Bone Health and Coronary Heart Disease in Postmenopausal Women with Breast Cancer Treated with Tamoxifen: A Dissertation

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BONE HEALTH AND CORONARY HEART DISEASE IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER TREATED WITH TAMOXIFEN

A Dissertation Presented

By

Hongliu Ding

Submitted to the Faculty of the
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December 28, 2008

Ph.D. Program in Clinical and Population Health Research
BONE HEALTH AND CORONARY HEART DISEASE IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER TREATED WITH TAMOXIFEN

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ABSTRACT

Breast cancer, osteoporosis, and coronary heart disease (CHD) are three major threats to women's health. Postmenopausal women with breast cancer are also at high risk for osteoporosis and CHD. Adjuvant tamoxifen therapy is not only an effective treatment for breast cancer, but has been shown to have a beneficial effect on bone and the cardiovascular system. Although tamoxifen has been convincingly demonstrated to be able to preserve bone mineral density (BMD), an unexpected increase of risk of fractures in patients treated with tamoxifen has been reported. The findings of the association of tamoxifen and CHD from previous studies were either borderline or inconsistent. To clarify the discrepancy between BMD and fractures and test the potential beneficial effect of tamoxifen on CHD, I conducted a series of retrospective studies in postmenopausal women with breast cancer who participated in the Cancer Surveillance in HMO Administrative Data (IMPACT study) or the Study of Osteoporotic Fractures (SOF).

In patients who participated in the IMPACT study, I demonstrated that the association of tamoxifen and fracture incidence varied at different skeletal sites. Although the association of tamoxifen and fractures in the spine (HR=0.40, 95% CI: 0.09-1.85), wrist (HR=2.49, 95% CI: 0.88-7.06), and total body (HR=0.87, 95% CI: 0.49-1.55) was inconclusive, tamoxifen was associated with an apparent
reduction of the risk of hip fracture (HR=0.41, 95% CI: 0.17-1.03, p=0.0565).
Importantly, the pattern of observed association of tamoxifen with the risks of fractures among postmenopausal women with breast cancer is consistent with its widely reported preserving effect on bone mineral density.

Using SOF data, I found that the association between BMD and fractures in women with breast cancer varied at different skeletal sites, and type of BMD measured. Non-specific BMD was not associated with hip fracture (HR=1.12; 95% CI: 0.78, 1.59). Site-specific BMD was more likely linked with hip fracture (HR=1.43, 95% CI: 0.99, 2.08) while change in BMD did not predict hip fracture (HR=1.05; 95% CI: 0.63, 1.72). The association of spine morphometric fracture with either non-specific or spine-specific BMD was similar (OR=1.40; 95% CI: 1.04, 1.90; OR=1.35, 95% CI: 0.99, 1.85, respectively). Overall, the association of BMD and fracture in elderly women with breast cancer is weak. Only site-specific BMD appears to have a consistently modest association with fractures in the corresponding skeletal sites.

In the IMPACT study population, compared to patients without tamoxifen, the overall incidence of CHD in tamoxifen-treated patients was lower (adjusted HR=0.60, 95% CI: 0.40-0.88). For each year of tamoxifen use, there was a statistically significant decrease in the risk of CHD (HR=0.90, 95% CI: 0.82-0.98). Further analyses categorized by length of tamoxifen use showed that an
apparent association with a decreased CHD risk was found in patients who received tamoxifen for two to five years (HR=0.54, 95% CI: 0.33-0.86). No association was detected after the discontinuation of tamoxifen therapy.

In summary, I detected a possible benefit associated with tamoxifen on fractures in the hip, the most common fracture site. I also found that BMD did not predict osteoporotic fractures well in postmenopausal women with breast cancer. In addition, I demonstrated that tamoxifen was associated with a reduced risk of CHD in postmenopausal women with breast cancer in a dose-dependent manner. An apparent benefit was found in those patients who received tamoxifen therapy for at least two years.
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PREFACE

Part of the thesis work has been published previously as:


In addition, publications related to the Ph.D study but not presented in this thesis are listed as follows:

- Xiaoping Wang, **Hongliu Ding***. Alzheimer’s disease: epidemiology, genetics, and beyond. *Neurosci Bull.* 2008 Mar; 24(2): 105-9
  *Corresponding author.*

- Changsheng Yang, Xiaoping Wang, **Hongliu Ding***. Is coronary artery disease a multifactorial inherited disorder with a sex-influenced trait? *Medical Hypotheses.* 2008 71(3) 449-452. *Corresponding author.*


1.1 Breast cancer, osteoporosis, and CHD in postmenopausal women

Breast cancer is the most common cancer and the second leading cause of cancer death in women. In the United States alone, it is estimated that a total of 182,460 new female cases and 40,480 deaths will occur in 2008. However, over the last decade a steady decline in breast cancer deaths has been observed due to advancements in breast cancer diagnosis and treatment. The majority of these women are over the age of 65 and can expect a lengthy period of breast cancer survivorship.

Osteoporosis, a progressive process of bone mass loss, is another lethal disease threatening women’s health. About 25% of postmenopausal white women suffer from osteoporosis. More importantly, 1.3 million fractures are associated with osteoporosis in the United States each year, which leads to substantial morbidity and mortality. Therefore, osteoporosis may be a major additional concern in postmenopausal women with breast cancer. Risk of osteoporosis is enhanced by a combination of female gender, older age, hormonal change, and the cancer itself. Increased bone loss in women with
breast cancer may result from chemotherapy\textsuperscript{5} and from adjuvant therapy agents such as aromatase inhibitors.\textsuperscript{6,7} Thus, in addition to risk of fracture due to loss of BMD, women with breast cancer may be at additional risk of fractures because of these cancer related factors.

Typically considered as a disease that affects mainly men, CHD is actually the leading cause of death in women in the United States. While fewer women than men suffer from CHD before age 50, the difference dramatically decreases in postmenopausal women. CHD causes the death of 283,886 females annually compared with 40,460 deaths from breast cancer.\textsuperscript{8} Eventually, about one third of women die from CHD, causing the deaths of four times as many women as breast cancer.\textsuperscript{9}

Because of the high prevalence of breast cancer, osteoporosis, CHD, postmenopausal women with breast cancer are at an increased risk of morbidity and mortality. For these patients, anti-tumor effects should not be the only factor considered when selecting breast cancer treatment. It is imperative, when possible, to take into consideration the potential additional impact of treatment on osteoporosis and CHD in order to improve their survivorship and overall health.

1.2 Tamoxifen therapy in postmenopausal women with breast cancer
Breast cancer is one of the most treatable cancers. Although more than 10% of women develop breast cancer in their lifetime, only about 4% of them die from the disease. Effective treatment choices, including surgery, hormonal therapy, radiation, and chemotherapy, save the lives of most breast cancer patients. Among these, hormonal therapy is a unique and very effective option in the treatment of breast cancer. It specifically suppresses hormone-induced tumor cell growth. Since the majority of women with breast cancer have positive-hormone-receptor status, hormonal therapy often becomes the first adjuvant therapy after primary tumor therapy.

The most commonly used hormonal therapies are SERMs (Selective Estrogen Receptor Modulators). Unlike estrogen, the SERMs are a group of chemically synthetic agents that lack the steroid structure. However, they can still bind to estrogen receptors and exert tissue-specific actions. In general, the SERMs act as estrogen antagonists by competing with estrogen to bind to estrogen receptors in breast cells, thereby suppressing the cancer cell proliferation stimulated by estrogen. In other tissues such as bone, uterus, and the cardiovascular system, SERMS are estrogen agonists and exhibit some estrogen-like effects.

The most successful SERMs agent in the treatment of breast cancer is tamoxifen. Since its introduction into clinical practice in 1978, tamoxifen has been
shown to effectively reduce the risk of breast cancer recurrence and improve survival in women at all stages of breast cancer. The summarized findings from a meta-analysis of 55 trials in 37,000 women with breast cancer treated with tamoxifen for five years demonstrated a reduction of 47% in the rate of recurrence. Tamoxifen reduces annual death of patients with early breast cancer by 31% after five years of standard treatment, according to an overview of 194 randomized trials of adjuvant chemotherapy or hormonal therapy. In addition to its high efficacy, tamoxifen is well tolerated with few severe adverse effects. For three decades, tamoxifen has been the choice for hormonal therapy both in pre and post-menopausal women as well as in men with breast cancer.

Recently, another type of hormonal therapy agent, aromatase inhibitor, has emerged as an efficacious treatment for breast cancer. Unlike tamoxifen, which binds to estrogen receptors, aromatase inhibitors block aromatase activity, and therefore decrease estrogen levels both in the breast and in circulation. Several clinical trials have demonstrated the anti-tumor superiority of the third generation aromatase inhibitors over tamoxifen. Based on this evidence, the National Comprehensive Cancer Network (NCCN) guidelines (2006) recommend the use of the third-generation aromatase inhibitors for breast cancer treatment of postmenopausal women. Tamoxifen is still the first choice of hormonal
therapy treatment in premenopausal women but no longer for postmenopausal breast cancer patients.

While it is reasonable to replace tamoxifen with aromatase inhibitors in terms of cancer treatment, it may be questionable to apply it in postmenopausal women with breast cancer who are also at high risk of other diseases such as CHD. It is particularly problematic if such patients have osteopososis since aromatase inhibitors have been clearly linked to an increased risk of fractures. Thus, as the treatment of early stage breast cancer begins to leave tamoxifen and shift to aromatase inhibitors, a comprehensive assessment of the effects of tamoxifen outside of the paradigm of anti-tumor property is critical to make the most well-informed decisions for breast cancer treatment.

The common adverse events of tamoxifen treatment are hot flashes and vaginal dryness. The more severe, yet less common, side effects are thromboembolic events such as venous thromboses and pulmonary emboli. Increased risk of endometrial cancer is also a concern in patients treated with tamoxifen. However, tamoxifen has also been reported to have beneficial side effects, including the protection of bone against osteoporosis and the heart from cardiovascular events. These beneficial effects are especially important for postmenopausal women since they are at high risk of osteoporosis and CHD. Clarification of the quality and quantity of the benefit associated with tamoxifen
on bone and heart health in addition to its anti-tumor effect will help guide the clinical practice in breast cancer treatment among postmenopausal women.

1.3 Bone health in postmenopausal women with breast cancer: how protective is tamoxifen? (published previously in Cancer Treat Rev 2007;33:506-13)

(1) Abstract

Breast cancer is a leading threat to women’s health. Tamoxifen, the most successful selective estrogen receptor modulator, has been used in hormonal therapy for three decades. Along with its therapeutic effect on breast cancer, tamoxifen also demonstrates potential benefits for bone health. However, the extent and quality of such benefits have not been systematically evaluated. We conducted a comprehensive literature search and identified 27 peer-reviewed articles investigating the relationship between tamoxifen and bone health in postmenopausal women with early stage breast cancer. The majority of studies reported that tamoxifen therapy alone protected against the loss of spinal bone mineral density. The bones in the hip also benefited from tamoxifen treatment while there was no evidence demonstrating tamoxifen’s protection against bone loss in the wrist. When tamoxifen was combined with chemotherapy, it was found
to partially prevent or reverse the bone loss resulting from chemotherapy. Patients with a history of hormone replacement therapy experienced bone loss while patients without the history had increased bone mineral density during tamoxifen therapy. Despite an apparent impact of tamoxifen on bone mineral density, the few available studies of tamoxifen and bone fractures appear to suggest no protective effect but an increase in fracture incidence. More investigation is necessary to clarify the discrepancy between bone mineral density and fracture in postmenopausal breast cancer patients treated with tamoxifen.

**Key Words:** Tamoxifen; Breast cancer; Osteoporosis; Bone density.

(2) Introduction

Breast cancer is the most common cancer and the second leading cause of cancer death in women. In the United States alone, it is estimated that a total of 274,900 new female cases and 40,970 deaths will occur in 2006.\(^1\) However, over the last decade a trend of a steady decline in breast cancer deaths has been observed due to advancements in breast cancer diagnosis and treatment. Most of the women currently diagnosed with breast cancer are over the age of 65 and can expect lengthy periods of breast cancer survivorship.
Osteoporosis, a progressive process of bone mass loss, is a potential concern in these older breast cancer patients. The risk of osteoporosis is enhanced by a combination of female gender, older age, hormonal change, and the cancer itself. Increased bone loss in women with breast cancer may result from chemotherapy and from adjuvant therapy agents such as aromatase inhibitors.

The majority of breast cancer tumors in postmenopausal women are hormone receptor positive and therefore sensitive to hormone deprivation therapy. Selective estrogen receptor modulation (SERM) was a revolutionary development in the history of breast cancer treatment. It suppresses cancer cells in the breast tissue by its anti-estrogenic effect while acting as an estrogen analog in other tissues. Tamoxifen is the most commonly used SERM drug in hormonal therapy for breast cancer and has been a major component of treatment for women with hormone receptor positive breast cancer for three decades. The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of adjuvant endocrine therapy in women with hormone receptor-positive breast cancer. While it has been clearly demonstrated that tamoxifen increases the survival rate in breast cancer patients, it has some severe side effects such as venous thrombosis and endometrial cancer due to its estrogen-like effect. However, tamoxifen has also been reported to have beneficial side effects, including the protection of bone from osteoporosis because of this estrogenic action.
Since both breast cancer and osteoporosis strike mainly women, especially postmenopausal women, postmenopausal women with breast cancer might receive an extra benefit from tamoxifen therapy. As the treatment of early stage breast cancer begins to leave tamoxifen and shift to aromatase inhibitors, it is important to clarify the amount of protection against bone loss that tamoxifen has been found to confer in postmenopausal women with breast cancer. It is particularly important to quantify the extent to which tamoxifen prevents fractures in these patients. To that end, we performed a systematic review of the literature to clarify the evidence on the effectiveness of the tamoxifen on bone health.

(3) Methods

1. Literature search strategy

Bone health has been documented by a variety of measures including serum calcium level, the biomarkers of bone metabolism, bone mineral density (BMD), and bone fracture. We focused on BMD and fracture, the two most clinically relevant bone health indicators. A PubMed search was made by a combination of MeSH terms (breast neoplasm and tamoxifen plus bone or osteoporosis or bone density or bone fracture), limited to human, female, adults (≥45 years old), and published in English. Initially, three hundred and seven articles were identified. Forty-six reviews were first excluded. Of the remaining 261 articles, 229 were either not relevant to bone health, without appropriate controls or studied the impact of aromatase inhibitors on bone and therefore
were not of interest for this review. After further excluding studies in healthy women (N=2), premenopausal women (N=1), and articles not available in full text (N=3), 26 articles were identified. Searching related studies and the references of identified articles resulted in identifying one additional study. Finally, 27 articles were included in this study (Figure 1).

2. Methods used to measure bone density

Bone mineral density, as recommended by the World Health Organization, is the gold standard for bone loss measurement. In the studies reviewed, three methods were adopted for measuring BMD. Most studies conducted in the 1980’s and early 1990’s used photon absorptiometry (PA), a technique typically based on the transmission of isotope I-125 or Gd-153 for bone scanning. Although it generally produces a good and reproducible result, the amount of radiation that a patient is exposed to is a concern. Quantitative computed tomography is a good alternative to photon absorptiometry. It is more precise and sensitive in detecting BMD change. However, it can only be used for spinal bone density measurement. The high cost also makes it less accessible.

Dual energy X-ray (DXA) absorptiometry is currently the most widely used technology for BMD measure. It depends on a safer X-ray instead of an isotope source for bone mass detection. Because of its low radiation exposure, high precision, short scan times, and suitability for any skeletal sites including whole body scanning, DXA has essentially replaced PA for BMD measure.
3. Quality assessment

Each study was assessed for methodological quality using a checklist designed for both randomized and non-randomized studies. The checklist includes 27 items in five categories (reporting, external validity, internal validity-bias, internal validity-confounding, and statistical power). The maximal score of quality assessment is 32. The highest score achieved by the studies included in this review was 23 with an average score of 12.78 (Table 1).

(4) Results

1. Tamoxifen alone

Changes in spinal BMD. The majority of studies of adjuvant treatment using tamoxifen alone focused on changes in spinal BMD. An early investigation in 10 postmenopausal breast cancer women treated for one year with tamoxifen demonstrated a significant preservation of BMD compared to matched healthy women. A similar finding was obtained by Ward et al. Four other studies that used healthy women as controls, showed marginal or no BMD increase.

To observe BMD change over time, several studies adopted baseline value as a control. Ryan conducted a preliminary study in 1991 in eight breast cancer patients receiving one year of tamoxifen therapy and noticed a continuous increase from 3.6% (6 months) to 4.3% (12 months) in spine BMD in these patients. Three more studies in the early and mid 1990’s also using photon absorptiometry, failed to find a significant BMD change over baseline. Using the
most recent BMD measuring technology DXA, Marttunen found a range of 0.4 to 2% difference in BMD after one year of tamoxifen therapy in 30 patients with stage II breast cancer.\textsuperscript{38, 39} In Japan, Yoneda found a 3.3% increase in BMD at 6 months and 2.7% at 12 months.\textsuperscript{40} In the most recent study in the United Kingdom, Estell et al reported an intermediate finding from the five-year Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial in postmenopausal women with invasive breast cancer: at year two, an increase of 2.2% in lumbar spinal BMD was observed.\textsuperscript{41} However, a recent randomized control trial conducted in 36 postmenopausal patients with either stage II or stage III breast cancer did not find a change in BMD over a three-year period.\textsuperscript{42} Similarly, no BMD change was detected in a recent prospective study in 44 estrogen-receptor-positive patients.\textsuperscript{43}

Using patients without adjuvant therapy as controls, Kristensen found statistically significant BMD differences in 50 patients with early breast cancer after two years of tamoxifen therapy.\textsuperscript{44} Lumbar spine BMD in the tamoxifen treatment group increased 2% in the first year and became stable in the following year while a steadily decrease to 5% was observed in patients without tamoxifen. In a cohort of breast cancer patients (N=111) followed for five years, Resch demonstrated a significantly lower BMD in patients without tamoxifen therapy.\textsuperscript{45}

Love et al conducted a randomized placebo-controlled trial in 140 patients with axillary node-negative breast cancer.\textsuperscript{46, 47} In the first two years after the administration of tamoxifen, lumbar spinal BMD increased 0.61% per year in the tamoxifen group while it decreased 1.0% per year in placebo group. A further
follow-up study examining the BMD change in 62 patients who completed a five year regimen revealed a 0.8% BMD increase in the tamoxifen group compared to a 0.7% decrease in the placebo group.

Changes in hip BMD. Ten studies measured the BMD change in the hip bone. Marttunen found a 5% BMD increase at Ward’s triangle in a study of 30 stage II breast cancer patients treated with tamoxifen for one year. Rodriguez noted a significant BMD increase after one year of treatment with tamoxifen alone in the trochanter area of the hip bone in recent research conducted in a subgroup of 22 patients. Ward et al also observed a 1.4% BMD increase after one year of treatment with tamoxifen compared to a 2.3% decrease in healthy controls. A statistically significant association between tamoxifen therapy and BMD change in the hip over two years was observed by Cameron and his colleagues. In the ATAC trial, a 1.2% increase of BMD at total hip was observed. The increased BMD in the hip was not significant or not seen in seven other studies.

Changes in wrist BMD. BMD in the wrist was explored in seven studies. No significant increase was seen in any of these studies. A slower BMD loss was observed in patients with tamoxifen in a randomized controlled trial of 50 patients with breast cancer. A similar trend was seen in the study conducted by Love et al, but was not statistically significant. The remaining five studies did not see BMD change.

2. Tamoxifen plus chemotherapy
In a study exploring the tamoxifen effect on BMD after chemotherapy, Rodriguez found significant BMD increases in both intertrochanter and total hip in women who received 12 months of tamoxifen after chemotherapy. BMD at other sites of the hip such as the femoral neck, trochanter, and Ward’s triangle remained stable. Spinal BMD was unchanged as well. When tamoxifen was administered with chemotherapy, no BMD change was detected in either the spine or forewrist as demonstrated by Love. Crandall studied 280 subjects and compared joint adjuvant tamoxifen therapy and chemotherapy to a control group of healthy women. BMD in the spine, hip, and total body was increased, but this was not statistically significant.

3. Tamoxifen and hormonal replacement therapy

Two studies involved the influence of hormonal replacement therapy (HRT) on the effect of tamoxifen on BMD. Both investigated the BMD change after three years of tamoxifen use. Tiitinen demonstrated a 4.0% spinal BMD decrease in patients who had received HRT prior to breast cancer diagnosis while patients without an HRT history remained unchanged. Saarto had a similar finding of spinal BMD, showing a 3.0% decrease for patients with an HRT history and a 1.2% increase for patients without a HRT history. He also found a similar pattern of BMD change in the hip, although to a smaller extent.
4. Tamoxifen and fractures

In a large randomized controlled trial (N=1716) directly investigating the femoral fractures in postmenopausal breast cancer patients treated with tamoxifen for one year, Kristensen et al found a higher incidence in the tamoxifen group compared to patients not receiving tamoxifen. Following a cohort of 352 breast cancer patients in which 79% received either tamoxifen alone or in combination with chemotherapy, Kanis et al observed an increase in the rate of spinal fracture 4.7 times that of healthy controls. Findings from both studies were statistically significant.

(5) Discussion

Tamoxifen has been the dominant hormonal treatment for breast cancer patients for three decades. In addition to its efficacy, it has also been perceived as having a beneficial effect on bone health. In this review, the majority of published studies demonstrated a protective effect of tamoxifen therapy on spinal BMD in postmenopausal patients with early stage breast cancer (Figure 2). In the hip, the benefit varies depending on the site. The highest BMD increase from baseline was found at Ward’s triangle (5%). No bone protection was reported in the wrist. Studies of the hip and wrist are relatively fewer than those focused on the spine. Because the fractures in postmenopausal women caused by osteoporosis increase exponentially in the hip, where the outcomes are more
serious than from fractures of the spine or wrist, the most important form of protection for bone would affect the hip.

When chemotherapy is included in the treatment of breast cancer, it is frequently combined with hormonal therapy. The high toxicity of chemotherapy can cause many unwanted outcomes including early menopause and thus an increased risk of osteoporosis. In three studies investigating the protective effect of tamoxifen on BMD in a combined treatment with chemotherapy, one showed that tamoxifen reversed the bone loss after chemotherapy. This protective effect is likely due to tamoxifen’s estrogenic action on bone. When tamoxifen is used simultaneously with chemotherapy, such a protection is not clear. The negative effect of chemotherapy on estrogen may outweigh the estrogenic action of tamoxifen.

Hormone replacement therapy has been a common treatment for postmenopausal women. Many patients have a history of HRT use when diagnosed with breast cancer. The bone loss caused by discontinuing HRT at the time of breast cancer treatment is not fully offset by the effect of tamoxifen on BMD, as demonstrated by the studies in this review.

Overall, these studies provide convincing evidence that tamoxifen preserves BMD at least in the spine and hip in postmenopausal women with breast cancer. This protection gradually decreases over time. However, tamoxifen therapy after five years still showed a beneficial effect on bones. The mechanism of the protection is not fully understood. Part of the explanation is the
estrogenic action of tamoxifen outside of breast tissue.\textsuperscript{15} This hypothesis is supported by the studies in this review, which demonstrated that a reduced level of estrogen by chemotherapy or HRT withdrawal weakened or offset the protective effect of tamoxifen on BMD.\textsuperscript{30, 42, 48, 51, 52} Tamoxifen has also been shown to behave differently in premenopausal women by decreasing rather than increasing BMD \textsuperscript{55-57}, indicating a strong influence of estrogen on the effect of tamoxifen on bone health. The decrease in bone turnover biomarkers in patients treated with tamoxifen further suggests its estrogenic effect.\textsuperscript{38, 40, 43} Although many studies have demonstrated that tamoxifen protects against loss of BMD in postmenopausal women with breast cancer, the extent of such protection is not clear or consistent. Few studies directly investigated the net BMD increase.\textsuperscript{44-47, 50} Most studies used baseline BMD value as the control. This comparison may underestimate the impact of tamoxifen on BMD because BMD naturally decreases over time in postmenopausal women (Figure 2). Thus, the full impact of tamoxifen on BMD can not be obtained using women as their own controls. Similarly, healthy controls are not ideal because the bone mass density and its change in normal persons have been found to differ from that of women with breast cancer. Depending on their estrogen receptor status and anti-tumor therapy received, these patients could have a higher BMD value\textsuperscript{58} or increased bone loss.\textsuperscript{5-7} The scientific benefits of tamoxifen on bone health would be more convincing if data were obtained from randomized placebo controlled trials directly comparing breast cancer patients with and without tamoxifen.
The only two identified studies that directly investigated fractures in patients treated with tamoxifen found no beneficial effects but negative impacts on both spinal and hip bones,\textsuperscript{53, 54} compared to breast cancer patients who did not receive tamoxifen or to an age matched general population. In fact, the fracture risk in overall breast cancer survivors regardless of tamoxifen treatment status is not well known.\textsuperscript{59, 60} This may be partially due to the complexity of measuring fracture risk in elderly women. It is difficult to differentiate a disease specific fracture from common fractures in the population. Also important is that although low BMD has been linked with the likelihood of fracture,\textsuperscript{61, 62} the change in BMD has predicted the fracture risk poorly in patients with osteoporosis after raloxifene treatment.\textsuperscript{63, 64} This may also be true in breast cancer patients treated with tamoxifen. In addition, bone health in cancer patients is not only determined by bone metabolism, cancer itself is a major contributor. Women with breast cancer may be weaker and therefore more likely to fall, leading to a bone fracture. Thus, tamoxifen may protect women without breast cancer against fractures as demonstrated by the Breast Cancer Prevention Trial (P-1),\textsuperscript{65} while such protection is not evident in breast cancer patients. In the absence of further information from randomized trials, clarification of the relationship of tamoxifen therapy and fracture in breast cancer patients requires further studies of fracture incidence in breast cancer patients with and without tamoxifen with adjustments for potential confounding factors.
There are several limitations in the studies included in this review. Small sample size is a prevalent problem. More than half had a study population of less than 100 people. Since BMD change is often subtle with the known highest increase less than 8% (Figure 2), these studies may have failed to detect a difference due to inadequate statistical power. The complexities of disease features and treatments in these patients also add to the difficulties of determining the effect of tamoxifen on bone health. Few studies included hormone receptor information and many patients had mixed treatment at a given time period of disease. This led to problematic variation in study groups. The quality assessment demonstrated that most of the studies included in this review scored poorly with an average below the 50% of maximal score of 32. Although many studies indicated that the BMD change resulting from tamoxifen treatment for both hip and spinal bones was around 4%, the limited studies scoring above 50% of maximal score found a lower increase of 2% (Figure 3). These studies may better reflect the true effect of tamoxifen on BMD. Finally, it is important to note that no studies were found that assessed BMD change in relationship to fracture incidence in patients with tamoxifen treatment.

Tamoxifen has been the first choice for hormonal therapy for women with breast cancer. Other agents such as toremiphene are not widely adopted in clinical practice because of their relatively lower efficacy and/or inadequate information on benefit and safety profile. However recently, third-generation aromatase inhibitors have replaced tamoxifen in guideline recommendations for
breast cancer treatment of postmenopausal women.\textsuperscript{21} One important implication of this review is that tamoxifen may still be a valuable choice for postmenopausal women with breast cancer who also suffer from osteoporosis. However, because of the discrepancy between the BMD change and fracture incidence in the studies in this review, recommendations for clinical practice are not clear. Finally, it must be pointed out that the protective effect of tamoxifen on bone may have extra benefit for some breast cancer patients, but it cannot and should not replace osteoporosis prevention and anti-osteoporotic therapy for breast cancer patients at high risk of or with osteoporosis. BMD screening for such patients during tamoxifen treatment is necessary and a clinical recommendation for starting anti-osteoporotic therapy can be decided at an appropriate time.

**ACKNOWLEDGMENT**

We thank Drs. Jerry H. Gurwitz, Mary Costanza and Wenjun Li for advice and critically reading this manuscript.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Study design</th>
<th>Age (range, average)</th>
<th>Stage of breast cancer</th>
<th>Tamoxifen therapy</th>
<th>Dose (mg/d)</th>
<th>Method of BMD measure</th>
<th>Control</th>
<th>BMD change</th>
<th>Total body</th>
<th>Quality score</th>
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<td>40</td>
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<td>RCT</td>
<td>58.1</td>
<td>Non-skeletal metastasis</td>
<td>2 yrs</td>
<td>20 PA</td>
<td>Baseline</td>
<td>5.073(Z-score)</td>
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<td>Cohort</td>
<td>Post-menopausal 50-70</td>
<td>Breast Cancer Survivors</td>
<td>T2, T4</td>
<td>2 yrs</td>
<td>Baseline</td>
<td>0.74(Z-score)</td>
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<td>52-70</td>
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<td>40 PA</td>
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<td>0.278(Z-score)</td>
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<td>51-75/63</td>
<td>Stage II</td>
<td>1 yr</td>
<td>40 PA</td>
<td>Healthy Control</td>
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<td>Stage II, III</td>
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<td>T1-T2M0DM</td>
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<td>13</td>
<td></td>
<td></td>
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</table>

* = Increase; – = Decrease; ± = No change; p<0.05, **p<0.01.
PA=Photon absorptiometry, DXA=Dual energy X-ray absorptiometry, QCT=Quantitative computed tomography.
Breast Cancer AND Tamoxifen OR Bone OR Osteoporosis OR Bone Density OR Bone Fracture (limited to Human+Female +Age>=45+English) (N=307 articles)

Original studies (N=261)

Studies relevant to tamoxifen with appropriate bone health information and control (N=32)

Available studies in post menopausal women with breast cancer (N=25)

Studies included (N=26)

Reviews (N=46)

Non-tamoxifen studies; Preventive setting; No BMD/Fracture data; No self/healthy/non-tamoxifen control (N=229)

Studies in healthy or premenopausal women; Studies not retrievable (N=7)

Reference search (N=1)

**Figure 1** Literature search strategy
Figure 2  Effect of tamoxifen on BMD at different skeletal sites

'Self control uses patients' baseline BMD values.
†Matched control is either patients without tamoxifen therapy or healthy subjects.
Figure 3  Relationship between the quality of studies and findings of BMD change
1.4 Tamoxifen and CHD

Coronary heart disease (CHD) in women has a clear association with estrogen. It has been perceived that postmenopausal women are at a similar risk of CHD as their male counterparts mainly because of the decreased level of estrogen resulting from menopause.\textsuperscript{66} Hormone replacement therapy has been hypothesized to be a powerful tool to lower cardiovascular incidence in postmenopausal women. However, despite the positive evidence from many observational studies,\textsuperscript{67-71} some randomized trials,\textsuperscript{72, 73} especially the Women's Health Initiative study,\textsuperscript{74} failed to support the hypothesis. In the search for alternatives to hormone replacement therapy, SERMs emerge as a promising candidate. Due to the fact that SERMs are not steroids, they may avoid a summation of the effects of estrogen while mimicking the estrogenic action on coronary arteries. In postmenopausal women with breast cancer, tamoxifen has been proven to lower serum lipid levels.\textsuperscript{45, 75-77} More directly, tamoxifen has demonstrated an association with a reduced risk of CHD in several clinical trials.\textsuperscript{78-80} Recently, in a cohort of 11,045 women with breast cancer, Geiger et al showed no change in the risk of myocardial infarction (MI) in patients treated with tamoxifen.\textsuperscript{81} In a nested, matched, case-control study among 7263 women, Brandbury and his colleagues demonstrated that five years of tamoxifen therapy reduced the risk of acute MI or angina (adjusted OR, 0.4; 95% CI, 0.2–0.7) compared to patients without tamoxifen.\textsuperscript{82} Taken together, the current evidence from both clinical trials and observational studies appear to suggest that tamoxifen may reduce the risk of CHD in
women with breast cancer. Future cohort studies with a focus specifically on postmenopausal breast cancer women will add valuable information about CHD in this high-risk population.

1.5 Summary

Breast cancer is one of the leading threats to women’s health. Tamoxifen, the most successful SERM agent, has been used in hormonal therapy for three decades. Along with its therapeutic effect on breast cancer, tamoxifen also demonstrates potential benefits for bone and heart health. However, many questions associated with the beneficial effects remain to be answered: 1). Why have the few available studies failed to show a protection from tamoxifen on fractures while the majority of research demonstrated an increased BMD resulting from tamoxifen? How well does BMD predict the risk of fractures in patients with breast cancer? 2). Does tamoxifen protect breast cancer patients from fractures? 3). Whether and to what extent does tamoxifen reduce the risk of CHD?

As hormone replacement therapy for aging-associated female health problems has become controversial after the WHI trial, it is essential to clarify the role of SERMs and tamoxifen in particular on the prevention or treatment of osteoporosis and CHD. The proposed study is an attempt to enrich the knowledge on this issue and potentially generate valuable
information for both breast cancer treatment and the health of postmenopausal women.

1.6 References


41. Eastell, Richard Hannon, Rosemary A Cuzick, Jack Dowsett, Mitch Clack, Glen Adams, Judith E. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the anastrozole, tamoxifen, alone or in
combination (ATAC) trial (18233230). *Journal of bone and mineral research* 2006;21:1215.


CHAPTER II

Tamoxifen use and the risk of fractures in postmenopausal women with breast cancer

2.1 ABSTRACT

Adjuvant tamoxifen therapy in postmenopausal women with breast cancer has been repeatedly demonstrated to preserve bone mineral density. However, whether it prevents bone fractures is not clear. In fact, the few available studies exploring the association of tamoxifen use and fractures indicated an increased risk of fractures. We conducted a retrospective cohort study on the association of tamoxifen use and risk of fractures in an insured population of patients with breast cancer aged 55 or older by comparing those under tamoxifen therapy to patients who did not receive the treatment. Our results showed that the association between tamoxifen use and fracture risk varied at different skeletal sites. Although the relationship of tamoxifen and fractures in the spine (HR=0.40, 95% CI: 0.09-1.85), wrist (HR=2.49, 95% CI: 0.88-7.06), and total body (HR=0.87, 95% CI: 0.49-1.55) was inconclusive, tamoxifen was associated with an apparent reduction of the risk of hip fracture (HR=0.41, 95% CI: 0.17-1.03, p=0.0565). Importantly, the pattern of observed association of tamoxifen with fractures in postmenopausal women with breast cancer is consistent with its widely reported preserving effect on bone mineral density. Further study is necessary to evaluate the precise magnitude of benefit conferred by tamoxifen on bone fractures.
2.2 INTRODUCTION

Bone health is a concern in the treatment of breast cancer. Postmenopausal women who represent the largest portion of elderly women with breast cancer may be at higher risk of fractures through a combination of risk factors including female gender, older age, and hormonal change. Increased bone loss in these postmenopausal breast cancer patients may also result from chemotherapy [1] and adjuvant therapy agents such as aromatase inhibitors [2, 3]. Thus, in order to improve the overall survivorship of this specific patient population, the impact of cancer treatment on bone health in addition to its anti-tumor effect deserves consideration.

Adjuvant tamoxifen therapy is, theoretically, an ideal treatment for postmenopausal women with breast cancer who have a fracture concern. Due to the fact that tamoxifen is a SERM (Selective Estrogen Receptor Modulator) which suppresses tumor cells in the breast but has an estrogenic effect in other tissues such as bone [4-8], it has been speculated to mimic the estrogen protection on bone. Indeed, studies investigating the association of tamoxifen and bone mineral density (BMD) in postmenopausal women with breast cancer have repeatedly demonstrated increased BMD in the hip and spine, although a similar association was not seen in the wrist [9]. In addition, when combined with chemotherapy, tamoxifen has been found to partially prevent
or reverse the bone loss resulting from chemotherapy [10, 11]. Studies also found that patients with a history of hormone replacement therapy experienced bone loss during tamoxifen therapy compared to an increased BMD seen in those without such history [12, 13]. Overall, the evidence suggests the benefit associated with tamoxifen on BMD appear to be consistent with the estrogenic effect of tamoxifen.

Few studies investigating the association of tamoxifen and fractures, the ultimate outcome of deteriorated bone health, are available. Despite the widely reported apparent beneficial effect of tamoxifen on BMD in postmenopausal women with breast cancer, whether it prevents bone fractures is not clear. In fact, the only two original studies of tamoxifen on bone fractures in postmenopausal breast cancer patients who received tamoxifen therapy found no protective effect but an increase in spine or hip fracture incidence [14, 15] while a cross-study comparison based on data from three different studies failed to find a difference in overall fracture incidence [16]. The unexpected increase of fracture incidence in those studies requires further investigation.

In the present study, we conducted a retrospective cohort study on the association of tamoxifen use and risk of fractures in an insured patient population aged 55 or older. By comparing breast cancer patients taking tamoxifen to those who did not receive the treatment, we investigated the
relationship between tamoxifen use and the risk of fractures in a setting of community-based treatment. As adjuvant hormonal therapy shifts from tamoxifen to aromatase inhibitors (AIs), our study provides information to clarify the discrepancy between BMD and fractures and to evaluate the added value of tamoxifen use in postmenopausal women with breast cancer due to its potential benefit on bone health.

2.3 METHODS

Study population

The data we used for this study is from four large integrated health care delivery systems (HealthPartners, Minneapolis/St Paul, MN; Fallon Clinic, Worcester, MA; Kaiser Permanente Northern California, San Francisco/Sacramento, CA; and Henry Ford Health System, Detroit, MI) that participate in the Cancer Research Network (CRN) which consists of 14 health care delivery systems [17, 18]. Postmenopausal patients (aged 55 or older) with newly diagnosed breast cancer between January 1, 1996 and December 31, 1997 were included in this study. These patients were followed for a maximum of seven years to the date of death, or disenrollment, or the last day of the follow-up, (December 31, 2002) with a follow-up rate of 85.8%. This study was approved by the institutional review boards of all sites.

Identification of breast cancer cases and study parameters
Breast cancer patients were identified through health system registries at two sites (Henry Ford and Kaiser Permanente) with tumor registries. At two sites without such access (HealthPartners, Fallon Clinic), automated data bases with medical record confirmation were used. In-situ and invasive cases were included and tumor stage was categorized as 0 (in-situ), I, II, III, or other (IV or unknown) according to the criterion of the American Joint Commission on Cancer (AJCC). All breast cancer patients with AJCC stage 2 or greater plus an age-stratified random sample of patients with stage 1 or less as well as all patients at the two sites without tumor registries were selected. At the largest site (Kaiser Permanente), one-fifth of patients with stage 0 or 1 breast cancer were sampled. In total, 897 women with breast cancer were included. All cases were confirmed through medical record reviews by trained abstractors [19].

In addition to the breast cancer information, data including demographics (age and race), tumor stage, cancer treatments (surgery, chemotherapy, and radiotherapy), comorbidities, plus tamoxifen use were collected by the chart abstractors supplemented by electronic pharmacy data. A modified Charlson comorbidity score [20] for the two years prior to diagnosis of breast cancer was derived from the abstracted information, weighted as originally developed, and categorized as 0, 1, 2, or 3 and above.
The outcome parameter, fracture, was extracted from administrative, electronic medical utilization data that included inpatient and outpatient diagnoses and procedures. Osteoporotic fractures were identified using the following criterion [21]: at least one of ICD-9-CM diagnosis codes (805.xx-vertebral, 807.0x or 807.1x-rib, 813.xx or 814.xx-wrist, and 820.xx-hip) or one of The Current Procedural Terminology (CPT) procedure codes (7607x and 7835x) from inpatient data, or at least two of ICD-9-CM diagnosis codes for the same fracture on different dates or one diagnosis code plus one CPT procedure code from outpatient data. Patients with a fracture during the two years prior to diagnosis of breast cancer were excluded from this analysis. For BMD testing status, the ICD-9-CM diagnosis code 88.98 and CPT codes 76070, 76071, 76075, 76076, 76078, 76499, 76977, 76999, 78350, 78351 were used for the data extraction [22, 23]. Finally, information about anti-osteoporosis treatment was obtained from pharmacy data using NDC (National Drug Code) codes for raloxifene, calcitonin, alendronate, and risedronate. Anti-osteoporotic pharmacy data were not collected at one study site (Kaiser Permanente North California).

Statistical analysis

Outliers with potential impact on study results were checked and all patients were kept in the data analyses because the exclusion of outliers did not change the association of tamoxifen use with fractures. Age was categorized into six groups from 55-59 to 80+ by five year intervals. All
other characteristics of patients included in the study are either dichotomous or categorical variables. Chi-square tests were used for the comparison of characteristics between patients treated with tamoxifen and those who did not receive such treatment.

To compare of the incidence of fractures over time between patients who did and did not receive tamoxifen, we used the Kaplan-Meier survival method. Both overall and site specific fractures in the spine, hip, and wrist of patients were compared by tamoxifen use status. The association between tamoxifen use and risk of first fracture at a specific skeletal site (spine, hip, and wrist) as well all sites combined (total body) was examined using Cox proportional hazards regression, providing hazard ratio (HR) estimates and 95% confidence intervals (95% CI), with a series of adjustments for potential confounders. Tamoxifen use was treated as a time-dependent covariate in regression models. The time prior to the beginning of tamoxifen therapy was considered as non-tamoxifen use status. Because of the limited number of fractures at individual skeletal sites and the similarity of fracture incidence between the time periods of during and after tamoxifen therapy (data not shown), we did not further differentiate these two stages of tamoxifen use in the data analyses. For comparison, we also tested tamoxifen use as a dichotomous variable as well as fitting Poisson models (using generalized estimating equations) and obtained similar results (data not shown). Although Charlson comorbidity score, BMD testing status, and anti-osteoporotic therapy are
potential predictors of fractures, these factors were not associated with
tamoxifen use (Table 1), and the inclusion of these factors in the model did
not significantly affect the results (data not shown). In addition, the
hormone receptor status (ER/PR) was not used in the regression analyses
because the data are only available at two out of four study sites, and the
pattern of the association of tamoxifen and fractures at different skeletal
sites observed from the analyses restricted to the two sites with the ER/PR
information did not differ from the one using the whole dataset. Given the
clinical and epidemiological significance as well as the preliminary
analyses, we included age, race, surgery status, and cancer stage in the
final model. Statistical significance was defined at the $\alpha=0.05$ level.
Analyses were performed using SAS software, version 9.1 (SAS Institute,
Inc., Cary, NC).

2.4 RESULTS

The baseline characteristics of patients are presented in Table 1. After
the exclusion of patients with a fracture prior to the diagnosis of breast cancer,
there are 866 women with breast cancer included in this study. Of these, more
than half (487) received tamoxifen therapy. Age distribution in each age group
is similar between tamoxifen users and non-users. However, there is a higher
percent of black patients in the non-tamoxifen group (11.87% vs 9.65%).
Tamoxifen users were generally hormone-receptor-positive (83.81%) while far
fewer non-tamoxifen users had positive hormone receptor status (40.98%). As
expected, few patients with in-situ breast cancer received tamoxifen (2.26% vs 29.29%). A significantly higher percent of non-tamoxifen users had breast-conserving surgery (BCS) than those taking tamoxifen (60.16% vs 49.28%, P=0.0016). For other major cancer treatments (chemotherapy and radiotherapy), no difference is seen between the two patient groups. Comorbidity conditions are similar in patients with or without tamoxifen therapy although a slightly higher percent of patients in the category of score 0 of Charlson index are found in the tamoxifen user group (66.53% vs 62.01%, P=0.1961). In terms of osteoporosis associated medical utilization, an almost identical percent of patients in both groups received BMD testing (25.67% vs 25.07%) as well as anti-osteoporotic therapy (12.77% vs 11.61%), suggesting a similar perceived fracture risk at baseline.

Fractures at three common fracture sites (spine, hip, and wrist) and total body are visualized using Kaplan-Meier survival functions in Figure 1. A reduced fracture event trend can be observed in the spine over time, and this trend is more noticeable in the hip. However, an increase of fracture events is seen in the wrist, while the combined fracture events of all skeletal sites do not differ between patients with and without tamoxifen therapy at any time in the follow-up period. Due to the fact that fracture events are low at all sites (ranging from 1% to 7%), the differences by tamoxifen use status at the individual skeletal sites are small, and none are statistically significant at the p<0.05 level.
Table 2 presents the risk of fractures for patients with and without tamoxifen therapy. Fracture cases identified at each skeletal site are relatively few, especially in the spine, where only 11 fractures were found. The total number of patients with incident fractures after the diagnosis of breast cancer is 59, with some patients having fracture events at multiple skeletal sites on a given date. Compared to non-tamoxifen users, the fracture incidence over the period of follow-up time is lower among the tamoxifen users in the spine (1.64 vs 3.89/1,000 person years) and hip (4.13 vs 7.35/1,000 person years). A higher incidence of fracture is seen in the wrist among the patients with tamoxifen therapy. Results of the Cox proportional hazards regression analyses find that tamoxifen users have a 60% (95% CI: 0.10-1.55) reduction in risk of fracture in the spine, 44% (95% CI: 0.24-1.30) in the hip, and no change for total body before model adjustment (Unadjusted Model), but a 121% (95% CI: 0.89-5.45) increase in the wrist. The addition of age and race, two common confounders, has little impact on the estimates of risk (Model 2 and Model 3). Similarly, surgery status does not dramatically affect risk estimates (Model 4). However, the stage of cancer has a strong effect on the prediction of the fracture risk by tamoxifen use status. After the inclusion of this factor in the final model, the risk of fracture (HR) was changed from 0.56 (95% CI: 0.24-1.30) to 0.41 (95% CI: 0.17-1.03) in the hip, from 2.21(95% CI: 0.89-5.45) to 2.49 (95% CI: 0.88-7.06) in wrist, and from 0.99 (95% CI: 0.58-1.68) to 0.87 (95% CI: 0.49-1.55) in total body. The hazard ratios in the final adjusted models are not statistically significant except for hip fractures.
where the reduction of fracture risk is of borderline statistical significance (HR: 0.41; 95% CI: 0.17-1.03; P=0.0565).

2.5 DISCUSSION

Compelling evidence from previous studies demonstrated that tamoxifen preserved BMD in postmenopausal patients with breast cancer. This preservation is evident in the hip and spine but not detectable in the wrist [9]. However, opposite to common speculation, observations documented in the few available studies regarding the association of tamoxifen and fractures showed an unexpected increase of the risk of fractures in patients taking tamoxifen. One study conducted as a randomized controlled trial of 1716 breast cancer patients with an average age of 54 years for one year found a significant increase of spinal fracture (OR=2.12, 95% CI: 1.12-4.01) in those taking tamoxifen [15]. Furthermore, a nearly five times higher risk of hip fracture among patients taking tamoxifen (OR=4.7, 95% CI: 2.3-9.9) was observed in a two to three year cohort study in which 79% of 352 breast cancer patients received either tamoxifen alone or in combination with chemotherapy (14). Although these studies have many strengths, their findings could be biased by several factors such as the complexity of the patient population, the suitability of the controls, the length of tamoxifen use, the accuracy of identification of fractures, and the short follow-up.
In the present study, we investigated the association of tamoxifen and fractures in three common skeletal fracture sites (spine, hip, and wrist) plus combined sites (total body) in postmenopausal women with breast cancer in an insured population. Our results showed that the association of tamoxifen and fractures varied at different skeletal sites. While the association of tamoxifen and the risk of fractures in the spine (HR=0.40, 95% CI: 0.09-1.85), wrist (HR=2.49, 95% CI: 0.88-7.06), and total body (HR=0.87, 95% CI: 0.49-1.55) was inconclusive, an apparent reduction of fracture risk was found in the hip (HR=0.41, 95% CI: 0.17-1.03) with borderline statistical significance (p=0.0565). The effect estimates, especially in the spine where subtle fractures are likely to be under-diagnosed, are imprecise. However, the pattern of the associations of tamoxifen and various fracture sites found in this study was similar to its preserving effect on BMD in a recent systematic review of 27 studies [9] which demonstrated a site-specific preservation on the spine and hip but not the wrist. In addition, the reduced fracture risk seen in this study was consistent with the findings reported in a breast cancer prevention setting using tamoxifen [24], further supporting the possibility of a benefit associated with tamoxifen on fractures.

Our study is strengthened by several factors. The study population we used is insured and received care in integrated health care systems. This study setting ensures a diverse patient population with equal health service access so that treatment decisions such as tamoxifen use are
likely to be based on medical needs. The collection of data in this study, including breast cancer diagnosis, medical utilization, and follow-up is complete. The use of medical record reviews by trained medical abstractors further reduces selection and information biases. In fact, the majority of patients had at least two years of tamoxifen therapy (data not shown) enhancing the chance of detection of changed risk of fractures resulting from longer tamoxifen use. The relatively long follow-up period of a maximum of seven years enables us to accumulate more information on fracture, so that this relatively rare medical outcome can be studied.

Although this study is carefully designed to overcome or circumvent common problems, there are some weaknesses that could affect the study results. Despite an identified trend of reduced risk of fracture in patients under tamoxifen therapy, the findings were not statistically significant except for a borderline significant change in hip fractures. One explanation is the limited sample size. A power calculation shows that in order to detect a relative risk (HR) of 0.41 in the hip found in this study at the $\beta=0.8$ level in this patient population, a sample size of 1,588 is required. Our study sample ($N=897$) does not meet that requirement. Thus, we were only able to detect the trend but not statistical significance for spine and wrist fractures as well as total fractures. However, the study population is large enough to confirm a 4.7 times risk of spine fracture [15] for which only 175 patients would be needed. Since we did not observe an increase but a decrease of the risk of hip fracture, the large increased risk of hip fracture observed in the previous study is more
likely the result of other factors than tamoxifen, and the possibility of a potential benefit associated with tamoxifen on fractures in the hip still holds. Given the magnitude of findings (no reduction to 65% reduction) from major clinical trials including the MORE trial (the Multiple Outcomes of Raloxifene Evaluation) [25] which was conducted in 7705 women with postmenopausal osteoporosis treated with raloxifene, a SERM for the treatment of osteoporosis, and the trials of bisphosphonates such as VERT (the Vertebral Efficacy with Risedronate Therapy) [26, 27], HIP (Hip Intervention Program) [28], and FIT (the Fracture Intervention Trial) [29, 30], it is understandable that we found a trend of rather than a large and statistically significant reduction of the risk of fractures associated with tamoxifen, a weaker protection of bone than these pharmacologic agents for osteoporosis. Other limitations of the study include reliance on administrative data for the identification of fractures. Fractures in some patients, especially those who have numerous comorbidities might not be documented or documented as a secondary diagnosis. The low rate of spine fractures [16] reinforces the potential underestimation of fractures identified in this study. The lack of information about some risk factors of osteoporosis associated fractures such as body mass index, BMD measures, T-score, smoking status, hormone replacement therapy, the history of fractures [31] as well as aromatase inhibitor use may leave uncontrolled confounding. An additional limitation is that although all patients included in this study are postmenopausal women, a population with high risk of osteoporosis, one third of them who are 65 or younger. We could have more power to clarify the association of tamoxifen and fracture if these
patients were older. The inconclusive findings observed in this study could be clarified if we had a similar size but older patient population.

Tamoxifen has been the first-line adjuvant hormonal therapy in postmenopausal women with breast cancer for three decades and is currently being replaced by third-generation aromatase inhibitors (AIs) [32]. Although AIs have been proven to be equal to or better than tamoxifen as treatment for hormone-receptor-positive breast cancer [33], the fact that they increase the risk of fractures [2, 3] restricts their application in patients who are also at high risk of osteoporosis. Tamoxifen appears an ideal choice in this situation because of its preservation of BMD. However, since initial studies found an unexpected increase of fracture risk in patients under tamoxifen therapy, no subsequent studies have been conducted to answer the question. Since AIs, the current recommended adjuvant hormonal therapy, increase the risk of fractures, the clarification of tamoxifen use on fracture risk in postmenopausal women with breast cancer is important. Our study suggests a reduced risk of fractures in the hip and possibly in the spine. While we were preparing this manuscript, a case control study set in a large administrative database without full information on breast cancer status demonstrated a similar protection of tamoxifen on fractures in a predominantly non-breast cancer population (97%) [34]. Future studies in different settings are necessary to elucidate the precise magnitude of the benefit associated with tamoxifen on
fractures and help to clarify confusion resulting from the increased fracture risk associated with tamoxifen therapy in previous studies.

ACKNOWLEDGMENTS

We thank Dr. Jerry H. Gurwitz, Dr. Mary Costanza, and Dr. Wenjun Li for their advice and help in this study.
Table 1. Characteristics of women with breast cancer by tamoxifen-use status (%)

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen user (N=487)</th>
<th>Non-tamoxifen user (N=379)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>18.89</td>
<td>20.58</td>
<td>0.9583</td>
</tr>
<tr>
<td>60-64</td>
<td>16.84</td>
<td>15.30</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>17.25</td>
<td>16.62</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>17.45</td>
<td>17.94</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>18.89</td>
<td>16.89</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>10.68</td>
<td>12.66</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>0.9131</td>
</tr>
<tr>
<td>White</td>
<td>81.93</td>
<td>81.27</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.85</td>
<td>1.32</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9.65</td>
<td>11.87</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific</td>
<td>4.11</td>
<td>3.17</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2.46</td>
<td>2.37</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone receptor status (ER/PR)†</strong></td>
<td>(n=247)</td>
<td>(n=205)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive</td>
<td>83.81</td>
<td>40.98</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4.45</td>
<td>16.10</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11.74</td>
<td>42.93</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer Stage</strong></td>
<td></td>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>0</td>
<td>2.26</td>
<td>29.29</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>49.90</td>
<td>45.12</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>32.65</td>
<td>16.36</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8.83</td>
<td>2.90</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6.37</td>
<td>6.33</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td>0.0016</td>
</tr>
<tr>
<td>None</td>
<td>5.13</td>
<td>3.43</td>
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<tr>
<td>BCS</td>
<td>49.28</td>
<td>60.16</td>
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<tr>
<td>Mastectomy</td>
<td>45.59</td>
<td>36.41</td>
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</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
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<td>0.1443</td>
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<td>20.53</td>
<td>16.62</td>
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</tr>
<tr>
<td>No</td>
<td>79.47</td>
<td>83.38</td>
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<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
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<td>0.5093</td>
</tr>
<tr>
<td>Yes</td>
<td>46.82</td>
<td>49.09</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53.18</td>
<td>50.92</td>
<td></td>
</tr>
<tr>
<td><strong>Charlson score</strong></td>
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<td>0.1961</td>
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<tr>
<td>0</td>
<td>66.53</td>
<td>62.01</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19.51</td>
<td>21.11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6.98</td>
<td>9.23</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>6.98</td>
<td>7.65</td>
<td></td>
</tr>
<tr>
<td><strong>BMD testing</strong></td>
<td></td>
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<td>0.8403</td>
</tr>
<tr>
<td>Yes</td>
<td>25.67</td>
<td>25.07</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74.33</td>
<td>74.93</td>
<td></td>
</tr>
<tr>
<td>Anti_osteoporotic therapy††</td>
<td>(n=321)</td>
<td>(n=267)</td>
<td>0.6689</td>
</tr>
<tr>
<td>Yes</td>
<td>12.77</td>
<td>11.61</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87.23</td>
<td>88.39</td>
<td></td>
</tr>
</tbody>
</table>

† Data not available at two HMO sites (Fallon Clinic, MA and Henry Ford Health, MI). †† Data not available at one HMO site (Kaiser Permanente, CA).
Figure 1. Survival possibility from fractures at different skeletal sites in patients by tamoxifen use status
Table 2. Comparison of fractures in breast cancer patients with versus without tamoxifen therapy

<table>
<thead>
<tr>
<th>Fracture site</th>
<th>Number of Cases</th>
<th>Fracture Incidence (/1000 yrs)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen user</td>
<td>Non-tamoxifen user</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Spine</td>
<td>11</td>
<td>1.64</td>
<td>3.89</td>
</tr>
<tr>
<td>Hip</td>
<td>23</td>
<td>4.13</td>
<td>7.35</td>
</tr>
<tr>
<td>Wrist</td>
<td>24</td>
<td>6.65</td>
<td>4.45</td>
</tr>
<tr>
<td>Total Body</td>
<td>59</td>
<td>13.04</td>
<td>16.03</td>
</tr>
</tbody>
</table>

Unadjusted Model: Tamoxifen only (reference: non-tamoxifen user)
Model 2: age adjusted
Model 3: age+race adjusted
Model 4: age+race+surgery adjusted
Full model: Tamoxifen+age+race+surgery+cancer_stage
2.6 REFERENCES


12. Saarto T, Vehmanen L, Elomaa I, Valimaki M, Makela P, Blomqvist C. The effect of clodronate and antioestrogens on bone loss associated with...


CHAPTER III

Association between bone mineral density and fractures in elderly women with breast cancer

3.1 Abstract

Bone mineral density (BMD) is the gold standard for the diagnosis of osteoporosis. However, the association of osteoporotic fractures and BMD is not fully understood. BMD has been linked with different risks of fractures between sexes, races, and at different skeletal sites. In addition, studies have reported a null association of BMD and fractures among patients treated with anti-osteoporotics and a paradoxical discrepancy between BMD and fractures in breast cancer women under tamoxifen therapy. In the present study, we investigated the association of BMD and fractures among elderly women with breast cancer who participated in the Study of Osteoporotic Fractures in comparison to women without breast cancer. Our results demonstrate that women with breast cancer have a higher BMD value and lower risk of fractures. Compared with the consistent association of BMD and fractures in those without breast cancer, the association between BMD and fractures in women with breast cancer varies by different skeletal sites, and type of BMD. Non-specific BMD was not associated with hip fracture (HR=1.12; 95% CI: 0.78, 1.59). Site-specific BMD was more likely linked with hip fracture (HR=1.43, 95% CI: 0.99, 2.08) while change in BMD did not predict hip fracture (HR=1.05; 95% CI: 0.63, 1.72). The
association of spine morphometric fracture with either non-specific or spine-specific BMD was similar (OR=1.40; 95% CI: 1.04, 1.90; OR=1.35, 95% CI: 0.99, 1.85, respectively). In conclusion, the association of BMD and fracture in elderly women with breast cancer is weak. Thus, these finding suggest that BMD may have reduced value in predicting and monitoring the risk of fractures in this patient population. Alternative risk factors that are unique or better predictors of fractures in women with breast cancer need to be identified.

**Key words:** Bone mineral density, Fracture, Osteoporosis, Breast cancer

### 3.2 Introduction

Osteoporosis is one of the leading threats to women’s health. Postmenopausal women are at an increased risk of this disease because of aging-associated progressive bone loss. While bone loss itself may not have severe clinical symptoms, fracture, the ultimate outcome of osteoporosis, causes tremendous suffering and life loss in patients with this disease, and the social and economical burdens are overwhelming. Understanding the likelihood of a fracture in patients with osteoporosis is an important element of osteoporosis management. A preventive strategy and necessary treatment based on an accurate assessment of fracture risk could save many lives in patients with osteoporosis.
Although the risk of osteoporotic fractures is associated with many factors, bone mineral density (BMD) is the most important risk factor in most cases. The decrease of BMD has been linked to an increase of fracture risk in many studies. In general, one standard deviation (SD) reduction of BMD leads to about 1.6 fold increase of fractures depending on the site. However, despite the fact that BMD has been successfully used in the assessment of fracture risk, its value varies in different study populations. BMD has been linked with a different risk of fractures in men. Studies have also reported a null association of BMD and fractures among patients treated with anti-osteoporotics. Therefore, it is important to explore the association of BMD and fractures in specific populations with features that could affect the association.

Women with breast cancer differ from their non-breast cancer counterparts in terms of osteoporosis risk. An inverse relationship between breast cancer and osteoporosis/fractures has been reported, (i.e. patients with osteoporosis/fractures are less likely to develop breast cancer and vice versa). In addition, the risk of developing osteoporosis in women with breast cancer could be changed for a variety of reasons including the breast cancer treatment such as aromatase inhibitor use and withdrawal of hormone replacement therapy. Although the underlying mechanism of the association between osteoporosis and breast cancer is not fully understood, estrogen may
play an important role. Because of a relatively high level of circulating estrogen found in women with breast cancer\textsuperscript{20-25}, it is speculated that elevated estrogen leads to a reduction of the risk of osteoporosis in this population. Indeed, estrogen has a proven beneficial effect on BMD\textsuperscript{26-30}, and it has been reported that BMD is higher in women with breast cancer\textsuperscript{16, 31-34}. However, whether the increased BMD results in a decreased risk of osteoporotic fracture is not certain. In fact, a surprising discrepancy between increased BMD and an increased rather than decreased risk of fractures in breast cancer women treated with tamoxifen\textsuperscript{35} indicates a possibility that BMD may not be of value in the prediction of fracture in this patient population.

To test the hypothesis that the inter-relationship among BMD, fracture, and breast cancer could change the role of BMD as a major predictor of fractures in women with breast cancer, we investigated the association of BMD and fracture in the elderly women who participated in the Study of Osteoporotic Fractures (SOF). Using women without breast cancer as the comparison group, we studied the value of baseline peripheral foot (calcaneal) BMD, site-specific BMD (hip, spine, wrist), and BMD change over time in the assessment of fracture risk at different skeletal sites in women with breast cancer. The findings of this study will enhance our understanding of the prediction of BMD on fractures and help to clarify confusion on the change in the risk of osteoporosis resulting from anti-breast cancer treatment.
3.3 Methods

Study population

The data used in this study were collected in the SOF study. The design and study population of that study have been described previously \textsuperscript{26, 36}. In brief, 9704 white women aged 65 or older were recruited during the period of 1986-1988 in four metropolitan clinical centers across the United States (Baltimore, Pittsburgh, Minneapolis, and Portland OR). Participants were followed-up every four months by postcard or telephone; medical examinations were conducted at each visit every two years. A follow-up rate of 98\% was achieved for vital information and fracture status. Data from six visits are available for public use. This study was approved by the SOF study committee.

Breast cancer status

The diagnosis of breast cancer was obtained from self-report by study participants and validated by review of their medical records. Participants with breast cancer before the enrollment were excluded from this analysis. Also collected was the date of the diagnosis; women with breast cancer were excluded if the diagnosis was after a fracture. In total, 563 participants were diagnosed with breast cancer during the SOF follow up. After the re-classification
of breast cancer status according to the dates of the diagnosis of breast cancer and fractures, 444 were identified as women who developed breast cancer during follow-up. Participants without a diagnosis of breast cancer during the follow-up were also included in data analyses (N=8525).

_BMD measures and fracture information_

Peripheral BMD measures including those at calcaneus, distal radius, and proximal radius were conducted at baseline (visit 1) using single photon absorptiometry. Subsequent measures starting at year two adopted duel X-ray absorptiometry and data were available at a variety of skeletal sites. However, only hip BMD was measured at multiple visits (2, 4, 5, 6) in the whole study population. BMD measures in spine and wrist were either only available at one visit or not measured at the last visit (visit 6) while whole body BMD was measured in a subset of the population. Therefore, peripheral calcaneal BMD was used to substitute for whole body BMD, and change in BMD was only calculated in the hip for these analyses.

Information about incident fractures was ascertained by mail and phone and validated by x-ray reports or a review of pre-operative radiographs. Data were collected and calculated based on a specific starting visit. Spine x-rays were performed at baseline (visit 1) and visit 3. Prevalent spinal fractures were
determined by morphometric change compared with women without vertebral deformities. Data from the two visits (1 and 3) were combined and calculated as morphometric spine fractures.

Data analysis

The general comparisons of characteristics between SOF participants who did and did not develop breast cancer were performed by either t test or chi square as appropriate. The incidence rate of fractures was defined as the number of fractures per 1000 person years. These rates were further stratified by age groups in 5-year intervals for comparisons by breast cancer status. To quantify the relationship among BMD, fractures, and breast cancer, Cox proportional hazards regression analysis was performed with breast cancer as a time-dependent variable, (i.e. the time before diagnosis of breast cancer was counted as non-breast cancer status). The overall risk of any incident fracture was first assessed using baseline BMD in women with breast cancer. The predictive value of baseline BMD in the development of breast cancer was also explored. Furthermore, the potential interaction of baseline BMD and breast cancer in the occurrence of fractures was tested. Eventually, a comprehensive assessment of the association between BMD and the first fracture incidence at a specific skeletal site (hip and wrist) was examined. Because of the lack of follow-
up information on the timing of spine fracture, logistic regression was used for the estimation of BMD on spinal morphometric fractures.

Three types of BMD measures were used in this study: baseline non-specific BMD, site-specific BMD, and change in BMD. Baseline peripheral calcaneal BMD was used as the non-specific BMD. The site-specific BMD measures included distal wrist BMD and proximal wrist BMD, total hip BMD, and total spine BMD at visit 2. The change in BMD for the hip was calculated by comparing the measures at visit 6 to those at visit 2. To better describe the association of BMD and fracture, BMD measures were transformed and SD (per SD decrease) was used as the unit for the establishment of the regression models instead of using absolute measures. In addition, a T-score was calculated for each woman based on the hip BMD compared with the mean BMD of normal young people adopted from the National Health and Nutrition Examination Survey, and osteoporosis status was determined using the WHO (World Health Organization) standard \(^{37, 38}\) (normal BMD: T-score\(\geq\)-1.0; osteopenia (low BMD): -1\(\geq\)T-score\(\geq\)-2.5; osteoporosis: T-score\(\leq\)-2.5).

Based on the statistical tests, three potential confounders (age, BMI, and smoking status) were controlled in the analyses. Hazard ratios (HR) or odds ratios (OR) and 95% confidence interval (95% CI) were obtained for the estimation of the change of fracture risk resulting from per SD decrease of BMD.
Statistical significance was defined as the $\alpha=0.05$ level. Analyses were carried out using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

### 3.4 Results

The characteristics of SOF participants by breast cancer status are shown in Table 1. Compared to women who were not diagnosed with breast cancer during the follow-up period, those with breast cancer were slightly younger (about 9% more under 70 years old), heavier (weight: 69.86 kg vs 67.53 kg) and had higher Body Mass Indices (BMI) (27.25 vs 26.37). Both baseline calcaneal BMD and site-specific BMD (in wrist, hip and spine) were significantly higher among women who developed breast cancer, although the loss of BMD from visit 2 to visit 6 (BMD change) was similar to women without breast cancer. Correspondingly, fewer women with breast cancer had very low bone density with a T-score less than -2.5 SD (osteoporosis). No statistical difference was seen for other demographic characteristics and bone health-associated risk factors.

The incidence rate of fracture was about half or less for women who developed breast cancer than for their non-breast cancer counterparts across age groups. While the overall rate of fractures increased over time in women without breast cancer, it remained relatively stable in those who developed
breast cancer (Fig. 1). A higher percentage of women without breast cancer experienced a fracture at each skeletal site (Table 2).

Analyses of the relationship of baseline BMD (calcaneal), breast cancer and fractures demonstrated that baseline BMD was associated with both risks of breast cancer and fractures (Table 3). Each SD decrease in calcaneal BMD, was associated with a statistically significant increased risk of fractures (HR=1.44, 95% CI: 1.38-1.49) and a decreased risk of breast cancer (HR=0.85, 95% CI: 0.76-0.95). Breast cancer itself was associated with a decreased risk of fractures (HR=0.59, 95% CI: 0.50-0.70) and this association was independent from baseline BMD (HR=0.61, 95% CI: 0.51, 0.73 after adjustment for baseline BMD). In addition, breast cancer status did not affect the association of baseline BMD and overall fracture risk (interaction: p=0.6431).

Table 4 summarizes the association of incident fractures in the hip and wrist with three different types of BMD measures. Unlike the association of BMD and fractures seen in women without breast cancer, the risk of fractures associated with BMD in those with breast cancer varied by skeletal sites and the types of BMD. Baseline calcaneal BMD did not predict hip well (HR=1.12; 95% CI: 0.78, 1.59). Change in BMD was not associated with the fracture risk at the corresponding site (hip) (HR=1.05, 95% CI: 0.63, 1.72). Hip-specific BMD was more closely associated with the hip fractures than non-site-specific calcaneal
BMD (HR=1.43, 95% CI: 0.99, 2.08). A higher hazard ratio of wrist fractures in women with breast cancer was associated with all three BMD measures. The association of baseline calcaneal BMD and spine-specific BMD on morphometric fractures in the spine are represented in Table 5. Unlike the non-vertebral incident fractures, spinal fractures had a similar association with site-specific (spine) and non-specific BMD (OR=1.40, 95% CI: 1.04, 1.90; OR=1.35, 95% CI: 0.99, 1.85, respectively), but the association was not as strong as in women without breast cancer.

3.5 Discussion

BMD is the gold standard for the screening and diagnosis of osteoporosis. It is also perceived as the most valuable predictor of fractures in people with low bone density and patients with osteoporosis. However, it has been reported that BMD is not well associated with fractures in some populations such as patients who received anti-osteoporotic therapy. In the present study, we investigated the association of BMD and fractures in a specific population, (i.e. women with breast cancer, who differ from their non-breast cancer counterparts in terms of the risk of fractures).

Our results demonstrated that women with breast cancer have a higher BMD. While BMD did show a consistent association with fracture risk in women
without breast cancer, the association between BMD and fractures seen in women with breast cancer varied by skeletal sites and the types of BMD measures. Among the three types of BMD measures used in this study, non-specific BMD was less efficient. Site-specific BMD in the hip was better associated with hip fracture, but BMD change at this site did not predict fractures (Table 4). Unlike incident fractures, spine morphometric fractures were predicted by either non-specific or spine-specific BMD (Table 5). Although BMD predicted wrist fractures better in women with breast cancer, it is not conclusive partially because of the low number of wrist fracture cases identified in this study population. Overall, the predictive value of BMD on fracture in women with breast cancer is weak. Only site-specific BMD appears to have a modest association with fractures in those women diagnosed with breast cancer.

The weak association of BMD and fractures in women with breast cancer could be attributable to multiple factors. Breast cancer itself certainly plays the most important role. BMD is a predictor not only for bone health but also for the risk of breast cancer. Although how much their relatively higher BMD benefits bone health is not clear, women with breast cancer have been found to have a decreased risk of fractures which was also demonstrated in this study. The inter-relationship among BMD, fractures, and breast cancer could lead to a change of association between BMD and fracture in women with breast cancer. While a low fracture incidence is likely a major reason for finding an overall lower
risk of fractures associated with a given risk factor, the association of BMD and
fractures could be further weakened by breast cancer itself through a decreased
risk of fractures that is independent from BMD (Table 3).

The different association between fractures and non-specific, site-specific
BMD and change in BMD has been demonstrated in previous studies in general
populations \(^{41-44}\). In women with breast cancer, this difference is more apparent.
While only site-specific BMD has a modest predictive value at the corresponding
skeletal sites, neither the non-specific baseline BMD nor a change in BMD was
associated with an increased risk of fracture.

Several limitations of this study could affect the findings. The SOF study
was designed to study osteoporotic fractures among elderly women in general.
Within the large cohort of 9704 participants, there are a relatively small number
of women who developed breast cancer (N=563). Of those with breast cancer,
less than 10% of women suffered from osteoporosis (Table 1) or wrist/hip
fracture (Table 2). The sample size is likely an important contributor to the
inability to detect a statistically significant association between BMD and
fractures. In addition, due to data unavailability, analyses did not adjust for the
breast cancer and treatment characteristics. Since some breast cancer
treatments such as adjuvant hormonal therapy and the disease itself (bone
metastasis) are associated with the risk of fractures $^{45-47}$, the lack of this information prevents adjustment for potential confounding factors and adequate explanation of the study findings.

Assessing the risk of bone fracture is of great importance in clinical practice. Due to the fact that BMD accounts for 75% to 85% of bone strength $^{48}$, it is highly related to the risk of fractures. However, bone fracture is a clinical outcome associated with multiple risk factors and disease conditions. Although BMD is the most commonly used measure in the assessment of the risk of fractures, other factors such as falls $^{49}$ and the history of fractures $^{50}$ are also associated with fractures. Each risk factor, including BMD, may play a slightly different role in the overall risk of fractures in a given population. In women with breast cancer, it appears that the weight of BMD in predicting fractures is decreased. While the higher BMD measure and estrogen level in this population could be important contributors to the change in the predictive value, the lower risk of fractures in women with breast cancer that is independent from BMD indicates that breast cancer itself might have more of a role in the association of BMD and fractures. It is possible that this population has a different combination of risk factors, so that not only the role of BMD in the prediction of fracture is changed but the overall risk of fracture is lower. Because of the low predictive value of BMD shown in this study, BMD should be used cautiously, especially non-site specific BMD and change in BMD, to predict and monitor the risk of
fractures in women with breast cancer. Alternative measures and tools should be
developed and studied to replace BMD. Future study to identify the unique risk
factors in women with breast cancer is important for accurately assessing the risk
of fracture for this patient population.

Acknowledgments

We thank the SOF study committee for providing data and support to this
study, and Drs. Jerry H. Gurwitz, Mary Costanza, and Wenjun Li for their advice
and help in this work.
<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer (N=444)</th>
<th>Non-Breast Cancer (N=8525)</th>
<th>P value</th>
</tr>
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<tr>
<td>Age (%)</td>
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<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>65-69</td>
<td>50.62</td>
<td>42.57</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>32.50</td>
<td>31.14</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>11.01</td>
<td>16.22</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>5.86</td>
<td>10.06</td>
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<td>Education (%)</td>
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<td></td>
<td>0.4375</td>
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<tr>
<td>Elementary</td>
<td>0.38</td>
<td>1.25</td>
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<td>High school</td>
<td>65.19</td>
<td>66.98</td>
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<td>College training</td>
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<td>21.53</td>
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<tr>
<td>Post graduate</td>
<td>13.46</td>
<td>10.24</td>
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<td>Smoking (%)</td>
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<td></td>
<td>0.0632</td>
</tr>
<tr>
<td>Never</td>
<td>64.11</td>
<td>60.09</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>27.32</td>
<td>29.93</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>8.57</td>
<td>9.98</td>
<td></td>
</tr>
<tr>
<td>Physical activity(past wk) (%)</td>
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<td></td>
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</tr>
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<td>67.43</td>
<td></td>
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<tr>
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<td>28.77</td>
<td>32.57</td>
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<tr>
<td>Weight (kg)</td>
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<td>69.29</td>
<td>66.88</td>
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<td>Waist/hip ratio</td>
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<td>0.81</td>
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<td>Calcium use (%)</td>
<td></td>
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<td>0.3815</td>
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<tr>
<td>Never</td>
<td>47.07</td>
<td>49.45</td>
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</tr>
<tr>
<td>Past</td>
<td>9.06</td>
<td>7.93</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>43.87</td>
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<td>Estrogen use (%)</td>
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<td>Never</td>
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<td>93.74</td>
<td></td>
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<tr>
<td>Past</td>
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<tr>
<td>Current</td>
<td>0.00</td>
<td>0.17</td>
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<tr>
<td>History of fall (%)</td>
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<td></td>
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<td>No</td>
<td>28.65</td>
<td>30.27</td>
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<td>Site-specific BMD (gm/cm^2)</td>
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<td></td>
<td></td>
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<tr>
<td>Wrist</td>
<td></td>
<td></td>
<td></td>
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<td>Distal radius</td>
<td>0.38</td>
<td>0.36</td>
<td>&lt;0.0001</td>
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<td>Proximal radius</td>
<td>0.66</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hip</td>
<td>0.79</td>
<td>0.76</td>
<td>&lt;0.0001</td>
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<td>Spine</td>
<td>0.88</td>
<td>0.86</td>
<td>&lt;0.0001</td>
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<td>BMD change (Hip, %)</td>
<td>-4.90</td>
<td>-4.61</td>
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<td></td>
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<td>Normal (T&gt;= -1)</td>
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<td>24.12</td>
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<td>Osteopenia (-2.5&lt;T&lt;-1)</td>
<td>46.89</td>
<td>44.36</td>
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<td>Osteoporosis (T&lt;=-2.5)</td>
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<td>Arthritis (%)</td>
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<td></td>
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<td>63.62</td>
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<td>36.83</td>
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<tr>
<td>Diabetes (%)</td>
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<td>Yes</td>
<td>7.71</td>
<td>6.93</td>
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<td>No</td>
<td>92.29</td>
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<tr>
<td>Anti-osteoportics (%)</td>
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<td>Reloxifene</td>
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<td>All-cause death (%)</td>
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<td>Breast Cancer (N=444)</td>
<td>Non-Breast Cancer (N=8525)</td>
<td>P value</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>No. of Fracture</td>
<td>%</td>
<td>No. of Fracture</td>
</tr>
<tr>
<td>Wrist</td>
<td>24</td>
<td>5.41</td>
<td>881</td>
</tr>
<tr>
<td>Hip</td>
<td>42</td>
<td>9.46</td>
<td>1110</td>
</tr>
<tr>
<td>Spine (morphometric)</td>
<td>74</td>
<td>17.01</td>
<td>2148</td>
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</table>

Table 2. Fractures at different skeletal sites among SOF participants by breast cancer status.
Fig 1. Fracture incidence among SOF participants by breast cancer status
Table 3. Association of baseline BMD (per SD decrease in calcaneal BMD), breast cancer and fractures among SOF participants

<table>
<thead>
<tr>
<th></th>
<th>Fractures (any)</th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Baseline BMD</td>
<td>1.44 (1.38, 1.49)</td>
<td>0.85 (0.76, 0.95)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.59 (0.50, 0.70)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer+baseline BMD</td>
<td>0.61 (0.51, 0.73)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer*baseline BMD</td>
<td>0.96 (0.82, 1.13)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, BMI, and smoking status.
Table 4. Association of BMD (per SD decrease) and fractures among SOF participants

<table>
<thead>
<tr>
<th></th>
<th>Hip</th>
<th>Wrist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast cancer HR (95% CI)</td>
<td>Breast cancer HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Non-breast cancer HR (95% CI)</td>
<td>Non-breast cancer HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>Baseline BMD</td>
<td>1.12 (0.78, 1.59)</td>
<td>1.93 (1.18, 3.13)</td>
</tr>
<tr>
<td>Site-specific BMD</td>
<td>1.42 (1.32, 1.52)</td>
<td>1.57 (1.44, 1.70)</td>
</tr>
<tr>
<td>Hip</td>
<td>0.0754</td>
<td>0.0005</td>
</tr>
<tr>
<td>Distal radius</td>
<td>1.43 (0.99, 2.08)</td>
<td>1.75 (1.20, 2.79)</td>
</tr>
<tr>
<td>Proximal radius</td>
<td>1.91 (1.76, 2.09)</td>
<td>1.69 (1.56, 1.82)</td>
</tr>
<tr>
<td>BMD change (Hip)</td>
<td>1.05 (0.63, 1.72)</td>
<td>1.58 (1.01, 2.47)</td>
</tr>
<tr>
<td></td>
<td>1.42 (1.29, 1.55)</td>
<td>1.39 (1.29, 1.50)</td>
</tr>
<tr>
<td></td>
<td>0.1319</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Adjusted for age, BMI, and smoking status
Table 5. Association of BMD (per SD decrease) and spinal morphometric fractures

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer OR (95% CI)</th>
<th>Non-breast cancer OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Baseline Calcaneal BMD</td>
<td>1.40 (1.04, 1.90)</td>
<td>1.73 (1.63, 1.84)</td>
</tr>
<tr>
<td>Site-specific BMD (spine)</td>
<td>1.35 (0.99, 1.85)</td>
<td>1.72 (1.61, 1.84)</td>
</tr>
</tbody>
</table>

Adjusted for age, BMI, and smoking status.
3.6 References


42. Gnudi S, Malavolta N, Lisi L, Ripamonti C. Bone mineral density and bone loss measured at the radius to predict the risk of nonspinal osteoporotic fracture. \textit{J Bone Miner Res} 2001;16:1130-1135.


CHAPTER IV

Coronary heart disease among tamoxifen-treated postmenopausal women with breast cancer

4.1 ABSTRACT

Postmenopausal women with breast cancer are members of a population that is also at high risk of coronary heart disease (CHD). Adjuvant tamoxifen therapy has been shown to have a beneficial effect on the cardiovascular system. However, the association between tamoxifen and CHD reported in previous studies was either borderline or inconsistent. We conducted a retrospective study in four integrated healthcare delivery systems to investigate the association of tamoxifen use and the incidence of CHD among 820 postmenopausal women with breast cancer. This association was further explored with stratification of the duration of tamoxifen use to examine the dose-response association of tamoxifen therapy and CHD. Compared to patients without tamoxifen, the overall incidence of CHD in tamoxifen-treated patients was lower (adjusted HR=0.60, 95% CI: 0.40-0.88). For each year of tamoxifen use, there was a statistically significant decrease in the risk of CHD (HR=0.90, 95% CI: 0.82-0.98). Further analyses categorized by length of tamoxifen use showed that an apparent association with a decreased CHD risk was found in patients who received tamoxifen for two to five years (HR=0.54, 95% CI: 0.33-0.86). No association was detected after the discontinuation of tamoxifen therapy. In summary, tamoxifen reduces the risk of
CHD in postmenopausal women with breast cancer in a dose-dependent manner. The favorable association is particularly evident in those patients who continued their tamoxifen use for at least two years.

**KEYWORDS:** Tamoxifen; Breast cancer; Coronary heart disease.

### 4.2 INTRODUCTION

Coronary heart disease (CHD) and breast cancer are two of the leading diseases threatening women’s health.\(^1\)\(^2\) Although the etiologies of both diseases are not well-understood, the age and sex-dependent risk of these two diseases indicates that female hormones play an important role. While the risk of CHD increases after menopause,\(^3\)\(^-\)\(^5\) high estrogen exposure has been linked to a protective effect on CHD as well as an increased risk of breast cancer.\(^6\)\(^-\)\(^12\) Since postmenopausal women are also at high risk for CHD, a treatment that suppresses the action of estrogen in the breast while mimicking an estrogenic effect on coronary arteries might provide additional benefit to these patients.

Tamoxifen, the most commonly used and successful SERM (Selective Estrogen Receptor Modulator) in the history of breast cancer treatment, is potentially such a candidate. Unlike estrogen, tamoxifen is a chemically synthetic agent that lacks the steroid structure but can still bind to estrogen receptors and
exert tissue-specific actions.\textsuperscript{13, 14} Since its introduction into clinical practice in 1978, tamoxifen has been shown to effectively reduce the risk of breast cancer recurrence and improve survival in women at all stages of breast cancer due to its anti-estrogenic effect.\textsuperscript{15-17} Tamoxifen has also been reported to have a beneficial effect on the cardiovascular system where it acts as an estrogen analog in postmenopausal women with breast cancer. For example, tamoxifen has been found to lower serum lipid levels\textsuperscript{18-21}, a proven risk factor for CHD. More directly, it has been linked with a reduced risk of CHD in several clinical trials.\textsuperscript{22-25} Recently, an observational study was also able to reproduce the benefit associated with tamoxifen on CHD.\textsuperscript{26}

Despite the fact that the current evidence appears to suggest that tamoxifen may reduce the risk of CHD in postmenopausal women with breast cancer, the beneficial effects found have been either borderline or not statistically significant.\textsuperscript{27} Inconsistent findings in both randomized controlled trials\textsuperscript{28, 29} and observational study settings\textsuperscript{30} have also been reported. In addition, the majority of the evidence was not based on clinical outcomes such as myocardial infarction and angina.\textsuperscript{31} Therefore, the association of tamoxifen and CHD needs further investigation.

In the present study, we explored the association of tamoxifen use and CHD incidence in postmenopausal women with breast cancer in four integrated
healthcare delivery systems. To better estimate the magnitude of the potential benefit associated with tamoxifen on CHD, we also studied the dose-response relationship based on the duration these patients received tamoxifen. As adjuvant hormonal therapy switches from tamoxifen to the third generation aromatase inhibitors (AIs),32 our study provides important information on the risk/benefit ratio of this switch in the treatment of breast cancer for postmenopausal women who are also exposed to a high risk of CHD.

4.3 MATERIALS AND METHODS

Data Sources and Study Population

The data sources used in this study have been described previously.33-35 In brief, patients from four sites of the Cancer Research Network (CRN), were the targeted study population. Newly diagnosed breast cancer patients aged 55 or above (between January 1, 1996 and December 31, 1997) were identified and followed for up to seven years. Initially, 897 patients were eligible for this study. After the exclusion of those with CHD before the diagnosis of breast cancer, 809 patients were included in the final study population.

Identifying breast cancer, tamoxifen use, CHD, and other parameters
Among the four study sites, two (Henry Ford Health System, Detroit, MI; and Kaiser Permanente Northern California, San Francisco/Sacramento, CA) have access to tumor registries while the other two (HealthPartners, Minneapolis/St. Paul, MN; Fallon Clinic, Worcester, MA) do not. Breast cancer cases were identified through either tumor registry or a chart review. All cases were confirmed by trained medical abstractors by a review of patients’ medical records. The criterion of the American Joint Commission on Cancer was used for categorization of the stage of breast cancer \{0 (in-situ), I, II, III, other (IV or unknown)\} at diagnosis.

Tamoxifen use information was collected from both chart review and automated pharmacy data. Patients with an indication of tamoxifen use in either source were considered tamoxifen users. For the duration of tamoxifen use, if the discontinuation was recorded in chart review, this date was used for the calculation of the years of tamoxifen treatment received. Otherwise, the date of last prescription of tamoxifen in pharmacy data plus the days of supply were extracted. Based on the actual length of tamoxifen use, a variable reflecting the years of therapy was created and categorized in four levels (non-tamoxifen, tamoxifen: <2 years, 2-5 years, and >5 years).

CHD cases were identified from inpatient and outpatient automated utilization data using a combination of diagnosis and procedure codes. Three
coding systems (The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); The Current Procedural Terminology (CPT); and The Healthcare Common Procedure Coding System (HCPCS)) were adopted for the data extraction. ICD-9-CM codes '410-414' and '429' were used to identify MI and angina/ischemic heart disease; the procedure codes '3601', '3602', '3605', '3609' (ICD-9-CM), '3351', '33521-33523', '33533', '33535', '33536' (CPT) were applied for identifying coronary artery bypass graft (CABG); and the codes '361x-36.3x' (ICD-9-CM), '92980-92984', '92995', '92996' (CPT), plus 'G0290', 'G0291' (HCPCS) were adopted for extracting percutaneous coronary intervention (PCI). In patients with either one diagnosis or procedure code and outpatients with two diagnosis codes or one procedure code were defined as patients with CHD.37

Other information abstracted from medical records include general demographic characteristics (age and race), breast cancer specific data (hormone receptor status and cancer treatments), and comorbidity information. A modified Charlson score was calculated and categorized into four levels (0, 1, 2, 3 or above) after weighting as originally developed. Since there is a possibility that patients who received tamoxifen also actively seek other health care services, we used preventive services as an indicator for this potential confounding factor affecting the association of tamoxifen and CHD. Preventive services received by the study population were collected from automated
utilization data. Similar to the identification of CHD, ICD-9-CM, CPT, AND HCPCS codes were used to identify receipt of mammograms, colorectal cancer screening, influenza vaccination, and BMD testing from the automated utilization data.

**Data analyses**

The dataset was first checked for outliers. Since the exclusion of those outliers with a high deviance residual did not change predicted value for outcomes, we included all patients in the data analyses (Appendix 1). Descriptive statistics were used to compare the characteristics of tamoxifen users and non-users. All variables included in this study were either dichotomous or categorical, thus, chi square tests were performed to identify differences between patients with and without tamoxifen therapy. Tamoxifen use was treated as a time-dependent variable in this study. The effect of tamoxifen on CHD was also analyzed based on the timing of tamoxifen use, (i.e., before, during, and after tamoxifen therapy). The time prior to the start of tamoxifen therapy was categorized as non-tamoxifen use. For CHD cases, time to event was calculated from the time of diagnosis of breast cancer to the CHD event. For those patients who did not develop CHD during the follow-up period of study, time was estimated to the date of disenrollment, last day of follow-up, or death, whichever came first. Cox proportional regression analyses were performed to calculate the difference of the risk of developing CHD in patients with tamoxifen versus those
without tamoxifen. The association of tamoxifen and CHD was addressed separately by the timing of tamoxifen use. While we focused on the period of time when tamoxifen was actually used, the CHD incidence after tamoxifen use was also explored. Since there is a possible residual effect after the discontinuation of tamoxifen, we did not group the post-tamoxifen time into the non-tamoxifen category but evaluated it as an independent time period. The crude hazard ratio (HR) was first obtained, followed by the establishment of a model adjusted for potential confounding factors. The inclusion of potential confounding variables was based on clinical significance and statistical considerations. After testing the adjusted model with different combinations of potential confounding factors, the final model was established with demographic variables (age and race), disease specific factors (cancer stage and surgery), and preventive services (colorectal cancer screening and influenza vaccination). The full model did not violate proportional hazard assumption as demonstrated by BPHREG procedure in SAS (Appendix 2). All analyses were performed using SAS for Windows, Version 9.1.3 Service Pack 4 (SAS Institute, Inc., Cary, NC).

4.4 RESULTS

The general comparison of patient characteristics is presented in Table 1. Similar proportions of patients were seen in each age category between the
tamoxifen and non-tamoxifen groups. Slightly more white patients received tamoxifen (82.02% vs. 80.79%), and a somewhat higher percent of black patients were non-tamoxifen users (11.24% vs. 10.15%), but these differences are not statistically significant (p=0.7152). Although data for hormone receptor status {estrogen receptor (ER) and progestin receptor (PR)} are only available at two of four sites, a much higher percent of patients with tamoxifen compared to those without tamoxifen were ER/PR positive (84.07% vs. 39.38%, p<0.0001), suggesting the reliability of these data. Patients who did not receive tamoxifen therapy were more often diagnosed at in situ stage (stage 0: 30.34% vs. 2.21%), were more likely to receive breast conserving surgery (BCS) (60.39% vs. 49.10%) and had less severe comorbidity (Charlson score 0: 65.17% vs. 69.76%); while patients in both tamoxifen and non-tamoxifen groups were almost equal in receiving chemotherapy and radiotherapy. The utilization of preventive services differed between tamoxifen users and non-users. Among the four most frequently used services, patients with tamoxifen were more likely to also obtain colorectal cancer screening (60.71% vs. 49.44%, p=0.0014) and influenza vaccination (35.54% vs. 29.49%, p=0.0694), but are similar to those without tamoxifen in receipt of mammograms and bone mineral density (BMD) testing.

The identified CHD cases stratified by coding systems are summarized in Table 2. Of the total 160 CHD cases identified in this study population, 138 were found through diagnosis codes of which most (117) were from outpatient data.
Using procedure codes for PCI and CABG identified fewer than half of the CHD events (56/160=35.00%); while the majority of cases were also found in the outpatient data (36/56=64.28%). Comparing CHD incidence in patients with tamoxifen to those without tamoxifen, there is no significant difference when restricted to the cases identified using diagnosis codes from either inpatient data (11.04% vs. 9.83%, p=0.5789) or outpatient data (15.01% vs. 13.76%, p=0.6169) as well as the two combined (17.44% vs. 16.57%, p=0.7452). However, the percent of CHD found though procedure codes differed between tamoxifen users and non-users (6.18% vs. 7.87%), especially for those identified from inpatient data (2.43% vs. 3.65%). Overall, the CHD incidence is almost identical in patients who did or did not receive tamoxifen therapy (19.87% vs. 19.66%).

The quantitative risk of CHD in patients with tamoxifen compared to those without tamoxifen was estimated using a Cox proportional regression model, and the results are presented in Table 3. Although the overall incidence of CHD in patients with tamoxifen is almost identical to non-tamoxifen users (44.18 vs 46.05 per 1000 person years); the final estimate of the risk of CHD differs. For each year of tamoxifen use, there was a statistically significant decrease of the risk of CHD (HR=0.90, 95% CI: 0.82-0.98). For patients who received tamoxifen for less than two years, the risk of CHD could not be accurately assessed because of the small number of cases (N=3). A large reduction in risk was seen in patients on tamoxifen for two to five years (adjusted HR=0.54, 95% CI: 0.33-0.86). For
patients who continued tamoxifen beyond the five years of standard therapy, the association of tamoxifen and CHD was inconclusive (adjusted HR=0.77, 95% CI: 0.44-1.25). Overall, the risk of CHD in patients on tamoxifen therapy is lower than non-tamoxifen users (adjusted HR=0.60, 95% CI: 0.40-0.88). The benefit associated with tamoxifen on CHD was only observed during tamoxifen use.

4.5 DISCUSSION

Tamoxifen has been perceived to have a beneficial effect on CHD in postmenopausal women with breast cancer because of its estrogen-like action. However, the current evidence is not consistent, and the effect is not well determined.27, 31 In the present study, we examined the relationship between tamoxifen use and CHD in postmenopausal breast cancer patients in multiple community-based health delivery systems. Our results demonstrated an overall benefit associated with tamoxifen use on CHD. Furthermore, the benefit is dose-dependent. The reduction of CHD risk was more likely seen in patients who received tamoxifen for at least two years. No reduction was found after the discontinuation of tamoxifen therapy.

Previous studies have reported a potential benefit associated with tamoxifen on the risk of CHD.27 Most of these studies were clinical trials in a diverse patient population. On average, 26% decrease of the risk of CHD was
found among patients with tamoxifen therapy (RR=0.74, 95% CI: 0.47-1.16), but the decrease lacks statistical significance. In those trials conducted specifically in postmenopausal women with breast cancer, the magnitude of the association of tamoxifen and CHD was even smaller (RR=0.89, 95% CI: 0.48-1.64). While the findings could reflect the real effect of tamoxifen on CHD, these results may be biased by the fact that in most studies the tamoxifen therapy did not complete a standard regimen with an average exposure of 2.2 years among postmenopausal patients. In the limited number of observational studies, the results are even more controversial. The association of tamoxifen and CHD in patients with breast cancer treated in community settings needs to be clarified.

One advantage of our study is that we investigated the relationship of tamoxifen and CHD among women with health insurance receiving health care in integrated systems. All patients included in this study have equal access to health care so that the likelihood of under-service is lessened. This enables us to assess the association of tamoxifen and CHD in a community setting where the length of the tamoxifen use is the actual treatment time rather than an artificial cutoff by study design. Thus, we identified a study population with an average use of tamoxifen for 3.5 years, much longer than most previous studies. In addition, the geographically diverse population reduces bias. The results generated from this study population (overall HR: 0.60) are within the range of summarized findings from multiple clinical trials (0.48-1.64). In addition, we
were able to demonstrate a dose-dependent relationship of tamoxifen use and risk of CHD in postmenopausal women with breast cancer, which not only explains the failure of the observation of protection in some previous studies, but also furthers our understanding of the benefit associated with tamoxifen on CHD.

Nevertheless, our study is limited by several factors. While we used a combination of chart review and automated data extraction supplemented with the confirmation of medical records and pharmacy data for identifying breast cancer and tamoxifen use, the search for CHD cases was solely dependent on automated utilization data. However, unlike many studies which simply adopt diagnosis codes for identifying CHD, we conducted a comprehensive search in both inpatient and outpatient data bases using not only diagnosis codes but procedure codes as well, and thus, avoided missing some cases. More importantly, without the confirmation from medical records, it is possible that some cases were mistakenly identified. Due to the lack of information of characteristics such as smoking and serum cholesterol levels, we were not able to adjust all risk factors known to be relevant to CHD. The lack of access to the data about hormone receptor status at two study sites prevented us from further studying the association of tamoxifen and CHD in patients who are hormone receptor positive. Some important information about medication associated CHD specific risk factors such as statin and aromatase inhibitor use was not available, and thus, not adjusted in this study, which could potentially either exaggerate
(biased by statins) or underestimate the benefit of tamoxifen use (biased by aromatase inhibitors) on CHD.

CHD is the leading cause of death in postmenopausal women. Together with breast cancer, the most common cancer and the second leading cause of cancer death in women postmenopausal patients with breast cancer are at heightened risk. Our study agrees with previous reports of the benefit associated with tamoxifen on CHD and further demonstrates a dose-dependent pattern of beneficial effect. Therefore, patients who receive the standard five years of tamoxifen therapy could benefit from a significant decrease in risk of CHD. Since there is a high prevalence of CHD in postmenopausal women, a slight reduction of the risk of CHD could save many of them from this lethal disease. While tamoxifen has been recently replaced by more potent AIs as the first choice of adjuvant hormonal therapy for breast cancer, the lack of similar beneficial effect of the latter on CHD raises the importance of an assessment of overall risk/benefit ratio during recommendations for breast cancer treatment. For a postmenopausal patient with breast cancer who is known to be at a high risk of CHD, tamoxifen could outweigh AIs and thus be recommended as the first choice of adjuvant hormonal therapy. In addition, because the significant benefit of tamoxifen on CHD appears to occur in patients on tamoxifen for at least two years, a good adherence to the standard five-year tamoxifen therapy would confer more benefits to those who tolerate the treatment. Future study
investigating the benefit of tamoxifen therapy on CHD is necessary to determine the overall risk/benefit ratio in postmenopausal women with breast cancer.

ACKNOWLEDGMENTS

We thank Dr. Jerry H. Gurwitz, Dr. Mary Costanza, and Dr. Wenjun Li for their advice and help in this study.
| Table 1. Characteristics of patients in IMPACT study by tamoxifen use status |
|-------------------------------------------------|-------------------------------------------------|
| Age                                             | P value                                         |
| 55-59                                           | 0.6552                                          |
| 60-64                                           |                                                |
| 65-69                                           |                                                |
| 70-74                                           |                                                |
| 75-79                                           |                                                |
| 80+                                             |                                                |
| Race                                            | 0.7152                                          |
| White                                           |                                                |
| Hispanic                                        |                                                |
| Black                                           |                                                |
| Asian/Pacific                                   |                                                |
| Unknown                                         |                                                |
| Hormone receptor status                         | <0.0001                                         |
| (ER/PR)†                                        | (n=226)                                         |
| Positive                                        | (n=193)                                         |
| Negative                                        |                                                |
| Unknown                                         |                                                |
| Cancer Stage                                    | <0.0001                                         |
| 0                                               |                                                |
| I                                               |                                                |
| II                                              |                                                |
| III                                             |                                                |
| Other                                           |                                                |
| Surgery                                         | 0.0014                                          |
| BCS                                             |                                                |
| Mastectomy                                      |                                                |
| None                                            |                                                |
| Chemotherapy                                    | 0.1004                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| Radiotherapy                                    | 0.4123                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| Charlson score                                  | 0.0423                                          |
| 0                                               |                                                |
| 1                                               |                                                |
| 2                                               |                                                |
| 3                                               |                                                |
| Duration of Tamoxifen use (years)               | N/a                                             |
| <2                                              |                                                |
| 2-5                                             |                                                |
| >=5                                             |                                                |
| Mammogram                                       | 0.4045                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| Colorectal cancer screening                     | 0.0014                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| Influenza vaccination                           | 0.0694                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| BMD testing                                     | 0.5675                                          |
| Yes                                             |                                                |
| No                                              |                                                |
| † Data not available at two HMO sites (Fallon Clinic, MA and Henry Ford Health, MI). |
Table 2. Identified CHD among the patients in IMPACT study

<table>
<thead>
<tr>
<th>Coding system used</th>
<th>Number of cases†</th>
<th>Tamoxifen (%)</th>
<th>Non-Tamoxifen (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>138</td>
<td>17.44</td>
<td>16.57</td>
<td>0.7452</td>
</tr>
<tr>
<td>Inpatient</td>
<td>85</td>
<td>11.04</td>
<td>9.83</td>
<td>0.5789</td>
</tr>
<tr>
<td>outpatient</td>
<td>117</td>
<td>15.01</td>
<td>13.76</td>
<td>0.6169</td>
</tr>
<tr>
<td>Procedure (PCI, CABG)</td>
<td>56</td>
<td>6.18</td>
<td>7.87</td>
<td>0.3492</td>
</tr>
<tr>
<td>Inpatient</td>
<td>24</td>
<td>2.43</td>
<td>3.65</td>
<td>0.3089</td>
</tr>
<tr>
<td>Outpatient</td>
<td>36</td>
<td>4.42</td>
<td>4.49</td>
<td>0.9567</td>
</tr>
<tr>
<td>Diagnosis+Procedure</td>
<td>160</td>
<td>19.87</td>
<td>19.66</td>
<td>0.9422</td>
</tr>
</tbody>
</table>

†These numbers are not mutually exclusive.
<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Number of Cases</th>
<th>CHD Event (/1000 pys)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Tamoxifen</td>
<td>70</td>
<td>46.05</td>
<td>Reference</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>90</td>
<td>44.18</td>
<td>0.64 (0.45, 0.93)*</td>
</tr>
<tr>
<td>Before treatment</td>
<td>17</td>
<td>102.27</td>
<td>1.45 (0.82, 2.67)</td>
</tr>
<tr>
<td>During treatment</td>
<td>44</td>
<td>31.98</td>
<td>0.64 (0.45, 0.93)*</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>3</td>
<td>31.43</td>
<td>0.51 (0.16, 1.64)</td>
</tr>
<tr>
<td>2-5 years</td>
<td>25</td>
<td>29.17</td>
<td>0.59 (0.38, 0.93)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>16</td>
<td>37.82</td>
<td>0.79 (0.46, 1.35)</td>
</tr>
<tr>
<td>Each year</td>
<td>N/a</td>
<td>N/a</td>
<td>0.92 (0.85, 0.99)*</td>
</tr>
<tr>
<td>After treatment</td>
<td>29</td>
<td>58.59</td>
<td>1.08 (0.71, 1.67)</td>
</tr>
</tbody>
</table>

† Adjusted for age, race, surgery, cancer stage, colorectal screening, and influenza vaccination. Asterisk (*) indicates p<0.05.
4.6 REFERENCES


41. Geiger AM, Bernstein L. Tamoxifen-treated breast carcinoma patients and the risk of acute myocardial infarction and newly diagnosed angina. *Cancer* 2006;106:480-1; author reply 481.

CHAPTER V

Summary

5.1 Study findings

Previous studies demonstrated that tamoxifen preserved BMD in postmenopausal patients with breast cancer. This preservation is evident in the hip and spine but not detectable in the wrist. However, observations documented in the few available studies regarding the association of tamoxifen and fractures showed an unexpected increase of risk of fractures in patients treated with tamoxifen.

We investigated the relationship of tamoxifen and fractures in the three common fracture skeletal sites (spine, hip, and wrist) plus the combined sites (total body) in postmenopausal women with breast cancer in an insured population. Our results showed that the association of tamoxifen and fracture incidence varied at different skeletal sites. Although the associations between tamoxifen and fractures in the spine (HR=0.40, 95% CI: 0.09-1.85), wrist (HR=2.49, 95% CI: 0.88-7.06), and total body (HR=0.87, 95% CI: 0.49-1.55) were imprecise and inconclusive, an apparent reduction of the risk of fracture was found in the hip (HR=0.41, 95% CI: 0.17-1.03) with borderline statistical significance (p=0.0565). Although the effect estimates, especially in the spine where subtle fractures are likely to be under-diagnosed, are imprecise, the
pattern of the association of tamoxifen and fractures found in this study was similar to its benefit on BMD in a recent systematic review of 27 studies which demonstrated a site-specific preservation on spine and hip but not wrist. In addition, the reduced fracture risk seen in this study was consistent with the findings reported in a breast cancer prevention setting using tamoxifen, further supporting the possibility of a benefit associated with tamoxifen on fractures.

BMD is the gold standard for the screening and diagnosis of osteoporosis. It is also perceived as the most valuable indicator for the prediction of fracture risk in both people with low bone density and patients with osteoporosis. However, it has been reported that BMD did not predict fractures well in some populations such as patients who received anti-osteoporotic therapy.

Using SOF data, we demonstrated that, while BMD did show a consistent association with fracture risk in women without breast cancer, the association of BMD and fractures seen in women with breast cancer varied by different skeletal sites, osteoporosis status, and the type of BMD measure. Among the three types of BMD measures used in this study, non-specific BMD has a weak association with fractures. Site-specific BMD (hip) had a stronger association with hip fracture, but BMD change at this site was not associated with fractures. Unlike non-vertebral incident fractures, the spine morphometric fracture had a similar association with either non-specific or spine-specific BMD. Overall, the association of BMD and fractures in women with breast cancer is weak. Only
site-specific BMD appears to have a consistently modest association with fractures in those women diagnosed with breast cancer.

In addition to bone health, tamoxifen has been perceived to have a beneficial effect on CHD in postmenopausal women with breast cancer because of its estrogen-like action. However, the current evidence is not consistent, especially in observational settings, and the effect is not fully characterized. We examined the relationship between tamoxifen use and CHD in postmenopausal breast cancer patients in a large managed care system with multiple study sites. Our results demonstrated an overall protective association with tamoxifen use on CHD (HR=0.60, 95% CI: 0.40-0.88). In addition, the association of tamoxifen and CHD is dose-dependent. The longer a patient received the tamoxifen therapy, the more likely this person would have a lower incidence of CHD.

The protective association for tamoxifen with bone and CHD in this study is likely due to the fact that tamoxifen is a selective estrogen receptor modulator which has tissue-specific actions. Tamoxifen acts as an estrogen antagonist in breast cells and thus suppresses the cancer cell proliferation stimulated by estrogen. In other tissues such as bone, uterus, and cardiovascular system, tamoxifen is an estrogen agonist and exhibits some estrogen-like effects. Although still controversial, estrogen itself has been linked to the protection against bone loss and a low risk of CHD. Since tamoxifen can mimic estrogen in
bone and cardiovascular system it could reduce the risk of osteoporosis and CHD. Whether there are other mechanisms underlying the protective association we observed of tamoxifen on bone and CHD is not clear but certainly can not be excluded.

5.2 Conclusions

In the current attempt to investigate the association of tamoxifen and bone and heart health using two cohorts of postmenopausal women, I detected a possible benefit associated with tamoxifen use on fractures in the hip, the fracture site with high morbidity and mortality. I also found that BMD did not predict the risk of fracture well in postmenopausal women with breast cancer. In addition, I demonstrated that tamoxifen was associated with a reduced risk of CHD in postmenopausal women with breast cancer in a dose-dependent manner. An apparent benefit was seen in those patients who receive tamoxifen therapy for at least two years.

Based on the findings, I conclude that the discrepancy between BMD and fractures reported in previous studies among tamoxifen-treated postmenopausal women with breast cancer could be an artifact possibly resulting from factors such as the complexity of patient population, the suitability of controls, the length of tamoxifen use, the accuracy of identification of fractures, and the short follow-
up. The weak association of BMD and fractures in breast cancer patients as
demonstrated in my study could also contribute to the discrepancy. I also
conclude that tamoxifen may have a beneficial effect on CHD if a patient receives
tamoxifen for two years or longer. Thus, tamoxifen could provide additional
benefits to postmenopausal women with breast cancer when they are at high risk
of bone fractures and/or CHD.
Appendix 1

Identifying outliers and testing their influence on the association of tamoxifen use (each year) and CHD

HR=0.90
(All data points included)

HR=0.91
(Most influential outliers excluded)
Appendix 2

Test of proportional hazard assumption

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum Absolute Value</th>
<th>Replications</th>
<th>Seed</th>
<th>Pr &gt; MaxAbsVal</th>
</tr>
</thead>
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<tr>
<td>tamoxifen</td>
<td>1.1931</td>
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<td>19</td>
<td>0.1330</td>
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<td>Age_ca2Ageca6569</td>
<td>1.0858</td>
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<td>Age_ca2Ageca7579</td>
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<td>RACE_C2</td>
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<td>RACE_C3</td>
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<td>RACE_C7</td>
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<td>19</td>
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<td>19</td>
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