Bone Mineral Density Testing Disparities Among Patients With Breast Cancer Prescribed Aromatase Inhibitors

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Abstract

Objectives: Aromatase inhibitors (AIs) are standard adjuvant therapy for postmenopausal women with early-stage, estrogen receptor–positive breast cancer. We designed our study to determine whether women initiating adjuvant therapy with an AI underwent baseline bone mineral density testing, as well as what factors predicted adherence with testing guidelines. **Methods:** Medicare Parts A, B, and D claims were used to identify a cohort of women aged 67 years and older with incident breast cancer in 2006 and 2007 who started AI therapy. Medicare claims provided information about bone density testing, as well as demographic and other treatment data through 2012. We also ascertained which patients were treated with bisphosphonates and studied the relationship of bisphosphonate therapy with bone density testing. **Results:** Approximately two-thirds of patients had baseline bone density testing. Older age, comorbidity, low income, and black race were associated with lower rates of baseline bone density testing. Testing rates decreased substantially with increasing age from 73% for women aged 67 to 70 years to 51% for those 85 years of age and older (adjusted odds ratio for not being tested, 2.48 [CI, 2.17–2.82]). The proportion of women who had neither bone density testing nor bisphosphonate therapy increased with age as well. **Conclusions:** Despite the importance of age as a risk factor for fractures, older women starting treatment with AIs for treatment of breast cancer are less likely to undergo recommended bone density assessment.

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Background

Aromatase inhibitors (AIs), tamoxifen, and the sequential use of these agents are all standard options for adjuvant hormonal therapy (HT) for postmenopausal women with early-stage, estrogen receptor (ER)–positive breast cancer. At least 70% of these women are prescribed AIs alone.[1] AI use is associated with a decrease in bone mineral density (BMD) and an increased fracture risk, relative to both tamoxifen and placebo.[2–4] Clinical assessment of fracture risk in postmenopausal women starting AI therapy with bone density testing with dual x-ray absorptiometry (DXA) or other technologies is recommended by current ASCO and NCCN guidelines.[5,6] Subsequent treatment decisions should be based on results of bone density tests along with other risk factors for fracture.[3,5–8]

Although a few studies early in the use of AIs suggested that adherence to these guidelines was suboptimal,[9–13] there are few recent data. As consensus about the importance of AIs in HT regimens has grown, it is likely that AIs are increasingly given to patients with substantially higher fracture risk, making understanding current patterns in guideline adherence even more

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important. The aim of this study was to investigate whether older women in a population-based sample from across the United States treated with AIs as adjuvant breast cancer therapy are undergoing appropriate guideline-based bone risk assessments. We used a population-based sample with a number of older and other high-risk women. In addition, we also examined how testing in this population compared with testing in patients without cancer, and, to account for the possibility that higher-risk patients were empirically treated without testing, also examined prescription osteoporosis treatment.

Methods

Study Cohort and Data Sources

To establish a cohort of older women receiving AIs as adjuvant breast cancer treatment, we used Medicare Parts A, B, and D claims to identify Medicare-enrolled women aged 67 years or older who underwent initial breast cancer surgery in 2006 or 2007 and who initiated AI therapy within 1 year after surgery.[14] AI initiation was defined as filling one or more prescriptions for anastrozole, exemestane, or letrozole within 365 days of breast cancer surgery. We used 67 years as the lower age limit to allow us to identify prior claims for BMD testing (nearly all patients in this period entered Medicare at age 65 years). To minimize inclusion of patients with metastatic cancer, women receiving intravenous bisphosphonates at intervals less than 90 days were excluded.

Medicare files from 2 years before until 6 months after AI initiation were the source of cohort members' demographic data, outpatient and inpatient diagnoses, and information about whether a Medicare Part D low-income subsidy (LIS) was received. Claims were also available for patients who started in a Medicare D plan and then subsequently switched into a Medicare Advantage plan. Per capita income (PCI) at the zip code level was obtained from census data. BMD testing was identified using Medicare claims for procedure codes for peripheral or central DXA, or ultrasound. Medicare Part D Prescription Drug Event files were used to determine oral medication prescription fills, and Medicare Parts A and B were used to identify cytotoxic chemotherapy and intravenous bisphosphonate use.

To allow comparison of testing with non–breast cancer controls, a cohort of female Medicare enrollees aged 67 years and older was also drawn from a random sample of 5% of all Medicare enrollees.

Analysis

We defined our primary outcome of baseline BMD testing as testing performed between 24 months prior and 6 months after AI initiation. As a secondary outcome, we also measured receipt of at least one prescription for an oral bisphosphonate (risedronate, alendronate, or ibandronate) between 12 months before and 12 months after AI initiation. Because denosumab was not FDA-approved for any indication until June 2010, we did not examine its use. Covariates included age, race, rural versus urban dwelling, comorbidity score (using a breast cancer–specific NCI algorithm based on claims diagnoses),[15] zip code PCI by quartile, receipt of LIS, and whether patients were treated with chemotherapy.

Unadjusted rates of baseline BMD testing and use of oral bisphosphonates were calculated for all patients and in subgroups by patient age. Logistic regression models adjusted for the covariates were developed to investigate the degree to which demographic and clinical factors were associated with failure to undergo baseline BMD testing. For comparison, annualized bone density testing rates from the 6 months before and 6 months after AI initiation were compared with a random 5% sample of Medicare enrollees in 2008. In addition, the rate of bisphosphonate use was measured in relationship to BMD testing. Finally, as a sensitivity analysis, to assess whether clinicians become more aware of bone risks over the time of our study or as their patients continued on medications, we measured testing though December 2012.

Results

Our cohort consisted of 19,585 older women with incident breast cancer in 2006 and 2007 who started adjuvant AI therapy (Table 1). Most women initiating adjuvant AI therapy (67.7%) underwent baseline BMD testing. The annualized BMD testing rate for the complete breast cancer cohort was 53.9%, substantially higher than the noncancer random sample of Medicare patients (15.4% rate) (Figure 1).

BMD testing rates, unadjusted for socioeconomic or health variables, were lowest in the oldest age group. In contrast, the rates of bisphosphonate use without BMD testing during our study interval

Table 1. Baseline Characteristics (N=19,585)

Characteristic	Cohort n, (%)
Age, y	
67–70	5,005 (25.6)
71–75	5,512 (28.1)
76–80	4,663 (23.8)
80–85	3,102 (15.8)
≥86	1,303 (6.7)
Race	
White	16,701 (85.3)
Black	1,478 (7.6)
Hispanic	938 (4.8)
Asian	319 (1.6)
Other	149 (0.8)
Low-income support	
No	13,586 (69.4)
Yes	5,999 (30.6)
Rural residence	
No	14,412 (73.6)
Yes	5,173 (26.4)
Comorbidity score	
0	10,031 (51.2)
1	5,080 (25.9)
≥2	3,815 (19.5)
Unknown	659 (3.4)
Received chemotherapy	
No	15,946 (81.4)
Yes	3,639 (18.6)
Baseline bone mineral density testing	
No	6,326 (32.3)
Yes	13,259 (67.7)
Received bisphosphonate	
No	13,293 (67.9)
Yes	6,292 (32.1)

were slightly higher among older women (Figure 2). Nonetheless, the percentage of women initiating adjuvant AI therapy without evidence of any measure of bone care, that is, who neither underwent BMD testing nor received bisphosphonates, increased from 24% in the 67-to 70-year-old age group to 40% in the oldest group (aged ≥86 years).

In adjusted models, older age, comorbidity, low income (by zip code PCI and receipt of LIS), and race (black women) were all associated with a higher likelihood of starting an AI without baseline BMD testing (Table 1). Women treated with chemotherapy were also less likely to undergo baseline BMD testing, and baseline BMD testing decreased progressively with increasing age (relative risk, 2.49 [2.17–2.82] for women aged ≥85 years vs those aged 67–70 years) and with comorbidity (Table 2). An additional 2,953 patients who had not previously been tested received a BMD test during their treatment, so that 81.8% of patients received a BMD test at some point shortly before or during cancer care.

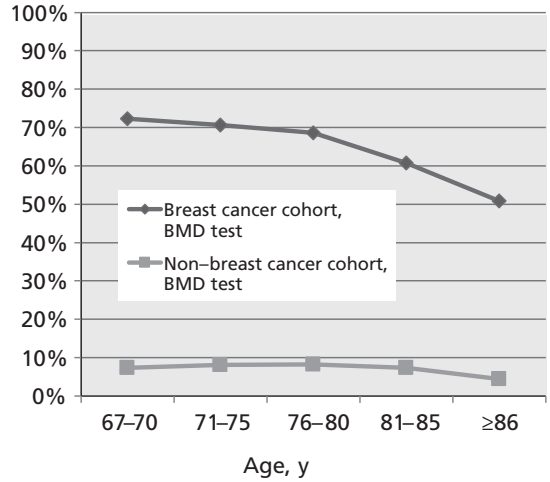

Figure 1. Annualized bone mineral density (BMD) testing rates by age, compared with a non–breast cancer sample. The annual rate of BMD testing in our cohort, by age group, in comparison to a random 5% sample of Medicare beneficiaries.

Discussion

In a 2006–2007 population-based cohort of older US Medicare patients starting adjuvant AIs who were followed through 2012, approximately one-third of patients did not undergo recommended baseline BMD testing. Several factors, including race and comorbidity, were associated with testing, but older age was the variable most strongly associated with lower likelihood of testing. Although there was a slightly higher rate of bisphosphonate use without testing in older women, this increase was much smaller than the decrease in testing by age, thus despite their substantially higher risk, older patients received less bone-related care overall.

Our results are important to the quality of cancer care, because randomized controlled trials of AIs compared with tamoxifen demonstrated substantially higher fracture rates with AIs. Fractures were the most common adverse effect in most of the AI trials,

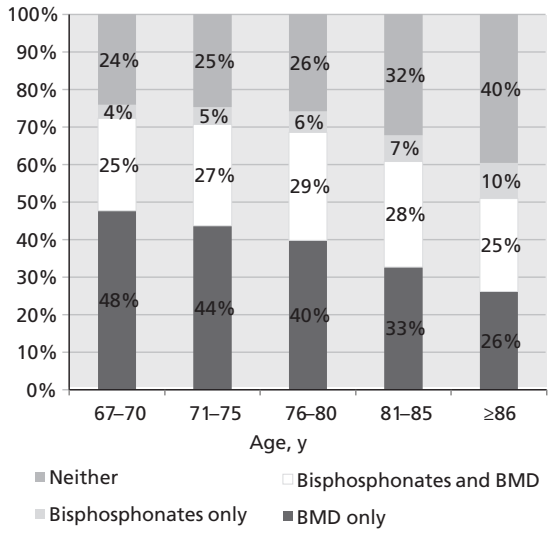

Figure 2. Treatment strategies by age group. The percentage of patients in each age group of the study cohort who are treated according to 1 of 4 different bone health strategies: bone mineral density (BMD) testing without bisphosphonate treatment, bisphosphonate treatment without BMD testing, BMD testing and bisphosphonate treatment, and no testing or treatment. Bisphosphonate use was determined by Medicare Part D claims for an oral bisphosphonate during the period 12 months before to 12 months after initiation of aromatase inhibitor therapy.

with an absolute risk in the largest trial of upfront AI versus upfront tamoxifen (ATAC) of 11.0% versus 7.7% at 5 years.[16] Most trials' estimated hazard ratios for fractures associated with AIs compared with tamoxifen were between 1.4 and 1.6.[2,13] Fracture risk was also found to be 2.2% higher for 5 years of AI treatment versus sequential treatment with tamoxifen followed by an AI (2.5 years of each).[17] Studies that compared AIs with placebo were substantially smaller and did not have the statistical power to assess fracture risk, but reported reductions in bone density with AIs.[4,18] Given these data, NCCN and ASCO recommend baseline bone density testing for all patients starting AIs. Other studies' results regarding overall use of BMD testing are mixed. One study found that patients with breast cancer were more likely to undergo DXA relative to controls,[9] but another showed that breast cancer survivors were less likely than noncancer controls to have undergone several health maintenance procedures, including bone densitometry.[10] Perhaps because those studies were performed just after adjuvant AIs were recommended, in our contemporary cohort, patients with breast cancer on AIs were substantially more likely than a noncancer cohort to receive testing (annualized testing rate, 53.9% vs 15.4%).

Table 2. Multivariate Analysis of Factors Predicting Lack of Baseline Bone Density Testing Among Women Starting Aromatase Inhibitors

Factor	Odds Ratio	95% CI	*P* Value
Age, y			<.01
67–70	–		
71–75	1.09	0.99–1.19	.07
76–80	1.21	1.11–1.33	<.01
80–85	1.69	1.53–1.87	<.01
≥86	2.48	2.17–2.82	<.01
Race			<.01
White	–		
Asian	0.79	0.61–1.01	.06
Black	1.55	1.38–1.75	<.01
Hispanic	0.98	0.85–1.14	.80
Other	1.22	0.87–1.72	.26
Comorbidity			<.01
None	–		
1	1.17	1.09–1.27	<.01
≥2	1.41	1.30–1.53	<.01
Low-income support			<.01
No	–		
Yes	1.74	1.62–1.87	<.01
Per capita income in zip code			<.01
≥$25,000 (upper quartile)	–		
<$25,000	1.35	1.25–1.46	<.01
Rural residence			.21
No			
Yes	1.05	0.97–1.13	.21
Treated with chemotherapy			.03
No			
Yes	1.098	1.011–1.192	.03

Despite this overall relatively high rate of testing, we also found that several groups of patients at highest risk of fracture were among the least likely to receive testing. Fracture risk increases substantially with age,[19] and women in the oldest age groups are at particularly high risk for hip fracture.[20] Hip fracture rates are approximately 7 times higher in women aged 70 to 74 years compared with those aged 50 to 54 years.[21] Higher comorbidity is also strongly linked to fractures.[3] Despite the importance of age and comorbidity in fracture risk, our study found that screening occurs in a pattern that is inverse with

risk; results that were consistent with one other large study in cancer[11] and several studies in osteoporosis.[22,23] One smaller cohort study[12] did not identify an inverse relationship of age with testing, but was probably underpowered for this question. Compared with the other breast cancer studies, our study includes a much larger and nationally representative cohort, as we included all patients with breast cancer aged 67 years and older enrolled nationally in Medicare Part D, including more than 4,000 women older than 80 years. Unlike earlier studies, we also examined whether use of osteoporosis medication without testing might explain the large age disparities in testing. It was also during this study's measurement period, through 2012, that data continued to emerge suggesting a potential role for bisphosphonates in reducing breast cancer recurrence rates.[24–26] Although a larger number of older patients did receive bisphosphonates, this did not explain the disparities in bone density findings, or even substantially change our finding that attention to bone health was higher in the lower-risk younger patients.

BMD testing may be even more important in patients with breast cancer than in noncancer patients. Although patients with a prior fracture or a higher bone density are actually less likely to develop breast cancer,[27–29] fracture risk increases for patients after treatment, such that some studies suggest that breast cancer history is an independent risk factor for fracture.[30] ASCO and NCCN Guidelines recommend that patients at increased risk of fracture consider treatment with antiresorptive therapy.[5,6] For women with premenopausal breast cancer, premature ovarian failure after chemotherapy is a major determinant of that risk and is generally reflected in rapid losses in BMD. For postmenopausal women, fracture risk factors other than AI use appear to be similar to those in women without breast cancer.[3,6] A strategy of baseline BMD testing followed by treatment (with oral bisphosphonates) for women with osteoporosis or osteopenia and fracture risk factors was shown to be a more cost-effective intervention for bone health than universal treatment with bisphosphonates for all women on AIs.[31] These data perhaps influenced clinicians in our study, few of whom appeared to treat without testing.

Limitations of this study include the lack of access to results of BMD tests; we are therefore unable to comment on appropriateness of prescription treatment. Although it is notable that in our study a subset of the cohort on bisphosphonates did not have a baseline BMD test, and the proportion of women in this category also increased with age, it is unknown whether these women were previously diagnosed with osteoporosis and were already on therapy. It is also noted that since our study period, evidence has accumulated supporting the use of zoledronic acid and denosumab as adjuvant cancer treatment in postmenopausal women with breast cancer, which may lead to changes in bone health guidelines for this population. Nonetheless, to our knowledge this is the largest and most contemporary population-based study to date assessing quality of bone health management in postmenopausal patients with breast cancer initiating adjuvant AI therapy, with BMD testing examined through 2012; the first to both assess screening and empiric treatment; and the first to include large numbers of older women.

This study highlights suboptimal US compliance with guideline recommendations for baseline BMD testing when starting AI therapy. Older women, at higher risk for fractures in general, are least likely to obtain BMD testing, and the slight increase in empiric treatment for those women did not close the gap. The reason for this deficiency is unknown, but clinicians should be aware of it so that efforts can be focused on maximizing the therapeutic index in adjuvant breast cancer treatment.

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