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Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer

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Abstract

Background—Breast cancer tends to occur in an older age group of women also burdened with comorbidities such as cardiovascular disease (CVD). Numerous medications used to manage CVD (e.g., statins and antihypertensives) are hypothesized to alter breast cancer risk, but there are few studies on breast cancer outcomes. The COMBO (COMmonly used Medications and Breast Cancer Outcomes) cohort was developed to study how medications and co-morbidities influence breast cancer prognosis.

Methods—Cohort study among adult women, diagnosed with incident early stage breast cancer, and enrolled in an integrated health plan. Data sources included health plan administrative databases, Surveillance, Epidemiology, and End Results tumor registry, and medical records. Statins, angiotensin converting enzyme inhibitors (ACEI), beta blockers (BB), calcium blockers, and diuretics were the exposures of interest. The outcome was second breast cancer events (SBCE) defined as recurrence or second primary breast cancer. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for SBCE and components of SBCE.

Results—4,216 women were followed for a median of 6.3 years, and 13.2% experienced a SBCE (first of: n=415 recurrences and n=143 second primary breast cancers). Compared to non-users, we observed an increased risk of second primary breast cancer with ACEI use (HR=1.66; 95% CI, 1.06–2.58) and an increased risk of recurrence with BB use (HR=1.29; 95% CI, 1.01–1.64). There was suggestion of a reduced risk of SBCE with statin use (HR=0.82; 95% CI, 0.62–1.08) and second primary breast cancer with BB use (HR=0.77; 95% CI, 0.50–1.19). No differences in outcomes were observed by duration of medication use.

Conclusions—The majority of CVD medications evaluated in this study appear safe with respect to SBCE, but ACEI and BB use warrant further evaluation. The study presented is one example of the questions that can be addressed using the COMBO cohort.

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Keywords

Breast cancer; statins; antihypertensive medication; recurrence; cardiovascular disease

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, and there are an estimated 2.8 million breast cancer survivors in the US.[1] These women are at risk for recurrence, second primary breast tumors, and long-term sequelae of their original treatment. Each of these outcomes can have negative consequences and are important to prevent.[2]

Breast cancer tends to occur in an older age group also burdened with co-morbidities.[3] Numerous medications used to manage these co-morbidities (e.g., statins for high cholesterol and antihypertensives) are hypothesized to alter breast cancer risk and recurrence [4–17] including concerning new evidence that statins,[18] and calcium channel blockers[19] are associated with substantial increases in breast cancer risk. Statins' inhibition of HMG-CoA reductase prevents the conversion of HMG-CoA to mevalonate, and thereby reduces levels of mevalonate and its downstream products.[20] Many products of the mevalonate pathway are necessary for cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression.[20, 21] Disruptions of these processes may alter tumor initiation, growth, and metastasis.[21–25] A recent article in the journal *Science* provides compelling data to suggest that lowering circulating cholesterol or preventing conversion of cholesterol to 27-hydroxycholesterol may be a useful strategy to prevent and/or treat breast cancer.[26]

Angiotensin-converting enzyme inhibitors (ACEIs), beta blockers (BBs), calcium channel blockers (CCBs), and diuretics to treat hypertension impact various pathways that can alter cancer development and progression. ACEIs may reduce cancer risk and improve prognosis by reducing the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates neovascularization, a requirement for tumor growth and possibly a growth factor in stimulating cell replication and increased expression of genes that control cell growth in tumors.[27, 28] ACEIs show strong cytostatic properties on in vitro cultures of normal and neoplastic cells, including two lines of human breast carcinomas.[29] BBs target epinephrine and norepinephrine, which induce tumor cell invasion and migration.[30–35] β -adrenergic signaling is also involved in immune response regulation, apoptosis inhibition, and expression of vascular endothelial growth factor.[32–35] Inhibition of these receptors by BBs may prevent cancer from metastasizing.[12, 13] Through decreasing intracellular calcium, CCBs are hypothesized to increase the risk of cancer by inhibiting apoptosis.[36–38] Diuretics are hypothesized to increase breast cancer risk and progression through increasing insulin resistance,[39, 40] an established risk factor for breast carcinoma.[41, 42]

The association between commonly used cardiovascular disease (CVD) medications and cancer risk, including breast cancer, are well studied but few studies exist on cancer outcomes. Here, we describe the Commonly used Medications and Breast Cancer Outcomes (COMBO) study, initiated to improve understanding of how medications used in the

management of co-morbidity alter breast cancer outcomes,[43, 44] and the association between common CVD medications and second breast cancer events (SBCE).

METHODS

Population and Setting

COMBO is a retrospective cohort study within Group Health (GH), a nonprofit integrated delivery system that provides comprehensive health care on a pre-paid basis to approximately 620,000 individuals throughout Washington State and parts of Idaho. GH is located within the geographic reporting region of the western Washington Cancer Surveillance System, a population-based cancer registry and member of the NCI Surveillance, Epidemiology, and End Results (SEER) program.[45, 46]

Women were selected if: 1) 18 years; 2) residing within the 13 counties covered by the Washington State SEER; 3) diagnosed with an incident, histologically confirmed stage I or II breast cancer[47] between January 1, 1990 and December 31, 2008; 4) no bilateral disease; and 5) enrolled in GH's integrated group practice for 1+ year before and after the breast cancer diagnosis (unless they died).

A total of 4,426 potentially eligible subjects underwent medical record review, of which a subset (1,268 women diagnosed 1990–1999) was partially abstracted in prior studies.[48–50] Based on medical record review, we further excluded women with no medical record (n=72), bilateral disease (n=6), recurrent or second primary breast cancers that were incorrectly identified as incident breast cancer (n=79), and no definitive surgery (n=44). We required women be alive and recurrence-free for 120 days after completing surgery, yielding a final cohort of 4,216 women (after excluding 5 deaths and 4 metastases prior to 120 days). The GH Institutional Review Board approved this study.

Data collection

Data were collected from one year before incident breast cancer through the earliest of death, disenrollment from GH (> 90 days lapse), or end of study (chart abstraction date). Data collection was through health plan administrative databases including GH's Breast Cancer Screening Recruitment and Reminder (BSRR) survey on breast cancer risk factors at the time of each mammography,[51] SEER, and medical record review (paper and electronic). The sources for each COMBO data component are outlined in Table 1.

GH's administrative data files include demographics, enrollment, inpatient and outpatient diagnoses and procedures, breast services and results, pharmacy dispensings, laboratory results, vital signs, and death.[52] The pharmacy database includes all medications dispensed at GH's outpatient pharmacies as well as claims from contracting pharmacies. Pharmacy data are estimated to be 97% complete.[52–54] Automated death data is from an on-going link to Washington State death tapes.[55]

Chart abstraction began in 2009 and continued through August 2011. Data with medical record as the source in Table 1 were abstracted by 5 trained abstractors and entered into an Access database. Three inter- and intra-rater reliability tests[56] revealed good agreement

(per overall kappa) for key variables such as recurrence (0.93), second primaries (0.95), and death (0.94).

Exposures

Use of statins and common antihypertensive classes after breast cancer diagnosis were our exposures of interest. Women were defined as a user of a particular medication class of interest during the follow-up period if they had any dispensing of a medication in the class of interest after the incident breast cancer diagnosis (Figure 1). Dispensing data are continuous and thus exposure status can be updated daily. Women were allowed to be users of multiple medication classes. Statin use was further categorized as hydrophilic (pravastatin and rosuvastatin) vs. lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin).[57]

Exposures of interest were further characterized by total duration of use. Duration was estimated by first organizing medication dispensings into episodes of continuous use. The first episode for a class of interest began with the first dispensing of a medication in that class. For each dispensing, the date when the pills would run out (run-out date) was estimated based on the days' supply field of the dispensing record multiplied by 1.25 to account for an assumed 80% compliance.[58] Successive dispensings with 60-day gap between the run-out date of one dispensing and fill date of the subsequent dispensing were considered continuous. The end date of a continuous episode was the run-out date of the last dispensing in that episode. A new run out date was set for each dispensing (i.e., no accumulation allowed when prescriptions overlapped). A new episode began each time a patient experienced a gap in use of > 60 days and then was once again dispensed a medication of interest. Duration was defined as the difference between the start and end dates of the episode. Periods of continuous episodes were summed for total duration of use which was then categorized as <1 year, 1–<3 years, and 3+ years of medication use.

Outcomes

The endpoint of interest was second breast cancer event (SBCE), defined as the first of a ductal carcinoma in situ or invasive cancer of the ipsilateral (recurrence) or contralateral (second primary) breast or in any regional or distant sites (Figure 1).[59]

Statistical Analysis

We estimated the adjusted hazard ratios (HR) and 95% confidence intervals using the Cox proportional hazards models to assess whether commonly used classes of cardiovascular medications were associated with risks of SBCE while accounting for competing risks.[60] We modeled time from the incident breast cancer (time scale) with a delayed entry at 120 days post-surgery (at risk date)[50] to SBCE as a function of exposure to the medication classes of interest while adjusting for potential confounders. They were followed until the first SBCE, death, disenrollment from the health plan, or end of study date. Individual events (i.e., recurrence and second primary) that make up the composite outcome, SBCE, were also modeled separately to obtain a comprehensive assessment of the medication effects.[60] In analysis of individual events such as recurrence, women were censored at the earliest of disenrollment, end of follow-up, and other competing events (e.g., death and

second primary). Primary exposures were ever use of each medication class of interest (with all medication classes in the same model). Secondary exposures were type of statin use (hydrophilic vs. lipophilic) and subgroup analyses were duration of medication use (while adjusting for ever use of other medication classes in both models). All medication exposures were modeled as time-varying covariates and women were only allowed unidirectional transition (i.e., non-user to user or low to high duration categories of exposure). In order for all subjects to have the opportunity to be in any of the duration exposure categories at the beginning of the duration of use analysis (<1 year, 1–<3 years, and 3+ years of medication use), women were eligible to enter the duration of use analysis once they had three years of follow-up (n=3,467). Linear trend test of duration use categories were also performed.

Similar to other studies,[7–9, 14, 16] all models were adjusted for age at diagnosis; calendar year of incident breast cancer diagnosis; AJCC stage;[47] hormone receptor; primary treatment for initial breast cancer; endocrine therapy for the incident breast cancer (time-varying); body mass index (BMI) at diagnosis; smoking status at diagnosis; menopausal status at diagnosis; Charlson co-morbidity score (time-varying);[61] diabetes;[62–64] non-steroidal anti-inflammatory (NSAID) medication use which included traditional NSAIDs, aspirin, and Cox-2 inhibitors (time-varying); and receipt of screening mammogram in the prior 12 months (time-varying). Our unadjusted model included only age at diagnosis and AJCC stage.

In sensitivity analyses, we evaluated change in the HRs with adjustment for medication use in the year prior to incident diagnosis as well as co-morbidities (hypertension and dyslipidemia) associated with medication use.

Proportional hazards assumptions were evaluated by testing the interaction between the medication classes of interest (ever vs. never use) and the logarithm of follow-up time. The assumptions held for all exposure-outcome pairs except for diuretics and SBCE. To further assess the non-proportional hazards for diuretics, we divided the follow-up time into 2 periods at 3.3 years following incident diagnosis, each containing equal number of outcomes. We then included an interaction term between the 2 time periods and ever use of diuretics in the multivariate models. Separate HRs for the 2 time periods were estimated.

All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The median age of the cohort at initial breast cancer diagnosis was 63 years. The majority were post-menopausal, Caucasian, non-Hispanic, never smokers, and had at least some college education or more, and a Charlson co-morbidity score of zero (Table 2). The 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. During follow-up, 29% used statins, 36% ACEI, 36% BB, 21% CCB, and 42% diuretics. The median number of dispensings per user of each

therapeutic class over the follow-up period was 12 to 16, varying only slightly by class. Median number of pills dispensed was 90 for all antihypertensive medication classes and 60 for statins. Forty-seven percent of women used multiple medication classes of interest. The specific medications used for each therapeutic class are listed in Appendix A. Briefly, lisinopril was the predominant drug used among ACEI users (97%), atenolol (72%) and metoprolol (24%) among BB users, hydrochlorothiazide with or without triamterene (97%) among diuretic users, and simvastatin (63%) and lovastatin (49%) among statin users. CCB medication use was more varied but the three most commonly used medications were nifedipine (29%), diltiazem (27%), and amlodipine (24%). Specific drug used is not mutually exclusive due to switching within therapeutic class.

The median follow-up was 6.3 years (interquartile range, 3.7–9.7 years). Median duration of follow-up varied by diagnosis date with women diagnosed during the early study years having the longest follow-up: median 12.7 years for women diagnosed in 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, 13.2% experienced a SBCE (first of: n=415 recurrences and n=143 second primary breast cancers). 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 cancers, 21% were DCIS, 49% stage I, 21% stage II, 4% stage III/IV, and 5% unknown stage. Age adjusted cumulative hazards of SBCE are shown in Figure 2.

Women experiencing a SBCE were more likely to be peri- or premenopausal, and diagnosed with AJCC stage II (especially IIB), 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 detected by a diagnostic versus screening mammography compared to women without a SBCE during the follow-up period.

Unadjusted and adjusted models did not differ substantially so we present only adjusted model results. From multivariate models, we observed associations between ACEI use and an increased risk of second primary breast cancer (HR=1.66; 95% CI, 1.06–2.58) and BB use and an increased risk of recurrence (HR=1.29; 95% CI, 1.01–1.64) (Figure 3). Point estimates suggested a reduced risk of SBCE with statin use compared to non-users (HR=0.82; 95% CI, 0.62–1.08) and a non-significant reduced risk of second primary breast cancer with BB use (HR=0.77; 95% CI, 0.50–1.19). After splitting the time periods at 3.3 years following incident diagnosis due to violation of the proportional hazards assumption, the HRs for diuretics on risk of SBCE compared to no diuretic was 0.91 (95% CI, 0.68–1.20) in the first time period and 1.25 (95% CI, 0.97–1.62) in the second time period. We observed no difference in risk of SBCE by statin type (HR=0.81; 95% CI, 0.61–1.07 for lipophilic; HR=0.76; 95% CI, 0.31–1.86 for hydrophilic), non-significant reduced risk of recurrence with lipophilic statin use (HR=0.76; 95% CI, 0.54–1.05) vs. no association with hydrophilic statin use (HR=1.01; 95% CI, 0.37–2.76), and data were sparse on risk of second primary breast cancer by statin type (HR=0.94; 95% CI, 0.57–1.57 for lipophilic; HR=0.34; 95% CI, 0.05–2.50 for hydrophilic).

No patterns of association with SBCE, recurrence or second primary breast cancer were observed by duration of the CVD medication classes (Table 3).

Our main results for post-diagnosis exposure to the medication classes of interest changed little when we adjusted for use of the medication classes of interest in the year prior to incident breast cancer diagnosis, a diagnosis of hypertension, and a diagnosis of dyslipidemia. Exposure to ACEI (HR=1.15; 95% CI, 0.82–1.60), BB (HR=0.96; 95% CI, 0.70–1.32), CCB (HR=1.02; 95% CI, 0.68–1.53), diuretics (HR=0.94; 95% CI, 0.71–1.25), and statins (HR=0.96; 95% CI, 0.60–1.53) during the one year prior to incident breast cancer was not significantly associated with SBCEs. The average length of use during the year prior for all medication classes was approximately 9–10 months. Hypertension (HR=1.00; 95% CI, 0.78–1.29) and dyslipidemia (HR=0.90; 95% CI, 0.70–1.16) were also not associated with SBCE.

DISCUSSION

In the first comparative safety study to evaluate commonly used CVD medications and SBCE, we found no association between most medication classes of interest and SBCE among a large cohort of women diagnosed with early stage breast cancer. However, we observed an increased risk of second primary breast cancer with ACEI use and an increased risk of recurrence with BB use. Dose response analyses did not support any increased risk in outcomes with ACEI or BB use.

There are only a few studies on CVD medications and recurrence and no studies that specifically evaluated the recommended composite endpoint of SBCE.[59] Our observation on BB use and increased risk of recurrence is similar to that reported by Sorensen et al. (HR= 1.3; 95% CI, 1.1–1.5) in a cohort study of 18,733 Danish women with non-metastatic breast cancer.[17] The same study found ACEI use was associated with an increased risk of recurrence (HR = 1.2, 95% CI, 0.97–1.4). Ganz and colleagues observed point estimates for recurrence among 1,779 women with early stage breast cancer that were in the opposite direction of our point estimates - increased risk with ACEI use (HR=1.56; 95% CI, 1.02–2.39) and a non-significant reduced risk with BB use (HR=0.86; 95% CI, 0.57–1.32).[14] In contrast, Chae et al. reported a reduced risk of breast cancer recurrence in 703 women with stage II/III breast cancer among users of ACEI/angiotensin-receptor blockers (ARB) compared to non-users (HR=0.49; 95% CI, 0.31–0.76) in a 2011 publication.[7] Recently, Chae and colleagues studied 1,449 women treated with neoadjuvant therapy for stage I–III incident breast cancer.[16] In this cohort, Chae et al. observed only suggestion of differences by ACE/ARB use versus no use in pathologic complete response (16% vs 18.1%, $p=0.50$), relapse-free survival (HR=0.81; 95% CI=0.54–1.21), disease-specific survival (HR=0.83; 95% CI=0.52–1.31), and overall survival (HR=0.91; 95% CI =0.61–1.37). In Chae 2011, a protective association was observed for recurrence among statin users (HR=0.40; 95% CI, 0.24–0.67) and combined users of both drug classes (HR=0.30; 95% CI, 0.15–0.61) compared to respective non-users. Results from at least three other studies support a reduced risk of recurrence with statin use (Kwan et al.: relative risk=0.67; 95% CI, 0.39–1.13;[9] Nickels et al.: HR=0.83; 95% CI, 0.54–1.24)[15] and lipophilic statin use (HR=0.73; 95% CI, 0.60–0.89).[8] The majority of statin use in our study was lipophilic and our point

estimate for recurrence was similar. These studies differed from COMBO in that they included women with stage IIIA tumors and thus had higher recurrence rates (16.4% to 21.2%).[7–9, 14] The studies by Ganz and Kwan were conducted at Kaiser Permanente Northern California, a similar setting to our study. Our study and the previous studies overlapped with respect to covariates but our study was more complete with potential confounders including data on surveillance.

COMBO is one of only a few population based cohorts of breast cancer survivors that contains comprehensive and high quality data on incident breast cancer characteristics and treatment through both a validated registry and medical charts, demographics, vital signs, unbiased health care utilization including medication use 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 and informative censoring and other cancers. The study presented here is just one example of the numerous questions that can be rigorously addressed using such a rich datasource.

Our study is not without limitations. COMBO uses data from a single health plan and includes an insured, educated, and primarily Caucasian population (89% vs. 73% in the US [65]). This may limit generalizability to some populations but the results are generalizable to a large majority of women and we do not hypothesize a difference in association by race. Managed care organizations such as GH are common in the US among insured individuals; as of 2008, 25% of the US population was enrolled in an HMO.[65] Our decades of research within the HMO Research Network (HMORN) suggests that GH medical practice and prescribing patterns are similar to other HMORN plans.[66] Loss to follow-up is a possible source of bias with 18% censored due to disenrollment from the health plan. 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, physical activity, over-the-counter (OTC) aspirin use, and alcohol intake. Lack of OTC data restricted our ability to test whether aspirin use modified the association between medication use and breast cancer outcomes.[67] Our analyses were however adjusted for all prescription NSAID use including aspirin which was 14% of NSAID users. Because the medication classes of interest are not used to treat breast cancer nor do their underlying indications for use cause or share a known cause of SBCEs, confounding by indication is less of a concern. In addition, there was little change in the results when we adjusted for potential indications of use (i.e., hypertension and dyslipidemia) in sensitivity analyses. People who fill a prescription but do not ingest the medication and who obtain medications at non-GH pharmacies with no claim submitted to GH may be misclassified, but GH enrollees obtain almost all of their prescription medications at GH pharmacies or contracting pharmacies[52–54] and any misclassification is likely non-differential. Due to limited statistical power, we did not evaluate other hypotheses related to risk of SBCEs such as the interaction between combinations of medication classes, suggested reduction in risk with ARBs, [7, 68] or use of beta-1 specific BB vs non-specific BBs use. [13, 35]

Our study provides some reassurance that many commonly used CVD medications are safe with respect to SBCE, but ACEI and BB use warrant further evaluation. The signals

generated that ACEIs may increase second primaries (and recurrences in other studies) and BBs may increase recurrence could be due to real changes and warrant further investigation. The relative lack of documentation on these associations and somewhat discordant findings in the few studies conducted is of concern given the wide spread use of these agents worldwide, a growing number of breast cancer survivors,[1] and an aging population with multi-morbidity.[3] Our results should be used in planning future studies in this area. Further research on other classes of medications hypothesized to alter cancer outcomes is also warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schematic of data collection and exposure and outcome assessment in Commonly Used
Medications and Breast Cancer Outcomes (COMBO) Study

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

Figure 2.
Cumulative hazard of second breast cancer events including recurrence and second primary breast cancer

Figure 3.

Risk of second breast cancer events (SBCE) by ever/never medication use

Abbreviations: HR – hazard ratio; CI – confidence interval; ACEI- angiotensin converting enzyme inhibitor; BB – beta blocker; CCB – calcium channel blocker.

HR adjusted for all other medication classes of interest (ever/never use, time-varying), age at diagnosis (18–49, 50–59, 60–69, 70–79, 80+ years); diagnosis year (1990–1994, 1995–1999, 2000–2004, 2005–2008); AJCC stage (I, IIA, IIB); hormone receptor status (estrogen receptor [ER] –/progesterone receptor [PR] –, ER +/PR –, ER –/PR +, ER +/PR +, and ER and/or PR unknown); primary treatment for initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation); endocrine therapy for the incident breast cancer (yes/no, time-varying); body mass index (BMI) at diagnosis (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35+ kg/m²); smoking status at diagnosis (current, past, never/unknown); menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal); Charlson co-morbidity score (0, 1, 2+, time-varying each year); diabetes (yes/no, time-varying); prescription non-steroidal anti-inflammatory medication use, Cox-2 inhibitors, and aspirin (yes/no, time-varying); and receipt of screening mammogram in the 12 months prior to events (yes/no, time-varying).

Table 1Data and data sources for Commonly Used Medications and Breast Cancer Outcomes (COMBO)

Variable	Primary Data Source	Comments
<i>At Incident Breast Cancer Diagnosis</i>		
Age at diagnosis	SEER	
Menopausal status	BSRR	Women with missing data assumed to be menopausal if age 55 years[69]
Race and ethnicity	SEER	Medical chart if missing from SEER
Education	BSRR	
Smoking status	Administrative	No mention was considered non-smoker
Tumor characteristics (stage, size, histology, lymph node status, hormone receptor status, HER-2/neu status)	SEER	Medical chart if missing from SEER
Surgical procedures	Medical chart	Type (partial mastectomy, subcutaneous mastectomy, total mastectomy, modified radical mastectomy, radical mastectomy, extended radical mastectomy), surgical margins, date of surgical pathology report, node evaluations (sentinel and axillary), number positive nodes,
Chemotherapy	Medical chart	Specific agents; date of first and last course; completion status per medical oncologist report; reason for no referral; reasons for non-completion; side effects
Radiation	Medical chart	Date of first and last sessions; completion status; reason for no referral; reasons for non-completion; side effects
Mode of incident breast cancer detection	Administrative (1997+) Missing before 1997	First mammogram in 12 months prior to diagnosis taken as mode of detection. Considered diagnostic if no screening mammograms occurred in the 12-months prior to diagnosis or if a woman reported a lump.
<i>Collected throughout follow-up</i>		
Endocrine therapy	Medical chart	Agent, date prescribed, date discontinued, side effects, and reasons for discontinuation
Body mass index	Medical chart	Administrative data (BSRR) if missing from chart One weight abstracted for each year post diagnosis. Value closest to year of interest was recorded. Height closest to breast cancer diagnosis used to calculate all BMIs.
Co-morbidities Charlson Co-morbidity score[61]	Administrative 1993+ Medical chart before 1993	Updated each year post diagnosis
Laboratory values	Administrative	
Surveillance mammograms	Administrative 1997+ Medical chart before 1997	Defined as asymptomatic screening exams or SIFU exams <9 months following a screening exam. Symptoms had to be coded as "none" or completely missing.
Prescription medication use (including endocrine therapy)	Administrative	Drug name, dispensing date, quantity, strength, days supply, route, and prescriber
Recurrence	Medical chart	Location (local, regional, distant, DCIS), 1 st vs 2 nd recurrence, date of pathological and clinical diagnosis, side, metastasis, histology, symptoms, treatment
Second primary breast cancer	Medical chart	AJCC stage (T, N, and M), date of pathological and clinical diagnosis, side, histology, symptoms, ER/PR, Her-2/neu, treatment
Other primary cancers	SEER	Site, date
Death	State death registry	Date, underlying cause

Abbreviations: SEER – Surveillance, Epidemiology, and End Results (SEER) tumor registry; BSRR – Group Health's Breast Cancer Screening Recruitment and Reminder survey.

Characteristics of women included in commonly used medications and breast cancer outcomes (COMBO) study, overall and by second breast cancer event (SBCE) status

Table 2

Participant characteristics		All		SBCE ¹	
		N=4,216		No (n=3658)	Yes (n=558)
		n (column %)			
At incident breast cancer diagnosis					
Year of diagnosis					
1990–1994		950	(22.5)	755	(20.6)
1995–1999		1191	(28.2)	1020	(27.9)
2000–2004		1201	(28.5)	1073	(29.3)
2005–2008		874	(20.7)	810	(22.1)
Age, years					
Median (Interquartile range)		63	(52–73)	63	(52–73)
18–39		139	(3.3)	112	(3.1)
40–49		646	(15.3)	544	(14.9)
50–59		995	(23.6)	866	(23.7)
60–69		1018	(24.1)	889	(24.3)
70–79		940	(22.3)	824	(22.5)
80+		478	(11.3)	423	(11.6)
Menopausal status					
Peri- or Premenopausal		1145	(27.2)	956	(26.1)
Postmenopausal		3071	(72.8)	2702	(73.9)
Race					
White		3719	(88.5)	3232	(88.7)
African American		136	(3.2)	104	(2.9)
American Indian/Alaska Native		113	(2.7)	104	(2.9)
Asian/Pacific Islander		233	(5.5)	203	(5.6)
Unknown		15		15	0

Participant characteristics	All N=4,216	SBCE ¹			
		n (column %)			
		No (n=3658)			
Ethnicity		Yes (n=558)			
		n (column %)			
Hispanic	229 (5.4)	209 (5.7)	20 (3.6)		
Non-Hispanic	3976 (94.6)	3438 (94.3)	538 (96.4)		
Unknown	11	11	0		
Education					
High school or less	418 (23.4)	393 (23.5)	25 (21.4)		
Some college	634 (35.4)	594 (35.5)	40 (34.2)		
College or post graduates	737 (41.2)	685 (41)	52 (44.4)		
Unknown	2427	1986	441		
Body mass index (kg/m²)					
<18.5	69 (1.6)	55 (1.5)	14 (2.5)		
18.5–24.9	1453 (34.6)	1269 (34.8)	184 (33.3)		
25.0–29.9	1362 (32.5)	1186 (32.6)	176 (31.8)		
30.0–34.9	766 (18.3)	666 (18.3)	100 (18.1)		
35+	546 (13)	467 (12.8)	79 (14.3)		
Unknown	20	15	5		
Smoking status					
Current	253 (6.0)	230 (6.3)	23 (4.1)		
Past	352 (8.3)	318 (8.7)	34 (6.1)		
Never/Unknown	3611 (85.6)	3110 (85)	501 (89.8)		
AJCC stage					
I	2648 (62.8)	2384 (65.2)	264 (47.3)		
IIA	1078 (25.6)	906 (24.8)	172 (30.8)		
IIB	490 (11.6)	368 (10.1)	122 (21.9)		
Lymph node status					
Negative	2847 (75.6)	2525 (77.3)	322 (64.3)		
Positive	918 (24.4)	739 (22.7)	179 (35.7)		

Participant characteristics	All		SBCE ¹	
	N=4,216		No (n=3658)	Yes (n=558)
	n (column %)			
Unknown	451		394	57
ER/PR status				
ER-/PR-	667	(15.8)	531	136 (24.4)
ER+/PR-	383	(9.1)	319	64 (11.5)
ER-/PR+	61	(1.4)	47	14 (2.5)
ER+/PR+	2888	(68.5)	2572	316 (56.6)
ER &/or PR unknown	217		189	28 (5)
Tumor size				
2 cm	3110	(73.8)	2785	325 (58.5)
> 2 cm	1104	(26.2)	873	231 (41.5)
Unknown	2		0	2
Her-2				
Test done	2074	(49.2)	1874	200 (35.8)
Positive/Borderline	353	(17.0)	311	42 (21.0)
Negative	1714	(82.6)	1556	158 (79.0)
No result	7	(0.3)	7	0 (0)
Surgical procedure				
Mastectomy including radical				
+/- radiation	1521	(36.1)	1289	232 (41.6)
Breast conserving, + radiation	2172	(51.5)	1927	245 (43.9)
Breast conserving, no radiation	523	(12.4)	442	81 (14.5)
Other treatment				
Any chemotherapy	1376	(32.6)	1142	234 (41.9)
Completed course	1212	(88.1)	1003	209 (89.3)
Any endocrine therapy	2363	(56.0)	2101	262 (47.0)
Charlson co-morbidity score				

Participant characteristics		All	SBCE ^I	
		N=4,216	No (n=3658)	Yes (n=558)
n (column %)				
0		3229 (76.6)	2784 (76.1)	445 (79.7)
1		704 (16.7)	625 (17.1)	79 (14.2)
2+		283 (6.7)	249 (6.8)	34 (6.1)
Medication use during year prior to incident breast cancer ²				
Statins		359 (8.5)	329 (9)	30 (5.4)
ACE inhibitors		559 (13.3)	493 (13.5)	66 (11.8)
Beta blockers		706 (16.7)	620 (16.9)	86 (15.4)
Calcium channel blockers		417 (9.9)	367 (10.0)	50 (9.0)
Diuretics		949 (22.5)	829 (22.7)	120 (21.5)
Non-steroidal anti-inflammatory agents				
		1527 (36.2)	1304 (35.6)	223 (40.0)
Throughout follow-up				
Years of follow-up, median (interquartile range)		6.3 (3.7–9.7)	6.7 (4.2–10.2)	3.3 (1.8–5.9)
Diabetes		610 (14.5)	539 (14.7)	71 (12.7)
Medication use from incident breast cancer diagnosis through end of follow-up ²				
Statins		1210 (28.7)	1128 (30.8)	82 (14.7)
ACE inhibitors		1515 (35.9)	1379 (37.7)	136 (24.4)
Beta blockers		1501 (35.6)	1348 (36.9)	153 (27.4)
Calcium channel blockers		893 (21.2)	811 (22.2)	82 (14.7)
Diuretics		1770 (42)	1577 (43.1)	193 (34.6)
Non-steroidal anti-inflammatory agents		3081 (73.1)	2704 (73.9)	377 (67.6)
% follow-up years with yearly surveillance mammography				
<50%		939 (22.3)	793 (21.7)	146 (26.2)
50%–80%		1439 (34.1)	1284 (35.1)	155 (27.8)
>80%		1838 (43.6)	1581 (43.2)	257 (46.1)

¹ SBCE=second breast cancer event includes recurrence or second primaries, in-situ and invasive. Characteristics were significantly different by SBCE status at p<0.005 except for age at diagnosis, ethnicity, education, body mass index, smoking status, chemotherapy completion, Charlson co-morbidity score, and all medication use during the year prior to incident breast cancer.

²Not mutually exclusive.

Table 3
Risk of second breast cancer events (SBCE) by duration of cardiovascular medication use after breast cancer diagnosis.

Duration	SBCE		Recurrence		Second Primary	
	HR*	95% CI	HR*	95% CI	HR*	95% CI
Statin						
< 1 yr	1.16	0.72–1.86	0.94	0.51–1.75	1.68	0.80–3.52
1–2.9 yrs	0.79	0.47–1.34	0.66	0.34–1.30	1.11	0.48–2.56
3+ yrs	0.75	0.46–1.22	0.77	0.42–1.41	0.73	0.31–1.71
Trend**	0.91	0.78–1.05	0.89	0.74–1.08	0.94	0.74–1.20
Angiotensin Converting Enzyme Inhibitors						
< 1 yr	1.15	0.78–1.72	0.96	0.59–1.56	1.75	0.87–3.51
1–2.9 yrs	0.80	0.48–1.32	0.56	0.29–1.08	1.43	0.63–3.25
3+ yrs	0.96	0.64–1.44	0.73	0.44–1.21	1.61	0.83–3.16
Trend**	0.97	0.85–1.10	0.87	0.74–1.03	1.16	0.94–1.43
Beta Blockers						
< 1 yr	0.98	0.64–1.51	1.45	0.90–2.32	0.29	0.09–0.93
1–2.9 yrs	1.14	0.72–1.80	1.24	0.70–2.20	0.94	0.43–2.03
3+ yrs	1.04	0.74–1.46	1.29	0.86–1.92	0.65	0.34–1.23
Trend**	1.02	0.91–1.14	1.09	0.96–1.24	0.87	0.71–1.08
Calcium Channel Blockers						
< 1 yr	0.90	0.52–1.55	0.77	0.38–1.54	1.26	0.52–3.07
1–2.9 yrs	0.80	0.44–1.45	0.66	0.30–1.44	1.10	0.42–2.86
3+ yrs	1.08	0.71–1.65	1.00	0.58–1.70	1.34	0.67–2.68
Trend**	1.00	0.88–1.15	0.96	0.81–1.14	1.09	0.88–1.37
Diuretics						
< 1 yr	1.09	0.75–1.57	1.24	0.80–1.91	0.80	0.39–1.67
1–2.9 yrs	1.35	0.92–1.97	1.47	0.93–2.32	1.16	0.58–2.30
3+ yrs	1.17	0.84–1.62	1.30	0.87–1.95	0.93	0.52–1.68
Trend**	1.07	0.96–1.19	1.11	0.98–1.26	0.99	0.82–1.20

Abbreviations: SBCE – second breast cancer event; HR- hazard ratio; CI - confidence interval; yrs - years

* HR adjusted for all other medication classes of interest, age at diagnosis (18–49, 50–59, 60–69, 70–79, 80+ years); diagnosis year (1990–1994, 1995–1999, 2000–2004, 2005–2008); AJCC stage (I, IIA, IIB); hormone receptor status (estrogen receptor [ER] –/progesterone receptor [PR] –, ER +/PR –, ER –/PR +, ER +/PR +, and ER and/or PR unknown); primary treatment for initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation); endocrine therapy for the incident breast cancer (yes/no, time-varying); body mass index (BMI) at diagnosis (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35+ kg/m²); smoking status at diagnosis (current, past, never/unknown); menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal); Charlson co-morbidity score (0, 1, 2+, time-varying each year); diabetes (yes/no, time-varying); prescription non-steroidal anti-inflammatories, Cox-2 inhibitors, and aspirin (yes/no, time-varying); and receipt of screening mammogram in the 12 months prior to events (yes/no, time-varying). Analyses limited to women with at least 3 years of follow-up.

** HR of duration groups as a linear term