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ARTICLE

Bisphosphonate Use After Estrogen Receptor–Positive Breast Cancer and Risk of Contralateral Breast Cancer

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Background A growing body of evidence suggests that nitrogenous bisphosphonates may reduce the risk of developing a first breast cancer and may prevent metastases among breast cancer survivors. However, their impact on risk of second primary contralateral breast cancer is uncertain.

Methods Within a nested case–control study among women diagnosed with a first primary estrogen receptor–positive invasive breast cancer at ages 40–79 years, we assessed the association between post-diagnostic bisphosphonate use and risk of second primary contralateral breast cancer. We used multivariable-adjusted conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) comparing 351 contralateral breast cancer case subjects with 662 control subjects (ie, breast cancer patients not diagnosed with contralateral breast cancer) who were incidence density–matched on county; race/ethnicity; and age at, year of, and stage at first breast cancer diagnosis. We performed sensitivity analyses with respect to bisphosphonate type and confounding by indication. All statistical tests were two-sided.

Results Current use of any nitrogenous bisphosphonate and use specifically of alendronate were both associated with reduced risks of contralateral breast cancer compared with never use (OR = 0.41, 95% CI = 0.20 to 0.84 and OR = 0.39, 95% CI = 0.18 to 0.88, respectively). The risk of contralateral breast cancer further declined with longer durations of bisphosphonate use among current users (P_{trend} = .03). Results were similar in analyses restricted to patients with a history of osteoporosis or osteopenia.

Conclusions Bisphosphonate use was associated with a substantial reduction in risk of contralateral breast cancer. If this finding is confirmed in additional studies, nitrogenous bisphosphonate therapy may be a feasible approach for contralateral breast cancer risk reduction.

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Breast cancer survivors have an estimated two to six times greater risk of being diagnosed with a second primary breast cancer in their contralateral breast compared with the risk of being diagnosed with a first breast cancer for women in the general population (1). Established strategies for preventing second primary breast cancers include adjuvant hormonal therapy and prophylactic contralateral mastectomy (2). Given the increasing number of breast cancer survivors, it is imperative to identify effective and well-tolerated ways to prevent second primary breast cancers. One possible approach is the use of bisphosphonates, which are commonly prescribed to prevent osteoporosis-related comorbidities (3) and, more recently, to prevent and treat bone metastasis and cancer treatment–induced bone loss and comorbidity (4–7). There is a growing body of evidence suggesting that bisphosphonates have additional direct and indirect antitumor effects (8,9), including solo and synergistic (with cytotoxic chemotherapy, selective estrogen receptor modulators, or aromatase inhibitors) activities in breast cancer relapse prevention (10,11).

In addition, three recent studies (12–14) suggest that nitrogen-containing bisphosphonates are associated with a reduced risk of first breast cancer, and in preliminary data from the randomized Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) (15), slightly fewer incident contralateral breast cancers in the trial arms that received adjuvant nitrogenous bisphosphonate therapy were observed compared with arms that did not receive adjuvant nitrogenous bisphosphonate therapy. These findings motivated us to assess the association between bisphosphonate use and the risk of contralateral breast cancer using data from a population-based case–control study that was conducted in women who had been diagnosed with a first primary estrogen receptor–positive (ER+) breast cancer. To our knowledge, this is the first population-based study to examine the relationship between bisphosphonate use and the risk of contralateral breast cancer among breast cancer survivors.

Participants and Methods

Study Design and Data Collection

The study design and data collection methods have been previously described (16). In brief, we used the Surveillance, Epidemiology,

and End Results (SEER) population-based cancer registry covering Western Washington State to identify 17 628 women who were 40–79 years old and resided in the four-county Seattle–Puget Sound region when they were diagnosed with a first primary invasive, localized or regional SEER historic stage (17) ER+ breast cancer between January 1, 1990, and September 30, 2005. This study (and the parent study) was restricted by age and to ER+ breast cancers to focus on women who were most likely to have received tamoxifen therapy (the primary exposure of the parent study) (16). Within this cohort, we identified 446 women who were diagnosed from July 1, 1990, to March 31, 2007, with a second primary invasive contralateral breast cancer 6 or more months after their first breast cancer diagnosis (case subjects). Of these women, 369 (83%) were enrolled. Eligible control subjects were women who were alive and residing in the county in which they were diagnosed with a first primary ER+ breast cancer and who had not developed a contralateral breast cancer for at least the period between their matched case subject's first breast cancer and subsequent contralateral breast cancer diagnosis. Of 982 eligible control subjects, 734 (75%) were enrolled. An average of two control subjects were matched to each case subject on age at and year of first breast cancer diagnosis, race/ethnicity, SEER historic stage of first breast cancer (localized vs regional) (17), and county of residence at first breast cancer diagnosis. To prevent a survivor bias, eligible women were included in the study regardless of vital status at the time of case and control subject ascertainment. Deceased women (n = 246) were enrolled through a waiver of consent granted by the Fred Hutchinson Cancer Research Center's Institutional Review Board. Primary study data were collected through SEER and detailed medical record reviews. Women who were alive at the time of the parent study provided verbal informed consent (n = 857). This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Information on bisphosphonate use between the index date (date of first breast cancer diagnosis) and the reference date (case subject reference date: date of contralateral breast cancer diagnosis; control subject reference date: date of the matched case subject's contralateral breast cancer diagnosis) was abstracted from the medical records of the oncology and/or primary care provider for 351 (95%) of the 369 matched case–control sets (351 case subjects and 662 control subjects). Data on potential confounders and effect modifiers came from several sources, including SEER (eg, age, year of diagnosis, SEER historic stage, and county of residence), interviewer-administered telephone questionnaires (eg, a variety of established breast cancer risk factors and treatments), and the medical record abstractions described above (ie, detailed information on breast cancer treatments, medical history). Sources of the information for all variables are annotated in Table 1.

For descriptive purposes, we derived the American Joint Committee on Cancer (AJCC) stage of the initial breast cancer diagnosis. AJCC stage derivations for diagnoses made before 2004 were made according to version 1.1 of the SEER Program: Comparative Staging Guide for Cancer (18); subsequent diagnoses were staged according to the 10th edition of the North American Association for Central Cancer Registries Standards for Cancer Registries Volume II (19).

CONTEXT AND CAVEATS

Prior knowledge

Nitrogenous bisphosphonates are commonly prescribed to prevent osteoporosis-related comorbidities and, more recently, to prevent and treat bone metastasis and cancer treatment–induced bone loss and comorbidity. A growing body of evidence suggests that bisphosphonates have additional direct and indirect antitumor effects, including the prevention of breast cancer relapse.

Study design

A nested case–control study among women diagnosed with a first primary estrogen receptor–positive invasive breast cancer at ages 40–79 years that assessed the association between bisphosphonate use after the first breast cancer diagnosis and the risk of second primary contralateral breast cancer.

Contribution

Current use of bisphosphonates and use for longer durations were both associated with large reductions in the risk of contralateral breast cancer.

Implication

Nitrogenous bisphosphonate therapy may be a feasible approach to reduce the risk of contralateral breast cancer.

Limitations

The observed associations could be due to chance or residual confounding. Factors that influence the ability to tolerate bisphosphonates or to adhere to their use could explain the observed dose–response relationship with duration of use. The findings may not be generalizable to risk of breast cancer recurrences, premenopausal use of bisphosphonates, ER-negative or advanced-stage breast cancer survivors, or use of nonnitrogenous bisphosphonates.

From the Editors

Statistical Analysis

Bisphosphonate use was defined according to ever use, the recency of use, and the cumulative duration of use following the first breast cancer diagnosis. Ever use was defined as having used bisphosphonates for 6 months or longer between the index and reference dates. Short-term use was defined as bisphosphonate use for fewer than 6 months during this period, and never use was defined as never having used bisphosphonates during this period. Current users were defined as ever users who had used bisphosphonates within 6 months of their reference date. Former users were defined as ever users who last used bisphosphonates more than 6 months before their reference date. This 6-month threshold was chosen to define current use and short-term use because it reflects the minimum possible duration between the index and reference dates. In analyses of the duration of use following the first breast cancer diagnosis, we assessed thresholds of 6, 12, and 24 months of use. We restricted these analyses to women with greater than or equal to 6, 12, or 24 months, respectively, between their index and reference dates. Thresholds of 12 and 24 months were chosen to facilitate interpretation and comparison of our findings to those of other studies.

We excluded from the analysis bisphosphonates that were specifically given to treat breast cancer according to the medical

Table 1. Characteristics of second primary contralateral breast cancer case subjects and control subjects*

Characteristic	Contralateral breast cancer case subjects (n = 351) No. (%)	Control subjects (n = 662) No. (%)	*P*†
Data obtained through the cancer registry			
Age at first breast cancer diagnosis, y			
40–49	69 (19.7)	122 (18.4)	
50–59	88 (25.1)	175 (26.4)	
60–69	108 (30.8)	203 (30.7)	
70–79	86 (24.5)	162 (24.5)	NA
Year of first breast cancer diagnosis			
1990–1994	153 (43.6)	289 (43.7)	
1995–1999	143 (40.7)	261 (39.4)	
2000–2005	55 (15.7)	112 (16.9)	NA
AJCC stage‡			
I	228 (65.0)	447 (67.5)	
II	107 (30.5)	186 (28.1)	
III	16 (4.6)	29 (4.4)	NA
County of residence from first breast cancer diagnosis to reference date			
King	171 (48.7)	338 (51.1)	
Pierce	83 (23.6)	153 (23.1)	
Snohomish	67 (19.1)	118 (17.8)	
Thurston	30 (8.5)	53 (8.0)	NA
Progesterone receptor status of first breast cancer			
Negative	44 (12.5)	95 (14.4)	
Positive	307 (87.5)	567 (85.6)	.49
Vital status at enrollment			
Alive	260 (74.1)	532 (80.4)	
Deceased	91 (25.9)	130 (19.6)	.005
Data obtained primarily by medical record review			
Height at first breast cancer diagnosis, in			
<62	42 (12.3)	94 (14.9)	
62 to <64	120 (35.1)	247 (39.3)	
64 to <66	96 (28.1)	160 (25.4)	
≥66	84 (24.6)	128 (20.3)	
Missing	9	33	.19
Weight at first breast cancer diagnosis§, kg			
<61	63 (18.2)	160 (24.3)	
61 to <69	81 (23.4)	171 (26.0)	
69 to <82	85 (24.6)	158 (24.0)	
≥82	117 (33.8)	169 (25.7)	
Missing	5	4	.02
BMI at first breast cancer diagnosis§, kg/m^2			
<25	123 (35.8)	286 (43.7)	
25 to <30	115 (33.4)	196 (30.0)	
≥30	106 (30.8)	172 (26.3)	
Missing	7	8	.04
Osteoporosis or osteopenia diagnosis before reference date			
No	255 (73.5)	465 (70.3)	
Yes	92 (26.5)	196 (29.7)	
Missing	4	1	.28
No. of surveillance mammograms from first breast cancer diagnosis to reference date§			
0	5 (1.4)	54 (8.3)	
1–4	159 (45.8)	299 (45.7)	
5–9	152 (43.8)	254 (38.8)	
10–14	29 (8.4)	42 (6.4)	
≥15	2 (0.6)	5 (0.7)	
Missing	4	8	<.001

(Table continues)

Table 1 (Continued).

Characteristic	Contralateral breast cancer case subjects (n = 351) No. (%)	Control subjects (n = 662) No. (%)	*P*†
Treatment with aromatase inhibitors, mo			
None	330 (94.6)	598 (90.6)	
1–5	7 (2.0)	16 (2.4)	
≥6	12 (3.4)	46 (7.0)	
Missing	2	2	.02
Treatment with tamoxifen, mo			
None	139 (39.7)	212 (32.3)	
1–5	30 (8.6)	45 (6.8)	
≥6	181 (51.7)	400 (60.9)	
Missing	1	5	.01
Treatment with chemotherapy§			
No	261 (74.8)	485 (73.4)	
Yes	88 (25.2)	176 (26.6)	
Missing	2	1	.45
Treatment with radiation§			
No	122 (34.8)	226 (34.2)	
Yes	229 (65.2)	435 (65.8)	
Missing	0	1	.97
Data obtained primarily by telephone interview			
Race/ethnicity‖			
Non-Hispanic white	322 (92.3)	609 (92.3)	
Black	9 (2.6)	18 (2.7)	
Asian or Pacific Islander	10 (2.9)	21 (3.2)	
Native American	5 (1.4)	9 (1.4)	
Hispanic white	3 (0.9)	3 (0.5)	
Missing	2	2	NA
No. of full-term pregnancies by first breast cancer diagnosis‖			
0	56 (16.4)	102 (15.7)	
1	43 (12.6)	81 (12.5)	
2	106 (31.1)	193 (29.7)	
3	67 (19.6)	147 (22.7)	
≥4	69 (20.2)	126 (19.4)	
Missing	10	13	.76
Menopausal status at first breast cancer diagnosis			
Natural menopause	129 (52.9)	261 (51.9)	
Premenopause	45 (18.4)	86 (17.1)	
Induced menopause	30 (12.3)	63 (12.5)	
Simple hysterectomy	40 (16.4)	93 (18.5)	
Missing	107	159	.90
Average weekly alcohol consumption in the 5 years before first breast cancer diagnosis			
None	105 (42.0)	226 (43.5)	
<3 drinks	74 (29.6)	150 (28.9)	
≥3 drinks	71 (28.4)	143 (27.6)	
Missing	101	143	.55
Smoking status at first breast cancer diagnosis			
Never smoker	120 (47.6)	274 (52.5)	
Former smoker	49 (19.4)	77 (14.8)	
Current smoker	83 (32.9)	171 (32.8)	
Missing	99	140	.16
Use of unopposed estrogen or estrogen and progestin pill or patch for ≥6 mo before first breast cancer diagnosis‖			
Ever	161 (49.4)	319 (51.9)	
Never	165 (50.6)	296 (48.1)	
Missing	25	47	.41

(Table continues)

Table 1 (Continued).

Characteristic	Contralateral breast cancer case subjects (n = 351) No. (%)	Control subjects (n = 662) No. (%)	P†
First-degree family history of breast cancer at reference date‖			
No	231 (70.9)	467 (74.2)	
Yes	95 (29.1)	162 (25.8)	
Missing	25	33	.35

* For each matched case–control set, the reference date was defined at the date on which the case subject was diagnosed with a second primary contralateral breast cancer. AJCC = American Joint Committee on Cancer; BMI = body mass index.

† Likelihood ratio test *P* value comparing conditional logistic regression models with and without adjustment for the given characteristic. Models are implicitly adjusted for matching factors (age at and year of diagnosis with first primary breast cancer, Surveillance, Epidemiology and End Results historic stage [localized vs regional] of the first primary breast cancer, county of residence, and race/ethnicity).

‡ AJCC stage derivations for diagnoses made before 2004 were made according to version 1.1 of the SEER Program: Comparative Staging Guide for Cancer (18); subsequent diagnoses were staged according to the 10th edition of the North American Association for Central Cancer Registries Standards for Cancer Registries Volume II (19).

§ Supplemented by interview.

‖ Supplemented by medical record review.

record data (this exclusion influenced the exposure classification of three women). Information on bisphosphonate use before the first breast cancer diagnosis and self-reported bisphosphonate use were not available due to the design of the parent study. In these analyses, we assessed risks associated with use of any type of bisphosphonate and use specifically of the most prevalent bisphosphonate (alendronate alone).

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression to estimate the relative risk of developing contralateral breast cancer. We performed all analyses using STATA/SE 11.1 statistical software (STATA Corporation, College Station, TX). Reported *P* values are two-sided and, unless otherwise noted, were obtained using the Wald test. Statistical significance was defined as *P* less than or equal to .05. To test for trends in the duration of use among ever users and current users, we modeled the cumulative months of bisphosphonate use as a continuous variable and estimated the per-month change in the log odds of contralateral breast cancer.

By using conditional logistic regression, we implicitly adjusted for all of the matching factors in our statistical models. We also evaluated the potential confounding effects of the following factors selected a priori because of their potential to influence breast cancer susceptibility and bisphosphonate use: progesterone receptor status of the first primary breast cancer (positive or negative), height (<62, 62 to <64, 64 to <66, or ≥66 inches), weight (<61, 61 to <69, 69 to <82, ≥82 kg), body mass index (BMI; <25, 25 to <30, or ≥30 kg/m^2), having been diagnosed with osteoporosis or osteopenia (yes, no), surveillance mammography (none, 1–4, 5–9, 10–14, or ≥15 mammograms), therapies received for first breast cancer (ie, aromatase inhibitors [none, 1–5, ≥6 months], tamoxifen [none, 1–5, ≥6 months], chemotherapy [yes, no], radiation [yes, no]), parity (0, 1, 2, 3, 4, ≥4 full-term pregnancies), menopausal status (natural menopause, premenopause, induced menopause, simple hysterectomy), alcohol consumption (none, <3, or ≥3 drinks per week in the 5 years before first breast cancer diagnosis), smoking status (never, former, current), use of menopausal hormone therapy for 6 months or longer (ever, never), and first-degree family history of breast cancer (yes, no). Cut points were chosen to reflect those used in clinical practice and the distribution of the characteristic among the control subjects. To assess whether each potential confounder was associated with bisphosphonate use independent of its influence on contralateral breast cancer risk and the matching factors in the study population, among the control subjects, we compared unconditional logistic regression models of bisphosphonate ever use adjusted for the matching factors that included and excluded the given confounder. Of the variables listed in Table 1, only height, weight, BMI, osteoporosis or osteopenia diagnosis, aromatase inhibitor use, chemotherapy use, and surveillance mammography habits were associated with bisphosphonate use (likelihood ratio test $P \leq .2$). Of these, only adjustment for weight or BMI resulted in a meaningful change (judged as a change ≥10%) in the odds of contralateral breast cancer among women who had ever used bisphosphonates following their first breast cancer diagnosis relative to women who had not. Concurrent adjustment for weight and BMI yielded no change in the odds ratio compared with the model adjusted for BMI alone (OR of 0.53 vs OR of 0.53). Therefore, the final models were adjusted only for BMI and matching factors.

We used multiple approaches to assess potential confounding by indication. We conducted a subanalysis that was restricted to the 284 women in the original analysis who had been diagnosed with osteoporosis or osteopenia. To prevent the loss of those matched case–control sets in which either the case subject or all of the control subjects lacked a diagnosis of osteoporosis or osteopenia, we applied unconditional logistic regression adjusted for matching factors (in addition to adjustment for BMI). We were unable to perform an equivalent analysis among women who did not have a diagnosis of osteoporosis or osteopenia because only 10 of the 709 women in the original analysis without osteoporosis or osteopenia had used bisphosphonates. We performed two additional sensitivity analyses to further assess potential confounding by indication: one in which we excluded women with unknown bisphosphonate indication from the analysis, and another in which we excluded women who were using bisphosphonates at the time of their first breast cancer diagnosis in an attempt to remove the effects of

bisphosphonate use before breast cancer diagnosis on the observed associations. Varying the modeling assumptions regarding the potential confounding variables and applying different thresholds for bisphosphonate duration did not alter our interpretation of the data.

Results

Of the 121 women who had used bisphosphonates, 106 (88%) had used alendronate. Other bisphosphonates that were used by the women in this study included bisedronate, ibandronate, etidronate, pamidronate intravenous infusion, and zoledronate intravenous infusion. Of the 121 women who had used bisphosphonates, 109 (90%) had used only one type of bisphosphonate and 94 (78%) had used only alendronate. None of the women in this study had used a nonnitrogenous bisphosphonate.

Contralateral breast cancer case subjects were similar to control subjects with respect to the matching factors (age at and year of breast cancer diagnosis, breast cancer stage, race or ethnicity, and county of residence at breast cancer diagnosis), receipt of chemotherapy or radiation therapy, and progesterone receptor status of their first breast cancer. At the date of their first breast cancer diagnosis, the contralateral breast cancer case subjects were comparable to the control subjects with respect to average alcohol use in the last 5 years, current smoking status, menopausal status, the number of full-term pregnancies, and ever use of hormone therapy. A greater proportion of control subjects than case subjects received hormonal therapy as a treatment for breast cancer (aromatase inhibitors: 9.4% vs 5.4%; tamoxifen: 67.7% vs 60.3%). Contralateral breast cancer case subjects were, on average, heavier, had a higher BMI at the time of their first breast cancer diagnosis, and were much less likely to have received no surveillance mammograms over the study period compared with control subjects. Slightly more case subjects than control subjects had a first-degree family history of breast cancer (29.1% vs 25.8%) or had received a diagnosis of osteoporosis or osteopenia before the reference date (73.5% vs 70.3%) (Table 1).

Analyses that adjusted for matching factors and BMI revealed that women who ever used bisphosphonates for 6 months or longer following their first primary breast cancer diagnosis had a 47% lower risk of contralateral breast cancer compared with women who had never used bisphosphonates (OR = 0.53; 95% CI = 0.30 to 0.93) and that current users had a 59% lower risk (OR = 0.41; 95% CI = 0.20 to 0.84) (Table 2). By contrast, neither short-term nor former use of bisphosphonates was associated with risk of contralateral breast cancer. Restricting the analyses to women who had longer durations of bisphosphonate use (≥12 and ≥24 months) increased the magnitude and strength of the association with ever use (OR for ever use for ≥12 months vs never use = 0.38, 95% CI = 0.19 to 0.75; OR for ever use for ≥24 months vs never use = 0.36, 95% CI = 0.14 to 0.88) and with current use (OR for current use for ≥12 months vs never use = 0.31, 95% CI = 0.13 to 0.72; OR for current use for ≥24 months vs never use = 0.21, 95% CI = 0.06 to 0.73). We assessed linear trends for associations between increasing durations of bisphosphonate use and the log odds of contralateral breast cancer and found that the

Table 2. Nitrogenous bisphosphonate use and risk of second primary contralateral breast cancer*

Use following diagnosis with estrogen receptor–positive breast cancer	Any nitrogenous bisphosphonate				Alendronate			
	No. of case subjects	No. of control subjects	OR (95% CI)	*P*	No. of case subjects	No. of control subjects	OR (95% CI)	*P*
Ever use								
Never	308	532	1.00 (referent)		307	526	1.00 (referent)	
Short-term (<6 mo)	15	20	1.34 (0.67 to 2.70)	.41	12	16	1.28 (0.59 to 2.74)	.53
Ever (≥6 mo)	17	65	0.53 (0.30 to 0.93)	.03	13	50	0.51 (0.27 to 0.98)	.04
Duration of use among ever users								
≥12 mo	11	55	0.38 (0.19 to 0.75)	.005	9	42	0.40 (0.19 to 0.85)	.02
≥24 mo	6	31	0.36 (0.14 to 0.88)	.03	4	26	0.27 (0.09 to 0.79)	.02
Per year†	16	63	0.74 (0.58 to 0.95)	.02	13	48	0.73 (0.55 to 0.95)	.02
Recency of use among ever users‡								
Former use	6	15	0.76 (0.29 to 2.03)	.59	5	9	1.04 (0.33 to 3.32)	.94
Current use								
≥6 mo duration	10	48	0.41 (0.20 to 0.84)	.02	8	39	0.39 (0.18 to 0.88)	.02
≥12 mo duration	7	43	0.31 (0.13 to 0.72)	.006	6	34	0.33 (0.13 to 0.82)	.02
≥24 mo duration	3	24	0.21 (0.06 to 0.73)	.01	2	21	0.16 (0.04 to 0.71)	.02
Per year†	10	47	0.71 (0.52 to 0.96)	.03	8	38	0.71 (0.52 to 0.97)	.03

* ORs and 95% CIs were estimated using conditional logistic regression to account for matching factors (age and year of diagnosis with first primary breast cancer, Surveillance, Epidemiology and End Results historic stage of the first primary breast cancer, county of residence, and race/ethnicity). All models were additionally adjusted for body mass index at first breast cancer diagnosis. The alendronate-specific analyses exclude users of other types of bisphosphonates. *P* values (two-sided) were obtained using the Wald test. CI = confidence interval; OR = odds ratio.

† The relative change associated with a 1-year increase in duration of bisphosphonate use among ever and current users, extrapolated from the relative change associated with a 1-month increase. *P* value reflects the P_{trend}.

‡ Former use was defined as last use more than 6 months before the reference date, and current use was defined as use within 6 months before the reference date. For each matched case–control set, the reference date was defined at the date on which the case subject was diagnosed with a second primary contralateral breast cancer.

trends among both ever users and current users were statistically significant (P_{trend} of .02 and .03, respectively). The magnitudes and directions of these risk estimates did not change meaningfully in analyses focused specifically on alendronate use (Table 2). For example, current alendronate use was associated with a slightly lower risk of contralateral breast cancer compared with current use of any bisphosphonate (current alendronate use vs never use: OR = 0.39, 95% CI = 0.18 to 0.88; current use of any bisphosphonate vs never use: OR = 0.41, 95% CI = 0.20 to 0.84).

Adjustment for BMI shifted the odds ratio for ever use vs never use of bisphosphonates 11% toward the null (OR of 0.47 vs the above reported OR of 0.53). Adjustment for the other potential confounders did not meaningfully change the odds ratio: history of osteoporosis or osteopenia (3% change in OR), frequency of surveillance mammograms (4% change), use of aromatase inhibitors (7% change), and use of chemotherapy (1% change). Concurrent adjustment for weight and BMI yielded no change in the odds ratio compared with the model adjusted for BMI alone (OR of 0.53 vs OR of 0.53).

We explored potential confounding by indication by restricting the analyses to the 284 women diagnosed with osteoporosis or osteopenia with a known BMI. Risk estimates for this subgroup were similar to those in the overall analysis with respect to ever use ($OR_{subgroup}$ = 0.61, 95% CI = 0.31 to 1.20; $OR_{overall}$ = 0.53, 95% CI = 0.30 to 0.93), current use ($OR_{subgroup}$ = 0.43, 95% CI = 0.19 to 0.99; $OR_{overall}$ = 0.41, 95% CI = 0.20 to 0.84), and long-term (ie, ≥24 months) ever use ($OR_{subgroup}$ = 0.41, 95% CI = 0.16 to 1.09; $OR_{overall}$ = 0.36, 95% CI = 0.14 to 0.92) of bisphosphonates. Furthermore, neither exclusion of the 11 women with unknown indication (ie, analyses were restricted to women who use bisphosphonates for osteoporosis, arthritis, gout, or musculoskeletal problems) nor the eight women who reported current use of bisphosphonates at the time of their first breast cancer diagnosis meaningfully changed our risk estimates (data not shown).

Discussion

Our data provide evidence to support the hypothesis that nitrogen-containing bisphosphonates may reduce risk of a second primary breast cancer among ER+ breast cancer survivors. In this study, current use of bisphosphonates and use for longer durations were both associated with large reductions in risk. If these findings are confirmed by subsequent studies, the observed reduction in risk of contralateral breast cancer associated with prolonged bisphosphonate use may imply that these agents have antitumor effects outside of the adjuvant setting.

To our knowledge, the ABCSG-12 and Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trials are the only clinical trials of bisphosphonate use among breast cancer survivors to report contralateral breast cancer events; however, to date, the total number of events in these trials is low, and formal analyses have not yet been published (20,21). In ABCSG-12, 1803 premenopausal women with stage I or II ER+ breast cancer who were taking goserelin, an ovarian suppressor, were randomly assigned to receive tamoxifen or anastrozole and seven doses of adjuvant intravenous zoledronic acid over the course of 3 years or endocrine therapy alone (15). After a median of 62 months of follow-up, treatment with zoledronic acid improved disease-free survival (which included contralateral breast cancer) by 32% relative to endocrine therapy alone (20). In the AZURE trial, 3340 women diagnosed with stage II or III breast cancer were randomly assigned to receive standard chemotherapy with or without 19 doses of intravenous zoledronic acid over the course of 5 years. After a median follow-up of 62 months, there was no overall effect of zoledronic acid with respect to disease-free survival; however, when the analyses were restricted to postmenopausal women, an increase in disease-free survival in the zoledronic acid arm was observed (22). Our study population is more similar to that in the ABCSG-12 trial (in which goserelin created an artificial menopause) than to the AZURE study population because only 18% of the women in this study were premenopausal, all women had ER+ breast tumors, and 96% of the tumors were AJCC stage I or II.

There is a lack of studies on bisphosphonate use and contralateral breast cancer risk. Our findings with respect to ever use of bisphosphonates and duration of bisphosphonate use are consistent with four recent observational studies that evaluated the potential chemopreventive effect of bisphosphonate use in relation to risk of first primary breast cancer (12,13,23,24). These studies observed 20%–32% lower risks of first breast cancer associated with ever use of nitrogenous bisphosphonate therapy compared with never use. Three of these studies (13,23,24) evaluated duration of bisphosphonate use in relation to the risk of a first breast cancer, and similar to our results, two of them (13,23) observed stronger inverse associations with longer durations of bisphosphonate use. The third study (24) observed an inverse association only among women who used bisphosphonates for 2 years or less. The reasons for this discrepancy are uncertain, and more work is also needed to clarify the relationship between bisphosphonate use and the risk of a first breast cancer.

A range of theories has been proposed to explain the association between bisphosphonate use and a lower risk of breast cancer (9). Within hours of administration, bisphosphonates are deposited in the bone or transported to the kidneys for elimination; they remain in the skeleton until they are resorbed into the circulation (within days to weeks) and are then redeposited in the bone or transported to the kidneys (25). This constant release and reabsorption by bone contributes to the long half-life of bisphosphonates in the body. Potential direct effects of bisphosphonate include the induction of tumor cell apoptosis and inhibition of tumor cell invasion, viability, and proliferation (9). Potential indirect effects of bisphosphonates include reduction in the levels of cytokines and growth factors, inhibition of angiogenesis, and activation of gammadelta T cells (9). Our observation that current bisphosphonate use (but not former use) is associated with a reduced risk of contralateral breast cancer suggests that the effects of bisphosphonates with respect to breast cancer are transient. Although our data also suggest that longer-term use of bisphosphonates is inversely associated with risk, our sample size was insufficient to characterize if there is a duration of use after which the efficacy of bisphosphonates either plateaus or declines.

It is also important to consider potential confounding by indication when interpreting our results. Bisphosphonates are approved for the treatment of low bone density, which itself may be a marker

of past estrogen exposure. Longitudinal data on bone mineral density, beginning before the initiation of the first primary breast cancer, could provide insight into potential confounding by indication. However, data on bone density is not routinely included in medical records or known by a study participant; thus, individuals for whom bone density is available are unlikely to represent a random sample of the underlying population. This issue of confounding by indication is likely to become more of a challenge in future observational studies because bisphosphonates have become a standard treatment for cancer- and therapy-related side effects. Of the four observational studies discussed above, three (13,23,24) approached this challenge through adjustment of analyses for a variety of proxy measures of bone density, such as age, weight, height, physical activity, and history of fractures, and observed no meaningful change in the observed risk estimates. In the fourth study, Chlebowski et al. (12) measured bone mineral density for a subset of participants. They found that further adjustment for bone mineral density did not influence findings currently adjusted for 5-year risk of hip fracture, as modeled by proxy measures. We used multiple approaches to assess potential confounding by indication, including adjusting for a broad range of factors thought to be associated with bone density or hormone exposure (eg, height, weight, BMI, use of adjuvant hormonal therapy, chemotherapy, radiation, diagnosis with osteoporosis or osteopenia) and performing sensitivity analyses that were restricted to women who had been diagnosed with osteoporosis or osteopenia, excluded patients with an unknown indication for bisphosphonate use, or excluded those who were using bisphosphonates at the time of their first breast cancer diagnosis. The results of all of these analyses were consistent with our overall findings, suggesting that confounding by indication is unlikely to explain fully the relationships we observed.

The strengths of this study are the high participation rates and the ascertainment of participants without respect to vital status, which decreases the potential for selection biases such as survivor bias. Recall bias was prevented by using data abstraction from medical records. Potential surveillance bias was assessed by evaluating the impact of mammography use and was found not to influence our risk estimates. Our finding of an inverse association between bisphosphonate use and contralateral breast cancer risk is consistent with in vitro and in vivo evidence of direct and indirect antitumor effects of bisphosphonates (26). In addition, this study is relatively large for a study of contralateral breast cancer risk in women diagnosed with ER+ breast cancer. However, this study has several limitations. We cannot rule out chance or residual confounding as causes of the observed associations. Factors that influence the ability to tolerate bisphosphonates or to adhere to their use (a frailty effect) could explain the observed dose–response relationship with duration. Lastly, our findings may not be generalizable to risk of breast cancer recurrences, premenopausal use of bisphosphonates, ER-negative or advanced-stage breast cancer survivors, nonnitrogenous bisphosphonate use, or other less common forms of bisphosphonates.

To our knowledge, this is the first study to evaluate the association between bisphosphonate use and the risk of contralateral breast cancer in detail. Recent literature related to risk of relapse, treatment-induced bone loss, and metastasis to the bone [reviewed in (26)] suggests that bisphosphonates may confer multiple benefits to breast cancer survivors; however, these benefits need to be weighed against the potential adverse effects of bisphosphonates, which include osteonecrosis of the jaw and atrial fibrillation. A reduced risk of contralateral breast cancer may be among the potential benefits of bisphosphonates, and large ongoing clinical trials should, in the future, be able to provide additional clarity about the influence of bisphosphonates on second primary breast cancer risk, relapse, and comorbidity. Given the perceived tolerance for and potential benefits of bisphosphonates in this high-risk population, nitrogenous bisphosphonate therapy may prove to be a feasible approach for contralateral breast cancer risk reduction and merits further investigation both during and after adjuvant therapy.

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