EMERGING BONE HEALTH ISSUES IN WOMEN
WITH BREAST CANCER IN HAWAII

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MASTER OF SCIENCE

IN

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[Names of the Thesis Committee Members]
ACKNOWLEDGMENTS

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ABSTRACT

Purpose: Aromatase inhibitors have improved breast cancer outcomes for early stage, postmenopausal women who have hormone receptor positive disease. Aromatase inhibitors have replaced the prior gold standard treatment, tamoxifen, a selective estrogen receptor modulator. However, aromatase inhibitors markedly reduce estradiol and have the potential to increase the risk for osteoporosis and associated bone fractures. Guidelines for monitoring bone health in women with breast cancer exist but it is unclear whether these recommendations are the standard of care in Hawaii. This study addresses adjuvant chemotherapy among women with early stage breast cancer and related issues of bone health in Hawaii.

Methods: The patients were women age 50 and older with early stage breast cancer who were taking an aromatase inhibitor or tamoxifen and enrolled with the largest insurer in Hawaii from 1999 to 2006. Their clinical histories were obtained from administrative data including their prior use of hormone replacement therapy and whether they had received radiation or adjuvant chemotherapy. Spine, hip, and wrist fractures, bisphosphonate therapy, and dual energy X-ray absorptiometry scans were the measured outcomes.

Results: In 2006, the percentage of women on tamoxifen was 29% compared to 71% for aromatase inhibitors. Women taking aromatase inhibitors were significantly more likely to have bone fractures than those on tamoxifen (rate ratio=2.42). More patients on aromatase inhibitors received bone density scans as well as medications to prevent bone loss (odds ratio=1.86).
Conclusions: In this Hawaii population, the use of aromatase inhibitors has increased steadily since 2002 when the initial adjuvant trial for postmenopausal women with early breast cancer was reported. However, tamoxifen remained a commonly prescribed agent. Women taking aromatase inhibitors were at increased risk of developing fractures. In addition, preventative strategies, such as dual energy absorptiometry scans and bone health agents, were underutilized
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INTRODUCTION

Breast cancer affects over 200,000 women annually and the majority of patients are candidates for adjuvant endocrine therapy. Until recently, tamoxifen, a selective estrogen receptor modulator, had been the standard drug of choice. Studies of postmenopausal women with early stage, hormone receptor positive breast cancer have shown improvement in disease free survival, time to recurrence, contralateral breast cancer development, and distant metastases with the third generation aromatase inhibitors compared to tamoxifen in the upfront setting. (1, 2) Studies examining sequential adjuvant endocrine therapy using tamoxifen followed by an aromatase inhibitor have demonstrated an improvement in overall survival in women with early breast cancer. (3, 4)

In postmenopausal women, tamoxifen acts as an estrogen agonist on bone and is associated with protection from osteoporosis. A major side effect of aromatase inhibitors, by contrast, is the effect on bone health likely due to the marked reduction in estradiol affecting bone physiology. Studies have reported a decrease in bone mineral density, changes in biomarkers of bone turnover, and an increase in the number of bone fractures. (5) Currently, the American Society of Clinical Oncology guidelines for bisphosphonate and bone health recommend a baseline dual energy X-ray absorptiometry (DEXA) scan before initiation of aromatase inhibitors, and annual DEXA scans thereafter. (6) The guidelines also encourage lifestyle modifications such as exercise and calcium with vitamin D intake.
Osteoporosis is a skeletal disorder characterized by compromised bone strength resulting in a predisposition for an increased risk of fracture. (8) The prevalence of osteoporosis is difficult to assess accurately but it is estimated that osteoporosis affects 30% of postmenopausal women and osteopenia affects 54%. (9) The risk of osteoporosis is multi-factorial with non-modifiable risk factors including age, female gender, Caucasian or Asian race and family history. Currently, the most common tool to measure bone mineral density is the dual energy X-ray absorptiometry (DEXA) scan. The World Health Organization has published diagnostic criteria for osteopenia and osteoporosis based upon DEXA scans. (10)

The current study examined whether the rising use of aromatase inhibitors impacted bone health among postmenopausal women diagnosed with breast cancer in Hawaii. The study also determined whether community practice followed national guidelines for bone health among these women. The study compared aromatase inhibitors and tamoxifen by evaluating fracture rates, frequency of DEXA scans, and use of bone modeling agents.

**METHODS**

**Database**

Data used were administrative data from the major party payer for health insurance in Hawaii which insures approximately half of the state’s population. Information on ethnicity was obtained from respondents to a satisfaction survey mailed to a random sample of members. Response rates averaged about 50%
across the study years. Bone mineral density studies were identified using CPT-4 codes 76070, 76071, 76075, 76076, 76078, 76977, 78350, G0130, G0131, and G0132. Fractures were recorded using the ICD-9 codes for femur and hip (820, 821), vertebra (805, 806), and wrist fractures (814).

Study Population

Women were eligible for the study if they were age 50 or older, had a diagnosis of breast cancer (ICD-9 diagnosis code 174), and a prescription for an aromatase inhibitor or tamoxifen between the years 1999 and 2006. As the administrative database did not specifically identify post-menopausal status, the age minimum was set at 50 to limit the study primarily to postmenopausal women. Aromatase inhibitors included anastrazole, letrozole, and exemestane. Bisphosphonate use by the patients included oral regimens like ibandronate, risedronate, and alendronate, but intravenous forms like pamidronate and zolendronic acid were excluded since these drugs are used in women with metastatic breast cancer to bone. Calcitonin use was also included as a bone health agent. For the analyses, patients were divided into those women ages 50 to 59 years, 60 to 69 years, and those greater than 70 years.

The protocol for this study was granted an exemption from institutional review board (IRB) review by the University of Hawaii IRB.
Statistical Analysis

Descriptive variables of interest included use of chemotherapy and radiation therapy, age, and prior use of hormone replacement therapy. Dependent outcomes included fracture, DEXA scans, and bisphosphonate or calcitonin use. All analyses were performed using the SAS Enterprise Guide version 3.0. Regression analyses employed generalized estimating equations. Information for regression analyses were summarized by year and the analyses were corrected for the clustering of repeated years of measurements within patients. Use of a bisphosphonate or calcitonin was modeled as an outcome using logistic regression. The number of fractures was modeled using Poisson regression. The denominator was based on the patients' length of enrollment and not by calendar year. Therefore, the Poisson model included an ‘offset,’ a known constant giving the days of enrollment with the insurer during the year. The Poisson regression model included the Pearson adjustment of the standard errors to account for possible overdispersion.
RESULTS

Table 1 shows the distribution of characteristics for the 1,043 patients included in the analyses.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PERCENT (NUMBER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>33.8% (353)</td>
</tr>
<tr>
<td>60-69</td>
<td>33.4% (348)</td>
</tr>
<tr>
<td>70 and older</td>
<td>32.8% (342)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>43.5% (316)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>24.8% (180)</td>
</tr>
<tr>
<td>Hawaiian</td>
<td>12.8% (93)</td>
</tr>
<tr>
<td>Chinese</td>
<td>7.3% (53)</td>
</tr>
<tr>
<td>Filipino</td>
<td>5.6% (41)</td>
</tr>
<tr>
<td>Other</td>
<td>6.0% (44)</td>
</tr>
<tr>
<td>Past estrogen use</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44.5% (579)</td>
</tr>
<tr>
<td>No</td>
<td>55.5% (464)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39.0% (639)</td>
</tr>
<tr>
<td>No</td>
<td>61.0% (407)</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63.0% (657)</td>
</tr>
<tr>
<td>No</td>
<td>37.0% (386)</td>
</tr>
</tbody>
</table>

316 participants were missing ethnicity

Patient age was evenly distributed between ages 50 to 59, 60 to 69, and greater than 70 years old. For this study, ethnicity was established through survey responses. Patients of Japanese ethnicity were the most common respondents followed by Caucasian and Hawaiian women. Forty four percent of women had a history of estrogen use. Thirty nine percent of women received chemotherapy for breast cancer and 63% received radiation therapy for breast conserving therapy.
As shown in Figure 1, tamoxifen was the principal agent used to treat early stage breast cancer patients in Hawaii during 1999.

![Graph showing the frequency of aromatase inhibitor and tamoxifen use from 1999 through 2006.](image)

A decline in tamoxifen use began during 2002; however, it remained a commonly prescribed agent. In 2006, 29% of women were treated with tamoxifen. While the use of tamoxifen decreased, aromatase inhibitor use steadily increased from 2002 to 2006. During 2006 aromatase inhibitors were prescribed 71% of the time.
Compared to women taking tamoxifen, women taking aromatase inhibitors in Hawaii had an increased rate of fractures as shown in Figure 2.

Figure 2. Age-adjusted relative rate of fractures comparing endocrine therapies for breast cancer patients

There were 19 hip fractures, 20 spine fractures, and 4 wrist fractures during the 8 year interval. After adjusting for age, the relative rate for fractures over the length of follow-up was 2.42.
Use of DEXA scans for postmenopausal women on tamoxifen has remained essentially stable with about a quarter of patients receiving bone imaging (Table 2).

<table>
<thead>
<tr>
<th>YEAR</th>
<th>TAMOXIFEN (%)</th>
<th>AROMATASE INHIBITORS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>21.6</td>
<td>26.3</td>
</tr>
<tr>
<td>2003</td>
<td>25.1</td>
<td>33.7</td>
</tr>
<tr>
<td>2004</td>
<td>23.1</td>
<td>38.1</td>
</tr>
<tr>
<td>2005</td>
<td>34.8</td>
<td>37.7</td>
</tr>
<tr>
<td>2006</td>
<td>28.0</td>
<td>30.8</td>
</tr>
</tbody>
</table>

Although there was an initial rise in the use of dual energy absorptiometry scans for patients on aromatase inhibitors, there has been a slight decline in use since 2005. Usage peaked in 2004 when 38.1% of patients on aromatase inhibitors also received DEXA scans. Approximately one third of patients on aromatase inhibitors received dual energy absorptiometry scans.
Figure 3 describes the response to the use of bone health agents.

Figure 3. Age-adjusted odds ratio of using bone health medications by women while on endocrine therapy.

The use of bone health agents to prevent osteoporosis was greater in women on aromatase inhibitors with an age-adjusted odds ratio of 1.86.
DISCUSSION

We wanted to investigate trends in endocrine therapy use in Hawaii. Since aromatase inhibitors may adversely affect bone health, we compared fracture rates among the treatment groups and frequency of DEXA scans and bone health modulators. While aromatase inhibitors may have better clinical efficacy, the effect on health care costs is not insubstantial.

Since 2002, use of aromatase inhibitors has increased dramatically when results of the anastrazole, tamoxifen, and combination (ATAC) trial were initially reported. (1) However, tamoxifen remains a commonly prescribed endocrine agent for the treatment of breast cancer in postmenopausal women despite its higher toxicity profile. The continued use of tamoxifen could be related to concerns over the skeletal effects of aromatase inhibitors. Despite the negative effects of aromatase inhibitors on bone health, there was less use of dual energy absorptiometry scans than recommended by national guidelines. The insurer allows bone mineral density testing every two years so the 30.8% use of DEXA scans during 2006, for example, is less than expected. The use of DEXA scans among patients taking tamoxifen remained relatively consistent across the study years. Bisphosphonates or calcitonin were used about twice as often by women taking aromatase inhibitors compared to women taking tamoxifen.

Our study limitations include a short length of follow-up, lack of cancer staging information, and potential problems regarding the accuracy of administrative data. In order to address some of these limitations, we attempted to capture early breast cancer patients by type of chemotherapy, use of breast
conserving therapy, and excluded some medications approved in the metastatic setting.

We found that women in Hawaii with breast cancer on an aromatase inhibitor are 2.5 times more likely to have suffered a fracture compared to women on tamoxifen. The evidence also suggested that these women were not receiving DEXA scans as often as recommended which may contribute to an under diagnosis of osteoporosis and osteopenia. This in turn could affect bone health by limiting the use of bisphosphonates and other bone health agents. It is unclear from our study whether the lack of screening with DEXA scans is due to the practices of prescribing physicians or to lack of compliance by the patient population. More community-based education and awareness is essential to prevent the substantial morbidity and potential mortality from fractures among the population of breast cancer survivors in Hawaii.
REFERENCES


