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Research Article

Femur fracture classification in women with a history of breast cancer

Stephanie Chau [a], Malini Chandra [b], Christopher D. Grimsrud [c], Joel R. Gonzalez [b], Rita L Hui [d], Joan C. Lo [a,b,*]

[a] Department of Medicine, Kaiser Permanente Oakland Medical Center, USA
[b] Division of Research, Kaiser Permanente Northern California, USA
[c] Department of Orthopedic Surgery, Kaiser Permanente Oakland Medical Center, USA
[d] Pharmacy Outcomes Research Group, Kaiser Permanente California, Oakland, CA, USA

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ABSTRACT

Purpose: Women with breast cancer are at increased risk for femur fracture. Contributing factors include estrogen deficiency, cancer-related therapies, or direct bone involvement. This study examines fracture subtypes in women with prior breast cancer experiencing a femur fracture.
Methods: Women age ≥ 50 years old with a history of invasive breast cancer who experienced a femur fracture were identified during 2005–2012. Fracture site was classified by hospital diagnosis (for hip) and/or radiologic findings (for femoral diaphysis), with subtype classification as pathologic, atypical or fragility fracture. Clinical characteristics were ascertained using health plan databases and disease registries.
Results: There were 802 women with prior breast cancer who experienced a femur fracture. The mean age at fracture was 80.5 ± 9.6 years, with most fractures (93.8%) occurring in the hip and only 6.2% in the femoral diaphysis. However, diaphyseal fractures accounted for 23.6% of fractures in younger women (age ≤ 65 years). Pathologic fractures comprised 9.6% of total fractures (56.0% of diaphyseal fractures) and accounted for half the fractures in younger women. An atypical fracture pattern was seen in 1% of all femur fractures and 16.0% of diaphyseal fractures, with prior bisphosphonate exposure in all atypical fracture cases.
Conclusion: Most femur fractures in women with prior breast cancer occurred in the hip. Among younger women and those experiencing diaphyseal fractures, a larger proportion were pathologic and some were found to be atypical. Further studies should examine risk factors for femur fracture in women with breast cancer with specific attention to fracture subtype and pharmacologic exposures.

1. Introduction

Breast cancer is the leading cause of cancer among adult U.S. women, with over 200,000 new cases estimated to have occurred in 2013 [1]. Treatment strategies have included both endocrine and cytotoxic therapies, with tamoxifen and aromatase inhibitors as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer [2]. Treatment with aromatase inhibitors has been associated with accelerated bone loss and increased fracture risk [3–10], prompting greater attention towards bone health and fracture outcomes in women with breast cancer. Other factors contributing to greater fracture risk in women with breast cancer include estrogen deficiency, chemotherapeutic regimens, nutritional status, frailty, local cytokine factors and metastatic bone disease [7,9,11–13].

Melton et al. studied 608 women with invasive breast cancer in Olmsted County, Minnesota, and found that the overall risk of fracture was elevated 1.8-fold, although the relative risk was only 1.2 after exclusion of pathologic and incidentally discovered fractures [14]. This study, conducted among women with breast cancer diagnosed in 1990–1999 followed for up to 15 years, found that various breast cancer therapies were associated with increased fracture risk, with the strongest associations seen for pathologic fracture [14]. The Women's Health Initiative found a 1.5-fold increased risk of hip fracture in postmenopausal women with breast cancer and an even higher risk among those treated with aromatase inhibitors [15]. Compared to tamoxifen, aromatase inhibitor therapy has been associated with a 3- to 4-fold increased risk of hip fracture [3,4].

Of additional interest have been rare cases of atypical femur fracture reported in women with breast cancer [16,17], described

* Corresponding author at: Kaiser Permanente Northern California Division of Research, 2000 Broadway, Oakland, CA 94612, USA.
Tel.: +1 510 891 3492; fax: +1 510 891 3508.
E-mail address: Joan.C.Lo@kp.org (J.C. Lo).

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as transverse fractures with focal cortical hypertrophy occurring in the femoral diaphysis with minimal trauma [18]. While atypical fractures were initially reported in women receiving oral bisphosphonate therapy for osteoporosis [19], several reports have been published describing atypical femur fractures in patients with cancer receiving high dose intravenous bisphosphonate therapy [17,20–22]. Within Kaiser Permanente Northern California (KPNC), we found that up to 1 in 10 femur fractures occurring in breast cancer patients who received high dose intravenous bisphosphonate therapy (e.g. for bone metastases) demonstrated an atypical fracture pattern [16].

Collectively, these studies demonstrate that the majority of femur fractures among female breast cancer survivors occur in the proximal femur and are likely secondary to postmenopausal bone loss or cancer-specific therapy. However, some fractures are pathologic, attributable to direct skeletal metastases, and rare cases of atypical femur fracture in women receiving bisphosphonate therapy have also emerged. Given the paucity of studies in the current era examining fracture subtypes in women with breast cancer, the primary goal of this study was to characterize fracture site and subtype in a contemporary population of women with a history of invasive breast cancer who experienced a fracture of the hip or diaphyseal femur.

2. Methods

Kaiser Permanente Northern California (KPNC) is an integrated healthcare delivery system that serves more than 3 million members annually, of whom approximately one-fifth are women aged 50 years and older. Since 1995, electronic databases have been utilized for hospitalization and ambulatory care diagnoses, pharmacy records, and operative and radiology reports, with digital radiologic images since 2005. An extensive KPNC Cancer Registry has also been maintained, with high-quality information on tumor histology and stage of disease at initial presentation [23].

2.1. Cohort identification and fracture site adjudication

The source cohort was derived from a large population study of KPNC women aged 50 years and older identified as having a principal hospital discharge diagnosis of femur fracture at a KPNC hospital between January 1, 2005 and December 31, 2012, based on International Classification of Diseases, 9th edition (ICD-9) discharge diagnoses codes 820.x, and 821.x, excluding open fractures (ICD-9 820.1x, 820.3x, 820.9x and 821.1x), distal femur fractures (821.2x and 821.3x) and those associated with high energy trauma (secondary ICD-9 E800-848). Women were also included in the source cohort if they were identified by a principal hospital discharge diagnosis of pathologic femur fracture (733.14 and 733.15). The study cohort was then established by identifying the subset of women with femur fracture who had a history of invasive breast cancer diagnosed since 1988 using the KPNC Cancer Registry. Women with *in situ* disease ($N=122$) or missing stage ($N=14$) at initial breast cancer diagnosis were excluded. For women experiencing two femur fractures during the study observation period, the first fracture occurring after breast cancer diagnosis within the study observation period was ascertained.

Proximal femur (hip) fractures were classified as femoral neck (ICD-9 820.0x and 820.8x) and pertrochanteric (ICD-9 820.20 and 820.21) fractures based on principal hospital discharge diagnosis. For diaphyseal fractures, subtrochanteric-coded (820.22) and femoral shaft-coded (821.0x) fractures were adjudicated by an orthopedic surgeon (CDG) after review of radiologic images to classify subtrochanteric fractures as those occurring within 5 cm below the lesser trochanter (based on Orthopedic Trauma Association criteria) [24–26] and femoral shaft fractures as those occurring below this region and up to but not including the metaphyseal flare [27]. This approach was selected due to the large proportion of subtrochanteric-coded fractures occurring above the lower margin of the lesser trochanter (reclassified as pertrochanteric fracture) and periprosthetic fractures of the femoral diaphysis (identified for exclusion) as previously described [24]. Cases of femur fracture initially ascertained by a principal hospital discharge diagnosis of pathologic femur fracture (ICD-9 733.14 and 733.15, $N=100$) were also adjudicated by fracture site based on radiologic findings, with review of radiologic images for all diaphyseal fractures. Women found to have other malignancies involving the fracture site ($N=4$), those with impending fracture ($N=6$), and periprosthetic fracture ($N=3$), fractures found to be not specific to the femoral neck, pertrochanter, subtrochanter or femoral shaft ($N=3$) or adjudication uncertain ($N=4$) were excluded.

2.2. Demographic and clinical characteristics

Age and race/ethnicity were obtained using health plan demographic databases. Pharmacy dispensing records were used to characterize use of aromatase inhibitors, tamoxifen and bisphosphonate drugs (both oral and intravenous) prior to femur fracture. Dates of breast cancer diagnosis and initial cancer staging were obtained from the KPNC Cancer Registry. Prior fracture history (occurring after age 40 years and prior to the femur fracture event) was obtained from outpatient and hospitalization diagnoses of fractures involving the spine, trunk, upper and lower extremities (ICD-9 805.0x, 805.2, 805.4, 805.6, 805.8, 807.0x, 807.2, 808.0, 808.2, 808.4x, 808.8, 809.0, 810.0x, 811.0x, 812.0x, 812.2x, 812.4x, 813.0x, 813.2x, 813.4x, 813.8x, 814.0x, 815.0x, 817.0, 818.0, 819.0, 820.0x, 820.2x, 820.8, 821.0x, 821.2x, 822.0, 823.0x, 823.2x, 823.4x, 823.8x, 824.0, 824.2, 824.4, 824.6, 824.8, 825.0, 825.2x, 827.0, 828.0, and 829.0) excluding open fractures, fractures involving spinal cord injury, fractures of the face/skull, fingers and toes, and fractures associated with high energy trauma.

2.3. Identification of pathologic and atypical fractures

Two approaches were used to identify pathologic fractures. First, fractures were considered pathologic if there was evidence of biopsy-proven metastases to bone. Second, fractures were considered pathologic in patients who had a coded diagnosis of pathologic femur fracture (ICD-9 733.14 and 733.15) or secondary malignancy to bone (ICD-9 198.5) if there were radiologic or clinical findings consistent with metastatic disease to the femur (e.g. lytic, blastic or sclerotic lesions, known bone/bone marrow involvement, or prior targeted radiation therapy).

Atypical fractures were adjudicated by an orthopedic trauma surgeon (CDG) based on the following radiographic criteria: presence of a primarily transverse fracture (with or without oblique progression or a medial spike), localized periosteal or endosteal thickening at the lateral cortex of the fracture site, minimal or no comminution, and occurring in the presence of minimal or no trauma [18,27]. These criteria are consistent with the Second Task Force Report by the American Society of Bone and Mineral Research on atypical femur fractures [18].

2.4. Statistical analyses

Differences between subgroups were compared using the chi-square test (or Fisher exact test) for categorical variables and Student's *t*-test (or Wilcoxon test) for continuous variables. The Cochrane-Armitage test was used to examine the trend in proportions across categories. A *p*-value of <0.05 was chosen as

Table 1
Characteristics of women with a history of breast cancer experiencing femur fracture. Numbers represent column percentages, BC=breast cancer.

	Overall $N=802$	Age 50–64 y $N=72$	Age 65–79 y $N=236$	Age ≥80 y $N=494$
Race/ethnicity		*,†		
White	659 (82.2%)	48 (66.7%)	187 (79.2%)	424 (85.8%)
Black	27 (3.4%)	8 (11.1%)	7 (3.0%)	12 (2.4%)
Hispanic	44 (5.5%)	6 (8.3%)	13 (5.5%)	25 (5.1%)
Asian	35 (4.4%)	7 (9.7%)	14 (5.9%)	14 (2.8%)
Other/unk	37 (4.6%)	3 (4.2%)	15 (6.4%)	19 (3.9%)
Initial BC stage		*,†	*	
Localized	564 (70.3%)	32 (44.4%)	157 (66.5%)	375 (75.9%)
Regional	212 (26.4%)	35 (48.6%)	65 (27.5%)	112 (22.7%)
Metastatic	26 (3.2%)	5 (6.9%)	14 (5.9%)	7 (1.4%)
Prior fracture	341 (42.5%)	25 (34.7%)	96 (40.7%)	220 (44.5%)
Fracture site		*,†	*	
Femoral neck	417 (52.0%)	33 (45.8%)	139 (58.9%)	245 (49.6%)
Pertrochanter	335 (41.8%)	22 (30.6%)	79 (33.5%)	234 (47.4%)
Diaphyseal	50 (6.2%)	17 (23.6%)	18 (7.6%)	15 (3.0%)
Fracture subtype		*,†	*	
Fragility[a]	717 (89.4%)	34 (47.2%)	203 (86.0%)	480 (97.2%)
Pathologic	77 (9.6%)	36 (50.0%)	28 (11.9%)	13 (2.6%)
Atypical	8 (1.0%)	2 (2.8%)	5 (2.1%)	1 (0.2%)
Time from BC DX		*	*	
≤5 years	258 (32.2%)	32 (44.4%)	88 (37.3%)	138 (27.9%)
6–10 years	209 (26.1%)	19 (26.4%)	60 (25.4%)	130 (26.3%)
>10 years	335 (41.8%)	21 (29.2%)	88 (37.3%)	226 (45.8%)

unk = unknown; DX = diagnosis; y = years.

* $p<0.05$ when compared to age ≥80 years.

† $p<0.05$ when compared to age 65–79 years.

[a] Those not classified as pathologic or atypical fractures were considered as fragility fracture.

the criterion for statistical significance. All analyses were conducted using SAS, version 9.3 (Cary, NC).

3. Results

From the source cohort of KPNC women age ≥50 years old experiencing a femur (including pathologic femur) fracture during 2005–2012 ($N=12,891$), we identified a final femur fracture cohort of 802 women with a prior history of invasive breast cancer, meeting inclusion/exclusion criteria. The mean age at fracture was 80.5 ± 9.6 years, with the majority of women age ≥80 years and older (61.6%) and predominantly of white race (82.2%). More than two-thirds of the study cohort (70.3%) had localized cancer at initial breast cancer diagnosis with a median time between breast cancer diagnosis and fracture of 9.0 years (interquartile range 4.6–14.2 years). The median time to fracture was 7.3 years (interquartile range 3.2–12.3 years) for those who initially presented with regional disease (lymph node or local extension) and only 3.1 years (interquartile range 0.9–6.5) for those with metastatic disease at initial diagnosis ($p<0.05$ for all comparisons). Table 1 shows the demographic and clinical characteristics of the women with prior breast cancer at the time of fracture by age group.

Half of all femur fractures occurred in the femoral neck, with an increasing proportion of pertrochanteric fractures among older patients. Diaphyseal fractures accounted for only 6.2% of fractures, but contributed to 23.6% of fractures in the youngest age group (50–64 years old). Fig. 1 shows the stratification of the cohort by age, fracture site and fracture subtype, with women classified as having a fragility fracture in the absence of adjudicated pathologic or atypical fracture. Overall, 77 (9.6%) fractures were found to be pathologic, with a much greater proportion of fractures that were pathologic in the diaphyseal femur (56.0%) and among younger women (50.0% for age 50–64 years old). Among the 77 women with pathologic fractures, 88.3% were initially identified by a primary or secondary ICD-9 diagnosis for pathologic fracture of the femur (733.14 or 733.15) and an additional 7.8% were identified by ICD-9 198.5 (metastases to bone). However, one fourth (26.9%) of the 93 women with a principal or secondary ICD-9 diagnosis of 733.14 or 733.15 did not have evidence of metastatic disease at the fracture site, where the designation of pathologic fracture reflected osteoporosis, atypical fracture or other non-malignant processes.

We identified a total of eight atypical femur fracture cases among women with a history of invasive breast cancer, accounting for 16.0% of those presenting with diaphyseal femur fracture. Three of the eight cases with atypical fracture had received high dose intravenous bisphosphonate therapy and were previously reported [16]. The remaining five cases with atypical fracture received oral bisphosphonate therapy for a total duration of 4–12 years prior to fracture. Of note, there were three additional women classified as having a pathologic fracture (based on positive bone pathology) whose fracture pattern also appeared atypical; these women had also previously received intravenous bisphosphonate therapy [16].

We examined pharmacologic exposures among the subset of women diagnosed with breast cancer on or after 1995 ($N=620$) and found that over two thirds (70.8%) received adjuvant endocrine therapy prior to hip or femur fracture, including 30.8% who received tamoxifen only, 23.1% who received aromatase inhibitor only, and 16.9% who received both tamoxifen and aromatase inhibitor at some point during the interval between breast cancer diagnosis and subsequent fracture. Compared to women who received only tamoxifen therapy, women receiving any aromatase inhibitors were significantly younger at the time of fracture (77.7 ± 10.6 vs 81.1 ± 9.4 years old, $p<0.001$). Even after exclusion of pathologic and atypical fractures, there was a trend towards greater receipt of aromatase inhibitor therapy in younger women with fracture (46.7%, 41.3% and 33.4% for ages 50–64, 65–79 and ≥80 years, p=0.04 for trend) but not for receipt of tamoxifen-only therapy (20.0%, 33.5% and 32.6%, respectively). Overall, 35.5% of women received oral bisphosphonates prior to fracture (median duration 1.3 years, interquartile range 0.3–3.9 years), including one third (35.1%) of women with aromatase inhibitor exposure.

4. Discussion

This study of more than 800 women is one of the largest studies to date examining femur fracture site and subtype among contemporary women with a history of invasive breast cancer. We found that approximately half of all ascertained fractures occurred in the femoral neck, with a slightly smaller proportion in the femoral pertrochanter (increasing proportionately with age as expected) and only 6% of fractures localized to the femoral diaphysis. These distributions were similar to those ascertained for our health plan population of women age 60 years and older [24,27], except for a higher proportion of diaphyseal fractures in women with breast cancer that were more likely to be pathologic.

Overall, nearly 1 in 10 fractures were pathologic, with an even greater proportion of pathologic fractures among younger women age 50–64 years old (50%). We used several algorithms to identify pathologic fracture in this study, including examination of available bone histopathology findings for the entire cohort and clinical/radiologic findings in women with a coded diagnosis of pathologic fracture or metastases to bone. Our study demonstrates that pathologic fractures of the femur remain an important consideration in younger women with breast cancer and may be increasingly relevant in population-based studies examining fragility fracture outcomes in early postmenopausal women with breast cancer. Melton et al. also found that 45% of fractures occurring in premenopausal women with breast cancer were pathologic, in contrast to 12% among

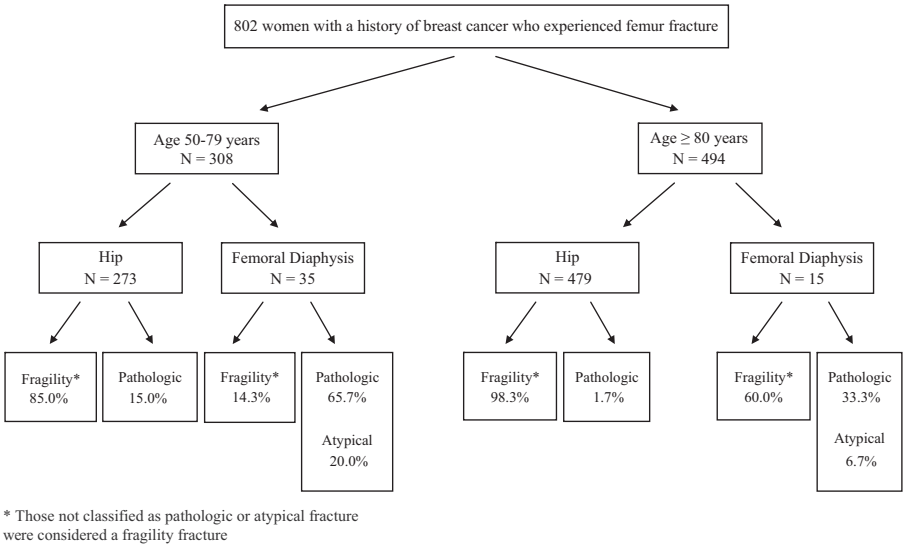

Fig. 1. Women with a history of breast cancer and subsequent femur fracture classified by age, fracture site and subtype.

postmenopausal women [14]. Others have reported that up to 14% of femoral neck fractures in patients with co-existing cancer (one-third with breast cancer) have histopathologic evidence of bone metastases [28]. Use of ICD-9 diagnosis codes for pathologic hip fracture identified the majority of cases, although pathologic-coded fractures do include a subset of fragility fractures due to osteoporosis where exclusion based solely on ICD-9 codes may underestimate the burden of fractures secondary to osteoporosis [29].

While atypical fractures accounted for only 1% of femur fractures in this cohort, we noted with interest that 16% of diaphyseal fractures demonstrated an atypical fracture pattern, occurring mostly in women <80 years old. Furthermore, all atypical fracture cases occurred in the setting of prior intravenous or oral bisphosphonate therapy. These findings contrast with previously reported data from our health plan, where 48% of diaphyseal fractures (in women age ≥ 60 years old) demonstrated an atypical pattern, with atypical fractures accounting for more than 1% of hip and femur fractures [27]. These differences are likely attributable to the larger proportion of pathologic fractures among diaphyseal fracture cases in women with breast cancer and potential differences in race/ethnicity and bisphosphonate exposure which also impact atypical fracture risk [27]. Others have found that 17–29% of subtrochanteric and femoral shaft fractures meet the criteria for atypical fractures among older women [19].

In the current era, nearly all cases of hormone-receptor positive breast cancer are treated with adjuvant endocrine therapy irrespective of staging, with preference for aromatase inhibitors over tamoxifen because of side effect profile, survival outcome and tumor recurrence rates [4,11]. In our study we found that women who received aromatase inhibitors were younger at the time of hip fracture compared to women who received tamoxifen therapy, similar to findings from Edwards et al. [5] who demonstrated that hip fractures associated with aromatase inhibitors tend to occur at a younger age than otherwise expected. While we cannot exclude the possibility that differences by endocrine therapy reflect changes in breast cancer care over the past two decades (with more recent use of aromatase inhibitors), epidemiologic data demonstrating increased bone loss and fracture risk with aromatase inhibitors [3–5,7,8] also emphasize the need to further examine contemporary fracture risk in women with treated breast cancer. As osteoporosis therapy is currently recommended for patients initiating aromatase inhibitor treatment known to be at high fracture risk [2,7,12,30] and high dose intravenous bisphosphonate therapy remains a primary treatment modality in the setting of skeletal metastases, long term treatment strategies in women with breast cancer should also consider monitoring for rare atypical fractures in the setting of potent antiresorptive therapy.

Our study has some limitations. First, the true proportion of pathologic fractures may have been higher than reported since cases of impending fracture (which are generally pathologic) were excluded, bone histopathology was not uniformly available [16], and systematic review of clinical and radiologic findings was not conducted for the entire cohort. In addition, other risk factors for hip fracture, chemotherapeutic exposures and cancer progression [5,12] were not examined, and pharmacologic care outside our health system or prior to 1995 were not available for this study. Finally, our cohort was not large enough to differentiate outcomes by breast cancer subtype and extent of primary disease. Nonetheless, this study represents one of the largest contemporary cohorts of breast cancer survivors in whom femur fracture site and subtype have been carefully examined. Importantly, population studies examining hip fracture outcome in younger women with breast cancer should note that a significant proportion of fractures may be pathologic rather than fragility in nature. In addition to pathologic fractures, a small number of diaphyseal femur fractures in bisphosphonate-treated women may be atypical. Finally, with the increasing use of adjuvant aromatase inhibitor and bisphosphonate therapy, future studies should examine long term clinical outcomes associated with optimization of bone health in women with a history of breast cancer.

Conflict of interest statement

Joan Lo, Malini Chandra and Rita Hui have received prior research funding from Amgen Inc. None of the remaining authors have any conflict of interest to report.

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