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Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval

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ABSTRACT

Objectives: Since population-based data on prognostic factors affecting survival in patients with breast cancer with bone metastasis (BM) are currently limited, we conducted this nationwide retrospective cohort study to examine the prognostic role of disease stage at breast cancer diagnosis and length of BM-free interval (BMFI).

Setting: Denmark.

Participants: 2427 women with a breast cancer diagnosis between 1997 and 2011 in the Danish Cancer Registry and a concurrent or subsequent BM diagnosis in the Danish National Registry of Patients.

Primary and secondary outcome measures: Survival (crude) based on Kaplan-Meier method and mortality risk (crude and adjusted for age, year of diagnosis, estrogen receptor status and comorbidity) based on Cox proportional hazards regression analyses by stage of disease at breast cancer diagnosis and by length of BMFI (time from breast cancer to BM diagnosis), following patients from BM diagnosis until death, emigration or until 31 December 2012, whichever came first.

Results: Survival decreased with more advanced stage of disease at the time of breast cancer diagnosis; risk of mortality during the first year following a BM diagnosis was over two times higher for those presenting with metastatic versus localised disease (adjusted HR=2.12 (95% CI 1.71 to 2.62)). With respect to length of BMFI, survival was highest in women with a BMFI <1 year (ie, in those who presented with BM at the time of breast cancer diagnosis or were diagnosed within 1 year). However, among patients with a BMFI ≥1 year, survival increased with longer BMFI (1-year survival: 39.9% (95% CI 36.3% to 43.6%) for BMFI 1 to <3 years and 52.6% (95% CI 47.4% to 57.6%) for BMFI ≥5 years). This pattern was also observed in multivariate analyses.

Conclusions: Stage of disease at breast cancer diagnosis and length of BMFI appear to be important prognostic factors for survival following BM.

Strengths and limitations of this study

- The primary strength of this study is its use of a nationwide cohort with complete follow-up (because registration of all cancer cases in Denmark is mandatory, the ascertainment of breast cancer is virtually complete and availability of free access to hospitals through the National Health System essentially eliminates private inpatient or outpatient treatment for breast cancer).
- A major limitation of this study is its dependence on diagnosis codes in the Danish National Registry of Patients (DNRP) to identify bone metastases; a previous study on the validity of these codes in patients with breast cancer in the DNRP demonstrated high specificity, but only a moderate level of sensitivity.
- Other limitations include lack of clinical data on cancer therapy and missing data on progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) receptor status in half of the patients.

INTRODUCTION

Globally, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in women.[1] In Denmark, breast cancer represents 27% of all cancers and 16% of all cancer deaths in women.[2 3]

Approximately, 5% of women present with metastatic disease during breast cancer diagnosis[1 4] and bone is the most frequent site of metastatic lesions.[5] In population-based cohort studies of patients with newly diagnosed breast cancer, 1–2% have bone metastasis (BM) at diagnosis and another 5–6% are diagnosed to have BM within the next 5 years.[4 6] Given the high prevalence of breast cancer, the burden of metastatic bone disease secondary to this disease is important. In the USA, it was estimated that approximately 91 000 women were living with BM from breast cancer at the end of 2008.[7]

BM can cause considerable morbidity and reduced quality of life in women with advanced breast cancer.[8] The accelerated bone resorption associated with BM results in a range of skeletal-related events (SREs), including radiation or surgery to bone, pathological fractures and spinal cord compression. Studies have demonstrated that at least one of these SREs occurs in nearly 50% of patients with breast cancer with BM and is associated with a poor prognosis.[4 6 9] Still, the estimated life expectancy in this patient population is quite long. The rate of 1-year survival in patients with breast cancer with BM, with and without subsequent SREs, has been reported to be 40% and 59%, respectively.[9]

Although recent population-based research has improved our empirical understanding of the occurrence of metastatic bone disease secondary to breast cancer, and have quantified the impact of BM and subsequent SREs on breast cancer survival,[4 6 7 9] important gaps in the data remain. It is well recognised that patients with breast cancer with BM represent a diverse group in terms of survival, prognosis and risk of SREs.[10–17] However, real-world data on the prognostic value of specific patient, tumour and treatment characteristics following the onset of BM are limited. Given the heterogeneity of patients with breast cancer with BM, such information can assist in counselling patients, in determining appropriate treatment strategies and in suggesting new therapeutic targets.

We undertook this nationwide study in Denmark to examine the prognostic role of two specific factors affecting survival among patients with breast cancer with BM: (1) initial breast cancer stage at diagnosis; and (2) time between diagnoses of breast cancer and BM (ie, length of the BM-free interval (BMFI)).

METHODS

Study design and setting

This nationwide historical cohort study was conducted in Denmark (~2.8 million female inhabitants), whose entire population receives tax-supported healthcare from the Danish National Health Service. Since 1968, the Civil Registration System (CRS) has assigned to every Danish citizen a unique 10-digit civil registration number encoded for date of birth and gender.[18] The CRS also tracks address changes, dates of emigration and changes in vital status, and allows for unambiguous linkage among all Danish population-based administrative and health registries.[19]

The nationwide Danish Cancer Registry (DCR) has recorded all incident cases of cancer in Denmark since 1943.[20] The DCR collects data on patient demographics, tumour site, tumour morphology and tumour stage at diagnosis. The Danish National Registry of Patients (DNRP) has collected electronic data on hospitalisations since 1977 and on outpatient and emergency room visits since 1995.[21] For each hospital contact, the DNRP records dates of admission and discharge, surgical procedures, and up to 20 diagnoses coded by physicians at discharge as per the Danish version of the *International Classification of Diseases*, 10th revision (ICD-10).

Patients with breast cancer with BM

Our study included all women aged ≥18 years with an incident diagnosis of breast cancer in the DCR between 1 January 1997 and 31 December 2011, who also had a diagnosis of BM in the DNRP within 30 days before the breast cancer diagnosis (date of cancer diagnosis is generally recorded as month and year) or at any point after the breast cancer diagnosis. To ensure that BM originated from breast cancer, we excluded patients who had an additional incident cancer diagnosis at another site during the time period between the breast cancer and BM diagnoses.

Breast cancer stage and length of the BMFI

Disease stage at breast cancer diagnosis (recorded as the extent of tumour spread—localised (confined within the breast), regional (spread to the lymph nodes) or metastatic (spread to other organs)) was obtained from the DCR. Length of BMFI was calculated as the time from the breast cancer diagnosis in the DCR to the BM diagnosis in the DNRP. Length of BMFI was categorised as follows: <1 year (women who presented with BM at the time of breast cancer diagnosis were included in this category); 1 to <3; 3 to <5 and ≥5 years.

Other patient and clinical characteristics

Level of comorbidity was assessed using the Charlson Comorbidity Index (CCI)—a weighted index based on 19 chronic conditions.[22] A CCI score (excluding breast cancer and metastatic solid tumours) was calculated for each patient using all hospital diagnoses recorded in the DNRP during the 5 years prior to the diagnosis date of BM. CCI scores were categorised as low (score of 0); medium (score of 1–2) or high (score >2). We also determined whether there were distant metastases to other sites prior to or on the diagnosis date of BM. In addition, we obtained information from the DNRP on SREs occurring on or after the diagnosis date of BM, including radiation to bone, pathological fractures, surgery to bone and spinal cord compression. It is important to note that we assumed that administration of any conventional external radiation was radiation to

bone, since the code for radiation does not specify location and all patients in the study cohort had BM.

We used information from the Danish National Pathology Registry to assess immunohistochemistry expression among the breast cancer cases within ±90 days of their diagnosis (estrogen receptor (ER)-positive/negative, progesterone receptor (PR)-positive/negative and HER2 (human epidermal growth factor receptor 2)-positive/negative).[23] Data in the Pathology Registry are coded according to the Systematized Nomenclature of Medicine (http://www.snomed.org). We classified breast cancer cases according to ER status (positive vs negative) and into one of the following three subsets: (1) ER/PR-positive and HER2-negative; (2) HER2-positive (regardless of ER and PR status); and (3) ER/PR-negative and HER2-negative.

Mortality

We obtained data on mortality and migration from the CRS, which is updated daily. Each patient with breast cancer in our cohort was followed from the date of BM diagnosis until the date of death, emigration or until 31 December 2012, whichever came first.

Statistical analysis

Kaplan-Meier curves were constructed to describe survival by stage at the time of breast cancer diagnosis and by length of BMFI. On this basis, 1-year, 3-year and 5-year survival was estimated. For the estimates of 3-year survival, we restricted the study cohort to patients with breast cancer diagnosed with BM before the year 2010 to ensure the potential for at least 3 years of follow-up for each patient and limit the influence of changes related to calendar year (including changes in treatment over time) on length of BMFI and hence, on any analyses with length of BMFI as a covariate. Likewise, for the estimates of 5-year survival, we restricted the study cohort to those diagnosed with BM before the year 2008.

We also used Cox proportional hazards regression analyses and associated 95% CIs to assess whether the hazard (risk) of death in patients with breast cancer with BM during the first year after a diagnosis of BM varied by stage at the time of breast cancer diagnosis and by length of BMFI, after adjusting for the following other important characteristics: age at breast cancer diagnosis, time period of breast cancer diagnosis, ER status (as a surrogate for treatment received for breast cancer), level of comorbidity and presence/absence of other distant metastases at or prior to diagnosis of BM. For these analyses, patients with breast cancer were followed from the date of BM diagnosis until the date of death, emigration or the end of 1 year of follow-up, whichever came first. We restricted these analyses to the first year of follow-up because not only is this a clinically relevant time period following a diagnosis of BM, but it also minimises the impact of calendar year on length of BMFI and subsequent analyses involving comparisons based on length of BMFI, as previously discussed.

A complete list of codes for all primary study definitions is provided in online supplementary appendix 1. All analyses were conducted using SAS software (V.9.2; SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Patient characteristics

We identified 2427 women diagnosed with breast cancer in Denmark between 1997 and 2011, who also had a diagnosis of BM secondary to their breast cancer. Median follow-up from the time of BM diagnosis until the date of death, emigration or until 31 December 2012 was 1.12 years (IQR 0.24–2.73 years). Median time between the diagnoses of breast cancer and BM was 1.85 years (IQR 0.16–3.78 years).

The patient and clinical characteristics of the study cohort are presented overall and stratified by initial breast cancer stage at diagnosis in table 1 and by length of BMFI in table 2. Approximately half of patients initially presented with regional disease at the time of their breast cancer diagnosis. The remaining cases were classified as localised (17%), metastatic (25%) or unknown (8%) at the time of diagnosis. The distribution of patients across the BMFI groups was as follows: 38% had a BMFI of <1 year; 28% had a BMFI of 1 to <3 years; 19% had a BMFI of 3 to <5 years and 15% had a BMFI of ≥5 years. Patients who presented with more advanced disease stages at the time of breast cancer diagnosis progressed to BM more quickly. Among patients diagnosed with localised disease, the median time to BM was 3 years, while among those presenting with metastatic disease, the median time to BM was less than 1 year.

Over half of the study cohort was diagnosed with breast cancer at age 60 years or older, and the median age at diagnosis of BM was 63 years (range 28–97 years). Just over one-third (36%) of our study cohort were diagnosed with breast cancer in the earliest time period (1997–2001); 42% were diagnosed in 2002–2006; and 22% were diagnosed in 2007–2011. There was greater representation of metastatic disease at breast cancer diagnosis and shorter lengths of BMFI in women diagnosed with breast cancer in recent years. Importantly, this simply reflects the fact that these women had less time to develop BM and be included in our study compared with women diagnosed with breast cancer in earlier years. For example, women diagnosed with breast cancer in 1997–2001 had 10–14 years (1998–2011) for their development of BM, whereas women diagnosed with breast cancer in 2007–2011 had <1 to 4 years (2008–2011) for the development of BM. If women diagnosed with breast cancer in recent years been followed longer, more would have developed BM and been included in our study. Also, these patients would have been distributed more evenly across stage of disease at breast cancer diagnosis and length of BMFI, as seen in patients diagnosed with breast cancer in 1997–2001.

Approximately, 77% of women were diagnosed with ER-positive tumours. Additionally, the majority of women

Table 1 Study cohort of patients with breast cancer with BM (N=2427) by stage of disease at BC diagnosis

	Stage of disease at BC diagnosis				
	Localised BC N=420 N (%)	Regional BC N=1204 N (%)	Metastatic BC N=606 N (%)	Unknown N=197 N (%)	Overall N=2427 N (%)
Age at BC diagnosis (years)					
25–49	94 (22%)	319 (27%)	89 (15%)	30 (15%)	532 (22%)
50–59	103 (25%)	340 (28%)	129 (21%)	45 (23%)	617 (25%)
60–69	120 (29%)	321 (27%)	201 (33%)	56 (28%)	698 (29%)
≥70	103 (25%)	224 (19%)	187 (31%)	66 (34%)	580 (24%)
Time period of BC diagnosis					
1997–2001	211 (50%)	492 (41%)	135 (22%)	36 (18%)	874 (36%)
2002–2006	161 (38%)	528 (44%)	242 (40%)	80 (41%)	1011 (42%)
2007–2011	48 (11%)	184 (15%)	229 (38%)	81 (41%)	542 (22%)
Hormone receptor and HER2 status					
ER-positive	313 (75%)	890 (74%)	500 (83%)	156 (79%)	1859 (77%)
ER-negative	99 (24%)	295 (25%)	98 (16%)	35 (18%)	527 (22%)
Unknown	8 (2%)	19 (2%)	8 (1%)	6 (3%)	41 (2%)
ER/PR-positive and HER2-negative	61 (15%)	200 (17%)	180 (30%)	50 (25%)	491 (20%)
HER2-positive (any ER/PR status)	46 (11%)	216 (18%)	97 (16%)	34 (17%)	393 (16%)
ER/PR-negative and HER2-negative	42 (10%)	128 (11%)	51 (8%)	17 (9%)	238 (10%)
Unknown	271 (65%)	660 (55%)	278 (46%)	96 (49%)	1305 (54%)
Charlson Comorbidity Index score					
0	316 (75%)	925 (77%)	476 (79%)	145 (74%)	1862 (77%)
1–2	87 (21%)	245 (20%)	111 (18%)	42 (21%)	485 (20%)
>2	17 (4%)	34 (3%)	19 (3%)	10 (5%)	80 (3%)
Median age (range) at BM diagnosis	64 years (28–92)	62 years (28–97)	65 years (28–95)	67 years (34–92)	63 years (28–97)
Length of BMFI					
0 to <1 year	79 (19%)	264 (22%)	491 (81%)	84 (43%)	918 (38%)
1 to <3 years	131 (31%)	426 (35%)	71 (12%)	58 (29%)	686 (28%)
3 to <5 years	108 (26%)	281 (23%)	38 (6%)	35 (18%)	462 (19%)
≥5 years	102 (24%)	233 (19%)	6 (1%)	20 (10%)	361 (15%)
25th centile	1.43 years	1.16 years	0.02 years	0.12 years	0.16 years
Median	3.01 years	2.54 years	0.07 years	1.52 years	1.85 years
75th centile	4.87 years	4.34 years	0.44 years	3.30 years	3.78 years
Other metastases recorded at or before BM diagnosis	200 (48%)	691 (57%)	296 (49%)	105 (53%)	1292 (53%)
Skeletal-related events at BM diagnosis*					
Radiation to bone	81 (19%)	258 (21%)	124 (20%)	21 (11%)	484 (20%)
Pathological fracture	11 (3%)	41 (3%)	14 (2%)	1 (1%)	67 (3%)
Spinal cord compression	12 (3%)	33 (3%)	12 (2%)	6 (3%)	63 (3%)
Surgery to bone	10 (2%)	29 (2%)	19 (3%)	5 (3%)	63 (3%)

*Categories not mutually exclusive.
BC, breast cancer; BM, bone metastasis; BMFI, bone metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

had no additional underlying disease recorded in the 5 years before their diagnosis of BM. Evidence of most types of SREs on diagnosis of BM was also relatively infrequent; 20% of patients had documentation of radiation, but 3% had pathological fracture, 3% had spinal cord compression and 3% had surgery to bone. We were unable to categorise over half of the cohort into one of the three hormone receptor and HER2 status groupings (ER/PR-positive and HER2-negative; HER2-positive (regardless of ER and PR status); and ER/PR-negative and HER2-negative), because only 53% of cases had data on PR status and 43% had information on HER2 status.

Survival

Survival was relatively poor in this cohort of patients with breast cancer with BM (1-year, 3-year and 5-year survival: 52.4% (95% CI 50.4% to 54.4%), 26.4% (95% CI 24.5% to 28.3%) and 13.1% (95% CI 11.4% to 14.8%), respectively; table 3). Survival was highest in women who had localised disease at their breast cancer diagnosis (1-year survival: 59.0% (95% CI 54.2% to 63.6%), and 5-year survival: 19.6% (95% CI 15.3% to 24.5%)) compared with those diagnosed with regional or metastatic disease (table 3). After adjusting for important prognostic factors, patients who presented with metastatic disease at

Table 2 Study cohort of patients with BC with BM (N=2427) by length of BM-free interval

	Length of BM-free interval				
	0 to <1year N=918 N (%)	1 to <3 years N=686 N (%)	3 to <5 years N=462 N (%)	≥5 years N=361 N (%)	Overall N=2427 N (%)
Age at BC diagnosis (years)					
25–49	146 (16%)	158 (23%)	126 (27%)	102 (28%)	532 (22%)
50–59	209 (23%)	187 (27%)	111 (24%)	110 (30%)	617 (25%)
60–69	277 (30%)	197 (29%)	145 (31%)	79 (22%)	698 (29%)
≥70	286 (31%)	144 (21%)	80 (17%)	70 (19%)	580 (24%)
Time period of BC diagnosis					
1997–2001	214 (23%)	215 (31%)	198 (43%)	247 (68%)	874 (36%)
2002–2006	377 (41%)	311 (45%)	209 (45%)	114 (32%)	1011 (42%)
2007–2011	327 (36%)	160 (23%)	55 (12%)	0 (0%)	542 (22%)
Stage of disease at BC diagnosis					
Localised	79 (9%)	131 (19%)	108 (23%)	102 (28%)	420 (17%)
Regional	264 (29%)	426 (62%)	281 (61%)	233 (65%)	1204 (50%)
Metastatic	491 (53%)	71 (10%)	38 (8%)	6 (2%)	606 (25%)
Unknown	84 (9%)	58 (8%)	35 (8%)	20 (6%)	197 (8%)
Hormone receptor and HER2 status					
ER-positive	714 (78%)	474 (69%)	367 (79%)	304 (84%)	1859 (77%)
ER-negative	188 (20%)	199 (29%)	89 (19%)	51 (14%)	527 (22%)
Unknown	16 (2%)	13 (2%)	6 (1%)	6 (2%)	41 (2%)
ER/PR-positive and HER2-negative	233 (25%)	135 (20%)	84 (18%)	39 (11%)	491 (20%)
HER2-positive (any ER/PR status)	156 (17%)	131 (19%)	72 (16%)	34 (9%)	393 (16%)
ER/PR-negative and HER2-negative	90 (10%)	91 (13%)	41 (9%)	16 (4%)	238 (10%)
Unknown	439 (48%)	329 (48%)	265 (57%)	272 (75%)	1305 (54%)
Charlson Comorbidity Index score					
0	717 (78%)	521 (76%)	341 (74%)	283 (78%)	1862 (77%)
1–2	173 (19%)	141 (21%)	104 (23%)	67 (19%)	485 (20%)
>2	28 (3%)	24 (4%)	17 (4%)	11 (3%)	80 (3%)
Median age (range) at BM diagnosis	64 years (28–95)	62 years (28–91)	63 years (29–97)	65 years (36–92)	63 years (28–97)
Other metastases recorded at or before BM diagnosis	437 (48%)	352 (51%)	283 (61%)	220 (61%)	1292 (53%)
Skeletal-related events at BM diagnosis*					
Radiation to bone	159 (17%)	140 (20%)	112 (24%)	73 (20%)	484 (20%)
Pathological fracture	10 (1%)	26 (4%)	14 (3%)	17 (5%)	67 (3%)
Spinal cord compression	13 (1%)	19 (3%)	18 (4%)	13 (4%)	63 (3%)
Surgery to bone	18 (2%)	24 (4%)	11 (2%)	10 (3%)	63 (3%)

*Categories not mutually exclusive.
BC, breast cancer; BM, bone metastasis; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

breast cancer diagnosis had over twice the risk of death during the first year following a diagnosis of BM compared with those who presented with localised disease (adjusted HR=2.12 (95% CI 1.71 to 2.62); table 4).

With respect to length of BMFI, survival was highest in women who either presented with BM or were diagnosed with BM within the first year after breast cancer diagnosis (1-year and 5-year survival: 64.4% (95% CI 61.2% to 67.4%) and 21.0% (95% CI 17.9% to 24.2%), respectively; table 3). After the first year, survival increased with longer length of BMFI (1-year survival: 39.9% (95% CI 36.3% to 43.6%) vs 52.6% (95% CI 47.4% to 57.6%) in women diagnosed with BM 1 to <3 vs ≥5 years after breast cancer diagnosis; 5-year survival: 6.7% (95% CI 4.7% to 9.2%) vs 8.6% (95% CI 4.8% to 13.7%) in women diagnosed with BM 1 to <3 vs ≥5 years after breast cancer diagnosis (table 3)). This pattern was also observed in the multivariate analyses (table 5).

DISCUSSION

In this nationwide historical cohort study of 2427 Danish women with metastatic bone disease secondary to breast cancer, 1-year survival was just over 52%. Approximately 13% survived 5 years after their diagnosis of BM. More advanced initial stage of disease at breast cancer diagnosis was associated with a higher risk of death in these patients, independent of age, time period of breast cancer diagnosis, ER status, level of comorbidity, presence of other metastases at or prior to diagnosis of BM and length of BMFI. Shorter BMFI was also independently associated with decreased survival among patients

Table 3 Survival in patients with BC with bone metastases (N=2427) by stage of disease at BC diagnosis and by length of bone metastasis-free interval

	1-year survival % (95% CI)	3-year survival* % (95% CI)	5-year survival† % (95% CI)
Stage of disease at BC diagnosis			
Localised	59.0 (54.2 to 63.6)	35.2 (30.2 to 40.2)	19.6 (15.3 to 24.5)
Regional	50.7 (47.9 to 53.5)	25.0 (22.4 to 27.7)	12.4 (10.2 to 14.9)
Metastatic	52.0 (47.9 to 55.9)	22.8 (19.3 to 26.6)	9.5 (6.9 to 12.6)
Unknown	49.7 (42.6 to 56.5)	27.3 (20.2 to 34.9)	13.3 (7.3 to 21.2)
Length of bone metastasis-free interval (years)			
<1	64.4 (61.2 to 67.4)	37.8 (34.4 to 41.2)	21.0 (17.9 to 24.2)
1 to <3	39.9 (36.3 to 43.6)	16.4 (13.5 to 19.5)	6.7 (4.7 to 9.2)
3 to <5	47.0 (42.4 to 51.4)	18.5 (14.7 to 22.6)	7.4 (4.7 to 10.9)
≥5	52.6 (47.4 to 57.6)	25.7 (20.5 to 31.3)	8.6 (4.8 to 13.7)
Overall	52.4 (50.4 to 54.4)	26.4 (24.5 to 28.3)	13.1 (11.4 to 14.8)

*Restricted to patients with bone metastasis diagnosed prior to 2010.
†Restricted to patients with bone metastasis diagnosed prior to 2008.
BC, breast cancer.

with breast cancer who were diagnosed with BM ≥1 year following their breast cancer diagnosis.

Our finding that initial stage of disease at breast cancer diagnosis represents an important prognostic factor for survival among patients with breast cancer with BM is consistent with the published literature on this topic.[12 13 15 17] Kuru *et al*[13] studied the medical records of 470 patients with breast cancer from a single institution in Turkey who had T1–T3 tumours and developed distant skeletal or visceral metastases following modified radical mastectomy. In multivariate analyses, stage IIIC disease (vs stage I disease) at breast cancer presentation was associated with a nearly twofold increase in mortality after distant metastasis. Another single-institution Turkish study specifically focused on BM produced similar findings. The study included data on 248 patients with breast cancer with localised or regional stage disease whose first distant metastasis after surgical treatment was in the skeleton (with or without visceral metastases).[17] Multivariate modelling of prognostic factors for survival after BM demonstrated that more advanced disease stage was independently associated with increased mortality risk. These results are consistent with older but similar research on patients with metastatic breast cancer in the UK and in the USA.[14 15] Our study extends these previous investigations, since our cohort included all women with metastatic bone disease secondary to breast cancer, regardless of initial stage of disease, presence of metastasis to other distant sites, and first-line treatment received.

We also found that survival was longest among patients diagnosed with BM at the time of breast cancer presentation or within the following year. But among patients diagnosed with BM at least 1 year following their initial breast cancer diagnosis, longer BMFI was associated with decreased mortality risk. Previous research on this association has produced conflicting results.[10 12–17] For example, in a study of 648 patients with consecutive metastatic breast cancer treated at a German academic institution between 1977 and 1985, shorter BMFI (<2 vs ≥2 years) was associated with a nearly twofold increased risk of death in patients whose site of first metastasis was the bone.[14] Conversely, in the recent Turkish study of patients with breast cancer with BM, length of BMFI (≤12 vs >12 months) did not show prognostic significance in multivariate modelling.[17]

In contrast to our study, the majority of studies examining the relationship between length of the metastasis-free interval and survival in patients with metastatic breast cancer have excluded women who presented with distant metastases at breast cancer diagnosis. Thus, most

Table 4 Crude and adjusted associations between stage of disease at breast cancer diagnosis and mortality during the first year following a diagnosis of bone metastasis in patients with breast cancer (N=2427)

	Crude HR (95% CI)	Adjusted HR* (95% CI)
Stage of disease at breast cancer diagnosis		
Localised	Reference	Reference
Regional	1.29 (1.08 to 1.52)	1.34 (1.13 to 1.60)
Metastatic	1.23 (1.02 to 1.49)	2.12 (1.71 to 2.62)
Unknown	1.33 (1.03 to 1.70)	1.55 (1.20 to 2.00)

*Adjusted for age at breast cancer diagnosis, time period of breast cancer diagnosis, estrogen receptor status, level of comorbidity, other metastases recorded at or before bone metastasis diagnosis and length of bone metastasis-free interval.

Table 5 Crude and adjusted associations between length of bone metastasis-free interval and mortality during the first year following a diagnosis of bone metastasis in patients with breast cancer (N=2427)

	Crude HR (95% CI)	Adjusted HR* (95% CI)
Length of bone metastasis-free interval (years)		
<1	Reference	Reference
1 to <3	2.00 (1.73 to 2.31)	2.64 (2.23 to 3.12)
3 to <5	1.74 (1.48 to 2.06)	2.45 (2.02 to 2.97)
≥5	1.47 (1.23 to 1.77)	2.21 (1.77 to 2.76)

*Adjusted for age at breast cancer diagnosis, time period of breast cancer diagnosis, estrogen receptor status, level of comorbidity, other metastases recorded at or before bone metastasis diagnosis and stage of disease at breast cancer diagnosis.

previous work focused only on women with recurrent breast cancer. To our knowledge, only one other relevant study was similar to ours in its inclusion of women with metastatic bone lesions at the time of breast cancer diagnosis as well as women who developed BM later in their disease course. In that study, the medical records of 82 Japanese patients with breast cancer with metastasis initially confined to bone were reviewed.[16] Women with a longer BMFI (≥24 months) or a BMFI of 0 (BM at time of breast cancer diagnosis) demonstrated longer survival compared with those who had a shorter BMFI (<24 months), but this association was not statistically significant. Estimates of 1-year and 5-year survival from this study were 100% and 37%, respectively, in 12 patients with BMFI of 0; 73% and 21%, respectively, in 15 patients with BMFI <24 months; and 84% and 27%, respectively, in 55 patients with BMFI ≥24 months.[16] Although the study was relatively small and included only women diagnosed with breast cancer prior to 1988, the nature of the relationship between length of BMFI and survival is consistent with that observed in our study.

It is possible that the prolonged survival we observed among patients with a BMFI of <1 year at least partly results from occurrence of BM that are asymptomatic or less severe than those diagnosed later. There is likely to be intensive follow-up during the first year after a diagnosis of breast cancer, which could uncover these types of BM. Consequently, longer survival time observed in these patients could simply reflect lead-time bias. This hypothesis is supported by our finding that the proportion of patients presenting with at least one SRE at the time of BM diagnosis was lowest in those with a BMFI of <1 year. Alternatively, detection of bone metastases in asymptomatic patients could allow for early and targeted therapy, leading to better outcomes.

It is also possible that patients with breast cancer who present with BM at the time of breast cancer diagnosis may have an indolent, chronic disease course with prolonged survival, particularly when the metastatic breast cancer remains confined to the skeletal system.[24–26] We attempted to explore this premise by examining the distribution of ER, PR and HER2 status in the patients with breast cancer by length of BMFI, given that ER-positive tumours are generally more indolent and less aggressive but more likely to metastasise to bone.[27] We found that there was no clear pattern in the proportion of ER-positive breast cancer tumours by length of BMFI. Unfortunately, approximately half of the patients lacked key information on PR and HER2 status needed for a more comprehensive analysis, and the data did not appear to be missing at random. Missing PR or HER2 status was relatively more frequent in women who presented with earlier stages of disease at breast cancer diagnosis (65% of women who presented with localised disease at their breast cancer diagnosis had missing PR or HER2 status vs 46% who presented with metastatic disease) and in those with a longer BMFI (75% of women who were diagnosed with BM at least 5 years after their breast cancer diagnosis had missing PR or HER2 status vs 48% who presented with or were diagnosed with BM within the first year after breast cancer diagnosis).

The primary strength of our study is its use of a nationwide cohort with complete follow-up. Given mandatory registration of all cancer cases in Denmark, ascertainment of breast cancer is virtually complete. As well, availability of free access to hospitals through the National Health System essentially eliminates private inpatient or outpatient treatment for breast cancer.

A major study limitation was our dependence on diagnosis codes in the DNRP to identify BM. The validity of recorded ICD-10 diagnosis codes of BM in patients with breast cancer in the DNRP was previously characterised using data from medical chart reviews as the reference.[28] Although the DNRP's specificity was 0.99 (95% CI 0.93 to 1.00), the sensitivity was only 0.32 (95% CI 0.13 to 0.57). Possible explanations for this high level of undercoding include lack of incentive to code BM in patients who are believed to have a poor prognosis, failure to clinically recognise BM, and non-mandatory reporting of BM in Denmark.[28] As we examined relative mortality exclusively among patients with BM, it is unlikely that undercoding could significantly bias our estimates or modify our conclusions.

Several additional concerns must be noted. Since metastases to other distant sites have an effect on mortality and are associated with initial stage of disease at breast cancer diagnosis and possibly length of BMFI, we attempted to control for presence of other metastases prior to or at the time of diagnosis of BM. However, the validity of the DNRP coding of metastases to other distant sites is unknown. Also, although we measured the level of comorbidity using the CCI, which has been

well studied and validated to predict mortality in patients with breast cancer,[29] we were unable to include additional clinical data that may have informed our analyses, such as information on cancer-directed therapy (beyond using ER status as a proxy), detailed data on pathological node status, tumour grade, TNM staging and menopausal status.

In conclusion, this nationwide cohort study of patients with breast cancer with BM in Denmark showed that initial stage of disease at breast cancer diagnosis and length of BMFI are important prognostic factors for survival following BM. A thorough understanding of these prognostic factors can help identify subsets of patients likely to benefit from certain treatments or inspire new therapeutic strategies.

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