences, 67% were distant, 32% local or regional, and 1% DCIS. Among second primary breast cancers, 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 breast cancer, be peri- or premenopausal, lymph node positive, ER and/or PR negative, tumor size >2 cm, HER-2 positive, treated by mastectomy, treated with chemotherapy, not treated with endocrine therapy and have incident breast cancer detected by diagnostic

versus surveillance mammography. Overall, 6% of women experienced breast cancer-specific deaths and 22% of women died overall.

In multivariate-adjusted models, we observed an association between having ≥3 MetS components and an increased risk of SBCE (HR=1.50, 95% CI 1.08-2.07) (Table 1.4). Weight risk (BMI ≥27.7 kg/m^2), adjusted for other MetS conditions, was also independently associated with increased risk of SBCE (HR=1.37, 95% CI 1.14-1.64). These associations were stronger with risk of recurrence 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 breast cancer 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 a potential increased risk. Presence of DM or impaired glucose tolerance was suggestive of an increased risk of SBCE overall (HR=1.24, 95% CI 0.78-1.41) but confidence intervals included 1.0. Point estimates suggest a possible increased risk of SBCE among women with full DM (HR=1.34, 95% CI 0.98-1.52) but not impaired glucose tolerance (HR=1.03, 95% CI 0.83-1.28) compared to women with neither DM nor impaired glucose tolerance. No significant associations were observed with presence of hypertension or low HDL and risk of SBCE, including recurrence or second primary breast cancer separately. High triglycerides were also not associated with SBCE or recurrence alone. However, our results did indicate a more than 8-fold increased risk (95% CI 1.04-67.69) of second primary breast cancer associated with high triglycerides; though, this result should be interpreted cautiously and its confidence limits reflect the small number of cases and very low prevalence of hypertriglyceridemia in these women. Sensitivity of the exposure definition for high triglycerides (i.e., using only laboratory data, diagnostic codes or fibrates dispensed) did not alter the significance or direction of the risk estimate for second primary breast cancer (Appendix Table A.4). Among the 143 women that developed a second primary breast cancer, 4.9% of women had high triglycerides during follow-up, whereas prevalence of hypertriglyceridemia was 1.5% in women with no SBCE (n=3,658) and 0.9% in women that had a recurrence (n=415).

With regard to breast cancer-specific mortality, presence of ≥3 MetS components was associated with increased risk of breast cancer-specific death (HR=1.65, 95% CI 1.02-2.69) compared to women with 0 MetS components (Table 1.5). Weight risk was also associated with increased risk of breast cancer-

specific mortality (HR=1.36, 95% CI 1.04-1.78), whereas no other individual MetS components were significantly associated with breast cancer-specific mortality. With regard to overall mortality, compared to women with 0 MetS components, presence of 1 only (HR=1.17, 95% CI 1.00-1.38), 2 only (HR=1.36, 95% CI 1.12-1.65) and ≥3 MetS components (HR=1.81, 95% CI 1.44-2.29) was associated with increased risk of death (Table 1.5). 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.

Our main results for number of MetS components, as well as individual components, in relation to SBCE and breast cancer-specific mortality changed little when we adjusted for time-varying, annually calculated Charlson comorbidity scores (0, 1, ≥2). However, estimates for the association between number of MetS components and overall mortality were attenuated toward the null with adjustment for Charlson scores when 1 MetS component (HR=1.10, 95% CI 0.93-1.30), 2 MetS components (HR=1.22, 95% CI 1.00-1.49) and ≥3 MetS components (HR=1.69, 95% CI 1.39-2.07) were present (Appendix Table A.5).

DISCUSSION

Prior studies have demonstrated that the number and severity of comorbid conditions at the time of cancer diagnosis strongly influence the probability of dying from non-cancer causes and also may influence cancer-specific survival.[59] In this population-based, retrospective cohort study, presence of ≥3 MetS components was associated with risk of breast cancer recurrence and breast cancer-specific mortality but not second primary breast cancer.

Few studies have examined combined MetS risk factors or the "syndrome" per se in relation to SBCE. Our observation of a positive association between ≥3 MetS components and recurrence is consistent with increased risk of recurrence reported by Pasanisi et al.[60] (HR=3.0, 95% CI 1.2-7.1) in a dietary intervention trial including 110 postmenopausal breast cancer patients, although we observed a more modest increase in recurrence risk. Our findings of increased risk of SBCE with weight risk (BMI ≥27.7 kg/m^2) in MetS concurs with some studies[35, 40-42] reporting a relationship between increased BMI and prognosis following breast cancer but not others.[39, 43] In a study of 18,967 women in a population-

based Danish cohort, Ewertz et al.[35] reported no association between increased BMI with locoregional recurrence, but showed increased risk of distant metastases with BMI 25-29 kg/m^2 (HR=1.42, 95% CI 1.17-1.73) and BMI ≥30 kg/m^2 (HR=1.46, 95% CI 1.11-1.92) compared with BMI <25 kg/m^2. Our observed increased risk of breast cancer-specific mortality with ≥3 MetS components and weight risk further supports our findings on increased risk of SBCE. Also in agreement with our findings, women in the Danish cohort were at increased risk of breast cancer-specific mortality with BMI 25-29 kg/m^2 (HR=1.26, 95% CI 1.09-1.46) and BMI ≥30 kg/m^2 (HR=1.38, 95% CI 1.11-1.71) compared with BMI <25 kg/m^2.[35]

DM along with obesity epitomizes MetS and the etiologic processes underlying the syndrome's possible role in cancer.[61, 62] Presence of DM can impact breast cancer 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 side effects and complications of chemotherapy.[63] While our results were not statistically significant, the point estimates suggest that diabetes but not impaired glucose tolerance increases risk of recurrence and second primary breast cancer. On the other hand, in a retrospective cohort study of 3,124 women with stages I-III breast cancer by Kiderlen et al.,[64] results were suggestive of decreased risk of recurrence (greater relapse-free period) in women with diabetes compared to women without diabetes (HR=0.77, 95% CI 0.59-1.01) after accounting for competing risks and other comorbidity, particularly in patients ages ≥75 years (HR=0.67, 95% CI 0.45-0.98). One possible explanation for results indicating no statistically significant association or possibly an inverse relationship is that the adverse influences of DM or impaired glucose tolerance on breast cancer prognosis could be counterbalanced by possible protective effects of some DM medications, such as metformin.[65] Metformin is among the recommended first-line interventions for medical management of hyperglycemia,[66] and its relevance to breast cancer outcomes is supported by the effects of metformin in reducing circulating insulin levels and activation of the adenosine monophosphate-activated protein kinase pathway.[67] Kiderlen et al., suggested that the majority of women with DM in their study used metformin on the basis of Dutch DM treatment guidelines primarily recommending metformin use.[68] Likewise, DM management at GH largely includes metformin use, particularly in more recent years, and throughout follow-up 62% of women with DM had ≥1 pharmacy dispensings of metformin. 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[69] to help further substantiate their potential role in breast cancer prognosis.

Studies evaluating MetS risk factors in relation to second primary breast cancer risk are also limited. No statistically significant association was observed between number of MetS components and risk of second primary breast cancer; although our results were suggestive of an increased risk of second primary breast cancer with weight risk and DM. The low number of second primary breast cancers (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 breast cancer. Some studies describe increased risk of second primary breast cancer with increased weight,[43, 70-73] but others that report no association with increased BMI or obesity.[74-76] We observed a possibly increased risk of second primary breast cancer with DM but not with impaired glucose tolerance only. In kind, a population-based case-control study[77] of women ages 40-79 years diagnosed with ER-positive, stages I-III, incident primary breast cancer found that women with DM had an increased risk (OR=2.2, 95% CI 1.3-3.6) of second primary contralateral breast cancer compared to women with no history of DM.

No other studies have examined the role of hypertriglyceridemia (TG >150 mg/dl) specifically with risk of second primary breast cancer. In our study, we observed an increased risk of second primary breast cancer with elevated triglycerides (HR=8.38, 95% CI 1.04-67.69). The role of serum triglycerides in breast cancer is not clear, and studies examining primary breast cancer incidence related to elevated triglycerides are inconsistent, showing no association in some prospective cohort studies,[25, 26] but a positive association in other cohort[27] and case-control studies.[28, 29] It has been suggested that lipoprotein lipase may regulate the clearance of triglycerides from blood to tissue and its activity in adipose tissue decreases in cancer patients, contributing to hypertriglyceridemia.[15] While tamoxifen is associated with reduced risk of second primary breast cancer,[78] tamoxifen and estrogen also have a known role in increasing serum triglyceride levels and sometimes inducing severe hypertriglyceridemia.[79] Additional studies are needed to evaluate the relationship between risk of second primary breast cancer and elevated triglycerides.

In early stage breast cancer, the risk of death due to causes other than cancer is high, particularly with increasing age.[3] Risk of overall mortality in the general population is increased with presence of MetS. In a large cohort study of 9,677 women ages ≥65 years,[80] 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. In our study of breast cancer survivors, we observed an increased risk of overall mortality associated with an increasing number of MetS components and with DM and hypertension individually. Similar to our findings, multiple studies support an association between DM and an increased risk of overall mortality in women with a history of breast cancer.[34, 44, 81-84] In a meta-analysis by Peairs et al.,[34] pre-existing diabetes was associated with a 49% increased risk (95% CI 1.35-1.65) for all-cause mortality in women with breast cancer.

The strengths of this study include the use of a population-based cohort of breast cancer survivors, which contains comprehensive and high quality data on incident breast cancer characteristics and treatment through both a validated registry and medical charts, demographics, vital signs, health care utilization including medication use details and breast services, breast cancer 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 includes an insured, educated 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.[85] Loss to follow-up is a possible source of bias with 18% 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 that may influence prevalence of MetS and breast cancer outcomes and survival. We did not include adjustment for annual Charlson comorbidity scores in our main analysis because of the contribution of MetS components to the calculation of the scores. There was little change in the results in our multivariate models for SBCE and

breast cancer-specific mortality with adjustment for time-varying Charlson scores, but as expected, our estimates indicating increased risk of overall mortality were modestly attenuated.

Our ability to detect associations between MetS components and SBCE is also limited by the number of cases observed and the prevalence of exposures. We evaluated power using the Wald test (hazard metric) for Cox regression[86] to determine the minimum detectable effect size for exposures with β=0.20, sample size of N=4,216 and probability of SBCE of 13%: ≥3 MetS components (HR=1.30), weight risk (HR=1.18), hypertension (HR=1.23), low HDL-cholesterol (HR=1.22), hypertriglyceridemia (HR=2.02) and DM or impaired glucose tolerance (HR=1.26). Therefore, the low occurrence of some events (i.e., second primary breast cancer, 3.4%) and the typically low prevalence of some MetS components (i.e., hypertriglyceridemia, 1.6%) may have limited our ability to detect a true association if one was present.

We performed sensitivity analyses to describe the patterns of missing data among the covariates used to define exposure to MetS components. Classification of exposure using automated and electronic health record data obtained in the course of clinical practice can lead to measurement error and bias when covariate data are missing,[87, 88] such as infrequent laboratory testing of triglycerides in earlier years of follow-up. Our approach included the use of data elements as surrogates for direct clinical measurement of MetS components (i.e., documented diagnosis in the medical chart or dispensing of medications used for treatment).[5, 87] As expected, there was strong agreement between surrogate measures to define MetS components (i.e., documented diagnosis and dispensing of medication for treatment). A slightly greater proportion of missing data on laboratory values and/or clinical measurements to define MetS components was present among women considered to be unexposed per our main classification scheme with a strong assumption of data not missing at random (NMAR). We evaluated our assumptions regarding reasons for missing data (e.g., no hypertriglyceridemia diagnosis, no fibrates dispensed and no TG laboratory tests documented = MetS component not present) in sensitivity analyses assuming MAR. Application of multiple imputation under MAR to account for missing covariates yielded results similar to our main analysis for SBCE (Appendix Table A.4) and breast cancer-specific mortality (Appendix Table A.5) and suggests that our data are not substantially influenced by varying assumptions made with respect to missing data on MetS components.

CONCLUSION

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

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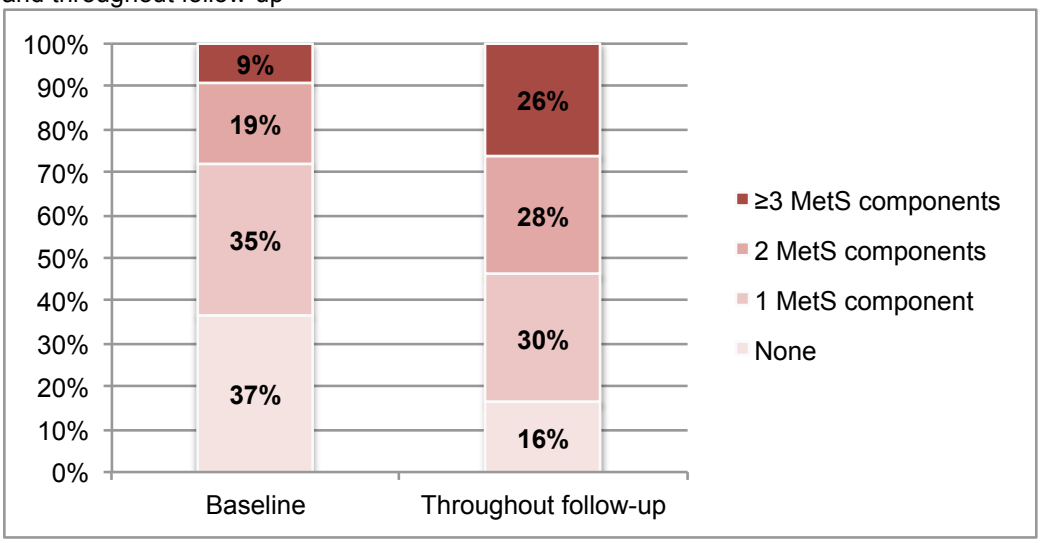
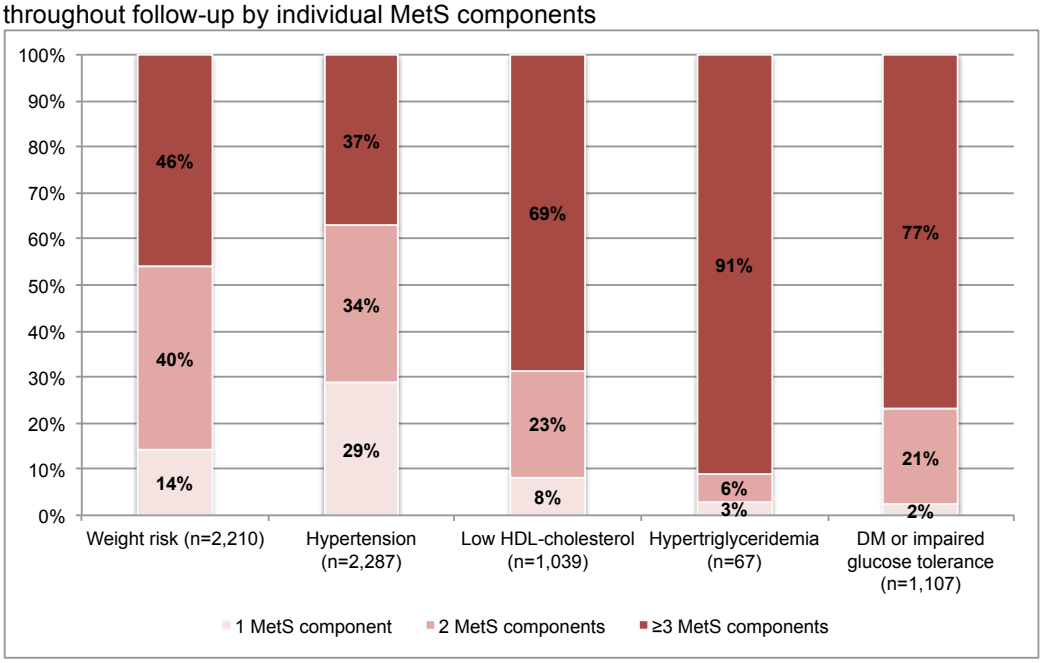
Figure 1.1. Prevalence of metabolic syndrome (MetS) components in the COMBO study

(A) Prevalence of metabolic syndrome (MetS) components in the COMBO study at baseline and throughout follow-up

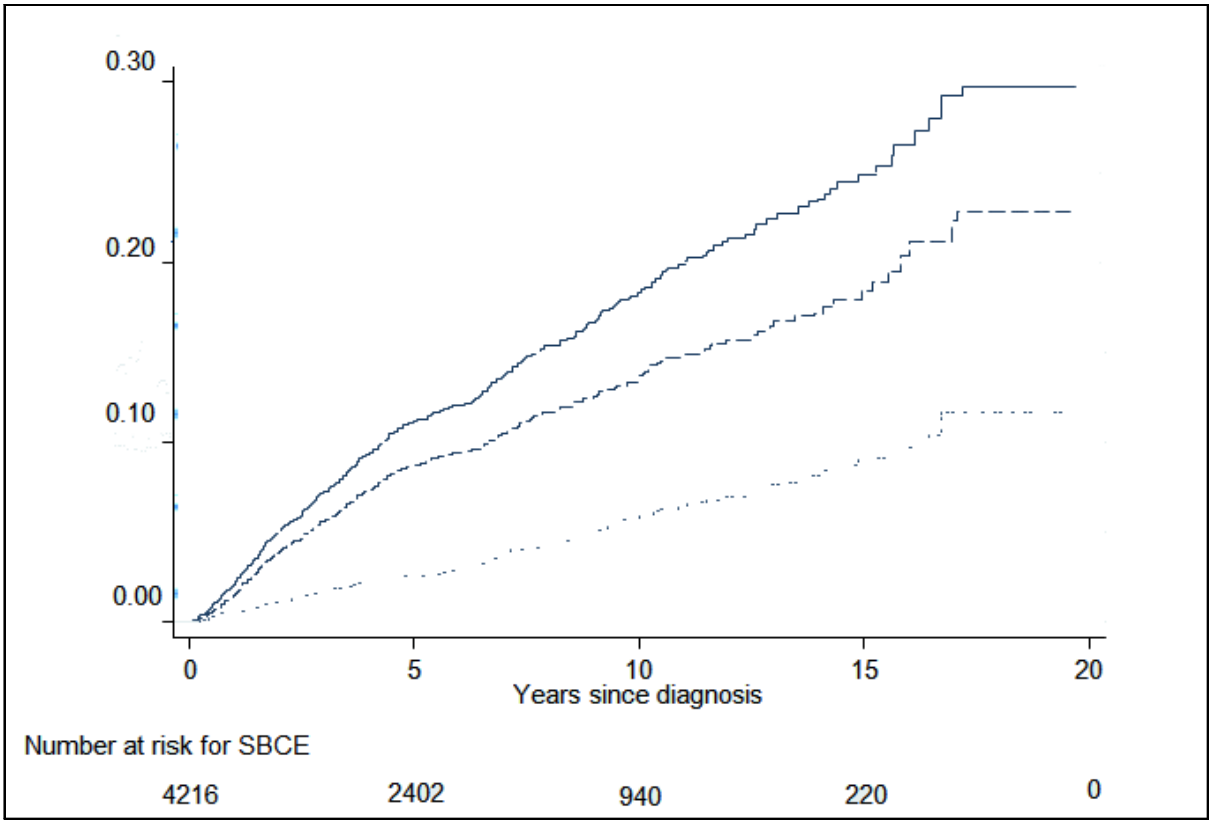


(B) Number of co-occurring metabolic syndrome (MetS) components in the COMBO study throughout follow-up by individual MetS components



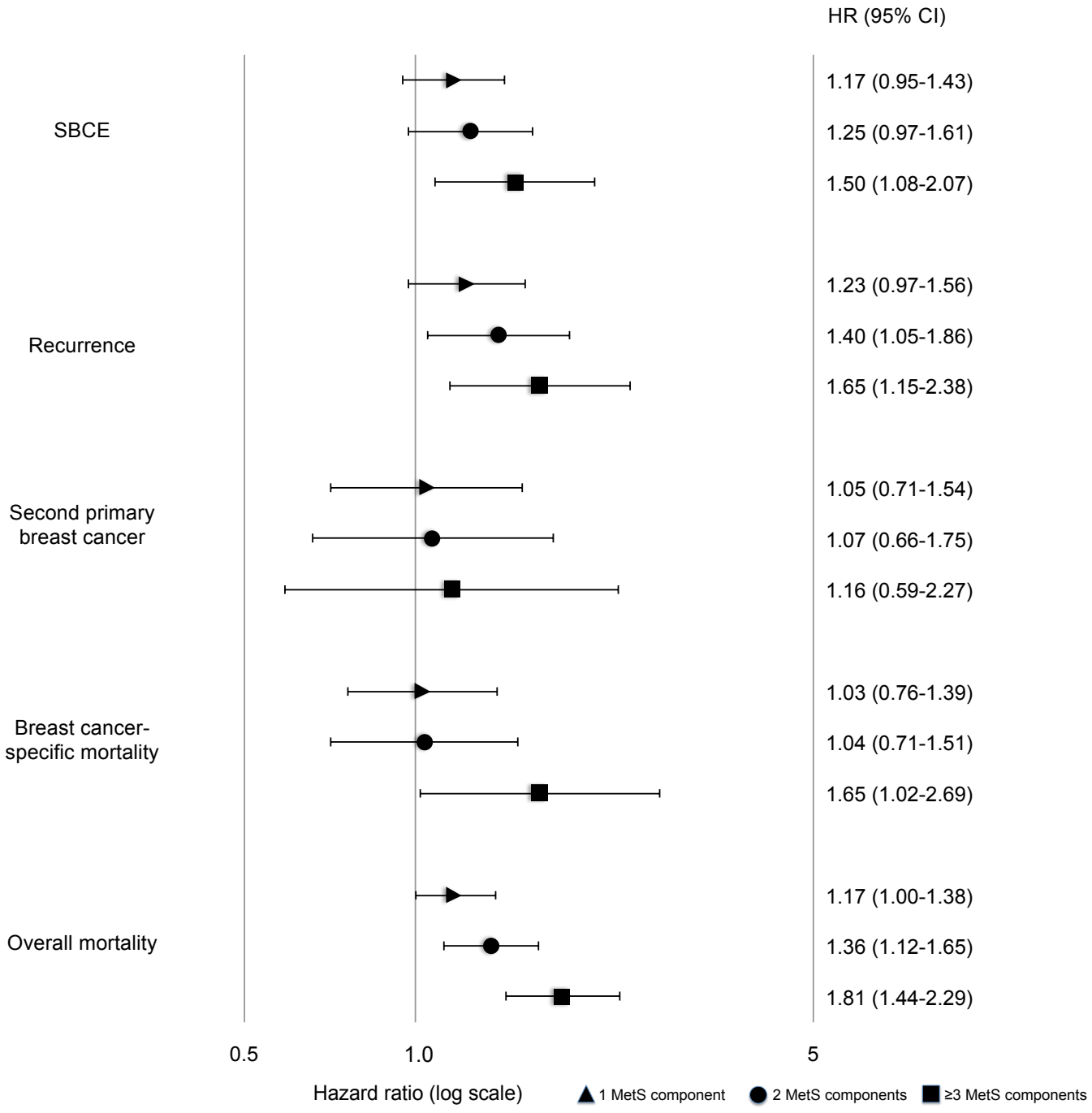
Note: Number of MetS components throughout follow-up indicates highest ever total

Figure 1.2. Cumulative hazard of second breast cancer events including recurrence and second primary breast cancer



KEY	
Age-Adjusted Cumulative Hazard of Second Breast Cancer Event	
Age-Adjusted Cumulative Hazard of Recurrence	
Age-Adjusted Cumulative Hazard of Second Primary	

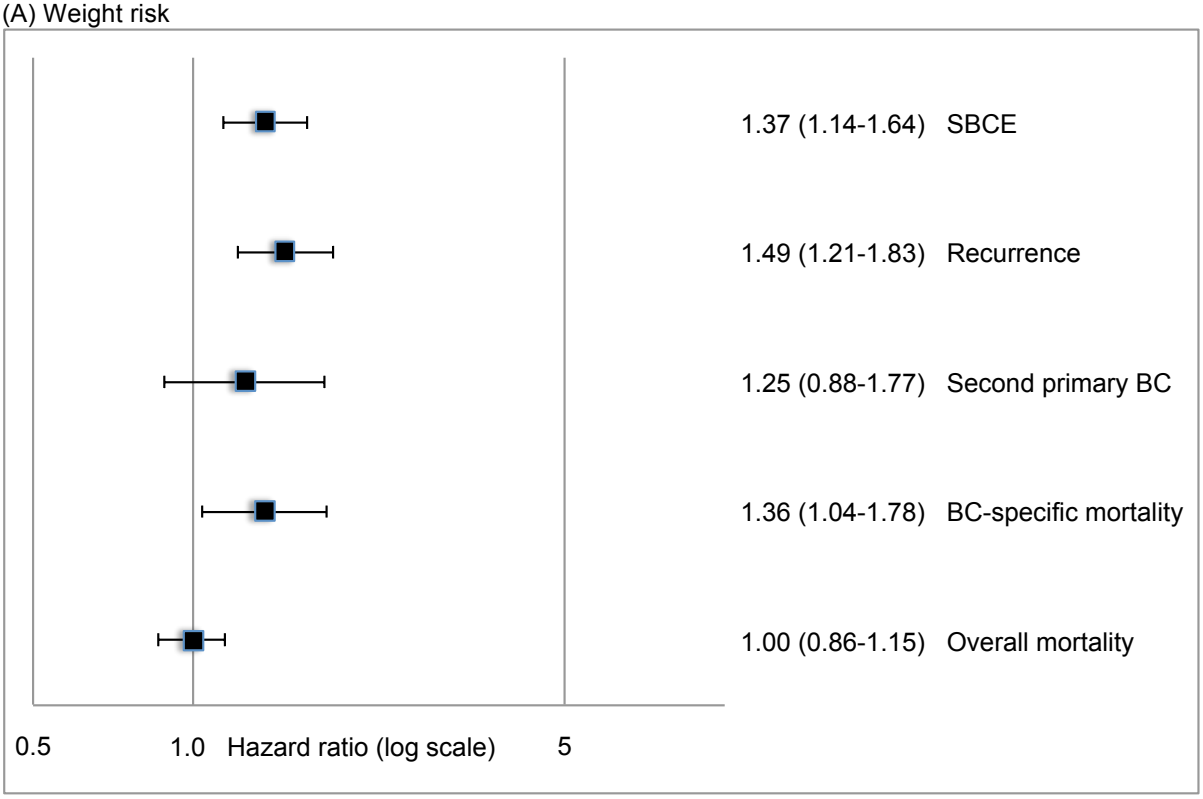
Figure 1.3. Adjusted hazard ratios and 95% confidence intervals for metabolic syndrome (MetS) components with risk of SBCE, breast cancer-specific mortality and overall mortality



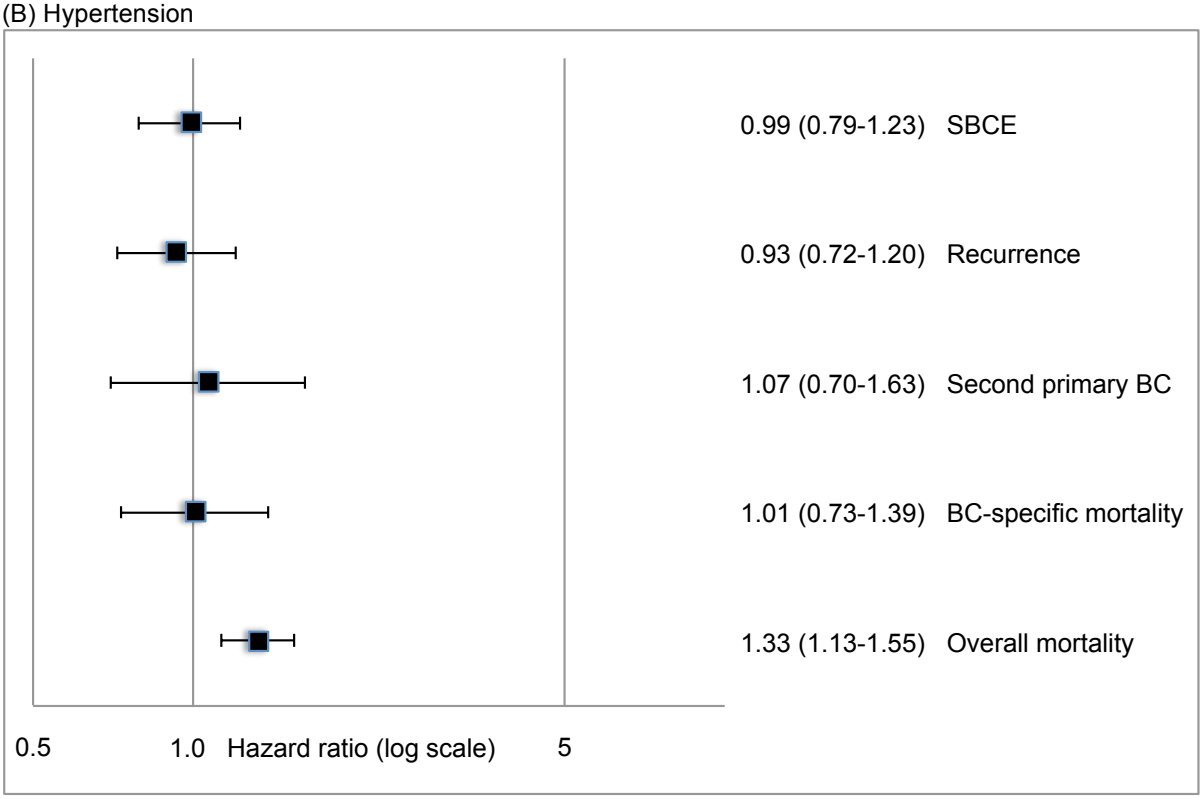
Note: Hazard ratios are adjusted for age (18-39, 40-49, 50-59, 60-69, 70-79, 80+ years), incident breast cancer diagnosis year, AJCC stage (I, IIA, IIB), hormone receptor status (ER-/PR-, ER+/PR-, ER-/PR+, ER+/PR+), primary treatment for the initial breast cancer (mastectomy +/- radiation, BCS + radiation,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

Figure 1.4. Adjusted hazard ratios and 95% confidence intervals for individual metabolic syndrome (MetS) components with risk of SBCE, breast cancer-specific mortality and overall mortality

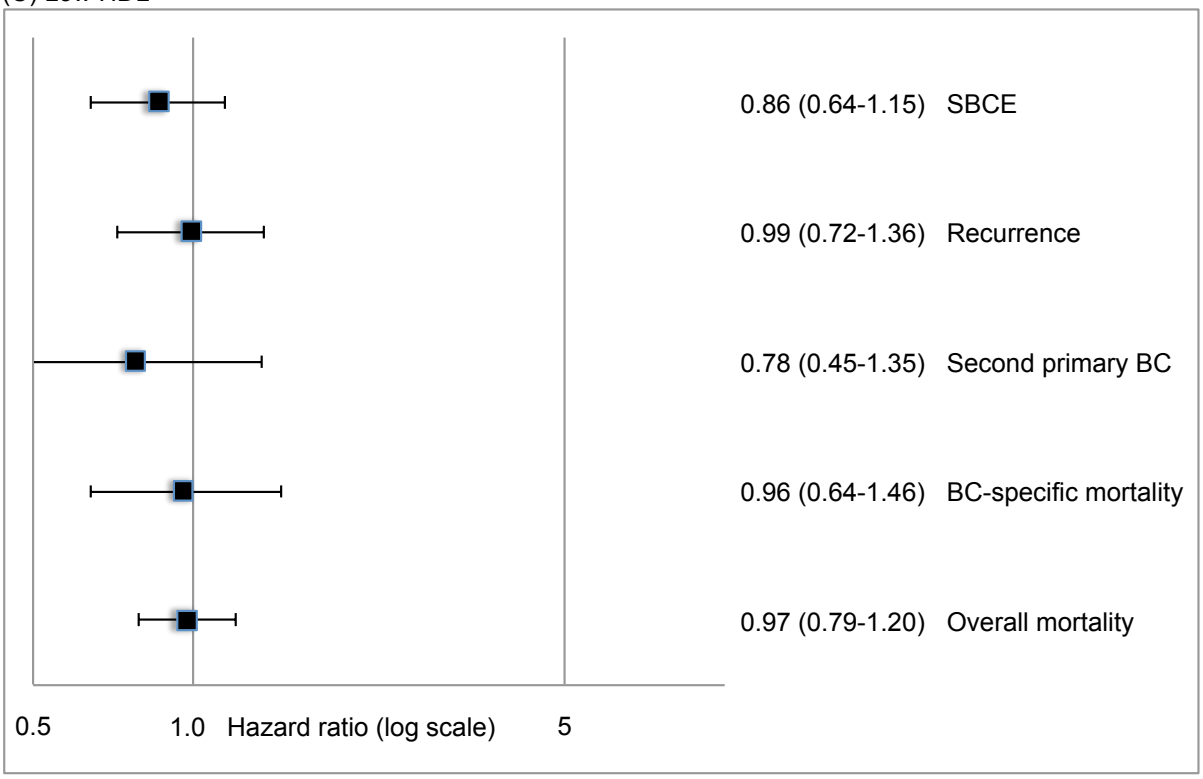
(A) Weight risk



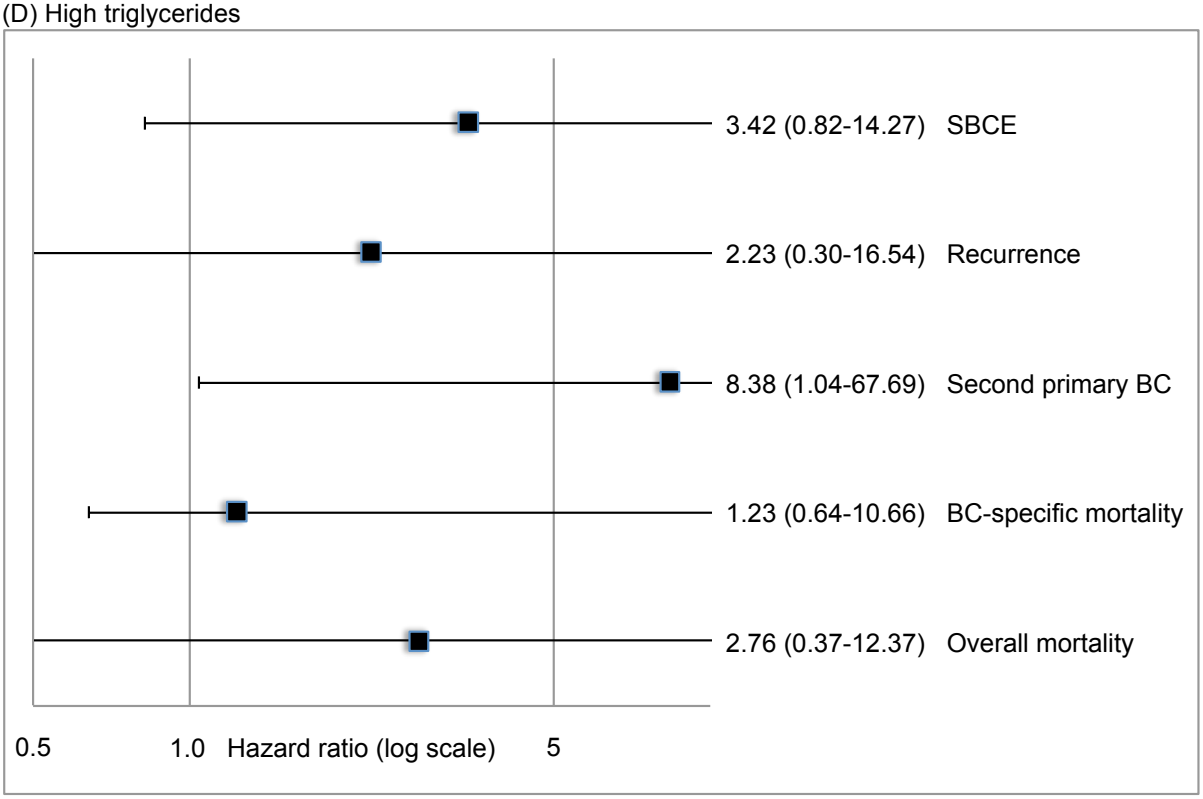
(B) Hypertension



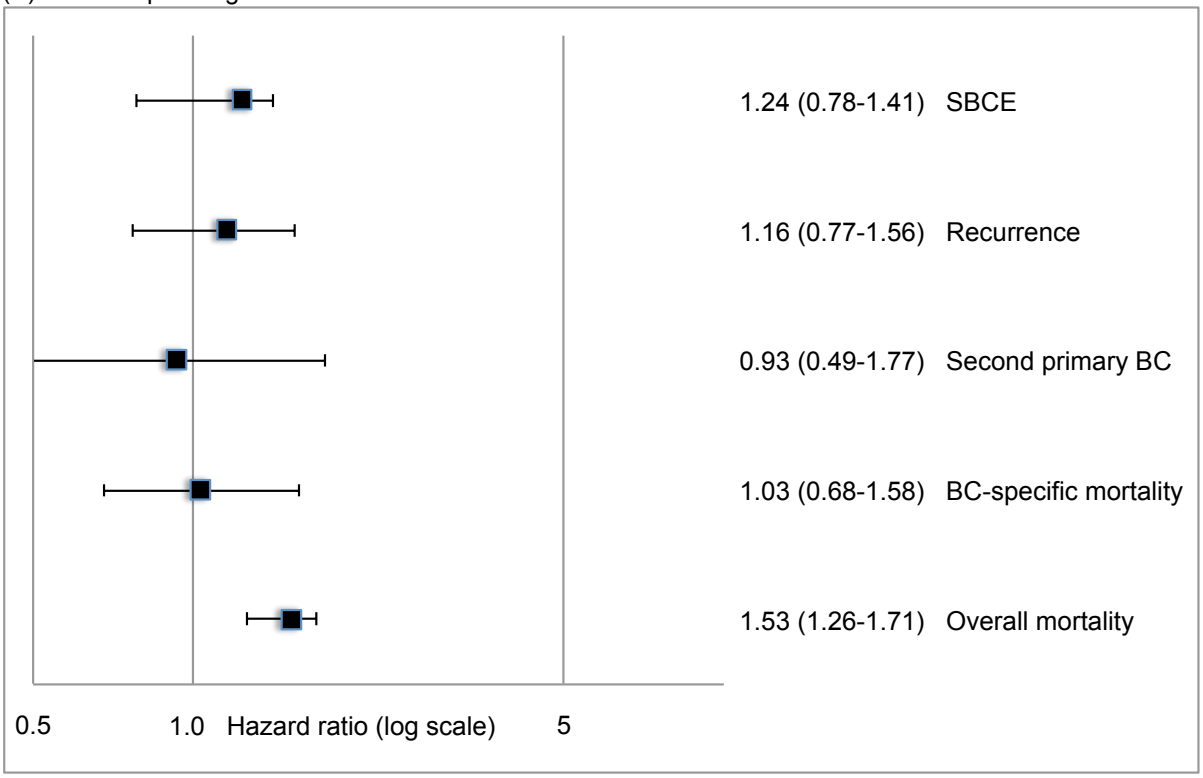
(C) Low HDL



(D) High triglycerides



(E) DM or impaired glucose tolerance



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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables; receipt of surveillance mammography (yes/no in prior 12 months) as time-varying; accounting for competing risks in multivariate-adjusted models.

Table 1.1. Classification of metabolic syndrome components in the COMBO study

Weight risk	BMI ≥27.7 kg/m^2 as a proxy for waist circumference ≥88 cm
Hypertension	≥2 blood pressure measurements ≥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} ≥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

Table 1.2. Descriptive characteristics of women in the COMBO study 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/m^2)				
<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)
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)

Table 1.2. Descriptive characteristics of women in the COMBO study by SBCE status

	SBCE (*N* = 4,216)			
	No (*n*=3,658)		Yes (*n*=558)	
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)
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	860	(23.5)	124	(22.2)

Table 1.2. Descriptive characteristics of women in the COMBO study by SBCE status

	SBCE (*N* = 4,216)	
	No (*n*=3,658)	Yes (*n*=558)
glucose tolerance 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

[a] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; Hypertension: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

[b] Arterburn 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 1.3. Descriptive characteristics of women in the COMBO study 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/m^2)								
<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)

Table 1.3. Descriptive characteristics of women in the COMBO study 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)	
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)

Table 1.3. Descriptive characteristics of women in the COMBO study 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)	
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)
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

[a] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; Hypertension: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

[b] Arterburn 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 1.4. Adjusted hazard ratios and 95% confidence intervals for the association of metabolic syndrome (MetS) and its individual components as time-varying throughout follow-up with risk of second breast cancer events (recurrence and second primary breast cancer) in the COMBO study

	Person-years of follow-up	All SBCE cases (*n*=558) MV-adjusted HR (95% CI) [a]	Recurrence (*n*=415) MV-adjusted HR (95% CI) [a]	Second primary BC (*n*=143) MV-adjusted HR (95% CI) [a]
# of MetS components [b]				
0 present (112 cases)	8,193	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1 only (163 cases)	9,282	1.17 (0.95-1.43)	1.23 (0.97-1.56)	1.05 (0.71-1.54)
2 only (145 cases)	7,308	1.25 (0.97-1.61)	1.40 (1.05-1.86)	1.07 (0.66-1.75)
≥3 (138 cases)	5,029	1.50 (1.08-2.07)	1.65 (1.15-2.38)	1.16 (0.59-2.27)
P-trend		0.010	0.002	0.649
Individual components [b]				
Weight risk [c]				
No (249 cases)	14,598	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (309 cases)	15,215	1.37 (1.14-1.64)	1.49 (1.21-1.83)	1.25 (0.88-1.77)
Hypertension (HTN)				
No (234 cases)	18,679	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (324 cases)	11,132	0.99 (0.79-1.23)	0.93 (0.72-1.20)	1.07 (0.70-1.63)
Low HDL cholesterol				
No (420 cases)	21,954	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (138 cases)	7,858	0.86 (0.64-1.15)	0.99 (0.72-1.36)	0.78 (0.45-1.35)
High triglycerides				
No (546 cases)	29,668	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (12 cases)	144	3.42 (0.82-14.27)	2.23 (0.30-16.54)	8.38 (1.04-67.69)
Diabetes (DM) or impaired glucose tolerance				
No - neither (417 cases)	23,717	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes - both (141 cases)	6,095	1.24 (0.78-1.41)	1.16 (0.77-1.56)	0.93 (0.49-1.77)
Diabetes (DM)	4,209	1.34 (0.98-1.52)	1.36 (0.95-1.49)	1.29 (0.85-1.97)
Impaired glucose tolerance	1,886	1.03 (0.83-1.28)	0.98 (0.76-1.25)	0.90 (0.47-1.71)

Note: We excluded 20 women from analyses due to missing BMI information; cases and person-years of follow-up are for all SBCE

[a] Multivariate models 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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables; receipt of surveillance mammography (yes/no in prior 12 months) as time-varying; accounting for competing risks in multivariate-adjusted models. Estimates for individual MetS components are mutually adjusted for all other MetS components in addition to above covariates.

[b] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; HTN: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

[c] Arterburn 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 1.5. Adjusted hazard ratios and 95% confidence intervals for the association of metabolic syndrome (MetS) and its individual components as time-varying throughout follow-up with risk of breast cancer-specific mortality and overall mortality in the COMBO study

	Person-years of follow-up	Breast cancer-specific mortality (*n*=259) MV-adjusted HR (95% CI) [a]	Overall mortality (*n*=929) MV-adjusted HR (95% CI) [a]
# of MetS components [b]			
0 present (54/133 cases)	8,117	1.00 (ref.)	1.00 (ref.)
1 only (84/298 cases)	9,206	1.03 (0.76-1.39)	1.17 (1.00-1.38)
2 only (66/255 cases)	7,259	1.04 (0.71-1.51)	1.36 (1.12-1.65)
≥3 (55/243 cases)	4,933	1.65 (1.02-2.69)	1.81 (1.44-2.29)
P-trend		0.102	<0.001
Individual components [b]			
Weight risk [c]			
No (120/462 cases)	14,042	1.00 (ref.)	1.00 (ref.)
Yes (139/467 cases)	14,577	1.36 (1.04-1.78)	1.00 (0.86-1.15)
Hypertension (HTN)			
No (174/285 cases)	17,929	1.00 (ref.)	1.00 (ref.)
Yes (85/643 cases)	10,691	1.01 (0.73-1.39)	1.33 (1.13-1.55)
Low HDL cholesterol			
No (194/699 cases)	21,060	1.00 (ref.)	1.00 (ref.)
Yes (65/230 cases)	7,559	0.96 (0.64-1.46)	0.97 (0.79-1.20)
High triglycerides			
No (255/924 cases)	28,480	1.00 (ref.)	1.00 (ref.)
Yes (4/5 cases)	140	1.23 (0.64-10.66)	2.76 (0.37-12.37)
Diabetes (DM) or impaired glucose tolerance			
No – neither (198/671 cases)	22,770	1.00 (ref.)	1.00 (ref.)
Yes – both (61/258 cases)	5,849	1.03 (0.68-1.58)	1.53 (1.26-1.71)
Diabetes (DM)	4,012	1.04 (0.66-1.72)	1.54 (1.32-1.87)
Impaired glucose tolerance	1,837	1.02 (0.59-1.35)	1.37 (1.16-1.61)

Note: We excluded 20 women from analyses due to missing BMI information; cases refer to number of BC-specific deaths/overall deaths

[a] Multivariate models 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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables; receipt of surveillance mammography (yes/no in prior 12 months) as time-varying; accounting for competing risks in multivariate-adjusted models for breast cancer-specific mortality. Estimates for individual MetS components are mutually adjusted for all other MetS components in addition to above covariates.

[b] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; HTN: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

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CHAPTER 2

Adherence to Oral Diabetes Medications and Glycemic Control During and Following Breast Cancer Treatment

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ABSTRACT

BACKGROUND: We evaluated changes in oral DM medication adherence and persistence, as well as glycemic control for the year prior to breast cancer (BC) diagnosis (Year -1), during BC treatment, and in subsequent years.

METHODS: Cohort study of 4,216 women diagnosed with incident early stage (I,II) invasive BC from 1990-2008, enrolled in Group Health Cooperative. Adherence was measured in prevalent users at baseline (N=509), during treatment, and 1-3 years post-diagnosis using medication possession ratio (MPR), %-adherent (MPR≥0.80) and discontinuation rates (DR). Laboratory data on glycosylated hemoglobin (HbA_{1C}) was obtained for the corresponding periods.

RESULTS: Compared to Year -1, mean MPR for metformin/sulfonylureas (0.86 versus 0.49, $P<0.001$) and %-adherent (75.3% versus 24.6%, $P<0.001$) declined during BC treatment. MPR and %-adherent rose slightly during years 1-3 post diagnosis but never returned to baseline. DR increased from treatment to Year +1 (59.3% versus 75.6%, $P<0.001$) and remained elevated during subsequent observation periods. Compared to baseline, increased HbA_{1C} (7.0% versus 7.4%, $P=0.001$) and % women with high HbA_{1C} >7.0% (34.9% versus 51.1%, $P<0.001$) coincided with decreased adherence.

CONCLUSION: DM medication adherence declined following BC diagnosis while discontinuation rates were relatively stable but poor overall. The proportion of adherent users increased only marginally following treatment, while the proportion of women meeting goals for HbA_{1C} decreased considerably. These data support the hypothesis that adherence and subsequent glycemic control are sensitive to BC diagnosis and treatment. Confirmatory studies in other settings, on reasons for reduced adherence post-cancer diagnosis, and on subsequent indicators of glycemic control are warranted.

INTRODUCTION

The incidence of breast cancer (BC) increases with age,[1] as does the incidence and prevalence of comorbid conditions such as diabetes mellitus (DM)[2] that are managed by multiple medications. Breast cancer patients with DM are part of a growing population of aging individuals with multi-morbidity, and oncologists can expect more than half of the patients they see ages 65 years and older to have ≥1 other meaningful chronic condition that may affect their treatment.[3] However, overall adherence to DM medications in the general population is low, between 50-75% on average,[4-6] and attainment of DM treatment goals with oral medications is strongly tied to adherence.[6] Further, nonadherence to DM medications is associated with increased risk of glycometabolic disturbance and all-cause mortality,[7] as well as increased costs and all-cause hospitalization.[8] Adherence to DM therapy is known to decrease following major life events and with psychological stressors,[9] although little is known about DM management following cancer diagnosis.

Numerous studies including meta-analyses support an association between diabetes and increased risk of breast cancer.[10-12] Diabetes is also hypothesized to be an indicator of poor prognosis[13-16] and possibly a risk factor for second contralateral breast cancer.[17] DM may promote carcinogenesis through increased insulin-like growth factors and sex-steroid bioavailability, hyperglycemia, and chronic inflammation.[18, 19] Other factors may influence the association between diabetes and breast cancer, including extent of glycemic control and impacts of certain drugs such as metformin used to manage DM.[20, 21] As such, adherence to DM medications has the potential to not only alter DM outcomes but also breast cancer outcomes. The need for high quality management of comorbid conditions will continue to increase as improvements in diagnosis and treatment lead to longer lives for cancer survivors. For cancers such as early stage breast cancer with 5-year survival rates of >90%,[1] increasing numbers of survivors are burdened with the challenges of polypharmacy and chronic condition care, and are more likely to die from causes other than cancer.[3] While there are considerable data documenting the decline in medication adherence for adjuvant hormone therapies,[22] there is relatively little evidence regarding adherence to medications used to control important comorbid conditions post-breast cancer.

The estimated 2.8 million breast cancer survivors living in the U.S.[1] and the increasingly high prevalence of DM[2] warrants a better understanding of adherence to medications for DM and goals for

glycemic control. The objective of our study was to estimate adherence to commonly used oral DM medications, biguanides (i.e., metformin) and sulfonylureas, in the year before breast cancer diagnosis, during cancer treatment, and in subsequent years among a retrospective cohort of women diagnosed with early stage breast cancer. Further, we evaluated glycemic control, measured by glycosylated hemoglobin (HbA_{1C}), among women taking oral DM medications in the corresponding periods.

METHODS

We sampled women from the previously established Commonly Used Medications and Breast Cancer Outcomes (COMBO) cohort of 4,216 women diagnosed with incident early stage (I, II), invasive breast cancer between 1990 and 2008 at Group Health Cooperative (GH).[23, 24] Women without at least 1 year of GH enrollment prior and after breast cancer diagnosis (unless they died) and women with bilateral breast cancer were excluded. GH is a large integrated delivery system that provides comprehensive medical care to approximately 620,000 enrollees in Washington State and parts of Idaho. Incident breast cancers and tumor characteristics were identified through linkage to the Surveillance, Epidemiology and End Results Seattle-Puget Sound registry.[25] In this study, we included all women diagnosed through August 2007 so each woman had the potential for 3 years of follow-up. Follow-up was then through the earliest of second breast cancer event (SBCE), death, disenrollment, or end of the study period (August 2010). SBCE is defined as the first of a recurrence or second primary ductal carcinoma in situ or invasive cancer of the ipsilateral or contralateral breast. Patient characteristics were obtained through GH automated data files,[26] which include laboratory results, inpatient and outpatient diagnoses, procedures, enrollment, pharmacy dispensings, and death (internal records and Washington state death tapes).[27] Information on breast cancer treatment and outcomes (e.g., recurrence) were obtained through review of medical records. For the current study, we selected only women with ≥1 dispensings of GH's first-line DM medications, metformin and/or sulfonylureas (N=509) alone or in combination, out of the 516 women treated with oral DM medications in the year before breast cancer diagnosis. Since the majority of oral DM medication users were taking metformin or sulfonylureas, we refer to these women as users of oral DM medication. Insulin use was also identified for women using oral DM medications.

Measures of medication adherence

Medication adherence and persistence were measured using medication possession ratio (MPR) and discontinuation rate (DR), respectively. Shorter days' supply associated with repeated DM medication dispensings prompted calculation of measures to incorporate both information on oversupply and medication gaps, a more recently validated method using automated pharmacy/claims data.[28] Recent reviews in the scientific literature identify MPR and DR among the most commonly used and reproducible measures of medication adherence.[29] We defined MPR as the proportion of days' supply of medication dispensed over the number of days for which the patient had been prescribed oral DM medication, or the intended period of treatment. For example, in a period of 180 days, five dispensings of 30 days' supply (150 days) of glyburide would result in an estimated MPR of 0.83 (150/180). MPR ≥0.80 was considered the threshold for which women were adherent to DM pharmacotherapy.[29] DR was calculated using the observed number of discontinuation episodes, defined as a gap of ≥90 days between the end of a previous days' supply and the subsequent dispensing of DM medication.[29] DR is equal to the proportion of users with ≥1 discontinuation episode within an observation period. Thus, for periods of one year, DR is the one-year cumulative incidence of discontinuation and persistence among users (i.e., continuous treatment with no gaps ≥90 days) in that period is represented as 1–DR.

Observation periods

Using dispensing data from the GH automated pharmacy database, MPR and DR were calculated for the 1-year period before breast cancer diagnosis (Year −1, t_0 − 1 year ↔ t_0), treatment period ($t_0 \leftrightarrow t_{tx} = t_{rx}$ + 90 days), 1-year period following end of treatment (Year +1, $t_x \leftrightarrow t_x$ + 1 year), and two subsequent 1-year periods (Years +2 and +3) following end of treatment (Figure 2.1). The treatment period was defined as time from diagnosis to 120 days post-final treatment (last of surgery, radiation, or chemotherapy) plus 90 days. Among women on oral DM medication at any point during the year before breast cancer diagnosis (n=509), mean time to end of primary treatment (last of surgery, radiation or chemotherapy) was 133.5 days (SD 112.9) (Table 2.1). Sensitivity analyses were conducted on the definition of the treatment period (Appendix Tables B.1 to B.3). Specifically, we examined differences in varying definitions of treatment length (range: 180 to 365 days). No substantial differences were observed, and thus, we present results only on the treatment period defined as 120 days post-final treatment plus

90 days. Women contributed to the four post-diagnosis observation periods only if they were using DM medication (i.e., no discontinuation) in the prior observation period.

Glycemic control

We obtained laboratory data on HbA_{1C} for DM medication users within corresponding time periods in which medication adherence was calculated. Approximately 85% of DM medication users received ≥1 laboratory measurement of HbA_{1C} in the year prior to breast cancer diagnosis. Similar proportions (80-85%) of users had HbA_{1C} data in subsequent observation periods. The highest of HbA_{1C} in a given period of interest was used to determine glycemic control and standard goals for management of DM[30] (defined as HbA_{1C} ≤7.0%) as well as a less rigid measure of glycemic control (HbA_{1C} ≤8.0%). We performed sensitivity analyses using the lowest HbA_{1C} and mean value of multiple measures (Appendix Tables B.4 to B.9). We also limited our analysis of medication adherence to only women with complete HbA_{1C} data in all periods. Results from these sensitivity analyses were not appreciably different from our first approach, and thus, we report on only our main analyses. All analyses of medication adherence and glycemic control were also stratified by concurrent insulin use.

Statistical analysis

Statistical tests for within-subjects' comparisons of measures of adherence and glycemic control were performed. Statistical methods for the analysis of paired data were used to test the hypothesis of no difference between the year prior to diagnosis and each subsequent year. Paired t-tests were used for the continuous measures of mean MPR and HbA_{1C}. McNemar exact tests were used to test the hypothesis of no difference for dichotomous measures of persistence and adherence to DM therapy and glycemic control goals met. Our analyses tested differences between Year -1 and subsequent years' mean MPR, % adherent, % persistent, mean HbA_{1C} and % at goal overall and by adherence status yielding a total of 48 comparisons. To account for these multiple comparisons, we set an alpha level of 0.001 for determining statistical significance, following the approach of Bonferroni.[31] This alpha level allows us to conduct up to 50 hypothesis tests without exceeding a family-wise type I error rate of 0.05. Analyses were performed using Stata 13 (College Station, TX: StataCorp LP).

RESULTS

Of the 509 women using metformin and/or sulfonylureas in the year prior to BC diagnosis (Year-1), the median age at BC diagnosis was 65 years, the majority presented with AJCC Stage I tumors (61.6%), and 23.6% of women scored ≥2 on the Charlson comorbidity index (Table 2.1).[32] Prevalence of other comorbidities was high with 121 (23.4%) women having a history of ischemic heart disease and 440 (85.3%) having a history of hypertension. Compared with adherent users during the diagnosis through treatment period, nonadherent users of oral DM medications were more likely to be diagnosed with Stage II tumors (40.9% versus 31.7%), and more likely treated with adjuvant chemotherapy (31.9% versus 22.0%) and endocrine therapy (60.1% versus 52.8%). Nonadherent users also had a marginally higher proportion of women with 0-1 visit only to a primary care provider (30.1% versus 22.8%) within the year following diagnosis. Per pharmacy dispensings, nonadherent oral DM medication users were more likely to be also concurrently using ≥4 CVD medications compared with adherent users (37.2% versus 26.8%). Between the year before diagnosis and Year +3, 124 women were censored from analyses due to discontinuation of oral DM therapy (n=64), death (n=23), disenrollment (n=17), or SBCE (n=20) (Table 2.2).

Medication adherence and persistence

Estimated MPR and DR among oral DM medication users are reported in Table 2.2. Mean MPR for oral DM medication use in the year before diagnosis (Year -1) was highest overall, 0.85. In Year -1 there were 383 (75.3%) DM medication users adherent (MPR ≥0.80) to medication therapy. Mean MPR was lower in the treatment period, 0.49 (P <0.001) compared to Year-1. Accordingly, DM medication users considered adherent during treatment declined to only 24.6%. In the subsequent three years of observation, mean MPR and proportion adherent remained considerably low (Figure 2.2). Adherence was poorest in Year +2, MPR = 0.48 and proportion adherent of 24.2%, but overall similar to that observed during the treatment period. The proportion of persistent users, those that did not experience a discontinuation episode (1–DR), was 25.3% at Year-1 and greatest in the treatment period (40.7%, P<0.001), although in each of the 3 years following treatment persistence levels were similar to that of baseline. While adherence throughout the follow-up period was similar between oral DM medication users

on insulin therapy and those on oral medications only, persistence (1–DR) was greater among insulin users in all observation periods (Table 2.3).

Glycemic control

Results on measured HbA_{1C} are reported in Table 2.4. Among DM medication users with laboratory values for HbA_{1C} during periods of interest (n=433), mean HbA_{1C} and proportion not at goal HbA_{1C} were higher during the treatment period (HbA_{1C} 7.32%, *P*=0.001 and 47.8% not at goal HbA_{1C}, *P*<0.001) in comparison to Year-1 (HbA_{1C} 6.96% and 34.9% not at goal HbA_{1C}). Achievement of treatment goal HbA_{1C} continued to decline slightly through Year +3 (Figure 2.3). Despite the trend in increasing mean HbA_{1C} over time, the majority of women maintained relatively good control with fewer women having HbA_{1C} >8.0% (24.7% in Year +1, 24.2% in Year +2, and 21.8% in Year +3).

Glycemic control also varied by adherence status (Table 2.5). Among adherent oral DM medication users mean HbA_{1C} increased from Year-1 to the treatment period (6.45% to 6.83%, *P*<0.001) and remained elevated throughout subsequent years of follow-up. Adherent users had a slightly higher proportion with high HbA_{1C} (>7.0%) during treatment and Year +1 (40.0%, *P*=0.343 and 46.5%, *P*=0.032) compared with Year-1 (34.7% high HbA_{1C}). Nonadherent DM medication users (MPR <0.80) also had a marginally increased mean HbA_{1C} from baseline to treatment (7.32% to 7.46%, *P*=0.390) that remained similarly elevated and consistently higher compared to adherent users. The proportion of nonadherent users with high HbA_{1C} at Year-1 (35.5%) was higher during treatment (50.3%, *P*=0.009) and was greatest in Year +3 (64.7%, *P*<0.001). Insulin users consistently had higher mean HbA_{1C} throughout all observation periods (Table 2.6).

DISCUSSION

A non-trivial number of women diagnosed with breast cancer will have ≥1 concurrent, comorbid conditions for which a need for evidence on quality of survivor care has been identified.[33-35] Our results suggest that adherence to oral DM medications as measured by MPR and DR may be sensitive to timing of breast cancer diagnosis and treatment, and that these effects continue in the years that follow. Medication adherence decreased in the treatment period and remained low in the years following breast cancer diagnosis. Achieving goals for glycemic control in DM treatment also appeared to vary in the years

following diagnosis with increased mean HbA_{1C} compared to baseline. While many factors influence glycemic control among women with DM, these results signal a possible opportunity for improved management of DM among breast cancer survivors particularly with respect to medication adherence.

There is evidence from some but not all epidemiological studies that diabetes and abnormal glucose tolerance are associated with cancer-related death,[36, 37] and several reports link pre-existing diabetes to increased risk of all-cause mortality in breast cancer.[14-16] In a meta-analysis comparing overall survival in cancer patients with and without pre-existing diabetes,[14] there was a 61% increased risk (95% CI, 1.46-1.78) of long-term, all-cause mortality in breast cancer patients with diabetes. It is hypothesized that less aggressive primary breast cancer treatment or diabetes care, both of which could compromise survival, are responsible for such observed associations.[15] Here we consider the latter scenario, in which management of DM through adherence to medications and glycemic control may be compromised during breast cancer treatment and the following years of recovery. Also, certain DM medications, such as metformin, are hypothesized to improve breast cancer prognosis and survival.[21, 38-40] Such a protective effect is potentially mediated through metformin's role in reducing hyperglycemia, decreasing circulating insulin levels and suppressing several metabolic processes that contribute to tumorigenesis.[41] Therefore, adherence to DM medications may become important for improving cancer outcomes in addition to diabetes management and glycemic control.

Relevant epidemiological studies for direct comparison are limited. In a large, independent practice model health maintenance organization (HMO), a cross-sectional study of 6,000 patients in a DM management program[6] described correlations between HbA_{1C} and MPR for use of sulfonylureas (r=-0.295, P<0.001) and metformin (r=-0.285, P<0.001). As such, mean MPR of patients at goal HbA_{1C} ≤7.0% compared with those that did not meet glycemic goals was higher for users of sulfonylureas (0.82 versus 0.72, P<0.001) and metformin users (0.77 versus 0.62, P<0.001) over two years. Using data from an integrated health system, Rolnick et al[5] described medication adherence among a sample of 4,631 patients taking a single oral DM medication and having no other major chronic disease diagnoses. In this select group of patients, median MPR over a 12-month period was 0.81, and only 50% of female and 55% of male DM medication users were considered adherent (MPR ≥0.80). These estimates are similar to women in this study with regard to adherence in the year before diagnosis (MPR=0.86, 75% adherent)

and differ from our MPR observed during treatment (MPR=0.49, 25% adherent). However, while observed adherence declined post-diagnosis and remained low in subsequent years, glycemic control among DM medication users in our cohort was only marginally clinically worse and seems to improve or stabilize by Year +3, particularly for insulin users.

The Institute of Medicine report, *From Cancer Patient to Cancer Survivor: Lost in Transition*,[34] describes the lack of guidelines for and possible inconsistencies on the transfer from cancer-directed care back to primary care providers. Illustrating this possibly complex transition, Snyder et al[35] compared 23,731 breast cancer survivors in the 366 to 730 days post-cancer diagnosis. Women seeing both a primary care provider and oncology specialist versus only a single provider were the most likely to receive recommended cancer screenings (i.e., colorectal cancer and mammography) and other preventive care (i.e., influenza vaccination, cholesterol screening, bone densitometry). Our results add to this limited body of work on chronic comorbid condition care in cancer patients because, to our knowledge, this analysis is the first to report on longitudinal measures of medication adherence and glycemic control among women diagnosed with breast cancer.

Some important limitations to our study should be noted. Although use of automated pharmacy records provides objective and reproducible adherence measures, this methodology has its drawbacks. First, a dispensed medication does not guarantee patients ingested medication as directed, potentially overestimating adherence. Similarly, patients may receive medications from other sources not captured by health plan data and therefore DR may be overestimated. However, this is unlikely given that approximately 97 % of GH enrollees fill their medications at GH-owned or contracted pharmacies.[26, 42, 43] We used two of the most commonly reported and reproducible measures of medication adherence (MPR and DR), but results using other methods to measure adherence and discontinuation may yield different results, particularly with longer periods of observation.[29] We accounted for therapeutic interchange in DM management by considering all days' supply from metformin and sulfonylureas together when calculating MPR and DR. Therefore, this approach was conservative in that changes in therapy would tend toward medication oversupply in MPR and not inflate DR. We note the possible limitations in our study's generalizability. GH enrollees represent a predominantly White, insured population in the United States, thereby excluding a proportion of breast cancer survivors. This is noteworthy given that minority,

uninsured, and/or low-income women may have worse adherence due to financial constraints or problems with access to services. Although we can make broad comparisons to studies of DM medication adherence in the general population, adherence among women in our population without a history of breast cancer would be informative, but beyond the scope of this analysis.

Data from the parent study only went back one year before breast cancer diagnosis, limiting our ability to evaluate the influence of duration of DM medication use before breast cancer diagnosis on post-diagnosis adherence. Analysis of prevalent users, women followed from Year -1 versus incident "new users," may introduce selection bias because prevalent users have, by definition, survived under treatment. The mix of incident and prevalent users stands to dilute differences in adherence behavior between those recently starting DM medications and those on long-term treatment. Also, HbA_{1C} estimates average plasma glucose in the prior 4-12 weeks. Therefore, this measure may not reflect glycemic control entirely throughout each observation period. We lacked information on other factors that can alter glycemic control such as health behaviors (e.g., diet and exercise), short-term corticosteroids co-administered with adjuvant chemotherapy, and nausea/anorexia side effects of chemotherapy. Long-term changes in health behaviors post-breast cancer diagnosis (e.g., adopting healthier eating habits or increasing exercise) could improve glycemic control and lead to medication dose reductions or even warranted discontinuation of medication. We were unable to measure dose reductions but the drop in glycemic control and relatively constant discontinuation rate (except for the treatment period) does not support this argument in our data. Short-term changes in diet coinciding with chemotherapy such as nausea and anorexia may preclude use of oral DM medications and potentially lower MPR. If chemotherapy-related nausea or loss of appetite alone accounted for our observed decreases in adherence then we would perhaps expect adherence to promptly return to pre-diagnosis levels. Although the role of chemotherapy side effects as a cause for glycometabolic disturbance warrants further investigation, the observed sustained decline in MPR suggests that these short-term changes are not the sole explanation for poor adherence. It is also possible that corticosteroids altered glycemic control in the short term, which could actually result in improved adherence and/or addition of therapies. To that end, goal HbA_{1C} and glycemic control are intermediate therapeutic outcomes, not end-point clinical outcomes such as hospitalizations or emergency department visits. Rather, we answer a specific question regarding

how clinical management (often driven by HbA_{1C} values) varies from prior to and in the years following breast cancer diagnosis and treatment. Loss to follow-up due to disenrollment is a potential limitation since these women may differ from women who stay with a health plan longer. However, only 17 (3.3%) cohort members disenrolled during the study period so this did not substantively affect out results.

In the Cochrane review of interventions to improve medication adherence,[44] confounding by severity of disease is noted to be particularly problematic in studies of DM management. For example, intensive insulin therapy is indicated to be added to oral DM therapy when oral therapies alone have failed and glycemic control has worsened. Poorly controlled diabetes also often triggers closer management by nutritionists and diabetes educators to monitor therapy and titrate insulin dosing, which in turn influences both measured adherence and glycemic control.[30] Reporting one of these measures not in the context of other data (e.g., DR with no information on MPR or HbA_{1C}) may limit interpretation of continuance/discontinuation of therapy.[45] Thus, by design, we chose to use multiple measures to examine DM management (i.e., adherence, discontinuation, and glycemic control) and stratify glycemic control and adherence to oral DM medications by insulin use. Understanding adherence to intensive insulin therapy would also be informative but is less reliably measured using automated pharmacy dispensing data.

Our study adds to the current literature and has many strengths including a large population-based cohort of women with (1) automated pharmacy records considered to be valid, complete, and used in other epidemiologic studies; (2) longitudinal, long-term follow-up; (3) complete capture of cancer and recurrences through the SEER registry and medical charts; (4) cancer and treatment characteristics; and (5) information on diagnoses, laboratory values, and demographics. Also, our approach uses multiple measures of adherence and glycemic control such that comparison to future studies and potential interventions to improve outcomes modifiable by drug therapy are possible.[46] Further studies allowing for comparison of medication adherence in both incident and prevalent users among breast cancer survivors and the general population will be important for understanding any differences in the reasons for nonadherence and the role providers may have in managing comorbidities among cancer survivors.

CONCLUSION

Efforts to understand multiple-comorbidity following cancer diagnosis and improve self-management are important to the growing population of breast cancer survivors. We believe our results lend further evidence to and raise awareness of the importance of DM management following breast cancer diagnosis and subsequent years following treatment. Population-level measures to improve diabetes care have been identified and applied to integrated primary care models at GH,[47, 48] and multidisciplinary, tailored approaches such as these may be important tools for addressing adherence and glycemic control among these women. We hope that our results further motivate efforts to address the complex needs for comorbidity care in breast cancer survivorship. While not the focus of this study, patient characteristics (e.g., treatment with adjuvant chemotherapy, frequency of visits to primary care providers) identified to be more prevalent among the nonadherent group versus adherent group during the breast cancer treatment period may provide clues for further research and potential interventions.

NOTES TO CHAPTER 2

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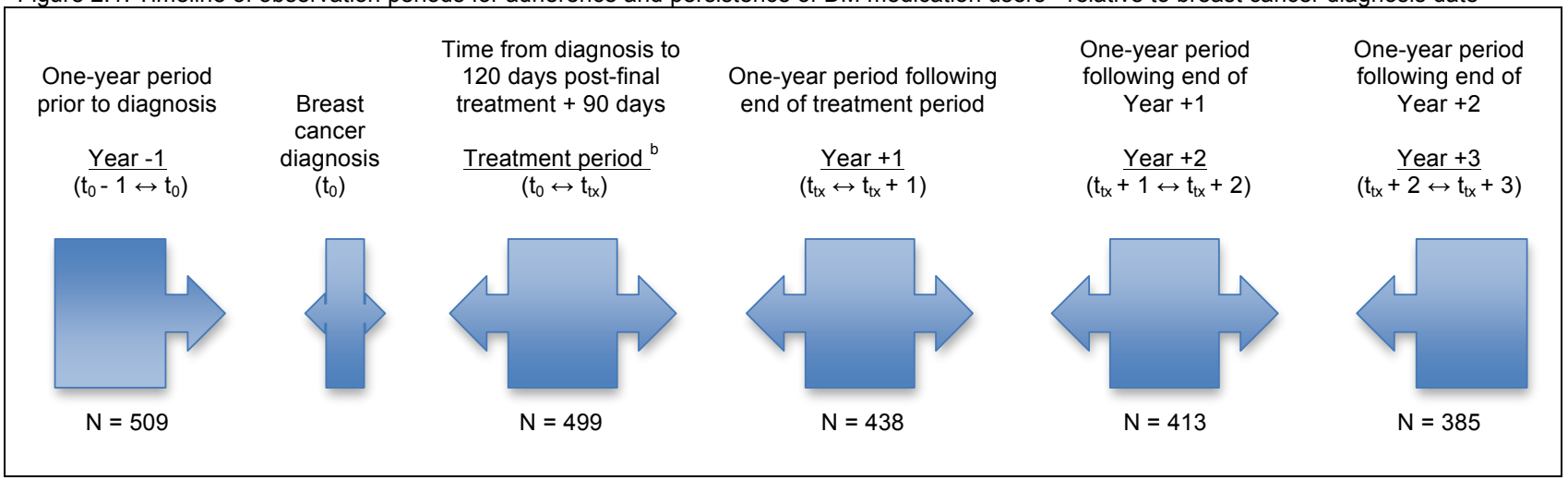
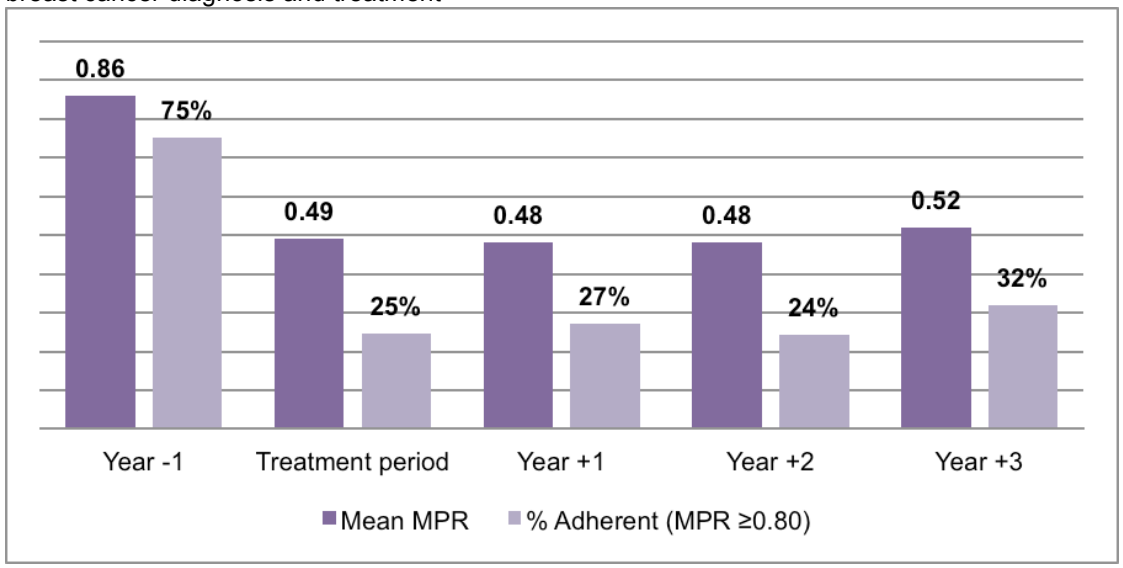
Figure 2.1. Timeline of observation periods for adherence and persistence of DM medication users [a] relative to breast cancer diagnosis date



a. ≥1 Dispensing of metformin and/or sulfonylureas in the year prior to breast cancer diagnosis
b. Treatment period: SEER diagnosis date to 120 days post-final breast cancer treatment noted in the medical chart (surgery, radiation, or chemotherapy) plus 90 days

Figure 2.2. Medication adherence for users of metformin and sulfonylureas prior to and following breast cancer diagnosis and treatment



Abbreviation: MPR, medication possession ratio

Figure 2.3. Glycemic control among users of metformin and sulfonylureas prior to and following breast cancer diagnosis and treatment

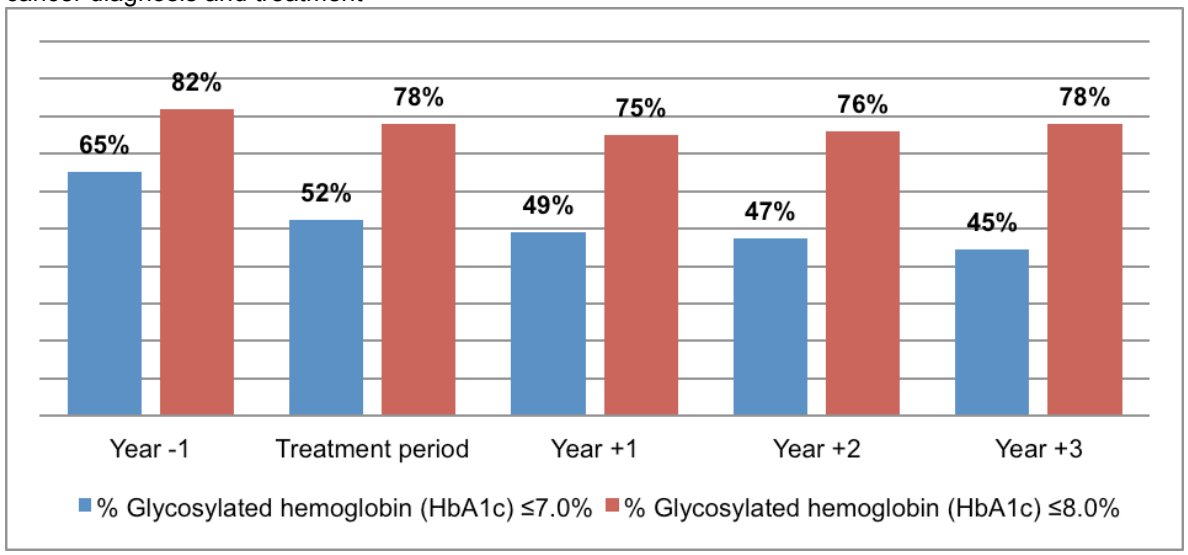


Table 2.1. Characteristics of oral DM medication users at breast cancer diagnosis

	All DM medication users [a] (n=516)		During breast cancer treatment period: Adherent DM medication users [b] (n=123)		During breast cancer treatment period: Nonadherent DM medication users [b] (n=376)	
Year of breast cancer diagnosis						
1990-2000	302	(58.5)	66	(53.7)	232	(61.7)
2001-2004	120	(23.3)	39	(31.7)	77	(20.5)
2005-2008	94	(18.2)	18	(14.6)	67	(17.8)
Length of cancer treatment period (days) [c]						
Median (IQR)	110	(59-185)	113	(76-191)	109	(57-193)
Age (years)						
Median (IQR)	64.3	(11.4)	68	(55-71)	63	(56-76)
18-39	9	(1.8)	1	(0.8)	8	(2.1)
40-49	57	(11.4)	13	(10.6)	44	(11.7)
50-59	116	(23.2)	22	(17.9)	89	(23.7)
60-69	150	(30.1)	32	(26.0)	115	(30.6)
70-79	132	(26.5)	38	(30.9)	91	(24.2)
≥80	51	(10.2)	17	(13.8)	29	(7.7)
Menopausal status						
Premenopausal	105	(20.3)	23	(18.7)	80	(21.3)
Postmenopausal	411	(79.7)	100	(81.3)	296	(78.7)
Race						
White	423	(82.0)	107	(87.0)	293	(77.9)
African American	26	(5.0)	3	(2.4)	23	(6.1)
American Indian / Alaska Native	20	(3.9)	3	(2.4)	20	(5.3)
Asian / Pacific Islander	44	(8.5)	9	(7.3)	39	(10.4)
Unknown	3		1		2	
Ethnicity						
Hispanic	36	(7.0)	7	(5.7)	29	(7.7)
Not Hispanic	480	(93.0)	116	(94.3)	347	(92.3)
Education						
High school or less	82	(31.5)	16	(13.0)	46	(12.2)
Some college	106	(40.8)	18	(14.6)	65	(17.3)
College or post graduate	72	(27.7)	16	(13.0)	50	(13.3)
Unknown	256		73		215	
Body mass index (kg/m^2)						
Mean (SD)	32.3	(6.3)	33.2	(7.4)	31.4	(6.5)
<18.5	4	(0.8)	2	(1.6)	2	(0.5)
18.5-24.9	69	(13.4)	12	(9.8)	56	(14.9)

Table 2.1. Characteristics of oral DM medication users at breast cancer diagnosis

	All DM medication users [a] (n=516)		During breast cancer treatment period: Adherent DM medication users [b] (n=123)		During breast cancer treatment period: Nonadherent DM medication users [b] (n=376)	
25.0-29.9	139	(26.9)	33	(26.8)	106	(28.2)
30.0-34.9	139	(26.9)	31	(25.2)	108	(28.7)
35.0+	165	(32.0)	50	(40.7)	103	(27.4)
Smoking status						
Ever	79	(15.3)	17	(13.8)	55	(14.6)
Never	433	(84.7)	106	(86.2)	321	(85.4)
AJCC stage						
I	318	(61.6)	84	(68.3)	222	(59.0)
IIA	138	(26.7)	25	(20.3)	108	(28.7)
IIB	60	(11.6)	14	(11.4)	46	(12.2)
Lymph node status [d]						
Negative	383	(74.4)	82	(66.7)	253	(67.3)
Positive	132	(25.6)	22	(17.9)	91	(24.2)
Unknown	1		19		32	
Comorbidities						
Hypertension	440	(85.3)	104	(84.5)	320	(85.1)
Ischemic heart disease	175	(35.1)	53	(43.1)	122	(32.4)
Charlson comorbidity index [e]						
0	177	(34.2)	28	(22.8)	175	(46.5)
1	197	(38.2)	51	(41.5)	118	(31.4)
2+	122	(23.6)	37	(30.1)	72	(19.1)
Missing (pre-1993)	20		7		11	
Surgical procedure						
Mastectomy ± radiation	195	(39.7)	57	(46.3)	138	(36.7)
Breast conserving, radiation (+)	258	(51.5)	60	(48.8)	191	(50.8)
Breast conserving, radiation (-)	63	(12.2)	13	(10.6)	40	(10.6)
Other breast cancer treatments						
Chemotherapy	153	(29.7)	27	(22.0)	120	(31.9)
Endocrine therapy	301	(58.3)	65	(52.8)	226	(60.1)
Completed 5 years endocrine therapy	130	(43.2)	26	(40.0)	104	(46.0)
Chemotherapy + Endocrine therapy	109	(21.1)	16	(13.0)	78	(20.7)
# Primary care physician visits within one year post-diagnosis						
Mean (SD)	4.0	(3.9)	4.3	(3.6)	3.9	(4.0)
0-1 visit only	147	(28.5)	28	(22.8)	113	(30.1)

Table 2.1. Characteristics of oral DM medication users at breast cancer diagnosis

	All DM medication users [a] (n=516)	During breast cancer treatment period: Adherent DM medication users [b] (n=123)	During breast cancer treatment period: Nonadherent DM medication users [b] (n=376)
≥2 visits	369 (71.5)	95 (77.2)	263 (69.9)
DM medication use			
Metformin only	149 (28.9)	38 (30.9)	111 (29.5)
Sulfonylureas only	195 (37.8)	48 (39.0)	147 (39.1)
Metformin plus sulfonylureas	165 (32.0)	37 (30.1)	128 (34.0)
Any DM medication plus insulin	220 (42.6)	39 (31.7)	148 (39.4)
Other DM medications only [f]	7 (1.4)		
# CVD prescriptions used concurrently throughout study period [g]			
1 medication only	102 (19.8)	23 (18.7)	67 (17.8)
≥2 medications	414 (80.2)	100 (81.3)	309 (82.2)
≥3 medications	248 (48.1)	52 (42.3)	195 (51.9)
≥4 medications	150 (29.1)	33 (26.8)	140 (37.2)

Abbreviations: *IQR* interquartile range, *SD* standard deviation, *AJCC* American Joint Committee on Cancer
Note: Values are presented as *n* (%) unless otherwise noted

a. ≥1 dispensing of oral DM medication in the year prior to breast cancer diagnosis
b. Post-diagnosis adherence defined as MPR ≥0.80 to metformin/sulfonylureas, breast cancer diagnosis through treatment period
c. Last date of primary breast cancer treatments (surgery, radiation or chemotherapy)
d. From SEER registry or chart when missing from SEER
e. Deyo RA, Cherkin DC, Ciol MA. J Clin Epidemiol. 1992;45: 613-619.
f. Other DM medications: meglitinides, thiazolidinediones or DPP-4 inhibitors
g. CVD prescriptions used: highest number through Year +3 of concurrent oral medications to treat DM, dyslipidemias or hypertension

Table 2.2. Adherence and persistence of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment

		Adherence					Persistence						
		MPR			Adherent users (MPR ≥0.80)		Discontinuation episodes				DR	Persistent users (1–DR)	
	N	Mean	SD	IQR	n	(%)	Mean	SD	Median	IQR	(%)	n	(%)
Year -1	509	0.86	0.26	0.67-0.99	383	75.3%	1.23	1.41	1	0-2	74.7%	129	25.3%
Treatment period	499	0.49*	0.31	0.25-0.67	123	24.6%*	1.06	1.25	1	0-1	59.3%	186	40.7%*
Year +1	438	0.48*	0.32	0.25-0.82	118	27.1%*	1.16	1.50	1	0-2	75.6%	107	24.4%
Year +2	413	0.48*	0.30	0.25-0.74	100	24.2%*	1.22	1.56	1	0-2	71.5%	118	28.5%
Year +3	385	0.52*	0.32	0.25-0.87	122	31.8%*	1.97*	2.57	2	0-2	70.5%	113	29.5%

Abbreviations: MPR, medication possession ratio; DR, discontinuation rate; SD, standard deviation; IQR, interquartile range
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table 2.3. Adherence and persistence of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment among oral DM medication users on concurrent insulin therapy and users of oral DM medications only

		Adherence					Persistence						
		MPR			Adherent users (MPR ≥0.80)		Discontinuation episodes				DR	Persistent users (1–DR)	
	N	Mean	SD	IQR	n	(%)	Mean	SD	Median	IQR	(%)	n	(%)
Insulin users													
Year -1	220	0.86	0.26	0.82-0.99	168	76.4%	2.12	2.44	1	0-3	69.5%	68	30.5%
Treatment period	187	0.47*	0.29	0.25-0.99	39	20.9%*	1.16*	1.43	1	0-2	58.3%	78	41.7%
Year +1	186	0.47*	0.31	0.25-0.82	48	25.8%*	2.15	2.45	1	0-3	74.7%	47	25.3%
Year +2	184	0.46*	0.30	0.25-0.82	42	22.8%*	2.12	2.45	2	0-3	65.8%	63	34.2%
Year +3	182	0.50*	0.32	0.25-0.82	59	32.4%*	1.67	1.97	1	0-3	65.4%	63	34.6%
Insulin non-users													
Year -1	289	0.85	0.26	0.74-0.99	213	73.7%	2.34	2.37	2	1-3	81.7%	53	18.3%
Treatment period	272	0.52*	0.33	0.25-0.99	82	30.1%*	0.92*	0.91	1	0-1	61.0%	106	39.0%*
Year +1	251	0.51*	0.32	0.25-0.82	73	29.1%*	2.17	2.56	1	1-3	76.9%	58	23.1%
Year +2	231	0.50*	0.31	0.25-0.82	60	26.0%*	2.35	2.69	2	1-3	78.8%	49	21.2%
Year +3	201	0.54*	0.31	0.25-0.82	62	30.8%*	2.29	3.07	2	1-3	76.1%	48	23.9%

Abbreviations: MPR, medication possession ratio; DR, discontinuation rate; SD, standard deviation; IQR, interquartile range
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table 2.4. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment

	Glycemic control							
			HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.32*	0.072	7.18-7.46	191	47.9%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.42*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.064	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table 2.5. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment by adherence status

		Glycemic control						
		HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Adherent users (MPR ≥0.80)								
Year -1	326	6.45	0.049	6.35-6.55	113	34.7%	52	16.0%
Treatment period	105	6.83*	0.081	6.67-6.99	42	40.0%	19	18.1%
Year +1	101	6.90*	0.078	6.75-7.05	47	46.5%	21	20.8%
Year +2	84	6.96*	0.087	6.79-7.13	31	36.9%	27	32.1%*
Year +3	103	6.96*	0.081	6.80-7.12	36	35.0%	22	21.4%
Nonadherent users (MPR <0.80)								
Year -1	107	7.32	0.157	7.01-7.63	38	35.5%	19	17.8%
Treatment period	294	7.46	0.080	7.30-7.62	148	50.3%	67	22.8%
Year +1	271	7.52	0.081	7.36-7.68	143	52.8%	70	25.8%
Year +2	267	7.53	0.081	7.37-7.69	154	57.7%*	60	22.5%
Year +3	224	7.42	0.073	7.28-7.56	145	64.7%*	51	22.8%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table 2.6. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment among oral DM medication users on concurrent insulin therapy and users of oral DM medications only

	Glycemic control							
		HbA_{1C}			HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Insulin users								
Year -1	187	8.12	0.141	7.84-8.40	127	67.9%	76	40.6%
Treatment period	159	7.85	0.121	7.61-8.09	104	65.4%	57	35.8%
Year +1	158	7.80	0.117	7.57-8.03	100	63.3%	56	35.4%
Year +2	156	7.67	0.118	7.44-7.90	95	60.9%	50	32.1%
Year +3	148	7.43*	0.100	7.23-7.63	90	60.8%	38	25.7%
Insulin non-users								
Year -1	246	6.40	0.071	6.26-6.54	46	18.7%	16	6.5%
Treatment period	230	6.84*	0.073	6.70-6.98	74	32.2%*	22	9.6%
Year +1	214	6.98*	0.078	6.83-7.13	80	37.4%*	27	12.6%
Year +2	195	7.05*	0.081	6.89-7.21	80	41.0%*	25	12.8%
Year +3	179	7.04*	0.075	6.89-7.19	80	44.7%*	29	16.2%*

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

CHAPTER 3

Overall Summary

This dissertation provides evidence from a large population-based cohort study that presence of metabolic syndrome risk factors (i.e., weight risk, hypertension, low HDL-cholesterol, hypertriglyceridemia and diabetes or impaired glucose tolerance) may increase risk of second breast cancer events in early stage breast cancer. Our results suggest that compared to women with no metabolic syndrome components, presence of ≥3 metabolic syndrome components increases risk of breast cancer recurrence (HR=1.65, 95% CI 1.15-2.38), breast cancer-specific mortality (HR=1.65, 95% CI 1.02-2.69) and overall mortality (HR=1.81, 95% CI 1.44-2.29), whereas the association with second primary breast cancer (HR=1.16, 95% CI 0.59-2.27) was not statistically significant. Similarly, weight risk increased risk of breast cancer recurrence (HR=1.49, 95% CI 1.21-1.83) and point estimates were suggestive of an association with second primary breast cancer (HR=1.25, 95% CI 0.88-1.77). Point estimates for DM were also suggestive of an association with breast cancer recurrence (HR=1.36, 95% CI 0.95-1.49) and second primary breast cancer (HR=1.29, 95% CI 0.85-1.97) but the confidence limits included 1.0. Describing these relationships is especially important given the increasing number of breast cancer survivors and the high prevalence of comorbid conditions in this population. Therefore, although the role of MetS requires additional research to confirm a distinct etiology, efforts to prevent or improve management of these conditions may have benefits in both cancer-related and non-cancer-related outcomes for these women.

Interpretation of results from our study should be made in the context of the limitations previously discussed in Chapter 1. The women included in this cohort were sampled from an insured, primarily Caucasian population and enrolled on a health plan. This may limit the generalizability of our results to minority women in the United States among whom national data suggests the prevalence of metabolic syndrome is higher than in White women. Also, while we ascertained and considered many potential

confounders, we lacked data on certain lifestyle factors such as diet and physical activity that influence the presence of metabolic syndrome risk factors and outcomes in breast cancer.

Our study also supports the hypothesis that adherence to oral diabetes medications and glycemic control may be sensitive to breast cancer diagnosis and treatment, and declines in medication adherence and glycemic control may persist in subsequent years and lag in returning to pre-diagnosis levels. Some epidemiologic studies support a beneficial role of metformin, a first-line oral diabetes medication, in breast cancer outcomes and clinical trials of metformin in the breast cancer adjuvant therapy setting are ongoing. If the role of metformin in chemoprevention is confirmed, then medication adherence to this commonly used diabetes medication could have implications for both outcomes in cancer and diabetes.

To our knowledge, this study is one of the first of its kind to report on longitudinal measures of adherence to oral diabetes medications and glycemic control among women diagnosed and treated for early stage breast cancer. The limitations described in Chapter 2 should be considered when interpreting data from automated pharmacy dispensing records for prevalent users of diabetes medications. Indeed, this study sought to answer a specific question related to clinical management of diabetes therapy prior to and following breast cancer diagnosis. With high potential of long-term survival following successful treatment of early stage breast cancer, improved management of diabetes with regard to medication adherence and glycemic control could have clinically meaningful consequences and also reduce the substantial healthcare costs associated with nonadherence. Additional study in this area should consider factors related to poor adherence to medications for chronic conditions and further guide clinicians to address the needs for high quality comorbid condition care among breast cancer survivors. Moving forward from the stresses of cancer diagnosis and treatment, optimization of care for cancer survivors will require a better understanding of patients' preferences, self-efficacy and communication barriers between patients and providers or systems of care.

We hope that our study highlights the considerable prevalence of comorbidity in the growing breast cancer survivor population and emphasizes the importance of surveillance for and management of metabolic syndrome risk factors. If our findings are borne out and confirmed in further studies, then this knowledge could be used to improve prevention of both cardiovascular and cancer-related outcomes in breast cancer survivors at risk for metabolic syndrome.

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APPENDIX A

Sensitivity Analyses of Criteria for and Approaches to Missing Data on Metabolic Syndrome Exposures

The objectives of these sensitivity analyses were to describe the missing data in covariates defining metabolic syndrome components and to determine how our results could be influenced by missingness assumptions. Classification of exposure using automated and electronic health record data obtained in the course of clinical practice can lead to measurement error and bias when covariate data are missing.[1, 2] For instance, the potential for this bias to affect our observed results is present with the MetS exposure constituent condition hypertriglyceridemia due, in part, to infrequent laboratory testing of triglycerides in women overall and particularly in women followed in earlier years of the study period.

In our study design, we used alternative electronic data elements as surrogates for direct measurement of MetS factors. For example, women potentially misclassified as unexposed to a MetS factor (e.g., no TG tests performed in the year prior to diagnosis) were considered exposed as of the date of an ICD-9 diagnosis code in the medical record or dispensing of medication used for treatment (e.g., hypertriglyceridemia diagnosis or fibrates dispensed) (Table A.1). In adopting this exposure classification scheme, we make a strong not missing at random (NMAR) assumption. This informative missingness assumes that with no direct measures of a MetS component available, nor any surrogate measure from the medical chart or pharmacy dispensings present, the MetS constituent condition is absent (unexposed) at that point in time. Further, a woman diagnosed and treated for hypertriglyceridemia, hyperglycemia, or hypertension with normal laboratory values could potentially be misclassified as unexposed if not taking into account diagnosis of the condition or its treatment (i.e., documented diagnosis and/or medications dispensed).

We examined the agreement between the varying criteria for MetS component exposure. The proportion of women in the COMBO cohort with “complete” (non-missing) clinical/laboratory data

available to classify MetS exposure is described in Table A.2, indicating women with missing data on these covariates overall. The prevalence of MetS exposures throughout the study period is described in Table A.3, indicating women with prevalent conditions based on one or more data elements (and proportion with missing laboratory data). From these data we see that there tends to be strong agreement between exposure surrogates. For instance, of the 2,756 women with a diagnosis of hypertension throughout follow, 2,375 (86.2%) also had an antihypertensive medication dispensed but only 728 (26.4%) with elevated blood pressure measurements. Also, in women with a surrogate-classified exposure, the proportion of missing data is lower. For example, in the overall cohort of 4,216 women, there were 802 (19.0%) with no BP measurements. Whereas, among the 2,756 women with antihypertensive medication dispensed, there were 272 (9.9%) with no BP measurements.

To evaluate the sensitivity of our results to missingness assumptions we performed a post hoc sensitivity analysis using multiple imputation (MI) with an assumption of data missing at random (MAR). Using MI under MAR, we imputed datasets and estimated risks of SBCE and death for women with missing data to define MetS criteria (e.g., for hypertriglyceridemia, no laboratory values for TG available with no diagnosis documented and no dispensings of fibrates). The working assumption of MI that data are MAR implies that the reason for the missing data does not depend on the unseen data given the observed data. While our strong a priori assumption (NMAR) relies on the data being informatively missing, it is likely that other data among our large number of covariates explains, in part, the reason for missingness.[3] If such overlap in the MAR and NMAR distributions exists, our sensitivity analysis provides insight to the degree that our main approach relies on NMAR assumptions.

We performed multiple imputation for estimates of adjusted hazard ratios and confidence intervals based on M=500 datasets of the 4,216 women eligible for SBCE, in which covariate data on laboratory values or clinical measurements to define MetS exposures were missing at baseline. Models for multiple imputation were specified in SAS PROC MI[4] separately for number of MetS components present and presence of each of the MetS components fit to a multivariate normal distribution. The procedure applied to the models for multiple imputation used the Markov Chain Monte Carlo (MCMC) method with a single chain to create 500 imputed datasets. MCMC was selected versus parametric regression methods to account for the non-monotone patterns of missingness in the data. The starting

value for the chain was computed from the expectation-maximization (EM) algorithm as the posterior mode with a non-informative prior, the highest observed-data posterior density. The imputation procedure took 200 burn-in iterations before the first imputation and 100 iterations between imputations to eliminate the series of dependence on the starting value of the Markov chain and to achieve the stationary distribution. The between-imputation iterations in a single chain were used to eliminate the series' dependence between two imputations. Results from the analyses for the imputed datasets were combined using Rubin's rules with MIANALYZE.[5] Examination of the trace and autocorrelation confirmed the model had converged.

Covariates included in the models for MI under MAR were those included in the multivariate-adjusted models (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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables, as well as presence of other MetS components.

Results from our application of MI under MAR are described in Table A.4 (second breast cancer events, recurrence, second primary breast cancer) and Table A.5 (breast cancer-specific mortality, overall mortality). Compared with our main analyses with a strong NMAR assumption, estimates from MI under MAR did not differ substantially in the effects of number of MetS components present with respect to statistical significance nor direction. Some variance in the estimates for individual MetS components was present but remained not statistically significant, and therefore, did not influence inference made in our main analyses.

SUMMARY

We performed sensitivity analyses to describe the patterns of missing data among the covariates used to define exposure to MetS components. As expected, there was strong agreement between surrogate measures to define MetS components (i.e., documented diagnosis and dispensing of medication for treatment). A slightly greater proportion of missing data on laboratory values and/or clinical

measurements to define MetS components was present among women considered to be unexposed per our main classification scheme with a strong assumption of NMAR. Application of multiple imputation under MAR to account for these missing covariates yielded results similar to our main analysis and suggests that our data are not substantially influenced by varying assumptions made with respect to missing data on MetS components.

NOTES TO APPENDIX A

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Table A.1. Classification of metabolic syndrome components in the COMBO study

Weight risk	BMI ≥27.7 kg/m^2 as a proxy for waist circumference ≥88 cm
Hypertension	≥2 blood pressure measurements ≥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} ≥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

Table A.2. Frequency of clinical measurements for metabolic syndrome components

	At baseline, pre-diagnosis year		Throughout study period	
	n	(%)	n	(%)
BMI measurement	4,196	(99.5)	4,196	(99.5)
Missing BMI	20	(0.5)	20	(0.5)
≥1 BP measurements	3,211	(76.2)	3,789	(89.9)
≥2 BP measurements	1,639	(38.9)	1,967	(46.7)
Missing (no BP measurements)	1,005	(23.8)	427	(10.1)
≥1 HDL laboratory values	2913	(69.1)	3,408	(80.8)
Missing (no HDL lab values)	1303	(30.9)	808	(19.2)
≥1 TG laboratory values	1645	(39.0)	1,810	(42.9)
Missing (no TG lab values)	2571	(61.0)	2,406	(57.1)
≥1 FPG laboratory values	1,054	(25.0)	1,202	(28.5)
≥1 HbA_{1C} laboratory values	870	(20.6)	1,009	(23.9)
≥1 FPG or HbA_{1C} laboratory values	1,138	(27.0)	1,331	(31.6)
Missing (no glucose lab values)	3,078	(73.0)	2,885	(68.4)

Table A.3. Prevalence of metabolic syndrome components throughout study period by exposure criteria

	n	(%)
Weight risk		
BMI ≥27.7 kg/m^2 (main analysis)	2,210	(52.4)
Hypertension		
≥1 of exposure criteria (main analysis)	2,877	(68.2)
Missing BP (no BP measurements available)	222	(7.7)
Documented hypertension diagnosis	2,756	(65.4)
with blood pressure medication dispensed	2,375	(86.2)
with elevated BP measurements	728	(26.4)
Missing BP (no BP measurements available)	272	(9.9)
Blood pressure medication dispensed	2,522	(59.8)
with documented hypertension diagnosis	2,284	(90.6)
with elevated BP measurements	702	(27.8)
Missing BP (no BP measurements available)	248	(9.8)
Elevated BP measurements	802	(19.0)
with documented hypertension diagnosis	762	(95.0)
with blood pressure medication dispensed	702	(87.5)
Low HDL		
HDL laboratory values <50 mg/dl (main analysis)	1,039	(24.6)
Hypertriglyceridemia		
≥1 of exposure criteria (main analysis)	67	(1.6)
Missing TG (no TG laboratory values available)	1	(1.5)
Documented hypertriglyceridemia diagnosis	67	(100)
with hypertriglyceridemia medication dispensed	66	(98.5)
with elevated TG laboratory values	65	(97.0)
Missing TG (no TG laboratory values available)	1	(1.5)
Hypertriglyceridemia medication dispensed	66	(98.5)
with documented hypertriglyceridemia diagnosis	66	(100)
with elevated TG laboratory values	65	(98.5)
Missing TG (no TG laboratory values available)	0	
Elevated TG laboratory values	65	(97.0)
with documented hypertriglyceridemia diagnosis	65	(100)
with hypertriglyceridemia medication dispensed	65	(100)
Diabetes or impaired fasting glucose		
≥1 of exposure criteria (main analysis)	1,107	(26.3)
Missing glucose (no glucose laboratory values available)	148	(13.4)
Documented diabetes diagnosis	647	(15.3)
with diabetes medication dispensed	534	(82.5)
with elevated glucose laboratory values	169	(26.1)
Missing glucose (no glucose laboratory values available)	71	(11.0)
Diabetes medication dispensed	547	(13.0)
with documented diabetes diagnosis	534	(97.6)
with elevated glucose laboratory values	169	(30.9)

Missing glucose (no glucose laboratory values available)	65	(11.9)
Elevated glucose laboratory values	453	(10.7)
with documented diabetes diagnosis	298	(65.8)
with diabetes medication dispensed	169	(37.3)

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

Table A.4. Adjusted hazard ratios and 95% confidence intervals for the association of metabolic syndrome (MetS) and its individual components as time-varying throughout follow-up with risk of second breast cancer events (recurrence and second primary breast cancer) in the COMBO study with multiple imputation of missing MetS covariates

	All SBCE cases (*n*=558) MV-adjusted HR (95% CI) [a]	Recurrence (*n*=415) MV-adjusted HR (95% CI) [a]	Second primary BC (*n*=143) MV-adjusted HR (95% CI) [a]
# of MetS components [b,c]			
0 present (112 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1 only (163 cases)	1.18 (0.88-1.54)	1.22 (0.95-1.48)	0.96 (0.58-1.66)
2 only (145 cases)	1.40 (0.92-1.37)	1.50 (1.16-1.93)	1.16 (0.67-2.01)
≥3 (138 cases)	1.47 (1.10-2.26)	1.72 (1.17-2.64)	1.22 (0.49-2.24)
P-trend	0.047	0.046	0.316
Individual components [b,c]			
Weight risk [d]			
No (249 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (309 cases)	1.25 (1.01 -1.78)	1.27 (1.12-1.50)	1.24 (0.78-2.08)
Hypertension (HTN)			
No (234 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (324 cases)	1.01 (0.78-1.08)	1.08 (0.62-1.44)	1.20 (0.63-1.74)
Low HDL cholesterol			
No (420 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (138 cases)	0.77 (0.48-1.05)	1.03 (0.61-1.18)	0.82 (0.58-1.61)
High triglycerides			
No (546 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (12 cases)	4.04 (0.86-11.56)	2.65 (0.33-16.37)	9.72 (1.12-76.49)
Diabetes (DM) or impaired glucose tolerance			
No - neither (417 cases)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes - both (141 cases)	1.41 (0.90-1.20)	1.45 (0.85-1.64)	0.80 (0.45-2.02)
Diabetes (DM)	1.48 (0.92-1.61)	1.54 (0.96-1.55)	1.50 (0.71-2.03)
Impaired glucose tolerance	1.13 (0.71-1.27)	1.04 (0.71-1.46)	0.98 (0.55-1.59)

[a] Multivariate models 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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables; receipt of surveillance mammography (yes/no in prior 12 months) as time-varying; accounting for competing risks in multivariate-adjusted models. Estimates for individual MetS components are mutually adjusted for all other MetS components in addition to above covariates.

[b] Multiple imputation for estimates of adjusted hazard ratios and confidence intervals were based on M=500 datasets of 4,216 women eligible for SBCE, in which covariate data on laboratory values or clinical measurements to define MetS exposures were missing at baseline under an assumption of missing at random (MAR); models for multiple imputation were specified for number of MetS components present and presence of each of the MetS components in SAS PROC MI by fitting to a multivariate normal distribution

[c] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; HTN: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

[d] Arterburn 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 A.5. Adjusted hazard ratios and 95% confidence intervals for the association of metabolic syndrome (MetS) and its individual components as time-varying throughout follow-up with risk of breast cancer-specific and overall mortality in the COMBO study with multiple imputation of missing MetS covariates

	Breast cancer-specific mortality (*n*=259) MV-adjusted HR (95% CI) [a]	Overall mortality (*n*=929) MV-adjusted HR (95% CI) [a]
# of MetS components [b,c]		
0 present (54/133 cases)	1.00 (ref.)	1.00 (ref.)
1 only (84/298 cases)	0.97 (0.76-1.47)	1.10 (0.93 -1.30)
2 only (66/255 cases)	1.09 (0.68-1.53)	1.22 (1.00 -1.49)
≥3 (55/243 cases)	1.62 (1.09 -2.61)	1.69 (1.39-2.07)
P-trend	0.252	0.001
Individual components [b,c]		
Weight risk [d]		
No (120/462 cases)	1.00 (ref.)	1.00 (ref.)
Yes (139/467 cases)	1.40 (1.20-1.58)	0.92 (0.79-1.29)
Hypertension (HTN)		
No (174/285 cases)	1.00 (ref.)	1.00 (ref.)
Yes (85/643 cases)	0.86 (0.71-1.31)	1.28 (1.06-1.63)
Low HDL cholesterol		
No (194/699 cases)	1.00 (ref.)	1.00 (ref.)
Yes (65/230 cases)	0.95 (0.55-1.50)	1.06 (0.78-1.26)
High triglycerides		
No (255/924 cases)	1.00 (ref.)	1.00 (ref.)
Yes (4/5 cases)	1.33 (0.69-11.30)	2.26 (0.33-13.12)
Diabetes (DM) or impaired glucose tolerance		
No – neither (198/671 cases)	1.00 (ref.)	1.00 (ref.)
Yes – both (61/258 cases)	1.14 (0.61-1.58)	1.38 (1.22-1.84)
Diabetes (DM)	1.15 (0.65-1.71)	1.70 (1.47-1.93)
Impaired glucose tolerance	1.01 (0.67-1.22)	1.22 (1.12-1.83)

Note: We excluded 20 women from analyses due to missing BMI information; cases refer to number of BC-specific deaths/overall deaths

[a] Multivariate models 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), race (White, African American, American Indian/Alaska Native, Asian/Pacific Islander, unknown), smoking status (current, past, never), menopausal status (pre- or perimenopausal, postmenopausal) as categorical variables; receipt of surveillance mammography (yes/no in prior 12 months) as time-varying; accounting for competing risks in multivariate-adjusted models for breast cancer-specific mortality. Estimates for individual MetS components are mutually adjusted for all other MetS components in addition to above covariates.

[b] Multiple imputation for estimates of adjusted hazard ratios and confidence intervals were based on M=500 datasets of 4,216 women eligible for SBCE, in which covariate data on laboratory values or clinical measurements to define MetS exposures were missing at baseline under an assumption of missing at random (MAR); models for multiple imputation were specified for number of MetS components

present and presence of each of the MetS components in SAS PROC MI by fitting to a multivariate normal distribution

[c] Metabolic syndrome components defined as Weight risk: BMI ≥27.7 kg/m^2 as proxy for waist circumference ≥88 cm; HTN: ≥2 blood pressure measurements ≥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} ≥5.7%, DM diagnosis or DM medications dispensed

[d] Arterburn 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

APPENDIX B

Sensitivity Analyses of Observation Periods for Treatment Period and Glycemic Control

Use of automated pharmacy dispensing to determine medication adherence and discontinuation has advantages of providing reproducible estimates of medication possession ratio (MPR) and discontinuation rates (DR), two of the most commonly reported measures reported in the adherence literature.[1] They are both, however, sensitive to the length of observation periods in epidemiologic studies.[2] We also further examined how the use of multiple glycosylated hemoglobin laboratory values in an observation period medication influences our results on glycemic control among users of oral DM medications. The objectives of these sensitivity analyses were to determine if results from our analyses on medication adherence and glycemic control are dependent on the definitions of length of treatment period and measures used to define glycemic control.

In our approach, we estimated medication adherence and discontinuation prior to and following diagnosis of incident breast cancer by defining periods of medication use that include a treatment period where women undergo primary breast cancer treatments (i.e., surgery, radiation, and chemotherapy). We tested the hypothesis that medication adherence and glycemic control vary post-breast cancer diagnosis and that these changes persist into the years following. In sensitivity analyses, we examined if the observed changes in medication adherence and glycemic control could be explained by varying lengths of treatment for breast cancer. If shorter (or longer) length of observation periods during treatment accounted entirely for the observed changes in medication adherence or glycemic control, then we would could perhaps expect these measures to return to pre-diagnosis levels promptly thereafter.

Our main results describe glycemic control using the highest of HbA_{1C} laboratory values within each observation period for users of oral DM medications and how these compare with clinical treatment goals of ≤7% and ≤8% for DM pharmacotherapy.[3] We evaluated how our results differ when using the

lowest of HbA_{1C} laboratory values and the mean of multiple measurements to determine glycemic control. Explanations for multiple HbA_{1C} laboratory values in a given observation period include the possibility that providers are following some women more closely (e.g., monitoring of laboratory values occurs more every 3-6 months versus only annually) or possibly that multiple tests are performed as a result of poor glycemic control where medication is titrated. We selected the highest of HbA_{1C} laboratory values in a given observation period in our main analysis to determine if poor glycemic control or unmet treatment goals coincided with changes in medication adherence. Certainly, other determinants of glycemic control exist and other HbA_{1C} laboratory values could be considered as indications of glycemic control.

Results from our sensitivity analyses with varying definitions of post-breast cancer diagnosis treatment periods are described in Tables B.1 to B.6 and with varying definitions of HbA_{1C} laboratory value to determine glycemic control in Tables B.7 to B.9. Compared with our main analysis, few differences were observed in our results. With regard to length of treatment period, some modest changes occurred that reflect the time sensitivity of MPR and DR, particularly greater opportunity to "discontinue" treatment with a longer observation period. Very minor differences were observed with regard to HbA_{1C} laboratory values to define glycemic control, including meeting treatment goals of ≤7% and ≤8%.

SUMMARY

We performed sensitivity analyses to describe changes in our results as we varied the length of observation periods and the selection of which laboratory values define glycemic control. As mentioned in Chapter 2, few studies offer longitudinal measures of medication adherence, discontinuation, or clinical control when evaluating pharmacotherapy. Our findings of few changes in our results provide some assurance that the observed changes in adherence and glycemic control are not determined solely by length of the treatment period. As expected, minimal differences were observed when we used different criteria to select HbA_{1C} laboratory values in measuring glycemic control. Compared with other clinical measurements used to monitor DM therapies, such as fasting plasma glucose, HbA_{1C} laboratory values measure average glycemic control over longer periods (i.e., prior 4-12 weeks). Further, most women in this setting had only ≤2 HbA_{1C} laboratory values during observation periods, where perhaps drastic differences in glycemic control based on these measurements in a single period would be less likely.

NOTES TO APPENDIX B

1. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. 2006;15: 565-574; discussion 575-567.

2. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008: CD000011.

3. American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care. 2013;36 Suppl 1: S11-66.

Table B.1. Adherence and persistence of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 120 days post-final treatment + 90 days, main analysis)

		Adherence					Persistence						
		MPR			Adherent users (MPR ≥0.80)		Discontinuation episodes				DR	Persistent users (1–DR)	
	N	Mean	SD	IQR	n	(%)	Mean	SD	Median	IQR	(%)	n	(%)
Year -1	509	0.86	0.26	0.67-0.99	383	75.3%	1.23	1.41	1	0-2	74.7%	129	25.3%
Treatment period	499	0.49*	0.31	0.25-0.67	123	24.6%*	1.06	1.25	1	0-1	59.3%	186	40.7%*
Year +1	438	0.48*	0.32	0.25-0.82	118	27.1%*	1.16	1.50	1	0-2	75.6%	107	24.4%
Year +2	413	0.48*	0.30	0.25-0.74	100	24.2%*	1.22	1.56	1	0-2	71.5%	118	28.5%
Year +3	385	0.52*	0.32	0.25-0.87	122	31.8%*	1.97*	2.57	2	0-2	70.5%	113	29.5%

Abbreviations: MPR, medication possession ratio; DR, discontinuation rate; SD, standard deviation; IQR, interquartile range
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.2. Adherence and persistence of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 180 days)

		Adherence					Persistence						
		MPR			Adherent users (MPR ≥0.80)		Discontinuation episodes				DR	Persistent users (1–DR)	
	N	Mean	SD	IQR	n	(%)	Mean	SD	Median	IQR	(%)	n	(%)
Year -1	509	0.86	0.26	0.67-0.99	383	75.3%	1.23	1.41	1	0-2	74.7%	129	25.3%
Treatment period	499	0.45*	0.32	0.25-0.67	120	24.0%*	1.01	1.21	1	0-1	59.7%	201	40.3%*
Year +1	438	0.49*	0.32	0.25-0.82	118	26.9%*	1.20	1.43	1	0-2	71.5%	125	28.5%
Year +2	413	0.48*	0.30	0.25-0.74	104	25.2%*	1.22	1.56	1	0-2	71.7%	117	28.3%
Year +3	385	0.52*	0.32	0.25-0.87	120	31.2%*	1.97*	2.57	2	0-2	70.9%	112	29.1%

Abbreviations: MPR, medication possession ratio; DR, discontinuation rate; SD, standard deviation; IQR, interquartile range
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.3. Adherence and persistence of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 365 days)

		Adherence					Persistence						
		MPR			Adherent users (MPR ≥0.80)		Discontinuation episodes				DR	Persistent users (1–DR)	
	N	Mean	SD	IQR	n	(%)	Mean	SD	Median	IQR	(%)	n	(%)
Year -1	509	0.86	0.26	0.67-0.99	383	75.3%	1.23	1.41	1	0-2	74.7%	129	25.3%
Treatment period	499	0.47*	0.31	0.25-0.67	129	25.9%*	1.06	1.25	1	0-1	65.3%	173	34.7%*
Year +1	438	0.49*	0.30	0.25-0.82	119	27.2%*	1.16	1.50	1	0-2	76.3%	104	23.7%
Year +2	413	0.48*	0.30	0.25-0.74	103	24.9%*	1.22	1.56	1	0-2	71.2%	119	28.8%
Year +3	385	0.52*	0.32	0.25-0.87	124	32.2%*	1.97*	2.57	2	0-2	70.4%	114	29.6%

Abbreviations: MPR, medication possession ratio; DR, discontinuation rate; SD, standard deviation; IQR, interquartile range
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.4. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 120 days post-final treatment + 90 days, main analysis)

	Glycemic control							
		HbA_{1C}			HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.32*	0.072	7.18-7.46	191	47.9%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.42*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.064	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.5. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 180 days)

	Glycemic control							
			HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.93	0.079	6.78-7.12	150	34.6%	77	17.8%
Treatment period	399	7.32*	0.072	7.18-7.46	191	47.9%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.42*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.28	0.062	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.6. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Treatment period = 365 days)

	Glycemic control							
			HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.33*	0.074	7.18-7.46	191	47.9%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.42*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.064	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.7. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Highest HbA_{1C} laboratory value per observation period, main analysis)

	Glycemic control							
		HbA_{1C}			HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.32*	0.072	7.18-7.46	191	47.9%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.42*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.064	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.8. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Lowest HbA_{1C} laboratory value per observation period)

	Glycemic control							
			HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.31*	0.072	7.18-7.46	189	47.4%	86	21.6%
Year +1	372	7.35*	0.072	7.27-7.55	190	51.1%*	92	24.7%
Year +2	351	7.32*	0.074	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.064	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

Table B.9. Glycosylated hemoglobin (HbA_{1C}) of metformin and sulfonylureas users prior to and following breast cancer diagnosis and treatment (Mean of all HbA_{1C} laboratory values per observation period)

	Glycemic control							
			HbA_{1C}		HbA_{1C} >7.0%		HbA_{1C} >8.0%	
	N	Mean	SE	95% CI	n	(%)	n	(%)
Year -1	433	6.96	0.080	6.80-7.12	151	34.9%	77	17.8%
Treatment period	399	7.31*	0.075	7.18-7.46	188	47.1%	87	21.8%
Year +1	372	7.41*	0.072	7.27-7.55	189	50.8%*	92	24.7%
Year +2	351	7.42*	0.077	7.28-7.56	185	52.7%*	85	24.2%
Year +3	327	7.30	0.065	7.17-7.43	181	55.4%*	73	22.3%

Abbreviations: SE, standard error; CI, confidence interval of the mean
Note: Statistical hypothesis tests were performed comparing means and proportions to baseline, Year -1 values; (*) indicates difference of statistical significance at $P<0.001$

VITA

Gregory S. Calip, PharmD, MPH, PhD

Gregory Calip was born and raised in Chicago, Illinois. He earned a Doctor of Pharmacy degree with honors in 2008 from the University of Illinois at Chicago. In 2010 he earned a Master of Public Health degree with highest honors from the New York University Graduate School of Arts and Science. In 2014 he earned a Doctor of Philosophy degree in Epidemiology from the University of Washington and started as Assistant Professor at the University of Illinois at Chicago in the Center for Pharmacoepidemiology and Pharmacoeconomic Research and the Department of Pharmacy Systems, Outcomes and Policy.

EDUCATION		
Ph.D.	Epidemiology, University of Washington	2014
M.P.H. *summa cum laude*	Biostatistics & Epidemiology, New York University	2010
Pharm.D. *cum laude*	Pharmacy, University of Illinois at Chicago	2008

RESEARCH EXPERIENCE		
Data Analyst	University of Washington, Global Medicines Program	2013-2014
Postdoctoral Fellow	Fred Hutchinson Cancer Research Center, Cancer Prevention Program	2010-2014
Research Fellow	New York University School of Medicine, Health Disparities Research Training Program	2008-2010
Data Analyst	New York University School of Medicine, Tobacco Control Program	2008-2009

CLINICAL CERTIFICATION	
Washington State	
Registered Pharmacist (RPh), License # PH60190480	2010
New York State	
Registered Pharmacist (RPh), License # 20052683	2008
Pharmacy Provider, NPI # 1962734236	2008
APhA Certified Immunization Provider, Certificate # 305837502	2008
American Red Cross CPR-AED Training, Registration # 9603853	2010
Illinois State	
Registered Pharmacist (RPh), License # 051293452	2008

FELLOWSHIPS

Postdoctoral Fellow	Cancer Prevention Training Grant in Nutrition, Exercise and Genetics (NIH R25CA094880, PI: J. Emily White) Fred Hutchinson Cancer Research Center	2010-2014

CLINICAL EXPERIENCE

Clinical Staff Pharmacist	New York University Langone Medical Center New York, New York	2008-2010
Staff Pharmacist	Duane Reade, Inc. New York, New York	2008-2010
Pharmacist Intern	University of Illinois Medical Center Chicago, Illinois	2005-2008

TEACHING EXPERIENCE

Teaching Assistant	Department of Epidemiology University of Washington	2011

Course: Epidemiology of Infectious Diseases in Resource-Limited Settings

Clinical Instructor	Center for the Study of Asian American Health New York University School of Medicine	2010-2011

Courses: Community Health Worker Training Program – Clinical measurements of anthropometrics and blood pressure; Chronic medication therapy management in hypertension, dyslipidemias and diabetes mellitus

PUBLICATIONS IN PREPARATION

Calip GS, Malone KE, Gralow JR, Hubbard RA, Stergachis A, Boudreau DM: Association between metabolic syndrome risk factors and breast cancer outcomes. (in preparation)

Calip GS, Hubbard RA, Stergachis A, Malone KE, Gralow JR, Boudreau DM: Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. (accepted in *Pharmacoepidemiology and Drug Safety*)

Calip GS, Malmgren JA, Atwood MK, Kaplan HG: Clinical and cytogenetic characteristics of breast cancer therapy-related myelodysplastic syndrome and acute myeloid leukemia: an institutional case series. (in preparation)

Kaplan HG, Malmgren JA, Atwood MK, Calip GS: 5-year breast cancer disease specific survival improvement over time: detection method or treatment (in preparation)

Sevene E, Halidou T, Dellicour S, Calip GS, Stergachis A, ter Kuile FO: Active surveillance methodologies for assessing the safety of antimalarial drug use during early pregnancy (in preparation)

PUBLICATIONS

Kaplan HG, Malmgren JA, Li CI, Calip GS: Age related risk of myelodysplastic syndrome and acute myeloid leukemia among breast cancer survivors. *Breast Cancer Res Treat* 2013 Dec; 142(3):629-36. PMID: 24265034

Monahan LJ, Calip GS, Novo PM, Sherstinsky M, Casiano M, Mota E, Dourado I: Impact of the Family Health Program on gastroenteritis in children in Bahia, Brazil: an analysis of primary care-sensitive conditions. *J Epidemiol Global Health* 2013 Sep; 3(3):175-85. PMID: 23932060

Calip GS, Boudreau DM, Loggers ET: Changes in adherence to statins and subsequent lipid profiles during and following breast cancer treatment. *Breast Cancer Res Treat* 2013 Feb; 138(1):225-33. PMID: 23358904

Calip GS, McDougall JA, Wheldon MC, Li CI, De Roos AJ: Evaluation of seasonality in the diagnosis of acute myeloid leukaemia among adults in the United States, 1992-2008. *Br J Haematol* 2013 Feb; 160(3):343-50. PMID: 23189956

Schenk JM, Calip GS, Tangen CM, Goodman P, Parsons JK, Thompson IM, Kristal AR: Indications for and use of nonsteroidal antiinflammatory drugs and the risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol* 2012 Jul; 176(2):156-63. PMID: 22759721

Shelley D, Anno J, Tseng TY, Calip GS, Wedeles J, Lloyd M, Wolff MS: Implementing tobacco use treatment guidelines in public health dental clinics in New York City. *J Dent Educ* 2011 Apr; 75(4):527-33. PMID: 21460273

POSTERS AND PRESENTATIONS

Calip GS, Boudreau DM: Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. 29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Oral Presentation, Montreal, QC; Aug 2013 *Pharmacoepidemiol Drug Saf* 2013 Oct; 22(s1): 22. doi: 10.1002/pds.3512

Kaplan HG, Malmgren JA, Calip GS, Li CI: MDS/AML risk post-breast cancer and association with age: SEER data 2001-2009. 2013 American Society of Clinical Oncology (ASCO) Annual Meeting, General Poster Session, Chicago, IL; June 2013. *J Clin Oncol* 31, 2013 (suppl; abstr 554).

Calip GS, Bell GA, Drieling RL: Associations between cesarean delivery and public or private insurance: a retrospective cohort study of Washington State births. Washington State Public Health Association (WSPHA) Joint Conference on Health, General Poster Session, Vancouver, WA; Oct 2011.

Calip GS, Jones DC: The role of sociocultural factors on medication adherence and control of hypertension among Filipino Americans in Metropolitan New York City: a qualitative study. Yale University Unite for Sight Conference, Poster and Roundtable Sessions, New Haven, CT; Apr 2010.

Calip GS: Associations between sociocultural factors on medication adherence and control of hypertension among Filipino Americans in Metropolitan New York City: preliminary results from Project AsPIRE.New York University (NYU) 4th Annual Asian American Health Conference, Oral Presentation & Discussion Section, New York, NY; Dec 2009.

Calip GS, Kannankeril AJ, Chan J: HAVE-A: Adherence to hepatitis A vaccination protocol among patients with chronic liver disease in the ambulatory care setting. American Society of Health-System Pharmacists (APhA-ASHP) Mid-Year Clinical Meeting, General Poster Session Las Vegas, NV; Dec 2007.

HONORS AND DISTINCTIONS

New York University, Graduate School, *summa cum laude*, May 2010	May 2010
Excellence in Global Public Health Award, New York University, May 2010	May 2010
University of Illinois at Chicago College of Pharmacy, *cum laude*, May 2008	May 2008
Nathan Stoller Pharmacy Scholarship, University of Illinois at Chicago College of Pharmacy	April 2007
Chancellor's Committee Graduate Research Award, University of Illinois at Chicago	April 2007

SCHOOL AND PUBLIC SERVICE

University of Washington School of Public Health, Seattle, WA

Member	Diversity Committee School of Public Health, Office of the Dean	2013-2014
Chairperson	EPI Expo Student Planning Committee Department of Epidemiology	2011
Student Housing Coordinator	Prospective Student Visit Days Department of Epidemiology	2011-2013

Rosehedge / Multifaith Works AIDS Housing and Health Care, Seattle, WA

CareTeam Volunteer	HIV/AIDS Support Services Volunteer Staff	2013-2014

Washington Junior Science & Humanities Symposium, Seattle, WA

Judge	STEM Conference Oral Presentation Session Seattle Pacific University	2013

PROFESSIONAL AFFILIATIONS

Associate Editor	*Clinical Case Reports*	2013-2014
Ad hoc reviewer	*Journal of the American Pharmacists Association*	2013-2014
Ad hoc reviewer	*Breast Cancer Research and Treatment*	2012-2014
Ad hoc reviewer	*Journal of General Internal Medicine*	2012-2014
Ad hoc reviewer	*American Journal of Public Health*	2011-2014
Student Member	International Society for Pharmacoepidemiology	2011-2014
Student Member	American Society of Clinical Oncology	2011-2014
Member	Washington State Public Health Association	2011-2014
Member	American Pharmacists Association	2011-2014
Member	American Society of Health Systems Pharmacists	2011-2014