Published in final edited form as:
J Bone Miner Res. 2012 May ; 27(5): 1196–1205. doi:10.1002/jbmr.1556.

Fracture Risk in Women With Breast Cancer: A Population-Based Study

L. Joseph Melton III, M.D.[1,4], **Lynn C. Hartmann, M.D.**[2], **Sara J. Achenbach, M.S.**[3], **Elizabeth J. Atkinson, M.S.**[3], **Terry M. Therneau, Ph.D.**[3], and **Sundeep Khosla, M.D.**[4]

[1]Division of Epidemiology, College of Medicine, Mayo Clinic, Rochester, MN

[3]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN

[2]Department of Oncology, College of Medicine, Mayo Clinic, Rochester, MN

[4]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Internal Medicine, College of Medicine, Mayo Clinic, Rochester, MN

Abstract

A positive association has been reported between greater bone density and higher breast cancer risk, suggesting that these women could be at reduced risk of fracture. To estimate fracture risk among unselected community women with breast cancer, and to systematically assess associations with various risk factors including breast cancer treatments, we conducted a population-based historical cohort study of 608 Olmsted County, MN women with invasive breast cancer first diagnosed in 1990-99 (mean age, 61.6 ± 14.8 years), who were followed for 5776 person-years. Altogether, 568 fractures were observed in 270 women (98 per 1000 person-years). Overall fracture risk was elevated 1.8-fold; but the absolute increase in risk was only 9%, and 56% of the women did not experience a fracture during follow-up. Excluding pathologic fractures (15%) and those found incidentally (24%), to allow for ascertainment bias, the standardized incidence ratio was 1.2 (95% CI, 0.99–1.3) for total fracture risk and 0.9 (95% CI, 0.7–1.2) for osteoporotic fracture risk alone. Various breast cancer treatments were associated with an increased risk of fracture, but those associations were strongest for pathologic fractures, which were relatively more common among the women who were premenopausal when their breast cancer was diagnosed. Moreover, underlying clinical characteristics prompting different treatments may have been partially responsible for the associated fracture outcomes (indication bias). These data thus demonstrate that breast cancer patients in general are not at greatly increased risk of fracture but neither are they protected from fractures despite any determinants that breast cancer and high bone density may have in common.

Send correspondence and reprint requests to Dr. L. J. Melton III, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905., Telephone: (507)284-5550; Fax: (507)284-1516; melton.j@mayo.edu.

Disclosures

All authors state that they have no conflicts of interest.

Authors' roles

Study design: LJM, LCH, TMT. Study conduct: LJM. Data collection: LJM, SJA. Data analysis: SJA, EJA, TMT. Data interpretation: LJM, LCH, TMT, SK. Drafting manuscript: LJM. Revising manuscript: LJM, LCH, SJA, SK. Approving final version: LJM, LCH, SJA, EJA, TMT, SK. Responsibility for integrity of data analysis: TMT.

Keywords

CANCER TREATMENTS; EPIDEMIOLOGY; FRACTURES; POPULATION-BASED; BREAST CANCER

Introduction

We previously assessed fracture risk among the 235 Rochester, MN women first diagnosed with breast cancer in 1965-74,[1] an era which antedated widespread use of adjuvant radiation and systemic therapy. Allowing for the expected excess of pathologic fractures, there was no increase in the risk of other fractures compared to age- and sex-matched community controls; there was even suggestion of a reduction in subsequent hip fractures as seen also by some investigators[2] but not others.[3] To the extent that breast cancer is linked to excessive endogenous or exogenous estrogen exposure,[4] one would expect these women to have greater bone mass[5] and a lower risk for fracture.[6] Indeed, there is evidence that breast cancer is more common among women with the highest bone density.reviewed in (7) Consistent with this observation, the risk of breast cancer is less among women with a prior hip or distal forearm fracture,[8–11] who presumably had low bone density.[12] Other fracture types have not been addressed in population-based studies of breast cancer even though vertebral fractures are likely a more sensitive indicator of abnormal bone metabolism.[13]

Any positive association between breast cancer and bone density, however, might be countered by the fact that many breast cancer patients receive hormonal therapy, to block estrogen, and/or chemotherapy, which can induce ovarian failure.[14] While rapid bone loss is seen following ovarian failure, the effect of this on long-term fracture risk has not been well quantified.[15] The likelihood of ovarian failure increases with age among premenopausal women,[16] but it is not clear whether chemotherapy also has adverse effects on postmenopausal women analogous to our findings for bilateral oophorectomy at a late age.[17] Moreover, low circulating estrogen levels are associated with reduced bone density even among older women,[18] and treatment with hormonal therapy, especially aromatase inhibitors (AIs), results in rapid bone loss.[19] Such treatment also appears to have an adverse effect on fractures, the clinically important outcome, as previous population studies found an increase in fractures among breast cancer patients treated with AIs.[20–22]

It may be possible to mitigate bone loss and reduce the risk of fractures,[15] but data are conflicting[23] and little information is available with respect to bone sparing treatments in actual clinical practice.[24] In addition, use of tamoxifen or other selective estrogen receptor modulators (SERMs) might have beneficial skeletal effects.[25] However, there is a question whether tamoxifen used as an estrogen antagonist (AE) has differential effects on the skeleton depending on menopausal status,[19] ie, bone loss in premenopausal women but stabilization in postmenopausal women. Although tamoxifen in postmenopausal women with breast cancer was not associated with any overall reduction in hip fracture risk in one trial,[26] a protective effect of concurrent tamoxifen use against hip fractures, as well as osteoporotic fractures generally, was seen in a large population-based study in Canada.[27]

A large number of women residing in Rochester and the balance of Olmsted County, MN have been diagnosed with breast cancer since our initial investigation, and systemic therapies are more complex.[28,29] The objective of this study was to determine whether long-term fracture risk, exclusive of pathologic fractures, is now greater than expected (and as compared with the Rochester women diagnosed with breast cancer in an earlier era). If so, it is important to know whether this is associated with breast cancer treatment and whether fracture risk is differentially modulated by chemotherapy or hormonal therapies in women

who are premenopausal versus postmenopausal at diagnosis. These data will be relevant to over 207,000 women who are diagnosed with invasive breast cancer each year, the majority of whom will be long-term survivors.[30]

Materials and Methods

Olmsted County is well suited for disease association studies such as this because comprehensive medical records are accessible through a centralized index to diagnoses made by essentially all medical care providers used by the local population.[31] Following approval by the Institutional Review Boards of Mayo Clinic and the Olmsted Medical Center, we used this unique database (the Rochester Epidemiology Project) to identify all women who resided in Olmsted County when first diagnosed with tissue-confirmed, invasive breast cancer in 1990-99, allowing for a decade or more of subsequent follow-up. Of 1599 potential cases screened, 284 women did not have invasive cancer; 159 were not residents at diagnosis; and 546 were initially diagnosed before 1990 or after 1999; 2 additional patients declined to authorize the use of their medical records for research.[32] The remaining 608 women were followed forward in time (historical cohort study) until death or the most recent clinical contact. Their medical records were reviewed by trained nurse abstractors to collect information about the breast cancer and its treatment, as well as demographic and lifestyle factors and a diverse array of conditions predisposing to secondary osteoporosis or to falls.[33] The age- and severity-weighted Charlson comorbidity index was used to assess serious comorbidity generally.[34] Body mass index (BMI) was recorded at the time of diagnosis, and obesity was defined as BMI ≥ 30. Physical activity was assessed qualitatively on a six-point scale, with subjects in the highest two categories (sedentary/normal activities but no exercise; active/walks at a brisk pace) classified as physically active. Cigarette smoking and alcohol use were classified as ever/never, while self-reported or clinically documented excessive alcohol consumption was considered heavy use (ie, alcoholism). In addition, data were collected from contemporary clinical notes regarding the use of various classes of drugs (excluding over-the-counter supplements) associated with bone loss or with osteoporosis therapy. No attempt was made to record the actual indication for specific treatments, since this was frequently unclear, nor did we track changes in dosage.

The inpatient and outpatient records of local medical care providers were also searched for the occurrence of any fracture. Mayo Clinic records, for example, contain the details of every inpatient hospitalization, every outpatient office or clinic visit, all emergency room and nursing home care, as well as all laboratory results, all radiographic and pathology reports, including autopsies, and all correspondence with each patient.[31] The records contained the clinical history and the radiologist's report of each fracture, but original radiographs were not available for review. Thus, the diagnosis of vertebral fracture, whether symptomatic or not, was accepted on the basis of a radiologist's report of compression or collapse of one or more thoracic or lumbar vertebrae.[35] Ascertainment of clinically-evident fractures following the breast cancer diagnosis is believed to be complete,[36] although we only recorded fractures prior to diagnosis that occurred at the traditional osteoporotic (hip, spine or wrist) sites. Fractures were classified according to the circumstances of the injury: By convention, daily activities and falls from standing height or less were considered moderate trauma, while motor vehicle accidents and falls from a greater height were deemed severe trauma. In addition, based on review of complete contemporary medical record documentation, we distinguished fractures that were attributed by attending physicians to a specific bone lesion, mainly metastatic malignancy (pathologic fractures), and we also identified fractures that were only discovered because of radiographic monitoring of patients for bone metastases or were found on radiographs taken in the course of care for an unrelated clinical problem (incidental fractures).

The influence of breast cancer on fracture risk was evaluated using three basic methods of analysis, all carried out in SAS (SAS Institute Inc., Cary, NC). The primary analysis compared the number of fractures observed at each skeletal site (based on the first fracture of a given type per person) to the number expected in this cohort during their follow-up in the community, ie, standardized incidence ratios (SIRs). As delineated elsewhere,[37] expected numbers were derived by applying local calendar year-, age- and sex-specific incidence rates for these fractures to the calendar year- and age-specific person-years of follow-up in the breast cancer cohort and summing over the strata. Ninety-five percent confidence intervals (95% CI) for the SIRs were calculated assuming the expected rates are fixed and the observed fractures follow a Poisson distribution.[38]

The cumulative incidence of a new fracture was then estimated for up to 15 years following breast cancer confirmation using the Kaplan-Meier method.[39] In the customary approach, patients who die are censored, although this overestimates cumulative fracture incidence as perceived by attending physicians when the death rate is high. Therefore, we treated death as a competing event in an alternative analysis.[40] Patients were also censored when lost to follow-up, but this happened infrequently. Kaplan-Meier methods were used to assess survival as well, with expected death rates from the Minnesota white population. Observed and expected cumulative incidence estimates, as well as observed and expected survival curves, were compared using the log-rank test.[41]

In the final approach, Andersen-Gill time-to-fracture regression models[42] were used to assess the impact of various covariates (eg, clinical stage, chemotherapy) on subsequent fracture risk among all women with breast cancer and, separately, for those who were pre- versus postmenopausal at the time of diagnosis. These models allow for the use of multiple fractures per subject, while appropriately accounting for the correlation structure. Using an age scale, univariate relations between the risk of specific types of fractures and each clinical characteristic under consideration were first assessed, and stepwise methods with forward selection and backward elimination were then used to choose independent variables for the final models. The dependent variable was time until fracture, and the independent variables were the various clinical characteristics; drug exposures were handled as time-dependent variables which may have preceded the breast cancer diagnosis. When counts were low for a particular model, and coefficient estimates thereby unstable, Firth's penalized maximum likelihood estimation was used.[43]

Results

All but 15 of the 608 Olmsted County women with invasive breast cancer first diagnosed in 1990-99 were white (by self-report), reflecting the racial composition of the community (96% white in 1990). Their mean (± SD) age at diagnosis was 61.6 ± 14.8 years (median, 60.9 years; range, 26 to 103 years). The cancer was in the left breast in 52%, the right breast in 47% and bilateral in 9 women (laterality unknown in one); if bilateral, the most severe side was analyzed. Clinical characteristics of these unselected community patients are delineated in Table 1, both overall and, separately, for the women who were premenopausal or postmenopausal at diagnosis. Altogether, 326 women (54%) had localized (Stage I) breast cancer; only 10% had locally advanced or distant disease (Stage III or IV), although bone metastases developed ultimately in 13%. The two groups were fairly similar in many respects, but women who were premenopausal were more likely to undergo chemotherapy, often accompanied by glucocorticoid use (as an anti-emetic), and radiation treatment. Women who were postmenopausal when their breast cancer was diagnosed, on the other hand, were more often exposed to tamoxifen, and they had a greater prevalence of prior osteoporotic fractures, as well as risk factors for secondary osteoporosis and for falls. On average, this cohort of breast cancer patients had been attended in the community for 35

years prior to recognition of their disease, and for 9.5 years afterward (median, 10.4 years; 42% followed until death). Only 51% of the women remained alive after 15 years compared to 67% expected (p<.001).

During 5776 person-years (p-y) of observation (range, 1 day to 18 years per subject), 270 women experienced 568 different fractures (crude incidence, 98 per 1000 p-y; 95% CI, 90–107). Altogether, 338 women (56%) had no subsequent fracture, while 139 (23%) had a single fracture and 131 (22%) had two or more. Only 81 fractures (14%) were caused by severe trauma (eg, motor vehicle accident), while 373 (66%) were attributed to no more than moderate trauma (Table 2). Of the latter, 160 fractures were due to a fall from standing height or less, and 213 (mostly vertebral fractures) occurred “spontaneously” in the course of everyday activities. Eighty-seven fractures (15%) resulted from a specific pathological lesion (almost all in the axial skeleton due to metastatic malignancy). The etiology of the remaining 27 fractures was uncertain.

After 15 years of follow-up, an estimated 57% of these patients had experienced at least one new fracture, which was more than the expected 43% (p<.001) when follow-up was censored at death; with death treated as a competing risk, the observed cumulative incidence at 15 years was 49%, with an absolute increase in fracture risk of 9%. Compared to expected fracture rates, there was a statistically significant 1.8-fold (95% CI, 1.6–2.1) increase in overall fracture risk following the breast cancer diagnosis. The relative risk of fractures at specific skeletal sites is delineated in Table 3. Statistically significant increases were seen for most fractures of the axial skeleton, particularly the vertebrae (SIR, 5.7; 95% CI, 4.8–6.6). Overall, the relative risk of any axial fracture was 3.1 (95% CI, 2.7–3.6) compared to only 1.1 (95% CI, 0.9–1.3) for all limb fractures combined.

The overall risk of a subsequent fracture remained elevated (SIR, 1.7; 95% CI, 1.5–1.9) when the pathologic fractures were excluded; further exclusion of an additional 137 fractures that were only discovered incidentally, including 120 asymptomatic vertebral fractures (29 found in the course of cancer monitoring and 91 on radiographs taken for some other purpose), reduced the relative risk to a level that was no longer statistically significant (SIR, 1.2; 95% CI, 0.99–1.3). However, the fractures traditionally ascribed to bone loss include only those due to moderate trauma. These detailed site-specific data are also shown in Table 3. The risk of any subsequent moderate trauma vertebral fracture, excluding pathologic fractures and those found incidentally, was only elevated 1.9-fold (95% CI, 1.4–2.5) compared to the nearly 6-fold increase when all thoracic and lumbar spine fractures were included. The only other increased risks were for cervical vertebrae (SIR, 5.3; 95% CI, 1.1–15) and rib fractures (SIR, 1.6; 95% CI, 1.1–2.3). The risk of any osteoporotic fracture (hip, spine or wrist fracture due to moderate trauma but not pathologic nor incidental) was not elevated (SIR, 0.9; 95% CI, 0.7–1.2). After 15 years, an estimated 22% of the breast cancer patients had experienced at least one such fracture compared to an expected 23% (p=.474).

At the time of breast cancer diagnosis, 102 women were premenopausal and 503 were postmenopausal (the menopausal status of three women was uncertain). Compared to expected fracture rates in the community, cumulative fracture incidence was elevated by 46% among the premenopausal women (35% versus 24%; p=.011) compared to 35% among the women who were postmenopausal at diagnosis (62% versus 46%; p<.001), although absolute fracture risk was almost twice as high among the older women (Fig. 1). The risk factors for fracture also appeared to differ between the two groups as shown in Table 4, which includes all variables that were statistically significant in any specific analysis; the other patient characteristics delineated in Table 1 were not associated with risk by menopausal status, by fracture type or overall. Note, however, that the variables linked to

breast cancer and its treatment were more closely associated with the pathologic fractures, whereas those customarily linked to age-related fractures were more closely associated with osteoporotic fractures among the postmenopausal women. Indeed, including those found incidentally, 45% of all fractures in postmenopausal women were considered osteoporotic compared to 22% among the women who were premenopausal at diagnosis. Conversely, 45% of all fractures in the premenopausal group were pathologic fractures compared to just 12% among postmenopausal women.

Since fracture type seemed more important than menopausal status at diagnosis, we focused the remainder of the analysis on pathologic versus osteoporotic (excluding the incidentally detected ones) versus all other fractures as shown in Table 5. After adjusting for age (hazard ratio [HR] per 10-year increase, 1.4; 95% CI, 1.2–1.6), associations with most variables related to breast cancer and its treatment were accounted for by the pathological fractures. These included significantly increased pathologic fracture risk with Stage III/IV disease at diagnosis and with bone metastasis as a time-dependent variable, along with use of AIs (53 on letrozole, 42 on anastrozole and 13 on exemestane, with some women using more than one) and EAs (346 on tamoxifen, 64 on megestrol and 10 on a GnRH agonist), thoracic irradiation, various chemotherapy regimens and glucocorticoid use, as well as treatment with bisphosphonates (124 on an oral bisphosphonate [110 on alendronate, 16 on risedronate, and 6 on ibandronate] and 38 on an intravenous bisphosphonate [20 on pamidronate and 24 on zoledronic acid]). The Charlson index of significant comorbidity was also associated with pathologic fracture risk. In the age-adjusted analysis, osteoporotic fractures were significantly associated with more advanced disease at diagnosis, chemotherapy and use of osteoporosis drugs.

In multivariable analyses, the independent predictors of pathologic fractures in this cohort included bone metastases, use of EAs other than tamoxifen and general comorbidity (Table 5). By contrast, the independent predictors of an osteoporotic fracture included exposure to bisphosphonates, along with chemotherapy and alcoholism. All other fractures combined were associated with bone metastases, prior osteoporotic fracture, general comorbidity and alcoholism.

Discussion

In this inception cohort of unselected community women with breast cancer, the overall risk of any subsequent fracture was elevated 1.8-fold. Although fractures in this patient population have often been attributed to so-called cancer treatment-induced bone loss (CTIBL), 15% of all fractures seen in this cohort were pathologic fractures compared to just 2% of all fractures in the adult population generally.[36] The elevated risk was mainly confined to fractures of the axial skeleton, but many vertebral fractures were asymptomatic and only discovered incidentally. To the extent that breast cancer patients undergo more imaging procedures than community women generally, this raises the possibility of ascertainment bias. It is not clear how this problem should be handled. Excluding incidental vertebral fractures potentially underestimates the problem among women with breast cancer since even asymptomatic vertebral fractures can be associated with adverse sequelae,[44] and some mild, asymptomatic vertebral deformities exhibit characteristics of unequivocal vertebral fractures.[45] On the other hand, these so-called “morphometric” fractures are not the same as the symptomatic vertebral fractures considered clinically significant,[46] so including them certainly overestimates the fracture problem.

In any event, if the pathological fractures and those found incidentally are excluded, the overall relative risk is 1.2 and no longer statistically significant. The latter result is entirely consistent with the 1.19 odds ratio (OR) for overall fracture risk associated with breast

cancer that was reported from a large case-control study in Denmark,[47] but lower than the 1.3 HR for a hip, spine or wrist fracture among prevalent breast cancer cases in the Women's Health Observational Study.[48] All three estimates are greater than the OR of 0.86 for a hip, spine or wrist fracture from a case-control study in Canada[27] or the HR of 1.02 for total self-reported (70% agreement with chart review) fracture risk following an incident breast cancer as documented in the Women's Health Initiative.[49] However, the latter study excluded some fracture sites that were elevated in the present investigation (eg, ribs); excluding, as they did, fractures of the face/skull, hands/feet, and ribs/other chest, along with the pathological and incidental fractures, our SIR was a comparable 1.1 (95% CI, 0.9–1.3). Our earlier study also found no overall association of breast cancer with non-pathologic fractures.[1]

There is less consistency with respect to the association of breast cancer with fractures at specific skeletal sites. Thus, subsequent hip fracture risk has been reported as elevated[49] or not,[1–3,47,48] while an increase in distal forearm fractures was observed by Chen and colleagues[48] but not by others.[1,47,49] Relative risk estimates of around 1.3 have been reported for vertebral fractures in some studies[47,49] but not others.[1] However, ascertainment of vertebral fractures by self-report[49] or through administrative data[47] is highly suspect. In this investigation, we had access to the original X-ray reports on all subjects during their entire period of residency in the community, and we documented 246 fractures of the thoracic/lumbar spine (93 of which were found incidentally on routine radiographs, including 2 pathologic fractures) among 152 breast cancer patients. Consequently, the ascertainment of clinically diagnosed, though not necessarily clinically significant, vertebral fractures is more complete in our setting.[46]

Fracture risk did appear to be greater among women undergoing specific breast cancer treatments, especially those who were premenopausal at diagnosis. Thus, compared to postmenopausal women, fracture risk was greater among premenopausal women exposed to chemotherapy (HR, 5.2; 95% CI, 2.1–13 versus 1.9; 95% CI, 1.5–2.6) and tamoxifen (HR, 2.5; 95% CI, 1.1–5.6 versus 1.4; 95% CI, 1.1–1.8), as well as those premenopausal women treated with AIs after becoming menopausal (HR, 11; 95% CI 5.0–27 versus 2.0; 95% CI, 1.3–3.2). However, these differences appeared to be accounted for mainly by the strong association these risk factors had with pathologic fractures, which were relatively much more common among the women who were premenopausal when their breast cancer was diagnosed. It was not possible to disentangle these effects since treatment patterns were confounded by age, menopausal status and disease stage. However, the increased risk of a symptomatic vertebral fracture seen in the Women's Health Initiative Observational Study was confined to the women whose breast cancer had been diagnosed before age 55 years.[48]

Associations with various treatments could also be indirect ones to the extent that any increase in fracture risk was actually due to the clinical characteristics that dictated such treatment (indication bias), which is a particular concern in observational studies of treatment outcomes.[50] For example, randomized clinical trials indicate that treatment with AIs may increase fractures,[19] but use of AIs was more frequent among women who did, compared to those who did not, have Stage III/IV breast cancer at diagnosis (20% versus 8%), bone metastases (45% versus 7%) or who were treated with chemotherapy (82% versus 31%) or radiation (75% versus 51%); women prescribed AI therapy were also more likely to have had a bilateral oophorectomy (30% versus 18%) or used glucocorticoids (73% versus 48%). AIs did not independently predict pathological fracture risk after bone metastases were included in the model because the majority of AI-exposed women who experienced such an event also had bone metastases. An increased risk of osteoporotic fractures was also seen following bisphosphonate therapy, whether exposure was defined as of the onset of treatment or considered only the actual duration of use (data not shown), despite data from

large randomized clinical trials documenting the antifracture efficacy of these agents.[51] Thus, to the extent that women at high risk of fracture are disproportionately selected to receive bisphosphonate therapy, this can lead to "implausibly worse" outcomes.[52] By contrast, glucocorticoids are well known to cause bone loss and fractures[53] but did not independently predict fracture risk as 61% of glucocorticoid users in this study were also on chemotherapy. However, the increased fracture risk associated with chemotherapy, seen in this study and reported by others as well, could also be confounded by treatment indication as reviewed elsewhere.[54]

The present investigation has a number of strengths. The study was population-based, comprised of unselected community women followed from the time their breast cancer was first diagnosed (inception cohort); and it represents the current clinical spectrum of the disease. During extensive follow-up, a large number of fractures were documented in medical records that spanned each subject's entire period of residency in the community. Since most fractures come to medical attention,[36] ascertainment should be nearly complete with the possible exception of some vertebral fractures. Indeed, the overall incidence of fractures observed in this unselected community cohort (98 per 1000 p-y) was one-third higher than that reported in a cohort of breast cancer patients not given hormonal therapy (64 per 1000 p-y) and greater even than the 86 per 1000 p-y rate found in a high-risk AI-treated cohort.[20] In addition, access to complete inpatient and outpatient records allowed us to classify pathologic fractures on the basis of contemporary documentation by attending physicians, which is preferable to using "pathologic fracture" diagnoses in administrative databases that often refer to osteoporosis rather than to metastatic malignancy.[55] We were also able to identify clinical characteristics of the women with breast cancer that may have influenced treatment choices, and these potentially confounding clinical characteristics had been recorded prior to knowledge of subsequent fractures.

There are also corresponding limitations of a study based on medical records. One may be the generalizability of these data from a small Midwestern community that is predominantly white and better educated than the white population of the country as a whole,[31] although the incidence of hip fractures in this community is quite comparable to figures for United States whites generally.[56] Moreover, white women are at somewhat greater risk and account for the majority of breast cancer cases nationally.[30] In addition, measurements of bone density or bone turnover were not routinely performed so the contribution of bone loss to fracture risk could not be evaluated directly. Furthermore, we collected data on osteoporotic fractures but not other fractures that occurred prior to the breast cancer diagnosis and are thus unable to address the role of previous fractures generally. Finally, observational studies such as this do not represent a strong design for determining causality due to potential confounding by treatment indication as mentioned above.[52]

Conclusions

Although the incidence of breast cancer appears to be falling,[57] these women are living longer,[30] and more aggressive adjuvant therapy may be exacerbating bone loss and elevating their fracture risk.[19] While our results are generally consistent with reports of elevated fracture risk associated with various treatments for breast cancer, the treatment patterns observed were complex and difficult to partition. Randomized controlled clinical trials are required to establish causality with respect to adverse skeletal effects of specific treatments, as such associations in observational studies may be partly explained by underlying clinical characteristics that not only enhance fracture risk themselves but which also serve as indications for adjuvant radiation, hormone or chemotherapy (indication bias). Nonetheless, observational studies like this one are needed to estimate the positive and negative outcomes of treatment among unselected patients in routine clinical practice.

Moreover, putative associations of these fractures with disease- or treatment-related bone loss may be overstated somewhat by the fact that pathologic fractures were very common in the women with breast cancer, accounting for 15% of the total, while another 24% of the fractures observed here were only found incidentally (ascertainment bias). Most of the latter group was comprised of asymptomatic vertebral fractures of uncertain clinical significance. Even including pathologic fractures and those diagnosed incidentally, the absolute increase in fracture risk was only 9%, and 56% of the women did not experience a fracture in the decade following diagnosis. Thus, our data confirm most other reports that age-adjusted fracture risk is increased modestly, if at all, among women with breast cancer. Whereas breast cancer patients in general are not at greatly increased risk of fracture, neither are they protected from fractures despite any determinants that breast cancer and high bone density may have in common.

Acknowledgments

This project was supported by grants AG-04875 and AG-034676 from the National Institute on Aging, U.S. Public Health Service. The authors would like to thank Leona Bellrichard, R.N., Marcia Erickson, R.N., Wendy Gay, R.N., Joan LaPlante, R.N. and Barbara Nolte, R.N. for assistance with data collection and Mary Roberts for help in preparing the manuscript.

References

1. Utz JP, Melton LJ 3rd, Kan SH, Riggs BL. Risk of osteoporotic fractures in women with breast cancer: a population-based cohort study. J Chronic Dis. 1987; 40:105–13. [PubMed: 3818863]
2. Lamont EB, Lauderdale DS. Low risk of hip fracture among elderly breast cancer survivors. Ann Epidemiol. 2003; 13:698–703. [PubMed: 14599734]
3. Adami HO, Zack M, Kressner U, Persson I, Berglund A, Naessen T, Bergkvist L. Hip fractures in women with breast cancer. Am J Epidemiol. 1990; 132:877–83. [PubMed: 2239902]
4. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006; 354:270–82. [PubMed: 16421368]
5. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002; 23:279–302. [PubMed: 12050121]
6. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A. Predictive value of BMD for hip and other fractures. J Bone Miner Res. 2005; 20:1185–94. [PubMed: 15940371]
7. Tremollieres F, Ribot C. Bone mineral density and prediction of non-osteoporotic disease. Maturitas. 2010; 65:348–51. [PubMed: 20079983]
8. Olsson H, Hagglund G. Reduced cancer morbidity and mortality in a prospective cohort of women with distal forearm fractures. Am J Epidemiol. 1992; 136:422–7. [PubMed: 1415162]
9. Persson I, Adami HO, McLaughlin JK, Naessen T, Fraumeni JF Jr. Reduced risk of breast and endometrial cancer among women with hip fractures (Sweden). Cancer Causes Control. 1994; 5:523–8. [PubMed: 7827239]
10. Newcomb PA, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Baron JA, Storer BE, Willett WC, Stampfer MJ. Fracture history and risk of breast and endometrial cancer. Am J Epidemiol. 2001; 153:1071–8. [PubMed: 11390325]
11. Ganry O, Peng J, Dubreuil A. Is there a reduced risk of breast cancer among women with hip fractures? Eur J Epidemiol. 1999; 15:313–5. [PubMed: 10414370]
12. Cummings SR, Melton LJ 3rd. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002; 359:1761–7. [PubMed: 12049882]
13. Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. Br J Cancer. 1999; 79:1179–81. [PubMed: 10098755]

14. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol. 2000; 18:1570–93. [PubMed: 10735906]
15. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar RN, Shapiro CL, Shields A, Smith MR, Srinivas S, Van Poznak CH. NCCN Task Force Report: Bone Health in Cancer Care. J Natl Compr Canc Netw. 2009; 7 (Suppl 3):S1–32. [PubMed: 19555589]
16. Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, Trudeau M, Hood N, Redwood S. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol. 1999; 17:120–9. [PubMed: 10458225]
17. Melton LJ 3rd, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. J Bone Miner Res. 2003; 18:900–5. [PubMed: 12733730]
18. Khosla S, Riggs BL, Robb RA, Camp JJ, Achenbach SJ, Oberg AL, Rouleau PA, Melton LJ 3rd. Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. J Clin Endocrinol Metab. 2005; 90:5096–103. [PubMed: 15998772]
19. Vanderwalde A, Hurria A. Aging and osteoporosis in breast and prostate cancer. CA Cancer J Clin. 2011; 61:139–56. [PubMed: 21543824]
20. Mincey BA, Duh MS, Thomas SK, Moyneur E, Marynchencko M, Boyce SP, Mallett D, Perez EA. Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors. Clin Breast Cancer. 2006; 7:127–32. [PubMed: 16800971]
21. Vestergaard P, Rejnmark L, Mosekilde L. Effect of tamoxifen and aromatase inhibitors on the risk of fractures in women with breast cancer. Calcif Tissue Int. 2008; 82:334–40. [PubMed: 18463912]
22. Neuner JM, Yen TW, Sparapani RA, Laud PW, Nattinger AB. Fracture risk and adjuvant hormonal therapy among a population-based cohort of older female breast cancer patients. Osteoporos Int. 2011; 22:2847–55. [PubMed: 21170643]
23. Valachis A, Polyzos NP, Georgoulias V, Mavroudis D, Mauri D. Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: a meta-analysis. Gynecol Oncol. 2010; 117:139–45. [PubMed: 20061004]
24. Mahon SM, Williams MT, Spies MA. Screening for second cancers and osteoporosis in long-term survivors. Cancer Pract. 2000; 8:282–90. [PubMed: 11898145]
25. Ding H, Field TS. Bone health in postmenopausal women with early breast cancer: how protective is tamoxifen? Cancer Treat Rev. 2007; 33:506–13. [PubMed: 17573199]
26. Kristensen B, Ejlertsen B, Mouridsen HT, Andersen KW, Lauritzen JB. Femoral fractures in postmenopausal breast cancer patients treated with adjuvant tamoxifen. Breast Cancer Res Treat. 1996; 39:321–6. [PubMed: 8877012]
27. Cooke AL, Metge C, Lix L, Prior HJ, Leslie WD. Tamoxifen use and osteoporotic fracture risk: a population-based analysis. J Clin Oncol. 2008; 26:5227–32. [PubMed: 18838712]
28. Harlan LC, Abrams J, Warren JL, Clegg L, Stevens J, Ballard-Barbash R. Adjuvant therapy for breast cancer: practice patterns of community physicians. J Clin Oncol. 2002; 20:1809–17. [PubMed: 11919238]
29. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. J Natl Cancer Inst. 2008; 100:888–97. [PubMed: 18544740]
30. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60:277–300. [PubMed: 20610543]
31. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc. 1996; 71:266–74. [PubMed: 8594285]
32. Melton LJ 3rd. The threat to medical-records research. N Engl J Med. 1997; 337:1466–70. [PubMed: 9380105]
33. U.S.D.H.H.S. Bone Health and Osteoporosis: A Report of the Surgeon General. U.S. Department of Health and Human Services; Rockville, MD: 2004.
34. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992; 45:613–9. [PubMed: 1607900]

35. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res. 1992; 7:221–7. [PubMed: 1570766]
36. Melton LJ 3rd, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. Osteoporos Int. 1999; 9:29–37. [PubMed: 10367027]
37. Melton LJ 3rd, Alothman KI, Khosla S, Achenbach SJ, Oberg AL, Zincke H. Fracture risk following bilateral orchiectomy. J Urol. 2003; 169:1747–50. [PubMed: 12686824]
38. Cox DR. Some simple approximate tests for Poisson variates. Biometrika. 1953; 40:354–60.
39. Kaplan EL, Meier P. Non-parametic estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–81.
40. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]
41. Kalbfleisch, JD.; Prentice, RL. The Statistical Analysis of Failure Time Data. New York: John Wiley and Sons; 1980.
42. Therneau, TM.; Grambsch, PM. Modeling Survival Data: Extending the Cox Model. New York: Springer-Verlag; 2000.
43. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993; 80:27–38.
44. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. J Bone Miner Res. 2005; 20:1349–55. [PubMed: 16007332]
45. Melton LJ 3rd, Riggs BL, Achenbach SJ, Kopperdahl DL, Camp JJ, Rouleau PA, Amin S, Atkinson EJ, Robb RA, Therneau TM, Khosla S. Relation of vertebral fractures to bone density, structure and strength. J Bone Miner Res. 2010; 25:1922–30. [PubMed: 20533526]
46. Ettinger B, Black DM, Dawson-Hughes B, Pressman AR, Melton LJ 3rd. Updated fracture incidence rates for the US version of FRAX. Osteoporos Int. 2010; 21:25–33. [PubMed: 19705048]
47. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in patients with different types of cancer. Acta Oncol. 2009; 48:105–15. [PubMed: 18607871]
48. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med. 2005; 165:552–8. [PubMed: 15767532]
49. Chen Z, Maricic M, Aragaki AK, Mouton C, Arendell L, Lopez AM, Bassford T, Chlebowski RT. Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: results from the Women's Health Initiative. Osteoporos Int. 2009; 20:527–36. [PubMed: 18766294]
50. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. JAMA. 2010; 304:897–8. [PubMed: 20736474]
51. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med. 2008; 148:197–213. [PubMed: 18087050]
52. Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in determining outcomes from cancer therapy. Cancer. 2008; 112:2456–66. [PubMed: 18428196]
53. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton LJ 3rd, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res. 2004; 19:893–9. [PubMed: 15125788]
54. Vestergaard P, Rejnmark L, Mosekilde L. Methotrexate, azathioprine, cyclosporine, and risk of fracture. Calcif Tissue Int. 2006; 79:69–75. [PubMed: 16927044]
55. Curtis JR, Taylor AJ, Matthews RS, Ray MN, Becker DJ, Gary LC, Kilgore ML, Morrisey MA, Saag KG, Warriner A, Delzell E. "Pathologic" fractures: should these be included in

epidemiologic studies of osteoporotic fractures? Osteoporos Int. 2009; 20:1969–72. [PubMed: 19184268]

56. Melton LJ 3rd, Kearns AE, Atkinson EJ, Bolander ME, Achenbach SJ, Huddleston JM, Therneau TM, Leibson CL. Secular trends in hip fracture incidence and recurrence. Osteoporos Int. 2009; 20:687–94. [PubMed: 18797813]
57. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med. 2007; 356:1670–4. [PubMed: 17442911]

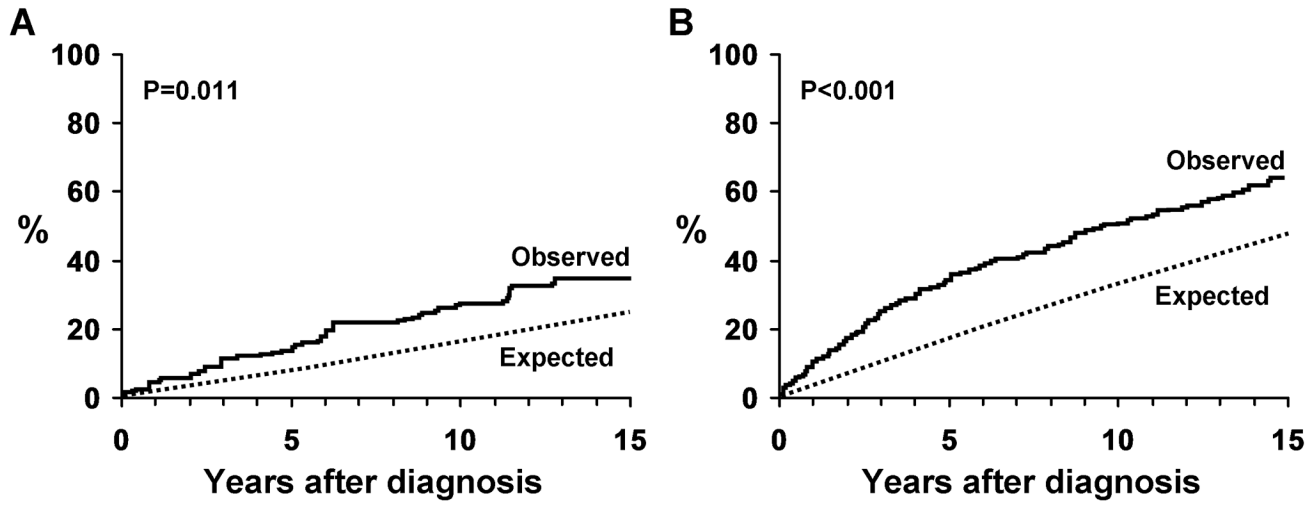

Fig. 1.

Observed versus expected cumulative incidence of any fracture among Olmsted County, MN women following breast cancer first diagnosed in 1990-99, comparing 102 women who were premenopausal at diagnosis (Panel A) and 503 women who were postmenopausal (Panel B).

Table 1

Clinical Characteristics of 608 Olmsted County, MN Women With Breast Cancer First Diagnosed in 1990-99, Comparing Women Who Were Premenopausal Versus Postmenopausal at Diagnosis

Characteristic	All women (N=608)	Premenopausal (N=102)	Postmenopausa l (N=503)
Age (median, years)	60.9	43.0	66.2
Stage III/IV at diagnosis (% yes)[a]	59 (10%)	11 (11%)	46 (9%)
Metastasis to bone (% ever)	78 (13%)	18 (18%)	59 (12%)
Bilateral oophorectomy (% ever)	123 (20%)	19 (19%)	104 (21%)
Hysterectomy (% yes)	238 (39%)	18 (18%)	219 (44%)
Used aromatase inhibitors (% ever)	93 (15%)	16 (16%)	76 (15%)
Used tamoxifen (% ever)	346 (57%)	45 (44%)	299 (59%)
Used other estrogen antagonists (% ever)	73 (12%)	19 (19%)	53 (11%)
Radiation therapy (% ever)	331 (55%)	63 (62%)	267 (53%)
Chemotherapy (% ever)	234 (39%)	67 (66%)	166 (33%)
Used glucocorticoids (% ever)	314 (52%)	66 (65%)	246 (49%)
Used other SERMs (% ever)	52 (9%)	10 (10%)	42 (8%)
Used bisphosphonates (% ever)	155 (25%)	24 (24%)	130 (26%)
Used calcitonin (% ever)	11 (2%)	0 (0%)	11 (2%)
Used birth control pills (% yes)	196 (32%)	61 (60%)	134 (27%)
Used other estrogens (% ever)	209 (34%)	6 (6%)	203 (40%)
Used progestins (% ever)	98 (16%)	13 (13%)	85 (17%)
Medical adrenalectomy (% ever)	9 (1%)	2 (2%)	7 (1%)
Prior osteoporotic fracture (% yes)[a]	93 (15%)	2 (2%)	91 (18%)
Risk factor for 2°osteoporosis (% ever)[b]	308 (51%)	32 (31%)	276 (55%)
Risk factor for falling (% ever)[c]	204 (34%)	16 (16%)	187 (37%)
Charlson comorbidity index (median score)	6.0	2.5	6.0
Obese (% yes)[a]	163 (27%)	14 (14%)	149 (30%)
Ever married (% yes)	571 (94%)	98 (96%)	471 (94%)
Gravidity > 0 (% yes)	522 (87%)	86 (84%)	434 (87%)
Parity > 0 (% yes)	510 (84%)	80 (78%)	428 (85%)
Smoked cigarettes (% ever)	282 (47%)	41 (40%)	239 (48%)
Used alcohol (% ever)	465 (78%)	86 (86%)	377 (76%)
Alcoholism (% ever)	63 (11%)	6 (6%)	56 (11%)
Used thiazide diuretics (% yes)	242 (40%)	17 (17%)	225 (45%)
Used anticoagulants (% ever)	101 (17%)	4 (4%)	97 (19%)
Limited activity (% yes)[a]	52 (9%)	0 (0%)	52 (10%)

[a] Baseline variable. Others could occur at any time point.

[b] If YES to any of the following: thyroid adenoma, increased thyroid function, thyroidectomy, peptic ulcer disease, gastric resection, resection of large or small bowel, renal failure/uremia, rheumatoid arthritis, decreased or increased adrenal function, increased parathyroid function, pancreatitis, cirrhosis of liver, malabsorption syndrome, pernicious anemia, emphysema, chronic bronchitis, or thyroid medication.

[c] If YES to any of the following: stroke, hemiparesis, hemiplegia, transient ischemic attack, dementia, vertebral-basilar insufficiency, vertigo, cataracts, blindness, other vision problems, heart arrhythmia, and postural/orthostatic hypotension, syncopal attacks, parkinsonism, polio sequelae, multiple sclerosis, seizure, or paraplegia.

Table 2

Distribution of Fractures Among 608 Olmsted County, MN Women Following a First Diagnosis of Breast Cancer in 1990-99, by Fracture Site and Immediate Cause

	Fracture cause									
	Severe trauma		Moderate trauma		Pathological		Uncertain		All causes	
Fracture site	**n**	**%[a]**	**n**	**%[a]**	**n**	**%[a]**	**n**	**%[a]**	**n**	**%[b]**
Skull/face	5	45.5	6	54.5	0	0.0	0	0.0	11	1.9
Hands/fingers	12	50.0	10	41.7	0	0.0	2	8.3	24	4.2
Distal forearm	6	27.3	16	72.7	0	0.0	0	0.0	22	3.9
Other arm	5	17.9	23	82.1	0	0.0	0	0.0	28	4.9
Clavicle/scapula/sternum	1	7.1	6	42.9	7	50.0	0	0.0	14	2.5
Ribs	10	13.5	28	37.8	22	29.7	14	18.9	74	13.0
Thoracic/lumbar vertebrae	6	2.4	197	80.1	43	17.5	0	0.0	246	43.3
Cervical vertebrae	0	0.0	3	50.0	3	50.0	0	0.0	6	1.1
Pelvis	2	6.7	16	53.3	9	30.0	3	10.0	30	5.3
Proximal femur	6	15.4	29	74.3	3	7.7	1	2.6	39	6.9
Other leg	15	32.6	29	63.0	0	0.0	2	4.3	46	8.1
Feet/toes	13	46.4	10	35.7	0	0.0	5	17.9	28	4.9
All sites	81	14.3	373	65.7	87	15.3	27	4.8	568	100

[a] Percentage (%) of each type of fracture.

[b] Percentage (%) of total.

Table 3

Fractures Observed (Obs) [a] Among 608 Olmsted County, MN Women Following Breast Cancer First Diagnosed in 1990-99 Compared With the Numbers Expected (Exp) and Standardized Incidence Ratios (SIR), With 95% Confidence Intervals (CI)

	All fractures			Non-pathological, non-incidental fractures due to moderate trauma		
Fracture site	**Obs**	**Exp**	**SIR (95% CI)[b]**	**Obs**	**Exp**	**SIR (95% CI)[b]**
Skull/face	11	4.03	**2.7 (1.4–4.9)**	6	2.30	2.6 (0.96–5.7)
Hands/fingers	24	14.1	**1.7 (1.1–2.5)**	12	8.44	1.4 (0.7–2.5)
Distal forearm	22	28.2	0.8 (0.5–1.2)	16	22.6	0.7 (0.4–1.2)
Other arm	26	21.6	1.2 (0.8–1.8)	21	17.9	1.2 (0.7–1.8)
Clavicle/scapula/sternum	14	6.13	**2.3 (1.2–3.8)**	6	3.45	1.7 (0.6–3.8)
Ribs	62	23.0	**2.7 (2.1–3.4)**	29	18.2	**1.6 (1.1–2.3)**
Thoracic/lumbar vertebrae	152	26.9	**5.7 (4.8–6.6)**	52	27.3	**1.9 (1.4–2.5)**
Cervical vertebrae	6	1.60	**3.8 (1.4–8.2)**	3	0.56	**5.3 (1.1–16)**
Pelvis	30	14.9	**2.0 (1.4–2.9)**	18	12.6	1.4 (0.8–2.2)
Proximal femur	33	25.6	1.3 (0.9–1.8)	25	23.0	1.1 (0.7–1.6)
Other leg	40	32.5	1.2 (0.9–1.7)	26	22.2	1.2 (0.8–1.7)
Feet/toes	26	24.0	1.1 (0.7–1.6)	12	8.60	1.4 (0.7–2.4)
Any site	270	146	**1.8 (1.6–2.1)**	148	132	1.1 (0.95–1.3)

[a] Note that the number of fractures observed at specific skeletal sites may differ from those reported in Table 2 because only the first fracture of each type per patient was counted in this analysis.

[b] Statistically significant ($p < 0.05$) associations are bolded.

Table 4

Predictors[a] of Fracture (Fx) Risk Among 608 Olmsted County, MN Women With Breast Cancer First Diagnosed in 1990-99, After Adjustment for Age at Diagnosis, by Menopausal Status at Diagnosis and Fracture Type

	All women	Premenopausal at diagnosis (N=102)		Postmenopausal at diagnosis (N=503)		
	Any Fx (n = 568)	Any Fx (n = 49)	Pathologic Fx (n =22)	Any Fx (n = 518)	Pathologic Fx (n =64)	Osteoporotic Fx[b] (n=119)
Risk factor	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**
Postmenopausal at diagnosis	**2.0 (1.1–3.4)**	NA	NA	NA	NA	NA
Stage III/IV at diagnosis	**2.9 (2.0–4.3)**	2.3 (0.6–8.2)	2.2 (0.3–17)	**2.9 (2.0–4.3)**	**10 (4.7–20)**	**2.7 (1.4–5.6)**
Metastasis to bone	**8.5 (5.3–14)**	**23 (11–47)**	**58 (14–240)**	**7.1 (4.2–12)**	**91 (45–184)**	1.7 (0.4–6.1)
Bilateral oophorectomy	1.1 (0.8–1.5)	3.0 (0.9–9.3)	**6.2 (1.1–35)**	1.0 (0.8–1.4)	1.5 (0.6–4.0)	0.9 (0.5–1.5)
Used aromatase inhibitors	**2.5 (1.6–3.7)**	**11 (5.0–27)**	**44 (11–178)**	**2.0 (1.2–3.2)**	**6.4 (2.9–14)**	0.9 (0.3–2.5)
Used tamoxifen	**1.4 (1.1–1.9)**	**2.5 (1.1–5.6)**	**6.1 (2.0–19)**	**1.4 (1.1–1.8)**	**2.6 (1.1–5.9)**	1.4 (0.9–2.2)
Used other estrogen antagonists	**2.4 (1.5–4.2)**	**3.0 (1.1–7.7)**	**4.7 (1.1–20)**	**2.4 (1.3–4.5)**	**6.8 (2.7–17)**	1.8 (0.5–6.5)
Any radiation therapy	1.2 (0.95–1.6)	1.8 (0.8–4.4)	**12 (1.4–106)**	1.2 (0.9–1.5)	**3.0 (1.1–8.4)**	1.1 (0.7–1.9)
Any chemotherapy	**2.1 (1.6–2.7)**	**5.2 (2.1–13)**	**20 (1.1–363)**	**1.9 (1.5–2.6)**	**9.5 (4.4–21)**	**2.4 (1.4–4.1)**
Used glucocorticoids	**1.4 (1.1–1.8)**	**3.4 (1.7–6.9)**	**13 (1.6–103)**	1.3 (0.99–1.7)	1.6 (0.7–3.7)	1.6 (0.97–2.5)
Prior osteoporotic fracture	**1.7 (1.2–2.4)**	**2.6 (1.3–5.3)**	18 (0.2–1630)	**1.7 (1.2–2.3)**	0.6 (0.2–2.0)	1.7 (0.95–2.9)
Used bisphosphonates	**1.6 (1.1–2.2)**	1.9 (0.7–5.3)	2.6 (0.4–18)	**1.6 (1.2–2.2)**	**3.0 (1.4–6.5)**	**1.9 (1.1–3.3)**
Charlson comorbidity index	**1.1 (1.04–1.1)**	**1.2 (1.7–1.3)**	**1.3 (1.1–1.7)**	**1.1 (1.03–1.1)**	**1.2 (1.1–1.4)**	1.0 (0.97–1.1)
Obesity	0.8 (0.6–1.1)	1.8 (0.6–5.2)	1.8 (0.3–11)	**0.7 (0.6–0.99)**	0.5 (0.2–1.2)	**0.6 (0.3–0.9)**
Alcoholism	**1.7 (1.1–2.6)**	0.2 (0.01–2.8)	0.2 (0.01–4.4)	**1.8 (1.1–2.7)**	0.6 (0.2–2.2)	2.1 (1.0–4.4)

[a] Age-adjusted univariable analyses; statistically significant ($p < 0.05$) associations are bolded. The numbers of affected women in each instance are shown in Table 1.

[b] Fractures of the proximal femur, distal radius or thoracic/lumbar vertebrae due to no more than moderate trauma, excluding pathologic fractures and those diagnosed incidentally on follow-up X-rays.

Table 5

Predictors[a] of Fracture (Fx) Risk Among 608 Olmsted County, MN Women With Breast Cancer First Diagnosed in 1990-99, by Fracture Type After Adjustment for Age and After Adjustment for Other Risk Factors

	Pathologic Fx (n=87)		Osteoporotic Fx [b] (n=122)		Other Fx (n=359)	
	Age-adjusted	Multivariable	Age-adjusted	Multivariable	Age-adjusted	Multivariable
Risk factor	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**	**HR (95% CI)[c]**
Postmenopausal at diagnosis	2.3 (0.8–6.8)		1.0 (0.2–5.3)		**1.9 (1.1–3.5)**	
Stage III/IV at diagnosis	**7.0 (2.8–17)**		**2.9 (1.5–5.7)**		**1.9 (1.3–2.9)**	
Metastasis to bone	**89 (48–166)**	**74 (35–157)**	1.6 (0.4–5.8)		**3.1 (1.6–6.0)**	**3.4 (1.8–6.4)**
Bilateral oophorectomy	1.9 (0.8–4.7)		0.9 (0.5–1.5)		1.0 (0.8–1.4)	
Used aromatase inhibitors	**7.7 (3.8–16)**		0.8 (0.3–2.4)		**1.8 (1.1–3.0)**	
Used tamoxifen	**3.3 (1.7–6.4)**		1.4 (0.9–2.3)		1.2 (0.9–1.6)	
Used other estrogen antagonists	**5.8 (2.7–13)**	**3.7 (1.6–8.4)**	2.0 (0.6–6.2)		1.6 (0.8–3.4)	
Any radiation therapy	**3.7 (1.5–8.9)**		1.1 (0.7–1.9)		1.0 (0.8–1.4)	
Any chemotherapy	**9.8 (4.8–20)**		**2.5 (1.5–4.2)**	**2.9 (1.7–4.8)**	**1.4 (1.1–1.9)**	
Used glucocorticoids	**2.0 (1.01–4.2)**		1.6 (0.99–2.5)		1.2 (0.9–1.6)	
Prior osteoporotic fracture	0.6 (0.2–2.0)		1.7 (0.95–2.9)		**1.9 (1.3–2.7)**	**1.9 (1.4–2.7)**
Used bisphosphonates	**2.7 (1.3–5.3)**		**1.8 (1.1–3.2)**	**1.7 (1.01–2.9)**	1.3 (0.9–1.9)	
Charlson comorbidity index	**1.3 (1.1–1.4)**	**1.2 (1.1–1.4)**	1.1 (0.98–1.1)		**1.1 (1.02–1.1)**	**1.1 (1.02–1.1)**
Obesity	0.7 (0.3–1.7)		0.6 (0.4–1.03)		0.9 (0.7–1.2)	
Alcoholism	0.5 (0.1–1.9)	_____	2.1 (0.99–4.4)	**2.4 (1.2–4.9)**	**1.9 (1.3–2.9)**	**1.8 (1.3–2.7)**
Concordance Index	-	0.94	-	0.64	-	0.62

[a] Age-adjusted univariable and multi-variable analyses; statistically significant ($p < 0.05$) associations are bolded.

[b] Fractures of the proximal femur, distal radius or thoracic/lumbar vertebrae due to no more than moderate trauma, excluding pathologic fractures and those diagnosed incidentally on follow-up X-rays.

[c] Hazard ratio (HR) and 95% confidence interval (CI).