Second Breast Cancer Events in Relation to Frequent Antibiotic Use

An Assessment of Risk and the Development of a Framework to Evaluate Detection Bias in Breast Cancer Pharmacoepidemiology Studies

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Abstract

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Background: Frequent antibiotic use is common and associated with increased primary breast cancer risk, but no study to date has evaluated the relation between antibiotic use and breast cancer outcomes among breast cancer survivors. Detection bias is commonly cited as a potential source of confounding in observational studies but rarely explored. We sought to evaluate the relation between frequent antibiotic use and second breast cancer events (SBCEs) and to develop a framework for investigating unexplored detection bias in breast cancer pharmacoepidemiology studies.

Methods: Retrospective cohort study among female health plan enrollees aged ≥18 years when diagnosed with stage I or II breast cancer between 1990 and 2008 via the Surveillance, Epidemiology, and End Results registry. We used Cox regression models to estimate the relation between frequent antibiotic use (≥4 dispensings in 12 months) and SBCEs (first of recurrence or second primary). We evaluated disease free survival (DFS) in secondary analyses. We used generalized estimating equations models to estimate associations of surveillance mammography over 10 years with exposure to two disparate medication classes, antibiotics and statins. We categorized antibiotic users as infrequent (1-3 dispensings in 12 months) and frequent (≥4 dispensings in 12 months), and statin users as less adherent (1 dispensing in 6 months) and more adherent (≥2 dispensings in 6 months).

Results: Among the 4,216 women in the SBCE cohort, 40% were frequent antibiotic users and 13% developed a SBCE. Frequent antibiotic use was associated with a non-significant higher risk of SBCE (HR 1.15, 95% CI 0.88-1.50) and a significantly higher risk of DFS events (HR 1.25, 95% CI 1.03-1.51). Of the 3,965 women evaluated for use of surveillance mammography over time, 79% received surveillance in year 1 and this decreased to 63% in year 10. Frequent antibiotic users were slightly less likely to receive mammograms during follow-up, though not significant (OR 0.93, 95% CI 0.84-1.02). More adherent statin users were more likely to receive mammograms (OR 1.15, 95% CI 1.03-1.28).

Conclusions: Breast cancer prognosis may be altered by frequent antibiotic use. Receipt of surveillance procedures may confound associations between medication exposure and breast cancer outcomes through detection bias.

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DEDICATION

To my boys, you are my heart and soul.

To JT, never forget.

CHAPTER 1:

Frequent Antibiotic Use and Risk of Second Breast Cancer Events

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ABSTRACT

Background: Frequent antibiotic use is common and associated with increased breast cancer risk and breast cancer mortality, but no study to date has evaluated the relation between antibiotic use and breast cancer outcomes among women with a history of breast cancer. We examined the association between frequent antibiotic use and second breast cancer events (SBCE) among an established cohort of women diagnosed with early stage invasive breast cancer.

Methods: Retrospective cohort study among female health plan enrollees aged ≥18 years who were diagnosed with a histologically confirmed incident invasive early stage (I, II) breast carcinoma between 1990 and 2008 via the Surveillance, Epidemiology, and End Results (SEER) registry. Information on antibiotic use and covariates was obtained from health plan automated databases and medical record review. We evaluated frequent antibiotic use defined as ≥4 antibiotic dispensings in 12 months. Our primary outcome measure was SBCE defined as the first occurrence of recurrence or second primary breast cancer. We evaluated disease free survival (DFS) in secondary analyses, defined as first occurrence of death, SBCE, or other cancers. We used multivariate Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) while accounting for competing risks.

Results: The final sample included 4,216 women who were followed for a median of 6.7 years (range 0.3-20.0 years). A total of 1,678 (40%) women were frequent antibiotic users and 558 (13%) developed a SBCE. Although not statistically significant, we observed a higher risk of SBCE among frequent antibiotic users compared to nonusers (HR 1.15, 95% CI 0.88-1.50). Frequent antibiotic use was associated with higher risk of experiencing a DFS event (HR 1.25, 95% CI 1.03-1.51).

Conclusions: Our findings suggest that frequent antibiotic use is associated with higher risk of experiencing a DFS event among women diagnosed with early stage invasive breast cancer but an association with SBCE remains to be established, though a higher risk of SBCE can't be ruled out. Additional evaluation in a different study population and further investigation of frequent use by antibiotic class would be a next step in understanding such an association. If the association differs by medication class, breast cancer survivors and their providers can make more informed decisions about which antibiotic is the optimal choice for managing medical conditions where frequent use is necessary.

INTRODUCTION

In the US, breast cancer is the most frequently diagnosed cancer in women,[1] with more than 200,000 new cases diagnosed each year.[2] Due to improvements in screening and treatment, breast cancer mortality rates have declined since 1990 and, as a result, there are an estimated 2.6 million breast cancer survivors living in the US today.[1] Given that these women are at risk for recurrence and second primary breast tumors, learning more about survivorship care and factors that influence breast cancer prognosis is essential.

Antibiotics were proposed as a risk factor for cancer over two decades ago.[3] Various hypotheses exist on how antibiotics may alter cancer risk, with some mechanisms suggesting an increased risk and others a decreased risk, depending on the antibiotic classification. Antibiotics disturb the intestinal microflora which limits the transformation of phytochemicals from plant-based food products into biologically active compounds hypothesized to protect against cancer.[3] Alternatively, antibiotic-induced disturbance of the intestinal microflora could decrease the risk of hormonal cancers by reducing intestinal metabolism of bound estrogens in the gut, resulting in lower levels of circulating estrogens and decreased risk of hormonal cancers.[4] Another potential pathway for antibiotic treatment to mediate cancer risk is by affecting immune and inflammatory responses, though further research into these biological mechanisms is necessary.[4] Through these effects, certain antibiotic classes have the potential to increase the risk of several different types of cancer while other classes could decrease risk.

Nine epidemiologic studies evaluated the relation between antibiotic use and incident breast cancer risk with conflicting results.[5-13] Five of these studies reported a positive association between antibiotic use and breast cancer risk,[6, 9, 10, 12, 13] and the remaining four studies found no association.[5, 7, 8, 11] The average duration of antibiotic use was shorter in the null studies, and information on many potential confounders was unavailable. A recent meta-analysis examined five of the nine epidemiologic studies that were eligible for an antibiotic ever use versus never use analysis. The pooled results indicated that antibiotic ever use was associated with a nonsignificant, slightly higher risk of incident breast cancer (pooled OR=1.175, 0.994–1.387).[14] No study to date has evaluated the relation between antibiotic use and second breast cancer events (SBCE) among women with a history of breast cancer.

It is clinically relevant to evaluate if frequent antibiotic use alters the risk of SBCE. Antibiotics are widely prescribed to treat a variety of infectious diseases, and frequent antibiotic use is common. The observational study by Velicer et al. of antibiotic use and breast cancer risk and mortality reported that, among antibiotic users, 38% of controls and 40% of cases were dispensed more than 10 antibiotic prescriptions.[13] Moreover, Velicer et al. demonstrated a dose-response trend of all antibiotic classes toward higher breast cancer risk and breast cancer related mortality with greater frequency of antibiotic use.[13] Importantly, antibiotics are often used inappropriately therefore a better understanding of risks associated with frequent use could bolster measures to improve antibiotic prescribing when frequent use is necessary. Consequently, the risk-benefit of antibiotic use among women with prior history of breast cancer is most relevant for chronic or frequent use, not short-term use. Thus, it was the objective of this study to evaluate the association between frequent antibiotic use and SBCE among women diagnosed with early stage invasive breast cancer.

METHODS

Study Population

This retrospective cohort study was conducted within Group Health Cooperative (GH), a nonprofit integrated delivery system that provides comprehensive health care on a pre-paid basis to approximately 650,000 individuals throughout western 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 Surveillance, Epidemiology, and End Results (SEER) registry.[1] Women were included in this study if they met the following criteria: 1) ≥18 years of age; 2) diagnosed with a histologically confirmed incident invasive breast carcinoma (stage I or II) between January 1, 1990 and December 31, 2008 via the SEER registry; 3) enrolled in GH's integrated group practice for at least 1 year before the initial breast cancer diagnosis and 1 year after diagnosis (unless died). A total of 4,426 subjects were identified and sent to chart review, of which a subset (1,268 women diagnosed 1990-1999) was already partially abstracted (first 5 years post diagnosis) as part of two previous studies.[15-17] After further excluding women per chart review due to no medical record (n=72), bilateral disease (n=6), breast cancers that were not first primaries (n=79), and women with no definitive surgery (n=44), our final sample size for the main outcome of SBCE was 4,225. The GH Institutional Review Board approved this study.

Data Collection

Data were collected on all eligible women through the earliest of death, disenrollment from GH, or end of study (i.e., date of chart abstraction). Disenrollment was defined as a lapse in membership of 90 or more days. Data were collected from medical record review (paper and electronic), SEER, health plan automated administrative databases, and GH's Breast Cancer Screening Recruitment and Reminder (BSRR) survey.[18] Tumor characteristics (unavailable or missing from SEER), breast cancer treatment, outcomes (i.e., recurrence and second primaries), and specific diagnoses, vitals, and breast cancer surveillance during years prior to availability of automated data were obtained through review of medical records. Data were abstracted directly from the medical record into an Access database by trained abstractors. GH's automated databases include demographics, enrollment, inpatient and outpatient diagnoses and procedures (available 1993 on), results of breast services (available 1997 on), pharmacy dispensings (available 1977 on), laboratory results, vitals, and death.[19]

Outcome Ascertainment

Second breast cancer events

The primary outcome was second breast cancer event (SBCE), including recurrence of the primary breast cancer or diagnosis of a second primary breast cancer. SBCE was defined as any ductal carcinoma in situ (DCIS) or invasive breast cancers of the ipsilateral (recurrence) or contralateral (second primary) breast or in any regional or distant sites.[20] A woman was at risk for a SBCE starting 120 days after completing definitive surgery for the incident breast cancer.[17] Of the 4,225 eligible women, 4,216 were at risk for a SBCE starting 120 days after completing definitive surgery (5 deaths and 4 metastases prior to 120 days). Medical records were reviewed to ascertain information on the SBCE. We used standard SEER definitions (local, regional, distant, and unknown) to describe the SBCE and relied on non-invasive test results and clinical examination if histology documentation was not available.

Disease free survival

We evaluated disease free survival (DFS) in secondary analyses. DFS included women alive and without a diagnosis of a SBCE or any other cancer.[20] A woman was at risk for DFS starting 120 days after completing definitive surgery for the incident breast cancer and free of other cancers (n=4,157). The diagnosis of other cancers was ascertained from SEER. GH data on death was derived from internal data (e.g., hospital notification, disenrollment, and survivor notification) and a link to Washington State death tapes.[21] Death date was also collected in the chart abstraction and used only when missing from automated data.

Antibiotic Exposure

We used the GH computerized pharmacy database to ascertain outpatient prescription medication use. The pharmacy database contains records of all prescriptions dispensed at GH's outpatient pharmacies as well as claims received from outside contracting pharmacies. The database contains one record per dispensing that includes: drug name, date of dispensing, quantity dispensed, route, strength, days supply, prescriber, and National Drug Code number. We identified prescriptions for any oral antibiotic dispensed in the year prior to each woman's incident breast cancer diagnosis through the end of follow-up. The value of GH's computerized pharmacy database derives from the size and accuracy of the database, as well as the accessibility of the data. Previous studies have indicated that IGP enrollees fill all or almost all of their prescriptions at GH pharmacies.[22, 23]

We included the following antibiotic classes in our exposure ascertainment: penicillins, cephalosporins, sulfonamides, fluoroquinolones, tetracyclines, nitrofurans, macrolides, ketolides, carbapenems, oxazolidinones (linezolid), glycopeptides (vancomycin), folate antagonists (trimethoprim), nitroimidazoles (metronidazole), and methenamine. All exposures were ascertained within any moving 12-month window after the SEER diagnosis date for the incident breast cancer. Frequent users included women with at least four dispensings for any antibiotic within any moving 12-month window. We arrived at this definition per communications with numerous clinicians and pharmacists. A dispensing was defined as a prescription with ≤30 days supply. If a dispensing had >30 days supply, we split that dispensing up into multiple dispensings reflective of days supply ≤30 days. For example, a dispensing of 90 days supply was counted as three 30 day dispensings. Nonusers were defined as women with no dispensings for an antibiotic. Nonusers were the reference category for all analyses. We modeled antibiotic use as a time varying exposure where women contributed person-time to the exposure category only after she met the definition of use. Women were only allowed to transition from being nonusers to frequent users over time.

In secondary analyses, we evaluated antibiotic exposure based on cumulative days of antibiotic use using similar categories as Velicer and colleagues (1-50, 51-100, 101-500, ≥501).[13] We restricted this analysis to include only women with ≥501 days of follow-up to allow only those who had the opportunity to meet all exposure-defining criteria into the analyses. Recency of use was investigated by categorizing frequent antibiotic use into two mutually exclusive time periods: <3 years and ≥3 years prior to SBCE diagnosis. We restricted the recency of use analysis to include only those women with ≥3 years of follow-up. We also explored frequent use by the top 5 most commonly dispensed antibiotic classes: penicillins, cephalosporins, sulfonamides, fluoroquinolones, and tetracyclines. In these analyses, women could contribute to multiple antibiotic classes if she filled at least one prescription for that class.

Covariates

We used automated GH pharmacy databases to ascertain information on antibiotic use and hormone therapy in the 12 months prior to the initial breast cancer diagnosis as well as post-diagnosis use of endocrine therapy. A woman was considered a pre-diagnosis antibiotic ever user if she was dispensed at least one antibiotic during the 12-month period prior to her SEER diagnosis date. Pre-diagnosis hormone therapy ever use was defined similarly. We characterized a woman as a pre-diagnosis frequent antibiotic user if she was dispensed 4+ antibiotics during the 12-month pre-diagnosis period. Endocrine therapy users included women who received a dispensing for tamoxifen and/or aromatase inhibitors for the initial breast cancer between her SEER diagnosis date and before her SBCE date or DFS date for cases or the end of follow-up for non-cases. Endocrine therapy was modeled as time-varying.

We used automated GH administrative databases to ascertain information on several potential confounders including age at breast cancer diagnosis, smoking status, the Charlson co-morbidity index (CCI) score,[24] and mammographic exams. The CCI score was modeled as time-varying and scores were allowed to only transition from a lower to a higher value over time. Prior to 1992 when diagnoses became available in GH automated data, we used data from the GH medical record to calculate the CCI score. Mammographic exams were available electronically from GH administrative databases from 1996 forward. Data on exam date, indication designated by the interpreting radiology (distinguishing screening from diagnostic exams) and Breast Imaging Reporting and Data System (BI-RADS®) initial and final assessments were collected on all women 12 months prior to diagnosis through the end of follow-up. Data from radiology exams performed prior to 1996 were obtained from the medical record. Surveillance mammograms included post-diagnosis exams where the patient reported no symptoms at the time of the exam and the indication was designated as screening by the interpreting radiologist. Surveillance mammograms also included all short interval follow-up (SIFU) exams following screening and only SIFU exams following a diagnostic exam if they were >9 months apart. A woman was categorized as having received surveillance mammography within the 12-month period prior to an event and was modeled as time-varying. Mode of detection for the initial breast cancer was defined as screening (positive/negative) or diagnostic (positive/negative) using pre-established criteria.[25] Information on screening mammographies was collected during the 12 months prior to the SEER diagnosis date. The first screening mammogram in 12 months prior to diagnosis was used to determine mode of detection. If there was no screening mammogram in the 12 months prior to diagnosis, we used the first diagnostic mammogram during this period.

We ascertained treatment information related to the incident breast cancer, including primary surgery (breast conserving surgery [BCS] or mastectomy), radiation therapy, and receipt of chemotherapy from the GH medical record. Completion of radiation and/or chemotherapy was ascertained directly from the medical chart. GH began performing HER2 tests in 1998 and information on HER2 status and test results were abstracted from the medical record. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. BMI at diagnosis was calculated from the weight and height ascertained from the medical record during 12 months prior to diagnosis. Co-morbid conditions related to recurrent or chronic antibiotic use, including chronic obstructive pulmonary disease (COPD), urinary tract infection (UTI), acne and/or rosacea, were collected from the medical record. A woman was considered to have the co-morbid condition of interest if noted in the chart on a date 12 months prior to the SEER diagnosis date through the event date for cases and the end of follow-up for non-cases. These co-morbidities were modeled as time-varying.

The BSRR, a self-administered questionnaire completed at each screening mammography, was used for information on education and menopausal status. If menopausal status was missing or unknown (19%), we characterized a woman as peri- or pre-menopausal if she was <55 years of age and post-menopausal if she was ≥55 years of age.

SEER was the gold standard for race, ethnicity and incident breast cancer characteristics including year of diagnosis, American Joint Committee on Cancer (AJCC) stage at diagnosis, lymph node status, hormone receptor status, and tumor size. If any of these data were missing from SEER, they were obtained from the medical record.

Sensitivity Analyses

We conducted sensitivity analyses to assess the influence of any assumptions used in the primary analyses. We evaluated other definitions of frequent antibiotic use, including 5+ and 6+ dispensings in any 12-month window post-diagnosis. We excluded antibiotic use in the year immediately prior to the SBCE diagnosis date to determine if this influences risk estimates since antibiotic use during this time frame may be associated with symptoms of undiagnosed SBCEs (i.e., protopathic bias). We also explored exclusion of antibiotic use during the first year post-diagnosis for the initial breast cancer to determine if this influences the risk estimates since antibiotic use may be related to immunosuppression due to the treatment regimen.

Data Analysis

The primary analysis evaluated whether frequent antibiotic use was associated with risk of SBCE. DFS was examined in secondary analyses. We evaluated additional post-diagnosis exposures including frequent antibiotic use by antibiotic class and cumulative days supply of antibiotic dispensings (all antibiotics and by antibiotic class). We used multivariate Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for SBCE and DFS for the *a priori* specified categories of antibiotic use. All exposures were modeled as time-varying. Time since breast cancer diagnosis was the time scale used in all analyses. Subjects were considered at risk beginning 120 days after the initial definitive surgery for the incident breast cancer. Women were followed until the earliest of death, disenrollment, or the end of follow-up. Nonusers were the reference category for all analyses. For the primary analysis evaluating SBCE, we performed a competing risks analysis to account for death as a competing risk. We also performed a competing risks analysis for the DFS composite endpoint.

All models were adjusted for variables we selected *a priori* to be confounders, including diagnosis year (1990-1994, 1995-1999, 2000-2004, 2005-2008), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status (current, past, never/unknown), Charlson score (0, 1, 2+, time-varying), acne and/or rosacea (yes/no, time-varying), COPD (yes/no, time-varying), UTI (yes/no, time-varying), and receipt of screening mammogram in the previous 12 months prior to the event-date (yes/no, time-varying). All models were further adjusted for precision variables predictive of SBCEs, including age at diagnosis (18-49, 50-59, 60-69, 70-79, 80+ years), AJCC stage (I, IIA, IIB), hormone receptor status (estrogen receptor [ER] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), and endocrine therapy for the initial breast cancer (yes/no, time-varying). We excluded 20 women from the analyses due to missing BMI information.

We examined the adequacy of the proportional hazards assumption by testing for an interaction between the exposure variable and the log of time since diagnosis. There was no evidence to suggest a violation of the proportional hazards assumption. All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Among the 4,216 eligible women for our main SBCE analysis, a total of 432 (10%) women experienced a recurrence and 153 (4%) experienced a second primary breast cancer, with 558 developing a SBCE (n=415 recurrences and n=143 second primary breast cancers). Among recurrences, 67% were distant, 32% were local or regional, and 1% were DCIS. Among second primary breast cancers, 4% were stage III/IV, 21% were stage II, 49% were stage I, 21% were DCIS, and staging was unavailable for 5%. The median follow-up was 6.7 years and the median time to first SBCE was 3.3 years. Among the 4,157 eligible women for the DFS event analysis, 1,320 (32%) experienced a DFS event (first of: n=536 SBCEs, n=519 deaths, and n=265 other cancers). The median follow-up was 6.7 years and the median time to first DFS event was 4.3 years.

During the study period, there were 3,691 (88%) women dispensed at least one antibiotic and 1,678 (40%) frequent antibiotic users with 9,112 person-years of follow-up. Penicillins and cephalosporins were the most commonly prescribed antibiotic classes overall, and this was consistent throughout the study period. The average time between the first and fourth antibiotic dispensings for frequent users was approximately 6 months and the average cumulative duration of use was 235 days.

Characteristics of the study cohort by SBCE and DFS status are described in Table 1. Due to the large sample size, many characteristics were statistically significantly different. Most notable, women who developed a SBCE had earlier year of diagnosis, shorter duration of follow-up, were pre- or peri-menopausal, and less likely to have acne and/or rosacea, COPD and UTIs compared to women who did not develop a SBCE. SBCE cases were also more likely to have initial breast cancers that were a higher AJCC stage and hormone receptor negative than women with no SBCEs. Consistent with these clinical characteristics, initial breast cancer treatment among SBCE cases was more likely to include mastectomy and chemotherapy but less likely to include endocrine therapy than women who did not develop a SBCE. The mode of detection of the initial breast cancer was more likely to be diagnostic detected among SBCE cases whereas non-cases were more likely to have screen-detected mammographic exams.

Characteristics of the study cohort by antibiotic use are described in Table 2. Frequent antibiotic users had earlier years of diagnosis, longer duration of follow-up, higher Charlson co-morbidity scores and were more likely to be White, non-Hispanic, and have acne and/or rosacea, COPD and UTIs compared to nonusers. Frequent antibiotic users were also more likely to have initial breast cancers that were lower AJCC stage than nonusers. Yet, frequent antibiotic users were more likely to be treated with mastectomy and endocrine therapy compared to nonusers.

Frequent antibiotic use was not associated with risk of SBCE compared to nonusers (HR 1.15, 95% CI 0.88-1.50) (Figure 1). There was also no association between SBCE and recent frequent antibiotic use (<3 years) (HR 0.78, 95% CI 0.53-1.17) or past frequent antibiotic use (≥3 years) (HR 0.91, 95% CI 0.48-1.72) compared to nonusers. In separate analyses, there were no differences in risk of SBCE comparing frequent antibiotic users to nonusers for any of the antibiotic classes studied (penicillins, cephalosporins, sulfonamides, fluoroquinolones, and tetracyclines) (Figure 1). Similar findings were observed when evaluating the risk of SBCE by cumulative days of antibiotic dispensings. For categories of increasing days of use, the corresponding HR and 95% CI were: 0.82 (0.63-1.08) for 1-50 days, 0.98 (0.71-1.37) for 51-100 days, 1.14 (0.81-1.61) for 101-500 days and 0.83 (0.42-1.66) for ≥501 days (Table 3). The test for trend of cumulative use was not significant (p=0.2461). We also observed no differences in risk of SBCE comparing the categories for increasing cumulative days of antibiotic use to never use for any of the antibiotic classes studied.

In addition to the composite SBCE outcome, we examined the cause-specific outcomes of breast cancer recurrence and second primary breast cancer. There were some statistically significant associations within the sulfonamide class for the second primary breast cancer outcome, but these data are likely a result of small numbers in this subanalysis. There were no statistically significant differences for any of the other antibiotic exposures we evaluated (Figure 1, Table 3).

In secondary analyses of DFS, frequent antibiotic use was associated with a higher risk of experiencing the composite endpoint of death, SBCE, or other cancers (HR 1.25, 95% CI 1.03-1.51) compared to nonusers (Figure 2). There was suggestion that the increased risk for these DFS events was most attributable to recent frequent antibiotic use (<3 years) (HR 1.27, 95% CI 0.96-1.68) but not past frequent antibiotic use (≥3 years) (HR 0.99, 95% CI 0.64-1.54) compared to nonusers. Frequent fluoroquinolone use was associated with higher risk of DFS events compared to nonusers (HR 1.48, 95% CI 1.13-1.95), but there were no differences for any of the other antibiotic classes studied (penicillins, cephalosporins, sulfonamides, and tetracyclines) (Figure 2). Overall, there was a trend for increasing risk of DFS events when we evaluated antibiotic exposure by categories of increasing cumulative days of antibiotic dispensings: 0.99

(0.81-1.22) for 1-50 days, 1.25 (0.99-1.58) for 51-100 days, 1.22 (0.96-1.55) for 101-500 days and 1.35 (0.95-1.94) for ≥501 days (Table 4). The test for trend of cumulative use was significant (p=0.0056). When we evaluated cumulative use by antibiotic class, fluoroquinolones was the only antibiotic class that demonstrated a trend for increasing risk of DFS events: HR 1.42 (1.24-1.63) for 1-50 days, HR 1.44 (1.03-2.03) for 51-100 days, and HR 2.10 (1.26-3.50) for ≥101 days (p<0.0001) (Table 4). We did not observe any differences in risk of DFS events comparing cumulative days of antibiotic use to never use for any of the other antibiotic classes studied.

In addition to the composite DFS outcome, we present the cause-specific outcomes of death and other cancers. Results for the cause-specific outcomes of recurrence and second primaries in the DFS analyses were similar to those already presented in the SBCE analyses. Although not statistically significant, we observed a higher risk of death (HR=1.41, 95% CI 0.98-2.01) and other cancers (HR=1.27, 95% CI 0.82-1.97) among frequent antibiotic users (Figure 2). The risk for death did approach statistical significance. There was an increased risk of other cancers among users with 1-50 days and ≥501 days of antibiotic dispensings (Table 4). We observed a significant trend for increasing risk of death when we evaluated antibiotic exposure by categories of increasing cumulative days of antibiotic dispensings (p=0.0014) (Table 4). We also observed a significant trend for increasing risk of death with increasing cumulative days of fluoroquinolone dispensings (p<0.0001) (Table 4). When we evaluated the remaining antibiotic classes, we observed no differences in risk which is likely attributable to low number of events for each individual outcome.

Study findings were robust to sensitivity analyses evaluating varying thresholds of frequent antibiotic use (5+ and 6+ dispensings in any moving 12-month window post-diagnosis). We also did not observe any appreciable changes in risk estimates when we excluded antibiotic dispensings during the first year post-diagnosis or the year immediately prior to the SBCE or DFS event date.

DISCUSSION

In this retrospective cohort study of women diagnosed with early stage invasive breast cancer, we found a slightly higher risk of SBCE among frequent antibiotic users, though this association was not statistically significant. Frequent antibiotic use was associated with a significantly higher risk of experiencing a DFS event. We also observed a significant trend for higher risk of DFS events with increasing cumulative days of antibiotic dispensings. Our findings were robust to sensitivity analyses. Importantly, the higher risk of DFS events persisted when analyses excluded antibiotic use in the year immediately prior to an event date.

Although we found no strong evidence of increased risk of SBCE or DFS events when we evaluated frequent antibiotic use by antibiotic class, this may be due to smaller number of events. The increased risk of DFS events and death observed among fluoroquinolone users in our study may be influenced by differences in health status and co-morbid conditions compared to nonusers since fluoroquinolones are generally used to treat more severe conditions. We found that frequent fluoroquinolone users were more likely to have higher baseline Charlson scores. Although we adjusted for Charlson scores in our analyses, this may not fully control for overall health status. Future research in this area would benefit from robust adjustment of health status, including functional status and co-morbid conditions.

This is the first study to evaluate the association between frequent antibiotic use and SBCE among women diagnosed with early stage invasive breast cancer. Nine epidemiologic studies have evaluated the relation between antibiotic use and incident breast cancer risk.[5-13] Five of these studies reported a positive association.[6, 9, 10, 12, 13] The first study followed a cohort of 9,461 cancer-free Finnish women during an 18-year follow-up period, and found long-term antibiotic treatment of UTIs was associated with an increased risk of incident breast cancer among women <50 years (RR=1.74 (1.13-2.68)).[10] The investigators evaluated confounding by indication by examining whether UTIs were associated with breast cancer risk and found no association. Antibiotic classes, cumulative use, and use for other infections/conditions were not evaluated. Velicer et al. conducted a population-based case-control study among 10,219 women enrolled at Group Health during a 23-year follow-up period.[13] Antibiotic use was associated with higher risk of incident breast cancer compared to nonusers and the association was stronger with increased duration of use (OR =1.45 (1.24-1.69) for 1-50 days use, 1.53 (1.28-1.83) for 51-100 days use, 1.68 (1.42-2.00) for 101-500 days use, 2.14 (1.60-2.88) for 501-1000 days use, and 2.07 (1.48-2.89) for ≥1001 days use). The findings were consistent across antibiotic classes. The Velicer and colleagues study is the only other study to date that also evaluated antibiotic use in relation to the risk of fatal breast cancer. The dose-response effect for breast cancer related death was still evident and the magnitude of the association was even stronger compared to those observed for incident breast cancer. Although our findings among Group Health enrollees also suggest a significant trend for higher risk of death, SBCE or other cancers with increasing cumulative days of antibiotic dispensings, the magnitude of response is much lower among our study population compared to Velicer et al. and we did not observe a consistent trend across antibiotic classes.[13] Friedman et al. conducted a cohort study of >2 million women at Kaiser Permanente in northern California and found an increased risk of breast cancer with antibiotic use compared to no use (HR = 1.14; 95% CI, 1.10-1.18).[6] A more recent study again involving Finnish women evaluated antibiotic use for conditions other than just UTIs.[9] This cohort study included over 1.6 million women in Finland and demonstrated antibiotic use was associated with an increased risk of incident breast cancer (RR = 1.0 for 0-1 prescriptions (referent), 1.16 (1.13-1.20) for 2-5 prescriptions, and 1.14 (1.09-1.20) for 6+ prescriptions).[9] The medication period examined was short and the exposure period was close to the diagnosis date. In a nested case-control study using the Saskatchewan Prescription Drug plan, Tamim et al. examined antibiotic use among individuals with at least 15 years of prescription drug coverage.[12] The authors found increasing number of antibiotic prescriptions was associated with increased risk for incident breast cancer compared to individuals who never used antibiotics (RR = 1.50 (1.26-1.79) for 1-3 prescriptions, 1.63 (1.36-1.94) for 4-7 prescriptions, 1.71 (1.43-2.05) for 8-13 prescriptions, and 1.79 (1.50-2.13) for 14+ prescriptions).

The four remaining studies did not confirm that antibiotic use is associated with increases in the risk of incident breast cancer.[5, 7, 8, 11] The average duration of antibiotic use was shorter in the null studies than the five studies with positive findings, and information on many potential confounders was unavailable. A matched case-control study conducted in Denmark by Sorensen et al. reported no evidence of an association between antibiotic use and the risk of breast cancer compared to nonusers (OR = 1.0 (0.86-1.15) for >10 prescriptions).[11] Antibiotic use was evaluated over a 9.5 year period so the shorter time frame for analyses is a limitation. They also did not have information on certain breast cancer risk factors. Didham et al. carried out a nested case-control study in New Zealand and also found that antibiotic use was not associated with increased risk of breast cancer (OR=1.02 (1.00-1.05)).[5] Patients had only 2-7 years of prescribing data and antibiotic exposure was categorized as ever vs. never use so dose-response effects could not be examined. Furthermore, hospital discharge records from 1998 to 2002 were used to identify cases. The electronic databases used in this study date back only to 1996 so it is possible that some patients were diagnosed with cancer prior to this but did not have a hospital discharge until after 1998. Therefore, some cases may have had post-diagnosis antibiotic exposure. In a case-control study using the General Practice Research Database in the United Kingdom, no association with breast cancer was identified among antibiotic users compared to nonusers, but the highest category of cumulative exposure did demonstrate a modest, nonsignificant increased risk (OR=1.2 (0.9-1.6) for >500 days use).[7] Using a similar design with the same database, Kaye and Jick also did not find evidence to support an association between overall antibiotic use and breast cancer risk, though again reported a modest, nonsignificant increased risk with >500 days of cumulative antibiotic use (OR=1.2 (0.6-2.4)).[8] The duration of follow-up in both of these studies was approximately 7-8 years and they lacked information on several hormonal risk factors for breast cancer including menarche, parity, and age at first live birth.

Major strengths of our study include: a large sample of population-based breast cancer cases with extensive follow-up; complete ascertainment of incident cancer cases and tumor characteristics through a validated registry; study subjects enrolled in a health plan, which mitigates disparities in breast cancer treatment, access to medications, and uniform follow-up post-diagnosis that may exist among women without health coverage; detailed information on incident breast cancer treatment; unbiased information on medications dispensed; and detailed information on primary and second breast cancer events, co-morbidities, and mammographic exams that enabled us to examine confounding in a robust manner.

A limitation of this study is that no prior epidemiologic studies evaluated frequent antibiotic use so we had to develop the exposure definition *de novo* based on clinician input. However, sensitivity analyses evaluating different thresholds for antibiotic use provided consistent results with the primary analysis. While being enrolled in an integrated health plan provides several strengths as noted above, a limitation of our study is also that subjects are from a single health plan which may not represent other care settings or populations. This should not compromise the validity of the results, but it may limit generalizability. The generalizability of our findings is further limited by defining study entry as 120 days after the initial definitive surgery for the incident breast cancer. This is necessary to be considered disease free and eligible to experience a recurrence at study entry. However, this requires that inclusion in the analyses is conditional on survival to study entry. Subjects with short survival times or those who are censored before study entry are not included in the analyses. Despite the many advantages of collecting exposure information from pharmacy records, we recognize there are limitations to this resource. Subjects dispensed a medication but do not subsequently take the medication may be misclassified as users, and subjects receiving medications at non-GH pharmacies without submitting a claim to GH may be erroneously classified as nonusers. We did not have information on medication use before or after disenrollment from GH. Any bias resulting from classifying a user as a nonuser will bias our findings towards the null. However, misclassification of medication use is relatively unlikely since previous GH studies have found GH enrollees obtain 97% of their medications at GH owned pharmacies or GH contracting pharmacies.[22, 23] Residual confounding is an ongoing concern in observational studies and one study limitation is the absence of information on potentially confounding factors, such as those related to socioeconomic status, that are not routinely collected in the medical records. However, GH's automated databases and medical charts provide detailed and unbiased access to medical information on breast cancer characteristics, treatment, diagnoses, medication use, and screening and surveillance history.

In conclusion, frequent antibiotic use is not associated with risk of SBCE but is associated with higher risk of experiencing the composite endpoint of death, SBCE, or other cancers among women with a history of early stage invasive breast cancer. While the management of conditions that require recurrent or chronic antibiotic use is warranted, breast cancer survivors should be educated on the potential risk of frequent antibiotic use and preventive measures should be taken to minimize antibiotic exposure whenever possible for numerous clinical reasons. This study is an original evaluation of this association and is part of ongoing efforts to improve cancer prognosis and address drug safety. Given the public health importance of learning more about survivorship care and factors that influence breast cancer prognosis, further investigation into this common exposure among women with a history of breast cancer is warranted. Additional evaluation in a different study population and further exploring frequent use by antibiotic class would be a next step in understanding such an association. If the association differs by medication class, breast cancer survivors and their providers can make more informed decisions about which antibiotic is the optimal choice for managing medical conditions where frequent use is necessary.

Table 1. Descriptive characteristics of women, by second breast cancer event and disease free survival status

	SBCE (N=4,216)				DFS (N=4,157)			
	No (n=3,658)		Yes (n=558)		No (n=2,837)		Yes (n=1,320)	
	n (%)							
Year of diagnosis								
1990-1994	755	(20.6)	195	(34.9)	480	(16.9)	453	(34.3)
1995-1999	1020	(27.9)	171	(30.6)	734	(25.9)	447	(33.9)
2000-2004	1073	(29.3)	128	(22.9)	895	(31.5)	293	(22.2)
2005-2008	810	(22.1)	64	(11.5)	728	(25.7)	127	(9.6)
Years of follow-up[1]								
Mean (SD)	7.5	(4.3)	4.4	(3.5)	7.6	(4.2)	5.3	(3.9)
Median	6.7		3.3		6.8		4.3	
Age, years								
Mean (SD)	62.8	(13.2)	61.1	(13.8)	60	(12.4)	67.9	(13.7)
18-39	112	(3.1)	27	(4.8)	108	(3.8)	31	(2.3)
40-49	544	(14.9)	102	(18.3)	514	(18.1)	129	(9.8)
50-59	866	(23.7)	129	(23.1)	789	(27.8)	199	(15.1)
60-69	889	(24.3)	129	(23.1)	725	(25.6)	276	(20.9)
70-79	824	(22.5)	116	(20.8)	524	(18.5)	391	(29.6)
80+	423	(11.6)	55	(9.9)	177	(6.2)	294	(22.3)
Menopausal status								
Peri- or pre-menopausal	956	(26.1)	189	(33.9)	896	(31.6)	245	(18.6)
Post-menopausal	2702	(73.9)	369	(66.1)	1941	(68.4)	1075	(81.4)
Race								
White	3232	(88.7)	487	(87.3)	2474	(87.6)	1192	(90.4)
African American	104	(2.9)	32	(5.7)	80	(2.8)	54	(4.1)
American Indian/Alaska Native	104	(2.9)	9	(1.6)	92	(3.3)	18	(1.4)
Asian/Pacific Islander	203	(5.6)	30	(5.4)	178	(6.3)	54	(4.1)
Other	1	(0)	0		0		1	(0.1)
Unknown	14		0		13		1	
Ethnicity								
Not Hispanic	3438	(94.3)	538	(96.4)	2633	(93.1)	1286	(97.6)
Hispanic	209	(5.7)	20	(3.6)	195	(6.9)	32	(2.4)
Unknown	11		0		9		2	
Education								
High school or less	393	(23.5)	25	(21.4)	340	(22.3)	73	(29.9)
Some college	594	(35.5)	40	(34.2)	547	(35.9)	77	(31.6)
College or post graduates	685	(41.0)	52	(44.4)	635	(41.7)	94	(38.5)
Unknown	1986		441		1315		1076	

	SBCE (N=4,216)				DFS (N=4,157)			
	No (n=3,658)		Yes (n=558)		No (n=2,837)		Yes (n=1,320)	
	n (%)							
Body mass index (kg/m^2)								
Mean (SD)	28	(6.2)	28.3	(6.6)	28.2	(6.2)	27.7	(6.3)
Median	26.7		27.5		26.9		26.6	
<18.5	55	(1.5)	14	(2.5)	28	(1.0)	39	(3.0)
18.5-24.9	1269	(34.8)	184	(33.3)	970	(34.2)	466	(35.8)
25.0-29.9	1186	(32.6)	176	(31.8)	924	(32.6)	419	(32.2)
30.0-34.9	666	(18.3)	100	(18.1)	531	(18.7)	226	(17.4)
35+	467	(12.8)	79	(14.3)	382	(13.5)	152	(11.7)
Unknown	15		5		2		18	
Smoking status								
Current	230	(6.3)	23	(4.1)	179	(6.3)	70	(5.3)
Past	318	(8.7)	34	(6.1)	270	(9.5)	75	(5.7)
Never/Unknown	3110	(85.0)	501	(89.8)	2388	(84.2)	1175	(89.0)
Charlson score								
0	2784	(76.1)	445	(79.7)	2283	(80.5)	910	(68.9)
1	625	(17.1)	79	(14.2)	416	(14.7)	273	(20.7)
2+	249	(6.8)	34	(6.1)	138	(4.9)	137	(10.4)
Co-morbidities[3]								
Acne and/or rosacea	329	(9.0)	31	(5.6)	283	(10.0)	67	(5.1)
COPD	574	(15.7)	58	(10.4)	325	(11.5)	274	(20.8)
UTI	1392	(38.1)	146	(26.2)	975	(34.4)	503	(38.1)
Other cancers	303	(8.3)	24	(4.3)	0		268	(20.3)
Medication use in year prior to diagnosis								
Antibiotic user, ever	1621	(44.3)	251	(45.0)	1240	(43.7)	595	(45.1)
Frequent antibiotic user	277	(7.6)	45	(8.1)	188	(6.6)	130	(9.8)
HRT	1282	(35.0)	197	(35.3)	1027	(36.2)	431	(32.7)
Antibiotic use post-diagnosis[1]								
Frequent	1476	(40.3)	202	(36.2)	1063	(37.5)	542	(41.1)
Infrequent	1762	(48.2)	251	(45.0)	1422	(50.1)	592	(44.8)
Nonuser	420	(11.5)	105	(18.8)	352	(12.4)	186	(14.1)
Max cumulative days supply	.		.		.		.	
0	420	(11.5)	105	(18.8)	352	(12.4)	186	(14.1)
1-50	1527	(41.7)	250	(44.8)	1238	(43.6)	548	(41.5)
51-100	723	(19.8)	89	(15.9)	543	(19.1)	245	(18.6)
101-500	838	(22.9)	104	(18.6)	599	(21.1)	291	(22.0)
≥501	150	(4.1)	10	(1.8)	105	(3.7)	50	(3.8)
AJCC stage								
I	2384	(65.2)	264	(47.3)	1827	(64.4)	778	(58.9)
IIA	906	(24.8)	172	(30.8)	710	(25.0)	359	(27.2)
IIB	368	(10.1)	122	(21.9)	300	(10.6)	183	(13.9)

	SBCE (N=4,216)				DFS (N=4,157)			
	No (n=3,658)		Yes (n=558)		No (n=2,837)		Yes (n=1,320)	
	n (%)							
Lymph node status								
Negative	2525	(77.4)	322	(64.3)	2050	(77.2)	760	(71.5)
Positive (1-3)	570	(17.5)	110	(22.0)	468	(17.6)	203	(19.1)
Positive (4+)	167	(5.1)	67	(13.4)	134	(5.0)	98	(9.2)
Positive (unknown #)	2	(0.1)	2	(0.4)	2	(0.1)	2	(0.2)
Unknown	394		57		183		257	
ER/PR status								
ER-/PR-	531	(14.5)	136	(24.4)	418	(14.7)	240	(18.2)
ER+/PR-	319	(8.7)	64	(11.5)	235	(8.3)	145	(11.0)
ER-/PR+	47	(1.3)	14	(2.5)	30	(1.1)	31	(2.3)
ER+/PR+	2572	(70.3)	316	(56.6)	2027	(71.4)	818	(62)
ER & PR unknown	189	(5.2)	28	(5.0)	127	(4.5)	86	(6.5)
Tumor size								
≤ 2 cm	2785	(76.1)	325	(58.5)	2157	(76.0)	905	(68.7)
> 2 cm	873	(23.9)	231	(41.5)	680	(24.0)	413	(31.3)
Unknown	0		2		0		2	
HER2 test result								
Test done	1874	(80.5)	200	(73.0)	1613	(82.8)	430	(69.9)
Positive/Borderline	311	(16.6)	42	(21.0)	269	(16.7)	79	(18.4)
Negative	1556	(83.0)	158	(79.0)	1340	(83.1)	348	(80.9)
No result	7	(0.4)	0		4	(0.2)	3	(0.7)
Surgical procedure								
Mastectomy +/- radiation	1289	(35.2)	232	(41.6)	967	(34.1)	526	(39.8)
BCS + radiation	1927	(52.7)	245	(43.9)	1540	(54.3)	609	(46.1)
BCS	442	(12.1)	81	(14.5)	330	(11.6)	185	(14.0)
Other treatment								
Chemotherapy	1142	(31.2)	234	(41.9)	1041	(36.7)	326	(24.7)
Completed course	1003	(87.8)	209	(89.3)	923	(88.7)	283	(86.8)
Endocrine therapy[1]	2101	(57.4)	262	(47.0)	1684	(59.4)	647	(49.0)
Mode of initial breast cancer detection								
Screen-detected	1212	(49.4)	82	(27.9)	1002	(49.3)	273	(40.4)
Screen interval-detected	303	(12.4)	40	(13.6)	244	(12.0)	92	(13.6)
Diagnostic-detected	862	(35.2)	158	(53.7)	725	(35.7)	287	(42.5)
Diagnostic interval-detected	75	(3.1)	14	(4.8)	62	(3.0)	24	(3.6)
Unknown[2]	1206		264		804		644	
% of follow-up years with yearly screening mammogram[1]								
<50%	793	(21.7)	146	(26.2)	521	(18.4)	407	(30.8)
50%-80%	1284	(35.1)	155	(27.8)	971	(34.2)	399	(30.2)
>80%	1581	(43.2)	257	(46.1)	1345	(47.4)	514	(38.9)

AJCC=American Joint Committee on Cancer; BCS=breast conserving surgery; ER=estrogen receptor; PR=progesterone receptor; SBCE=second breast cancer event, includes first occurrence of breast cancer recurrence and second primary breast cancer, in-situ and invasive; SD=standard deviation; COPD=chronic obstructive pulmonary disease; UTI=urinary tract infection; HRT=hormone replacement therapy

*Characteristics at diagnosis date for initial breast cancer (unless noted)

[1] Status ascertained from diagnosis through event date for cases or end of follow-up for non-cases.
[2] Mode of detection with mammography was collected from automated data available ≥1996; unknown mode of detection indicates pre-1996 diagnosis, diagnosis was ≥1996 with <12 month follow-up or there were no mammography data available.
[3] Status ascertained from 1 year before diagnosis through event date for cases or end of follow-up for non-cases.

Table 2. Descriptive characteristics of women, by antibiotic medication use[1] within second breast cancer event and disease free survival status

	SBCE (N=4,216)				DFS (N=4,157)			
	Nonuser (n=525)		Frequent Antibiotic User (n=1,678)		Nonuser (n=538)		Frequent Antibiotic User (n=1,605)	
	n (%)							
Year of diagnosis								
1990-1994	87	(16.6)	468	(27.9)	92	(17.1)	440	(27.4)
1995-1999	110	(21.0)	539	(32.1)	115	(21.4)	514	(32.0)
2000-2004	161	(30.7)	427	(25.4)	167	(31.0)	414	(25.8)
2005-2008	167	(31.8)	244	(14.5)	164	(30.5)	237	(14.8)
Years of follow-up[1]								
Mean (SD)	4.5	(3.3)	8.2	(4.5)	4.4	(3.3)	8	(4.4)
Median	3.7		7.6		3.6		7.4	
Age, years								
Mean (SD)	61.6	(13.5)	63.1	(13.3)	61.7	(13.5)	62.9	(13.4)
18-39	18	(3.4)	56	(3.3)	18	(3.3)	55	(3.4)
40-49	94	(17.9)	227	(13.5)	96	(17.8)	223	(13.9)
50-59	131	(25.0)	386	(23.0)	132	(24.5)	377	(23.5)
60-69	122	(23.2)	431	(25.7)	126	(23.4)	407	(25.4)
70-79	93	(17.7)	384	(22.9)	97	(18.0)	357	(22.2)
80+	67	(12.8)	194	(11.6)	69	(12.8)	186	(11.6)
Menopausal status								
Peri- or Pre-menopausal	158	(30.1)	442	(26.3)	160	(29.7)	436	(27.2)
Post-menopausal	367	(69.9)	1236	(73.7)	378	(70.3)	1169	(72.8)
Race								
White	436	(83.7)	1527	(91.2)	448	(83.9)	1459	(91.1)
African American	28	(5.4)	39	(2.3)	28	(5.2)	36	(2.2)
American Indian/Alaska Native	8	(1.5)	53	(3.2)	7	(1.3)	52	(3.2)
Asian/Pacific Islander	49	(9.4)	55	(3.3)	51	(9.6)	54	(3.4)
Other	0		1	(0.1)	0		1	(0.1)
Unknown	4		3		4		3	
Ethnicity								
Not Hispanic	483	(92.2)	1603	(95.9)	497	(92.6)	1532	(95.8)
Hispanic	41	(7.8)	69	(4.1)	40	(7.4)	67	(4.2)
Unknown	1		6		1		6	
Education								
High school or less	51	(21.2)	158	(25.5)	52	(21.4)	149	(24.9)
Some college	85	(35.3)	221	(35.7)	84	(34.6)	215	(35.9)
College or post graduates	105	(43.6)	240	(38.8)	107	(44.0)	235	(39.2)
Unknown	284		1059		295		1006	

	SBCE (N=4,216)				DFS (N=4,157)			
	Nonuser (n=525)		Frequent Antibiotic User (n=1,678)		Nonuser (n=538)		Frequent Antibiotic User (n=1,605)	
	n (%)							
Body mass index (kg/m^2)								
Mean (SD)	27.2	(6.0)	28.7	(6.7)	27.2	(6.0)	28.7	(6.6)
Median	26		27.3		26		27.4	
<18.5	13	(2.5)	27	(1.6)	12	(2.3)	26	(1.6)
18.5-24.9	209	(40.2)	519	(31.1)	214	(40.2)	491	(30.8)
25.0-29.9	157	(30.2)	546	(32.7)	164	(30.8)	521	(32.6)
30.0-34.9	85	(16.3)	316	(18.9)	86	(16.1)	308	(19.3)
35+	56	(10.8)	261	(15.6)	57	(10.7)	250	(15.7)
Unknown	5		9		5		9	
Smoking status								
Current	33	(6.3)	91	(5.4)	34	(6.3)	89	(5.5)
Past	51	(9.7)	119	(7.1)	50	(9.3)	117	(7.3)
Never/Unknown	441	(84.0)	1468	(87.5)	454	(84.4)	1399	(87.2)
Charlson score								
0	425	(81.0)	1183	(70.5)	433	(80.5)	1132	(70.5)
1	75	(14.3)	363	(21.6)	80	(14.9)	344	(21.4)
2+	25	(4.8)	132	(7.9)	25	(4.6)	129	(8.0)
Co-morbidities[3]								
Acne and/or rosacea	28	(5.3)	191	(11.4)	28	(5.2)	184	(11.5)
COPD	47	(9.0)	358	(21.3)	48	(8.9)	326	(20.3)
UTI	53	(10.1)	912	(54.4)	53	(9.9)	865	(53.9)
Other cancers	22	(4.2)	166	(9.9)	35	(6.5)	93	(5.8)
Medication use in year prior to diagnosis								
Antibiotic user, ever	132	(25.1)	974	(58.0)	133	(24.7)	935	(58.3)
Frequent antibiotic user	8	(1.5)	256	(15.3)	8	(1.5)	252	(15.7)
HRT	140	(26.7)	679	(40.5)	141	(26.2)	647	(40.3)
AJCC stage								
I	308	(58.7)	1049	(62.5)	313	(58.2)	1004	(62.6)
IIA	163	(31.0)	433	(25.8)	170	(31.6)	411	(25.6)
IIB	54	(10.3)	196	(11.7)	55	(10.2)	190	(11.8)
Lymph node status								
Negative	363	(78.1)	1095	(73.9)	368	(77.3)	1047	(73.9)
Positive (1-3)	75	(16.1)	293	(19.8)	81	(17.0)	279	(19.7)
Positive (4+)	27	(5.8)	92	(6.2)	27	(5.7)	90	(6.4)
Positive (unknown #)	0		1	(0.1)	0		1	(0.1)
Unknown	60		197		62		188	

	SBCE (N=4,216)				DFS (N=4,157)			
	Nonuser (n=525)		Frequent Antibiotic User (n=1,678)		Nonuser (n=538)		Frequent Antibiotic User (n=1,605)	
	n (%)							
ER/PR status								
ER-/PR-	90	(17.1)	255	(15.2)	90	(16.7)	246	(15.3)
ER+/PR-	47	(9.0)	167	(10.0)	51	(9.5)	159	(9.9)
ER-/PR+	8	(1.5)	35	(2.1)	8	(1.5)	33	(2.1)
ER+/PR+	350	(66.7)	1123	(66.9)	359	(66.7)	1074	(66.9)
ER & PR unknown	30	(5.7)	98	(5.8)	30	(5.6)	93	(5.8)
Tumor size								
≤ 2 cm	362	(69.0)	1257	(74.9)	372	(69.1)	1200	(74.8)
> 2 cm	163	(31.0)	421	(25.1)	166	(30.9)	405	(25.2)
HER2 test result								
Test done	322	(83.0)	678	(76.1)	326	(82.5)	660	(77.0)
Positive/Borderline	57	(17.7)	119	(17.6)	56	(17.2)	117	(17.7)
Negative	263	(81.7)	557	(82.2)	268	(82.2)	541	(82.0)
No result	2	(0.6)	2	(0.3)	2	(0.6)	2	(0.3)
Surgical procedure								
Mastectomy +/- radiation	176	(33.5)	681	(40.6)	179	(33.3)	644	(40.1)
BCS + radiation	262	(49.9)	802	(47.8)	270	(50.2)	772	(48.1)
BCS	87	(16.6)	195	(11.6)	89	(16.5)	189	(11.8)
Other treatment								
Chemotherapy	164	(31.2)	545	(32.5)	168	(31.2)	533	(33.2)
Completed course	147	(89.6)	472	(86.6)	151	(89.9)	462	(86.7)
Endocrine therapy[1]	269	(51.2)	969	(57.7)	277	(51.5)	932	(58.1)
Mode of initial breast cancer detection								
Screen-detected	187	(47.9)	451	(47.0)	191	(47.9)	435	(47.3)
Screen interval-detected	43	(11.0)	122	(12.7)	41	(10.3)	112	(12.2)
Diagnostic-detected	147	(37.7)	355	(37)	153	(38.3)	343	(37.3)
Diagnostic interval-detected	13	(3.3)	31	(3.2)	14	(3.5)	30	(3.3)
Unknowns[2]	135		719		139		685	
% follow-up years with yearly screening mammogram[1]								
<50%	146	(27.8)	391	(23.3)	154	(28.6)	377	(23.5)
50%-80%	130	(24.8)	627	(37.4)	131	(24.3)	584	(36.4)
>80%	249	(47.4)	660	(39.3)	253	(47.0)	644	(40.1)

Abbreviations: SBCE=second breast cancer event, includes first occurrence of breast cancer recurrence and second primary breast cancer, in-situ and invasive; DFS=disease-free survival, includes first occurrence of death, breast cancer recurrence, second primary breast cancer, and other cancers; AJCC=American Joint Committee on Cancer; BCS=breast conserving surgery; ER=estrogen receptor; PR=progesterone receptor; SD=standard deviation; COPD=chronic obstructive pulmonary disease; UTI=urinary tract infection

[1] Status ascertained from diagnosis through event date for cases or end of follow-up for non-cases.
[2] Mode of initial breast cancer detection was collected from automated data available ≥1996; unknown mode of detection indicates pre-1996 diagnosis, diagnosis was ≥1996 with <12 month follow-up or there were no mammography data available.
[3] Status ascertained from 1 year before diagnosis through event date for cases or end of follow-up for non-cases.

Table 3. Adjusted hazard ratios and 95% confidence intervals for cumulative days of antibiotic dispensings and second breast cancer events (breast cancer recurrence and second primary breast cancer).

	Adjusted Hazard Ratios and 95% Confidence Intervals		
Exposure	**SBCE**	**Recurrence**	**Second Primary Breast Cancer**
All			
1-50 days	0.82 (0.63-1.08)	0.79 (0.58-1.07)	0.94 (0.52-1.71)
51-100 days	0.98 (0.71-1.37)	0.82 (0.56-1.20)	1.56 (0.81-3.02)
101-500 days	1.14 (0.81-1.61)	1.11 (0.75-1.65)	1.37 (0.68-2.76)
>=501 days	0.83 (0.42-1.66)	0.96 (0.44-2.08)	0.59 (0.13-2.71)
Trend test p-value	0.2461	0.4118	0.3345
Penicillin			
1-50 days	1.25 (1.04-1.50)	1.23 (1.00-1.53)	1.28 (0.89-1.84)
51-100 days	1.14 (0.74-1.76)	1.06 (0.61-1.83)	1.37 (0.65-2.85)
>=101 days	1.22 (0.71-2.11)	1.19 (0.61-2.33)	1.31 (0.50-3.44)
Trend test p-value	0.0687	0.1571	0.2210
Cephalosporin			
1-50 days	1.20 (1.00-1.44)	1.13 (0.92-1.40)	1.39 (0.97-2.01)
51-100 days	1.12 (0.73-1.72)	1.00 (0.59-1.69)	1.48 (0.70-3.15)
>=101 days	1.18 (0.65-2.14)	1.13 (0.55-2.32)	1.52 (0.52-4.50)
Trend test p-value	0.1288	0.4223	0.0982
Sulfonamide			
1-50 days	0.90 (0.73-1.11)	0.99 (0.78-1.25)	0.71 (0.47-1.07)
51-100 days	0.74 (0.43-1.27)	1.08 (0.62-1.90)	0.12 (0.02-0.91)
>=101 days	1.14 (0.55-2.36)	1.20 (0.48-2.98)	1.11 (0.33-3.69)
Trend test p-value	0.3481	0.8162	0.0431
Fluoroquinolone			
1-50 days	1.03 (0.82-1.29)	1.13 (0.87-1.46)	0.70 (0.43-1.13)
51-100 days	1.09 (0.56-2.10)	1.32 (0.63-2.75)	0.65 (0.15-2.79)
>=101 days	1.79 (0.77-4.15)	2.12 (0.84-5.34)	1.02 (0.13-7.72)
Trend test p-value	0.4006	0.1702	0.2055
Tetracycline			
1-50 days	0.88 (0.68-1.14)	0.73 (0.52-1.00)	1.40 (0.90-2.16)
51-100 days	0.92 (0.43-1.96)	0.73 (0.27-2.00)	1.69 (0.51-5.56)
>=101 days	0.9 (0.45-1.79)	0.93 (0.40-2.14)	0.85 (0.26-2.86)
Trend test p-value	0.4201	0.1439	0.4114

Abbreviation: SBCE=second breast cancer event, includes first occurrence of breast cancer recurrence and second primary breast cancer, in-situ and invasive

Nonusers were the reference category for all analyses. A woman could contribute to multiple antibiotic classes if she filled at least one prescription for that class.

All models were adjusted for 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] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), Charlson score (0, 1, 2+, time-varying), acne and/or rosacea (yes/no, time-varying), COPD (yes/no, time-varying), UTI (yes/no, time-varying), and receipt of screening mammogram in the previous 12 months prior to the event-date (yes/no, time-varying).

Table 4. Adjusted hazard ratios and 95% confidence intervals for cumulative days of antibiotic dispensings and disease free survival (breast cancer recurrence, second primary breast cancer, death, and other cancers).

	Adjusted Hazard Ratios and 95% Confidence Intervals		
Exposure	**DFS**	**Death**	**Other Cancers**
All			
1-50 days	0.99 (0.81-1.22)	0.97 (0.65-1.45)	1.71 (1.03-2.83)
51-100 days	1.25 (0.99-1.58)	1.43 (0.93-2.19)	1.58 (0.89-2.80)
101-500 days	1.22 (0.96-1.55)	1.51 (0.98-2.33)	1.19 (0.65-2.18)
>=501 days	1.35 (0.95-1.94)	1.43 (0.81-2.52)	2.47 (1.14-5.32)
Trend test p-value	0.0056	0.0014	0.7437
Penicillin			
1-50 days	1.06 (0.94-1.20)	0.92 (0.75-1.12)	1.02 (0.78-1.34)
51-100 days	1.00 (0.78-1.30)	1.12 (0.77-1.61)	0.59 (0.30-1.15)
>=101 days	0.96 (0.70-1.31)	0.99 (0.63-1.56)	0.82 (0.40-1.66)
Trend test p-value	0.8243	0.9622	0.3487
Cephalosporin			
1-50 days	1.14 (1.01-1.29)	1.04 (0.85-1.26)	1.22 (0.93-1.60)
51-100 days	0.91 (0.70-1.18)	0.63 (0.42-0.95)	1.21 (0.69-2.12)
>=101 days	0.89 (0.62-1.28)	0.62 (0.35-1.09)	1.37 (0.65-2.90)
Trend test p-value	0.8167	0.0520	0.1729
Sulfonamide			
1-50 days	1.05 (0.92-1.19)	1.06 (0.86-1.29)	1.34 (1.02-1.77)
51-100 days	0.70 (0.50-0.97)	0.80 (0.50-1.29)	0.47 (0.19-1.17)
>=101 days	1.06 (0.67-1.68)	1.31 (0.65-2.62)	0.77 (0.24-2.47)
Trend test p-value	0.1279	0.3962	0.9328
Fluoroquinolone			
1-50 days	1.42 (1.24-1.63)	2.04 (1.64-2.53)	1.07 (0.79-1.46)
51-100 days	1.44 (1.03-2.03)	1.79 (1.12-2.87)	1.49 (0.70-3.18)
>=101 days	2.10 (1.26-3.50)	3.48 (1.78-6.80)	0
Trend test p-value	<0.0001	<0.0001	0.7845
Tetracycline			
1-50 days	0.84 (0.72-0.98)	0.89 (0.71-1.11)	0.75 (0.53-1.07)
51-100 days	0.59 (0.35-1.01)	0.67 (0.29-1.53)	0.36 (0.09-1.49)
>=101 days	1.11 (0.76-1.60)	1.02 (0.55-1.88)	1.85 (0.95-3.57)
Trend test p-value	0.1279	0.3962	0.9328

Abbreviation: DFS=disease-free survival, includes first occurrence of death, breast cancer recurrence, second primary breast cancer, and other cancers

Nonusers were the reference category for all analyses. A woman could contribute to multiple antibiotic classes if she filled at least one prescription for that class.

All models were adjusted for 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] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), Charlson score (0, 1, 2+, time-varying), acne and/or rosacea (yes/no, time-varying), COPD (yes/no, time-varying), UTI (yes/no, time-varying), and receipt of screening mammogram in the previous 12 months prior to the event-date (yes/no, time-varying).

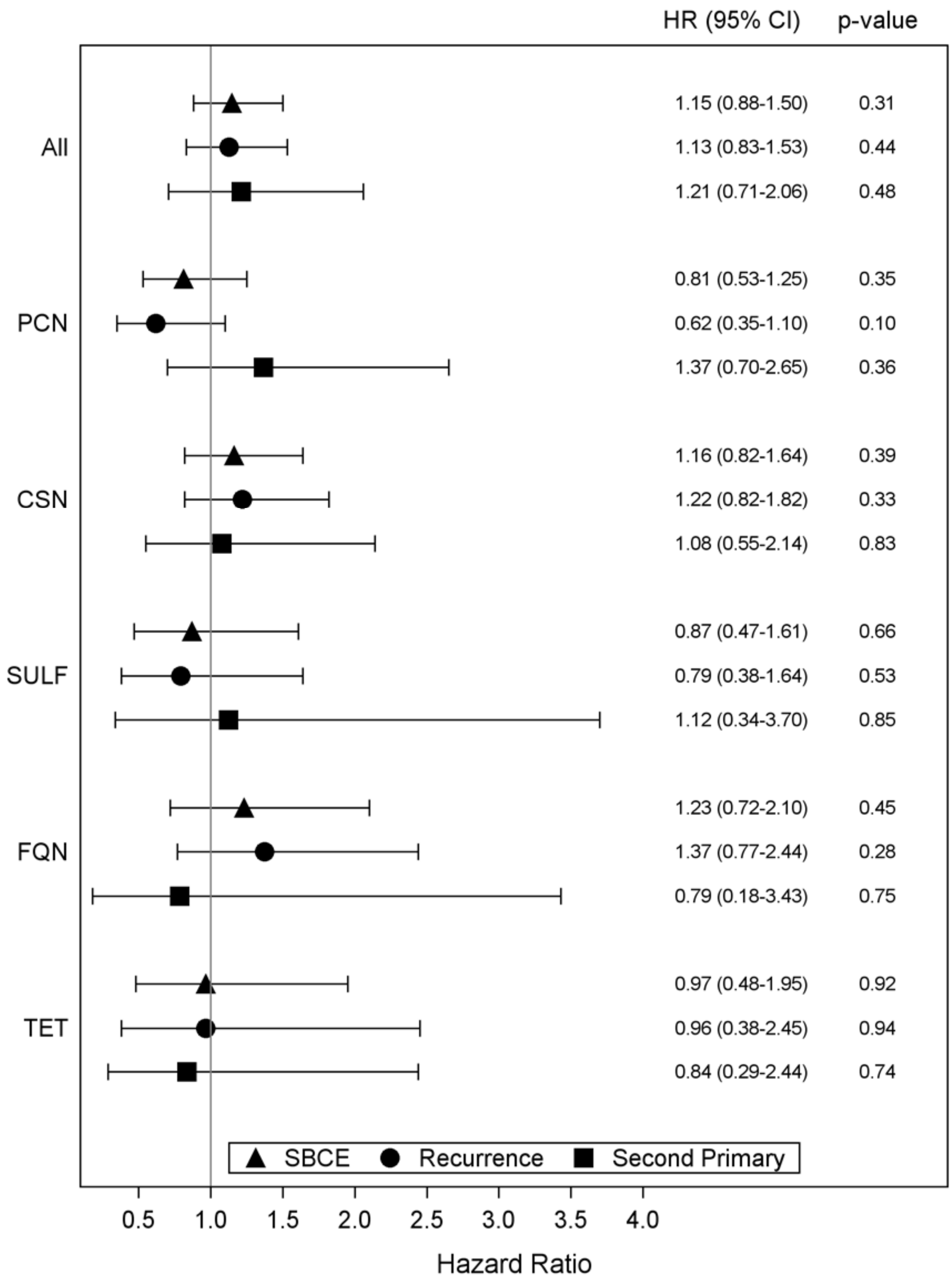

Figure 1. Adjusted hazard ratios and 95% confidence intervals for frequent antibiotic use and second breast cancer events (breast cancer recurrence and second primary breast cancer).

Abbreviations: 95% CI=95% confidence interval; CSN=cephalosporins; FQN=fluoroquinolones; PCN=penicillins; SBCE=second breast cancer event, includes first occurrence of breast cancer recurrence and second primary breast cancer, in-situ and invasive; SULF=sulfonamides; TET=tetracyclines.

Nonusers were the reference category for all analyses. A woman could contribute to multiple antibiotic classes if she filled at least one prescription for that class.

All models were adjusted for 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] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), Charlson score (0, 1, 2+, time-varying), acne and/or rosacea (yes/no, time-varying), COPD (yes/no, time-varying), UTI (yes/no, time-varying), and receipt of screening mammogram in the previous 12 months prior to the event-date (yes/no, time-varying).

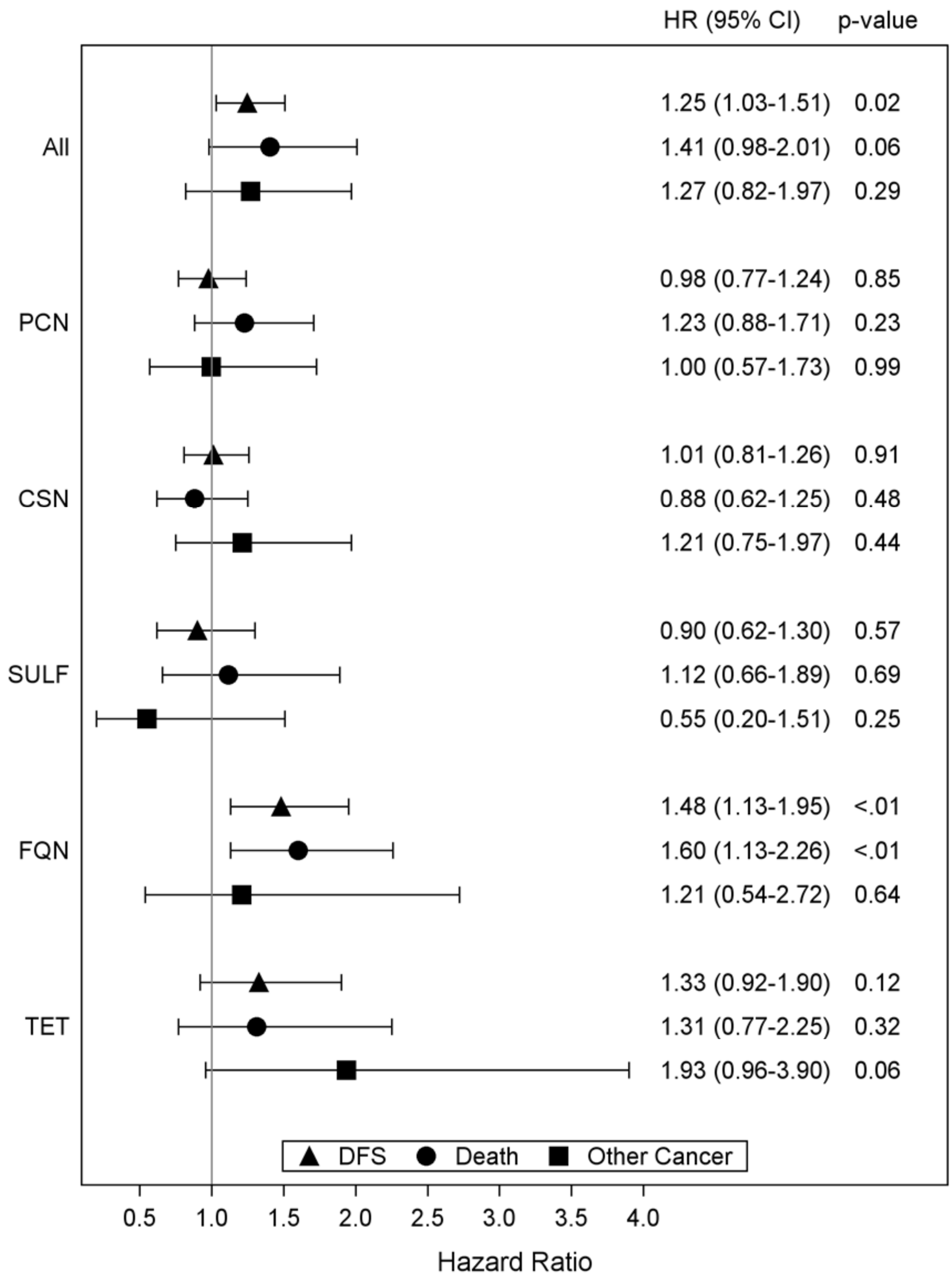

Figure 2. Adjusted hazard ratios and 95% confidence intervals for frequent antibiotic use and disease free survival (breast cancer recurrence, second primary breast cancer, death, and other cancers).

Abbreviations: 95% CI=95% confidence interval; CSN=cephalosporins; DFS=disease-free survival, includes first occurrence of death, breast cancer recurrence, second primary breast cancer, and other cancers; FQN=fluoroquinolones; PCN=penicillins; SULF=sulfonamides; TET=tetracyclines

Nonusers were the reference category for all analyses. A woman could contribute to multiple antibiotic classes if she filled at least one prescription for that class

All models were adjusted for 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] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), Charlson score (0, 1, 2+, time-varying), acne and/or rosacea (yes/no, time-varying), COPD (yes/no, time-varying), UTI (yes/no, time-varying), and receipt of screening mammogram in the previous 12 months prior to the event-date (yes/no, time-varying).

CHAPTER 2:

Framework for Evaluating Detection Bias Among Breast Cancer Survivors

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ABSTRACT

Background: Detection bias is commonly cited as a potential source of confounding in observational studies of commonly used medications and cancer outcomes but rarely explored. We sought to develop a framework for evaluating unexplored detection bias in breast cancer pharmacoepidemiology studies. Specifically, our objective was to evaluate if there were differences in yearly receipt of surveillance procedures by exposure to two disparate medication classes hypothesized to alter use of preventive services, antibiotics and statins.

Methods: Retrospective cohort study among health plan enrollees age ≥18 years and diagnosed between 1990 and 2008 with a histologically confirmed incident invasive early stage (I, II) breast carcinoma via the Surveillance, Epidemiology, and End Results (SEER) registry. Women were followed for up to 10 years after the completion of breast cancer treatment. We used automated health plan data to ascertain medication use, breast services, and covariates. We categorized antibiotic users as infrequent use (1-3 dispensings in 12 months) and frequent use (≥4 dispensings in 12 months). We categorized statin users as less adherent (1 dispensing in 6 months) and more adherent (≥2 dispensings in 6 months). Non-users were the reference category. In the main analyses, medication use was independently defined at each yearly surveillance interval. The main outcome measure was annual receipt of surveillance procedures, defined as mammography and breast magnetic resonance imaging (MRI). We used multivariate repeated measures generalized estimating equation (GEE) regression models to estimate odds ratios (ORs) and robust 95% confidence intervals (CI), combining all surveillance years, for annual receipt of surveillance procedures by exposure groups.

Results: Among the 3,965 women included in the analysis, 79% received surveillance procedures in year 1 and this steadily decreased to 63% in year 10. The median number of surveillance years was 6 and the median number of surveillance procedures received per patient during the study period was 4. Infrequent antibiotic use was not associated with receipt of surveillance procedures (OR 0.99, 95% CI 0.93-1.05) compared to nonusers. Although not significant, women who used frequent antibiotics were slightly less likely to receive surveillance during follow-up (OR 0.93, 95% CI 0.84-1.02). Statin use was associated with slightly higher odds of receiving surveillance procedures during follow-up than non-users, but differences were significant only for more adherent statin users (less adherent OR 1.08, 95% CI 0.84-1.35; more adherent OR 1.15, 95% CI 1.03-1.28). Other patient characteristics associated with lower surveillance use include: more advanced age, higher Charlson scores, increasing number of yearly visits to primary care physicians, initial breast cancers diagnosed at stage II and treated with mastectomy or breast conserving surgery without radiation. A greater number of yearly visits to an oncologist during follow-up was associated with higher odds of receiving surveillance procedures.

Conclusions: Breast cancer surveillance among breast cancer survivors steadily declines over time. Our results suggest receipt of surveillance procedures may confound associations between medication use and breast cancer outcomes. In addition to key patient characteristics, investigators should consider adjusting for receipt of surveillance in breast cancer pharmacoepidemiology studies among women with a history of early stage invasive breast cancer. Future research is needed to determine how to design studies or conduct analyses that minimize detection bias and to further investigate the degree of influence detection bias has on study findings.

INTRODUCTION

Biases are a major limitation of observational studies. Detection bias occurs in epidemiologic research when the comparison groups differ systematically in the measurement or diagnosis of the outcome.[26] Detection bias is commonly cited as a potential source of confounding in observational studies of medications and cancer outcomes.[27] For example, in breast cancer pharmacoepidemiology studies, the medication under investigation may be associated with higher or lower rates of breast cancer screening and therefore alter the likelihood and timing of breast cancer and breast cancer recurrence diagnoses. This association is attributed to systematic differences between patients who initiate and adhere to certain medications and those who do not.[28] For instance, patients who adhere to preventive therapies (e.g., statins in the management of cholesterol and prevention of cardiovascular events) may be more likely to engage in health-seeking behaviors such as cancer screening compared to those who do not.[29] On the contrary, severely ill patients who are often using numerous medications may stop using preventive services such as flu vaccination[30] and cancer screening[31]. This is relevant for breast cancer pharmacoepidemiology studies as it may be a source of detection bias.

Although long suspected as a source of bias, careful examination of detection bias in breast cancer pharmacoepidemiology studies has received little attention. Limited research has examined the relation between medications hypothesized to alter breast cancer risk and prognosis and mammography use. However, one study reported that more adherent statin users were more likely to receive screening mammograms than less adherent statin users.[29] Yet another study found only a borderline association between statin adherence and undergoing mammography.[28]

Among the many studies on medication use and breast cancer risk, few consider screening in their analyses,[32-34] and risk estimates may be biased if screening rates differ by exposure. Similarly, numerous studies of commonly used medication and breast cancer recurrence do not consider mammography surveillance in their analyses.[35-37] Examining receipt of screening or surveillance as a function of medication exposure provides a framework for evaluating unexplored detection bias in breast cancer pharmacoepidemiology studies. Developing this framework is important, given the growing number of studies conducted on commonly used medications (e.g., statins, hormone therapy, cardiovascular medications, and antidepressants) and breast cancer risk and recurrence.

For this study, we chose to evaluate the association between two disparate medication classes (statins and antibiotics) and adherence to recommended annual surveillance mammography among an already established cohort of women with early stage breast cancer as a first step in exploring detection bias by medication class. Statins were chosen as they are among the most commonly studied in relation to breast cancer risk and recurrence. Statin users have also been shown to be more health seeking than nonusers and thus more likely to receive surveillance,[28] and this is an important consideration for examining detection bias. We chose to also evaluate antibiotics since they are commonly prescribed, not a preventive therapy like statins, and the exposure of interest in Chapter 1. Therefore, we hypothesized that patients who frequently use antibiotics have different health-seeking behaviors than statin users. By evaluating surveillance within two medication classes used for different purposes (prevention vs. symptomatic treatment), we could investigate if detection bias differs by type of medication exposure. We compared differences in receipt of breast cancer surveillance procedures within the two medication classes over ten years of follow-up among women diagnosed with early stage invasive breast cancer.

METHODS

Study Population

The parent retrospective cohort study was conducted within Group Health Cooperative (GH), a nonprofit integrated delivery system that provides comprehensive health care on a pre-paid basis to approximately 650,000 individuals throughout western 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 Surveillance, Epidemiology, and End Results (SEER) registry.[1] Women were included in the parent study if they met the following criteria: 1) ≥18 years of age; 2) diagnosed with a histologically confirmed incident invasive breast carcinoma (stage I or II) between January 1, 1990 and December 31, 2008 via the SEER registry; 3) enrolled in GH's integrated group practice for at least 1 year before the initial breast cancer diagnosis and 1 year after diagnosis (unless died). A total of 4,426 subjects were identified and sent to chart review, of which a subset (1,268 women diagnosed 1990-1999) were After further excluding women per chart review due to no medical record (n=72), bilateral disease (n=6), breast cancers that were not first primaries (n=79), and women with no definitive surgery (n=44), the sample size was 4,225.

Study subjects were censored at 10 years or the earliest of death, disenrollment, or diagnosis of a second breast cancer event (SBCE), including recurrence of the primary breast cancer or diagnosis of a second primary breast cancer. SBCE was defined as any ductal carcinoma in situ (DCIS) or invasive breast cancers of the ipsilateral (recurrence) or contralateral (second primary) breast or in any regional or distant sites.[20] SBCE was the clinical endpoint we censored on because receipt of surveillance may dramatically change with the diagnosis of a SBCE. Censoring women who develop a SBCE also minimizes misclassification of diagnostic or treatment-related imaging as a surveillance procedure. A woman was at risk for a SBCE starting 120 days after completing definitive surgery for the incident breast cancer.[17] Of the 4,225 women, 4,216 were at risk for a SBCE starting 120 days after completing definitive surgery (5 deaths and 4 metastases prior to 120 days).

The GH Institutional Review Board approved this study.

Data Collection

Data were collected on all eligible women through the earliest of death, disenrollment from GH, or end of study (i.e., date of chart abstraction). Disenrollment was defined as a lapse in membership of 90 or more days. Data were collected from medical record review (paper and electronic), SEER, health plan automated administrative databases, and GH's Breast Cancer Screening Recruitment and Reminder (BSRR) survey, a self-administered questionnaire completed at each screening mammography.[18] Tumor characteristics (unavailable or missing from SEER), breast cancer treatment, breast cancer outcomes (i.e., recurrence and second primaries), vitals, and breast cancer surveillance during years prior to availability of automated data were obtained through review of medical records. Data were abstracted directly from the medical record into an Access database by trained abstractors. GH's automated databases include demographics, enrollment, inpatient and outpatient diagnoses and procedures (available 1993 on), results of breast services (available 1997 on), pharmacy dispensings (available 1977 on), laboratory results, vitals, and death.[19]

Outcome Ascertainment

We considered the first six months post-diagnosis as the treatment period and excluded from analyses all surveillance procedures performed during this time.[31, 38, 39] Therefore, we evaluated receipt of yearly surveillance procedures for each of the ten years of follow-up starting at month 7 after the SEER diagnosis date.

We ascertained both mammography and breast MRI exams to evaluate receipt of surveillance procedures. Mammographic and MRI exams were available electronically from GH administrative databases from 1997 forward, though breast MRI first began to be used within our cohort beginning 2003. Data on exam date, indication designated by the interpreting radiologist (distinguishing screening from diagnostic exams) and Breast Imaging Reporting and Data System (BI-RADS®) initial and final assessments were collected on all women 12 months prior to diagnosis through the end of follow-up. Information on mammographic exams performed prior to 1997 was obtained from the medical record.

We used the exam indication and symptomatic information reported by the patient to distinguish surveillance from diagnostic examinations. We defined surveillance procedures as post-diagnosis mammographic and breast MRI exams where the patient reported no symptoms at the time of the exam and the indication was designated as screening by the interpreting radiologist. Surveillance procedures also included all short interval follow-up (SIFU) exams following screening and only SIFU exams following a diagnostic exam if they were >9 months apart. A woman was categorized as having received at least one surveillance procedure (yes/no) within each 12-month surveillance interval. Only 0.7% of the surveillance procedures were breast MRI exams, therefore, we refer to surveillance procedures as surveillance mammography from here on out.

Medication Exposure

We used the GH computerized pharmacy database to ascertain outpatient oral medication use. The pharmacy database contains records of all prescriptions dispensed at GH's outpatient pharmacies as well as claims received from outside contracting pharmacies. The database contains one record per dispensing that includes: drug name, date of dispensing, quantity dispensed, route, strength, days supply, prescriber, and National Drug Code number. We identified prescriptions for any oral antibiotic and statin dispensed in the year prior to each woman's incident breast cancer diagnosis through the end of follow-up. The value of GH's computerized pharmacy database derives from the size and accuracy of the database, as well as the accessibility of the data. Previous studies indicate that IGP enrollees fill all or almost all of their prescriptions at GH owned or contracting pharmacies.[22, 23]

Women were categorized into exposure groups within each medication class, i.e., women could contribute data to both statin and antibiotic exposures if she met the definition of use for both.

Antibiotics

We included the following antibiotic classes in our exposure ascertainment: penicillins, cephalosporins, sulfonamides, fluoroquinolones, tetracyclines, nitrofurans, macrolides, ketolides, carbapenems, oxazolidinones (linezolid), glycopeptides (vancomycin), folate antagonists (trimethoprim), nitroimidazoles (metronidazole), and methenamine. We chose to evaluate frequent antibiotic use in our study because it was the exposure of interest in Chapter 1, is common,[13] and clinically relevant for evaluating the risk-benefit of antibiotic exposure over time.

Frequent antibiotic users included women with at least four dispensings for any antibiotic in 12 months. Infrequent antibiotic users consisted of women with one to three antibiotic dispensings in 12 months. Nonusers were defined as women with no dispensing for an antibiotic. Nonusers were the reference category for all antibiotic analyses. All antibiotic exposures were ascertained within any moving 12-month period throughout follow-up.

In our main analyses, antibiotic exposure was based on “per-interval” use, where exposure was evaluated separately during each sequential 12-month surveillance year (Figure 3). This treated the ten surveillance years as separate, cross-sectional ascertainment periods. If a subject met the exposure definition at any point during the specific surveillance year, she was classified as exposed for that entire surveillance year. Exposure status was then re-evaluated during the subsequent surveillance year, i.e., exposure status did not carry forward. We chose to classify exposure based on per-interval use because we hypothesize health care seeking behavior influences medication use over time. If there is a behavioral component to medication use, we anticipate it will change over time. For example, if a subject becomes sicker or is functionally declining she may be less likely to use a preventive medication such as a statin and more likely to use antibiotics for acute illnesses. This means that the health care seeking behavior that may have contributed to exposure status during year one may not reflect behavioral patterns during year ten. Therefore, we evaluated current medication exposure during each surveillance year.

<u>Statins</u>

We identified all statins dispensed during the study period (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin). We applied the same per-interval method as described above to define statin use except that we categorized statin use as more adherent and less adherent. We defined “more adherent statin users” as women with at least two dispensings for any statin within a six month period. We required two dispensings for a statin during a six-month period to minimize misclassifying unexposed women as exposed.[40] “Less adherent statin users” included women with only one statin dispensing within a six month period. Statin nonusers included women with no dispensings for a statin. Statin nonusers were the reference category for all statin analyses. All statin exposures were ascertained within any moving 6-month period throughout follow-up. Similar to antibiotics, our main analyses of statins were based on “per-interval” use, where statin exposure was evaluated separately during each sequential 12-month surveillance year.

Secondary analyses

Common to pharmacoepidemiology literature, a participant is included in an exposure category after she meets the definition of use and remains in that exposure category even if she discontinues use. We refer to this exposure classification as “ever-never” use throughout the entire study period and we based our medication exposures on this method in our secondary analyses. Similar to the per interval analysis, all exposures were defined within any moving 12-month window for antibiotics (e.g., frequent antibiotic user if 4+ dispensings for an antibiotic in 12 month window) or 6-month window for statins (e.g., more adherent statin user if 2+ dispensings for statin in any 6 month window), beginning at the diagnosis date of the initial breast cancer through end of the study period. However, antibiotic users were only allowed to transition from being nonusers to infrequent users to frequent users over the entire study period; statin users were only allowed to transition from being nonusers to less adherent users to more adherent users over the study period. Exposure status carried forward to the subsequent surveillance year and remained constant once the highest exposure category (e.g., frequent antibiotic user and adherent statin user) was reached (Figure 4). We required subjects meet the definition for exposure for at least 8 months of the surveillance year to be included in that exposure category for analyses; otherwise, they were included in that exposure category beginning with the next subsequent surveillance year. We tested the sensitivity of our ever-never results by changing the threshold requiring subjects to meet the definition for ever-never exposure to be at least 6 months of the surveillance year.

Covariates

We measured and defined 3 types of covariates: static covariates defined only once at either pre-diagnosis, diagnosis, or during treatment; time-varying per yearly surveillance interval that were independently measured at each surveillance year (i.e., variable status did not carry over to the subsequent years); and time varying "ever-never" measured and varied across the entire study or surveillance period of 10 years (i.e., variables carry over to subsequent years)

Static covariates

SEER was the gold standard for race, ethnicity and incident breast cancer characteristics including year of diagnosis, American Joint Committee on Cancer (AJCC) stage at diagnosis, lymph node status, hormone receptor status, and tumor size. If any of these data were missing from SEER, they were obtained from the medical record. Covariates such as treatment information related to the incident breast cancer, including primary surgery (breast conserving surgery [BCS] or mastectomy), radiation therapy, and receipt of chemotherapy from the GH medical record were defined only once using data at diagnosis date through treatment. BMI at diagnosis was calculated from the weight and height ascertained from the medical record during 12 months prior to diagnosis. Pre-diagnosis antibiotic and statin use as well as smoking status was estimated using data from the 12-month pre-diagnosis period. We used the BSRR completed during the year prior to diagnosis to inform menopausal status and education at diagnosis. If menopausal status was missing or unknown (19%), we characterized a woman as peri- or pre-menopausal if she was <55 years of age and post-menopausal if she was ≥55 years of age.

Time-varying per yearly surveillance interval covariates

We modeled age per yearly surveillance interval where we added one year to the age at diagnosis for each sequential surveillance year. Estimates of medical encounters included number of both primary care and oncology specialty outpatient visits. We captured the number of primary care and oncology specialty visits separately for each surveillance year.

Time-varying "ever-never" covariates over the entire study period

Both endocrine therapy and the Charlson co-morbidity index (CCI) scores[24] were modeled as time-varying covariates over the entire study period (Figure 5). Similar to the ever-never exposure method, a woman was required to meet the definition of covariate exposure for at least 8 months of the surveillance year to be included in that exposure category for analyses; otherwise, she was included as exposed beginning with the next subsequent surveillance year. Endocrine therapy users included women who received a dispensing for tamoxifen and/or aromatase inhibitors for the initial breast cancer before the SBCE date for cases or the end of follow-up for non-cases. The Charlson scores, calculated from ICD-9 diagnosis codes and diagnoses noted in the medical record prior to 1992, when diagnoses became available in the automated data, were allowed to transition from a lower to a higher value over the study period.

Data Analysis

The primary analyses evaluated whether per-interval medication use (i.e., frequent and infrequent antibiotic users vs. nonusers and more adherent and less adherent statin users vs. nonusers) was associated with receipt of yearly surveillance mammography over a 10-year period. Ever-never medication use was evaluated in secondary analyses. We used repeated measures generalized estimating equation (GEE) regression models to estimate odds ratios (ORs) and robust 95% confidence intervals for receipt of yearly surveillance mammography for each medication class (antibiotics and statins). A logit link based on a binomial distribution was implemented in the GEE models. We used an unstructured correlation covariance approach based on examination of the correlation matrix. The GEE method accounts for the correlation among the repeated observations for each subject in this longitudinal data set while also adjusting for different numbers of observations across individuals.[41] This analytic strategy has been used in previous studies on utilization of surveillance mammography over time.[31, 42, 43]

Women were evaluated during the following sequential, 12-month surveillance years following diagnosis of the initial breast cancer: months 7-18 (year 1), 19-30 (year 2), 31-42 (year 3), 43-54 (year 4), 55-66 (year 5), 67-78 (year 6), 79-90 (year 7), 91-102 (year 8), 103-114 (year 9), 115-126 (year 10). Within each surveillance year, women were categorized as receiving at least one surveillance mammography or not. Subjects were censored at 10 years or the earliest of death, disenrollment, or diagnosis of a SBCE. Subjects were included in the analyses for all surveillance years in which they had complete data (i.e., subjects must be alive and not censored through the end of the interval to be included in the analyses for that interval). We excluded 251 women because they did not complete the entire year 1 surveillance interval, resulting in a final cohort of 3,965 women eligible for this analysis.

All models were adjusted for surveillance year (linear continuous), age per-interval (21-34, 35-44, 45-54, 55-64, 64-74, 75+ years), diagnosis year (1990-1994, 1995-1999, 2000-2004, 2005-2008), AJCC stage (I, IIA, IIB), hormone receptor status (estrogen receptor [ER] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying ever-never), BMI at diagnosis (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35+ kg/m^2), smoking status at diagnosis (current, past, never/unknown), number of primary care visits per-interval (linear continuous), number of oncology visits per-interval (linear continuous), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), and Charlson score (0, 1, 2+, time-varying ever-never). In addition to the primary association of interest, we evaluated effect modification by a number of characteristics. We developed interaction terms between medication exposures and number of yearly primary care visits, number of yearly oncology visits, time (surveillance year), Charlson score (categorical, 0, 1, 2+), age group (<75, 75+ years), and age per-interval (dummy variables for each age group). We considered interaction terms with p-value <0.05 to be significant. We observed no strong evidence for effect modification for either medication class by any of the characteristics we evaluated; therefore, we did not include any of these interaction terms in the final models. We also examined the relation between all covariates and receipt of yearly surveillance mammography over time in exploratory analyses so that we could compare results of our model to previously published estimates. All analyses were performed using Stata/IC 12 software (StataCorp LP, College Station, TX).

RESULTS

Among the 3,965 women included in our analyses, the majority were White (89%), post-menopausal (73%), non-smokers (86%), normal BMI (34%), and score of 0 on Charlson (77%) at the time of incident breast cancer diagnosis. The mean (SD) age at diagnosis was 62.6 (13.2) years. Most women were stage I (64%), hormone receptor positive (69%), and treated with breast conserving surgery plus radiation (52%). The mean (SD) follow-up was 7.5 (4.1) years, ranging from 1.5 to 20.0 years (median 6.7 years). During the study period, the median number of surveillance years per patient was 6 (interquartile range 3-9) and the median number of surveillance mammograms per patient was 4 (interquartile range 2-6). The proportion of women who received a surveillance mammogram in year 1 was 79% (Figure 6). Receipt of surveillance declined through year 6 to 68% then became relatively stable at approximately 63-66% in years 7-10.

Characteristics of the study cohort by receipt of surveillance mammography for each surveillance year since the completion of initial breast cancer treatment are described in Table 5. Women who received surveillance mammograms were less likely to be frequent antibiotic users consistently throughout the study period and were less likely to be more adherent statin users for the majority of surveillance years, though these differences were not consistently statistically significant.

Women who received a surveillance mammogram in year 1 were more likely to be users of hormone therapy prior to diagnosis, non-smokers, diagnosed in earlier years, and have longer overall duration of follow-up compared to women who did not receive a surveillance mammogram in year 1. Mammography users were also more likely to have initial breast cancers of a lower stage, lymph node negative, smaller tumor size, and treated with breast conserving surgery plus radiation than women who did not use mammography in year 1. Initial breast cancers among women who received a surveillance mammogram in year 1 were more likely to be screen-detected. We observed trivial changes in population characteristics in subsequent surveillance years, however the differences in stage and lymph node status were no longer significant beginning in year 5 and differences in tumor size and mode of detection were no longer significant beginning in year 6. Any changes in these baseline characteristics over time were due to loss to follow-up.

Differences in age per-interval became more pronounced in later years where mammography users were more likely to be younger. Differences in visits between women who did and did not receive surveillance mammography were significant for the majority of surveillance years, though the actual differences were minimal and any statistical differences were likely attributed to sample size. Women who received surveillance mammograms were more likely to score 0 on Charlson beginning in year 2 and this persisted throughout all subsequent surveillance years. Mammography users were more likely use endocrine therapy but this difference was significant only in years 4, 5, and 9.

Characteristics of the study cohort by per-interval antibiotic use for each surveillance year are described in Table 6. Approximately 30% of women were infrequent antibiotic users throughout the ten year study period. Frequent antibiotic use was highest in year 1 at 18% and modestly declined to approximately 12-14% for the remainder of the surveillance years. Frequent antibiotic users in year 1 were more likely to have higher BMI and more primary care visits than nonusers. Initial breast cancers of frequent antibiotic users in year 1 were more likely to be higher stage, lymph node positive, smaller tumor size, and treated with mastectomy and chemotherapy compared to nonusers. Frequent antibiotic users in year 1 were more likely to have received hormone replacement therapy, any antibiotics, and to have been frequent antibiotic users in the 12 months pre-diagnosis period compared to nonusers. Infrequent antibiotic users were generally similar to nonusers in year 1 except infrequent users were more likely to have initial breast cancers with lower stage and smaller tumor size, and to have received pre-diagnosis antibiotics. The majority of the population did not change in subsequent surveillance years, however differences in initial breast cancer characteristics related to stage, lymph node status, tumor size and treatment with chemotherapy were no longer significant beginning in year 2 (except tumor size was significantly different in year 6). Frequent antibiotic users in subsequent surveillance years remained more likely to have undergone mastectomy compared to nonusers, though this difference was significant only in years 2, 6, and 10. Any changes in these baseline characteristics over time were due to loss to follow-up. When we evaluated the time-varying covariates, both frequent and infrequent antibiotic users were significantly more likely to have higher Charlson scores and more primary care visits than nonusers during each surveillance year.

Characteristics of the study cohort by per-interval statin use for each surveillance year are described in Table 7. Less than 1% of women were less adherent statin users in year 1 and it remained low throughout the study period. Due to the limited number of less adherent users, we only describe the characteristics for more adherent statin users here. In year 1, 10% of women were more adherent statin users and this rose steadily in each surveillance year to 24% by year 10. Compared to nonusers, more adherent statin users in year 1 were more likely to: be diagnosed in the later years of the parent study, have shorter duration of follow-up, be older, post-menopausal, smokers, of higher BMI, higher Charlson scores, higher number of primary care visits, and lower education. Initial breast cancers of more adherent statin users in year 1 were more likely to be screen-detected and hormone receptor positive but less likely to be treated with chemotherapy, a function of stage at diagnosis and tumor characteristics. More adherent statin users in year 1 were also more likely to be statin users and adherent statin users but less likely to take hormone replacement therapy in the 12 month pre-diagnosis period compared to nonusers. The majority of the population did not change in subsequent surveillance years; however, differences in hormone receptor status and receipt of chemotherapy diminished over time. Any changes in these baseline characteristics over time were due to loss to follow-up. When we evaluated the time-varying and per-interval covariates, we found that more adherent statin users were significantly more likely to have higher Charlson scores and more primary care visits than nonusers during each surveillance year.

We excluded 15 women from the multivariate models due to missing BMI information. In the multivariate models combining all surveillance years, infrequent antibiotic use was not associated with receipt of surveillance mammography (OR 0.99, 95% CI 0.93-1.05) compared to nonusers (Table 8). Frequent antibiotic use, however, was associated with slightly lower odds of receiving surveillance mammography during follow-up (OR 0.93, 95% CI 0.84-1.02) compared to nonusers, though this difference was not statistically significant. We observed similar findings from the unadjusted antibiotic models. When we evaluated statin use in the multivariate models, we found less adherent statin users had slightly higher odds of receiving surveillance mammography during follow-up (OR 1.07, 95% CI 0.84-1.35) compared to nonusers, though this difference was not statistically significant. This may be attributable to low numbers in this exposure category. More adherent statin users had significantly higher odds of receiving surveillance mammography than nonusers during follow-up (OR 1.15, 95% CI 1.03-1.28).

In secondary analyses where we evaluated medication exposure by the ever-never definition, we found that infrequent antibiotic use was associated with lower odds of mammography use during follow-up compared to nonusers (infrequent OR 0.93, 95% CI 0.84-1.03, frequent OR 0.85, 95% CI 0.75-0.96), though differences among infrequent users were not statistically significant. We found no association between less adherent statin use and receipt of surveillance mammography (OR 1.05, 95% CI 0.79-1.38) compared to nonusers. Although not significant, more adherent statin users had slightly higher odds of receiving a surveillance mammography during follow-up (OR 1.11, 95% CI 0.99-1.24) compared to nonusers. These findings were robust to sensitivity analyses where we changed the threshold for requiring women to meet the definition for exposure from 8 months to 6 months of the surveillance year in order to be categorized as a user for that year.

We evaluated clinical and demographic factors associated with receipt of surveillance mammography combining all surveillance years in multivariate models (Table 9). Compared to women 55-64 years of age, those age 21-34 and ≥75 years had lower odds of receiving mammography. The type of provider seen during follow-up affected receipt of mammography: higher number of oncology visits per surveillance year increased a woman's odds of receiving surveillance whereas higher number of primary care visits decreased her odds. Women who were sicker as demonstrated by higher Charlson scores had lower odds of receiving mammography compared to women with no co-morbidities and this finding was independent of age. Characteristics of the initial breast cancer also influenced receipt of surveillance mammography during follow-up. Women diagnosed with stage II cancer (significant only for stage IIA), women with hormone receptor negative tumors, and those who received mastectomy or breast conserving surgery without radiation had lower odds of receiving mammography compared to their respective referent groups of stage I, hormone receptor positive tumors, and breast conserving surgery plus radiation. Women who received hormone therapy during follow-up also had higher odds of receiving mammography.

DISCUSSION

In this large cohort study of women diagnosed with early stage invasive breast cancer, we found that women with frequent antibiotic use were less likely to receive surveillance mammography during follow-up, though this finding was not statistically significant. Infrequent antibiotic use was not associated with surveillance. Women with more adherent and less adherent statin use were slightly more likely to receive mammography during follow-up than non statin users. These differences, however, were statistically significant only for more adherent statin users.

No study to date has examined the relation between medication exposures and receipt of surveillance mammography among breast cancer survivors, and only limited information exists on screening mammography in women without a history of breast cancer. Receipt of mammography screening among antibiotic users has only been reported in one study to our knowledge. In contrast to our findings, Velicer et al. found that women with higher levels of antibiotic use were more likely to receive a screening mammogram.[44] However, Velicer et al. adjusted only for age which may limit the validity of the results. One hypothesis for why frequent antibiotic users were less likely to receive surveillance mammography in our study is these women are sicker and thus less concerned with early detection of second breast cancer events. Keating et al. demonstrated that receipt of surveillance mammography among breast cancer survivors reaches a threshold where women with increasingly more visits and co-morbidities receive fewer surveillance mammograms.[31] The authors suggest that patients reach a point where they are so ill they forgo surveillance mammography. Jackson et al. further demonstrated that seniors with limited functional status are less likely to seek the preventive service of influenza vaccination.[30] Therefore, it is possible that detection bias associated with surveillance mammography among frequent antibiotic use could spuriously lower the magnitude of association in observational studies whereby frequent antibiotic users do not engage in preventive care and detection of SBCEs is decreased or delayed. Our data indicate surveillance mammography may introduce detection bias among frequent antibiotic users, though our findings were not statistically significant.

We located only two studies that reported on receipt of mammography screening among patients who use statins. Brookhart et al. reported that adherent statin users, defined as ≥2 statin dispensings in a 12-month ascertainment period, were 22% more likely to receive screening mammograms compared to those who dispensed only one statin in a large cohort of Medicare enrollees.[29] However, in another study evaluating new statin users in British Columbia, investigators found only a small increase in the likelihood of receiving screening mammograms among more adherent statin users compared to those less adherent (HR 1.05, 95% CI 1.00-1.10).[28] Brookhart et al. attributed the increased screening mammography among statin adherers to healthy user bias whereby individuals who initiate and adhere to preventive therapies such as a statin are more likely to engage in health promoting behaviors than those who do not remain adherent.[29] Healthy user bias can contribute to detection bias if women who adhere to preventive therapies such as a statin are more likely to undergo continued surveillance for breast cancer and are therefore more likely to be detected with second events or detected earlier compared to nonusers or non-adherers. Healthy user bias and detection bias are therefore interrelated, and could confound risk estimates observed in breast cancer pharmacoepidemiology studies, depending upon the outcome evaluated. Detection bias could spuriously increase risk estimates between more adherent statin use and risk of breast cancer due to differentially higher screening rates and therefore, detection of disease among exposed individuals. However, detection bias could spuriously lower risk estimates associated with cancer tumor characteristics and breast cancer related death because a higher rate of mammography use among more adherent statin users could lead to a stage shift where women diagnosed with screen-detected breast cancer will have early stage tumors compared to women diagnosed with symptom-detected breast cancer. Therefore, women taking preventive therapy such as a statin may be less likely to be diagnosed with advanced or late stage breast cancer, and detection bias could contribute to this inverse association.

The NCCN clinical practice guidelines recommend yearly mammographic evaluation for breast cancer survivors,[45] yet our study and others confirm that many women do not undergo surveillance mammography[38, 39, 42, 43, 46] and the proportion of women who receive yearly mammography declines steadily over time.[42, 43, 47] Similar to our study results, another study found that surveillance mammography rates among women 65 years or older diagnosed with early stage invasive breast cancer were 82.1% in year 1 but dropped off to 68.5% by year 4 since completion of breast cancer treatment.[42] Similar patterns were observed in another study of breast cancer survivors age 55 years and older.[43] Onega et al. found slightly higher rates.[47] Women age 65 and older demonstrated surveillance mammography rates of 89.3% at 24 months post-diagnosis and rates remained steadily high at 81.5% at 78 months post-diagnosis.[47]

Inconsistencies in these findings could be attributed to different lengths of surveillance intervals. Onega et al. evaluated 18-month intervals as opposed to 12-months. The longer ascertainment period increased the opportunity for women to receive a mammogram and could account for the higher surveillance rates observed by Onega et al. We are among the few studies to date that have evaluated surveillance patterns for up to 10 years since treatment of the initial breast cancer. Receipt of surveillance mammograms gradually declined in our study population, yet our surveillance rates were generally higher over time than those reported previously. This could be due to differences in study populations, whereby our study population was younger compared to earlier studies.

Several prior studies have examined determinants to explain variability in receipt of surveillance mammography over time.[31, 42, 43, 47] Similar to our findings, factors consistently associated with lower rates of surveillance mammography include advanced age, higher stage of disease, and receipt of breast conserving surgery without radiation.[31, 38, 39, 42, 43] These factors could contribute to detection bias and failure to adjust for them could limit the validity of results in breast cancer pharmacoepidemiology studies. Outpatient visits to primary care physicians and oncologists during follow-up have been associated with higher rates of surveillance mammography, however the effect is largest for women who see oncologists.[31, 42, 43] We found that women were more likely to undergo surveillance mammography if they saw an oncologist but were less likely if they saw a primary care physician. Outpatient visits could contribute to detection bias. Frequency of ambulatory care visits is related to higher mammography use and early breast cancer stage at diagnosis.[48] Frequent contact with the delivery system introduces more opportunity for surveillance which could result in higher detection rates of asymptomatic breast cancer. These data suggest that investigators should consider adjusting for number of outpatient visits as well as type of physician seen during follow-up. Prior studies have also found that women with co-morbid illnesses are less likely to receive surveillance mammograms,[31, 43] therefore we expected that Charlson score would influence receipt of surveillance mammograms. We observed that women with higher Charlson scores were less likely to receive surveillance compared to women with no co-morbidities (Charlson score=1 OR 0.80, 95% CI 0.74-0.88; Charlson score=2+ OR 0.70, 95% CI 0.62-0.79). This may related to the "sick stopper effect" whereby patients who become increasingly ill, with a greater number of competing co-morbidities, forego preventive care. Therefore, co-morbidites appear to be important determinants for undergoing surveillance and should be adjusted for in pharmacoepidemiology studies.

There are several strengths in this study worth noting. GH's automated databases and medical charts provide detailed and unbiased access to medical information on breast cancer characteristics, treatment, diagnoses, medication use, and surveillance history. We evaluated a large, covered population with stable membership, minimal co-pays and co-insurance for preventive services such as mammography, and who receive almost all of their care within the system. Access to complete longitudinal data on surveillance mammograms for up to 10 years is typically unavailable in other settings. GH's consistent guidelines for surveillance mammography for all women with a history of breast cancer, regardless of age or other co-morbidities (guideline is surveillance every 12 months) provides for a clearly definable outcome. Care at GH for women with prior breast cancer diagnosis is well coordinated and managed by an oncology nurse case manager. While this is a strength, this setting may provide more intensive follow-up care, therefore surveillance rates may differ compared to other practice settings, limiting the generalizability of our results.

Our study has several additional limitations to note. We evaluated an insured population with access to complete medical care so estimates may be lower in populations with less access to medical services. Our study population is mainly white which limits generalizability to other races. Our results predominantly pertain to surveillance mammography and rates may be different for other modalities such as MRI. It was beyond the scope of our study to determine if there were differences in time of detection by medication use. For example, healthy user bias could result in cases being detected at earlier stage second primary breast cancer or local vs. regional or distant recurrence. There is potential for misclassification of medication exposure if patients filled a prescription but did not ultimately take it. However, this is minimized in our study because we required more than one prescription to be filled during a small time period. This increases the possibility that the patient actually took the medication. Patients who receive medications at non-GH pharmacies without submitting a claim to GH may be erroneously classified as nonusers. This would bias our results toward the null. However, this is unlikely since previous GH studies have found GH enrollees obtain 97% of their medications at GH owned pharmacies or GH contracting pharmacies.[22, 23] The intensity of follow-up care and decision about whether to seek preventive services such as mammography is complex. We did not capture patient beliefs or expectations regarding follow-up care, nor did we assess why women choose not to receive surveillance care. Further research is needed to fully understand how these factors influence receipt of surveillance mammography. There were also unmeasured variables that could influence receipt of surveillance mammography. For example, surveillance rates vary based on physician recommendations,[46] yet we did not capture this variable in our analyses. Furthermore, we did not address when to stop undergoing surveillance and this study did not identify subgroups of women who appropriately may not benefit from continued surveillance because of competing co-morbid conditions or poor prognosis.

In summary, our results suggest that studies investigating the association between common medication exposures, such as antibiotics and statins, and the risk of second breast cancer events may produce biased results if the study does not control for differences in opportunity for detection of disease. Factors that influence receipt of surveillance mammography during follow-up include: age, stage and treatment of the initial breast cancer, co-morbidities, primary care and oncology visits, as well as more adherent statin use. An association between frequent antibiotic use and surveillance mammography remain to be established. This is the first study to specifically evaluate if receipt of surveillance mammography confounds the association between medication exposure and risk of breast cancer outcomes. This framework for evaluating detection bias allows investigators to better understand methodological considerations in designing and interpreting breast cancer pharmacoepidemiology research. Further research is warranted, however, since our estimates for medication use were modest and several were not statistically significant. While this study suggests that breast cancer pharmacoepidemiology studies may be confounded by detection bias, we did not address methods for minimizing this bias. Further work is needed to determine how to design studies or conduct analyses that minimize detection bias in breast cancer pharmacoepidemiology studies. There are a large number of studies conducted on commonly used medications and breast cancer risk and recurrence, yet very few adjust for screening or surveillance. Therefore, it would be worthwhile to further investigate the influence of detection bias on study findings, such as determining the degree of bias that needs to exist to affect risk estimates. Additional research to identify populations that could benefit from interventions to improve surveillance care would also be beneficial.

Table 5. Distribution of covariates by receipt of mammography for all surveillance years since completion of treatment

	Year 1		Year 2		Year 3		Year 4		Year 5	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	823 (20.8%)	**3,142 (79.2%)**	**824 (22.5%)**	**2,839 (77.5%)**	**798 (24.5%)**	**2,461 (75.5%)**	**688 (24.3%)**	**2,148 (75.7%)**	**690 (29.0%)**	**1,689 (71.0%)**
Year of diagnosis										
1990-1994	125 (15.2)	773 (24.6)	136 (16.5)	703 (24.8)	141 (17.7)	633 (25.7)	170 (24.7)	556 (25.9)	187 (27.1)	486 (28.8)
1995-1999	152 (18.5)	962 (30.6)	176 (21.4)	851 (30)	188 (23.6)	772 (31.4)	177 (25.7)	710 (33.1)	224 (32.5)	604 (35.8)
2000-2004	322 (39.1)	812 (25.8)	325 (39.4)	718 (25.3)	308 (38.6)	659 (26.8)	245 (35.6)	641 (29.8)	266 (38.6)	561 (33.2)
2005-2008	224 (27.2)	595 (18.9)	187 (22.7)	567 (20)	161 (20.2)	397 (16.1)	96 (14)	241 (11.2)	13 (1.9)	38 (2.2)
Years of follow-up[1]										
Mean (SD)	6.1 (3.6)	7.8 (4.2)	6.8 (3.5)	8.2 (4.1)	7.7 (3.5)	8.8 (3.9)	8.7 (3.6)	9.3 (3.6)	9.5 (3.4)	10.2 (3.4)
Median	5.4	7	6.2	7.5	6.9	7.9	7.8	8.3	8.2	9.5
Age per-interval, years [2]										
Mean (SD)	64.5 (14.3)	63.3 (12.8)	65.8 (14.2)	64.2 (12.6)	66.1 (14.1)	65.3 (12.4)	68.1 (14.3)	66 (12.1)	69.3(14.1)	66.8 (12)
21-34	11 (1.3)	19 (0.6)	6 (0.7)	8 (0.3)	5 (0.6)	6 (0.2)	1 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)
35-44	50 (6.1)	210 (6.7)	44 (5.3)	157 (5.5)	34 (4.3)	116 (4.7)	29 (4.2)	71 (3.3)	26 (3.8)	37 (2.2)
45-54	156 (19)	669 (21.3)	153 (18.6)	558 (19.7)	153 (19.2)	434 (17.6)	105 (15.3)	368 (17.1)	95 (13.8)	267 (15.8)
55-64	209 (25.4)	728 (23.2)	180 (21.8)	706 (24.9)	186 (23.3)	606 (24.6)	154 (22.4)	535 (24.9)	139 (20.1)	417 (24.7)
65-74	169 (20.5)	833 (26.5)	194 (23.5)	725 (25.5)	170 (21.3)	644 (26.2)	147 (21.4)	566 (26.4)	146 (21.2)	460 (27.2)
75+	228 (27.7)	683 (21.7)	247 (30)	685 (24.1)	250 (31.3)	655 (26.6)	252 (36.6)	606 (28.2)	283 (41)	507 (30)
Menopausal status										
Peri- or premenopausal	221 (26.9)	851 (27.1)	218 (26.5)	762 (26.8)	226 (28.3)	633 (25.7)	183 (26.6)	557 (25.9)	181 (26.2)	440 (26.1)
Post-menopausal	602 (73.1)	2291 (72.9)	606 (73.5)	2077 (73.2)	572 (71.7)	1828 (74.3)	505 (73.4)	1591(74.1)	509 (73.8)	1249(73.9)
Race										
White	722 (88)	2780 (88.8)	719 (87.4)	2519 (89.1)	701 (87.8)	2191 (89.4)	610 (88.8)	1928(89.9)	616 (89.3)	1522(90.3)
African American	25 (3)	98 (3.1)	27 (3.3)	82 (2.9)	26 (3.3)	69 (2.8)	20 (2.9)	56 (2.6)	23 (3.3)	38 (2.3)
American Indian/Alaska Native	27 (3.3)	82 (2.6)	27 (3.3)	75 (2.7)	28 (3.5)	65 (2.7)	24 (3.5)	53 (2.5)	19 (2.8)	44 (2.6)
Asian/Pacific Islander	46 (5.6)	170 (5.4)	50 (6.1)	150 (5.3)	43 (5.4)	126 (5.1)	33 (4.8)	107 (5)	31 (4.5)	82 (4.9)
Other	0	1	0	1	0	1	0	1	1 (0.1)	0
Unknown	3	11	1	12	0	9	1	3	0	3
Ethnicity										
Not Hispanic	783 (95.1)	2956 (94.4)	779 (94.8)	2678 (94.6)	770 (96.6)	2319 (94.5)	661 (96.2)	2042(95.4)	661 (96.1)	1611(95.7)
Hispanic	40 (4.9)	175 (5.6)	43 (5.2)	152 (5.4)	27 (3.4)	134 (5.5)	26 (3.8)	98 (4.6)	27 (3.9)	72 (4.3)
Unknown	0	11	2	9	1	8	1	8	2	6

	Year 1		Year 2		Year 3		Year 4		Year 5	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	823 (20.8%)	**3,142 (79.2%)**	**824 (22.5%)**	**2,839 (77.5%)**	**798 (24.5%)**	**2,461 (75.5%)**	**688 (24.3%)**	**2,148 (75.7%)**	**690 (29.0%)**	**1,689 (71.0%)**
Education										
High school or less	86 (24.4)	323 (23.2)	75 (22.8)	314 (23.3)	71 (22.8)	280 (23.9)	61 (28)	239 (22.9)	55 (26.6)	188 (23.8)
Some college	111 (31.4)	510 (36.7)	116 (35.3)	482 (35.8)	110 (35.3)	407 (34.7)	66 (30.3)	365 (35)	74 (35.7)	260 (33)
College or post graduates	156 (44.2)	557 (40.1)	138 (41.9)	552 (40.9)	131 (42)	485 (41.4)	91 (41.7)	440 (42.1)	78 (37.7)	341 (43.2)
Unknown	470	1752	495	1491	486	1289	470	1104	483	900
Body mass index (kg/m^2)										
Mean (SD)	28 (6.3)	28 (6.1)	28 (6.5)	28 (6)	28.5 (6.3)	27.8 (6)	28.3 (6.6)	27.8 (5.9)	27.9 (6.1)	27.7 (5.9)
Median	27	26.8	26.8	26.9	27.5	26.6	27	26.6	26.7	26.6
<18.5	17 (2.1)	45 (1.4)	20 (2.4)	36 (1.3)	14 (1.8)	36 (1.5)	17 (2.5)	30 (1.4)	14 (2)	25 (1.5)
18.5-24.9	277 (33.9)	1082 (34.5)	275 (33.5)	978 (34.5)	252 (31.7)	865 (35.2)	228 (33.3)	764 (35.6)	240 (34.9)	608 (36)
25.0-29.9	262 (32.1)	1030 (32.9)	257 (31.3)	946 (33.4)	248 (31.2)	825 (33.6)	212 (30.9)	722 (33.6)	219 (31.8)	576 (34.1)
30.0-34.9	145 (17.7)	581 (18.5)	158 (19.3)	516 (18.2)	169 (21.3)	429 (17.5)	128 (18.7)	384 (17.9)	123 (17.9)	290 (17.2)
35+	116 (14.2)	395 (12.6)	110 (13.4)	357 (12.6)	111 (14)	303 (12.3)	100 (14.6)	246 (11.5)	92 (13.4)	188 (11.1)
Unknown	6	9	4	6	4	3	3	2	2	2
Smoking status										
Current	62 (7.5)	171 (5.4)	56 (6.8)	148 (5.2)	64 (8)	107 (4.3)	44 (6.4)	96 (4.5)	37 (5.4)	71 (4.2)
Past	79 (9.6)	251 (8)	64 (7.8)	238 (8.4)	64 (8)	174 (7.1)	37 (5.4)	116 (5.4)	18 (2.6)	58 (3.4)
Never/unknown	682 (82.9)	2720 (86.6)	704 (85.4)	2453 (86.4)	670 (84)	2180 (88.6)	607 (88.2)	1936(90.1)	635 (92)	1560(92.4)
Charlson score[3]										
0	612 (74.4)	2439 (77.6)	497 (60.3)	2001 (70.5)	465 (58.3)	1629 (66.2)	349 (50.7)	1365(63.5)	334 (48.4)	997 (59)
1	148 (18)	514 (16.4)	213 (25.8)	588 (20.7)	211 (26.4)	581 (23.6)	224 (32.6)	532 (24.8)	225 (32.6)	475 (28.1)
2+	63 (7.7)	189 (6)	114 (13.8)	250 (8.8)	122 (15.3)	251 (10.2)	115 (16.7)	251 (11.7)	131 (19)	217 (12.8)
# PCP visits per-interval [2]										
Mean (SD)	6.2 (7.2)	5.6 (6.5)	4.3 (4.1)	3.7 (3.2)	4.3 (4.1)	3.7 (3.4)	4.2 (4.1)	3.9 (3.5)	4.5 (4.3)	3.9 (3.5)
Median	4	4	4	3	3	3	3	3	4	3
# ONC visits per-interval [2]										
Mean (SD)	3 (3.7)	2.9 (2.9)	1.3 (1.7)	1.5 (1.4)	1.1 (1.3)	1.2 (1.4)	0.8 (1.3)	1.1 (1.3)	0.7 (1.2)	0.9 (1.1)
Median	2	2	1	2	1	1	1	1	0	1

	Year 1		Year 2		Year 3		Year 4		Year 5	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	823 (20.8%)	**3,142 (79.2%)**	**824 (22.5%)**	**2,839 (77.5%)**	**798 (24.5%)**	**2,461 (75.5%)**	**688 (24.3%)**	**2,148 (75.7%)**	**690 (29.0%)**	**1,689 (71.0%)**
AJCC stage										
I	477 (58)	2046 (65.1)	487 (59.1)	1880 (66.2)	474 (59.4)	1672 (67.9)	417 (60.6)	1478(68.8)	444 (64.3)	1163(68.9)
IIA	238 (28.9)	771 (24.5)	226 (27.4)	683 (24.1)	224 (28.1)	555 (22.6)	191 (27.8)	471 (21.9)	172 (24.9)	379 (22.4)
IIB	108 (13.1)	325 (10.3)	111 (13.5)	276 (9.7)	100 (12.5)	234 (9.5)	80 (11.6)	199 (9.3)	74 (10.7)	147 (8.7)
Lymph node status										
Negative	529 (72.3)	2174 (77.2)	539 (74.1)	1986 (77.6)	525 (74)	1751 (78.8)	432 (73.3)	1560(79.4)	447 (75.6)	1237(80.2)
Positive (1-3)	151 (20.6)	489 (17.4)	147 (20.2)	438 (17.1)	139 (19.6)	366 (16.5)	112 (19)	318 (16.2)	110 (18.6)	237 (15.4)
Positive (4+)	51 (7)	149 (5.3)	41 (5.6)	131 (5.1)	45 (6.3)	104 (4.7)	44 (7.5)	85 (4.3)	34 (5.8)	66 (4.3)
Positive (unknown #)	1 (0.1)	3 (0.1)	0	3 (0.1)	0	2 (0.1)	1 (0.2)	1 (0.1)	0	2 (0.1)
Unknown	91	327	97	281	89	238	99	184	99	147
ER/PR status										
ER-/PR-	119 (14.5)	474 (15.1)	113 (13.7)	412 (14.5)	129 (16.2)	325 (13.2)	94 (13.7)	279 (13)	91 (13.2)	216 (12.8)
ER+/PR-	69 (8.4)	288 (9.2)	80 (9.7)	254 (8.9)	71 (8.9)	233 (9.5)	61 (8.9)	218 (10.1)	76 (11)	175 (10.4)
ER-/PR+	14 (1.7)	43 (1.4)	14 (1.7)	37 (1.3)	9 (1.1)	35 (1.4)	13 (1.9)	27 (1.3)	16 (2.3)	22 (1.3)
ER+/PR+	579 (70.4)	2176 (69.3)	579 (70.3)	1987 (70)	552 (69.2)	1733 (70.4)	474 (68.9)	1505(70.1)	455 (65.9)	1181(69.9)
ER & PR unknown	42 (5.1)	161 (5.1)	38 (4.6)	149 (5.2)	37 (4.6)	135 (5.5)	46 (6.7)	119 (5.5)	52 (7.5)	95 (5.6)
Tumor size										
≤ 2 cm	580 (70.6)	2384 (75.9)	571 (69.4)	2197 (77.4)	567 (71.1)	1926 (78.3)	501 (72.9)	1697 (79)	519 (75.2)	1335 (79)
> 2 cm	242 (29.4)	757 (24.1)	252 (30.6)	641 (22.6)	230 (28.9)	534 (21.7)	186 (27.1)	451 (21)	171 (24.8)	354 (21)
Unknown	1	1	1	1	1	1	1	0	0	0
HER2 test result[4]										
Test done	546 (88.8)	1404 (76.9)	509 (87.6)	1286 (77.4)	471 (85.6)	1052 (76.1)	339 (81.5)	886 (75)	280 (74.1)	606 (71.5)
Positive/borderline	95 (17.4)	228 (16.2)	89 (17.5)	202 (15.7)	90 (19.1)	142 (13.5)	61 (18)	126 (14.2)	42 (15)	83 (13.7)
Negative	447 (81.9)	1174 (83.6)	419 (82.3)	1081 (84.1)	379 (80.5)	908 (86.3)	277 (81.7)	759 (85.7)	237 (84.6)	522 (86.1)
No result	4 (0.7)	2 (0.1)	1 (0.2)	3 (0.2)	2 (0.4)	2 (0.2)	1 (0.3)	1 (0.1)	1 (0.4)	1 (0.2)
Surgical procedure										
Mastectomy +/- radiation	376 (45.7)	1042 (33.2)	387 (47)	905 (31.9)	341 (42.7)	802 (32.6)	305 (44.3)	686 (31.9)	277 (40.1)	554 (32.8)
BCS + radiation	319 (38.8)	1759 (56)	328 (39.8)	1634 (57.6)	345 (43.2)	1417 (57.6)	295 (42.9)	1251(58.2)	328 (47.5)	987 (58.4)
BCS	128 (15.6)	341 (10.9)	109 (13.2)	300 (10.6)	112 (14)	242 (9.8)	88 (12.8)	211 (9.8)	85 (12.3)	148 (8.8)

	Year 1		Year 2		Year 3		Year 4		Year 5	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	823 (20.8%)	**3,142 (79.2%)**	**824 (22.5%)**	**2,839 (77.5%)**	**798 (24.5%)**	**2,461 (75.5%)**	**688 (24.3%)**	**2,148 (75.7%)**	**690 (29.0%)**	**1,689 (71.0%)**
Other treatment										
Chemotherapy	276 (33.5)	1015 (32.3)	272 (33)	914 (32.2)	274 (34.3)	761 (30.9)	225 (32.7)	645 (30)	197 (28.6)	516 (30.6)
Completed course	240 (87)	901 (88.8)	226 (83.1)	819 (89.6)	237 (86.5)	674 (88.6)	191 (84.9)	576 (89.3)	172 (87.3)	463 (89.7)
Endocrine therapy [3]	457 (55.5)	1812 (57.7)	460 (55.8)	1672 (58.9)	453 (56.8)	1451 (59)	368 (53.5)	1274(59.3)	368 (53.3)	998 (59.1)
Mode of initial cancer detection										
Screen-detected	258 (42.4)	986 (49.9)	232 (39.6)	933 (52.1)	236 (42.5)	797 (52.7)	182 (42.7)	677 (52.1)	172 (43.2)	496 (52)
Screen interval-detected	80 (13.1)	247 (12.5)	89 (15.2)	215 (12)	82 (14.8)	185 (12.2)	55 (12.9)	171 (13.2)	52 (13.1)	128 (13.4)
Diagnostic detected	253 (41.5)	674 (34.1)	240 (41)	590 (32.9)	215 (38.7)	481 (31.8)	176 (41.3)	402 (30.9)	153 (38.4)	294 (30.8)
Diagnostic interval-detected	18 (3)	68 (3.4)	25 (4.3)	53 (3)	22 (4)	49 (3.2)	13 (3.1)	50 (3.8)	21 (5.3)	35 (3.7)
Unknown	214	1167	238	1048	243	949	262	848	292	736
Medication use pre-diagnosis										
Antibiotic user, ever	369 (44.8)	1390 (44.2)	371 (45)	1239 (43.6)	360 (45.1)	1065 (43.3)	309 (44.9)	924 (43)	307 (44.5)	729 (43.2)
Frequent antibiotic user	69 (8.4)	231 (7.4)	75 (9.1)	190 (6.7)	69 (8.6)	160 (6.5)	58 (8.4)	137 (6.4)	58 (8.4)	108 (6.4)
Statin user, ever	79 (9.6)	261 (8.3)	76 (9.2)	234 (8.2)	68 (8.5)	177 (7.2)	52 (7.6)	124 (5.8)	35 (5.1)	89 (5.3)
More adherent statin user	64 (7.8)	233 (7.4)	60 (7.3)	213 (7.5)	55 (6.9)	163 (6.6)	45 (6.5)	113 (5.3)	32 (4.6)	82 (4.9)
HRT	256 (31.1)	1147 (36.5)	265 (32.2)	1053 (37.1)	266 (33.3)	944 (38.4)	229 (33.3)	872 (40.6)	238 (34.5)	731 (43.3)
Medication use post-diagnosis per-interval[2]										
Frequent antibiotic user	159 (19.3)	569 (18.1)	132 (16)	399 (14.1)	121 (15.2)	340 (13.8)	98 (14.2)	260 (12.1)	125 (18.1)	212 (12.6)
Infrequent antibiotic user	269 (32.7)	960 (30.6)	262 (31.8)	870 (30.6)	254 (31.8)	748 (30.4)	206 (29.9)	695 (32.4)	208 (30.1)	502 (29.7)
Antibiotic nonuser	395 (48)	1613 (51.3)	430 (52.2)	1570 (55.3)	423 (53)	1373 (55.8)	384 (55.8)	1193(55.5)	357 (51.7)	975 (57.7)
More adherent statin user	87 (10.6)	301 (9.6)	108 (13.1)	301 (10.6)	106 (13.3)	295 (12)	100 (14.5)	270 (12.6)	96 (13.9)	245 (14.5)
Less adherent statin user	7 (0.9)	25 (0.8)	7 (0.8)	28 (1)	13 (1.6)	25 (1)	11 (1.6)	32 (1.5)	11 (1.6)	20 (1.2)
Statin nonuser	729 (88.6)	2816 (89.6)	709 (86)	2510 (88.4)	679 (85.1)	2141 (87)	577 (83.9)	1846(85.9)	583 (84.5)	1424(84.3)

(table continues for years 6-10)

	Year 6		Year 7		Year 8		Year 9		Year 10	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	654 (31.9%)	**1393 (68.1%)**	**585 (34.2%)**	**1126 (65.8%)**	**458 (35.3%)**	**840 (64.7%)**	**398 (36.0%)**	**708 (64.0%)**	**338 (36.7%)**	**583 (63.3%)**
Year of diagnosis										
1990-1994	192 (29.4)	447 (32.1)	174 (29.7)	424 (37.7)	183 (40)	373 (44.4)	174 (43.7)	346 (48.9)	175 (51.8)	321 (55.1)
1995-1999	231 (35.3)	546 (39.2)	253 (43.2)	460 (40.9)	232 (50.7)	426 (50.7)	216 (54.3)	361 (51)	163 (48.2)	262 (44.9)
2000-2004	231 (35.3)	400 (28.7)	158 (27)	242 (21.5)	43 (9.4)	41 (4.9)	8 (2)	1 (0.1)	0	0
2005-2008	0	0	0	0	0	0	0	0	0	0
Years of follow-up[1]	.	.	.	.	.	.	.	.	.	.
Mean (SD)	10.2 (3.2)	10.9 (3.3)	10.7 (2.8)	11.7 (3.1)	12 (2.7)	12.7 (2.7)	12.7 (2.5)	13.2 (2.5)	13.3 (2.2)	13.9 (2.3)
Median	9.3	10.3	10	11.3	11.4	12.4	12.1	12.9	12.8	13.3
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.	.
Mean (SD)	69.5 (13.8)	67.6 (11.9)	71.5 (13.4)	67.7 (12)	72.3 (13.8)	68 (11.7)	72.4 (13.3)	68.6 (11.6)	72.9 (13.2)	69.3 (11.3)
21-34	2 (0.3)	0	0	1 (0.1)	1 (0.2)	0	1 (0.3)	0	0	0
35-44	21 (3.2)	22 (1.6)	7 (1.2)	20 (1.8)	6 (1.3)	10 (1.2)	3 (0.8)	7 (1)	5 (1.5)	2 (0.3)
45-54	84 (12.8)	206 (14.8)	76 (13)	154 (13.7)	55 (12)	113 (13.5)	41 (10.3)	92 (13)	32 (9.5)	64 (11)
55-64	142 (21.7)	339 (24.3)	107 (18.3)	278 (24.7)	88 (19.2)	200 (23.8)	82 (20.6)	165 (23.3)	63 (18.6)	145 (24.9)
65-74	145 (22.2)	359 (25.8)	116 (19.8)	300 (26.6)	70 (15.3)	240 (28.6)	75 (18.8)	182 (25.7)	62 (18.3)	150 (25.7)
75+	260 (39.8)	467 (33.5)	279 (47.7)	373 (33.1)	238 (52)	277 (33)	196 (49.2)	262 (37)	176 (52.1)	222 (38.1)
Menopausal status	.	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	170 (26)	383 (27.5)	146 (25)	331 (29.4)	130 (28.4)	254 (30.2)	115 (28.9)	226 (31.9)	95 (28.1)	193 (33.1)
Post-menopausal	484 (74)	1010(72.5)	439 (75)	795 (70.6)	328 (71.6)	586 (69.8)	283 (71.1)	482 (68.1)	243 (71.9)	390 (66.9)
Race	.	.	.	.	.	.	.	.	.	.
White	591 (90.4)	1253(90.1)	527 (90.1)	1014(90.2)	419 (91.7)	754 (89.9)	368 (92.5)	633 (89.7)	315 (93.5)	515 (88.5)
African American	25 (3.8)	32 (2.3)	17 (2.9)	29 (2.6)	13 (2.8)	21 (2.5)	10 (2.5)	20 (2.8)	13 (3.9)	15 (2.6)
American Indian/Alaska Native	18 (2.8)	36 (2.6)	18 (3.1)	30 (2.7)	11 (2.4)	25 (3)	10 (2.5)	19 (2.7)	4 (1.2)	20 (3.4)
Asian/Pacific Islander	20 (3.1)	68 (4.9)	23 (3.9)	50 (4.4)	14 (3.1)	38 (4.5)	10 (2.5)	33 (4.7)	5 (1.5)	32 (5.5)
Other	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)	0	0
Unknown	0	3	0	2	1	1	0	2	1	1
Ethnicity	.	.	.	.	.	.	.	.	.	.
Not Hispanic	628 (96)	1324(95.6)	567 (96.9)	1064(95.1)	445 (97.4)	798 (95.7)	383 (96.5)	674 (96)	330 (98.2)	550 (95.2)
Hispanic	26 (4)	61 (4.4)	18 (3.1)	55 (4.9)	12 (2.6)	36 (4.3)	14 (3.5)	28 (4)	6 (1.8)	28 (4.8)
Unknown	0	8	0	7	1	6	1	6	2	5

	Year 6		Year 7		Year 8		Year 9		Year 10	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	654 (31.9%)	**1393 (68.1%)**	**585 (34.2%)**	**1126 (65.8%)**	**458 (35.3%)**	**840 (64.7%)**	**398 (36.0%)**	**708 (64.0%)**	**338 (36.7%)**	**583 (63.3%)**
Education	.	.	.	.	.	.	.	.	.	.
High school or less	54 (27.1)	143 (23.5)	51 (29.7)	114 (25.6)	26 (27.4)	75 (28.7)	23 (29.1)	47 (24.9)	7 (17.1)	38 (29.7)
Some college	74 (37.2)	193 (31.7)	61 (35.5)	145 (32.6)	31 (32.6)	77 (29.5)	22 (27.8)	61 (32.3)	15 (36.6)	37 (28.9)
College or post graduates	71 (35.7)	272 (44.7)	60 (34.9)	186 (41.8)	38 (40)	109 (41.8)	34 (43)	81 (42.9)	19 (46.3)	53 (41.4)
Unknown	455	785	413	681	363	579	319	519	297	455
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.	.
Mean (SD)	28 (6.1)	27.6 (5.9)	28.2 (6.4)	27.4 (5.6)	27.7 (5.9)	27.5 (5.7)	27.8 (6.4)	27.4 (5.5)	27.3 (6.1)	27.6 (5.6)
Median	27	26.4	27.1	26.1	26.5	26.3	26.6	26.1	26.2	26.4
<18.5	12 (1.8)	21 (1.5)	12 (2.1)	13 (1.2)	10 (2.2)	10 (1.2)	8 (2)	8 (1.1)	6 (1.8)	7 (1.2)
18.5-24.9	223 (34.2)	509 (36.6)	187 (32.1)	435 (38.7)	162 (35.4)	318 (38)	146 (36.9)	269 (38.1)	119 (35.2)	222 (38.2)
25.0-29.9	209 (32)	477 (34.3)	189 (32.4)	383 (34.1)	153 (33.5)	277 (33.1)	121 (30.6)	237 (33.6)	127 (37.6)	185 (31.8)
30.0-34.9	125 (19.1)	225 (16.2)	120 (20.6)	166 (14.8)	80 (17.5)	136 (16.2)	75 (18.9)	112 (15.9)	54 (16)	94 (16.2)
35+	84 (12.9)	158 (11.4)	75 (12.9)	127 (11.3)	52 (11.4)	96 (11.5)	46 (11.6)	80 (11.3)	32 (9.5)	73 (12.6)
Unknown	1	3	2	2	1	3	2	2	0	2
Smoking status	.	.	.	.	.	.	.	.	.	.
Current	32 (4.9)	52 (3.7)	19 (3.2)	40 (3.6)	14 (3.1)	21 (2.5)	10 (2.5)	12 (1.7)	5 (1.5)	11 (1.9)
Past	17 (2.6)	38 (2.7)	15 (2.6)	35 (3.1)	12 (2.6)	32 (3.8)	15 (3.8)	25 (3.5)	7 (2.1)	18 (3.1)
Never/unknown	605 (92.5)	1303(93.5)	551 (94.2)	1051(93.3)	432 (94.3)	787 (93.7)	373 (93.7)	671 (94.8)	326 (96.4)	554 (95)
Charlson score[3]	.	.	.	.	.	.	.	.	.	.
0	307 (46.9)	792 (56.9)	240 (41)	620 (55.1)	179 (39.1)	451 (53.7)	147 (36.9)	366 (51.7)	122 (36.1)	284 (48.7)
1	213 (32.6)	397 (28.5)	201 (34.4)	339 (30.1)	163 (35.6)	257 (30.6)	149 (37.4)	222 (31.4)	134 (39.6)	193 (33.1)
2+	134 (20.5)	204 (14.6)	144 (24.6)	167 (14.8)	116 (25.3)	132 (15.7)	102 (25.6)	120 (16.9)	82 (24.3)	106 (18.2)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.	.
Mean (SD)	4.6 (4)	4 (3.6)	4.6 (4.1)	4 (3.6)	4.6 (4.2)	4 (3.5)	4.6 (4.2)	4.1 (3.9)	4.9 (4.5)	4.1 (3.5)
Median	4	3	4	3	4	3	4	3	4	3
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.	.
Mean (SD)	0.6 (1.3)	0.6 (1.2)	0.4 (1.4)	0.4 (0.9)	0.3 (0.7)	0.4 (1)	0.3 (1)	0.3 (0.8)	0.2 (0.9)	0.3 (0.9)
Median	0	1	0	0	0	0	0	0	0	0

	Year 6		Year 7		Year 8		Year 9		Year 10	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	654 (31.9%)	**1393 (68.1%)**	**585 (34.2%)**	**1126 (65.8%)**	**458 (35.3%)**	**840 (64.7%)**	**398 (36.0%)**	**708 (64.0%)**	**338 (36.7%)**	**583 (63.3%)**
AJCC stage	.	.	.	.	.	.	.	.	.	.
I	433 (66.2)	969 (69.6)	404 (69.1)	786 (69.8)	325 (71)	583 (69.4)	284 (71.4)	506 (71.5)	254 (75.1)	419 (71.9)
IIA	159 (24.3)	303 (21.8)	131 (22.4)	241 (21.4)	107 (23.4)	178 (21.2)	88 (22.1)	147 (20.8)	65 (19.2)	120 (20.6)
IIB	62 (9.5)	121 (8.7)	50 (8.5)	99 (8.8)	26 (5.7)	79 (9.4)	26 (6.5)	55 (7.8)	19 (5.6)	44 (7.5)
Lymph node status	.	.	.	.	.	.	.	.	.	.
Negative	439 (76.6)	1016(80.6)	404 (79.4)	822 (80.2)	317 (80.9)	608 (79.4)	276 (82.4)	532 (81.6)	243 (85.3)	450 (82.9)
Positive (1-3)	100 (17.5)	195 (15.5)	76 (14.9)	160 (15.6)	55 (14)	127 (16.6)	45 (13.4)	99 (15.2)	33 (11.6)	75 (13.8)
Positive (4+)	34 (5.9)	48 (3.8)	29 (5.7)	41 (4)	20 (5.1)	29 (3.8)	13 (3.9)	20 (3.1)	9 (3.2)	17 (3.1)
Positive (unknown #)	0	2 (0.2)	0	2 (0.2)	0	2 (0.3)	1 (0.3)	1 (0.2)	0	1 (0.2)
Unknown	81	132	76	101	66	74	63	56	53	40
ER/PR status	.	.	.	.	.	.	.	.	.	.
ER-/PR-	82 (12.5)	175 (12.6)	69 (11.8)	148 (13.1)	63 (13.8)	105 (12.5)	59 (14.8)	90 (12.7)	43 (12.7)	85 (14.6)
ER+/PR-	74 (11.3)	157 (11.3)	76 (13)	119 (10.6)	57 (12.4)	87 (10.4)	47 (11.8)	72 (10.2)	36 (10.7)	66 (11.3)
ER-/PR+	17 (2.6)	19 (1.4)	15 (2.6)	16 (1.4)	13 (2.8)	13 (1.5)	10 (2.5)	12 (1.7)	6 (1.8)	16 (2.7)
ER+/PR+	442 (67.6)	948 (68.1)	388 (66.3)	762 (67.7)	284 (62)	584 (69.5)	247 (62.1)	485 (68.5)	214 (63.3)	381 (65.4)
ER & PR unknown	39 (6)	94 (6.7)	37 (6.3)	81 (7.2)	41 (9)	51 (6.1)	35 (8.8)	49 (6.9)	39 (11.5)	35 (6)
Tumor size	.	.	.	.	.	.	.	.	.	.
≤ 2 cm	508 (77.7)	1103(79.2)	461 (78.8)	898 (79.8)	373 (81.4)	669 (79.6)	316 (79.4)	577 (81.5)	279 (82.5)	471 (80.8)
> 2 cm	146 (22.3)	290 (20.8)	124 (21.2)	228 (20.2)	85 (18.6)	171 (20.4)	82 (20.6)	131 (18.5)	59 (17.5)	112 (19.2)
Unknown	0	0	0	0	0	0	0	0	0	0
HER2 test result[4]	.	.	.	.	.	.	.	.	.	.
Test done	235 (68.9)	409 (65.9)	167 (62.1)	245 (55.8)	51 (34.7)	50 (22.6)	15 (14.4)	10 (7.3)	5 (11.1)	2 (3.6)
Positive/borderline	33 (14)	52 (12.7)	18 (10.8)	36 (14.7)	7 (13.7)	7 (14)	4 (26.7)	4 (40)	2 (40)	1 (50)
Negative	201 (85.5)	357 (87.3)	149 (89.2)	208 (84.9)	44 (86.3)	43 (86)	11 (73.3)	6 (60)	3 (60)	1 (50)
No result	1 (0.4)	0	0	1 (0.4)	0	0	0	0	0	0
Surgical procedure	.	.	.	.	.	.	.	.	.	.
Mastectomy +/- radiation	278 (42.5)	440 (31.6)	238 (40.7)	348 (30.9)	185 (40.4)	250 (29.8)	148 (37.2)	217 (30.6)	124 (36.7)	183 (31.4)
BCS + radiation	311 (47.6)	828 (59.4)	296 (50.6)	676 (60)	235 (51.3)	529 (63)	219 (55)	449 (63.4)	198 (58.6)	367 (63)
BCS	65 (9.9)	125 (9)	51 (8.7)	102 (9.1)	38 (8.3)	61 (7.3)	31 (7.8)	42 (5.9)	16 (4.7)	33 (5.7)

	Year 6		Year 7		Year 8		Year 9		Year 10	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
	654 (31.9%)	**1393 (68.1%)**	**585 (34.2%)**	**1126 (65.8%)**	**458 (35.3%)**	**840 (64.7%)**	**398 (36.0%)**	**708 (64.0%)**	**338 (36.7%)**	**583 (63.3%)**
Other treatment	.	.	.	.	.	.	.	.	.	.
Chemotherapy	201 (30.7)	402 (28.9)	150 (25.6)	336 (29.8)	113 (24.7)	241 (28.7)	101 (25.4)	191 (27)	81 (24)	155 (26.6)
Completed course	178 (88.6)	361 (89.8)	129 (86)	305 (90.8)	95 (84.1)	219 (90.9)	88 (87.1)	171 (89.5)	69 (85.2)	138 (89)
Endocrine therapy [3]	357 (54.6)	804 (57.7)	323 (55.2)	636 (56.5)	238 (52)	484 (57.6)	200 (50.3)	400 (56.5)	168 (49.7)	307 (52.7)
Mode of initial cancer detection	.	.	.	.	.	.	.	.	.	.
Screen-detected	174 (46.4)	352 (49.7)	155 (49.1)	231 (45.6)	93 (49.5)	133 (45.7)	74 (52.5)	83 (40.9)	37 (44.6)	54 (44.6)
Screen interval-detected	47 (12.5)	96 (13.6)	43 (13.6)	68 (13.4)	22 (11.7)	40 (13.7)	17 (12.1)	29 (14.3)	12 (14.5)	18 (14.9)
Diagnositic detected	134 (35.7)	233 (32.9)	99 (31.3)	187 (36.9)	65 (34.6)	105 (36.1)	43 (30.5)	82 (40.4)	30 (36.1)	42 (34.7)
Diagnostic interval-detected	20 (5.3)	27 (3.8)	19 (6)	21 (4.1)	8 (4.3)	13 (4.5)	7 (5)	9 (4.4)	4 (4.8)	7 (5.8)
Unknown	279	685	269	619	270	549	257	505	255	462
Medication use pre-diagnosis	.	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	290 (44.3)	605 (43.4)	287 (49.1)	467 (41.5)	206 (45)	375 (44.6)	186 (46.7)	320 (45.2)	146 (43.2)	267 (45.8)
Frequent antibiotic user	53 (8.1)	88 (6.3)	50 (8.5)	67 (6)	39 (8.5)	57 (6.8)	32 (8)	52 (7.3)	32 (9.5)	38 (6.5)
Statin user, ever	29 (4.4)	59 (4.2)	23 (3.9)	41 (3.6)	14 (3.1)	17 (2)	11 (2.8)	13 (1.8)	7 (2.1)	9 (1.5)
More adherent statin user	27 (4.1)	53 (3.8)	21 (3.6)	38 (3.4)	14 (3.1)	14 (1.7)	10 (2.5)	11 (1.6)	6 (1.8)	7 (1.2)
HRT	261 (39.9)	590 (42.4)	227 (38.8)	483 (42.9)	156 (34.1)	356 (42.4)	149 (37.4)	290 (41)	111 (32.8)	238 (40.8)
Medication use post-diagnosis per-interval[2]	.	.	.	.	.	.	.	.	.	.
Frequent antibiotic user	96 (14.7)	170 (12.2)	77 (13.2)	142 (12.6)	75 (16.4)	87 (10.4)	65 (16.3)	79 (11.2)	54 (16)	77 (13.2)
Infrequent antibiotic user	196 (30)	418 (30)	195 (33.3)	343 (30.5)	128 (27.9)	263 (31.3)	141 (35.4)	215 (30.4)	100 (29.6)	170 (29.2)
Antibiotic nonuser	362 (55.4)	805 (57.8)	313 (53.5)	641 (56.9)	255 (55.7)	490 (58.3)	192 (48.2)	414 (58.5)	184 (54.4)	336 (57.6)
More adherent statin user	102 (15.6)	232 (16.7)	123 (21)	208 (18.5)	91 (19.9)	153 (18.2)	91 (22.9)	150 (21.2)	76 (22.5)	143 (24.5)
Less adherent statin user	15 (2.3)	20 (1.4)	9 (1.5)	16 (1.4)	5 (1.1)	13 (1.5)	8 (2)	12 (1.7)	4 (1.2)	7 (1.2)
Statin nonuser	537 (82.1)	1141(81.9)	453 (77.4)	902 (80.1)	362 (79)	674 (80.2)	299 (75.1)	546 (77.1)	258 (76.3)	433 (74.3)

Abbreviations: SD=standard deviation; AJCC=American Joint Committee on Cancer; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; BCS=breast conserving surgery; PCP=primary care physician; ONC=oncology; HRT=hormone replacement therapy

*Characteristics at diagnosis date for initial breast cancer, unless otherwise noted; 0.7% of surveillance mammography included breast MRI

[1]Follow-up extended from diagnosis date through first of death, disenrollment, diagnosis of a second breast cancer event (i.e., recurrence or 2nd primary), or end of study (date of chart abstraction).
[2]Time-varying per-interval: variable exposure was ascertained during each surveillance year; variable status did not carry forward to the subsequent surveillance year.
[3]Time-varying ever-never: variable exposure was ascertained throughout the entire study period; once the subject mets the variable definition for use, she was included in that category and remained there until the end of follow-up; subjects must meet the variable definition for at least 8 months of the surveillance year to be included in that exposure category for analyses; otherwise, they were included in the exposure category beginning with the next subsequent surveillance year; if the variable included multiple categories (e.g., Charlson, ever-never medication use), subjects were only allowed to transition from a lower to a higher category over time.
[4]HER2 status ascertained 1998+ and abstracted from the medical record
[5]Ascertained in 12 months prior to the initial breast cancer diagnosis

Table 6. Distribution of covariates by per-interval antibiotic use for all surveillance years since completion of treatment

	Year 1			Year 2			Year 3		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	2,008 (50.6%)	**1,229 (31.0%)**	**728 (18.4%)**	**2,000 (54.6%)**	**1,132 (30.9%)**	**531 (14.5%)**	**1,796 (55.1%)**	**1,002 (30.7%)**	**461 (14.1%)**
Year of diagnosis									
1990-1994	442 (22)	283 (23)	173 (23.8)	419 (21)	285 (25.2)	135 (25.4)	390 (21.7)	257 (25.6)	127 (27.5)
1995-1999	535 (26.6)	346 (28.2)	233 (32)	548 (27.4)	307 (27.1)	172 (32.4)	518 (28.8)	299 (29.8)	143 (31)
2000-2004	592 (29.5)	365 (29.7)	177 (24.3)	579 (29)	324 (28.6)	140 (26.4)	535 (29.8)	298 (29.7)	134 (29.1)
2005-2008	439 (21.9)	235 (19.1)	145 (19.9)	454 (22.7)	216 (19.1)	84 (15.8)	353 (19.7)	148 (14.8)	57 (12.4)
Years of follow-up[1]									
Mean (SD)	7.4 (4.1)	7.5 (4.1)	7.5 (4.3)	7.8 (4)	8 (4)	7.9 (4)	8.3 (3.7)	8.8 (3.9)	8.8 (3.9)
Median	6.7	6.7	6.4	7	7.2	7	7.5	7.9	7.9
Age per-interval, years [2]									
Mean (SD)	63.4 (12.9)	64.2 (13.5)	63.2 (13.3)	63.8 (12.8)	65.3 (13.2)	66 (13.1)	65.1 (12.7)	65.5 (13.1)	67.2 (12.8)
21-34	9 (0.4)	10 (0.8)	11 (1.5)	5 (0.3)	5 (0.4)	4 (0.8)	6 (0.3)	4 (0.4)	1 (0.2)
35-44	134 (6.7)	77 (6.3)	49 (6.7)	120 (6)	62 (5.5)	19 (3.6)	84 (4.7)	45 (4.5)	21 (4.6)
45-54	423 (21.1)	247 (20.1)	155 (21.3)	409 (20.5)	202 (17.8)	100 (18.8)	331 (18.4)	189 (18.9)	67 (14.5)
55-64	509 (25.3)	270 (22)	158 (21.7)	510 (25.5)	267 (23.6)	109 (20.5)	450 (25.1)	237 (23.7)	105 (22.8)
65-74	500 (24.9)	308 (25.1)	194 (26.6)	489 (24.5)	275 (24.3)	155 (29.2)	441 (24.6)	246 (24.6)	127 (27.5)
75+	433 (21.6)	317 (25.8)	161 (22.1)	467 (23.4)	321 (28.4)	144 (27.1)	484 (26.9)	281 (28)	140 (30.4)
Menopausal status									
Peri- or premenopausal	544 (27.1)	328 (26.7)	200 (27.5)	566 (28.3)	291 (25.7)	123 (23.2)	489 (27.2)	258 (25.7)	112 (24.3)
Post-menopausal	1464 (72.9)	901 (73.3)	528 (72.5)	1434 (71.7)	841 (74.3)	408 (76.8)	1307 (72.8)	744 (74.3)	349 (75.7)
Race	.	.	.	.	.	.	.	.	.
White	1751 (87.5)	1089 (89)	662 (91.2)	1749 (87.8)	1008 (89.5)	481 (90.6)	1581 (88.3)	888 (88.9)	423 (91.8)
African American	70 (3.5)	38 (3.1)	15 (2.1)	65 (3.3)	31 (2.8)	13 (2.4)	61 (3.4)	25 (2.5)	9 (2)
American Indian/Alaska Native	41 (2)	40 (3.3)	28 (3.9)	51 (2.6)	31 (2.8)	20 (3.8)	46 (2.6)	35 (3.5)	12 (2.6)
Asian/Pacific Islander	139 (6.9)	56 (4.6)	21 (2.9)	128 (6.4)	55 (4.9)	17 (3.2)	102 (5.7)	50 (5)	17 (3.7)
Other	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)	0
Unknown	7	5	2	7	6	0	6	3	0
Ethnicity									
Not Hispanic	1880 (93.8)	1166 (95.3)	693 (95.6)	1883 (94.3)	1070 (95)	504 (95.1)	1699 (94.8)	949 (95.1)	441 (95.9)
Hispanic	125 (6.2)	58 (4.7)	32 (4.4)	113 (5.7)	56 (5)	26 (4.9)	93 (5.2)	49 (4.9)	19 (4.1)
Unknown	3	5	3	4	6	1	4	4	1

	Year 1			Year 2			Year 3		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	2,008 (50.6%)	**1,229 (31.0%)**	**728 (18.4%)**	**2,000 (54.6%)**	**1,132 (30.9%)**	**531 (14.5%)**	**1,796 (55.1%)**	**1,002 (30.7%)**	**461 (14.1%)**
Education	.	.	.	.	.	.	.	.	.
High school or less	202 (22.1)	133 (24.5)	74 (25.9)	206 (21.1)	125 (25.3)	58 (27.9)	207 (24.3)	94 (21.5)	50 (25.6)
Some college	314 (34.4)	202 (37.2)	105 (36.7)	352 (36.1)	157 (31.8)	89 (42.8)	290 (34.1)	156 (35.6)	71 (36.4)
College or post graduates	398 (43.5)	208 (38.3)	107 (37.4)	417 (42.8)	212 (42.9)	61 (29.3)	354 (41.6)	188 (42.9)	74 (37.9)
Unknown	1094	686	442	1025	638	323	945	564	266
Body mass index (kg/m^2)									
Mean (SD)	27.6 (5.9)	28.1 (6.1)	28.9 (6.8)	27.6 (6)	28.3 (6)	28.9 (6.8)	27.7 (5.8)	28 (6.1)	29.3 (7.2)
Median	26.6	26.8	27.8	26.4	27.2	27.6	26.7	26.8	28
<18.5	36 (1.8)	15 (1.2)	11 (1.5)	28 (1.4)	19 (1.7)	9 (1.7)	26 (1.5)	16 (1.6)	8 (1.7)
18.5-24.9	717 (35.8)	417 (34)	225 (31.1)	738 (37)	362 (32.1)	153 (29)	639 (35.6)	347 (34.7)	131 (28.5)
25.0-29.9	661 (33)	406 (33.1)	225 (31.1)	664 (33.2)	365 (32.3)	174 (33)	594 (33.1)	332 (33.2)	147 (32)
30.0-34.9	359 (17.9)	219 (17.9)	148 (20.5)	337 (16.9)	227 (20.1)	110 (20.9)	330 (18.4)	174 (17.4)	94 (20.5)
35+	228 (11.4)	169 (13.8)	114 (15.8)	230 (11.5)	156 (13.8)	81 (15.4)	204 (11.4)	131 (13.1)	79 (17.2)
Unknown	7	3	5	3	3	4	3	2	2
Smoking status									
Current	110 (5.5)	74 (6)	49 (6.7)	111 (5.6)	63 (5.6)	30 (5.6)	101 (5.6)	51 (5.1)	19 (4.1)
Past	164 (8.2)	99 (8.1)	67 (9.2)	176 (8.8)	84 (7.4)	42 (7.9)	133 (7.4)	75 (7.5)	30 (6.5)
Never/unknown	1734 (86.4)	1056 (85.9)	612 (84.1)	1713 (85.7)	985 (87)	459 (86.4)	1562 (87)	876 (87.4)	412 (89.4)
Charlson score [3]									
0	1620 (80.7)	941 (76.6)	490 (67.3)	1471 (73.6)	743 (65.6)	284 (53.5)	1243 (69.2)	618 (61.7)	233 (50.5)
1	274 (13.6)	209 (17)	179 (24.6)	380 (19)	256 (22.6)	165 (31.1)	391 (21.8)	264 (26.3)	137 (29.7)
2+	114 (5.7)	79 (6.4)	59 (8.1)	149 (7.5)	133 (11.7)	82 (15.4)	162 (9)	120 (12)	91 (19.7)
# PCP visits per-interval [2]									
Mean (SD)	5.1 (6.6)	6 (6.7)	6.8 (6.6)	3 (2.6)	4.4 (3.4)	6 (4.8)	3 (2.7)	4.4 (4)	6.3 (4.5)
Median	3	4	6	3	4	5	3	4	6
# ONC visits per-interval [2]									
Mean (SD)	2.8 (2.9)	2.9 (3)	3.3 (3.7)	1.4 (1.5)	1.4 (1.3)	1.5 (1.8)	1.1 (1.3)	1.2 (1.4)	1.3 (1.7)
Median	2	2	3	2	1	1	1	1	1

	Year 1			Year 2			Year 3		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	2,008 (50.6%)	**1,229 (31.0%)**	**728 (18.4%)**	**2,000 (54.6%)**	**1,132 (30.9%)**	**531 (14.5%)**	**1,796 (55.1%)**	**1,002 (30.7%)**	**461 (14.1%)**
AJCC stage									
I	1259 (62.7)	839 (68.3)	425 (58.4)	1285 (64.3)	741 (65.5)	341 (64.2)	1184 (65.9)	656 (65.5)	306 (66.4)
IIA	539 (26.8)	258 (21)	212 (29.1)	495 (24.8)	275 (24.3)	139 (26.2)	427 (23.8)	248 (24.8)	104 (22.6)
IIB	210 (10.5)	132 (10.7)	91 (12.5)	220 (11)	116 (10.2)	51 (9.6)	185 (10.3)	98 (9.8)	51 (11.1)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	1402 (77.9)	845 (77.5)	456 (69.3)	1404 (77.1)	783 (77.9)	338 (73.5)	1279 (78.5)	701 (77.2)	296 (75.1)
Positive (1-3)	302 (16.8)	179 (16.4)	159 (24.2)	311 (17.1)	181 (18)	93 (20.2)	267 (16.4)	162 (17.8)	76 (19.3)
Positive (4+)	92 (5.1)	65 (6)	43 (6.5)	103 (5.7)	40 (4)	29 (6.3)	83 (5.1)	44 (4.8)	22 (5.6)
Positive (unknown #)	3 (0.2)	1 (0.1)	0	2 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	0
Unknown	209	139	70	180	127	71	166	94	67
ER/PR status									
ER-/PR-	308 (15.3)	160 (13)	125 (17.2)	292 (14.6)	158 (14)	75 (14.1)	256 (14.3)	140 (14)	58 (12.6)
ER+/PR-	177 (8.8)	115 (9.4)	65 (8.9)	184 (9.2)	104 (9.2)	46 (8.7)	163 (9.1)	99 (9.9)	42 (9.1)
ER-/PR+	24 (1.2)	24 (2)	9 (1.2)	28 (1.4)	12 (1.1)	11 (2.1)	22 (1.2)	13 (1.3)	9 (2)
ER+/PR+	1398 (69.6)	864 (70.3)	493 (67.7)	1405 (70.3)	791 (69.9)	370 (69.7)	1275 (71)	694 (69.3)	316 (68.5)
ER & PR unknown	101 (5)	66 (5.4)	36 (4.9)	91 (4.6)	67 (5.9)	29 (5.5)	80 (4.5)	56 (5.6)	36 (7.8)
Tumor size									
≤ 2 cm	1463 (72.9)	958 (78)	543 (74.6)	1496 (74.8)	859 (76)	413 (77.8)	1368 (76.2)	769 (76.9)	356 (77.2)
> 2 cm	544 (27.1)	270 (22)	185 (25.4)	503 (25.2)	272 (24)	118 (22.2)	428 (23.8)	231 (23.1)	105 (22.8)
Unknown	1	1	0	1	1	0	0	2	0
HER2 test results									
Test done	1020 (80.2)	605 (80.7)	325 (77.6)	1033 (81.3)	535 (78.8)	227 (77.7)	883 (79.5)	445 (78.2)	195 (77.1)
Positive/borderline	163 (16)	93 (15.4)	67 (20.6)	171 (16.6)	86 (16.1)	34 (15)	137 (15.5)	70 (15.7)	25 (12.8)
Negative	853 (83.6)	510 (84.3)	258 (79.4)	861 (83.3)	446 (83.4)	193 (85)	745 (84.4)	373 (83.8)	169 (86.7)
No result	4 (0.4)	2 (0.3)	0	1 (0.1)	3 (0.6)	0	1 (0.1)	2 (0.4)	1 (0.5)
Surgical procedure									
Mastectomy +/- radiation	672 (33.5)	419 (34.1)	327 (44.9)	670 (33.5)	404 (35.7)	218 (41.1)	608 (33.9)	357 (35.6)	178 (38.6)
BCS + radiation	1096 (54.6)	665 (54.1)	317 (43.5)	1098 (54.9)	609 (53.8)	255 (48)	978 (54.5)	545 (54.4)	239 (51.8)
BCS	240 (12)	145 (11.8)	84 (11.5)	232 (11.6)	119 (10.5)	58 (10.9)	210 (11.7)	100 (10)	44 (9.5)

	Year 1			Year 2			Year 3		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	2,008 (50.6%)	**1,229 (31.0%)**	**728 (18.4%)**	**2,000 (54.6%)**	**1,132 (30.9%)**	**531 (14.5%)**	**1,796 (55.1%)**	**1,002 (30.7%)**	**461 (14.1%)**
Other treatment									
Chemotherapy	651 (32.4)	368 (29.9)	272 (37.4)	659 (33)	367 (32.4)	160 (30.1)	573 (31.9)	335 (33.4)	127 (27.5)
Completed course	574 (88.2)	329 (89.4)	238 (87.5)	584 (88.6)	323 (88)	138 (86.3)	507 (88.5)	293 (87.5)	111 (87.4)
Endocrine therapy [3]	1122 (55.9)	705 (57.4)	442 (60.7)	1154 (57.7)	660 (58.3)	318 (59.9)	1041 (58)	589 (58.8)	274 (59.4)
Mode of initial cancer detection									
Screen-detected	658 (49.2)	390 (48.5)	196 (44.2)	661 (48.7)	350 (50.3)	154 (47.7)	606 (51.1)	300 (49.5)	127 (46)
Screen interval-detected	164 (12.3)	101 (12.6)	62 (14)	167 (12.3)	98 (14.1)	39 (12.1)	159 (13.4)	73 (12)	35 (12.7)
Diagnostic-detected	474 (35.5)	282 (35.1)	171 (38.6)	483 (35.6)	229 (32.9)	118 (36.5)	383 (32.3)	209 (34.5)	104 (37.7)
Diagnostic interval-detected	41 (3.1)	31 (3.9)	14 (3.2)	47 (3.5)	19 (2.7)	12 (3.7)	37 (3.1)	24 (4)	10 (3.6)
Unknown	671	425	285	642	436	208	611	396	185
Medication use pre-diagnosis	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	697 (34.7)	573 (46.6)	489 (67.2)	686 (34.3)	542 (47.9)	382 (71.9)	631 (35.1)	473 (47.2)	321 (69.6)
Frequent antibiotic user	50 (2.5)	71 (5.8)	179 (24.6)	54 (2.7)	78 (6.9)	133 (25)	57 (3.2)	65 (6.5)	107 (23.2)
Statin user, ever	163 (8.1)	101 (8.2)	76 (10.4)	156 (7.8)	97 (8.6)	57 (10.7)	125 (7)	77 (7.7)	43 (9.3)
More adherent statin user	139 (6.9)	91 (7.4)	67 (9.2)	137 (6.9)	86 (7.6)	50 (9.4)	107 (6)	70 (7)	41 (8.9)
HRT	648 (32.3)	439 (35.7)	316 (43.4)	642 (32.1)	438 (38.7)	238 (44.8)	612 (34.1)	386 (38.5)	212 (46)

(table continues for years 4-6)

	Year 4			Year 5			Year 6		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	1,577 (55.6%)	**901 (31.8%)**	**358 (12.6%)**	**1,332 (56.0%)**	**710 (29.8%)**	**337 (14.2%)**	**1,167 (57.0%)**	**614 (30.0%)**	**266 (13.0%)**
Year of diagnosis									
1990-1994	382 (24.2)	232 (25.7)	112 (31.3)	372 (27.9)	196 (27.6)	105 (31.2)	368 (31.5)	187 (30.5)	84 (31.6)
1995-1999	479 (30.4)	294 (32.6)	114 (31.8)	460 (34.5)	256 (36.1)	112 (33.2)	427 (36.6)	246 (40.1)	104 (39.1)
2000-2004	514 (32.6)	278 (30.9)	94 (26.3)	469 (35.2)	246 (34.6)	112 (33.2)	372 (31.9)	181 (29.5)	78 (29.3)
2005-2008	202 (12.8)	97 (10.8)	38 (10.6)	31 (2.3)	12 (1.7)	8 (2.4)	0	0	0
Years of follow-up[1]									
Mean (SD)	9.1 (3.6)	9.3 (3.6)	9.2 (3.7)	9.9 (3.4)	10 (3.4)	10 (3.5)	10.7 (3.3)	10.4 (3.1)	10.6 (3.2)
Median	8.1	8.3	8.3	9	9.2	9.2	10.1	9.7	10
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	65.9 (12.6)	66.7 (12.7)	68.8 (12.8)	67 (12.8)	67.5 (12.7)	69.6 (12.1)	67.6 (12.6)	68.9 (12.6)	69.3 (12.2)
21-34	1 (0.1)	2 (0.2)	0	1 (0.1)	0	1 (0.3)	1 (0.1)	1 (0.2)	0
35-44	60 (3.8)	24 (2.7)	16 (4.5)	41 (3.1)	18 (2.5)	4 (1.2)	24 (2.1)	15 (2.4)	4 (1.5)
45-54	280 (17.8)	153 (17)	40 (11.2)	215 (16.1)	114 (16.1)	33 (9.8)	186 (15.9)	71 (11.6)	33 (12.4)
55-64	392 (24.9)	220 (24.4)	77 (21.5)	312 (23.4)	167 (23.5)	77 (22.8)	276 (23.7)	147 (23.9)	58 (21.8)
65-74	392 (24.9)	228 (25.3)	93 (26)	335 (25.2)	180 (25.4)	91 (27)	295 (25.3)	141 (23)	68 (25.6)
75+	452 (28.7)	274 (30.4)	132 (36.9)	428 (32.1)	231 (32.5)	131 (38.9)	385 (33)	239 (38.9)	103 (38.7)
Menopausal status	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	432 (27.4)	234 (26)	74 (20.7)	361 (27.1)	190 (26.8)	70 (20.8)	339 (29)	151 (24.6)	63 (23.7)
Post-menopausal	1145 (72.6)	667 (74)	284 (79.3)	971 (72.9)	520 (73.2)	267 (79.2)	828 (71)	463 (75.4)	203 (76.3)
Race	.	.	.	.	.	.	.	.	.
White	1395 (88.6)	811 (90.1)	332 (92.7)	1190 (89.5)	639 (90.1)	309 (91.7)	1046 (89.8)	552 (90)	246 (92.5)
African American	51 (3.2)	19 (2.1)	6 (1.7)	41 (3.1)	16 (2.3)	4 (1.2)	34 (2.9)	18 (2.9)	5 (1.9)
American Indian/Alaska Native	40 (2.5)	27 (3)	10 (2.8)	31 (2.3)	20 (2.8)	12 (3.6)	26 (2.2)	20 (3.3)	8 (3)
Asian/Pacific Islander	87 (5.5)	43 (4.8)	10 (2.8)	68 (5.1)	34 (4.8)	11 (3.3)	59 (5.1)	22 (3.6)	7 (2.6)
Other	1 (0.1)	0	0	0	0	1 (0.3)	0	1 (0.2)	0
Unknown	3	1	0	2	1	0	2	1	0
Ethnicity	.	.	.	.	.	.	.	.	.
Not Hispanic	1504 (95.7)	856 (95.1)	343 (96.3)	1275 (96.1)	673 (95.2)	324 (96.1)	1115 (96.1)	581 (94.8)	256 (96.2)
Hispanic	67 (4.3)	44 (4.9)	13 (3.7)	52 (3.9)	34 (4.8)	13 (3.9)	45 (3.9)	32 (5.2)	10 (3.8)
Unknown	6	1	2	5	3	0	7	1	0

	Year 4			Year 5			Year 6		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	1,577 (55.6%)	901 (31.8%)	358 (12.6%)	1,332 (56.0%)	710 (29.8%)	337 (14.2%)	1,167 (57.0%)	614 (30.0%)	266 (13.0%)
Education									
High school or less	162 (22.5)	104 (25.9)	34 (24.3)	134 (23.4)	72 (25.1)	37 (27.2)	93 (20.7)	77 (30.1)	27 (26.5)
Some college	250 (34.7)	132 (32.9)	49 (35)	184 (32.1)	101 (35.2)	49 (36)	146 (32.5)	82 (32)	39 (38.2)
College or post graduates	309 (42.9)	165 (41.1)	57 (40.7)	255 (44.5)	114 (39.7)	50 (36.8)	210 (46.8)	97 (37.9)	36 (35.3)
Unknown	856	500	218	759	423	201	718	358	164
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.
Mean (SD)	27.5 (5.9)	28 (6)	29.2 (6.8)	27.3 (5.7)	28.1 (5.8)	28.7 (6.8)	27.3 (5.5)	28 (5.8)	29.1 (7.6)
Median	26.4	26.9	28	26.1	27.1	27.3	26.1	26.9	27.9
<18.5	33 (2.1)	4 (0.4)	10 (2.8)	25 (1.9)	4 (0.6)	10 (3)	16 (1.4)	3 (0.5)	14 (5.3)
18.5-24.9	581 (36.9)	310 (34.4)	101 (28.3)	515 (38.8)	231 (32.6)	102 (30.3)	453 (38.9)	208 (34)	71 (26.7)
25.0-29.9	510 (32.4)	317 (35.2)	107 (30)	427 (32.1)	268 (37.8)	100 (29.7)	387 (33.2)	223 (36.4)	76 (28.6)
30.0-34.9	265 (16.8)	169 (18.8)	78 (21.8)	226 (17)	118 (16.6)	69 (20.5)	190 (16.3)	105 (17.2)	55 (20.7)
35+	185 (11.8)	100 (11.1)	61 (17.1)	136 (10.2)	88 (12.4)	56 (16.6)	119 (10.2)	73 (11.9)	50 (18.8)
Unknown	3	1	1	3	1	0	2	2	0
Smoking status	.	.	.	.	.	.	.	.	.
Current	78 (4.9)	49 (5.4)	13 (3.6)	72 (5.4)	20 (2.8)	16 (4.7)	46 (3.9)	23 (3.7)	15 (5.6)
Past	89 (5.6)	42 (4.7)	22 (6.1)	37 (2.8)	29 (4.1)	10 (3)	28 (2.4)	16 (2.6)	11 (4.1)
Never/unknown	1410 (89.4)	810 (89.9)	323 (90.2)	1223 (91.8)	661 (93.1)	311 (92.3)	1093 (93.7)	575 (93.6)	240 (90.2)
Charlson score [3]	.	.	.	.	.	.	.	.	.
0	1058 (67.1)	504 (55.9)	152 (42.5)	811 (60.9)	379 (53.4)	141 (41.8)	683 (58.5)	299 (48.7)	117 (44)
1	369 (23.4)	265 (29.4)	122 (34.1)	379 (28.5)	210 (29.6)	111 (32.9)	334 (28.6)	202 (32.9)	74 (27.8)
2+	150 (9.5)	132 (14.7)	84 (23.5)	142 (10.7)	121 (17)	85 (25.2)	150 (12.9)	113 (18.4)	75 (28.2)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	3 (2.8)	4.5 (3.6)	6.8 (5.3)	3.3 (3.1)	4.6 (3.5)	6.5 (5)	3.3 (3.1)	4.9 (3.8)	6.8 (4.5)
Median	3	4	6	3	4	6	3	4	6
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	1 (1.3)	1 (1.1)	1.2 (1.7)	0.9 (1.1)	0.8 (1)	0.9 (1.4)	0.6 (1.3)	0.6 (1.2)	0.6 (1.2)
Median	1	1	1	1	1	1	0	0	0

	Year 4			Year 5			Year 6		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	1,577 (55.6%)	901 (31.8%)	358 (12.6%)	1,332 (56.0%)	710 (29.8%)	337 (14.2%)	1,167 (57.0%)	614 (30.0%)	266 (13.0%)
AJCC stage	.	.	.	.	.	.	.	.	.
I	1042 (66.1)	605 (67.1)	248 (69.3)	891 (66.9)	484 (68.2)	232 (68.8)	780 (66.8)	438 (71.3)	184 (69.2)
IIA	383 (24.3)	205 (22.8)	74 (20.7)	316 (23.7)	158 (22.3)	77 (22.8)	266 (22.8)	135 (22)	61 (22.9)
IIB	152 (9.6)	91 (10.1)	36 (10.1)	125 (9.4)	68 (9.6)	28 (8.3)	121 (10.4)	41 (6.7)	21 (7.9)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	1117 (78)	631 (78.3)	244 (77.5)	962 (79.8)	497 (78.4)	225 (76.8)	843 (79.8)	432 (79.4)	180 (77.3)
Positive (1-3)	240 (16.8)	136 (16.9)	54 (17.1)	183 (15.2)	112 (17.7)	52 (17.7)	164 (15.5)	89 (16.4)	42 (18)
Positive (4+)	74 (5.2)	38 (4.7)	17 (5.4)	60 (5)	24 (3.8)	16 (5.5)	49 (4.6)	22 (4)	11 (4.7)
Positive (unknown #)	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.2)	0
Unknown	145	95	43	126	76	44	110	70	33
ER/PR status	.	.	.	.	.	.	.	.	.
ER-/PR-	204 (12.9)	127 (14.1)	42 (11.7)	178 (13.4)	86 (12.1)	43 (12.8)	147 (12.6)	77 (12.5)	33 (12.4)
ER+/PR-	150 (9.5)	95 (10.5)	34 (9.5)	155 (11.6)	60 (8.5)	36 (10.7)	136 (11.7)	71 (11.6)	24 (9)
ER-/PR+	24 (1.5)	12 (1.3)	4 (1.1)	21 (1.6)	11 (1.5)	6 (1.8)	15 (1.3)	13 (2.1)	8 (3)
ER+/PR+	1113 (70.6)	614 (68.1)	252 (70.4)	907 (68.1)	501 (70.6)	228 (67.7)	805 (69)	407 (66.3)	178 (66.9)
ER & PR unknown	86 (5.5)	53 (5.9)	26 (7.3)	71 (5.3)	52 (7.3)	24 (7.1)	64 (5.5)	46 (7.5)	23 (8.6)
Tumor size	.	.	.	.	.	.	.	.	.
≤ 2 cm	1216 (77.2)	697 (77.4)	285 (79.6)	1020 (76.6)	560 (78.9)	274 (81.3)	881 (75.5)	511 (83.2)	219 (82.3)
> 2 cm	360 (22.8)	204 (22.6)	73 (20.4)	312 (23.4)	150 (21.1)	63 (18.7)	286 (24.5)	103 (16.8)	47 (17.7)
Unknown	1	0	0						
HER2 test results	.	.	.	.	.	.	.	.	.
Test done	718 (77)	369 (75.9)	138 (77.1)	507 (72.1)	256 (71.7)	123 (74.5)	376 (70)	187 (61.9)	81 (65.9)
Positive/borderline	109 (15.2)	60 (16.3)	18 (13)	72 (14.2)	33 (12.9)	20 (16.3)	48 (12.8)	29 (15.5)	8 (9.9)
Negative	608 (84.7)	308 (83.5)	120 (87)	434 (85.6)	222 (86.7)	103 (83.7)	327 (87)	158 (84.5)	73 (90.1)
No result	1 (0.1)	1 (0.3)	0	1 (0.2)	1 (0.4)	0	1 (0.3)	0	0
Surgical procedure	.	.	.	.	.	.	.	.	.
Mastectomy +/- radiation	535 (33.9)	337 (37.4)	119 (33.2)	456 (34.2)	241 (33.9)	134 (39.8)	382 (32.7)	211 (34.4)	125 (47)
BCS + radiation	880 (55.8)	472 (52.4)	194 (54.2)	744 (55.9)	401 (56.5)	170 (50.4)	675 (57.8)	345 (56.2)	119 (44.7)
BCS	162 (10.3)	92 (10.2)	45 (12.6)	132 (9.9)	68 (9.6)	33 (9.8)	110 (9.4)	58 (9.4)	22 (8.3)

	Year 4			Year 5			Year 6		
	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User	Nonuser	Infrequent Antibiotic User	Frequent Antibiotic User
	1,577 (55.6%)	901 (31.8%)	358 (12.6%)	1,332 (56.0%)	710 (29.8%)	337 (14.2%)	1,167 (57.0%)	614 (30.0%)	266 (13.0%)
Other treatment	.	.	.	.	.	.	.	.	.
Chemotherapy	491 (31.1)	282 (31.3)	97 (27.1)	420 (31.5)	201 (28.3)	92 (27.3)	361 (30.9)	168 (27.4)	74 (27.8)
Completed course	431 (87.8)	249 (88.3)	87 (89.7)	378 (90)	176 (87.6)	81 (88)	323 (89.5)	152 (90.5)	64 (86.5)
Endocrine therapy [3]	925 (58.7)	494 (54.8)	223 (62.3)	770 (57.8)	391 (55.1)	205 (60.8)	662 (56.7)	343 (55.9)	156 (58.6)
Mode of initial cancer detection	.	.	.	.	.	.	.	.	.
Screen-detected	496 (49.7)	259 (49.1)	104 (51.5)	384 (49.5)	191 (47.9)	93 (52.8)	291 (48.2)	166 (48.5)	69 (50.4)
Screen interval-detected	136 (13.6)	71 (13.5)	19 (9.4)	104 (13.4)	54 (13.5)	22 (12.5)	75 (12.4)	50 (14.6)	18 (13.1)
Diagnostic-detected	334 (33.5)	172 (32.6)	72 (35.6)	260 (33.5)	135 (33.8)	52 (29.5)	211 (34.9)	117 (34.2)	39 (28.5)
Diagnostic interval-detected	31 (3.1)	25 (4.7)	7 (3.5)	28 (3.6)	19 (4.8)	9 (5.1)	27 (4.5)	9 (2.6)	11 (8)
Unknown	580	374	156	556	311	161	563	272	129
Medication use pre-diagnosis	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	569 (36.1)	427 (47.4)	237 (66.2)	488 (36.6)	324 (45.6)	224 (66.5)	437 (37.4)	284 (46.3)	174 (65.4)
Frequent antibiotic user	48 (3)	74 (8.2)	73 (20.4)	51 (3.8)	44 (6.2)	71 (21.1)	43 (3.7)	45 (7.3)	53 (19.9)
Statin user, ever	78 (4.9)	69 (7.7)	29 (8.1)	59 (4.4)	44 (6.2)	21 (6.2)	40 (3.4)	33 (5.4)	15 (5.6)
More adherent statin user	71 (4.5)	61 (6.8)	26 (7.3)	58 (4.4)	38 (5.4)	18 (5.3)	36 (3.1)	32 (5.2)	12 (4.5)
HRT	575 (36.5)	347 (38.5)	179 (50)	503 (37.8)	298 (42)	168 (49.9)	455 (39)	261 (42.5)	135 (50.8)

(table continues for years 7-9)

	Year 7			Year 8			Year 9		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	954 (55.8%)	**538 (31.4%)**	**219 (12.8%)**	**745 (57.4%)**	**391 (30.1%)**	**162 (12.5%)**	**606 (54.8%)**	**356 (32.2%)**	**144 (13.0%)**
Year of diagnosis									
1990-1994	331 (34.7)	199 (37)	68 (31.1)	311 (41.7)	174 (44.5)	71 (43.8)	295 (48.7)	160 (44.9)	65 (45.1)
1995-1999	414 (43.4)	204 (37.9)	95 (43.4)	385 (51.7)	195 (49.9)	78 (48.1)	309 (51)	191 (53.7)	77 (53.5)
2000-2004	209 (21.9)	135 (25.1)	56 (25.6)	49 (6.6)	22 (5.6)	13 (8)	2 (0.3)	5 (1.4)	2 (1.4)
2005-2008									
Years of follow-up[1]	.	.	.	.	.	.	.	.	.
Mean (SD)	11.4 (3)	11.4 (3.2)	11 (2.9)	12.6 (2.8)	12.4 (2.8)	12.2 (2.5)	13.1 (2.5)	13 (2.5)	12.9 (2.6)
Median	11	10.7	10.6	12.2	11.9	11.6	12.7	12.6	12.4
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	68.3 (12.5)	69.4 (12.7)	71.4 (12.7)	68.7 (12.6)	70 (12.2)	72.4 (13.1)	69.3 (12.1)	70.2 (12.9)	72.2 (11.7)
21-34	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.2)	0	0
35-44	13 (1.4)	8 (1.5)	6 (2.7)	7 (0.9)	4 (1)	5 (3.1)	4 (0.7)	4 (1.1)	2 (1.4)
45-54	147 (15.4)	67 (12.5)	16 (7.3)	116 (15.6)	42 (10.7)	10 (6.2)	76 (12.5)	50 (14)	7 (4.9)
55-64	217 (22.7)	122 (22.7)	46 (21)	168 (22.6)	85 (21.7)	35 (21.6)	150 (24.8)	65 (18.3)	32 (22.2)
65-74	239 (25.1)	124 (23)	53 (24.2)	182 (24.4)	100 (25.6)	28 (17.3)	144 (23.8)	84 (23.6)	29 (20.1)
75+	337 (35.3)	217 (40.3)	98 (44.7)	271 (36.4)	160 (40.9)	84 (51.9)	231 (38.1)	153 (43)	74 (51.4)
Menopausal status	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	283 (29.7)	148 (27.5)	46 (21)	235 (31.5)	111 (28.4)	38 (23.5)	195 (32.2)	111 (31.2)	35 (24.3)
Post-menopausal	671 (70.3)	390 (72.5)	173 (79)	510 (68.5)	280 (71.6)	124 (76.5)	411 (67.8)	245 (68.8)	109 (75.7)
Race	.	.	.	.	.	.	.	.	.
White	854 (89.7)	481 (89.4)	206 (94.1)	665 (89.5)	353 (90.3)	155 (95.7)	543 (89.8)	323 (91)	135 (93.8)
African American	29 (3)	14 (2.6)	3 (1.4)	20 (2.7)	14 (3.6)	0	17 (2.8)	10 (2.8)	3 (2.1)
American Indian/Alaska Native	19 (2)	24 (4.5)	5 (2.3)	23 (3.1)	8 (2)	5 (3.1)	14 (2.3)	11 (3.1)	4 (2.8)
Asian/Pacific Islander	49 (5.1)	19 (3.5)	5 (2.3)	34 (4.6)	16 (4.1)	2 (1.2)	30 (5)	11 (3.1)	2 (1.4)
Other	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.2)	0	0
Unknown	2	0	0	2	0	0	1	1	0
Ethnicity	.	.	.	.	.	.	.	.	.
Not Hispanic	908 (95.8)	511 (95.2)	212 (96.8)	711 (96.3)	378 (96.7)	154 (95.1)	576 (96)	338 (95.2)	143 (99.3)
Hispanic	40 (4.2)	26 (4.8)	7 (3.2)	27 (3.7)	13 (3.3)	8 (4.9)	24 (4)	17 (4.8)	1 (0.7)
Unknown	6	1	0	7	0	0	6	1	0

	Year 7			Year 8			Year 9		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	954 (55.8%)	**538 (31.4%)**	**219 (12.8%)**	**745 (57.4%)**	**391 (30.1%)**	**162 (12.5%)**	**606 (54.8%)**	**356 (32.2%)**	**144 (13.0%)**
Education	.	.	.	.	.	.	.	.	.
High school or less	81 (24.2)	59 (29.8)	25 (29.8)	52 (24.9)	35 (34.3)	14 (31.1)	39 (25.2)	21 (29.6)	10 (23.8)
Some college	104 (31)	70 (35.4)	32 (38.1)	66 (31.6)	27 (26.5)	15 (33.3)	47 (30.3)	18 (25.4)	18 (42.9)
College or post graduates	150 (44.8)	69 (34.8)	27 (32.1)	91 (43.5)	40 (39.2)	16 (35.6)	69 (44.5)	32 (45.1)	14 (33.3)
Unknown	619	340	135	536	289	117	451	285	102
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.
Mean (SD)	27.4 (5.8)	27.6 (5.7)	28.9 (6.6)	27.3 (5.8)	27.6 (5.7)	28.6 (6.1)	27.2 (5.8)	27.7 (5.6)	28.6 (6.2)
Median	26.1	26.7	27.6	26	26.8	27.4	25.8	26.7	27.4
<18.5	14 (1.5)	6 (1.1)	5 (2.3)	9 (1.2)	8 (2)	3 (1.9)	11 (1.8)	4 (1.1)	1 (0.7)
18.5-24.9	371 (39)	195 (36.4)	56 (25.6)	295 (39.7)	139 (35.5)	46 (28.8)	245 (40.6)	129 (36.2)	41 (28.7)
25.0-29.9	314 (33)	179 (33.4)	79 (36.1)	246 (33.1)	133 (34)	51 (31.9)	188 (31.2)	122 (34.3)	48 (33.6)
30.0-34.9	141 (14.8)	99 (18.5)	46 (21)	113 (15.2)	66 (16.9)	37 (23.1)	94 (15.6)	58 (16.3)	35 (24.5)
35+	112 (11.8)	57 (10.6)	33 (15.1)	80 (10.8)	45 (11.5)	23 (14.4)	65 (10.8)	43 (12.1)	18 (12.6)
Unknown	2	2	0	2	0	2	3	0	1
Smoking status	.	.	.	.	.	.	.	.	.
Current	29 (3)	22 (4.1)	8 (3.7)	23 (3.1)	10 (2.6)	2 (1.2)	14 (2.3)	6 (1.7)	2 (1.4)
Past	20 (2.1)	14 (2.6)	16 (7.3)	26 (3.5)	9 (2.3)	9 (5.6)	16 (2.6)	11 (3.1)	13 (9)
Never/unknown	905 (94.9)	502 (93.3)	195 (89)	696 (93.4)	372 (95.1)	151 (93.2)	576 (95)	339 (95.2)	129 (89.6)
Charlson score [3]	.	.	.	.	.	.	.	.	.
0	541 (56.7)	240 (44.6)	79 (36.1)	407 (54.6)	172 (44)	51 (31.5)	328 (54.1)	140 (39.3)	45 (31.3)
1	286 (30)	186 (34.6)	68 (31.1)	228 (30.6)	134 (34.3)	58 (35.8)	179 (29.5)	140 (39.3)	52 (36.1)
2+	127 (13.3)	112 (20.8)	72 (32.9)	110 (14.8)	85 (21.7)	53 (32.7)	99 (16.3)	76 (21.3)	47 (32.6)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	3.2 (2.7)	4.9 (4.2)	6.9 (5)	3.2 (2.8)	4.9 (4.3)	6.7 (4.7)	3.3 (3.1)	5 (4.3)	6.8 (5)
Median	3	4	6	3	4	6	3	4	6
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	0.4 (1)	0.5 (1.1)	0.5 (1.7)	0.3 (0.6)	0.4 (1.1)	0.5 (1.2)	0.3 (0.7)	0.3 (1)	0.5 (1.3)
Median	0	0	0	0	0	0	0	0	0

	Year 7			Year 8			Year 9		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	954 (55.8%)	**538 (31.4%)**	**219 (12.8%)**	**745 (57.4%)**	**391 (30.1%)**	**162 (12.5%)**	**606 (54.8%)**	**356 (32.2%)**	**144 (13.0%)**
AJCC stage	.	.	.	.	.	.	.	.	.
I	656 (68.8)	379 (70.4)	155 (70.8)	512 (68.7)	276 (70.6)	120 (74.1)	436 (71.9)	254 (71.3)	100 (69.4)
IIA	213 (22.3)	113 (21)	46 (21)	173 (23.2)	82 (21)	30 (18.5)	127 (21)	76 (21.3)	32 (22.2)
IIB	85 (8.9)	46 (8.6)	18 (8.2)	60 (8.1)	33 (8.4)	12 (7.4)	43 (7.1)	26 (7.3)	12 (8.3)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	682 (79.8)	394 (80.6)	150 (78.9)	528 (79.2)	281 (80.3)	116 (82.3)	449 (82.5)	258 (82.4)	101 (77.7)
Positive (1-3)	126 (14.7)	76 (15.5)	34 (17.9)	104 (15.6)	57 (16.3)	21 (14.9)	78 (14.3)	44 (14.1)	22 (16.9)
Positive (4+)	45 (5.3)	19 (3.9)	6 (3.2)	34 (5.1)	11 (3.1)	4 (2.8)	17 (3.1)	10 (3.2)	6 (4.6)
Positive (unknown #)	2 (0.2)	0	0	1 (0.1)	1 (0.3)	0	0	1 (0.3)	1 (0.8)
Unknown	99	49	29	78	41	21	62	43	14
ER/PR status	.	.	.	.	.	.	.	.	.
ER-/PR-	125 (13.1)	69 (12.8)	23 (10.5)	105 (14.1)	45 (11.5)	18 (11.1)	85 (14.0)	49 (13.8)	15 (10.4)
ER+/PR-	106 (11.1)	67 (12.5)	22 (10.0)	75 (10.1)	51 (13)	18 (11.1)	67 (11.1)	36 (10.1)	16 (11.1)
ER-/PR+	16 (1.7)	10 (1.9)	5 (2.3)	13 (1.7)	8 (2.0)	5 (3.1)	12 (2.0)	5 (1.4)	5 (3.5)
ER+/PR+	640 (67.1)	364 (67.7)	146 (66.7)	503 (67.5)	262 (67.0)	103 (63.6)	399 (65.8)	240 (67.4)	93 (64.6)
ER & PR unknown	67 (7.0)	28 (5.2)	23 (10.5)	49 (6.6)	25 (6.4)	18 (11.1)	43 (7.1)	26 (7.3)	15 (10.4)
Tumor size	.	.	.	.	.	.	.	.	.
≤ 2 cm	750 (78.6)	431 (80.1)	178 (81.3)	595 (79.9)	312 (79.8)	135 (83.3)	489 (80.7)	286 (80.3)	118 (81.9)
> 2 cm	204 (21.4)	107 (19.9)	41 (18.7)	150 (20.1)	79 (20.2)	27 (16.7)	117 (19.3)	70 (19.7)	26 (18.1)
Unknown	0	0	0	0	0	0	0	0	0
HER2 test results	.	.	.	.	.	.	.	.	.
Test done	215 (55.6)	141 (62.9)	56 (57.7)	57 (27.1)	28 (24.3)	16 (37.2)	12 (8.8)	8 (11.1)	5 (15.6)
Positive/borderline	30 (14.0)	16 (11.3)	8 (14.3)	10 (17.5)	2 (7.1)	2 (12.5)	5 (41.7)	2 (25.0)	1 (20.0)
Negative	184 (85.6)	125 (88.7)	48 (85.7)	47 (82.5)	26 (92.9)	14 (87.5)	7 (58.3)	6 (75.0)	4 (80.0)
No result	1 (0.5)	0	0	0	0	0			
Surgical procedure									
Mastectomy +/- radiation	314 (32.9)	188 (34.9)	84 (38.4)	256 (34.4)	120 (30.7)	59 (36.4)	180 (29.7)	126 (35.4)	59 (41.0)
BCS + radiation	549 (57.5)	306 (56.9)	117 (53.4)	429 (57.6)	243 (62.1)	92 (56.8)	388 (64.0)	205 (57.6)	75 (52.1)
BCS	91 (9.5)	44 (8.2)	18 (8.2)	60 (8.1)	28 (7.2)	11 (6.8)	38 (6.3)	25 (7.0)	10 (6.9)

	Year 7			Year 8			Year 9		
	Nonuser	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**	**Nonuser**	**Infrequent Antibiotic User**	**Frequent Antibiotic User**
	954 (55.8%)	**538 (31.4%)**	**219 (12.8%)**	**745 (57.4%)**	**391 (30.1%)**	**162 (12.5%)**	**606 (54.8%)**	**356 (32.2%)**	**144 (13.0%)**
Other treatment									
Chemotherapy	268 (28.1)	155 (28.8)	63 (28.8)	223 (29.9)	96 (24.6)	35 (21.6)	153 (25.2)	103 (28.9)	36 (25)
Completed course	247 (92.2)	136 (87.7)	51 (81.0)	200 (89.7)	83 (86.5)	31 (88.6)	135 (88.2)	92 (89.3)	32 (88.9)
Endocrine therapy [3]	532 (55.8)	294 (54.6)	133 (60.7)	423 (56.8)	205 (52.4)	94 (58)	331 (54.6)	194 (54.5)	75 (52.1)
Mode of initial cancer detection									
Screen-detected	220 (48.1)	114 (45.1)	52 (46.0)	124 (44.9)	76 (52.8)	26 (44.1)	90 (47.9)	48 (45.7)	19 (37.3)
Screen interval-detected	61 (13.3)	33 (13.0)	17 (15.0)	37 (13.4)	15 (10.4)	10 (16.9)	30 (16)	9 (8.6)	7 (13.7)
Diagnostic-detected	149 (32.6)	100 (39.5)	37 (32.7)	101 (36.6)	50 (34.7)	19 (32.2)	59 (31.4)	43 (41)	23 (45.1)
Diagnostic interval-detected	27 (5.9)	6 (2.4)	7 (6.2)	14 (5.1)	3 (2.1)	4 (6.8)	9 (4.8)	5 (4.8)	2 (3.9)
Unknown	497	285	106	469	247	103	418	251	93
Medication use pre-diagnosis	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	367 (38.5)	243 (45.2)	144 (65.8)	287 (38.5)	194 (49.6)	100 (61.7)	228 (37.6)	179 (50.3)	99 (68.8)
Frequent antibiotic user	36 (3.8)	41 (7.6)	40 (18.3)	31 (4.2)	28 (7.2)	37 (22.8)	22 (3.6)	32 (9)	30 (20.8)
Statin user, ever	29 (3)	20 (3.7)	15 (6.8)	12 (1.6)	11 (2.8)	8 (4.9)	13 (2.1)	4 (1.1)	7 (4.9)
More adherent statin user	26 (2.7)	20 (3.7)	13 (5.9)	11 (1.5)	10 (2.6)	7 (4.3)	11 (1.8)	4 (1.1)	6 (4.2)
HRT	369 (38.7)	226 (42)	115 (52.5)	283 (38)	146 (37.3)	83 (51.2)	230 (38)	131 (36.8)	78 (54.2)

(table continues for year 10)

	Nonuser 520 (56.5%)	Year 10 Infrequent Antibiotic User 270 (29.3%)	Frequent Antibiotic User 131 (14.2%)
Year of diagnosis			
1990-1994	292 (56.2)	145 (53.7)	59 (45)
1995-1999	228 (43.8)	125 (46.3)	72 (55)
2000-2004	0	0	0
2005-2008	0	0	0
Years of follow-up[1]	.	.	.
Mean (SD)	13.9 (2.3)	13.5 (2.2)	13.1 (2.2)
Median	13.5	13	12.7
Age per-interval, years [2]	.	.	.
Mean (SD)	69.5 (12)	71.9 (12.9)	72.7 (10.7)
21-34	0	0	0
35-44	4 (0.8)	1 (0.4)	2 (1.5)
45-54	59 (11.3)	32 (11.9)	5 (3.8)
55-64	134 (25.8)	48 (17.8)	26 (19.8)
65-74	124 (23.8)	57 (21.1)	31 (23.7)
75+	199 (38.3)	132 (48.9)	67 (51.1)
Menopausal status			
Peri- or premenopausal	182 (35)	76 (28.1)	30 (22.9)
Post-menopausal	338 (65)	194 (71.9)	101 (77.1)
Race	.	.	.
White	461 (89)	248 (91.9)	121 (92.4)
African American	21 (4.1)	6 (2.2)	1 (0.8)
American Indian/Alaska Native	11 (2.1)	6 (2.2)	7 (5.3)
Asian/Pacific Islander	25 (4.8)	10 (3.7)	2 (1.5)
Other	0	0	0
Unknown	2	0	0
Ethnicity	.	.	.
Not Hispanic	495 (96.5)	259 (95.9)	126 (96.2)
Hispanic	18 (3.5)	11 (4.1)	5 (3.8)
Unknown	7	0	0

	Nonuser 520 (56.5%)	Year 10 Infrequent Antibiotic User 270 (29.3%)	Frequent Antibiotic User 131 (14.2%)
Education	.	.	.
High school or less	27 (26)	12 (30)	6 (24)
Some college	27 (26)	15 (37.5)	10 (40)
College or post graduates	50 (48.1)	13 (32.5)	9 (36)
Unknown	416	230	106
Body mass index (kg/m^2)	.	.	.
Mean (SD)	27.2 (5.7)	27.1 (5.2)	29.5 (6.7)
Median	25.9	26	28
<18.5	7 (1.4)	3 (1.1)	3 (2.3)
18.5-24.9	204 (39.4)	108 (40)	29 (22.1)
25.0-29.9	175 (33.8)	89 (33)	48 (36.6)
30.0-34.9	76 (14.7)	47 (17.4)	25 (19.1)
35+	56 (10.8)	23 (8.5)	26 (19.8)
Unknown	2	0	0
Smoking status	.	.	.
Current	11 (2.1)	2 (0.7)	3 (2.3)
Past	12 (2.3)	5 (1.9)	8 (6.1)
Never/unknown	497 (95.6)	263 (97.4)	120 (91.6)
Charlson score [3]	.	.	.
0	271 (52.1)	105 (38.9)	30 (22.9)
1	174 (33.5)	102 (37.8)	51 (38.9)
2+	75 (14.4)	63 (23.3)	50 (38.2)
# PCP visits per-interval [2]	.	.	.
Mean (SD)	3.5 (3.3)	5 (4)	6.6 (5.1)
Median	3	4	6
# ONC visits per-interval [2]	.	.	.
Mean (SD)	0.2 (0.5)	0.3 (1.2)	0.4 (1.2)
Median	0	0	0

	Year 10		
	Nonuser 520 (56.5%)	Infrequent Antibiotic User 270 (29.3%)	Frequent Antibiotic User 131 (14.2%)
AJCC stage	.	.	.
I	376 (72.3)	197 (73)	100 (76.3)
IIA	104 (20)	61 (22.6)	20 (15.3)
IIB	40 (7.7)	12 (4.4)	11 (8.4)
Lymph node status	.	.	.
Negative	392 (82.5)	202 (86)	99 (83.9)
Positive (1-3)	66 (13.9)	28 (11.9)	14 (11.9)
Positive (4+)	16 (3.4)	5 (2.1)	5 (4.2)
Positive (unknown #)	1 (0.2)	0	0
Unknown	45	35	13
ER/PR status	.	.	.
ER-/PR-	74 (14.2)	37 (13.7)	17 (13)
ER+/PR-	58 (11.2)	35 (13)	9 (6.9)
ER-/PR+	10 (1.9)	7 (2.6)	5 (3.8)
ER+/PR+	341 (65.6)	165 (61.1)	89 (67.9)
ER & PR unknown	37 (7.1)	26 (9.6)	11 (8.4)
Tumor size	.	.	.
≤ 2 cm	422 (81.2)	219 (81.1)	109 (83.2)
> 2 cm	98 (18.8)	51 (18.9)	22 (16.8)
Unknown			
HER2 test results	.	.	.
Test done	5 (8.2)	1 (4)	1 (6.7)
Positive/borderline	2 (40)	1 (100)	0
Negative	3 (60)	0	1 (100)
No result			
Surgical procedure	.	.	.
Mastectomy +/- radiation	158 (30.4)	93 (34.4)	56 (42.7)
BCS + radiation	328 (63.1)	167 (61.9)	70 (53.4)
BCS	34 (6.5)	10 (3.7)	5 (3.8)

	Nonuser 520 (56.5%)	Year 10 Infrequent Antibiotic User 270 (29.3%)	Frequent Antibiotic User 131 (14.2%)
Other treatment	.	.	.
Chemotherapy	140 (26.9)	69 (25.6)	27 (20.6)
Completed course	124 (88.6)	62 (89.9)	21 (77.8)
Endocrine therapy [3]	265 (51)	142 (52.6)	68 (51.9)
Mode of initial cancer detection	.	.	.
Screen-detected	46 (41.8)	24 (40)	21 (61.8)
Screen interval-detected	21 (19.1)	6 (10)	3 (8.8)
Diagnostic-detected	34 (30.9)	30 (50)	8 (23.5)
Diagnostic interval-detected	9 (8.2)	0	2 (5.9)
Unknown	410	210	97
Medication use pre-diagnosis	.	.	.
Antibiotic user, ever	191 (36.7)	139 (51.5)	83 (63.4)
Frequent antibiotic user	22 (4.2)	21 (7.8)	27 (20.6)
Statin user, ever	7 (1.3)	7 (2.6)	2 (1.5)
More adherent statin user	5 (1)	6 (2.2)	2 (1.5)
HRT	197 (37.9)	89 (33)	63 (48.1)

Abbreviations: SD=standard deviation; AJCC=American Joint Committee on Cancer; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; BCS=breast conserving surgery; PCP=primary care physician; ONC=oncology; HRT=hormone replacement therapy

*Characteristics at diagnosis date for initial breast cancer, unless otherwise noted; 0.7% of surveillance mammography included breast MRI

[1] Follow-up extended from diagnosis date through first of death, disenrollment, diagnosis of a second breast cancer event (i.e., recurrence or 2nd primary), or end of study (date of chart abstraction).
[2]Time-varying per-interval: variable exposure was ascertained during each surveillance year; variable status did not carry forward to the subsequent surveillance year.

[3]Time-varying ever-never: variable exposure was ascertained throughout the entire study period; once the subject mets the variable definition for use, she was included in that category and remained there until the end of follow-up; subjects must meet the variable definition for at least 8 months of the surveillance year to be included in that exposure category for analyses; otherwise, they were included in the exposure category beginning with the next subsequent surveillance year; if the variable included multiple categories (e.g., Charlson, ever-never medication use), subjects were only allowed to transition from a lower to a higher category over time.
[4]HER2 status ascertained 1998+ and abstracted from the medical record
[5]Ascertained in 12 months prior to the initial breast cancer diagnosis

Table 7. Distribution of covariates by per-interval statin use for all surveillance years since completion of treatment

	Year 1			Year 2			Year 3		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	3,545 (89.4%)	**32 (0.8%)**	**388 (9.8%)**	**3,219 (87.9%)**	**35 (1.0%)**	**409 (11.2%)**	**2,820 (86.5%)**	**38 (1.2%)**	**401 (12.3%)**
Year of diagnosis									
1990-1994	882 (24.9)	0	16 (4.1)	818 (25.4)	4 (11.4)	17 (4.2)	748 (26.5)	3 (7.9)	23 (5.7)
1995-1999	1066 (30.1)	3 (9.4)	45 (11.6)	974 (30.3)	2 (5.7)	51 (12.5)	888 (31.5)	8 (21.1)	64 (16)
2000-2004	982 (27.7)	12 (37.5)	140 (36.1)	873 (27.1)	14 (40)	156 (38.1)	776 (27.5)	11 (28.9)	180 (44.9)
2005-2008	615 (17.3)	17 (53.1)	187 (48.2)	554 (17.2)	15 (42.9)	185 (45.2)	408 (14.5)	16 (42.1)	134 (33.4)
Years of follow-up[1]	.	.	.	.	.	.	.	.	.
Mean (SD)	7.7 (4.2)	5 (2.5)	5.5 (2.7)	8.2 (4.1)	6 (2.5)	5.9 (2.7)	8.8 (3.9)	6.6 (2.7)	6.8 (2.7)
Median	6.9	4.6	4.9	7.4	5.2	5.2	7.9	5.5	6.3
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	62.9 (13.3)	71.8 (10.7)	69.5 (9.7)	63.8 (13.2)	66.3 (11)	70.1 (9.7)	64.8 (13.1)	65.4 (11.2)	70.2 (9.8)
21-34	30 (0.8)	0	0	14 (0.4)	0	0	11 (0.4)	0	0
35-44	258 (7.3)	0	2 (0.5)	200 (6.2)	0	1 (0.2)	148 (5.2)	0	2 (0.5)
45-54	795 (22.4)	4 (12.5)	26 (6.7)	683 (21.2)	3 (8.6)	25 (6.1)	559 (19.8)	6 (15.8)	22 (5.5)
55-64	840 (23.7)	5 (15.6)	92 (23.7)	784 (24.4)	14 (40)	88 (21.5)	684 (24.3)	14 (36.8)	94 (23.4)
65-74	845 (23.8)	9 (28.1)	148 (38.1)	755 (23.5)	9 (25.7)	155 (37.9)	658 (23.3)	10 (26.3)	146 (36.4)
75+	777 (21.9)	14 (43.8)	120 (30.9)	783 (24.3)	9 (25.7)	140 (34.2)	760 (27)	8 (21.1)	137 (34.2)
Menopausal status	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	1044 (29.4)	2 (6.3)	26 (6.7)	943 (29.3)	7 (20)	30 (7.3)	816 (28.9)	9 (23.7)	34 (8.5)
Post-menopausal	2501 (70.6)	30 (93.8)	362 (93.3)	2276 (70.7)	28 (80)	379 (92.7)	2004 (71.1)	29 (76.3)	367 (91.5)
Race	.	.	.	.	.	.	.	.	.
White	3134 (88.7)	26 (81.3)	342 (88.4)	2849 (88.8)	29 (82.9)	360 (88.5)	2509 (89.2)	31 (83.8)	352 (88)
African American	106 (3)	2 (6.3)	15 (3.9)	92 (2.9)	2 (5.7)	15 (3.7)	78 (2.8)	3 (8.1)	14 (3.5)
American Indian/Alaska Native	99 (2.8)	1 (3.1)	9 (2.3)	88 (2.7)	1 (2.9)	13 (3.2)	79 (2.8)	2 (5.4)	12 (3)
Asian/Pacific Islander	192 (5.4)	3 (9.4)	21 (5.4)	178 (5.5)	3 (8.6)	19 (4.7)	147 (5.2)	1 (2.7)	21 (5.3)
Other	1	0	0	1	0	0	0	0	1 (0.3)
Unknown	13	0	1	11	0	2	7	1	1

	Year 1			Year 2			Year 3		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	3,545 (89.4%)	**32 (0.8%)**	**388 (9.8%)**	**3,219 (87.9%)**	**35 (1.0%)**	**409 (11.2%)**	**2,820 (86.5%)**	**38 (1.2%)**	**401 (12.3%)**
Ethnicity	.	.	.	.	.	.	.	.	.
Not Hispanic	3344 (94.6)	29 (90.6)	366 (94.3)	3038 (94.7)	32 (91.4)	387 (94.6)	2673 (95.1)	35 (92.1)	381 (95)
Hispanic	190 (5.4)	3 (9.4)	22 (5.7)	170 (5.3)	3 (8.6)	22 (5.4)	138 (4.9)	3 (7.9)	20 (5)
Unknown	11	0	0	11	0	0	9	0	0
Education	.	.	.	.	.	.	.	.	.
High school or less	307 (21.2)	8 (40)	94 (34.6)	289 (21.2)	6 (26.1)	94 (32.6)	254 (21.3)	4 (14.8)	93 (34.8)
Some college	514 (35.4)	7 (35)	100 (36.8)	478 (35)	9 (39.1)	111 (38.5)	400 (33.6)	17 (63)	100 (37.5)
College or post graduates	630 (43.4)	5 (25)	78 (28.7)	599 (43.9)	8 (34.8)	83 (28.8)	536 (45)	6 (22.2)	74 (27.7)
Unknown	2094	12	116	1853	12	121	1630	11	134
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.
Mean (SD)	27.7 (6)	29.8 (6.8)	30.7 (6.8)	27.6 (5.9)	32.3 (6.7)	30.9 (6.7)	27.5 (5.9)	30.8 (6)	31 (6.9)
Median	26.6	28.1	29.9	26.5	33.1	30	26.4	31	30
<18.5	57 (1.6)	0	5 (1.3)	52 (1.6)	0	4 (1)	48 (1.7)	0	2 (0.5)
18.5-24.9	1272 (36)	8 (25)	79 (20.4)	1166 (36.3)	8 (22.9)	79 (19.3)	1032 (36.7)	6 (15.8)	79 (19.7)
25.0-29.9	1169 (33.1)	10 (31.3)	113 (29.1)	1078 (33.6)	3 (8.6)	122 (29.8)	944 (33.6)	11 (28.9)	118 (29.4)
30.0-34.9	616 (17.5)	10 (31.3)	100 (25.8)	557 (17.4)	12 (34.3)	105 (25.7)	486 (17.3)	14 (36.8)	98 (24.4)
35+	416 (11.8)	4 (12.5)	91 (23.5)	356 (11.1)	12 (34.3)	99 (24.2)	303 (10.8)	7 (18.4)	104 (25.9)
Unknown	15	0	0	10	0	0	7	0	0
Smoking status	.	.	.	.	.	.	.	.	.
Current	203 (5.7)	4 (12.5)	26 (6.7)	172 (5.3)	4 (11.4)	28 (6.8)	139 (4.9)	5 (13.2)	27 (6.7)
Past	249 (7)	6 (18.8)	75 (19.3)	223 (6.9)	5 (14.3)	74 (18.1)	179 (6.3)	4 (10.5)	55 (13.7)
Never/unknown	3093 (87.2)	22 (68.8)	287 (74)	2824 (87.7)	26 (74.3)	307 (75.1)	2502 (88.7)	29 (76.3)	319 (79.6)
Charlson score [3]	.	.	.	.	.	.	.	.	.
0	2847 (80.3)	15 (46.9)	189 (48.7)	2336 (72.6)	10 (28.6)	152 (37.2)	1946 (69)	20 (52.6)	128 (31.9)
1	540 (15.2)	11 (34.4)	111 (28.6)	666 (20.7)	11 (31.4)	124 (30.3)	653 (23.2)	9 (23.7)	130 (32.4)
2+	158 (4.5)	6 (18.8)	88 (22.7)	217 (6.7)	14 (40)	133 (32.5)	221 (7.8)	9 (23.7)	143 (35.7)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	5.3 (6.4)	12.7 (11.4)	8.4 (7.9)	3.7 (3.2)	5.8 (4.4)	5.2 (4.7)	3.6 (3.2)	4.5 (4.2)	5.5 (5.3)
Median	4	7	5	3	5	4	3	4	4

	Year 1			Year 2			Year 3		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	3,545 (89.4%)	**32 (0.8%)**	**388 (9.8%)**	**3,219 (87.9%)**	**35 (1.0%)**	**409 (11.2%)**	**2,820 (86.5%)**	**38 (1.2%)**	**401 (12.3%)**
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	2.9 (3.2)	2.6 (2.3)	2.8 (2.5)	1.4 (1.5)	1.9 (2.1)	1.3 (1.2)	1.2 (1.4)	0.9 (0.8)	1.1 (1.3)
Median	2	2	3	2	2	2	1	1	1
AJCC stage	.	.	.	.	.	.	.	.	.
I	2239 (63.2)	21 (65.6)	263 (67.8)	2058 (63.9)	20 (57.1)	289 (70.7)	1837 (65.1)	26 (68.4)	283 (70.6)
IIA	912 (25.7)	9 (28.1)	88 (22.7)	815 (25.3)	11 (31.4)	83 (20.3)	693 (24.6)	8 (21.1)	78 (19.5)
IIB	394 (11.1)	2 (6.3)	37 (9.5)	346 (10.7)	4 (11.4)	37 (9)	290 (10.3)	4 (10.5)	40 (10.0)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	2401 (75.7)	22 (73.3)	280 (80.7)	2204 (76.4)	26 (78.8)	295 (80.2)	1955 (77.1)	25 (78.1)	296 (81.5)
Positive (1-3)	584 (18.4)	6 (20.0)	50 (14.4)	523 (18.1)	6 (18.2)	56 (15.2)	449 (17.7)	5 (15.6)	51 (14)
Positive (4+)	183 (5.8)	2 (6.7)	15 (4.3)	155 (5.4)	1 (3.0)	16 (4.3)	131 (5.2)	2 (6.3)	16 (4.4)
Positive (unknown #)	2 (0.1)	0	2 (0.6)	2 (0.1)	0	1 (0.3)	2 (0.1)	0	0
Unknown	375	2	41	335	2	41	283	6	38
ER/PR status	.	.	.	.	.	.	.	.	.
ER-/PR-	525 (14.8)	8 (25)	60 (15.5)	464 (14.4)	7 (20.0)	54 (13.2)	392 (13.9)	5 (13.2)	57 (14.2)
ER+/PR-	334 (9.4)	2 (6.3)	21 (5.4)	303 (9.4)	4 (11.4)	27 (6.6)	272 (9.6)	2 (5.3)	30 (7.5)
ER-/PR+	54 (1.5)	1 (3.1)	2 (0.5)	48 (1.5)	0	3 (0.7)	40 (1.4)	1 (2.6)	3 (0.7)
ER+/PR+	2440 (68.8)	21 (65.6)	294 (75.8)	2235 (69.4)	22 (62.9)	309 (75.6)	1961 (69.5)	29 (76.3)	295 (73.6)
ER & PR unknown	192 (5.4)	0	11 (2.8)	169 (5.3)	2 (5.7)	16 (3.9)	155 (5.5)	1 (2.6)	16 (4)
Tumor size	.	.	.	.	.	.	.	.	.
≤ 2 cm	2639 (74.5)	27 (84.4)	298 (76.8)	2416 (75.1)	23 (65.7)	329 (80.4)	2148 (76.2)	30 (78.9)	315 (78.6)
> 2 cm	904 (25.5)	5 (15.6)	90 (23.2)	801 (24.9)	12 (34.3)	80 (19.6)	670 (23.8)	8 (21.1)	86 (21.4)
Unknown	2	0	0	2	0	0	2	0	0
HER2 test result[4]	.	.	.	.	.	.	.	.	.
Test done	1599 (77.8)	29 (96.7)	322 (90.7)	1432 (77.7)	28 (93.3)	335 (91)	1190 (76.4)	27 (84.4)	306 (89.5)
Positive/borderline	262 (16.4)	6 (20.7)	55 (17.1)	228 (15.9)	5 (17.9)	58 (17.3)	186 (15.6)	2 (7.4)	44 (14.4)
Negative	1332 (83.3)	23 (79.3)	266 (82.6)	1201 (83.9)	23 (82.1)	276 (82.4)	1002 (84.2)	25 (92.6)	260 (85)
No result	5 (0.3)	0	1 (0.3)	3 (0.2)	0	1 (0.3)	2 (0.2)	0	2 (0.7)

	Year 1			Year 2			Year 3		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	3,545 (89.4%)	32 (0.8%)	388 (9.8%)	3,219 (87.9%)	35 (1.0%)	409 (11.2%)	2,820 (86.5%)	38 (1.2%)	401 (12.3%)
Surgical procedure	.	.	.	.	.	.	.	.	.
Mastectomy +/- radiation	1276 (36)	9 (28.1)	133 (34.3)	1136 (35.3)	11 (31.4)	145 (35.5)	989 (35.1)	11 (28.9)	143 (35.7)
BCS + radiation	1838 (51.8)	22 (68.8)	218 (56.2)	1714 (53.2)	21 (60.0)	227 (55.5)	1516 (53.8)	22 (57.9)	224 (55.9)
BCS	431 (12.2)	1 (3.1)	37 (9.5)	369 (11.5)	3 (8.6)	37 (9.0)	315 (11.2)	5 (13.2)	34 (8.5)
Other treatment	.	.	.	.	.	.	.	.	.
Chemotherapy	1198 (33.8)	10 (31.3)	83 (21.4)	1087 (33.8)	11 (31.4)	88 (21.5)	931 (33)	10 (26.3)	94 (23.4)
Completed course	1069 (89.2)	7 (70)	65 (78.3)	967 (89)	7 (63.6)	71 (80.7)	824 (88.5)	7 (70.0)	80 (85.1)
Endocrine therapy [3]	2025 (57.1)	14 (43.8)	230 (59.3)	1876 (58.3)	18 (51.4)	238 (58.2)	1658 (58.8)	19 (50.0)	227 (56.6)
Mode of breast cancer detection	.	.	.	.	.	.	.	.	.
Screen-detected	1024 (46.5)	14 (46.7)	206 (58.2)	936 (47.3)	15 (50.0)	214 (58.3)	823 (48.7)	18 (56.3)	192 (55.5)
Screen-interval detected	275 (12.5)	5 (16.7)	47 (13.3)	254 (12.8)	7 (23.3)	43 (11.7)	222 (13.1)	4 (12.5)	41 (11.8)
Diagnostic-detected	823 (37.4)	10 (33.3)	94 (26.6)	720 (36.4)	8 (26.7)	102 (27.8)	583 (34.5)	10 (31.3)	103 (29.8)
Diagnostic interval-detected	78 (3.5)	1 (3.3)	7 (2.0)	70 (3.5)	0	8 (2.2)	61 (3.6)	0	10 (2.9)
Unknown	1345	2	34	1239	5	42	1131	6	55
Medication use pre-diagnosis [5]	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	1566 (44.2)	17 (53.1)	176 (45.4)	1394 (43.3)	24 (68.6)	192 (46.9)	1215 (43.1)	16 (42.1)	194 (48.4)
Frequent antibiotic user	273 (7.7)	0	27 (7.0)	229 (7.1)	3 (8.6)	33 (8.1)	194 (6.9)	1 (2.6)	34 (8.5)
Statin user, ever	38 (1.1)	10 (31.3)	292 (75.3)	38 (1.2)	9 (25.7)	263 (64.3)	39 (1.4)	5 (13.2)	201 (50.1)
More adherent statin user	18 (0.5)	8 (25)	271 (69.8)	27 (0.8)	5 (14.3)	241 (58.9)	30 (1.1)	5 (13.2)	183 (45.6)
HRT	1293 (36.5)	6 (18.8)	104 (26.8)	1183 (36.8)	11 (31.4)	124 (30.3)	1055 (37.4)	12 (31.6)	143 (35.7)

(table continues for years 4-6)

	Year 4			Year 5			Year 6		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	2,423 (85.4%)	**43 (1.5%)**	**370 (13.0%)**	**2,007 (84.4%)**	**31 (1.3%)**	**341 (14.3%)**	**1,678 (82.0%)**	**35 (1.7%)**	**334 (16.3%)**
Year of diagnosis									
1990-1994	690 (28.5)	7 (16.3)	29 (7.8)	632 (31.5)	5 (16.1)	36 (10.6)	589 (35.1)	3 (8.6)	47 (14.1)
1995-1999	798 (32.9)	10 (23.3)	79 (21.4)	714 (35.6)	9 (29.0)	105 (30.8)	639 (38.1)	15 (42.9)	123 (36.8)
2000-2004	692 (28.6)	17 (39.5)	177 (47.8)	619 (30.8)	17 (54.8)	191 (56.0)	450 (26.8)	17 (48.6)	164 (49.1)
2005-2008	243 (10.0)	9 (20.9)	85 (23)	42 (2.1)	0	9 (2.6)			
Years of follow-up[1]	.	.	.	.	.	.	.	.	.
Mean (SD)	9.4 (3.7)	8 (3.1)	7.6 (2.7)	10.2 (3.5)	8.4 (2.4)	8.6 (2.5)	10.9 (3.3)	9.3 (2.3)	9.5 (2.6)
Median	8.4	7.5	7.1	9.5	8	7.9	10.2	8.3	8.4
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	65.9 (13)	68.6 (10.7)	70.3 (9.9)	67 (13.1)	69.1 (10.6)	70.6 (10)	67.7 (13)	70.9 (10.3)	70.6 (10.3)
21-34	3 (0.1)	0	0	2 (0.1)	0	0	2 (0.1)	0	0
35-44	98 (4)	0	2 (0.5)	62 (3.1)	0	1 (0.3)	41 (2.4)	0	2 (0.6)
45-54	445 (18.4)	4 (9.3)	24 (6.5)	337 (16.8)	2 (6.5)	23 (6.7)	262 (15.6)	3 (8.6)	25 (7.5)
55-64	592 (24.4)	11 (25.6)	86 (23.2)	475 (23.7)	9 (29)	72 (21.1)	406 (24.2)	5 (14.3)	70 (21)
65-74	570 (23.5)	18 (41.9)	125 (33.8)	471 (23.5)	10 (32.3)	125 (36.7)	382 (22.8)	13 (37.1)	109 (32.6)
75+	715 (29.5)	10 (23.3)	133 (35.9)	660 (32.9)	10 (32.3)	120 (35.2)	585 (34.9)	14 (40)	128 (38.3)
Menopausal status	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	695 (28.7)	8 (18.6)	37 (10)	577 (28.7)	4 (12.9)	40 (11.7)	503 (30)	5 (14.3)	45 (13.5)
Post-menopausal	1728 (71.3)	35 (81.4)	333 (90)	1430 (71.3)	27 (87.1)	301 (88.3)	1175 (70)	30 (85.7)	289 (86.5)
Race	.	.	.	.	.	.	.	.	.
White	2171 (89.7)	39 (90.7)	328 (88.6)	1812 (90.4)	28 (90.3)	298 (87.4)	1526 (91.1)	31 (88.6)	287 (85.9)
African American	65 (2.7)	2 (4.7)	9 (2.4)	50 (2.5)	2 (6.5)	9 (2.6)	44 (2.6)	2 (5.7)	11 (3.3)
American Indian/Alaska Native	64 (2.6)	1 (2.3)	12 (3.2)	49 (2.4)	0	14 (4.1)	38 (2.3)	0	16 (4.8)
Asian/Pacific Islander	119 (4.9)	1 (2.3)	20 (5.4)	93 (4.6)	1 (3.2)	19 (5.6)	67 (4)	2 (5.7)	19 (5.7)
Other	0	0	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.3)
Unknown	4	0	0	3	0	0	3	0	0
Ethnicity	.	.	.	.	.	.	.	.	.
Not Hispanic	2313 (95.8)	37 (88.1)	353 (95.4)	1921 (96.1)	29 (93.5)	322 (94.7)	1601 (95.8)	34 (97.1)	317 (95.2)
Hispanic	102 (4.2)	5 (11.9)	17 (4.6)	79 (4.0)	2 (6.5)	18 (5.3)	70 (4.2)	1 (2.9)	16 (4.8)
Unknown	8	1	0	7	0	1	7	0	1

	Year 4			Year 5			Year 6		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	2,423 (85.4%)	**43 (1.5%)**	**370 (13.0%)**	**2,007 (84.4%)**	**31 (1.3%)**	**341 (14.3%)**	**1,678 (82.0%)**	**35 (1.7%)**	**334 (16.3%)**
Education	.	.	.	.	.	.	.	.	.
High school or less	216 (21.7)	6 (31.6)	78 (31.6)	174 (22.6)	6 (40.0)	63 (30.0)	123 (20.7)	9 (40.9)	65 (33.9)
Some college	333 (33.4)	8 (42.1)	90 (36.4)	251 (32.6)	3 (20.0)	80 (38.1)	196 (33.1)	5 (22.7)	66 (34.4)
College or post graduates	447 (44.9)	5 (26.3)	79 (32.0)	346 (44.9)	6 (40.0)	67 (31.9)	274 (46.2)	8 (36.4)	61 (31.8)
Unknown	1427	24	123	1236	16	131	1085	13	142
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.
Mean (SD)	27.4 (5.9)	29.8 (5.9)	30.7 (6.6)	27.3 (5.7)	30.2 (6.1)	30.2 (6.4)	27.2 (5.8)	29.9 (6.7)	30 (6.2)
Median	26.2	29	29.9	26.1	29	29.4	26	28.7	29
<18.5	44 (1.8)	1 (2.3)	2 (0.5)	35 (1.7)	0	4 (1.2)	29 (1.7)	0	4 (1.2)
18.5-24.9	908 (37.6)	8 (18.6)	76 (20.5)	767 (38.3)	5 (16.1)	76 (22.3)	655 (39.1)	6 (17.1)	71 (21.3)
25.0-29.9	808 (33.4)	15 (34.9)	111 (30.0)	674 (33.6)	14 (45.2)	107 (31.4)	558 (33.3)	13 (37.1)	115 (34.4)
30.0-34.9	406 (16.8)	10 (23.3)	96 (25.9)	330 (16.5)	4 (12.9)	79 (23.2)	265 (15.8)	9 (25.7)	76 (22.8)
35+	252 (10.4)	9 (20.9)	85 (23)	197 (9.8)	8 (25.8)	75 (22.0)	167 (10.0)	7 (20.0)	68 (20.4)
Unknown	5	0	0	4	0	0	4	0	0
Smoking status	.	.	.	.	.	.	.	.	.
Current	116 (4.8)	4 (9.3)	20 (5.4)	87 (4.3)	4 (12.9)	17 (5)	61 (3.6)	1 (2.9)	22 (6.6)
Past	117 (4.8)	5 (11.6)	31 (8.4)	61 (3.0)	0	15 (4.4)	38 (2.3)	4 (11.4)	13 (3.9)
Never/unknown	2190 (90.4)	34 (79.1)	319 (86.2)	1859 (92.6)	27 (87.1)	309 (90.6)	1579 (94.1)	30 (85.7)	299 (89.5)
Charlson score [3]	.	.	.	.	.	.	.	.	.
0	1574 (65.0)	19 (44.2)	121 (32.7)	1223 (60.9)	10 (32.3)	98 (28.7)	994 (59.2)	8 (22.9)	97 (29)
1	631 (26.0)	15 (34.9)	110 (29.7)	581 (28.9)	11 (35.5)	108 (31.7)	500 (29.8)	12 (34.3)	98 (29.3)
2+	218 (9.0)	9 (20.9)	139 (37.6)	203 (10.1)	10 (32.3)	135 (39.6)	184 (11.0)	15 (42.9)	139 (41.6)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	3.8 (3.5)	4.2 (2.9)	5.2 (4.5)	3.9 (3.7)	5.5 (4.9)	5 (3.7)	4 (3.7)	4.6 (2.6)	5.2 (3.9)
Median	3	4	4	3	4	4	3	4	5
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	1 (1.3)	0.9 (0.9)	1 (1.4)	0.8 (1.1)	1.1 (1.6)	0.9 (1.1)	0.6 (1.2)	0.7 (0.8)	0.7 (1.3)
Median	1	1	1	1	1	1	0	1	1

	Year 4			Year 5			Year 6		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	2,423 (85.4%)	**43 (1.5%)**	**370 (13.0%)**	**2,007 (84.4%)**	**31 (1.3%)**	**341 (14.3%)**	**1,678 (82.0%)**	**35 (1.7%)**	**334 (16.3%)**
AJCC stage	.	.	.	.	.	.	.	.	.
I	1598 (66.0)	31 (72.1)	266 (71.9)	1342 (66.9)	17 (54.8)	248 (72.7)	1141 (68.0)	18 (51.4)	243 (72.8)
IIA	587 (24.2)	4 (9.3)	71 (19.2)	479 (23.9)	8 (25.8)	64 (18.8)	389 (23.2)	13 (37.1)	60 (18.0)
IIB	238 (9.8)	8 (18.6)	33 (8.9)	186 (9.3)	6 (19.4)	29 (8.5)	148 (8.8)	4 (11.4)	31 (9.3)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	1694 (77.5)	28 (73.7)	270 (82.1)	1423 (78.6)	17 (65.4)	244 (82.2)	1200 (79.3)	19 (61.3)	236 (81.7)
Positive (1-3)	379 (17.3)	9 (23.7)	42 (12.8)	296 (16.4)	7 (26.9)	44 (14.8)	243 (16.1)	11 (35.5)	41 (14.2)
Positive (4+)	111 (5.1)	1 (2.6)	17 (5.2)	89 (4.9)	2 (7.7)	9 (3.0)	69 (4.6)	1 (3.2)	12 (4.2)
Positive (unknown #)	2 (0.1)	0	0	2 (0.1)	0	0	2 (0.1)	0	0
Unknown	237	5	41	197	5	44	164	4	45
ER/PR status	.	.	.	.	.	.	.	.	.
ER-/PR-	321 (13.2)	5 (11.6)	47 (12.7)	261 (13.0)	4 (12.9)	42 (12.3)	205 (12.2)	5 (14.3)	47 (14.1)
ER+/PR-	242 (10.0)	5 (11.6)	32 (8.6)	217 (10.8)	3 (9.7)	31 (9.1)	200 (11.9)	4 (11.4)	27 (8.1)
ER-/PR+	37 (1.5)	1 (2.3)	2 (0.5)	34 (1.7)	0	4 (1.2)	30 (1.8)	1 (2.9)	5 (1.5)
ER+/PR+	1676 (69.2)	31 (72.1)	272 (73.5)	1368 (68.2)	23 (74.2)	245 (71.8)	1130 (67.3)	23 (65.7)	237 (71.0)
ER & PR unknown	147 (6.1)	1 (2.3)	17 (4.6)	127 (6.3)	1 (3.2)	19 (5.6)	113 (6.7)	2 (5.7)	18 (5.4)
Tumor size	.	.	.	.	.	.	.	.	.
≤ 2 cm	1868 (77.1)	33 (76.7)	297 (80.3)	1556 (77.5)	21 (67.7)	277 (81.2)	1313 (78.2)	26 (74.3)	272 (81.4)
> 2 cm	554 (22.9)	10 (23.3)	73 (19.7)	451 (22.5)	10 (32.3)	64 (18.8)	365 (21.8)	9 (25.7)	62 (18.6)
Unknown	1	0	0						
HER2 test result[4]	.	.	.	.	.	.	.	.	.
Test done	942 (74.3)	27 (90.0)	256 (85.6)	673 (71.2)	18 (81.8)	195 (75.6)	462 (65.4)	17 (77.3)	165 (70.5)
Positive/borderline	149 (15.8)	3 (11.1)	35 (13.7)	101 (15.0)	3 (16.7)	21 (10.8)	67 (14.5)	0	18 (10.9)
Negative	792 (84.1)	24 (88.9)	220 (85.9)	571 (84.8)	15 (83.3)	173 (88.7)	394 (85.3)	17 (100)	147 (89.1)
No result	1 (0.1)	0	1 (0.4)	1 (0.1)	0	1 (0.5)	1 (0.2)	0	0
Surgical procedure	.	.	.	.	.	.	.	.	.
Mastectomy +/- radiation	850 (35.1)	13 (30.2)	128 (34.6)	712 (35.5)	9 (29.0)	110 (32.3)	589 (35.1)	13 (37.1)	116 (34.7)
BCS + radiation	1311 (54.1)	26 (60.5)	209 (56.5)	1102 (54.9)	16 (51.6)	197 (57.8)	935 (55.7)	16 (45.7)	188 (56.3)
BCS	262 (10.8)	4 (9.3)	33 (8.9)	193 (9.6)	6 (19.4)	34 (10)	154 (9.2)	6 (17.1)	30 (9.0)

	Year 4			Year 5			Year 6		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	2,423 (85.4%)	**43 (1.5%)**	**370 (13.0%)**	**2,007 (84.4%)**	**31 (1.3%)**	**341 (14.3%)**	**1,678 (82.0%)**	**35 (1.7%)**	**334 (16.3%)**
Other treatment	.	.	.	.	.	.	.	.	.
Chemotherapy	772 (31.9)	10 (23.3)	88 (23.8)	620 (30.9)	9 (29)	84 (24.6)	506 (30.2)	10 (28.6)	87 (26.0)
Completed course	683 (88.5)	8 (80.0)	76 (86.4)	554 (89.4)	7 (77.8)	74 (88.1)	456 (90.1)	8 (80)	75 (86.2)
Endocrine therapy [3]	1416 (58.4)	23 (53.5)	203 (54.9)	1167 (58.1)	21 (67.7)	178 (52.2)	956 (57.0)	22 (62.9)	183 (54.8)
Mode of breast cancer detection	.	.	.	.	.	.	.	.	.
Screen-detected	675 (48.6)	15 (53.6)	169 (54.9)	509 (48.1)	10 (45.5)	149 (55)	386 (47.7)	12 (46.2)	128 (51.8)
Screen interval-detected	190 (13.7)	6 (21.4)	30 (9.7)	142 (13.4)	3 (13.6)	35 (12.9)	110 (13.6)	2 (7.7)	31 (12.6)
Diagnostic-detected	472 (34.0)	7 (25)	99 (32.1)	363 (34.3)	7 (31.8)	77 (28.4)	277 (34.2)	12 (46.2)	78 (31.6)
Diagnostic-interval detected	53 (3.8)	0	10 (3.2)	44 (4.2)	2 (9.1)	10 (3.7)	37 (4.6)	0	10 (4)
Unknown	1033	15	62	949	9	70	868	9	87
Medication use pre-diagnosis[5]	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	1038 (42.8)	21 (48.8)	174 (47)	863 (43)	16 (51.6)	157 (46)	727 (43.3)	15 (42.9)	153 (45.8)
Frequent antibiotic user	162 (6.7)	2 (4.7)	31 (8.4)	136 (6.8)	3 (9.7)	27 (7.9)	111 (6.6)	2 (5.7)	28 (8.4)
Statin user, ever	26 (1.1)	4 (9.3)	146 (39.5)	19 (0.9)	2 (6.5)	103 (30.2)	10 (0.6)	4 (11.4)	74 (22.2)
More adherent statin user	20 (0.8)	4 (9.3)	134 (36.2)	15 (0.7)	2 (6.5)	97 (28.4)	9 (0.5)	2 (5.7)	69 (20.7)
HRT	949 (39.2)	14 (32.6)	138 (37.3)	808 (40.3)	14 (45.2)	147 (43.1)	682 (40.6)	16 (45.7)	153 (45.8)

(table continues for years 7-9)

	Year 7			Year 8			Year 9		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	1,355 (79.2%)	**25 (1.5%)**	**331 (19.3%)**	**1,036 (79.8%)**	**18 (1.4%)**	**244 (18.8%)**	**845 (76.4%)**	**20 (1.8%)**	**241 (21.8%)**
Year of diagnosis									
1990-1994	541 (39.9)	4 (16.0)	53 (16.0)	500 (48.3)	2 (11.1)	54 (22.1)	447 (52.9)	7 (35.0)	66 (27.4)
1995-1999	547 (40.4)	14 (56.0)	152 (45.9)	478 (46.1)	13 (72.2)	167 (68.4)	392 (46.4)	13 (65.0)	172 (71.4)
2000-2004	267 (19.7)	7 (28.0)	126 (38.1)	58 (5.6)	3 (16.7)	23 (9.4)	6 (0.7)	0	3 (1.2)
2005-2008	.	.	.						
Years of follow-up[1]				.	.	.	.	.	.
Mean (SD)	11.7 (3.1)	10.2 (1.8)	10.2 (2.5)	12.7 (2.8)	11.3 (1.7)	11.6 (2.2)	13.3 (2.6)	12.8 (2.7)	12.3 (2.0)
Median	11.2	10.6	9.6	12.2	11.4	11.2	12.9	11.9	12.1
Age per-interval, years [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	68.4 (13.1)	68.4 (13.1)	71.8 (10.1)	69 (13)	67.2 (11.5)	72 (10.7)	69.4 (12.9)	69.2 (10.8)	71.8 (10.4)
21-34	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)	0	0
35-44	25 (1.8)	0	2 (0.6)	15 (1.4)	0	1 (0.4)	10 (1.2)	0	0
45-54	207 (15.3)	4 (16.0)	19 (5.7)	150 (14.5)	2 (11.1)	16 (6.6)	120 (14.2)	2 (10)	11 (4.6)
55-64	319 (23.5)	8 (32.0)	58 (17.5)	233 (22.5)	6 (33.3)	49 (20.1)	186 (22)	4 (20)	57 (23.7)
65-74	310 (22.9)	3 (12.0)	103 (31.1)	244 (23.6)	6 (33.3)	60 (24.6)	190 (22.5)	7 (35)	60 (24.9)
75+	493 (36.4)	10 (40.0)	149 (45)	393 (37.9)	4 (22.2)	118 (48.4)	338 (40)	7 (35)	113 (46.9)
Menopausal status	.	.	.	.	.	.	.	.	.
Peri- or premenopausal	421 (31.1)	10 (40.0)	46 (13.9)	329 (31.8)	6 (33.3)	49 (20.1)	282 (33.4)	5 (25)	54 (22.4)
Post-menopausal	934 (68.9)	15 (60.0)	285 (86.1)	707 (68.2)	12 (66.7)	195 (79.9)	563 (66.6)	15 (75)	187 (77.6)
Race	.	.	.	.	.	.	.	.	.
White	1231 (91)	19 (76.0)	291 (87.9)	936 (90.5)	16 (88.9)	221 (90.6)	762 (90.4)	19 (95.0)	220 (91.3)
African American	36 (2.7)	2 (8.0)	8 (2.4)	27 (2.6)	1 (5.6)	6 (2.5)	23 (2.7)	1 (5.0)	6 (2.5)
American Indian/Alaska Native	32 (2.4)	1 (4.0)	15 (4.5)	28 (2.7)	0	8 (3.3)	24 (2.8)	0	5 (2.1)
Asian/Pacific Islander	54 (4.0)	3 (12.0)	16 (4.8)	43 (4.2)	1 (5.6)	8 (3.3)	34 (4)	0	9 (3.7)
Other	0	0	1 (0.3)	0	0	1 (0.4)	0	0	1 (0.4)
Unknown	2	0	0	2	0	0	2	0	0
Ethnicity	.	.	.	.	.	.	.	.	.
Not Hispanic	1294 (95.9)	22 (88.0)	315 (95.5)	993 (96.4)	16 (88.9)	234 (96.3)	806 (96.1)	20 (100)	231 (96.3)
Hispanic	55 (4.1)	3 (12.0)	15 (4.5)	37 (3.6)	2 (11.1)	9 (3.7)	33 (3.9)	0	9 (3.8)
Unknown	6	0	1	6	0	1	6	0	1

	Year 7			Year 8			Year 9		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	1,355 (79.2%)	25 (1.5%)	331 (19.3%)	1,036 (79.8%)	18 (1.4%)	244 (18.8%)	845 (76.4%)	20 (1.8%)	241 (21.8%)
Education	.	.	.	.	.	.	.	.	.
High school or less	92 (21.8)	5 (38.5)	68 (37.4)	55 (22.2)	2 (20)	44 (44.9)	38 (20.4)	0	32 (41)
Some college	141 (33.4)	1 (7.7)	64 (35.2)	80 (32.3)	4 (40)	24 (24.5)	59 (31.7)	3 (75.0)	21 (26.9)
College or post graduates	189 (44.8)	7 (53.8)	50 (27.5)	113 (45.6)	4 (40)	30 (30.6)	89 (47.8)	1 (25.0)	25 (32.1)
Unknown	933	12	149	788	8	146	659	16	163
Body mass index (kg/m^2)	.	.	.	.	.	.	.	.	.
Mean (SD)	27.2 (5.8)	28.2 (5.8)	29.6 (5.8)	27.1 (5.8)	29.3 (6)	29.2 (5.7)	26.8 (5.4)	32.2 (10.0)	29.6 (6.2)
Median	25.9	26.7	28.9	25.8	28.1	28.5	25.7	30.6	28.8
<18.5	20 (1.5)	1 (4.0)	4 (1.2)	17 (1.6)	0	3 (1.2)	15 (1.8)	0	1 (0.4)
18.5-24.9	543 (40.2)	8 (32.0)	71 (21.5)	412 (39.9)	3 (16.7)	65 (26.6)	346 (41.1)	4 (20.0)	65 (27)
25.0-29.9	452 (33.5)	7 (28.0)	113 (34.1)	349 (33.8)	9 (50)	72 (29.5)	286 (34)	5 (25.0)	67 (27.8)
30.0-34.9	199 (14.7)	5 (20.0)	82 (24.8)	152 (14.7)	2 (11.1)	62 (25.4)	123 (14.6)	6 (30.0)	58 (24.1)
35+	137 (10.1)	4 (16.0)	61 (18.4)	102 (9.9)	4 (22.2)	42 (17.2)	71 (8.4)	5 (25.0)	50 (20.7)
Unknown	4	0	0	4	0	0	4	0	0
Smoking status	.	.	.	.	.	.	.	.	.
Current	39 (2.9)	2 (8.0)	18 (5.4)	23 (2.2)	1 (5.6)	11 (4.5)	17 (2)	0	5 (2.1)
Past	33 (2.4)	0	17 (5.1)	29 (2.8)	0	15 (6.1)	22 (2.6)	2 (10.0)	16 (6.6)
Never/unknown	1283 (94.7)	23 (92.0)	296 (89.4)	984 (95)	17 (94.4)	218 (89.3)	806 (95.4)	18 (90.0)	220 (91.3)
Charlson score [3]	.	.	.	.	.	.	.	.	.
0	774 (57.1)	5 (20.0)	81 (24.5)	561 (54.2)	4 (22.2)	65 (26.6)	442 (52.3)	9 (45.0)	62 (25.7)
1	423 (31.2)	9 (36.0)	108 (32.6)	338 (32.6)	8 (44.4)	74 (30.3)	292 (34.6)	4 (20.0)	75 (31.1)
2+	158 (11.7)	11 (44.0)	142 (42.9)	137 (13.2)	6 (33.3)	105 (43)	111 (13.1)	7 (35.0)	104 (43.2)
# PCP visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	3.9 (3.7)	5.7 (4.3)	5.2 (3.8)	4 (3.8)	3.4 (2.9)	5 (3.6)	4 (3.6)	5.4 (4.2)	5.4 (4.9)
Median	3	5	4	3	3	4	3	5	4
# ONC visits per-interval [2]	.	.	.	.	.	.	.	.	.
Mean (SD)	0.4 (1)	0.4 (1)	0.5 (1.6)	0.3 (0.9)	0.3 (0.6)	0.3 (0.9)	0.3 (0.9)	0.6 (1.3)	0.3 (0.9)
Median	0	0	0	0	0	0	0	0	0

	Year 7			Year 8			Year 9		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**	**Nonuser**	**Less Adherent Statin User**	**More Adherent Statin User**
	1,355 (79.2%)	**25 (1.5%)**	**331 (19.3%)**	**1,036 (79.8%)**	**18 (1.4%)**	**244 (18.8%)**	**845 (76.4%)**	**20 (1.8%)**	**241 (21.8%)**
AJCC stage	.	.	.	.	.	.	.	.	.
I	936 (69.1)	16 (64.0)	238 (71.9)	724 (69.9)	11 (61.1)	173 (70.9)	607 (71.8)	12 (60.0)	171 (71)
IIA	302 (22.3)	5 (20.0)	65 (19.6)	232 (22.4)	5 (27.8)	48 (19.7)	181 (21.4)	7 (35.0)	47 (19.5)
IIB	117 (8.6)	4 (16.0)	28 (8.5)	80 (7.7)	2 (11.1)	23 (9.4)	57 (6.7)	1 (5.0)	23 (9.5)
Lymph node status	.	.	.	.	.	.	.	.	.
Negative	975 (79.9)	16 (72.7)	235 (80.8)	749 (80.3)	14 (82.4)	162 (77.9)	628 (82.4)	16 (88.9)	164 (79.2)
Positive (1-3)	185 (15.2)	6 (27.3)	45 (15.5)	139 (14.9)	3 (17.6)	40 (19.2)	105 (13.8)	1 (5.6)	38 (18.4)
Positive (4+)	59 (4.8)	0	11 (3.8)	43 (4.6)	0	6 (2.9)	28 (3.7)	1 (5.6)	4 (1.9)
Positive (unknown #)	2 (0.2)	0	0	2 (0.2)	0	0	1 (0.1)	0	1 (0.5)
Unknown	134	3	40	103	1	36	83	2	34
ER/PR status	.	.	.	.	.	.	.	.	.
ER-/PR-	170 (12.5)	5 (20.0)	42 (12.7)	132 (12.7)	2 (11.1)	34 (13.9)	113 (13.4)	2 (10.0)	34 (14.1)
ER+/PR-	161 (11.9)	1 (4.0)	33 (10)	119 (11.5)	1 (5.6)	24 (9.8)	96 (11.4)	0	23 (9.5)
ER-/PR+	24 (1.8)	1 (4.0)	6 (1.8)	22 (2.1)	0	4 (1.6)	16 (1.9)	0	6 (2.5)
ER+/PR+	899 (66.3)	17 (68.0)	234 (70.7)	685 (66.1)	14 (77.8)	169 (69.3)	551 (65.2)	17 (85.0)	164 (68.0)
ER & PR unknown	101 (7.5)	1 (4.0)	16 (4.8)	78 (7.5)	1 (5.6)	13 (5.3)	69 (8.2)	1 (5.0)	14 (5.8)
Tumor size	.	.	.	.	.	.	.	.	.
≤ 2 cm	1071 (79.0)	18 (72.0)	270 (81.6)	832 (80.3)	12 (66.7)	198 (81.1)	685 (81.1)	13 (65)	195 (80.9)
> 2 cm	284 (21.0)	7 (28.0)	61 (18.4)	204 (19.7)	6 (33.3)	46 (18.9)	160 (18.9)	7 (35)	46 (19.1)
Unknown	0	0	0	0	0	0	0	0	0
HER2 test result[4]	.	.	.	.	.	.	.	.	.
Test done	277 (56.8)	7 (63.6)	128 (61.2)	71 (27.6)	2 (33.3)	28 (26.7)	17 (10.5)	1 (25)	7 (9.3)
Positive/borderline	40 (14.4)	1 (14.3)	13 (10.2)	11 (15.5)	1 (50.0)	2 (7.1)	7 (41.2)	0	1 (14.3)
Negative	236 (85.2)	6 (85.7)	115 (89.8)	60 (84.5)	1 (50.0)	26 (92.9)	10 (58.8)	1 (100)	6 (85.7)
No result	1 (0.4)	0	0	0	0	0	0	0	0
Surgical procedure	.	.	.	.	.	.	.	.	.
Mastectomy +/- radiation	465 (34.3)	8 (32.0)	113 (34.1)	347 (33.5)	5 (27.8)	83 (34.0)	280 (33.1)	7 (35.0)	78 (32.4)
BCS + radiation	771 (56.9)	14 (56.0)	187 (56.5)	616 (59.5)	12 (66.7)	136 (55.7)	515 (60.9)	9 (45.0)	144 (59.8)
BCS	759 (98.4)	14 (100)	185 (98.9)	606 (98.4)	12 (100)	134 (98.5)	506 (98.3)	9 (100)	143 (99.3)

	Year 7			Year 8			Year 9		
	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User	Nonuser	Less Adherent Statin User	More Adherent Statin User
	1,355 (79.2%)	**25 (1.5%)**	**331 (19.3%)**	**1,036 (79.8%)**	**18 (1.4%)**	**244 (18.8%)**	**845 (76.4%)**	**20 (1.8%)**	**241 (21.8%)**
Other treatment	.	.	.	.	.	.	.	.	.
Chemotherapy	399 (29.4)	9 (36.0)	78 (23.6)	285 (27.5)	6 (33.3)	63 (25.8)	223 (26.4)	5 (25.0)	64 (26.6)
Completed course	359 (90.0)	9 (100)	66 (84.6)	254 (89.1)	6 (100)	54 (85.7)	200 (89.7)	3 (60.0)	56 (87.5)
Endocrine therapy [3]	750 (55.4)	12 (48.0)	197 (59.5)	571 (55.1)	10 (55.6)	141 (57.8)	450 (53.3)	13 (65.0)	137 (56.8)
Mode of breast cancer detection	.	.	.	.	.	.	.	.	.
Screen-detected	267 (46.1)	7 (38.9)	112 (49.6)	159 (46.8)	5 (50.0)	62 (48.1)	107 (45.7)	2 (22.2)	48 (47.5)
Screen interval-detected	83 (14.3)	1 (5.6)	27 (11.9)	46 (13.5)	2 (20.0)	14 (10.9)	32 (13.7)	2 (22.2)	12 (11.9)
Diagnostic-detected	202 (34.9)	7 (38.9)	77 (34.1)	119 (35.0)	3 (30.0)	48 (37.2)	86 (36.8)	4 (44.4)	35 (34.7)
Diagnostic-interval detected	27 (4.7)	3 (16.7)	10 (4.4)	16 (4.7)	0	5 (3.9)	9 (3.8)	1 (11.1)	6 (5.9)
Unknown	776	7	105	696	8	115	611	11	140
Medication use pre-diagnosis[5]	.	.	.	.	.	.	.	.	.
Antibiotic user, ever	591 (43.6)	14 (56.0)	149 (45)	459 (44.3)	4 (22.2)	118 (48.4)	374 (44.3)	13 (65.0)	119 (49.4)
Frequent antibiotic user	87 (6.4)	5 (20.0)	25 (7.6)	75 (7.2)	0	21 (8.6)	61 (7.2)	1 (5.0)	22 (9.1)
Statin user, ever	6 (0.4)	2 (8.0)	56 (16.9)	4 (0.4)	1 (5.6)	26 (10.7)	2 (0.2)	0	22 (9.1)
More adherent statin user	5 (0.4)	2 (8.0)	52 (15.7)	4 (0.4)	0	24 (9.8)	2 (0.2)	0	19 (7.9)
HRT	536 (39.6)	13 (52.0)	161 (48.6)	395 (38.1)	6 (33.3)	111 (45.5)	318 (37.6)	8 (40.0)	113 (46.9)

(table continues for year 10)

	Year 10		
	Nonuser	Less Adherent Statin User	More Adherent Statin User
	691 (75.0%)	11 (1.2%)	219 (23.8%)
Year of diagnosis			
1990-1994	410 (59.3)	5 (45.5)	81 (37.0)
1995-1999	281 (40.7)	6 (54.5)	138 (63.0)
2000-2004			
2005-2008			
Years of follow-up[1]	.	.	.
Mean (SD)	13.9 (2.4)	12.8 (1.1)	13.1 (1.9)
Median	13.4	13.2	12.8
Age per-interval, years [2]	.	.	.
Mean (SD)	70.1 (12.7)	74.3 (9.9)	72.1 (10.2)
21-34	0	0	0
35-44	7 (1.0)	0	0
45-54	86 (12.4)	0	10 (4.6)
55-64	162 (23.4)	2 (18.2)	44 (20.1)
65-74	144 (20.8)	4 (36.4)	64 (29.2)
75+	292 (42.3)	5 (45.5)	101 (46.1)
Menopausal status	.	.	.
Peri- or premenopausal	235 (34.0)	2 (18.2)	51 (23.3)
Post-menopausal	456 (66.0)	9 (81.8)	168 (76.7)
Race	.	.	.
White	619 (89.8)	10 (90.9)	201 (91.8)
African American	21 (3.0)	1 (9.1)	6 (2.7)
American Indian/Alaska Native	21 (3.0)	0	3 (1.4)
Asian/Pacific Islander	28 (4.1)	0	9 (4.1)
Other	0	0	0
Unknown	2	0	0
Ethnicity	.	.	.
Not Hispanic	656 (95.8)	11 (100)	213 (97.7)
Hispanic	29 (4.2)	0	5 (2.3)
Unknown	6	0	1

	Year 10		
	Nonuser	Less Adherent Statin User	More Adherent Statin User
	691 (75.0%)	11 (1.2%)	219 (23.8%)
Education	.	.	.
High school or less	23 (19.2)	1 (100)	21 (43.8)
Some college	38 (31.7)	0	14 (29.2)
College or post graduates	59 (49.2)	0	13 (27.1)
Unknown	571	10	171
Body mass index (kg/m^2)	.	.	.
Mean (SD)	26.8 (5.4)	31.5 (7)	29.5 (6.2)
Median	25.7	31	28.6
<18.5	13 (1.9)	0	0
18.5-24.9	280 (40.6)	2 (18.2)	59 (26.9)
25.0-29.9	241 (35.0)	3 (27.3)	68 (31.1)
30.0-34.9	95 (13.8)	3 (27.3)	50 (22.8)
35+	60 (8.7)	3 (27.3)	42 (19.2)
Unknown	2	0	0
Smoking status	.	.	.
Current	13 (1.9)	0	3 (1.4)
Past	13 (1.9)	0	12 (5.5)
Never/unknown	665 (96.2)	11 (100)	204 (93.2)
Charlson score [3]	.	.	.
0	350 (50.7)	1 (9.1)	55 (25.1)
1	248 (35.9)	3 (27.3)	76 (34.7)
2+	93 (13.5)	7 (63.6)	88 (40.2)
# PCP visits per-interval [2]	.	.	.
Mean (SD)	4.1 (3.7)	8.5 (5.8)	5 (4.3)
Median	3	8	4
# ONC visits per-interval [2]	.	.	.
Mean (SD)	0.3 (1.0)	0.3 (0.5)	0.2 (0.4)
Median	0	0	0

	Year 10		
	Nonuser	**Less Adherent Statin User**	**More Adherent Statin User**
	691 (75.0%)	**11 (1.2%)**	**219 (23.8%)**
AJCC stage	.	.	.
I	507 (73.4)	9 (81.8)	157 (71.7)
IIA	138 (20)	2 (18.2)	45 (20.5)
IIB	46 (6.7)	0	17 (7.8)
Lymph node status	.	.	.
Negative	529 (84.4)	7 (87.5)	157 (81.3)
Positive (1-3)	78 (12.4)	1 (12.5)	29 (15)
Positive (4+)	20 (3.2)	0	6 (3.1)
Positive (unknown #)	0	0	1 (0.5)
Unknown	64	3	26
ER/PR status	.	.	.
ER-/PR-	100 (14.5)	0	28 (12.8)
ER+/PR-	81 (11.7)	0	21 (9.6)
ER-/PR+	15 (2.2)	0	7 (3.2)
ER+/PR+	437 (63.2)	10 (90.9)	148 (67.6)
ER & PR unknown	58 (8.4)	1 (9.1)	15 (6.8)
Tumor size	.	.	.
≤ 2 cm	561 (81.2)	10 (90.9)	179 (81.7)
> 2 cm	130 (18.8)	1 (9.1)	40 (18.3)
Unknown	0	0	0
HER2 test result[4]	.	.	.
Test done	5 (7.6)	0	2 (5.9)
Positive/borderline	3 (60)	0	0
Negative	2 (40)	0	2 (100)
No result	0	0	0
Surgical procedure	.	.	.
Mastectomy +/- radiation	229 (33.1)	2 (18.2)	76 (34.7)
BCS + radiation	425 (61.5)	9 (81.8)	131 (59.8)
BCS	37 (5.4)	0	12 (5.5)

	Year 10		
	Nonuser	Less Adherent Statin User	More Adherent Statin User
	691 (75.0%)	11 (1.2%)	219 (23.8%)
Other treatment	.	.	.
Chemotherapy	181 (26.2)	1 (9.1)	54 (24.7)
Completed course	160 (88.4)	1 (100)	46 (85.2)
Endocrine therapy [3]	345 (49.9)	9 (81.8)	121 (55.3)
Mode of breast cancer detection	.	.	.
Screen-detected	60 (43.5)	1 (50.0)	30 (46.9)
Screen-interval detected	24 (17.4)	1 (50.0)	5 (7.8)
Diagnostic-detected	48 (34.8)	0	24 (37.5)
Diagnostic interval-detected	6 (4.3)	0	5 (7.8)
Unknown	553	9	155
Medication use pre-diagnosis[5]	.	.	.
Antibiotic user, ever	305 (44.1)	5 (45.5)	103 (47.0)
Frequent antibiotic user	52 (7.5)	2 (18.2)	16 (7.3)
Statin user, ever	1 (0.1)	1 (9.1)	14 (6.4)
More adherent statin user	1 (0.1)	1 (9.1)	11 (5.0)
HRT	249 (36)	4 (36.4)	96 (43.8)

Abbreviations: SD=standard deviation; AJCC=American Joint Committee on Cancer; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; BCS=breast conserving surgery; PCP=primary care physician; ONC=oncology; HRT=hormone replacement therapy

*Characteristics at diagnosis date for initial breast cancer, unless otherwise noted; 0.7% of surveillance mammography included breast MRI

[1] Follow-up extended from diagnosis date through first of death, disenrollment, diagnosis of a second breast cancer event (i.e., recurrence or 2nd primary), or end of study (date of chart abstraction).
[2]Time-varying per-interval: variable exposure was ascertained during each surveillance year; variable status did not carry forward to the subsequent surveillance year.

[3]Time-varying ever-never: variable exposure was ascertained throughout the entire study period; once the subject mets the variable definition for use, she was included in that category and remained there until the end of follow-up; subjects must meet the variable definition for at least 8 months of the surveillance year to be included in that exposure category for analyses; otherwise, they were included in the exposure category beginning with the next subsequent surveillance year; if the variable included multiple categories (e.g., Charlson, ever-never medication use), subjects were only allowed to transition from a lower to a higher category over time.
[4]HER2 status ascertained 1998+ and abstracted from the medical record
[5]Ascertained in 12 months prior to the initial breast cancer diagnosis

Table 8. Odds ratios and 95% confidence intervals relating per-interval[1] medication use to receipt of surveillance mammography

	Unadjusted OR (95% CI)	p-value	Adjusted OR[2] (95% CI)	p-value
Antibiotics				
Nonuser	1.00 (Referent)		1.00 (Referent)	
Infrequent User	0.98 (0.91-1.04)	0.554	0.99 (0.93-1.05)	0.707
Frequent User	0.91 (0.83-1.00)	0.044	0.93 (0.84-1.02)	0.120
Statins				
Nonuser	1.00 (Referent)		1.00 (Referent)	
Less Adherent User	0.84 (0.69-1.06)	0.147	1.07 (0.84-1.35)	0.603
More Adherent User	0.81 (0.74-0.89)	<0.001	1.15 (1.03-1.28)	0.011

Abbreviations: OR=odds ratio; 95% CI=95% confidence interval
*0.7% of surveillance mammography includes breast MRI

[1] Time-varying per-interval: exposure was ascertained during each 12-month surveillance year; exposure status did not carry forward to the subsequent surveillance year.

[2]GEE model adjusted for: age per-interval (18-34, 35-44, 45-54, 55-64, 65-74, 75+ years), surveillance year since completion of treatment (linear continuous), diagnosis year (1990-1994, 1995-1999, 2000-2004, 2005-2008), AJCC stage (I, IIA, IIB), hormone receptor status (estrogen receptor [ER] negative/progesterone receptor [PR] negative, ER positive/PR negative, ER negative/PR positive, ER positive/PR positive), primary treatment for the initial breast cancer (mastectomy, breast conserving surgery plus radiation, breast conserving surgery without radiation), endocrine therapy for the initial breast cancer (yes/no, time-varying ever-never), 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 score (0, 1, 2+, time-varying ever-never), number of primary care visits per-interval (linear continuous, time-varying per-interval); number of oncology visits per-interval (linear continuous, time-varying per-interval).

Table 9. Adjusted odds ratios and 95% confidence intervals relating patient characteristics to receipt of surveillance mammography

	Adjusted OR (95% CI)[1]
Age per-interval[2], years	
21-34	0.50 (0.28-0.87)
35-44	0.91 (0.71-1.15)
45-54	1.01 (0.88-1.16)
55-64	1.00 (Referent)
65-74	1.06 (0.94-1.20)
75+	0.77 (0.68-0.88)
Charlson score3	
0	1.00 (Referent)
1	0.80 (0.73-0.87)
2+	0.67 (0.59-0.76)
# PCP visits per-interval[2]	0.99 (0.98-0.99)
# ONC visits per-interval[2]	1.03 (1.01-1.06)
Body mass index (kg/m2) at diagnosis	
<18.5	0.68 (0.46-1.02)
18.5-24.9	1.00 (Referent)
25.0-29.9	1.03 (0.93-1.16)
30.0-34.9	0.95 (0.83-1.09)
35+	0.90 (0.78-1.05)
Menopausal status at diagnosis	
Peri- or pre-menopausal	0.91 (0.77-1.07)
Post-menopausal	1.00 (Referent)
Smoking status at diagnosis	
Current	0.83 (0.69-1.01)
Past	1.04 (0.86-1.26)
Never/unknown	1.00 (Referent)

(table continues on next page)

	Adjusted OR (95% CI)[1]
AJCC stage	
I	1.00 (Referent)
IIA	0.83 (0.74-0.93)
IIB	0.87 (0.74-1.04)
ER/PR status	
ER-/PR-	1.19 (1.03-1.39)
ER+/PR-	0.90 (0.77-1.06)
ER-/PR+	0.84 (0.55-1.28)
ER+/PR+	1.00 (Referent)
ER & PR unknown	0.97 (0.79-1.19)
Surgical procedure	
Mastectomy +/- radiation	0.60 (0.53-0.66)
BCS + radiation	1.00 (Referent)
BCS	0.64 (0.55-0.74)
Endocrine therapy[3]	1.32 (1.19-1.47)

Abbreviations: OR=odds ratio; 95% CI=95% confidence interval; AJCC= American Joint Committee on Cancer; PCP=primary care physician; ONC=oncology; ER=estrogen receptor; PR=progesterone receptor; BCS=breast conserving surgery

*0.7% of surveillance mammography includes breast MRI

[1]Adjusted by medication use (infrequent antibiotic user, frequent antibiotic user, less adherent statin user, more adherent statin user) surveillance year and year of diagnosis in addition to all other variables in the table.
[2] Time-varying per-interval: exposure was ascertained during each 12-month surveillance year; exposure status did not carry forward to the subsequent surveillance year.
[3]Time-varying ever-never: variable exposure was ascertained throughout the entire study period; once the subject met the variable definition for use, she was included in that category and remained there until the end of follow-up.

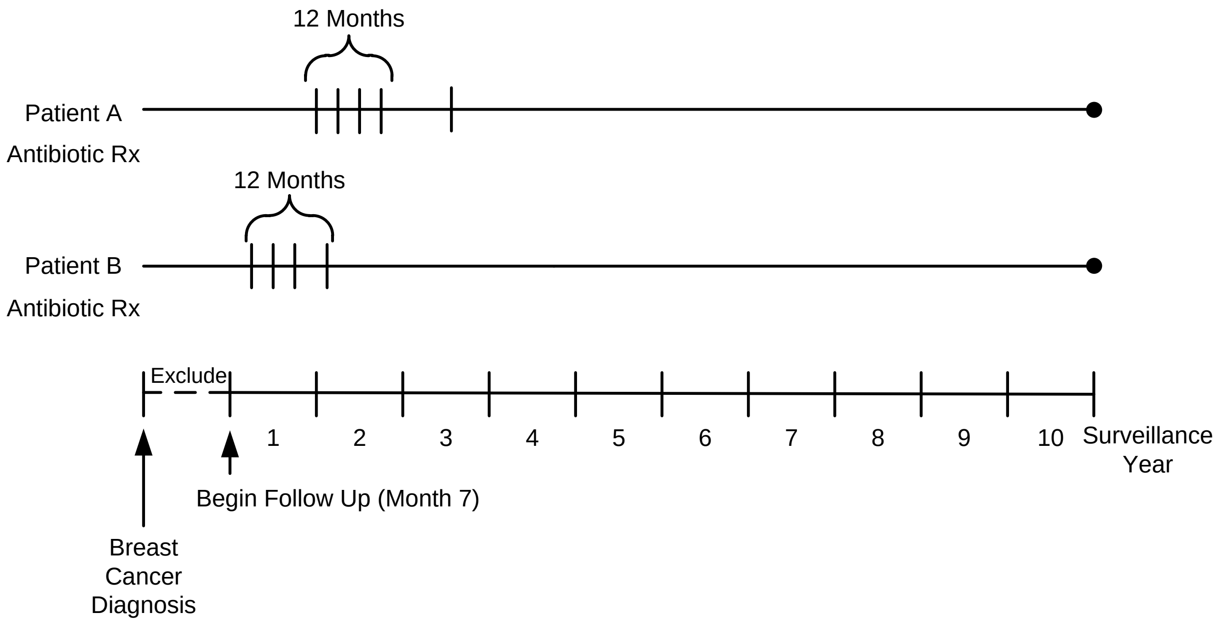

Figure 3. Schematic of per-interval exposure ascertainment

Illustrative example

- Scenario 1: Patient A fills 0 antibiotic prescriptions (Rx's) in year 1; 4 antibiotic Rx's in year 2; 1 antibiotic Rx in year 3; then 0 for all remaining surveillance years. Patient A is a nonuser in year1, a frequent user in year 2, an infrequent user in year 3, and a nonuser again in years 4-10.
- Scenario 2: Patient B fills 4 antibiotic Rx's in a 12-month window so she meets the definition for a frequent antibiotic user. Patient B filled 3 of the Rx's in year 1 and 1 of the Rx's in year 2. Patient B is an infrequent user in year 1 and a frequent user in year 2.

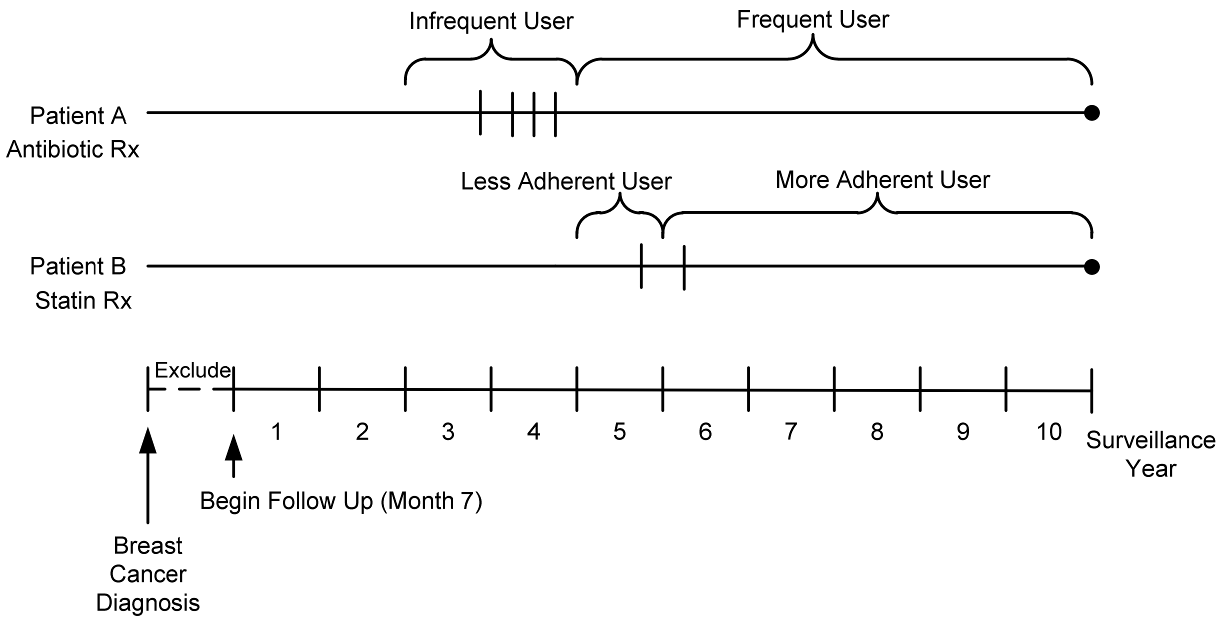

Figure 4. Schematic of ever-never exposure ascertainment.

- Scenario 1: Patient A fills 4 antibiotic prescriptions (Rx's) in a 12-month window so she meets the definition for a frequent antibiotic user. Patient A filled 1 of the Rx's in year 3 and 3 of the Rx's in year 4. She meets the definition for frequent antibiotic use at month 10 of year 4. Since she meets the exposure definition for frequent use only 2 months of year 4, she is classified as a frequent antibiotic user beginning in year 5. So Patient A is an antibiotic nonuser in years 1 and 2, an infrequent user in years 3 and 4, and a frequent user in year 5; she remains a frequent user for all subsequent surveillance years.

- Scenario 2: Patient B fills 2 statin Rx's in a 6-month window so she meets the definition for more adherent statin use. Patient B filled 1 of the statin Rx's in year 5 and 1 of them in year 6. She meets the definition for more adherent statin use at month 3 of year 6. Since she meets the exposure definition for more adherent use for at least 8 months of the surveillance year, she is classified as a more adherent statin user beginning in year 6. So Patient B is a statin nonuser in years 1-4, a less adherent statin user in year 5, and a more adherent statin user in year 6; she remains a more adherent statin user for all subsequent surveillance years.

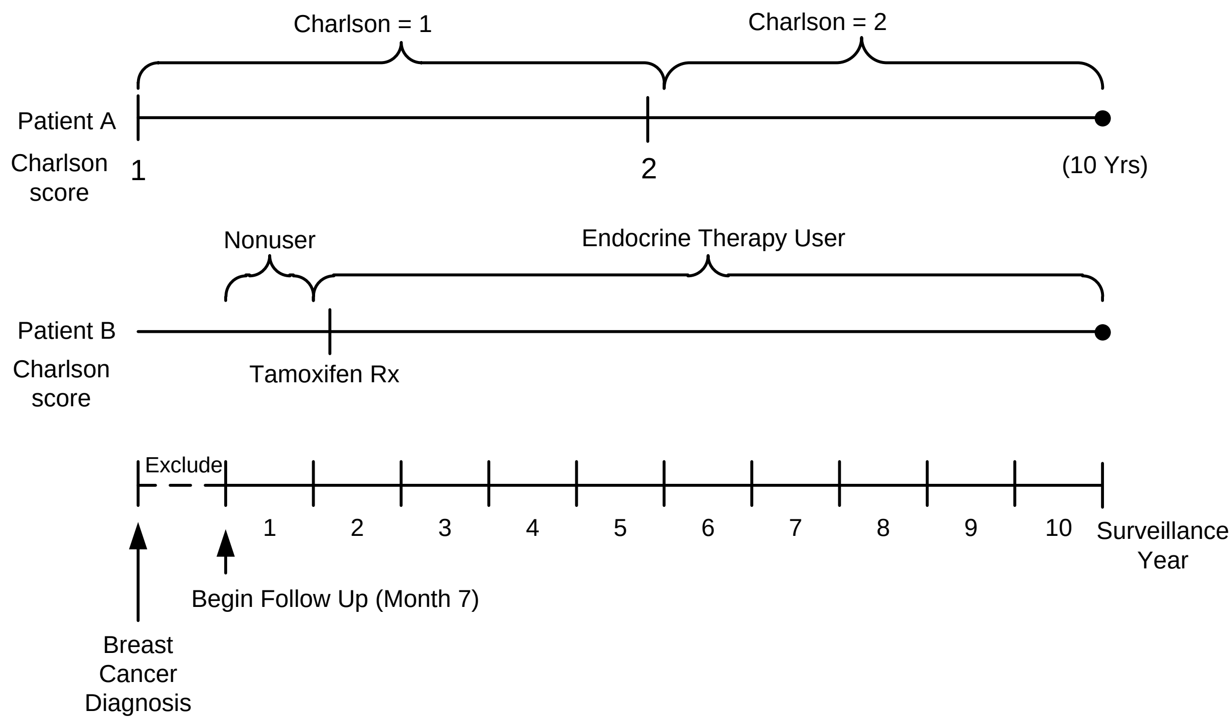

Figure 5. Schematic of time-varying “ever-never” covariates over the entire study period

Illustrative example:

- Scenario 1: Patient A has Charlson score = 1 at diagnosis; Charlson score = 2 beginning in month 7 of year 5, and no further changes to her Charlson score through year 10. Since she has a new Charlson score for only 5 months of year 5, her Charlson score remains 1 in year 5 and increases to 2 in year 6. She remains Charlson = 2 for all subsequent surveillance years.
- Scenario 2: Patient B fills her first tamoxifen prescription in month 1 of year 2. Since she meets the exposure definition for endocrine therapy use for at least 8 months of the surveillance year, she is classified as an endocrine therapy user beginning in year 2. She remains an endocrine therapy user for all subsequent surveillance years.

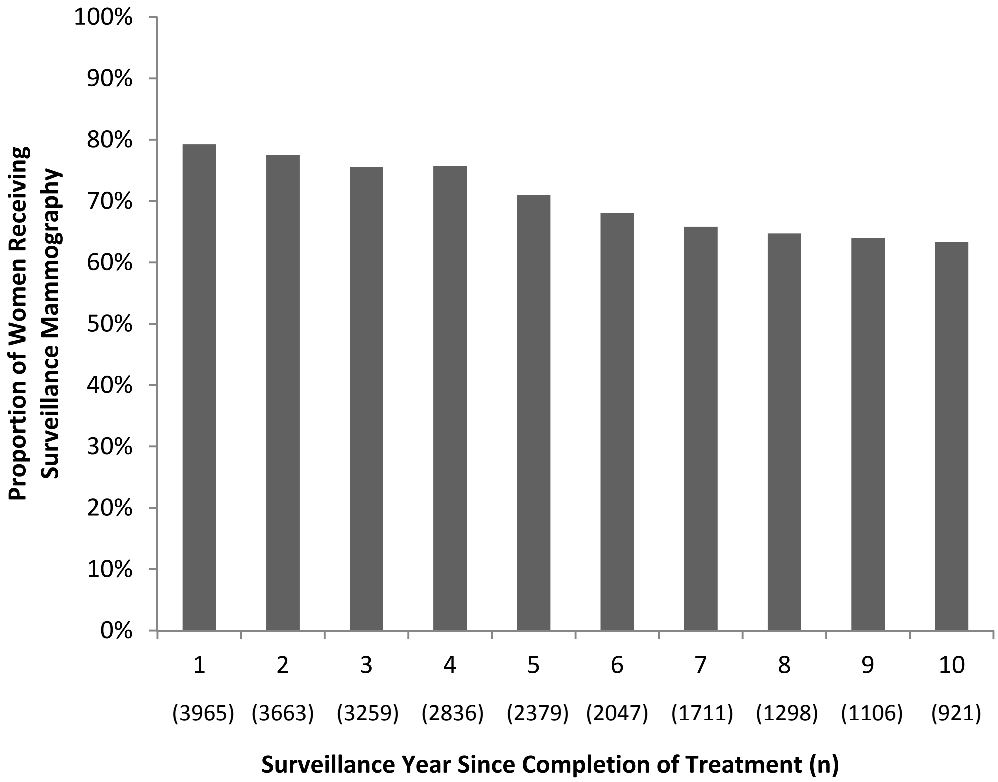

Figure 6. Receipt of yearly surveillance mammography since completion of breast cancer treatment among women with a history of early stage invasive breast cancer.

*0.7% of surveillance mammography includes breast MRI
Follow-up extended from month 7 post-SEER diagnosis date through 10 years or the earliest of death, disenrollment, or diagnosis of a second breast cancer event (i.e., recurrence or second primary breast cancer).

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Curriculum Vitae

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EDUCATION

Ph.D.	Pharmaceutical Outcomes Research and Policy Program, University of Washington	2012
Pharm.D. *summa cum laude*	Creighton University	2000
M.S.	Exercise Physiology, The University of Iowa	1996
B.S. *with honors*	Exercise Science, The University of Iowa	1994

RESEARCH EXPERIENCE

Research Assistant 2010-2012
University of Washington and Group Health Research Institute, Seattle, WA

TEACHING EXPERIENCE

Teaching Assistant 2008-2010
University of Washington School of Pharmacy, Seattle, WA

Courses: Pharmacy Law and Ethics; Evidence Based Medicine II: Applying and Interpreting Biostatistics in Clinical Research; Diabetes Care; Medication Safety in Patient Care

Adjunct Assistant Professor Spring 2002
Butler University College of Pharmacy and Health Sciences, Indianapolis, IN

Course: Pharmaceutical Drug Development

PROFESSIONAL EXPERIENCE

Inpatient Pharmacist (part-time) 2008-2010
Harborview Medical Center, Seattle, WA

Professional Education Scientific Manager – Neurology 2006-2008
Teva Neuroscience, Kansas City, MO; Regional responsibilities for Washington, Oregon, Idaho, Montana, Alaska

Senior Medical Education & Research Liaison – Rheumatology 2004-2006
TAP Pharmaceutical Products Inc., Lake Forest, IL; Regional responsibilities for Washington, Oregon, Colorado, Utah, Nevada, Idaho, Montana, and Wyoming

Regional Medical Scientist – Respiratory 2002-2004
GlaxoSmithKline, Research Triangle Park, NC; Regional responsibilities for Washington, Oregon, Idaho, and Alaska

Neuroscience Medical Liaison Associate 2002
Eli Lilly and Company, Indianapolis, IN

Visiting Scientist Fellowship – Neuroscience Clinical Research 2001-2002
Eli Lilly and Company, Indianapolis, IN

ASHP-Accredited Pharmacy Practice Residency 2000-2001
The University of Washington/ Harborview Medical Centers, Seattle, WA

HONORS & AWARDS

Achievement Rewards for College Scientists (ARCS) Foundation Scholar 2008-2011

Graduation with Honors, summa cum laude, Creighton University 2000

Merck and Company Award, Creighton University 2000
Presented to the graduating pharmacy student with the highest cumulative grade point average

Dean's List, Creighton University 1996-2000

Superior Scholastic Achievement Award, Creighton University 1997-2000

Rho Chi Recognition Certificate for Scholastic Achievement, Creighton University 1997

Graduation with Honors, The University of Iowa 1994

Dean's List, The University of Iowa 1991-1994

LEADERSHIP POSITIONS

President, International Society for Pharmacoeconomics and Outcomes Research Student Chapter 2011-2012
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Education Committee 2011-2012
International Society for Pharmacoeconomics and Outcomes
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Pharmaceutical Outcomes Research & Policy Program 2011
Admissions Committee
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Pharmaceutical Outcomes Research & Policy Program 2011
Retreat Planning Committee
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Investigator-Initiated Research Process Improvement Task Force 2005-2006
TAP Pharmaceutical Products Inc.

Health Outcomes Therapeutic Area Team, Regional Medical Scientist Chair 2003-2004
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University of Washington/Harborview Medical Centers

Rho Chi Honor Society, Vice President 1998-1999
Creighton University, School of Pharmacy & Health Professions

PUBLICATIONS

Boudreau DM, **Wirtz H**, Von Korff M, Catz SL, St. John J, Stang PE. A survey of patient awareness and use of medicine containing acetaminophen. Pharmacoepidemiol Drug Saf. 2012 Aug 13. doi: 10.1002/pds.3335. [Epub ahead of print]

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Heineman SM, Malesker KA, **Wirtz HS**. Kaposi's Sarcoma. US Pharmacist October 2000; 25(10): HS3-HS20.

MANUSCRIPTS SUBMITTED OR IN PREPARATION

Wirtz HS, Gray SL, Pettinger M, Carnahan R, Cauley JA, Bea J, LaCroix AZ. Anticholinergic medication use, falls and fractures in postmenopausal women: findings from the Women's Health Initiative. (in preparation for Arch Intern Med)

Wirtz HS, Buist DSM, Gralow JR, Barlow WE, Gray SL, Boudreau DM. Frequent antibiotic use and second breast cancer events. (in preparation)

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Hepp Z, Forrester S, Roth J. **Wirtz HS**, Devine EB. Cost-effectiveness of a computerized provider order entry system in improving medication safety: A case study in ambulatory care. (submitted to J Am Med Inform Assoc, September 2012)

Chubak J, Boudreau DM, **Wirtz HS**, McKnight B, Weiss NS. Threats to the validity of non-randomized studies of post-diagnosis exposures on cancer recurrence and survival. (submitted to J Clin Oncol)

Devine EB, Lau B, Overby CL, **Wirtz HS**. Use of stepwise clinical decision support to improve adherence to national drug-laboratory monitoring guidelines. (in preparation for Appl Clin Inform)

CONFERENCE PRESENTATIONS

Wirtz HS, Callaghan JT, Tatum DE, Cerimele BJ, Baker RW, Bergstrom RF. Effect of multiple-dose olanzapine on the steady-state pharmacokinetics of valproic acid in patients with bipolar or schizoaffective disorder. Poster presentation, 2002 American College of Clinical Pharmacy Annual Meeting, Albuquerque, NM, October 2002.

Wirtz HS, Gray SL, Pettinger M, Carnahan R, Cauley JA, Bea J, LaCroix AZ. Anticholinergic medication use, falls and fractures in postmenopausal women: findings from the Women's Health Initiative. Podium presentation, 2012 American Geriatric Society Annual Scientific Meeting, Seattle, WA, May 2012.

Lau B, Devine EB, Overby CL, **Wirtz HS**. Use of clinical decision support to improve adherence to national drug-laboratory monitoring guidelines. Podium presentation, National Research Service Award (NRSA) Trainees Research Conference, Academy Health Annual Research Meeting, Orlando, FL, June 2012.

Devine EB, Lau B, Overby CL, **Wirtz HS**. Use of clinical decision support to improve adherence to national drug-laboratory monitoring guidelines. Poster presentation, 34th Annual Meeting of the Society for Medical Decision Making, Phoenix, AZ, October 2012.

PROFESSIONAL ORGANIZATIONS

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