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SHORT REPORT

Hospital visits among women with skeletal-related events secondary to breast cancer and bone metastases: a nationwide population-based cohort study in Denmark

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Objective: Skeletal-related events (SREs) among women with breast cancer may be associated with considerable use of health-care resources. We characterized inpatient and outpatient hospital visits in a national population-based cohort of Danish women with SREs secondary to breast cancer and bone metastases.

Methods: We identified first-time breast cancer patients with bone metastases from 2003 through 2009 who had a subsequent SRE (defined as pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone). Hospital visits included the number of inpatient hospitalizations, length of stay, number of hospital outpatient clinic visits, and emergency room visits. The number of hospital visits was assessed for a pre-SRE period (90 days prior to the diagnostic period), a diagnostic period (14 days prior to the SRE), and a post-SRE period (90 days after the SRE). Patients who experienced more than one SRE during the 90-day post-SRE period were defined as having multiple SREs and were followed until 90 days after the last SRE.

Results: We identified 569 women with SREs secondary to breast cancer with bone metastases. The majority of women had multiple SREs (73.1%). A total of 20.9% and 33.4% of women with single and multiple SREs died in the post-SRE period, respectively. SREs were associated with a large number of hospital visits in the diagnostic period, irrespective of the number and type of SREs. Women with multiple SREs generally had a higher number of visits compared to those with a single SRE in the post-SRE period, eg, median length of hospitalization was 5 days (interquartile range 0–15) for women with a single SRE and 13 days (interquartile range 4–30) for women with multiple SREs.

Conclusion: SREs secondary to breast cancer and bone metastases were associated with substantial use of hospital resources.

Keywords: breast neoplasms, bone metastases, skeletal-related events, hospital services, utilization

Introduction

Breast cancer accounts for an annual estimated 1.4 million new cases worldwide, representing a leading cause of death in high-income countries and the main cause of cancer deaths among females.[1,2] Breast cancer is the most common cancer among women in Denmark, accounting for 26% of all new cancers among women in 2010.[3] Breast cancer treatment is associated with the highest costs of all cancer sites, and the cost is expected to increase due to the aging population and advances in diagnostic and treatment modalities.[4]

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Approximately 5%–6% of women have metastasized at breast cancer diagnosis, with bone metastases representing the most common site of metastatic lesions.[5–8] The clinical course of metastatic bone disease is relatively long and characterized by sequential skeletal complications, including bone pain, fractures, hypercalcemia, and spinal cord compression.[9] Metastatic bone disease represents a highly resource-intensive and costly stage of disease, primarily attributable to hospitalizations and hospital outpatient clinical visits.[9–13] Among patients presenting with bone metastases at the time of primary diagnosis, up to 43% develop skeletal-related events (SREs), defined as radiation to the bone, pathological fracture, bone surgery, or spinal cord compression,[5] probably adding substantially to the resource utilization and costs of metastatic bone disease.[14] However, published data about the use of hospital resources in breast cancer patients with SREs are scarce.[15,16] Having up-to-date information on the allocation of hospital resources would be important in health-care planning. Therefore, we analyzed the use of hospital visits in a cohort of Danish women with SREs secondary to breast cancer and bone metastases.

Methods

Setting and study period

This nationwide population-based cohort study was conducted in Denmark from 2003 through 2009, based on prospectively collected data from Danish medical registries. The entire Danish population receives tax-supported health care from the Danish National Health Service, with free access to hospital care.[17] All Danish citizens are assigned a unique ten-digit civil registration number, administered by the Central Office of Civil Registration, which allows unambiguous linkage among the registries.[18]

Data sources

The Danish Cancer Registry (DCR) includes data on the incidence of cancer in the Danish population since 1943. In 1987, it became mandatory for all physicians to report incident cancers. The quality of newly reported data is checked against any previous records in the DCR and linked to the pathology registry and the Danish registry of causes of death.[19] Recorded data include personal and tumor characteristics such as date of birth and diagnosis codes, and tumor staging. Since 2004, cancers have been classified according to the *International Classification of Diseases*, 10th revision (ICD-10). Coding of cancers diagnosed between 1978 and 2004 has been converted by the DCR from the ICD-7 to the ICD-10 system. Additional tumor staging at diagnosis was until 2004 recorded as local, regional, or distant (summary staging), and according to the tumor, nodes, metastasis (TNM) classification thereafter.[19] Conversion of TNM classifications to summary staging is presented in Table S1.[20]

The Danish National Patient Registry holds information on all Danish somatic hospitalizations since 1977, and on outpatient activities, emergency room contacts, and activities in psychiatric wards since 1995.[21] The registry serves as a basis for reimbursement in the Danish health-care system and holds information on hospital activity, including diagnosis codes according to the ICD-10 (since 1994), surgical procedures, major treatments performed, hospital and department identification codes, and date and time of activity.[21] The Danish Civil Registration System has kept up-to-date records on date of birth, sex, address, date of emigration, and changes in vital status for all Danish citizens since 1968.[18]

Study population

We identified all women diagnosed with incident breast cancer in the Danish Cancer Registry and subsequent bone metastases in the Danish National Patient Registry between January 1, 2003 and December 31, 2009. These women were followed through December 31, 2010 for development of SREs, defined as first date of spinal cord compression, pathological fracture, surgery to bone, or conventional external radiation therapy using the Danish National Patient Registry. The procedure code of conventional external radiation was not implemented before 2002. To make SRE identification consistent throughout the study period, we restricted the study period to 2003, allowing 1 year pre-SRE history (relevant codes are listed in Table S2).

Hospital contacts

We assessed the number of inpatient hospitalizations, inpatient bed days, hospital outpatient clinic visits, and emergency room visits. This hospital use was assessed for different observation periods, including a pre-SRE period (90 days prior to a diagnostic period), a diagnostic period (14 days prior to the SRE), and a post-SRE period (90 days after the SRE). Patients who experienced more than one SRE during the post-SRE period were defined as having multiple SREs and followed until 90 days after the last SRE.

Statistical analysis

The number of inpatient hospitalizations, inpatient bed days, hospital outpatient clinic visits, and emergency room visits was analyzed using frequency distributions, median, and interquartile range (IQR). Furthermore, the rate (and 95% confidence interval [CI]) of hospital contacts was assessed per 100 person-days according to the number of SREs (1 SRE, >1 SREs), the observation period (pre-SRE, diagnostic period, post-SRE), and type of SRE. We compared differences in rates of hospital contacts between the observation periods using rate ratios with the pre-SRE period as reference.

Results

We identified 569 women with SREs secondary to breast cancer and bone metastases among 30,700 women diagnosed with breast cancer from 2003 through 2009. Radiation therapy accounted for the vast majority of SREs. The median age at breast cancer diagnosis was 61.7 years (IQR 52.9–70.7), and the median length from first SRE to end of follow-up was 3.0 months (IQR 2.8–3.2) (Table 1). A total of 20.9% (32/153) and 33.4% (139/416) of women with single and multiple SREs died in the post-SRE period, respectively.

SREs were associated with a high rate of hospital visits in the diagnostic period, irrespective of the number and type of SREs (Table 2 and Figure 1). For example, the rate of bed days per 100 person-days was up to four times higher in the diagnostic period compared with the pre-SRE period (rate ratio for women with one SRE: 3.7, 95% CI 3.4–4.1) (Table 2). Conversely, the absolute number of hospital visits was lower in the diagnostic period compared with the pre- and post-SRE period, due to the shorter time window (14 days).

Table 1 Descriptive characteristics of 569 breast cancer patients with bone metastases and subsequent SREs

Characteristics	
Age at primary cancer diagnosis, years[a]	61.7 (52.9–70.7)
Tumor stage at primary cancer diagnosis, n (%)	
Local	78 (13.7)
Regional	253 (44.5)
Distant metastases	191 (33.6)
Unknown	47 (8.3)
SRE, n (%)	
One SRE	153 (100)
RT	117 (76.5)
PF	19 (12.4)
SSC	14 (9.2)
SB	3 (2.0)
Multiple SREs	416 (100)
Multiple treatments with RT alone	268 (64.4)
RT combined with PF, SSC, and/or SB	119 (28.6)
PF, SCC, and/or SB	29 (7.0)
Months from primary cancer diagnosis to bone metastases[a]	12.3 (0.8–29.0)
Months from bone metastases to first SRE[a]	0.8 (0.1–6.0)
Months from first SRE to end of follow-up[a]	3.0 (2.8–3.2)

Note: [a]Median (interquartile range).
Abbreviations: PF, pathological fracture; RT, radiation therapy; SB, surgery to bone; SCC, spinal cord compression; SREs, skeletal-related events.

Furthermore, women with multiple SREs generally had a higher rate of hospital visits compared to those with a single SRE, particularly in the post-SRE period (Table 2); the rate of inpatient bed days was 14.2 days per 100 person-days among women with a single SRE and 23.1 days per 100 person-days among women with multiple SREs. In addition, Figure 1 shows that patients with one SRE and diagnosed with pathologic fracture had a higher rate of inpatient bed days in the diagnostic period. In the post-SRE period, patients with spinal cord compression had a higher rate of inpatient bed days and outpatient clinic visits, whereas patients undergoing radiation therapy generally had fewer hospital contacts in this post SRE-period.

Discussion

In this population-based cohort of 569 Danish women with breast cancer, bone metastases, and subsequent SREs, we observed substantial use of hospital resources in relation to SREs. Notably, SREs were associated with more hospital visits in the diagnostic period, irrespective of the number and type of SRE. Furthermore, women with multiple SREs generally had more hospital visits compared to those with a single SRE.

Previous studies support our findings that SREs following metastatic bone disease are associated with considerable use of resources, particularly in relation to inpatient hospitalizations.[14–16] A Spanish study showed that patients with cancer who developed metastatic bone disease and subsequent SREs had longer inpatient lengths of stay and incurred higher inpatient costs compared to those with cancer only.[15] Furthermore, breast cancer patients who develop metastatic bone disease subsequent to their index hospital admission for cancer require more clinical attention from health-service providers than those who have cancer only, with this burden increasing further in those who subsequently develop an SRE.[15]

A Portuguese retrospective study on 121 women with breast cancer, bone metastases, and at least one SRE in the preceding 12 months (defined as spinal cord compression, pathologic fracture, hypercalcemia of malignancy, and radiation therapy) showed that patients diagnosed with spinal cord compressions had the highest total costs in the 12-month observation period, whereas patients undergoing radiation therapy had the lowest costs.[16] Similarly, the highest mean inpatient costs were observed among patients with spinal cord compression; however, patients with pathologic fracture had the lowest costs in a study from the US on 1542 patients with breast cancer, bone metastasis, and at least one subse-

Table 2 Hospital visits and follow-up time among 569 breast cancer patients with bone metastases and subsequent SREs

Hospital services	1 SRE (n = 153)			>1 SRE (n = 416)		
	Pre-SRE	Diagnostic period	Post-SRE	Pre-SRE	Diagnostic period	Post-SRE
Inpatient visits						
Patients, n (%)	79 (51.6)	85 (55.6)	105 (68.6)	226 (54.3)	233 (56.0)	335 (80.5)
Visits	128	96	184	433	271	734
Median (range)	1 (0–1)	1 (0–2)	1 (0–11)	1 (0–12)	1 (0–3)	1 (1–13)
Per 100 person-days (95% CI)	0.9 (0.8–1.1)	4.2 (3.4–5.1)	1.5 (1.3–1.8)	1.2 (1.1–1.3)	4.3 (3.9–4.9)	1.9 (1.8–2.1)
Rate ratio[a]	1 (ref)	4.5 (3.4–5.9)	1.7 (1.3–2.1)	1 (ref)	3.8 (3.2–4.4)	1.7 (1.5–1.9)
Bed days						
Patients, n (%)	79 (51.6)	85 (55.6)	105 (68.6)	226 (54.3)	233 (56.0)	335 (80.5)
Days	1201	742	1690	2415	1706	8757
Median (range)	1 (0–72)	2 (0–15)	5 (0–90)	2 (0–90)	1 (0–15)	13 (0–158)
Per 100 person-days (95% CI)	8.7 (8.2–9.2)	32.3 (30.1–34.7)	14.2 (13.5–14.9)	6.5 (6.2–6.7)	27.3 (26.1–28.7)	23.1 (22.6–23.6)
Rate ratio[a]	1 (ref)	3.7 (3.4–4.1)	1.6 (1.5–1.8)	1 (ref)	4.2 (4.0–4.5)	3.6 (3.4–3.7)
Emergency room visits						
Patients, n (%)	14 (9.2)	16 (10.5)	12 (7.8)	38 (9.1)	39 (9.4)	90 (21.6)
Visits	18	16	14	45	43	110
Median (range)	0 (0–2)	0 (0–1)	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–3)
Per 100 person-days (95% CI)	0.1 (0.1–0.2)	0.7 (0.4–1.1)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.7 (0.5–0.9)	0.3 (0.2–0.3)
Rate ratio[a]	1 (ref)	5.3 (2.5–11.1)	0.9 (0.4–1.9)	1 (ref)	5.7 (3.7–8.9)	2.4 (1.7–3.5)
Outpatient visits						
Patients, n (%)	139 (90.8)	109 (71.2)	145 (94.8)	359 (86.3)	325 (78.1)	395 (95.0)
Visits	675	196	760	1847	683	4154
Median (range)	3 (0–30)	1 (0–11)	4 (0–26)	4 (1–34)	1 (1–12)	8 (0–71)
Per 100 person-days (95% CI)	4.9 (4.5–5.3)	8.5 (7.4–9.8)	6.4 (5.9–6.9)	4.9 (4.7–5.2)	10.9 (10.2–11.8)	10.9 (10.6–11.3)
Rate ratio[a]	1 (ref)	1.7 (1.5–2.0)	1.3 (1.2–1.4)	1 (ref)	2.2 (2.0–2.4)	2.2 (2.1–2.3)
Follow-up time, days	13,770	2295	11,899	37,440	6240	37,948

Note: [a]The number of visits or days per person-day with the prediagnostic period as reference and 95% CIs.
Abbreviations: CI, confidence interval; SREs, skeletal-related events.

quent hospitalization for an SRE (defined as bone surgery, pathologic fracture, and spinal cord compression).[22] These observations support our finding that patients with spinal cord compression require substantial hospital resources in the post-SRE period. However, our study also suggests that patients diagnosed with pathologic fracture require substantial hospital resources in the diagnostic period.

To the best of our knowledge, this study is the first to compare the allocation of hospital use during adjacent time periods prior to and after the first SRE. However, our finding of a high number of hospital contacts in the diagnostic period (ie, 14 days prior to the SRE occurrence) is partly supported by previous studies. A study among Medicare beneficiaries suggests that the imaging costs in breast cancer patients have increased at a markedly higher rate than the increase in overall costs during 1999–2006.[23] These observations may denote a growing use of diagnostic modalities in cancer care. Furthermore, diagnostic evaluation is complex and may be conducted in a sequential process involving several investigations and referrals to hospital before a definitive diagnosis is made.[24]

A main strength of our study includes the nationwide population-based design, with up-to-date data on the number of hospital contacts in relation to inpatient bed days, emergency room visits, and hospital outpatient clinic visits reflecting major cost items in breast cancer care. The data were registered blind to the study hypothesis, minimizing the risk of differential misclassification and bias. Furthermore, patients who died during follow-up had a shortened observation time (which may be reflected in a moderated number of hospital contacts), but virtually complete information on vital status allowed for taking the observation time into account.

Limitations of the study include the inability to distinguish between the use of hospital resources for SRE and non-SRE-related purposes. Furthermore, we did not have information on other resource items that may impact costs,

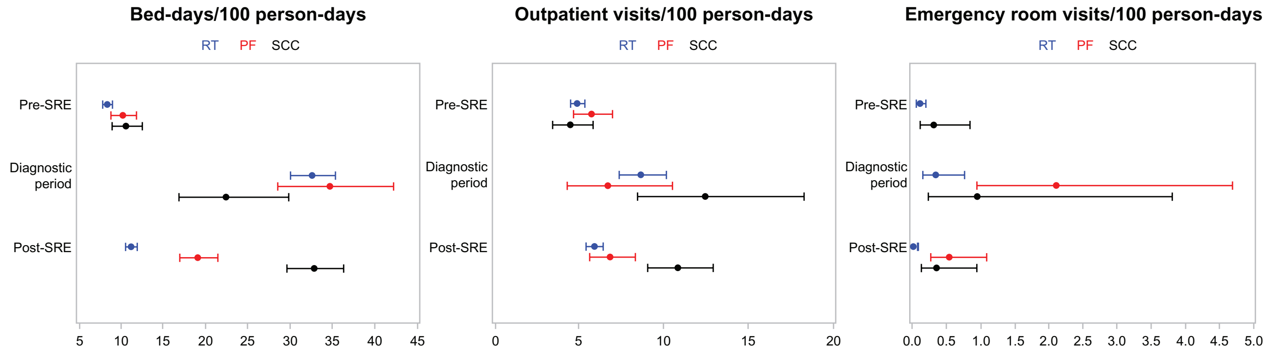

Figure 1 Hospital visits for women with only one SRE by SRE type.
Abbreviations: RT, radiation therapy; PF, pathological fracture; SCC, spinal cord compression; SRE, skeletal-related event.

including medications used during hospitalization, which may also represent a considerable cost category in SRE.[16] As a consequence, we likely underestimated the use of hospital resources in our study population. The generalizability of our findings may also be limited by the reliance on the diagnosis codes in the Danish National Patient Registry to identify bone metastases and SREs. A previous study showed that bone metastases secondary to breast cancer in the Danish National Patient Registry have a sensitivity of 0.32 (95% CI 0.13–0.57) and specificity of 0.99 (95% CI 0.93–1.00), and SREs secondary to breast cancer have a sensitivity of 0.75 (95% CI 0.43–0.95) and a specificity of 0.97 (95% CI 0.90–0.99).[25] In addition we used Danish procedure codes and ICD-10 codes to define SREs, and our results may not be directly applicable to other health-care systems using other coding systems and practice. Furthermore, it is necessary to evaluate whether any distinguishing factors in patient and health-service characteristics could somehow modify the observed findings before generalizing the results to other populations and settings, due to differences in the treatment of breast cancer across countries.[26]

Conclusion

In conclusion, SREs secondary to breast cancer and bone metastases were associated with substantial use of hospital resources.

Disclosure

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Appendix

Table S1 Conversion of TNM classification system to summary staging

Summary staging	TNM
Local	T1–4, N0, M0
	T1–2, N0, Mx
	T1, Nx, M0 or Mx
Regional	T1–4 or Tx, N1–3, M0
Distant	Any T, Any N, M1
Unknown	T2–4 or Tx, Nx, M0 or Mx
	T3–4 or Tx, N0, Mx
	T1–4 or Tx, N1–3, Mx
	T0, N1–3, M0–1 or Mx
	T0, N0 or Nx, M1

Note: x, variable not specified in the Danish Cancer Registry.
Abbreviation: TNM, tumor, nodes, metastasis.

Table S2 Codes to identify skeletal related events in the DNPR among patients with breast cancer and bone metastases

Pathologic fracture (ICD-10 codes)
M80.0: postmenopausal osteoporosis with pathological fracture
M84.4: fracture of bone in neoplastic disease
M90.7: fracture of bone in neoplastic disease
S12.0–12.9: fracture of neck
S22.0: fracture of thoracic vertebra
S22.1: multiple fractures of thoracic spine
S32.0–S32.8: fracture of lumbar spine and pelvis
S52.5–S52.6: fracture of lower end of radius and/or ulna
S72.0–72.9: fracture of femur
Spinal cord compression (ICD-10 codes)
M43.9: deforming dorsopathy, unspecified
M48.5: collapsed vertebra, not elsewhere classified
M49.5: collapsed vertebra I disease classified elsewhere; metastatic fracture of vertebrae
G95.2: cord compression, unspecified
G95.8: other specified diseases of spinal cord
Surgery to bone (NOMESCO classification of surgical procedure code)
KNxJxx: surgical fracture treatment
Radiation therapy (Danish treatment code)
BWGC1: conventional external radiation therapy

Abbreviations: DNPR, Danish National Patient Registry; ICD-10, 10th revision of the International Classification of Diseases; NOMESCO, Nordic Medicostatistical Committee.