Research Article

Frequent Antibiotic Use and Second Breast Cancer Events

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Abstract

Background: Antibiotic use may be associated with higher breast cancer risk and breast cancer mortality, but no study has evaluated the relation between antibiotic use and second breast cancer events (SBCE).

Methods: We conducted a retrospective cohort study among women ≥18 years, diagnosed with incident stage I/II breast cancer during 1990–2008. Antibiotic use and covariates were obtained from health plan administrative databases and medical record review. Frequent antibiotic use was defined as ≥4 antibiotic dispensings in any moving 12-month period after diagnosis. Our outcome was SBCE defined as recurrence or second primary breast cancer. We used multivariable Cox proportional hazards models to estimate HR and 95% confidence intervals (CI), accounting for competing risks.

Results: A total of 4,216 women were followed for a median of 6.7 years. Forty percent were frequent antibiotic users and 558 (13%) had an SBCE. Results are suggestive of a modest increased risk of SBCE (HR, 1.15; 95% CI, 0.88–1.50) among frequent antibiotic users compared with nonusers. Any potential increased risk was not supported when we evaluated recent use and past use. We observed no dose–response trends for SBCE with increasing duration of antibiotic use nor did we find evidence for altered SBCE risk in the antibiotic classes studied.

Conclusions: Frequent antibiotic use may be associated with modestly elevated risk of SBCEs, but the association was not significant.

Impact: Additional investigation by antibiotic class and underlying indication are important next steps given the high prevalence of frequent antibiotic use and growing number of breast cancer survivors. *Cancer Epidemiol Biomarkers Prev; 22(9); 1588–99. ©2013 AACR.*

Introduction

Each year in the United States more than 200,000 women are diagnosed with breast cancer (1) and currently there are an estimated 2.6 million breast cancer survivors (2). Breast cancer survivors are at risk for recurrence and second primary breast cancers (3).

Antibiotics were proposed as a risk factor for cancer over two decades ago (4). Biologic mechanisms have not been clearly established but suggest antibiotics could have different effects on cancer risk (5). Antibiotics may promote cancer by disrupting the ability of intestinal microflora to metabolize phytochemicals into biologically active compounds hypothesized to protect against cancer (4). Antibiotic-induced disturbance of intestinal microflora may also decrease the risk of some hormonal cancers by disrupting estrogen metabolism, resulting in lower levels of circulating estrogens (5).

Several epidemiologic studies report on antibiotic use and risk of incident breast cancer with conflicting results, as some studies showed no association (6–10) and others have suggested antibiotic use increases risk (11–15). Notably, one of these studies found a dose–response trend for both incident breast cancer risk and breast cancer–related mortality compared with nonusers; as much as a two-fold higher risk of incident breast cancer was found among women with more than 500 cumulative days of antibiotic use (15). To our knowledge, no study to date has evaluated antibiotic use and risk of recurrence and second primary breast cancers among women with a history of breast cancer.

The risk benefit of antibiotic use in relation to breast cancer outcomes is most relevant for chronic or frequent use. Antibiotics are widely prescribed and frequent antibiotic use is common (15) such as for the management of acne and/or rosacea, recurrent urinary tract infections (UTI), or chronic obstructive pulmonary disease (COPD). Antibiotics are often overused or prescribed inappropriately (16); therefore, a better understanding of risks associated with frequent use could bolster measures to improve antibiotic prescribing. We therefore evaluated the association between frequent

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antibiotic use and risk of recurrence and second primary breast cancer among women diagnosed with early-stage invasive breast cancer.

Materials and Methods

Study population

This retrospective cohort study was conducted within Group Health Cooperative (GH), a nonprofit integrated health care delivery system that provides comprehensive health care on a prepaid basis to approximately 620,000 individuals throughout Washington State and parts of Idaho. GH is located within the geographic reporting region of the western Washington Cancer Surveillance System, a population-based cancer surveillance, epidemiology, and end results (SEER) registry (2). Women were included if they were: (i) ≥18 years of age; (ii) diagnosed with an incident, histologically confirmed stage I or II (17) breast cancer between January 1, 1990 and December 31, 2008 via the SEER registry; (iii) had no evidence of bilateral disease per the SEER registry; and (iv) enrolled in GH's integrated group practice for at least 1 year before and 1 year after the breast cancer diagnosis (unless they 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 after diagnosis) as part of 2 previous studies (18–20). We verified the eligibility of 4,225 women per chart review [women were excluded for no medical record ($n = 72$), bilateral disease ($n = 6$), breast cancers that were not first primaries ($n = 79$), and no definitive surgery ($n = 44$)]. We required that women be alive and recurrence-free for 120 days after completing definitive surgery for the incident breast cancer, yielding a final cohort of 4,216 women (excluding 5 deaths and 4 metastases before 120 days). The GH Institutional Review Board approved this study.

Data collection

Information on patient and tumor characteristics, breast cancer treatment, outcomes (i.e., recurrence and second primaries), other cancers, comorbid conditions of interest, and breast cancer surveillance were obtained from GH automated databases, review of medical records by trained abstractors, and SEER. Data were collected on all eligible women from 1 year before diagnosis through the earliest of death, disenrollment from GH (a lapse in membership of 90+ days), or end of study (i.e., date of chart abstraction). GH's automated databases include demographics, enrollment, inpatient and outpatient diagnoses and procedures, breast imaging (e.g., mammography) results, pharmacy dispensings, laboratory results, vital signs, and death (21). Charlson comorbidity index scores (22) were collected annually from medical charts and automated databases. Deaths are determined through GH's link to Washington State death tapes (23). SEER was the gold standard for incident breast cancer characteristics including year of diagnosis, American Joint Committee on

Cancer (AJCC) stage (17), lymph node status, hormone receptor status, and tumor size. Education and menopausal status were collected from a self-administered questionnaire on breast cancer risk factors completed at each screening mammogram (24).

Antibiotic exposure

We identified all outpatient prescription medication use dispensed at any GH pharmacy 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 all antibiotics dispensed in the year before each woman's diagnosis through the end of follow-up.

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. A dispensing was defined as a prescription with ≤30-day supply. If a dispensing had >30-day supply, we split the dispensing into multiple dispensings reflective of supply ≤30 days. For example, a dispensing of 90-day supply was counted as three 30-day dispensings. On the basis of consensus of a group of prescribers and pharmacists, frequent antibiotic use was defined as having 4+ dispensings for any antibiotic within any moving 12-month period after breast cancer diagnosis. Women were categorized as frequent users at the time of the fourth dispensing. Infrequent antibiotic use was defined as having 1 to 3 antibiotic dispensings within any moving 12-month period. Nonusers were defined as women with no dispensings for an antibiotic. Exposure was time varying. Women were only allowed to transition from nonuser, to infrequent user, to frequent user over time. Once a woman was classified as a frequent user, she remained a frequent user throughout the rest of the follow-up period. We established *a priori* that frequent antibiotic use was the most clinically meaningful exposure so we only report frequent users versus nonusers in our study. Dispensings before breast cancer diagnosis were not included even though its use could potentially last past diagnosis.

In addition, we evaluated several secondary exposures. To investigate the influence of recency of use on second breast cancer event (SBCE) risk, we stratified frequent use according to the following mutually exclusive categories: nonuse, recent use (became frequent user <3 years before event date), and past use (became frequent user ≥3 years before event date). We restricted this analysis to person-time and events ≥3 years since diagnosis ($N = 3,475$). We further explored frequent use for each of the 5 most commonly dispensed antibiotic classes where a woman had to fill 4+ prescriptions from the antibiotic class of interest within any moving 12-month period after

diagnosis. Women could contribute to multiple antibiotic classes.

Duration of use was estimated by summing the days supply for each antibiotic prescription to obtain the cumulative days of antibiotic dispensings (15). Duration of use was time varying. We restricted this analysis to women with more than 500 days of follow-up ($N = 3,996$) to include only those who had the opportunity to be in any of the exposure categories (1–50 days, 51–100 days, 101–500 days and >500 days of antibiotic use). We also estimated duration of use by the top 5 most commonly dispensed antibiotic classes during follow-up. Women could contribute to multiple antibiotic classes if she filled at least one prescription for that class.

Outcome ascertainment

The primary outcome was SBCE, defined as the first ductal carcinoma *in situ* (DCIS) or an invasive cancer of the ipsilateral (recurrence) or contralateral (second primary) breast or in any regional or distant sites (25). A woman was at risk for a SBCE starting 120 days after completing definitive surgery for the incident breast cancer (index date; ref. 20).

Data analysis

We used multivariable Cox proportional hazards models to estimate HRs and 95% confidence intervals (CI) to assess whether frequent antibiotic use was associated with SBCEs while accounting for competing risks. We also stratified the primary analysis by tumor histology of the incident breast cancer (ductal, lobular, mixed/other). We modeled time from the incident breast cancer with a delayed entry at 120 days postsurgery (19, 20) to the composite and individual outcomes as a function of frequent antibiotic use while adjusting for precision variables (i.e., variables associated with the outcome) and potential confounders. Individual events (i.e., recurrence and second primaries) that make up the composite outcome were also modeled to obtain a comprehensive assessment of the medication effects (26). Women were followed from their index date until the first of SBCE, death, disenrollment, or end of study. In analyses of individual events (e.g., recurrence), women were censored at the earliest of disenrollment, end of follow-up, and other competing events (e.g., death and second primary). We evaluated secondary exposures including frequent antibiotic use by antibiotic class and duration of use (all antibiotics and by antibiotic class). Nonusers were the reference category in all analyses. All exposures were time varying.

All models were adjusted for confounders we selected *a priori*, including diagnosis year (1990–1994, 1995–1999, 2000–2004, and 2005–2008), age at diagnosis (18–49, 50–59, 60–69, 70–79, and 80+ years), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), body mass index (BMI) at diagnosis (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and 35+ kg/m^2), smoking status at diagnosis (current, past, and never/unknown), Charlson

comorbidity score (0, 1, 2+, and time-varying), conditions commonly managed with chronic antibiotic use (yes/no, time-varying for acne and/or rosacea, COPD, and UTI), and surveillance mammography receipt in the prior 12 months (yes/no, time-varying). All models were further adjusted for precision variables predictive of SBCEs, including AJCC stage (I, IIA, and IIB) hormone receptor status [estrogen receptor (ER)−/progesterone receptor (PR)−, ER+/PR−, ER−/PR+, and ER+/PR+], primary treatment for the incident breast cancer (mastectomy, breast conserving surgery with radiation, and breast conserving surgery without radiation), and endocrine therapy (yes/no, time-varying).

We evaluated the proportional hazards assumption by testing for an interaction between the exposure variable and the logarithm of time since diagnosis. There was no evidence suggesting a violation of the proportional hazards assumption. All analyses were conducted using SAS statistical software version 9.2 (SAS Institute Inc.).

Sensitivity analyses

We assessed the influence of assumptions about the antibiotic exposure on our results. We varied the definition of frequent antibiotic use to 5+ and 6+ dispensings in any 12-month period postdiagnosis. We excluded antibiotic use in the year immediately preceding the event to rule out protopathic bias. We also excluded antibiotic use during the first year postdiagnosis, as antibiotic use during this time may be related to immunosuppression from the treatment regimen. Finally, we considered frequent antibiotic use during the 12 months prediagnosis as a potential confounder.

Results

The median age of the cohort at initial breast cancer diagnosis was 63 years. The majority of women were postmenopausal (72.9%), White (88.5%), had some college or higher education (76.6%), were not smokers (85.6%), and had a Charlson comorbidity score of zero (76.5%).

During the study period, 1,678 (40%) were frequent antibiotic users with 9,112 person-years of follow-up. Penicillins and cephalosporins were the most commonly prescribed classes 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 antibiotic use are described in Table 1. Women who became frequent antibiotic users during follow-up were more likely to have received an antibiotic prescription and to have been frequent antibiotic users in the 12 months prediagnosis compared with nonusers. Frequent antibiotic users were diagnosed in earlier years, had longer duration of follow-up, higher Charlson scores, higher BMI, and were more likely to be older, White, and have acne and/or rosacea, COPD, UTIs, and other cancers

Table 1. Descriptive characteristics of women, by antibiotic medication use after early-stage breast cancer diagnosis

	Nonuser (*n* = 525)	Frequent antibiotic user (*n* = 1,678)	*P*[a]
Characteristics at diagnosis of initial breast cancer			
Year of diagnosis			
1990–1994	87 (16.6)	468 (27.9)	<0.001
1995–1999	110 (21.0)	539 (32.1)	
2000–2004	161 (30.7)	427 (25.4)	
2005–2008	167 (31.8)	244 (14.5)	
Years of follow-up			
Median (IQR)	3.7 (0.5–16.8)	7.6 (0.5–19.2)	<0.001
Age, y			
Median (IQR)	61 (34–91)	64 (27–93)	<0.01
18–39	18 (3.4)	56 (3.3)	0.03
40–49	94 (17.9)	227 (13.5)	
50–59	131 (25.0)	386 (23.0)	
60–69	122 (23.2)	431 (25.7)	
70–79	93 (17.7)	384 (22.9)	
80+	67 (12.8)	194 (11.6)	
Menopausal status			
Peri- or Premenopausal	158 (30.1)	442 (26.3)	0.09
Postmenopausal	367 (69.9)	1,236 (73.7)	
Race			
White	436 (83.7)	1,527 (91.2)	<0.001
African American	28 (5.4)	39 (2.3)	
American Indian/Alaska Native	8 (1.5)	53 (3.2)	
Asian/Pacific Islander	49 (9.4)	55 (3.3)	
Unknown	4	4	
Education			
High school or less	51 (21.2)	158 (25.5)	0.18
At least some college	190 (78.8)	461 (74.5)	
Unknown	284	1,059	
BMI (kg/m^2)			
<18.5	13 (2.5)	27 (1.6)	<0.001
18.5–24.9	209 (40.2)	519 (31.1)	
25.0–29.9	157 (30.2)	546 (32.7)	
30.0–34.9	85 (16.3)	316 (18.9)	
35+	56 (10.8)	261 (15.6)	
Unknown	5	9	
Smoking status			
Current	33 (6.3)	91 (5.4)	0.10
Past	51 (9.7)	119 (7.1)	
Never	441 (84.0)	1,468 (87.5)	
Charlson score			
0	425 (81.0)	1,183 (70.5)	<0.001
1	75 (14.3)	363 (21.6)	
2+	25 (4.8)	132 (7.9)	
Medication use in year before diagnosis			
Antibiotic use, ever	132 (25.1)	974 (58.0)	<0.001
Frequent antibiotic user	8 (1.5)	256 (15.3)	<0.001

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Table 1. Descriptive characteristics of women, by antibiotic medication use after early-stage breast cancer diagnosis (Cont'd)

	Nonuser (*n* = 525)	Frequent antibiotic user (*n* = 1,678)	*P*[a]
AJCC Stage (ref. 17)			
I	308 (58.7)	1,049 (62.5)	0.06
IIA	163 (31.0)	433 (25.8)	
IIB	54 (10.3)	196 (11.7)	
Lymph node status			
Negative	363 (78.1)	1,095 (73.9)	0.20
Positive	102 (21.9)	386 (26.1)	
Unknown	60	197	
ER/PR status			
ER−/PR−	90 (17.1)	255 (15.2)	0.73
ER+/PR−	47 (9.0)	167 (10.0)	
ER−/PR+	8 (1.5)	35 (2.1)	
ER+/PR+	350 (66.7)	1,123 (66.9)	
ER and PR unknown	30 (5.7)	98 (5.8)	
Tumor size			
≤2 cm	362 (69.0)	1,257 (74.9)	<0.01
>2 cm	163 (31.0)	421 (25.1)	
Tumor histology			
Ductal	435 (82.9)	1,290 (76.9)	<0.01
Lobular	31 (5.9)	168 (10.0)	
Mixed/other	59 (11.2)	220 (13.1)	
HER2 Test result			
Test done	322 (83.0)	678 (76.1)	<0.01
Positive/borderline	57 (17.7)	119 (17.6)	0.74
Negative	263 (81.7)	557 (82.2)	
No result	2 (0.6)	2 (0.3)	
Surgical procedure			
Mastectomy ± radiation	176 (33.5)	681 (40.6)	0.001
BCS + radiation	262 (49.9)	802 (47.8)	
BCS	87 (16.6)	195 (11.6)	
Other treatment			
Chemotherapy	164 (31.2)	545 (32.5)	0.59
Completed course	147 (89.6)	472 (86.6)	0.59
Endocrine therapy	269 (51.2)	969 (57.7)	<0.01
Characteristics throughout study period			
Comorbidities			
Acne and/or rosacea	28 (5.3)	191 (11.4)	<0.001
COPD	47 (9.0)	358 (21.3)	<0.001
UTI	53 (10.1)	912 (54.4)	<0.001
Other cancers	22 (4.2)	166 (9.9)	<0.001
% Follow-up years with yearly surveillance mammogram			
<50%	146 (27.8)	391 (23.3)	<0.001
50%–80%	130 (24.8)	627 (37.4)	
>80%	249 (47.4)	660 (39.3)	

NOTE: Data are represented as number (%) unless otherwise noted. Frequent antibiotic users included women with 4+ dispensing in any moving 12-month period after diagnosis. Infrequent antibiotic users are not presented here as this is not a clinically meaningful exposure.

Abbreviations: BCS, breast conserving surgery; IQR, interquartile range.

[a]To test for differences of the characteristics between the 2 groups, we used χ^2 test for categorical variables and Wilcoxon rank-sum test for medians.

compared with nonusers. Frequent antibiotic users were also more likely to initial tumors that were smaller, non-ductal carcinomas tested for HER2 and treated with mastectomy and endocrine therapy. During follow-up, frequent antibiotic users were less likely to receive surveillance mammography compared with nonusers.

Among the 4,216 women in our cohort, 432 (10%) women had a recurrence and 153 (4%) had a second primary breast cancer, a total of 558 having a SBCE ($n = 415$ recurrences and $n = 143$ second primary breast cancers). Among recurrences, 67% were distant, 32% were local or regional, and 1% was DCIS. Among second primary cancers, 21% were DCIS, 49% were stage I, 21% were stage II, 4% were stage III/IV, and staging was unavailable for 5%. Histologic types of the SBCEs were 35% ductal, 3% lobular, and 62% mixed/other. The distribution did not differ by exposure status. The median follow-up was 6.7 years and the median time to first SBCE was 3.3 years.

Characteristics of the study cohort by SBCE status are described in Table 2. SBCE cases were diagnosed in earlier years, had shorter duration of follow-up and were more likely to have initial cancers that were not tested for HER2, and were higher stage, larger tumor size, lymph node-positive, and hormone receptor-negative compared with noncases. Consistent with these clinical characteristics, SBCE cases were more likely to receive mastectomy and chemotherapy but less likely to receive endocrine therapy. Women experiencing a SBCE were also more likely to be younger, non White, pre- or peri-menopausal, less likely to be smokers and less likely to have acne and/or rosacea, COPD, UTIs, and other cancers compared with women who did not experience a SBCE. During follow-up, SBCE cases had shorter duration of antibiotic use and were less likely to be frequent antibiotic users and to receive surveillance mammography.

The unadjusted HRs for frequent use were 1.31 (95% CI, 1.02–1.68) for SBCE, 1.38 (95% CI, 1.03–1.84) for recurrences, and 1.11 (95% CI, 0.67–1.84) for second primaries. HRs from the multivariable-adjusted models suggest a modestly elevated risk of SBCE, including both recurrences and second primaries, with frequent antibiotic use versus no-use but the differences were not statistically significant: 1.15 (95% CI, 0.88–1.50) for SBCE, 1.13 (95% CI, 0.83–1.53) for recurrences, and 1.21 (95% CI, 0.71–2.06) for second primaries (Fig. 1). The potential association with SBCE was not supported when frequent antibiotic use was stratified by recent use (<3 years; HR, 0.78; 95% CI, 0.53–1.17) and past use (≥3 years; HR, 0.91; 95% CI, 0.48–1.72), or duration of use compared with no-use (Table 3). In the subgroup analysis by histologic type of the incident breast cancer, the adjusted HRs for frequent antibiotic use and risk of SBCEs were: 1.15 (95% CI, 0.86–1.54) for ductal, 2.99 (95% CI, 0.95–9.40) for lobular, and 0.62 (95% CI, 0.25–1.55) for mixed/other histologies. Findings for the individual outcomes of SBCE (i.e., recurrence and second

primaries) were similar to those observed for SBCEs (data not shown). The associations for frequent use and SBCE (or the individual outcomes of recurrence and second primaries) by antibiotic class varied from slightly reduced to slightly elevated risk but none were statistically significant and most of the CIs were wide (Fig. 1). We observed some significant associations when we examined duration of use by antibiotic class, though there are no clear trends overall (Table 3).

Study findings were robust to sensitivity analyses where we varied definitions of frequent antibiotic use and evaluated risk of SBCE and its individual outcomes. Consideration of frequent antibiotic use prediagnosis did not change our results. We also did not observe appreciable changes in risk estimates when we excluded antibiotic dispensings during the first year postdiagnosis or the year immediately before the SBCE event date.

Discussion

This study addresses an important gap in the literature as no prior studies have examined postdiagnosis antibiotic use among women with an early-stage breast cancer diagnosis. There was suggestion that risk of SBCEs and its individual outcomes of recurrence and second breast primaries may be modestly elevated with frequent antibiotic use following diagnosis, though CIs included 1.0. The least detectable HRs for SBCEs by frequent antibiotic use versus no-use was 1.20 for increased risk—two-sided test; $\alpha = 0.05$; $\beta = 0.80$. The potential association with SBCE was not supported when we compared duration of antibiotic use with no-use and evaluated dose–response trends. Mechanistic studies suggest antibiotics may alter the risk of cancer primarily through direct effects on intestinal microflora. We hypothesized, therefore, that recency of use would influence the risk of SBCEs, yet we found no differences in risk when stratified by recent use and past use. We did, however, observe differences in the association between frequent antibiotic use and risk of SBCEs by histologic subtype of the incident breast cancer. Women with ductal and lobular tumors showed elevated risk of SBCEs with frequent antibiotic use and mixed/other tumors showed reduced risk, though CIs were wide and included 1.0.

Although we found no strong evidence of increased risk of SBCEs by antibiotic class, we lacked sufficient power for this secondary aim (least detectable HRs for SBCEs varied by class but all were less than 0.60 for reduced risk and more than 1.50 for increased risk). We observed some statistically significant associations when we examined duration of use by antibiotic class (e.g., sulfonamide use). However, these results should be interpreted cautiously with multiple testing conducted and in the absence of any significant trends.

Because this is the first study on postdiagnosis antibiotic use and SBCEs, we are unable to directly compare our findings with others. A previous study, conducted at GH,

Table 2. Descriptive characteristics of women by SBCE status

	SBCE (N = 4,216)		
	No (n = 3,658)	Yes (n = 558)	Pa
Characteristics at diagnosis of initial breast cancer			
Year of diagnosis			
1990–1994	755 (20.6)	195 (34.9)	<0.001
1995–1999	1,020 (27.9)	171 (30.6)	
2000–2004	1,073 (29.3)	128 (22.9)	
2005–2008	810 (22.1)	64 (11.5)	
Years of follow-up			
Median (IQR)	6.7 (0.4–19.4)	3.3 (0.5–16.5)	<0.001
Age, y			
Median (IQR)	63 (28–95)	62 (29–89)	<0.01
18–39	112 (3.1)	27 (4.8)	0.06
40–49	544 (14.9)	102 (18.3)	
50–59	866 (23.7)	129 (23.1)	
60–69	889 (24.3)	129 (23.1)	
70–79	824 (22.5)	116 (20.8)	
80+	423 (11.6)	55 (9.9)	
Menopausal status			
Peri- or Premenopausal	956 (26.1)	189 (33.9)	<0.001
Postmenopausal	2,702 (73.9)	369 (66.1)	
Race			
White	3,232 (88.7)	487 (87.3)	<0.01
African American	104 (2.9)	32 (5.7)	
American Indian/Alaska Native	104 (2.9)	9 (1.6)	
Asian/Pacific Islander	203 (5.6)	30 (5.4)	
Unknown	15	0	
Education			
High school or less	393 (23.5)	25 (21.4)	0.83
At least some college	1,279 (76.5)	92 (78.6)	
Unknown	1,986	441	
BMI (kg/m^2)			
<18.5	55 (1.5)	14 (2.5)	0.37
18.5–24.9	1,269 (34.8)	184 (33.3)	
25.0–29.9	1,186 (32.6)	176 (31.8)	
30.0–34.9	666 (18.3)	100 (18.1)	
35+	467 (12.8)	79 (14.3)	
Unknown	15	5	
Smoking status			
Current	230 (6.3)	23 (4.1)	0.01
Past	318 (8.7)	34 (6.1)	
Never	3,110 (85.0)	501 (89.8)	
Charlson score			
0	2,784 (76.1)	445 (79.7)	0.16
1	625 (17.1)	79 (14.2)	
2+	249 (6.8)	34 (6.1)	
Medication use in year before diagnosis			
Antibiotic use, ever	1,621 (44.3)	251 (45.0)	0.77
Frequent antibiotic user	277 (7.6)	45 (8.1)	0.68
AJCC stage (ref. 17)			
I	2,384 (65.2)	264 (47.3)	<0.001
IIA	906 (24.8)	172 (30.8)	
IIB	368 (10.1)	122 (21.9)	

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Table 2. Descriptive characteristics of women by SBCE status (Cont'd)

	SBCE (N = 4,216)		
	No (n = 3,658)	**Yes (n = 558)**	**P[a]**
Lymph node status			
Negative	2,525 (77.4)	322 (64.3)	<0.001
Positive	739 (22.6)	179 (35.7)	
Unknown	394	57	
ER/PR Status			
ER−/PR−	531 (14.5)	136 (24.4)	<0.001
ER+/PR−	319 (8.7)	64 (11.5)	
ER−/PR+	47 (1.3)	14 (2.5)	
ER+/PR+	2,572 (70.3)	316 (56.6)	
ER and PR unknown	189 (5.2)	28 (5.0)	
Tumor size			
≤2 cm	2,785 (76.1)	325 (58.5)	<0.001
>2 cm	873 (23.9)	231 (41.5)	
Unknown	0	2	
HER2 Test result			
Test done	1,874 (80.5)	200 (73.0)	<0.01
Positive/borderline	311 (16.6)	42 (21.0)	0.21
Negative	1,556 (83.0)	158 (79.0)	
No result	7 (0.4)	0	
Surgical procedure			
Mastectomy ± radiation	1,289 (35.2)	232 (41.6)	<0.001
BCS + radiation	1,927 (52.7)	245 (43.9)	
BCS	442 (12.1)	81 (14.5)	
Other treatment			
Chemotherapy	1,142 (31.2)	234 (41.9)	<0.001
Completed course	1,003 (87.8)	209 (89.3)	0.74
Endocrine therapy	2,101 (57.4)	262 (47.0)	<0.001
Characteristics throughout study period			
Comorbidities			
Acne and/or rosacea	329 (9.0)	31 (5.6)	<0.01
COPD	574 (15.7)	58 (10.4)	<0.001
UTI	1,392 (38.1)	146 (26.2)	<0.001
Other cancers	303 (8.3)	24 (4.3)	<0.001
Antibiotic use postdiagnosis			
Frequent user	1,476 (40.3)	202 (36.2)	<0.001
Infrequent user	1,762 (48.2)	251 (45.0)	
Nonuser	420 (11.5)	105 (18.8)	
Max cumulative days supply			
0	420 (11.5)	105 (18.8)	<0.001
1–50	1,527 (41.7)	250 (44.8)	
51–100	723 (19.8)	89 (15.9)	
101–500	838 (22.9)	104 (18.6)	
≥501	150 (4.1)	10 (1.8)	
% of Follow-up years with yearly surveillance mammogram			
<50%	793 (21.7)	146 (26.2)	<0.01
50%–80%	1,284 (35.1)	155 (27.8)	
>80%	1,581 (43.2)	257 (46.1)	

NOTE: Data are represented as number (%) unless otherwise noted. Frequent antibiotic users included women with 4+ dispensing in any moving 12-month period after diagnosis. Infrequent antibiotic users included women with 1 to 3 dispensing in any moving 12-month period after diagnosis.

Abbreviations: BCS, breast conserving surgery; IQR, interquartile range.

[a]To test for differences of the characteristics between the 2 groups, we used χ^2 test for categorical variables and Wilcoxon rank-sum test for medians.
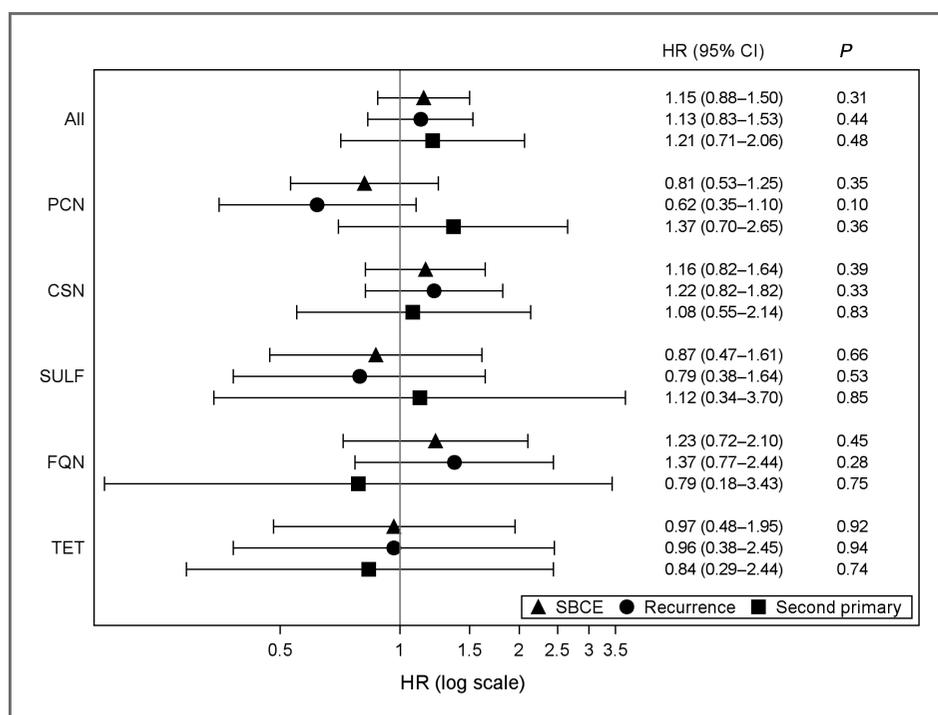
Figure 1. Adjusted HRs and 95% CIs for frequent antibiotic use and the risk of SBCEs. Abbreviations: CSN, cephalosporins; FQN, fluoroquinolones; PCN, penicillins; SULF, sulfonamides; TET, tetracyclines. Frequent antibiotic users included women with 4+ dispensings in any moving 12-month period after diagnosis. Nonusers were the reference category for all analyses. A woman could contribute to multiple antibiotic classes if she met the frequent use definition for that class. We excluded 20 women from analyses due to missing BMI information. All models adjusted for age, incident breast cancer diagnosis year, AJCC stage, hormone receptor status, primary treatment for the initial breast cancer, endocrine therapy, BMI, smoking status, menopausal status, Charlson comorbidity score, acne and/or rosacea, COPD, UTI, and receipt of surveillance mammography.

evaluated prediagnosis antibiotic use relative to incident breast cancer (15). In that case–control study of 2,266 women diagnosed in 1993–2001, prediagnosis antibiotic use was associated with higher risk of incident breast cancer compared with nonusers and the association was stronger with increased duration of use. ORs (95% CIs) for breast cancer were 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 501–1,000 days use, and 2.07 (1.48–2.89) for ≥1,001-day use (15). Although our findings among GH enrollees also suggest a higher risk of SBCEs, the magnitude of association is lower in our study, had wide CIs and showed no trend with increasing duration of use. The inconsistent results may be attributed to different exposures as Velicer and colleagues only evaluated antibiotic use preincident breast cancer diagnosis (15). We also evaluated different outcomes. As such, the risk of second primary breast cancers in our study is most comparable with the outcome of incident breast cancer in Velicer and colleagues. Our findings suggest frequent antibiotic use after diagnosis may increase risk of second breast primaries but CIs included 1.0. Our study was not powered to evaluate the development of new cancers and we only observed 143 second breast primaries (least detectable HRs for second primaries by frequent antibiotic use vs. no-use was 0.58 for reduced risk and 1.55 for increased risk).

We developed the definition of frequent antibiotic use *de novo* based on clinician input and coupled this with sensitivity analyses where different thresholds for frequent antibiotic use provided consistent results with the primary analysis. Compared with nonusers, frequent

antibiotic users were diagnosed in earlier years and had longer duration of follow-up, which gives more opportunity to observe a SBCE. Prediagnosis antibiotic exposure may confound the association between postdiagnosis frequent antibiotic use and risk of SBCEs. Including frequent antibiotic use during the 12 months prediagnosis did not change our results but it is possible that this was not a sufficient duration of prediagnosis exposure. Subjects were from a single health plan, which may not represent other care settings or populations. However, being enrolled in a health plan mitigates disparities in care that may exist among women without health coverage. There is always the potential for exposure misclassification for patients who receive a dispensing, but fail to take the drug. We required multiple dispensings in a year in order for a woman to be classified as a frequent user, which minimizes exposure misclassification as multiple dispensings in a defined period of time increase the possibility that women actually took the medication. Women who received medications at non-GH pharmacies without submitting a claim to GH may be erroneously classified as nonusers. This is likely minor as previous studies have found GH enrollees obtained 97% of their medications at GH owned or contracting pharmacies (27, 28). Residual confounding from unknown factors we did not adjust for and from known factors we did adjust for (e.g., diagnosis year, Charlson score, BMI) is always possible. Of importance, we adjusted for conditions associated with chronic antibiotic use. Other studies found no association between UTIs and breast cancer risk (13) and no differences in breast cancer risk comparing different indications for antibiotic use (15). We also

Table 3. Adjusted HRs and 95% CI for duration of antibiotic use and the risk of SBCEs

Antibiotic exposure	Adjusted HRs and 95% CIs[a]		
	SBCE (*n* cases = 558)	Recurrence (*n* cases = 415)	Second primary breast cancer (*n* cases = 143)
Any antibiotic			
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)
P_{trend}	0.25	0.41	0.33
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)
P_{trend}	0.07	0.16	0.22
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)
P_{trend}	0.13	0.42	0.10
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)
P_{trend}	0.35	0.82	0.04
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)
P_{trend}	0.40	0.17	0.21
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	0.90 (0.45–1.79)	0.93 (0.40–2.14)	0.85 (0.26–2.86)
P_{trend}	0.42	0.14	0.41

NOTE: Duration of antibiotic use is defined as cumulative days of dispensing. 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. We excluded 20 women from analyses due to missing BMI information.

[a]All models adjusted for age, incident breast cancer diagnosis year, AJCC stage, hormone receptor status, primary treatment for the initial breast cancer, endocrine therapy, BMI, smoking status, menopausal status, Charlson comorbidity score, acne and/or rosacea, COPD, UTI, and receipt of surveillance mammography.

found no association between any of the comorbidities of interest and SBCE.

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; detailed information on incident breast cancer characteristics and treatment; availability of medical charts to identify recurrences and details on recurrent cancer characteristics; unbiased information on medications dispensed; detailed information on comorbidities and mammographic exams that enabled us to examine confounding

in a robust manner; and application of robust analytic methods to address potential competing risks and informative censoring.

Although not statistically significant, our study provides a weak signal that frequent antibiotic use may be associated with a modestly elevated risk of SBCEs among women with a history of early-stage invasive breast cancer. This study is an important 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. As our findings provide only an initial signal, additional studies to better understand the role of frequent antibiotic use and SBCEs would be helpful. Furthermore, evaluations in different study populations and investigation of frequent use by antibiotic class and underlying indication would also be a next step in understanding such an association. This would allow breast cancer survivors and their providers to make more informed decisions about antibiotic selection for managing medical conditions where frequent use is necessary.

Disclosure of Potential Conflicts of Interest

Heidi S. Wirtz has ownership interest (including patents) in Teva Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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