JOURNAL OF WOMEN'S HEALTH
Volume 22, Number 2, 2013

DOI: 10.1089/jwh.2012.3687

Bone Mineral Density Screening Among Women with a History of Breast Cancer Treated with Aromatase Inhibitors

Leslie Spangler, PhD, VMD,[1] Onchee Yu, MS,[1]
Elizabeth Loggers, MD, PhD,[1,2] and Denise M. Boudreau, PhD, RPh[1,3]

Abstract

Background: Understanding adherence to bone mineral density (BMD) screening after breast cancer (BC) treatment with aromatase inhibitors (AI) is an important first step in preventing or treating BC-related osteoporosis.
Methods: This retrospective cohort study assessed receipt and adherence to BMD screening among 342 women diagnosed with BC who were at high risk for osteoporosis after BC treatment with AI between 2004 and 2007. Nonadherence to baseline and annual BMD screening (recommended by 2003 American Society of Clinical Oncology Guidelines) was assessed using descriptive statistics and Poisson regression models accounting for length of AI use and follow-up.
Results: In the year before AI initiation, 16% of women received BMD screening. Fifty-six percent had no BMD screening in the14 months after a minimum of 9 months of continuous AI use, and 75% and 66% failed to have BMD screens during the second (14.1–26 month) and third (26.1–38 month) annual time periods after continuous AI use for at least 23 and 35 months, respectively. Overall, 24% had no BMD screening after 35 months of continuous AI use. Statistically significant predictors of nonadherence included predominant exemestane use, BMD screening before AI initiation, and diabetes mellitus history. Postcollege education, geographic region of primary care clinic, and never smoking were associated with a reduced risk of nonadherence.
Conclusions: A significant proportion of breast cancer patients treated with AI did not receive guideline-recommended BMD screening. Findings should raise awareness of the importance of BMD screening and targeting women at increased risk of screening nonadherence.

Introduction

Osteoporosis affects approximately 12 million adults over the age of 50 years in the United States and is associated with increased rates of bone fractures.[1] Osteoporosis-related fractures are associated with excess mortality, morbidity, and dependency, resulting in 180,000 nursing home visits annually.[2] In addition to better known risk factors for osteoporosis (e.g., inadequate calcium and vitamin D intake and lower rates of exercise[3]), adjuvant breast cancer (BC) treatments can negatively affect bone health by inducing premature menopause (via ovarian suppression as a result of gonadotropin-releasing hormone [GRH] agonists, chemotherapy, or surgical ablation) or by reducing circulating estrogen levels (via adjuvant endocrine therapy).[4] As a result of cancer treatment, an estimated 2.9 million BC survivors, in the United States, almost 2% of the female population, may be at increased risk of osteoporosis and fracture, and this number is expected to increase.[5]

Endocrine therapy is particularly important in understanding BC-related osteoporosis risk, as it is a mainstay of adjuvant BC treatment for the approximately 80% of estrogen receptor-positive BC patients. The two recommended adjuvant endocrine therapies are tamoxifen (TAM) and aromatase inhibitors (AI).[6] The U.S. Food and Drug Administration (FDA) approved TAM for use in node-negative premenopausal and postmenopausal women in 1990. Late in 2002, the FDA approved the first AI as adjuvant therapy in postmenopausal women. In 2005, consideration of AI as a primary (5 years) or sequential (2–5 years after 2–5 years of TAM) adjuvant treatment option in postmenopausal women was recommended to improve disease-free survival.[6,7]

[1]Group Health Research Institute, Seattle, Washington.
[2]Fred Hutchinson Cancer Research Center, Seattle, Washington.
[3]School of Pharmacy, University of Washington, Seattle, Washington.

With respect to bone health, TAM may increase bone loss in premenopausal women with high levels of estrogen for the first 1–2 years of therapy, but enhanced bone mineral density (BMD) monitoring is not currently advocated.[4] In postmenopausal women, TAM is associated with a modest conservation of bone.[4,8–10] An increasing number of postmenopausal women are prescribed AI,[11] which are associated with both increased bone turnover[12] and higher fracture rates compared to TAM.[3,13]

In 2003, the American Society of Clinical Oncology (ASCO) published guidelines for managing bone health in women with BC, including those receiving adjuvant endocrine therapy.[11] In that guideline, BC patients were defined as high risk for osteoporosis if they were (1) older than 65 years, (2) aged 60–64 years with a family history of hip fracture, a prior nontraumatic fracture, a weight of <70 kg, or other risk factors for osteoporosis, (3) any age, if postmenopausal and receiving AI, or (4) diagnosed with BC therapy-associated premature menopause. For patients meeting high-risk criteria, initial BMD screening followed by annual assessments was recommended.[11] A recent cost-effectiveness study supports the use of these guidelines.[14] The objective of the current study was to describe adherence to BMD screening guidelines and predictors of nonadherence in a growing group of women with a history of early-stage breast cancer who are at high risk for osteoporosis by virtue of AI use.

Materials and Methods

Study setting

This retrospective cohort study used automated data from Group Health Cooperative (GH), a large mixed-model, nonprofit, healthcare insurer and delivery system based in Seattle, WA. GH provides comprehensive healthcare on a prepaid basis to approximately 600,000 enrollees either within its integrated group practice (IGP), served by employed staff physicians in typically GH-owned clinics, or by contracted, community-based providers. GH has extensive electronic data that capture detailed information on enrollment, medical encounters, laboratory services, medication dispensing, diagnoses, and procedures. Computer linkage between the GH population and the Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry provides complete ascertainment of validated cancer cases. Only enrollees receiving care within the IGP and residing in the 13-county SEER capture area were included in this study to ensure data accuracy and completeness.

Study population and data collection

The population included women of any age (1) identified in the SEER registry as diagnosed with early stage (I,II) incident BC, (2) enrolled in GH for at least 1 year before breast cancer diagnosis, and (3) initiating AI therapy between January 1, 2004, and May 31, 2007, with at least 9 months of continuous use. Subjects were followed for 38 months after AI initiation (or until death if it happened in the 38-month period). To determine the duration of AI use, all AI dispensing from time of BC diagnosis to the earliest of October 1, 2010, study end date, disenrollment from GH, or death was extracted from GH pharmacy data. The duration of each AI dispensing (or runout date) was estimated based on the days' supply variable recorded in pharmacy data multiplied by a 80% compliance factor of 1.25.[15] If the runout date of one AI dispensing and the next AI dispensing date were <60 days apart, the two dispensings were considered a continuous episode.[16,17] The first episode started on the date the first AI was dispensed and ended on the runout date of the last AI dispensed in the episode. Different AI could be used within the same AI episode. The predominate type of AI was defined as the AI with the longest days' supply.

To limit the population to women eligible for regular BMD screening (vs. monitoring osteoporosis), women were excluded if they had an indication for osteoporosis (*International Classification of Diseases*, 9th Revision, *Clinical Modification* [ICD9-CM] diagnosis codes 733.0, 733.00, 733.01, 733.02, 733.03, 733.09) or a dispensing for medications used to manage osteoporosis (i.e., alendronate, calcitonin, etidronate, risedronate, teriparatide, ibandronate, pamidronate, zoledronic acid, raloxifene) in the year before starting AI therapy. The final sample included 342 women. All study procedures were approved by Group Health's Institutional Review Board.

Outcomes

The outcomes of interest were presence/absence of any BMD tests, number of BMD tests, and nonadherence to BMD screening guidelines in a prespecified time period. BMD testing was defined as having an ICD9 procedure (88.98), Current Procedural Terminology (CPT) (76075, 76076, 76077, 77080, 77081, 77082, 76070, 76071, 77078, 77079, 76977, 77083, 76078, 78350, 78351, 0028T, 3095F, 3096F) or Healthcare Common Procedure Coding System (G0131, G0132, G0130, G8399) code in automated outpatient data. In our data, however, all procedures were identified through CPT codes for dual x-ray absorptiometry (DEXA) studies for either the appendicular (76076, 77081) or axial (76075, 77080) skeleton.

We describe the percent of women who did not receive any BMD testing during the 0–14 months, 14.1–26 months, and 26.1–38 months after AI initiation as well as the number of tests performed in different time periods. When BMD screening was assessed at 26 months, women were required to remain on AI continuously for at least 23 months with no indication of osteoporosis (i.e., no diagnosis code for osteoporosis or dispensing for medication used to manage osteoporosis) in the year before through 14 months after AI initiation ($n=251$). For the 38-month assessment, women were required to remain on AI continuously for at least 35 months with no indication of osteoporosis in the year before through 26 months after-AI initiation ($n=174$). Fourteen months, as opposed to 12 months, was chosen for the first interval in order to provide a grace period for scheduling the BMD test.

The definition of nonadherence to BMD screening was based on the ASCO 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer,[11] in which baseline and annual BMD screenings are recommended for high-risk patients. A conservative definition for nonadherence was used that accounted for both length of AI use and follow-up. Women who were on AI for at least 23 months were considered nonadherent if they had no BMD tests performed within 0–26 months after starting AI. Women on AI for at least 35 months were considered nonadherent if they did not have at least two BMD texts performed >9 months apart within 38 months of AI initiation.

Table 1. Characteristics of Eligible Breast Cancer Patients Prescribed Aromatase Inhibitors During January 1, 2004–May 31, 2007

Factor	n (n = *342*)	%
Age at AI start, years		
<50	23	6.7
50–54	49	14.3
55–64	155	45.3
65+	115	33.6
Race		
Caucasian	299	87.4
African American	14	4.1
American Indian /Alaskan Native	11	3.2
Asian	18	5.3
Education		
High school graduate or less	50	14.6
Some college	88	25.7
College graduate	55	16.1
Postcollege	66	19.3
Missing	83	24.3
Weight <70 kg (154 lbs)[a]	201	58.7
Smoking status[a]		
Current	18	5.3
Past	80	23.4
Never	242	70.7
Urban commuting area code	334	97.7
Insurance type		
Medicare	284	83.0
Individual	40	11.7
Commercial	18	5.3
Primary care clinic geographic region[a]		
Region 1 (Seattle)	169	49.4
Region 2 (South)	103	30.1
Region 3 (West)	17	5.0
Region 4 (North)	52	15.2
Charlson comorbidity score		
0	246	71.9
1	64	18.7
2+	32	9.4
History of fracture	28	8.1
Diabetes mellitus	93	27.2
Depression	56	16.4
Any medical conditions associated with osteoporosis (Appendix)	20	5.9
Corticosteroid use	58	17.4
Use of other medications associated with risk of osteoporosis (Appendix)	72	21.1
Incident breast cancer diagnosis year		
1990–1999	64	18.7
2000–2003	133	38.9
2004–2007	145	42.4
Breast cancer stage[a]		
I	161	47.1
IIA	106	31.0
IIB	74	21.6
Time from incident breast cancer diagnosis to AI start, years		
≤1	135	39.5
>1–3	66	19.3
>3–5	59	17.2
>5–16	82	24.0
AI start year		
2004	80	23.4
2005	129	37.7
2006	109	31.9
2007	24	7.0
Duration of AI use during study period, years		
<1	16	4.7
1–3	125	36.5
>3	201	58.8
Predominant type of AI used[b]		
Anastrozole	193	56.4
Exemestane	31	9.1
Letrozole	118	34.5
Tamoxifen (TAM) use since breast cancer diagnosis		
No TAM use	120	35.1
TAM use before AI start	203	59.3
TAM use after AI	19	5.6
Number of visits to oncologist in year before starting AI		
0	47	13.7
1–2	164	48.0
3–4	70	20.5
≥5	61	17.8
BMD test within 1 year before AI start	56	16.3

[a]Percentages calculated with missing as a separate category. Percent missing; weight 4.1%, smoking 0.6%, geographic region of clinic 0.3%, breast cancer stage 0.3%.
[b]Aromatase inhibitor (AI) with longest days' supply.
BMD, bone mineral density.

Covariates

Information was collected on covariates that were potentially related to receipt of BMD screening, including risk factors identified in the GH osteoporosis screening guidelines (Table 1). In the primary care setting, GH recommends BMD screening using DEXA with a minimum of 2 years between test for women aged 65–85 years or any age if they suffered a low-impact fracture, weigh <60 kg, or use medications or have medical conditions that put them at increased risk for osteoporosis. Breast cancer stage and race were obtained from the SEER registry. All other covariates were collected from GH automated data in the year before AI initiation. These covariates included education, weight, smoking status, history of fracture,[18] diabetes,[19] depression diagnoses, Charlson comorbidity score (Deyo version),[20] and corticosteroid use. Other medications and medical conditions listed in the GH osteoporosis screening guidelines as being associated with a higher risk of developing osteoporosis were also included. The Appendix lists medications and medical conditions associated with osteoporosis and additional details on covariate definitions. To assess any variability in adherence by geographic region, the location of the patient's primary care clinic was classified (as patients may not receive all care from their onchologists[21]) into four regions of western Washington (1: Seattle area, 2: South, 3: West, 4: North).

Analysis of nonadherence predictors

Because nonadherence to BMD screening guidelines was common, we performed Poisson regression with robust

Table 2. Percent of Patients not Receiving Bone Mineral Density Testing Within Selected Time Periods After Starting Aromatase Inhibitors

	% of patients who did not receive BMD testing		
Sample	*0–14 months*	*14.1–26 months*	*26.1–38 months*
Remained on AI ≥9 months with no indication of osteoporosis in 1 year before starting AI ($n=342$)	56	NA[a]	NA[a]
Remained on AI ≥23 months with no indication of osteoporosis 1 year before through 14 months after AI start ($n=251$)	56	75	NA[a]
Remained on AI ≥35 months with no indication of osteoporosis 1 year before through 26 months after AI start ($n=174$)	52	77	66

[a]NA, not applicable.

(sandwich) standard errors to evaluate the association between potential predictors and nonadherence to BMD screening guideline,[22] rather than logistic regression-based odds ratios (OR), which overestimate the relative risks (RR) for common outcomes. Factors associated with nonadherence at an alpha ≤0.05 in univariate analysis were included in a multivariate model. The multivariable models were simplified by removing nonsignificant variables ($p>0.05$) unless they changed coefficients of other significant variables by >10%. Separate models were fitted for the 26-month and 38-month time periods. All analyses were performed in Stata version 11 (StataCorp, College Station, TX).

Results

Descriptive characteristics

The median age of the study subjects was 62 years (range 36–89 years). Over 50% of women weighed <70 kg, never smoked, started TAM before starting AI, had a Charlson comorbidity score of 0, were Caucasian, and were insured by Medicare (Table 1). Sixteen percent of women had BMD testing in the year before AI initiation, and approximately 59% had >3 years of continuous AI use.

Fifty-six percent of women had no BMD tests performed within 14 months of starting AI (Table 2), and the percentages of women who had no BMD testing during the second (14.1–26 months) and third (26.1–38 months) annual time periods were 75% and 66%, respectively. During the 38 months after AI initiation, the median number of months from the first AI dispensing until the first BMD test was 11.3 (range 0–37.5 months). The median number of months between the first and second BMD tests was 23 months (range 3.4–37.5 months). When looking across the entire 0–26-month and 0–38-month time periods (rather than the annual period), 37% and 24% of women, respectively, had no BMD testing (Table 3).

Table 3. Number of Bone Mineral Density Tests During Selected Time Periods After Starting Aromatase Inhibitors

	0–26 months (n=*251*)	*0–38 months* (n=*174*)
Number of BMD tests	*%*	*%*
0	37	24
1	57	50
2	6	23
3	0	3

Predictors of nonadherence to BMD screening guidelines

Nonadherence to BMD screening guidelines was different among women who remained on AI for at least 23 months (37% without any BMD screens in the 26-month period) compared to women who remained on AIs for at least 35 months (74% without two or more BMD screens at least 9 months apart in the 38-month period). Factors associated with a statistically significantly higher likelihood of nonadherence in univariate models for both time periods included predominant exemestane use vs. anastrozole use (26-month period, $p<0.001$; 38-month period, $p<0.001$) and having a BMD screening performed in the year before starting AI (26-month period, $p=0.04$; 38-month period, $p<0.001$) (Table 4). Nonadherence varied by region of clinic: region 2 (South) compared to region 1 (Seattle) (26-month period, $p<0.001$; 38-month period, $p<0.001$). These same variables remained statistically significant in the multivariate analyses (Table 5). Additionally, in the 26-month univariate and mulitivariable analyses, postcollege education (vs. high school or less) ($p=0.01$) and never smoking (vs. current smoking) ($p=0.02$) were associated with a lower likelihood of nonadherence, whereas diabetes mellitus was associated with a higher risk of nonadherence ($p=0.01$).

Discussion

This is the largest and, to our knowledge, first study investigating adherence to BMD screening among women at high risk of osteoporosis because of BC treatment with AIs in a community setting. The results indicate that a large proportion of BC patients using AI therapy and, thus, at risk for osteoporosis are not receiving BMD screening as recommended by guidelines. However, BMD screening was highest around the time of initiating AI therapy, and women who remained on AI for 38 months vs. 26 months were more likely to have at least one BMD test.

Two other small studies conducted in cancer centers assessed attention to bone health in BC patients as described in the 2003 ASCO guidelines.[23,24] Gibson et al.[23] reported suboptimal adherence to BMD screening in 54 high-risk BC patients with an outpatient dispensing for AI between 2005 and 2006 who were not previously diagnosed with osteoporosis or taking bisphosphonate for bone metastases. Review of

Table 4. Predictors of Nonadherence to Bone Mineral Density Screening at 26 and 38 Months in Univariate Modified Poisson Model

	26 months		38 months	
	IRR	*95% CI*	*IRR*	*95% CI*
Age at AI start, years				
<65	Reference		Reference	
≥65	1.08	(0.76-1.53)	0.98	(0.80-1.20)
Race				
Caucasian	Reference		Reference	
African American	1.40	(0.69-2.88)	1.09	(0.70-1.71)
American Indian/Alaskan Native	0.70	(0.21-2.37)	1.17	(0.85-1.61)
Asian	1.40	(0.83-2.37)	0.91	(0.57-1.46)
Education				
High school graduate or less	Reference		Reference	
Some college	0.89	(0.58-1.36)	1.15	(0.82-1.62)
College graduate	0.90	(0.55-1.47)	1.03	(0.70-1.53)
Postcollege	0.43	(0.23-0.80)	1.09	(0.76-1.57)
Missing	0.76	(0.45-1.26)	1.16	(0.82-1.64)
Weight, kg				
≥70	Reference		Reference	
<70	0.85	(0.61-1.20)	0.94	(0.78-1.14)
Smoking status				
Current	Reference		Reference	
Past	0.65	(0.38-1.11)	1.02	(0.75-1.40)
Never	0.55	(0.34-0.89)	0.86	(0.64-1.16)
Insurance type				
Medicare	Reference		Reference	
Individual	1.08	(0.63-1.85)	1.02	(0.73-1.44)
Commercial	1.06	(0.52-2.16)	1.06	(0.74-1.53)
Primary care clinic geographic region				
Region 1	Reference		Reference	
Region 2	0.41	(0.25-0.68)	(0.48	(0.36-0.65)
Region 3	1.28	(0.76-2.14)	0.79	(0.54-1.14)
Region 4	1.28	(0.76-2.14)	0.86	(0.70-1.06)
Charlson comorbidity score[13]				
0	Reference		Reference	
1+	1.29	(0.92-1.83)	1.09	(0.90-1.32)
History of fracture				
No	Reference		Reference	
Yes	0.84	(0.50-1.41)	1.12	(0.89-1.40)
Diabetes mellitus				
No	Reference		Reference	
Yes	1.56	(1.13-2.15)	1.13	(0.94-1.36)
Depression				
No	Reference		Reference	
Yes	0.97	(0.62-1.51)	1.10	(0.89-1.35)
Any medical conditions associated with osteoporosis (AppendixA)				
No	Reference		Reference	
Yes	0.77	(0.33-1.79)	0.60	(0.31-1.16)
Corticosteroid use				
No	Reference		Reference	
Yes	0.84	(0.53-1.35)	1.26	(1.07-1.48)
Use of other medications associated with risk of osteoporosis (AppendixA)				
No	Reference		Reference	
Yes	1.10	(0.75-1.62)	1.15	(0.96-1.37)
Breast cancer stage				
I	Reference		Reference	
IIA	0.96	(0.65-1.42)	1.00	(0.81-1.23)
IIB	1.15	(0.78-1.70)	1.02	(0.82-1.28)
Time from incident breast cancer diagnosis to AI start, years				
≤1	Reference		Reference	
>1–3	1.31	(0.85-2.02)	1.05	(0.83-1.32)
>3–5	1.22	(0.74-2.02)	0.87	(0.60-1.27)
>5–16	1.36	(0.89-2.06)	0.87	(0.69-1.11)

(*continued*)

Table 4. (Continued)

	26 months		38 months	
	IRR	*95% CI*	*IRR*	*95% CI*
AI start year				
2004	Reference		Reference	
2005	1.41	(0.88-2.27)	1.07	(0.85-1.35)
2006	1.30	(0.79-2.13)	1.07	(0.84-1.36)
2007	0.63	(0.21-1.90)	0.82	(0.49-1.37)
Predominant AI type used				
Anastrozole	Reference		Reference	
Exemestane	1.99	(1.34-2.97)	1.30	(1.17-1.45)
Letrozole	1.13	(0.78-1.62)	0.87	(0.71-1.06)
BMD w/in 1 year of AI start				
No	Reference		Reference	
Yes	1.47	(1.02-2.11)	1.36	(1.19-1.56)
Tamoxifen use since breast cancer diagnosis				
No TAM use	Reference		Reference	
TAM use before AI start	1.40	(0.98-2.00)	0.96	(0.80-1.16)
TAM use after AI	0.41	(0.06-2.66)	1.35	(1.19-1.53)
Number of visits to oncologist in year before AI start				
0	Reference		Reference	
1–2	1.64	(0.87-3.08)	1.44	(0.95-2.16)
3–4	1.13	(0.54-2.38)	1.52	(0.97-2.37)
≥5	1.42	(0.71-2.87)	1.78	(1.19-2.65)

CI, confidence interval; IRR, incidence rate ratio.

Table 5. Predictors of Nonadherence to Bone Mineral Density Screening in 26 and 38 Month Multivariable Models

	0–26-month model		0–38-month model	
	IRR	*95% CI*	*IRR*	*95% CI*
Predominant type of AI used				
Anastrozole	Reference		Reference	
Exemestane	1.66	(1.09-2.53)	1.26	(1.06-1.50)
Letrozole	1.12	(0.79-1.59)	0.85	(0.71-1.01)
BMD w/in 1 year of AI start				
No	Reference		Reference	
Yes	1.50	(1.06-2.13)	1.52	(1.26-1.82)
Primary care clinic geographic region				
Region 1 (Seattle)	Reference		Reference	
Region 2 (South)	0.38	(0.24-0.62)	0.47	(0.35-0.62)
Region 3 (West)	1.35	(0.78-2.35)	0.81	(0.56-1.16)
Region 4 (North)	0.71	(0.45-1.11)	0.89	(0.72-1.10)
Education[a]				
High school graduate or less	Reference			
Some college	0.91	(0.58-1.43)		
College graduate	0.91	(0.57-1.46)		
Postcollege	0.45	(0.24-0..84)		
Missing	0.78	(0.48-1.27)		
Smoking Status[a]				
Current	Reference			
Past	0.72	(0.44-1.20)		
Never	0.58	(0.36-0.93)		
Diabetes[a]				
No	Reference			
Yes	1.39	(1.02-1.90)		

[a]Separate models were fitted for the 26-month and 38-month time periods.

electronic medical records revealed that 22% had no documentation of BMD tests and only 8% had baseline and yearly scans. Similar to our study results, they reported a greater number of BMD tests conducted before and at the start of AI dispensing compared to after AI initiation. In a 2004–2005 study of premenopausal women ≤50 years with chemotherapy-induced amenorrhea, 56% of respondents remembered discussing adjuvant chemotherapy and its relation to bone health with their doctors.[24] Forty percent of the women remembered being asked to undergo BMD testing; 32% did undergo BMD testing.

Lack of BMD screening in high-risk populations could be related to system, provider, or patient factors. One author postulated that the number of and diversity of recommendations between various osteoporosis screening, prevention, and treatment guidelines could affect their use in practice.[25] Management of bone health is addressed in both cancer treatment guidelines[11] and general osteoporosis guidelines, with AI being included under medications that contribute to osteoporosis.[26] In addition, different guidelines have provided varying recommendations on the interval between BMD screening since the 2003 ASCO guidelines were disseminated.[3,26,27] For example, the 2009 American College of Preventive Medicine[27] guidelines note that BMD testing by DEXA should not be performed more frequently than every 2 years, whereas the 2009 National Comprehensive Cancer Networks (NCCN) Task Force Report on Bone Health in Cancer Care[3] noted that cancer patients with elevated fracture risk should be evaluated every 24 months, with the added caveat that 12-month follow-up may be appropriate in situations when the risk of bone loss changes significantly. Medicare pays for BMD testing every 2 years but may pay for more frequent testing if medically necessary.[28] This scenario may be more complicated in women with BC, as these women are seen by both primary care physicians and oncologists; physicians appear to vary by specialty in their reports of barriers to BMD screening (e.g., patients too old or frail for testing).[29]

We found that nonadherence varied in at least one clinic location despite multiple available healthcare facilities with BMD testing and relatively similar demographic characteristics of BC patients in that region. This finding is consistent with other studies that report variation by clinic location in BMD screening rates of at-risk patients and receipt of other preventive care services in the general population.[30–32] For example, a multivariate analysis of 6,311 high-risk patients seen at 10 affiliated primary care practices in 2002 reported variation in adherence to local osteoporosis guidelines by physician and practice site.[30] This was also reported in a more recent study that evaluated BMD screening documented in 2005–2006 medical records in 833 women deemed high risk by virtue of their age >65 years; a wide range of physician-specific and practice-specific screening rates were observed.[31] At least one study suggested that clinic (university vs. hospital-based facility) was more important than patient characteristics in predicting adherence to preventive care services (e.g., mammogram, Pap smear, cholesterol testing, and retinal examination).[32]

There is still speculation about why the small percent (9%) of BC patients who used exemestane (irreversible steroidal inhibitor) had an increased risk of nonadherence to BMD screening compared to users of anastrozole (reversible non-steroidal inhibitor).[33] Some earlier animal research suggested that exemestane may have less effect on bone,[34] but subsequent research did not support this.[35,36] It is possible that exemestane was prescribed more in women who developed metastatic disease. We did not have data on metastatic disease to evaluate this hypothesis, but the time between BC diagnosis and AI initiation provided some evidence that exemestane was not used more frequently in the metastatic setting than letrozole (1080 days vs. 1524 days) but possibly was used more frequently than anastrazole (1080 days vs. 769 days). Women who used exemestane for at least 23 months did not appear to differ significantly from anastrozole or letrozole users in Charlson comorbidity score, BC stage at diagnosis, region of their primary care clinic (we were not able to assess prescriber), and age at AI start (data not shown). A higher percent of exemestane users did have prior TAM use (90% vs. 44% anastrozole and 76% letrozole, $p<0.01$) and BMD screening in the year before starting AI (30% vs. 11% and 21%, respectively, p 0.03), which may help explain the different risks of nonadherence.

Some aspects of this study merit consideration when interpreting the findings. First, we were not able to differentiate between BMD tests performed for screening vs. monitoring of already diagnosed osteoporosis or its treatment. We limited this misclassification by excluding women with an osteoporosis diagnosis or dispensing for a medication used to treat osteoporosis. Although AI use is indicated for postmenopausal women, we cannot ensure that all women were postmenopausal. Also, 24% of women started using AI >5 years after BC diagnosis (mean age at diagnosis 58 years). This opens the possibility that some women may have been treated with AI for recurrent (metastatic) disease. In sensitivity analyses restricted to women who started AI ≤5 years after BC diagnosis, there was little change in the percent of women receiving BMD testing. In this study, we required a minimum of 9 months of AI use. It is possible that women who were on AI for <9 months may have discontinued AI because they had a BMD screen that showed low BMD. In this scenario, the women would have received BMD screening but not be counted as such, which could cause a false elevation in the number of women with no BMD screening in the first year after AI initiation. The results of a sensitivity analysis that included all women who were on AI regardless of duration of use did not support this concern. Finally, this study was performed in women who had health insurance through a single health plan in western Washington and started AI treatment between 2004 and 2007; thus, results may not be generalizable to other populations, settings, or time periods. It is outside the scope of this study to address potential harms of BMD testing[27] or reasons for nonadherence (e.g., provider failing to refer for screening vs. patient noncompliance with recommendations).

Conclusions

A gap remains between clinical practice and guidelines for managing bone health in BC patients receiving AIs. Lack of adherence may have significant public health implications as the number of BC survivors increases and the population ages. Comparative effectiveness studies as well as consolidation or standardization of different osteoporosis guidelines should be considered. The risk of nonadherence to guidelines

was greater among women with certain characteristics. Effectiveness of primary care interventions to improve BMD screening that were successful in other high-risk populations, such as physician/patient education and notification[37] or universal bisphosphonate treatment,[14] could be explored in these nonadherent groups.

Acknowledgments

The project described was supported by award number R01CA120562 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Disclosure Statement

No competing financial interests exist.

References

1. U.S. Preventive Services Task Force (USPSTF). Screening for osteoporosis: recommendation statement. Am Fam Physician 2011;83:1197–1200.
2. National Osteoporosis Foundation (NOF). Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: NOF, 2010. Available at www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v2007.pdf Accessed July 2012.
3. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force report: Bone health in cancer care. J Natl Compr Canc Netw 2009;7 (Suppl 3):S1–S32.
4. Reid DM, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treat Rev 2008;34 (Suppl 1):S3–18.
5. De Angelis R, Tavilla A, Verdecchia A, et al. Breast cancer survivors in the United States: Geographic variability and time trends, 2005–2015. Cancer. 2009;115:1954–1966.
6. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28:3784–3796.
7. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004. J Clin Oncol 2005;23:619–629.
8. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992;326:852–856.
9. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996;14:78–84.
10. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–1388.
11. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042–4057.
12. Khan MN, Khan AA. Cancer treatment-related bone loss: A review and synthesis of the literature. Curr Oncol 2008;15: S30–40.
13. Neuner JM, Yen TW, Sparapani RA, Laud PW, Nattinger AB. Fracture risk and adjuvant hormonal therapy among a population-based cohort of older female breast cancer patients. Osteoporos Int 2011;22:2847–2855.
14. Ito K, Blinder VS, Elkin EB. Cost-effectiveness of fracture prevention in postmenopausal women who receive aromatase inhibitors for early breast cancer. J Clin Oncol 2012;30:1468–1475.
15. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995;274:620–625.
16. Boudreau DM, Yu O, Miglioretti DL, Buist DS, Heckbert SR, Daling JR. Statin use and breast cancer risk in a large population-based setting. Cancer Epidemiol Biomarkers Prev 2007;16:416–421.
17. Boudreau DM, Koehler E, Rulyak SJ, Haneuse S, Harrison R, Mandelson MT. Cardiovascular medication use and risk for colorectal cancer. Cancer Epidemiol Biomarkers Prev 2008; 17:3076–3080.
18. Lix LM, Yogendran MS, Leslie WD, et al. Using multiple data features improved the validity of osteoporosis case ascertainment from administrative databases. J Clin Epidemiol 2008;61:1250–1260.
19. Newton KM, LaCroix AZ, Heckbert SR, Abraham L, McCulloch D, Barlow W. Estrogen therapy and risk of cardiovascular events among women with type 2 diabetes. Diabetes Care 2003;26:2810–2816.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373–383.
21. Keating NL, Landrum MB, Guadagnoli E, Winer EP, Ayanian JZ. Surveillance testing among survivors of early-stage breast cancer. J Clin Oncol 2007;25:1074–1081.
22. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159: 702–706.
23. Gibson K, O'Bryant CL. Screening and management of osteoporosis in breast cancer patients on aromatase inhibitors. J Oncol Pharm Pract 2008;14:139–145.
24. Tham YL, Sexton K, Weiss HL, Elledge RM, Friedman LC, Kramer RM. The adherence to practice guidelines in the assessment of bone health in women with chemotherapy-induced menopause. J Support Oncol 2006;4:295–298, 304.
25. Lewiecki EM. Review of guidelines for bone mineral density testing and treatment of osteoporosis. Curr Osteoporos Rep 2005;3:75–83.
26. National Osteoporosis Foundation (NOF). Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation 2008. www.nof.org/professionals/Clinicians_Guide.htm
27. Lim LS, Hoeksema LJ, Sherin K. Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med 2009;36:366–375.
28. Centers for Medicare & Medicaid Services (CMS). National coverage determination (NCD) for bone (mineral) density studies (150.3). Available at www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=256&ver=251 Accessed July 2012.
29. Simonelli C, Killeen K, Mehle S, Swanson L. Barriers to osteoporosis identification and treatment among primary care

physicians and orthopedic surgeons. Mayo Clin Proc 2002;77:334–338.
30. Solomon DH, Brookhart MA, Gandhi TK, et al. Adherence with osteoporosis practice guidelines: A multilevel analysis of patient, physician, and practice setting characteristics. Am J Med 2004;117:919–924.
31. Cohen K, Maier D. Osteoporosis: Evaluation of screening patterns in a primary-care group practice. J Clin Densitom 2008;11:498–502.
32. Ramsey SD, Cheadle AD, Neighbor WE, et al. Relative impact of patient and clinic factors on adherence to primary care preventive service guidelines: An exploratory study. Med Care 2001;39:979–989.
33. American Society of Health-System Pharmacists. AHFS drug information 2011. Bethesda, MD: Authority of the Board of the American Society of Health-System Pharmacists, American Hospital Formulary Service, 2011.
34. Goss PE, Qi S, Cheung AM, Hu H, Mendes M, Pritzker KP. Effects of the steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariectomized rats. Clin Cancer Res 2004;10:5717–5723.
35. McCloskey EV, Hannon RA, Lakner G, et al. Effects of third generation aromatase inhibitors on bone health and other safety parameters: Results of an open, randomised, multicentre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. Eur J Cancer 2007;43:2523–2531.
36. Tang SC. Women and bone health: Maximizing the benefits of aromatase inhibitor therapy. Oncology 2010;79:13–26.
37. Laliberte MC, Perreault S, Jouini G, Shea BJ, Lalonde L. Effectiveness of interventions to improve the detection and treatment of osteoporosis in primary care settings: A systematic review and meta-analysis. Osteoporos Int 2011;22:2743–2768.

Address correspondence to:
Leslie Spangler, PhD, VMD
Group Health Research Institute
1730 Minor Avenue, Suite 1600
Seattle, WA 98101

E-mail: spangler.l@aghe.org

Appendix

Appendix. ICD9 Codes for Medical Conditions and Medications Associated with Osteoporosis and Additional Detail on Covariate Definitions

Medical conditions associated with osteoporosis

Condition	*ICD9 code*	*Condition*	*ICD9 code*
Adrenal insufficiency	255.4X, 255.5	Marfan's syndrome	759.82
Anorexia nervosa	307.1	Multiple myeloma	203.0X
Cushing syndrome	255.0	Osteogenesis imperfecta	756.51
Cystic fibrosis	277.0X	Hemochromatosis	275.0
Hepatic or renal disease chronic	571.XX, 585.X	Gaucher's disease	272.7
Hypercalciuria	791.9	Systemic mastocytosis	202.6
Hyperparathyroidism	588.81, 252.0X, 259.3	Rheumatologic diseases	710.0, 710.1, 710.3, 714.X
Hyperthyroidism/thyrotoxicosis	242.XX	Rickets/vitamin D deficiency	268.X
Hypogonadism	257.2	Spinal cord injury	806.XX, 952.X, 767.4
Hypophosphatasia	275.3	Malabsorption syndrome	579.X

Medications associated with osteoporosis

Heparin	Anticonvulsants	Other
Heparin	Phenytoin	Selective serotonin reuptake inhibitors
Enoxaparin	Primidone	Cyclosporine
Dalteparin	Phenobarbital	Depot medroxyprogesterone acetate
Enoxaparin	Carbamazepine	
Fondaparinux		
Tinzaparin		

Other covariates

History of fracture	ICD9 codes for fractures in hip (820.XX-821.XX), vertebral (805.XX), humerus (812.XX), forearm and wrist (813.XX-814.XX)
Diabetes	Defined as having 1) two fasting plasma glucoses ≥126 mg/dL, two nonfasting glucoses ≥200 mg/dL, or one of each, 2) one or more hemoglobin A1c ≥7.0%,3) one or more dispensing for insulin or oral diabetic agents, or 4) an inpatient diagnosis code of diabetes (250.XX)
Depression	ICD9 codes (296.2X, 293.3X, 311, 300.4, 309.0, 309.28)
Corticosteroid use	Oral forms of medications in the American Hospital Formulary Service (AHFS) class 68.04