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Research Article

Femur fracture classification in women with a history of breast cancer

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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.
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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

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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

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