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EPIDEMIOLOGY

Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999–2007)

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Abstract Bone lesions as a consequence of bone metastases in breast cancer patients can increase risk for skeletal-related events (SREs) (i.e., radiation to the bone, a pathological or osteoporotic fracture event, hypercalcemia, spinal cord compression, or surgery to the bone). The mortality risk for breast cancer patients with SREs subsequent to bone metastases is unclear. We assessed this relationship in a large, population-based cohort of breast cancer patients in Denmark. We identified 35,912 newly diagnosed breast cancer patients from January 1, 1999 to December 31, 2007 in the Danish National Patient Registry (DNPR) and followed them through April 1, 2008. Information on stage and treatment was obtained from the Danish Cancer Registry. We used the Kaplan–Meier method to estimate survival, and Cox's regression analysis to estimate the mortality rate ratio (MRR) by the presence of bone metastases with and without SREs, adjusting for age and comorbidity. The 5-year survival was 75.8% for breast cancer patients without bone metastases, 8.3% for patients with bone metastases, and 2.5% for those with both bone metastases and SREs. The adjusted MRR was 10.5 [95% confidence interval (CI) 9.5–11.6] for breast cancer patients with bone metastases, and 14.4 (95% CI 13.1–15.8) for those with bone metastases and SREs, compared with breast cancer patients with no bone metastases but possibly other sites of metastases. A similar pattern persisted when analyses were stratified by stage or treatment. Breast cancer patients with bone metastases and SREs have a poor prognosis compared to those with and without bone metastases regardless of cancer treatment or stage of disease at diagnosis.

Keywords Bone metastases · Skeletal-related events · Breast cancer · Epidemiology · Mortality risk

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Introduction

Breast cancer is the most commonly diagnosed cancer among women in the industrialized world, and accounts for 28% of all the new cancer cases in women in Denmark in 2008 [1]. Approximately 5–6% of breast cancer patients present with metastatic disease at diagnosis [2, 3]. Bone is the most common site of metastatic lesions with more than half of the women with metastatic breast cancer presenting with bone metastases [4]. Because bone metastases in breast cancer patients are primarily osteolytic lesions, breast cancer patients with bone metastases are at risk for skeletal-related events (SREs), defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopedic surgery [5].

To date, data on survival in breast cancer patients who develop bone metastases and SREs are scarce [6]. Saad et al. used data from three randomized controlled trials of bisphosphonate treatment to assess the effect of pathological fractures on survival in patients with malignant bone disease [6]. Among 1,130 women with stage IV breast

cancer who received bisphosphonate treatment, 393 (35%) developed pathological fractures. These patients were exposed to increased risk of death [adjusted hazard ratio = 1.32; 95% confidence interval (CI) 1.10–1.59] compared with those with no pathological fracture. However, given the restrictive study conditions of all the three randomized controlled trials, including requiring at least one bone metastasis and receiving antineoplastic therapy at the time of randomization among others for breast cancer patients, it may be difficult to extrapolate these data to the "real-world" clinical setting.

Population-based estimates of survival in breast cancer patients who develop bone metastases and SREs are needed to increase our understanding of the natural history of the disease. Therefore, we conducted a nationwide population-based cohort study in breast cancer patients in Denmark between 1999 and 2007 and examined all-cause mortality according to the presence of bone metastases with and without subsequent SREs.

Patients and methods

We conducted this population-based cohort study in Denmark, which has a population of approximately 5.4 million inhabitants. Its tax-supported health care system is regulated by the National Health Service (NHS) and provides free access to hospital care for the entire Danish population. Care for breast cancer patients is provided by specialized oncology centers within public hospitals operating under the NHS auspices. Since 1968, the Danish Civil Registration System (CRS) has maintained electronic records for each citizen, including date of birth, gender, change of address, date of emigration, and changes in vital status, with daily updates. A unique 10-digit civil registry number assigned to all Danish residents by the CRS allows linkage between registries [7].

Identification of breast cancer patients

From the Danish National Patient Registry (DNPR), we identified all the patients with a recorded first primary diagnosis of breast cancer during the period January 1, 1999 through December 31, 2007. The DNPR collects electronic data on all inpatient, outpatient, and emergency room visits. For each hospitalization, DNPR files contain data on date of admission and discharge, surgical procedure performed, if any, and up to 20 discharge diagnoses coded since 1994 according to the 10th revision of the International Classification of Diseases (ICD-10) [8]. Breast cancer patients were identified using ICD-10 code C50.x.

Bone metastases and SREs

We obtained information on the diagnosis of bone metastases (ICD-10 code: C79.5) through the DNPR. In the DNPR, surgical procedures are coded using the Danish version of the Nordic Classification of Surgical Procedures (NCSP). For each patient, the following SREs were recorded: (1) radiation to the bone (NCSP-code: BWGC1) given within 90 days after a bone metastasis diagnosis, (2) pathological or osteoporotic fractures in relation with a bone metastasis diagnosis (see Table 1 for codes), (3) surgery to the bone (NCSP-code: KNAGxx), (4) hypercalcaemia (ICD-10 code: DE835 C), and (5) spinal cord compression in conjunction with a bone metastasis diagnosis (see Table 1 for codes).

Stage at diagnosis

Information on stage at breast cancer diagnosis was obtained through linkage to the Danish Cancer Registry (DCR) until December 31, 2006. The DCR is a population-based nationwide registry containing data on incident cases of cancer in Denmark since 1943. Data in the DCR have a high degree of validity and completeness, and include cancer type, site, morphology, treatment within the first four months after cancer diagnosis, and date of diagnosis [9]. The Registry receives notifications of cancer diagnoses from hospital departments, institutes of forensic medicine, general practitioners, and practicing specialists. The extent of spread of the tumor at the time of diagnosis in the DCR was recorded as local, regional, or distant metastases (i.e., summary staging). From January 1, 2004 information on stage was recorded according to the TNM classification of malignant tumors cancer-staging system. A conversion of the TNM classification staging system to the summary staging system is presented in Table 2.

Treatment data at diagnosis

To determine whether breast cancer patients in our study cohort received adjuvant endocrine therapy or

Table 1 ICD-10 discharge diagnosis codes of skeletal-related events (SREs)

SRE category	ICD-10 codes
Fractures of the vertebrae, ribs and pelvis, femur and distal forearm	M80.0, M84.4, M90.7, S12.0–12.9, S22.0, S22.1, S32.0–S32.8, S72.0–S72.9, S52.5–S.52.6
Spinal cord compression	M43.9, M48.5, M54.5, M54.6, M54.9, G95.2, and G95.8

Table 2 American Joint Committee on Cancer groupings and summary staging for breast cancer

Stage	TNM categories
Localized	T1-4, N0, M0
Regional	T1-4, N1-3, M0
Distant	T1-4, N1-3, M1
0	Tis, N0, M0
I	T1, N0, M0
IIA	T0, N1, M0
	T1, N1, M0
	T2, N0, M0
IIB	T2, N1, M0
	T3, N0, M0
IIIA	T0, N2, M0
	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
IIIB	T4, N0, M0
	T4, N1, M0
	T4, N2, M0
IIIC	Any T, N3, M0
IV	Any T, Any N, M1

chemotherapy, we linked the DNPR to the DCR. Because data in the DCR are only complete for treatment up to 2003, information on adjuvant endocrine therapy administered to breast cancer patients within the first four months after diagnosis was available in our study through 2003. Of the 35,912 breast cancer patients identified during the period from January 1, 1999 through December 31, 2007, we had information from the DCR for 19,794 (55%) patients. Subset analyses were performed on this cohort of breast cancer patients.

Receptor status

We obtained information on receptor status at the time of diagnosis through the Danish Pathology Registry [10], which was established in 1977. Data in this registry are coded according to the Systematized Nomenclature of Medicine (http://www.snomed.org). We identified the following codes recorded within 90 days after the date of breast cancer diagnosis—F 29521: estrogen receptor positive (ER+), F 29525: estrogen receptor negative (ER−), F 29551: progesterone receptor positive (PR+), F 29555: progesterone receptor negative (PR−), F 29601: normal Human Epidermal growth factor Receptor 2 (HER2) expression (HER2−), and F 29603: HER2 overexpression (HER2+).

Comorbidity

Comorbidity is known to have an impact on breast cancer survival and mortality [11]. To control for this source of potential confounding, we used the Charlson Comorbidity Index score, which was originally developed to predict 1-year patient mortality based on data obtained from hospital chart review [12]. We computed the Index score (based on ICD-8 codes until December 31, 1993 and ICD-10 codes for the remaining time period) using all hospital diagnoses in the DNPR from January 1, 1977 to the date of breast cancer diagnosis for each patient. Three levels of comorbidity were defined: 0—"low" or no recorded underlying disease defined by the Charlson Index; 1–2—"medium"; and >2—"high" (Table 3) [13].

Follow-up

Mortality and migration updates were obtained from the CRS [14]. All the patients were followed from the date of first breast cancer diagnosis to the date of death, emigration, or April 1, 2008, whichever occurred first.

Statistical analyses

We constructed Kaplan–Meier curves for the following dynamic cohorts of breast cancer patients: (1) no bone metastases, (2) bone metastases but no SREs, and (3) bone metastases and SREs to estimate survival. Follow-up began at date of breast cancer diagnosis with patients contributing time-at-risk within each cohort. If patients developed a bone metastasis or an SRE, then they stopped contributing time-at-risk for their respective cohort. Patients would then enter the new cohort with delayed entry (i.e., left truncation). We estimated 1- and 5-year survival rates for each cohort and computed crude mortality rates (deaths per 1,000 person-years (PYs)). A Cox's proportional regression analysis was used to compute mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs), comparing mortality rates between patients by the presence of bone metastases with and without SREs as time-varying covariates, adjusting for age and level of comorbidity. Breast cancer patients without bone metastases but possibly other sites of metastases served as the reference group.

To evaluate whether tumor burden affected mortality risk in these breast cancer patients, we stratified by stage at breast cancer diagnosis. Furthermore, to assess whether adjuvant endocrine therapy or chemotherapy affected mortality risk, we stratified the analyses among the subsets of patients with data on therapy and on receptor status.

To estimate risk of death specifically associated with the occurrence of SREs, we followed breast cancer patients

Table 3 Diseases included in the Charlson Comorbidity Index according to ICD-8 and ICD-10 codes

Disease	ICD-8	ICD-10
Benign/malignant disease		
Any tumor	140–194	C00–C75
Leukemia	204–207	C91–C95
Lymphoma	200–203, 275.59	C81–C85, C88, C90, C96
Metastasis	195–198; 199	C76–C80
Cardiovascular/cerebrovascular		
Myocardial infarction	410	I21, I22, I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0 I13.0, I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Cerebrovascular disease	430–438	I60–I69, G45, G46
Hemiplegia	344	G81, G82
Gastrointestinal		
Ulcer disease	530.91, 530.98, 531–534	K22.1, K25–K28
Mild liver disease	571, 573.01, 573.04	B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Infectious		
Acquired immunodeficiency syndrome	079.83	B21-B24
Musculoskeletal		
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Neurological		
Dementia	290.09–290.19, 293.09	F00–F03, F05.1, G30
Renal/metabolic conditions		
Diabetes mellitus type 1 and 2	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Moderate to severe renal disease	403, 404, 580–583, 584, 590.09, 593.19, 753.10–753.19, 792	I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61
Diabetes with end organ failure	249.01–249.05, 249.08, 250.01–250.05, 250.08	E10.2–8, E11.2–8
Respiratory		
Chronic obstructive pulmonary disease	490–493, 515–518	J40–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3

with bone metastases with SRE as a time-varying covariate. Follow-up began at date of bone metastasis diagnosis with patients contributing time-at-risk until they experienced an SRE. We used Cox proportional hazards model to estimate the MRRs comparing mortality rates between patients with bone metastases and SREs and patients with bone metastases and no SREs, adjusting for level of comorbidity and stratifying by age using the following age-groups: <60 years, 60–69 years, 70+ years. The assumption of proportional hazards was satisfied in all Cox models.

This study was approved by the Danish Protection Agency (Record no. 2006-41-6387). The SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, NC), was used for all statistical analyses.

Results

Demographic characteristics

We identified 35,912 female patients with a diagnosis of first primary breast cancer from the DNPR. Of these, 1,494 (4%) developed bone metastases and of these, a further 722 (2% of the 35,912 newly diagnosed breast cancer patients) developed both bone metastases and SREs during the 138,295 PYs of follow-up. The median age at diagnosis for all breast cancer patients was 62 years (range: 18–104 years), 61 years (range: 25–95 years) for breast cancer patients with bone metastases, and 62 years (range: 25–95 years) for breast cancer patients with bone metastases and SREs. The distributions of comorbidities were

similar in all the three cohorts. A total of 1,090 (3%) of participants had a recorded use of a bisphosphonate before a recorded bone metastasis diagnosis, and an additional 245 participants had a recorded use of a bisphosphonate after a recorded bone metastasis diagnosis.

Survival among breast cancer patients according to presence of metastases and SREs, overall

Figure 1 shows the survival curves for (1) breast cancer patients with no bone metastases; (2) those with bone metastases; and (3) those with bone metastases and SREs. Both 1- and 5-year survivals were low for breast cancer patients with both bone metastases and SREs [1-year survival = 40.2 (32.8–47.4%); 5-year survival = 2.5 (95% CI 1.8–3.5%)], compared with breast cancer patients with bone metastases without SREs [1-year survival = 59.0% (95% CI 53.6–64.0%); 5-year survival = 8.3% (95% CI 6.6–10.4%)], and breast cancer patients with no evidence of bone metastases [1-year survival = 93.3% (95% CI 93.0–93.6%); 5-year survival = 75.8% (95% CI 75.3–76.3)]. To better illustrate survival among patients with bone metastases according to the occurrence of SREs, Fig. 2 shows the survival curves for breast cancer patients with bone metastases and later occurrence of SREs during follow up. The median survival for breast cancer patients with bone metastases was 16 months, and the median survival for breast cancer patients with bone metastases and a subsequent SRE was 7 months.

Mortality among breast cancer patients according to presence of metastases and SREs, stage of disease at diagnosis, and adjuvant endocrine therapy

Tables 4 and 5 present the mortality rates and MRRs, overall and by stage of disease at diagnosis, for the following breast cancer cohorts: (1) those with no bone metastases; (2) those with bone metastases; and (3) those with bone metastases and SREs. The mortality rate was the lowest in breast cancer patients without bone metastases [5-year average mortality rate = 58.0 (95% CI 56.7–59.5) per 1,000 PYs. The mortality rate was substantially increased for breast cancer patients with bone metastases [5-year mortality rate = 496.8 (95% CI 455.5–541.8) per 1,000 PYs], and increased even more in patients with a subsequent SRE [5-year mortality rate = 722.0 (95% CI 660.0–789.9) per 1,000 PYs]. Stage of disease at diagnosis had an impact on these estimates. The 5-year average mortality rate among breast cancer patients who presented with localized disease at breast cancer diagnosis with bone metastasis and SREs was 585.7 per 1,000 PYs (95% CI 219.8–1560.5). The corresponding 5-year average mortality rate among breast cancer patients with bone metastases and SREs who presented with distant metastasis at breast cancer diagnosis was 942.5 (95% CI 720.0–1233.6) per 1,000 PYs. For further details, see Table 4.

When adjusted for age and comorbidity, the one-year MRR was 7.2 (95% CI 6.1–8.6) and 10.8 (95% CI 8.9–13.2) in breast cancer patients with bone metastases and with bone metastases and a subsequent SRE, respectively, compared to breast cancer patients with no bone metastases. The adjusted MRR increased after 1 year of follow up to 10.5 (95% CI 9.5–11.6) and 14.4 (95% CI 13.1–15.8) for breast cancer patients with bone metastases and with bone metastases and a subsequent SRE, respectively, compared to those with no bone metastases (Table 5). The MRR was also affected by stage of disease at diagnosis, mainly due to differences in the mortality of the respective reference groups; however, bone metastases and SREs had the greatest impact on the MRR (Table 5).

After stratifying by receptor status, we found higher mortality rates in patients with ER−, PR−, and HER2+

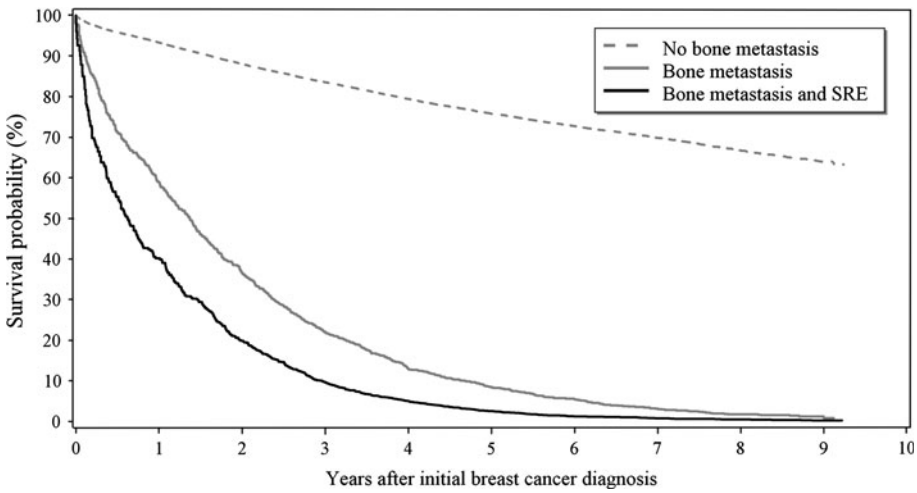

Fig. 1 Survival curves for breast cancer patients with no bone metastases, with bone metastases but no skeletal-related events (SREs), and with bone metastases and SREs during follow up

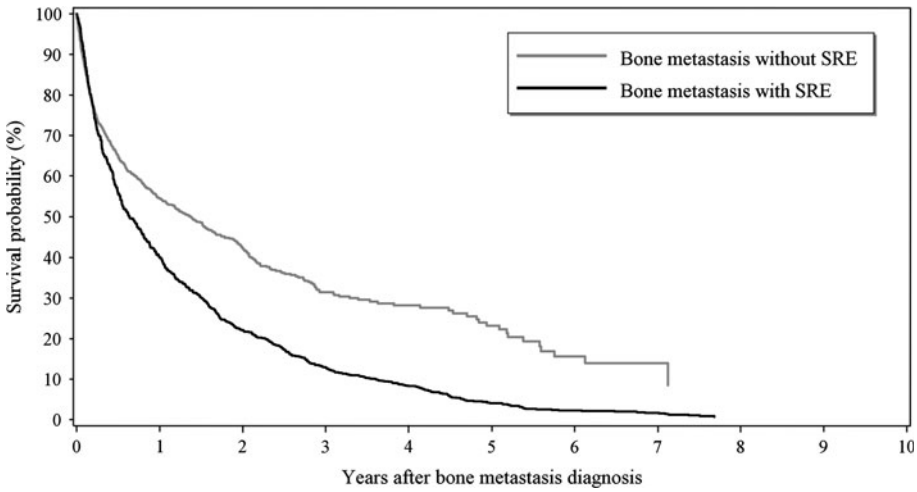

Fig. 2 Survival curves for breast cancer patients with bone metastases but no skeletal-related events (SREs) and with bone metastases and SREs during follow up

Table 4 Mortality rates in breast cancer patients with bone metastases and skeletal-related events (SREs), overall and by stage of disease at diagnosis[a]

	n	Mortality rate per 1,000 person-years (95% CI)		
		Year 1	Year 2 to Year 5	Year 1 to Year 5
Overall	35,912			
No bone metastasis	34,690	70.4 (67.6–73.4)	53.0 (51.4–54.6)	58.0 (56.7–59.5)
Bone metastasis	1,494	521.6 (442.0–615.6)	488.0 (440.8–540.3)	496.8 (455.5–541.8)
Bone metastasis + SRE	722	851.6 (702.0–1033.0)	692.9 (626.1–766.9)	722.0 (660.0–789.9)
Localized	13,515			
No bone metastasis	13,508	21.1 (18.7–23.7)	31.0 (29.3–32.8)	28.4 (27.0–29.9)
Bone metastasis	237	251.6 (113.0–559.9)	366.4 (279.2–480.8)	349.9 (270.5–452.6)
Bone metastasis + SRE	118	585.7 (219.8–1560.5)	499.4 (378.5–659.0)	504.9 (386.7–659.3)
Regional	12,452			
No bone metastasis	12,447	37.5 (34.2–41.1)	56.3 (53.8–59.0)	51.1 (49.1–53.3)
Bone metastasis	663	305.2 (201.0–463.6)	534.6 (466.2–613.0)	498.3 (437.5–567.5)
Bone metastasis + SRE	317	318.2 (159.1–636.3)	714.3 (618.7–824.7)	679.4 (590.2–782.1)
Distant	1,557			
No bone metastasis	1,429	569.1 (522.7–619.6)	279.2 (251.6–309.9)	402.1 (376.5–429.5)
Bone metastasis	358	603.4 (480.4–757.8)	468.1 (370.9–590.7)	528.6 (449.2–622.0)
Bone metastasis + SRE	177	942.5 (720.0–1233.6)	812.7 (666.0–991.6)	854.2 (727.9–1002.5)

[a] Analyses performed on a subset of the entire breast cancer patient cohort (1999–2006)

compared with patients with ER+, PR+, and HER2−, respectively. However, there were no differences in MRRs between receptor positive and receptor negative patients (data not shown). This pattern persisted regardless of age (Table 6) and treatment with adjuvant endocrine therapy or chemotherapy (data not shown).

Discussion

In this nationwide cohort study of breast cancer patients in Denmark, we found that patients who developed bone metastases and SREs have a poor prognosis compared to breast cancer patients with bone metastases and no SREs. Few breast cancer patients with bone metastases and SREs survived 5 years after diagnosis independent of age, stage of disease at diagnosis, and adjuvant therapy, including endocrine and chemotherapy during the first 4 months after primary breast cancer diagnosis.

Our findings showed a higher risk of mortality in breast cancer patients with bone metastases and SREs compared to the limited published data reporting on risk of death in breast cancer patients who developed a pathological fracture relative to breast cancer patients without a fracture [6]. Given that our data are from a nation-wide patient registry and published data are from randomized, controlled trials, this

Table 5 Mortality rate ratios (MRRs) and 95% confidence intervals (CIs) among breast cancer patients with bone metastases with and without skeletal related events (SREs) compared with breast cancer patients without bone metastases, overall, and by stage of disease at diagnosis[a]

Stage of disease at diagnosis	1-year Crude MRR (95% CI)	1-year Adjusted[b] MRR (95% CI)	>1 year Crude MRR (95% CI)	>1 year Adjusted[b] MRR (95% CI)
All patients ($N = 35{,}912$)				
No bone metastases ($n = 34{,}690$)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Bone metastases, no SREs ($n = 1{,}494$)	7.6 (6.4–9.0)	7.2 (6.1–8.6)	9.5 (8.7–10.5)	10.5 (9.5–11.6)
Bone metastases and SREs ($n = 722$)	13.0 (10.6–15.8)	10.8 (8.9–13.2)	13.4 (12.2–14.7)	14.4 (13.1–15.8)
Localized ($n = 13{,}515$)				
No bone metastases ($n = 13{,}508$)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Bone metastases, no SREs ($n = 237$)	11.9 (5.3–26.7)	10.0 (4.4–22.4)	12.3 (9.7–15.5)	12.5 (9.9–15.9)
Bone metastases and SREs ($n = 118$)	27.8 (10.3–74.6)	22.4(8.3–60.2)	14.2 (11.3–17.8)	15.5 (12.3–19.5)
Regional ($n = 12{,}452$)				
No bone metastases ($n = 12{,}447$)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Bone metastases, no SREs ($n = 663$)	7.9 (5.1–12.1)	7.9 (5.1–12.1)	9.5 (8.3–10.9)	10.4 (9.1–11.9)
Bone metastases and SREs ($n = 317$)	7.3 (3.6–14.7)	5.9 (2.9–11.9)	13.9 (12.2–15.8)	14.4 (12.6–16.3)
Distant ($n = 1{,}557$)				
No bone metastases ($n = 1{,}429$)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Bone metastases, no SREs ($n = 358$)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.8 (1.4–2.3)	2.0 (1.5–2.5)
Bone metastases and SREs ($n = 177$)	1.9 (1.4–2.5)	1.9 (1.4–2.5)	2.9 (2.3–3.6)	3.1 (2.4–3.8)

[a] Analyses performed on a subset of the entire breast cancer patient cohort (1999–2006)

[b] Adjusted for age and the Charlson Comorbidity Index

Table 6 Mortality rate ratios (MRRs) and 95% confidence intervals (CIs) among breast cancer patients with bone metastases and skeletal related events (SREs) compared with breast cancer patients with bone metastases and no SREs by age[a]

Age group	1-year Crude MRR (95% CI)	1-year Adjusted[b] MRR (95% CI)	>1 year Crude MRR (95% CI)	>1 year Adjusted[b] MRR (95% CI)
All patients	1.5 (1.3–1.7)	1.4 (1.2–1.7)	2.3 (1.9–2.8)	2.3 (1.9–2.8)
<60 years	1.6 (1.2–2.0)	1.5 (1.2–2.0)	2.3 (1.7–3.2)	2.4 (1.8–3.2)
60–69 years	1.4 (1.1–1.9)	1.4 (1.1–1.9)	2.2 (1.5–3.2)	2.2 (1.5–3.2)
70+ years	1.3 (1.0–1.7)	1.3 (1.0–1.7)	2.2 (1.5–3.2)	2.2 (1.5–3.3)

[a] Patients with bone metastases and no SREs are the reference group for each age group

[b] Adjusted for the Charlson Comorbidity Index

difference is not unexpected. Our median survival estimate of 16 months in breast cancer patients with bone metastases in the follow-up period is similar with another study that reported a median survival of 21 months after initial diagnosis of bone metastases or bone lesions subsequent to breast cancer [15]. Complications from bone metastases and SREs, such as bone pain, limited mobility, bone fractures, hypercalcaemia, and surgery [16], may account for some of the increased mortality in patients in our study. However, the differences between subgroups of breast cancer patients with and without bone metastases and with and without SREs are great enough to suggest that the occurrence of bone metastases and SREs may predict mortality.

Our findings raise the question of whether breast cancer patients with bone metastases and SREs should receive more aggressive anti-tumor therapy to prevent mortality. Our study did not account for bisphosphonate use among these women with breast cancer. Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption [17]; accordingly, it has been shown that use of bisphosphonates delay the time to a SRE among breast cancer patients [18]. Moreover, preclinical models have shown that bisphosphonates directly inhibit tumor growth and angiogenesis. Results from randomized trials, however, indicate that bisphosphonate treatments do not improve survival compared with placebo-treated patients [19, 20]. Clinical trials in women receiving adjuvant endocrine therapy, however, have shown a disease-free survival benefit with zoledronic acid [21, 22]. Although the clinical management of breast cancer, such as changes in systemic

therapy and the addition of osteoclast-inhibiting therapies may have changed over the course of our study, inclusion of year of diagnosis as a covariate in our analyses did not affect our estimates.

An advantage of our study is the use of a nationwide cohort with complete data on migration, vital status, and hospital admissions with low risk of referral and diagnostic bias. Ascertainment of breast cancer is thought to be virtually complete, because it is mandatory to register all breast cancer cases. In addition, health care is available to all residents, ensuring free access to hospitals and essentially eliminating all private in- or out-patient treatment for breast cancer.

A limitation of our study is our reliance on the DNPR diagnosis codes to identify bone metastases and SREs. In a previous study, the registration of bone metastases and SRE diagnoses secondary to breast cancer were under-ascertained in the DNPR. The completeness for bone metastases was 32%, and the positive predictive value was 86%. The completeness for SREs was 75%, and the positive predictive value was 75% [23]. Under-coding is most often seen in severely ill patients [24]. For example, very sick patients who have a number of comorbid conditions may have bone metastases and/or SREs moved to the end of the coding list or may not even include these conditions on their record. As such, the relative mortality estimates in our cohort study would likely lead to an underestimation of the underlying relative mortality [24]. Another limitation is that the Charlson Comorbidity Index [12], which is a widely used index that has been validated to predict mortality for a variety of outcomes, including breast cancer [25], may not be as effective in measuring comorbidity as clinical data [26]. Moreover, because the validity of the DNPR coding of metastasis to other vital organs, such as the brain, lung, or liver, were unknown, we did not control for these other sites of metastases. We would expect metastases to these sites to be associated with bone metastases and to have a major impact on mortality, and for this reason, the effects of these other sites of metastases may have provided more informative estimates. However, we stratified our analyses on stage of disease at diagnosis. Thus, distant disease with no bone metastases consists of breast cancer patients with metastases at sites other than bone.

The DCR recorded tumor spread as local, regional, or distant until 2003. This staging is expected to have a lower predicting ability than the TNM staging on mortality. This lower predicting ability is, however, not expected to explain the increased mortality we found in patients with bone metastases. We also did not have information on progressive or therapy refractory tumors, so we were not able to evaluate whether the poor prognosis in these patients explained the increased mortality in patients with bone metastases and SREs.

In conclusion, prognosis in breast cancer patients with bone metastases and SREs is poor compared to breast cancer patients with bone metastases and no SRE regardless of stage of disease at diagnosis and treatment. These findings suggest the potential for a mortality benefit from interventions for disease control that can prevent SREs in breast cancer patients with bone metastases.

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