Breast Cancer Res Treat (2018) 167:517–528
https://doi.org/10.1007/s10549-017-4510-3

EPIDEMIOLOGY

Breast cancer recurrence, bone metastases, and visceral metastases in women with stage II and III breast cancer in Denmark

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Received: 10 August 2017 / Accepted: 12 September 2017 / Published online: 25 September 2017

Abstract
Purpose We developed and validated algorithms to identify metastases and breast cancer recurrence in Danish medical registries. We computed the incidence rate (IR) and hazard ratios (HRs) to evaluate predictors of these outcomes in stage II/III breast cancer patients.
Methods We included all women in Denmark diagnosed during 1999–2011 with regional or stage II/III breast cancer. Demographic, tumor, and treatment data were ascertained from population-based health registries. To facilitate diagnostic work-up of the primary cancer, follow-up began 180 days after diagnosis and continued until recurrence/metastases, death, or 31 December 2012, whichever occurred first. We computed the positive predictive values (PPVs) of recurrence, bone metastases, and visceral metastases using medical records as a gold standard. We calculated the cumulative incidence, IR per 10,000 person years, and used Cox regression to compute the HRs and associated 95% confidence intervals (95% CI) for each outcome.
Results Among 23,478 patients, 7073 had regional stage and 16,405 had stage II/III breast cancer. The PPV for recurrence was 72.6% (95% CI 59.3, 83.3%). The PPVs for bone and visceral metastases were 92.3% (95% CI 69.3–99.2%) and 70.8% (95% CI 51.1, 85.9%), but had low sensitivity. Five-year cumulative incidence of recurrence, bone metastases, and visceral metastases were 18.4, 2.2, and 5.2%, with corresponding 5-year IRs of 540 (95% CI 524, 557), 60 (95% CI 55, 65), and 144 (95% CI 136, 152), respectively. Predictors of recurrence and metastases included age, stage, hormone receptor status, and cancer treatment.
Conclusion Our algorithms show moderate to high PPVs for recurrence and metastases. The IRs of metastases were lower compared with other registry-based cohort studies, so may be underestimated in Danish registries.

Keywords Breast cancer · Breast cancer recurrence · Incidence rate · Bone metastases · Visceral metastases · Mortality

Introduction

Breast cancer accounts for 23% of female cancers and is the leading cause of cancer-related death among women worldwide [1]. Each year, about 4500 women are diagnosed with breast cancer in Denmark [2]. Survival has improved over time due to earlier detection and more effective therapies [3]. Nonetheless, the increasing number of survivors requires better understanding of the breast cancer clinical course and survivorship, particularly the occurrence of disease recurrence, bone metastases, and visceral metastases [4, 5].

Women with non-metastatic disease at diagnosis in the UK and Canada have 6–8% incidence of bone metastases within the first 5 years of diagnosis [6, 7], and about 14% incidence of bone metastases by 15 years of follow-up. These estimates stem from a UK-based study, which incorporated registry-based data linking the Clinical Practice Research Database (CPRD) to the National Cancer Registry combining Read codes with International Classification of Disease codes [6]. The Canadian data are based

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on a single-center study incorporating questionnaire- and interview-based data assembled in the Henrietta Banting Breast Centre database, as well as follow-up information ascertained from medical record review and pathology reports [7]. In contrast, a registry-based cohort study of stage I–IV breast cancer patients in Denmark suggested that only 3.6% of patients developed bone metastases in a median follow-up of 3.5 years. This estimate is lower than that reported in countries with tax-supported healthcare, similar to Canada and the United Kingdom [6, 7]; therefore the incidence of bone metastases is likely underestimated in the Danish National Patient Registry (DNPR) [8, 9]. The underestimation of bone metastases in breast cancer as recorded using International Classification of Diseases, 10th edition (ICD-10) coding in the DNPR has been shown to be associated with low sensitivity 32% (95% confidence interval [CI] 13, 57%) but high specificity 99% (95% CI 93, 100%) [9].

Clinical and pathological factors correlate with the risk of breast cancer recurrence, bone metastases, and visceral metastases. The Canadian study suggested that younger patient age, estrogen receptor-positive (ER+) disease, larger tumor size, higher tumor grade, lymph node involvement at diagnosis, and receipt of adjuvant tamoxifen therapy correlated with increased risk of bone metastases [7]. Specifically, women with ER+ disease were more likely to develop metastases to the bone before the viscera compared with those with ER-negative (ER−) tumors [7].

Nonetheless, studies investigating breast cancer recurrence, bone metastases, and visceral metastases report limited information on cancer-directed treatment and breast cancer subtypes [ER, progesterone receptor (PR), and HER2 status], which are important for breast cancer prognosis [6, 10, 11]. Studies have also been restricted to subgroups of patients, such as those receiving particular treatments, those participating in clinical trials, or those diagnosed and treated at single institutions [6, 9–11].

We therefore used Danish population-based and medical registries to develop and validate algorithms to identify breast cancer recurrence, bone metastases, and visceral metastases. Our study's overall aim was to provide a better understanding of recurrence and incidence (incidence rates and proportions) and predictors of recurrence, bone metastases, and visceral metastases in a historical cohort of women initially diagnosed with non-metastatic breast cancer.

Methods

This study was approved by the Danish Data Protection Agency (J.nr. 2014-41-3250) and the Danish Health Board (J.nr. 3-3013-670/1).

Source population and data collection

The source population included women residing in Denmark from 1 January 1999 through 31 December 2011 who were (a) registered in the Danish Civil Registration System (CRS) and assigned a civil personal registration (CPR) number and (b) at least 18 years of age. The Danish National Health Service provides tax-supported healthcare for the entire population, guaranteeing unfettered access to all hospitals and primary medical care. The unique CPR numbers, assigned to every Danish citizen and resident since 1968, encode gender and date of birth and allow for individual-level electronic record linkage among multiple databases [12, 13].

From this source population, we identified all women with an incident diagnosis of breast cancer registered in the Danish Cancer Registry (DCR) between 1 January 1999 and 31 December 2011, with follow-up through 2012 (see Appendix for codes). The DCR has maintained records of patients diagnosed with malignant neoplasms in Denmark since 1943. The completeness and validity of DCR data are estimated at 95–98% [14, 15]. We restricted our study population to women with an incident diagnosis of regional stage (according to Summary Stage, available through 2003) or American Joint Committee on Cancer (AJCC) stage II and III (available from 2004 onwards) breast cancer. We excluded women with a history of any cancer before breast cancer diagnosis, except non-melanoma skin cancer (Appendix).

We used the CPR numbers to link across the registries. The DNPR has recorded data on inpatients since 1977 and data on outpatient and emergency room visits since 1995. This registry contains admission and discharge diagnoses, surgical procedures performed, and up to 20 discharge diagnoses recorded according to the ICD-10. Surgical procedures in the DNPR are coded according to the Nordic Classification of Surgical Procedures (NCSP). In 2004, the DNPR began to register information on cancer-directed treatments [16]. We also used the CPR numbers to link to the National Pathology Registry which was established in 1997 [17]. It routinely records information on all pathology examinations conducted in Denmark. For breast cancer, ER testing became routine in 1999. PR testing began in 2006 and phased out of clinical practice about 2011. HER-2 testing began in 2006. The Civil Registration System (CRS) was established in 1968 and is updated daily [13]. The CRS provided information on vital status, immigration, emigration, and death.

Validation of study outcomes

For the validation study, we conducted a detailed medical record review led by clinically trained and Danish registry-

certified abstractors (nurses) restricted to patients diagnosed between 2004 and 2010 and treated at two large teaching hospitals in the Central and Northern Denmark Regions (Aalborg University Hospital and Aarhus University Hospital). We included 155 patients in the validation study sample. Twenty percent of patients were diagnosed during 2004–2006; then approximately 20% were diagnosed each subsequent year up to 2011. The medical record review mainly included patients diagnosed between 2007 and 2010, to reflect the time period when HER2 testing was conducted in Denmark. For each hospital, we initially sampled 100 patients using a balanced design, which simultaneously stratified on year of diagnosis and hospital, and then selected the first ten patients in each stratum. The remaining patients were sampled into the validation study based on whether or not they had the outcome of interest (breast cancer recurrence, bone metastases, and/or visceral metastases as identified in the registries) in order to ensure sufficient patient numbers to calculate positive predictive values (PPVs).

Covariates

From the DCR we also retrieved information on age and cancer stage at diagnosis. As we lacked information on age of onset of menopause, we assumed post-menopausal status for women age $\geq$55 years. We retrieved information on cancer surgery (mastectomy and breast-conserving surgery) and cancer-directed treatments from the DNPR. All treatments were recorded as a yes/no variable denoting treatment received/not received within 180 days of the initial breast cancer diagnosis.

We obtained information from the DNPR on potentially confounding comorbid diseases diagnosed up to 10 years before breast cancer diagnosis and summarized them using a modified version of the Charlson Comorbidity Index (CCI), excluding breast cancer [18]. The CCI score for individual women (0 = no comorbidity; 1 = mild comorbidity; 2 = moderate comorbidity; 3+ = severe comorbidity) was calculated based on the presence of comorbid disease up to 10 years before the date of initial breast cancer diagnosis (Appendix).

Study outcomes

Breast cancer recurrence was defined as (1) tumor growth at or near the site of the original tumor and in the same organ, (2) metastases to tissue adjacent to the original tumor site, or (3) metastases to a distant organ (therefore breast cancer recurrence also incorporated bone and visceral metastases). The algorithm was a modified version of an existing algorithm (Appendix) [19].

We identified patients who developed *bone metastases* using the DNPR, by retrieving information on diagnosis of bone metastases (Appendix 1), as well as on the diagnosis of skeletal-related events (including surgical procedures for bone fractures) [8, 9]. *Visceral metastases* were also identified from the DNPR (Appendix).

Disease-free survival was defined as the time from the date of initial breast cancer diagnosis plus 180 days (implemented to avoid immortal person-time bias [20] due to the start time of our breast cancer recurrence algorithms) until the date of first treatment failure. *Treatment failure* was defined as breast cancer recurrence (therefore including bone or visceral metastases), a new primary breast cancer, or death from any cause (other new primary non-breast cancers were not included in the definition of disease-free survival).

Statistical analyses

We calculated the frequency and proportion of patients according to demographic, tumor, and treatment characteristics.

In the validation study, information from the medical records was considered the gold standard. We computed the positive predictive value (PPV) and 95% confidence interval (95% CI) for breast cancer recurrence, bone and visceral metastases, and patient and clinical variables, including menopausal status, lymph node involvement, ER, PR, and HER2 status, and receipt of chemotherapy. The PPV was defined as the number of patients with a particular parameter confirmed by the medical record review divided by the total number of patients in the validation cohort who had the characteristic documented in the DNPR. We computed sensitivity as the proportion of the patients with the outcome documented in medical records who also had a record of that outcome in the DNPR. We computed specificity as the proportion of patients without the outcome documented in their medical records who also had no record of that outcome in the DNPR.

Cumulative incidence proportions were calculated using the number of diagnoses of interest (e.g., bone metastases) as the numerator over a denominator that included all women at risk during a given time period, with time of follow-up specified (e.g., 1, 2, 5 years). We calculated cumulative incidence as the first occurrence of a study outcome, and subsequently calculated the cumulative incidence of each study outcome, accounting for competing risk of death. We also assessed the chronology of the occurrence of metastatic disease (visceral versus bone). Follow-up began 180 days after breast cancer diagnosis and continued to the outcome of interest, death, emigration, or 31 December 2012, whichever occurred first.

We used Cox regression models to calculate hazards ratios (HRs) for age, menopausal status, cancer stage, ER status, PR status, HER2 status, comorbidity, primary surgery type, and receipt of chemotherapy, radiotherapy, endocrine therapy, and anti-HER2 therapy as predictors of breast cancer recurrence, bone metastases, and visceral metastases.

Multiple imputation

We carried out sensitivity analyses in which AJCC stage was imputed for women diagnosed during 1999–2003. Variables that informed the imputation included breast cancer recurrence, comorbidity, age, surgery type, ER status, PR status, HER2 status, cancer stage, and receipt of chemotherapy, endocrine therapy, radiotherapy, or anti-HER2 treatment.

Bias analysis

To account for misclassification observed in the validation study, we conducted a bias analysis to compute the expected cumulative incidence proportions of breast cancer recurrence, bone metastases, and visceral metastases using the sensitivity and specificity estimates from the validation study. The observed incidence can be expressed as:

$$\hat{I} = \Delta I + I_{\mathrm{FP}},$$

where $\hat{I}$ = observed incidence proportion, Δ = sensitivity, I = true incidence proportion, and I_{FP} = false positive rate (equal to 1-specificity). Rearranging the terms, we obtain an expression for the true or expected incidence proportion:

$$I = \frac{\hat{I} - I_{\mathrm{FP}}}{\Delta}.$$

All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC).

Results

Among 23,478 breast cancer patients diagnosed with regional stage or stage II or III disease from 1999 through 2011, 80% were 50 years or older at diagnosis (Table 1). Overall, 73% of patients had ER+ tumors, 18% ER− tumors, and 9% unknown ER status. Among those diagnosed after 2006 (when HER2 testing became routine), 62% of patients were HER2−, 24% HER2+, and 13% had no registered HER2 status. About half of the cohort underwent mastectomy and 43% received breast-conserving surgery. Within the first 180 days following diagnosis, a total of 35% of patients received chemotherapy, <1% in a neoadjuvant setting. Endocrine therapy was given to 45% of patients and radiotherapy to 42% of patients. Overall, 18% of patients had comorbid disease at diagnosis (CCI score > 0).

We noted high PPV, NPV, sensitivity, and specificity for most prognostic and treatment variables (menopausal status, lymph node involvement, ER, PR, and HER2 status, and chemotherapy) (Table 2). The PPV for breast cancer recurrence was 72.6% (95% CI 59.3, 83.3%), with high sensitivity, specificity, and NPV. The PPV for bone metastases was high at 92.3% (95% CI 69.3, 99.2%), but sensitivity was low at 40.0% (95% CI 24.1, 57.8%). The PPV for visceral metastases was 70.8% (95% CI 51.1, 85.9%), but sensitivity was low at 46.0% (95% CI 30.7, 61.8%).

Figures 1 and 2 show the cumulative incidences of breast cancer recurrence, bone metastases, and visceral metastases, up to 5 years after breast cancer diagnosis and by calendar period of diagnosis (1999–2003, 2004–2007, and 2008–2011). The highest 5-year cumulative incidence of recurrence and bone metastases was evident among patients diagnosed in the earliest period. The cumulative incidence curves for visceral metastases overlapped for all three diagnostic periods, with highest incidence among patients diagnosed in 1999–2003, and little change among patients diagnosed from 2004 onwards.

The 5-year cumulative incidence of breast cancer recurrence was 18.4%, with a corresponding IR of 540.2 per 10,000 person years (95% CI 524.2, 556.6) (Table 3). The 5-year cumulative incidence of mortality was 18.8%, corresponding to an IR of 507.3 per 10,000 person years (95% CI 492.5, 522.5). The cumulative incidence of visceral metastases was higher than that of bone metastases (5.2% vs. 2.2% at 5 years, corresponding to 5-year IRs of 143.9 per 10,000 person years (95% CI 136.0, 152.2) and 60.0 per 10,000 person years (95% CI 54.9, 65.4), respectively). Given the low sensitivity of our algorithms in identifying bone and visceral metastases in the Danish registries, we also computed the expected incidence proportion and IR at 5 years for bone metastases, at 6.55 and IR = 150.0 per 10,000 person years, and for visceral metastases, at 12.95 and IR = 313.1 per 10,000 person years, respectively.

We observed higher cumulative incidence and IRs of bone metastases among patients with ER+/PR+/HER2+ disease, compared with those with triple-negative (ER−/PR−/HER2−) disease, ER−/PR−/HER2+ disease, and ER+/PR+/HER2− disease. In contrast, the cumulative incidence and IRs of recurrence and visceral metastases were higher among patients with hormone receptor-negative disease, irrespective of HER2 status.

Predictors of recurrence, metastases, and mortality included age, hormone receptor status, stage at diagnosis,

Table 1 Characteristics of non-metastatic breast cancer patients diagnosed 1999–2011 in Denmark, and registered in the Danish cancer registry, with follow-up through 2012

Characteristics	Registry data source population	
	N	%
Total	23,505	100.0
Age at diagnosis		
<40	1240	5.3
40–49	3834	16.3
50–59	6095	25.9
60–69	6366	27.1
70+	5970	25.4
Year of diagnosis		
1999	1241	5.3
2000	1354	5.8
2001	1436	6.1
2002	1621	6.9
2003	1421	6.0
2004	2010	8.6
2005	2096	8.9
2006	2080	8.8
2007	2104	9.0
2008	2196	9.3
2009	2199	9.4
2010	2001	8.5
2011	1746	7.4
Menopausal status at diagnosis		
Pre-menopausal	7890	33.6
Post-menopausal	15,615	66.4
Tumor size		
<2 cm	4306	18.3
2–5 cm	10,107	43.0
>5 cm	1333	5.7
Unknown	7759	33.0
Lymph node status		
Negative	5119	21.8
Positive	11,295	48.1
Not registered	7091	30.2
Stage at diagnosis		
AJCC: stage II	12,387	52.7
AJCC: stage III	4045	17.2
Summary stage: regional stage	7073	30.1
Surgery type		
Mastectomy	11,203	47.7
Breast-conserving surgery	10,013	42.6
Unspecified surgery	352	1.5
No registered breast cancer surgery	1937	8.2
Estrogen receptor		
ER−	4210	17.9
ER+	17,146	72.9
Not registered	2149	9.1
Progesterone receptor		
PR−	5556	23.6
PR+	8505	36.2
Not registered	9444	40.2
HER2		
HER2−	9168	39.0
HER2+	4010	17.1
Not registered	10,327	43.9
Triple-negative breast cancer		
No	7757	33.0
Yes	1241	5.3
Not tested	14,507	61.7
Chemotherapy	8110	34.5
Endocrine therapy	10,663	45.4
Radiation therapy	9810	41.7
Charlson Comorbidity Index score		
0	19,370	82.4
1	2676	11.4
2	914	3.9
3+	545	2.3

and treatment receipt. Compared with patients aged 50–59 years at breast cancer diagnosis, patients aged below 50 years had higher HRs of bone metastases, recurrence, and mortality (Table 4). Patients aged 70 years or older had increased HRs of recurrence and mortality compared with the other age groups. Increased HRs of recurrence or metastases correlated with receipt of systemic therapy (chemotherapy, endocrine therapy, and radiotherapy), and with stage III or regional stage disease. HRs for recurrence, metastases, and mortality were lower among patients who underwent breast-conserving surgery compared with mastectomy patients. Patients with ER+ disease had lower HRs of recurrence, visceral metastases, mortality, and possibly bone metastases.

Discussion

Our findings suggest that the Danish registries are a valid resource for identifying data on hormone receptor and HER2 status. However, sensitivity was low for diagnoses of bone and visceral metastases, so these outcomes may be underestimated. This may explain the slightly lower incidence rates of bone and visceral metastases observed in our

Table 2 PPV, NPV, sensitivity, specificity of data in the Danish registries compared with the gold standard medical record review of 155 patients diagnosed with stage II and III breast cancer in Denmark 2004–2011

Variable	Measure	Calculation	Estimate (95% CI)
Menopausal status	Sensitivity	94/109	86.24 (78.85–91.73)
	Specificity	34/37	91.89 (79.92–97.66)
	Positive predictive value	94/97	96.91 (91.98–99.12)
	Negative predictive value	34/49	69.39 (55.66–80.90)
Lymph node status	Sensitivity	115/124	92.74 (87.17–96.35)
	Specificity	21/30	70.00 (52.35–84.00)
	Positive predictive value	115/124	92.74 (87.17–96.35)
	Negative predictive value	21/30	70.00 (52.35–84.00)
Estrogen receptor	Sensitivity	112/114	98.25 (94.49–99.63)
	Specificity	33/34	97.06 (87.07–99.68)
	Positive predictive value	112/113	99.12 (95.94–99.90)
	Negative predictive value	33/35	94.29 (82.91–98.79)
Progesterone receptor	Sensitivity	41/45	91.11 (80.24–96.92)
	Specificity	28/31	90.32 (76.37–97.20)
	Positive predictive value	41/44	93.18 (82.91–98.04)
	Negative predictive value	28/32	87.50 (72.97–95.63)
HER2	Sensitivity	32/49	65.31 (51.41–77.46)
	Specificity	65/67	97.01 (90.77–99.37)
	Positive predictive value	32/34	94.12 (82.44–98.76)
	Negative predictive value	65/82	79.29 (69.57–86.94)
Receipt of chemotherapy	Sensitivity	68/80	85.00 (75.99–91.53)
	Specificity	67/72	93.06 (85.45–97.30)
	Positive predictive value	68/73	93.15 (85.64–97.34)
	Negative predictive value	67/79	84.81 (75.71–91.42)
Receipt of endocrine therapy	Sensitivity	72/101	71.29 (61.96–79.42)
	Specificity	37/41	90.24 (78.45–96.62)
	Positive predictive value	72/76	94.74 (87.97–98.20)
	Negative predictive value	37/66	56.06 (44.04–67.56)
Receipt of radiotherapy	Sensitivity	79/119	66.39 (57.59–74.40)
	Specificity	27/30	90.00 (75.66–97.10)
	Positive predictive value	79/82	96.34 (90.56–98.96)
	Negative predictive value	27/67	40.30 (29.17–52.25)
Recurrence	Sensitivity	37/42	88.10 (75.86–95.31)
	Specificity	99/113	87.61 (80.61–92.72)
	Positive predictive value	37/51	72.55 (59.31–83.31)
	Negative predictive value	99/104	95.19 (89.79–98.14)
Bone metastases	Sensitivity	12/30	40.00 (24.05–57.78)
	Specificity	120/121	99.17 (96.20–99.91)
	Positive predictive value	12/13	92.31 (69.29–99.16)
	Negative predictive value	120/138	86.96 (80.59–91.79)
Visceral metastases	Sensitivity	17/37	45.95 (30.70–61.80)
	Specificity	111/118	94.07 (88.71–97.31)
	Positive predictive value	17/24	70.83 (51.08–85.90)
	Negative predictive value	111/131	84.73 (77.84–90.11)
New primary cancer	Sensitivity	2/6	33.33 (7.68–71.36)
	Specificity	137/139	98.56 (95.46–99.70)
	Positive predictive value	2/4	50.00 (12.28–87.72)
	Negative predictive value	137/141	97.16 (93.40–99.04)

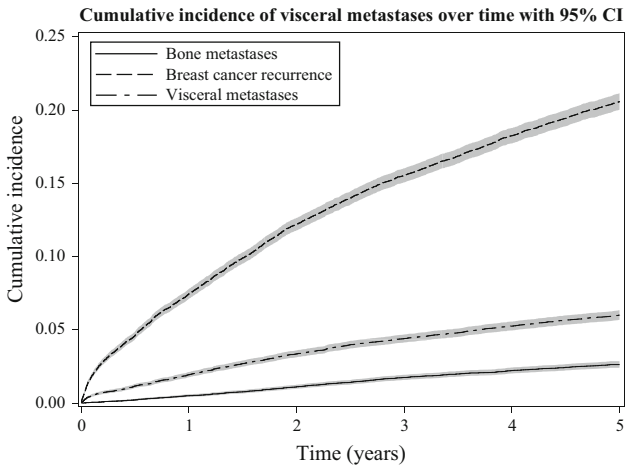

Fig. 1 Cumulative incidence of breast cancer recurrence, bone metastases, and visceral metastases among stage II, III, and regional stage breast cancer patients diagnosed in Denmark during 1999–2011 with follow-up through 2012

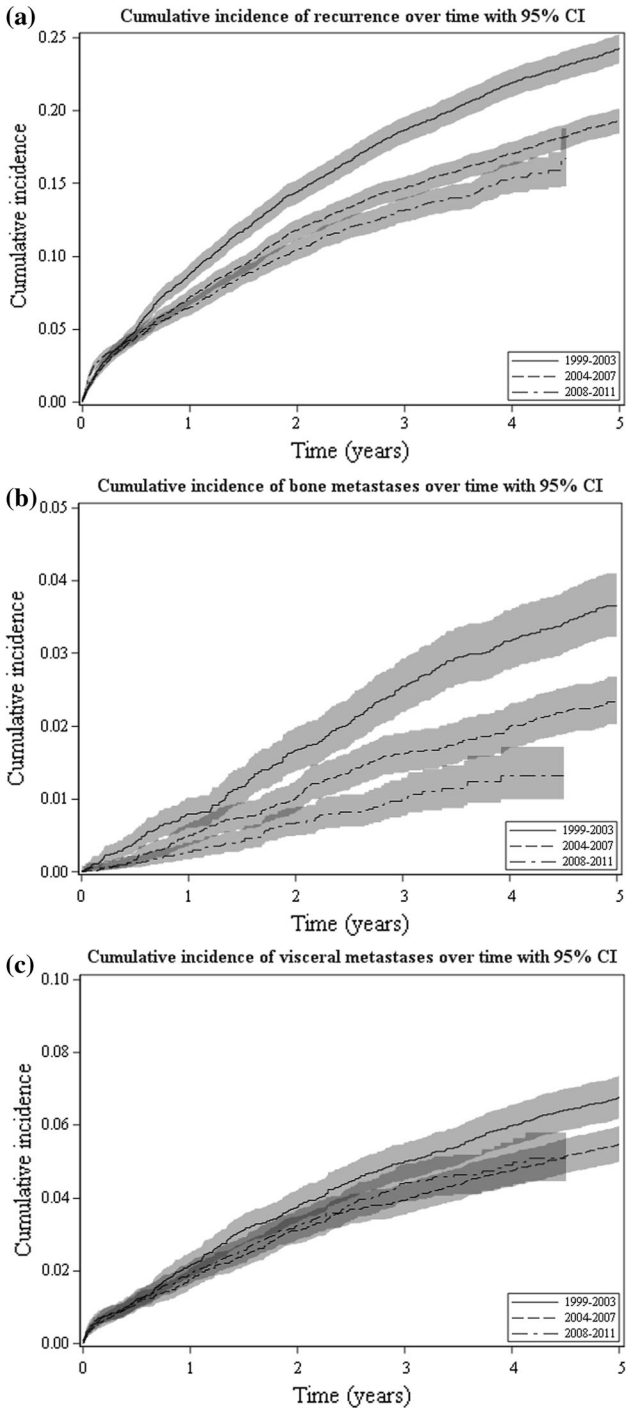

Fig. 2 Cumulative incidence of **a** breast cancer recurrence, **b** bone, and **c** visceral metastases according to calendar period of diagnosis among stage II, III, and regional stage breast cancer patients diagnosed in Denmark during 1999–2011 with follow-up through 2012

study compared with longitudinal studies from the UK and Canada [6, 7, 21]. Although the cumulative incidence of recurrence and bone metastases decreased in more recent calendar periods of diagnosis, that for visceral metastases has remained unchanged among patients diagnosed since 2004. In our study, predictors of recurrence, bone metastases, and visceral metastases include age, advanced stage, type of primary surgery, and the receipt of cancer-directed treatment within 180 days of diagnosis. These findings are consistent with the published work from countries with similar national healthcare systems in Canada and the United Kingdom [6, 7, 11].

Several strengths should be considered when interpreting our findings. The large size of our study and prospectively collected registry data ensured high validity of primary cancer diagnosis and treatment, and long and virtually complete follow-up. Use of population-based and medical registries in Denmark facilitated retrieval of a wide range of predictors. We validated the algorithms for the study outcomes using medical records as a gold standard. We restricted our study population to patients with non-metastatic disease and started follow-up at 180 days after diagnosis to ensure that our outcomes were unrelated to the primary breast cancer diagnosis [6]. We chose to assess specific outcomes, which are assigned an ICD diagnostic code, rather than to investigate these outcomes as causes of death. We thereby minimized potential disease misclassification.

Our study has some limitations. The generalizability of our findings may be limited as the Danish population is primarily Caucasian. For patients included in our cohort in the earliest time period, 1999–2004, only summary stage was available. Furthermore, the DCR only recorded treatment data during 1999–2004 if administered within the first 4 months after diagnosis. We therefore used multiple imputation to impute missing data in our cohort, noting little change to the observed estimates. Research suggests

Table 3 Cumulative incidence of each outcome, and Incidence rates (IR) per 10,000 person years (PY) and associated 95% CI for each outcome at 1, 2, 5 years and overall among 23,478 women diagnosed with regional stage (1999–2003) and stage II and III (2004–2011) breast cancer in Denmark

Outcome variable	IR time frame	Persons at risk	Outcome (*n*)	Outcome (%)	Expected cumulative incidence proportion	Person years	IR per 10,000 person years (95% CI)	Expected IR per 10,000 person years
Recurrence	1-year	23,478	1753	7.45 (7.12–7.79)	8.32	21,936	799.16 (762.18–837.46)	906.96
	2-year	23,478	2804	12.21 (11.79–12.64)	13.72	40,657	689.68 (664.38–715.69)	782.70
	5-year	23,478	4314	20.59 (20.03–21.16)	23.23	79,853	540.24 (524.24–556.61)	613.07
Mortality	1-year	23,478	972	4.20 (3.95–4.47)	–	22,857	425.24 (398.93–452.84)	–
	2-year	23,478	2047	9.15 (8.78–9.54)	–	43,109	474.84 (454.49–495.87)	–
	5-year	23,478	4419	22.58 (21.99–23.19)	–	87,106	507.31 (492.46–522.49)	–
Bone metastases	1-year	23,478	117	0.50 (0.42–0.60)	1.23	22,815	51.28 (42.41–61.46)	128.18
	2-year	23,478	247	1.12 (0.99–1.26)	2.78	42,960	57.50 (50.55–65.13)	143.73
	5-year	23,478	519	2.63 (2.41–2.86)	6.55	86,509	60.00 (54.94–65.38)	149.95
Visceral metastases	1-year	23,478	449	1.94 (1.77–2.12)	4.09	22,636	198.36 (180.43–217.58)	431.56
	2-year	23,478	758	3.36 (3.13–3.60)	7.18	42,499	178.36 (165.89–191.52)	388.03
	5-year	23,478	1228	6.01 (5.68–6.34)	12.95	85,324	143.92 (135.98–152.20)	313.08

that the incidence of bone and visceral metastases may be differential in luminal A (ER+/PR+/HER2−/low Ki67) compared with luminal B (ER+/PR+/HER2−/high Ki67) breast tumors [22]. Unfortunately, we were unable to distinguish between luminal A and luminal B tumor status, as information on the proliferation marker Ki67 was not routinely recorded in the National Pathology Registry for our cohort's diagnostic period. We also lacked information on tumor histologic grade and on the fibrotic focus of the tumor, which may predict bone metastases [23]. This residual confounding may be reflected in the finding that surgery type and receipt of cancer-directed treatment were predictive of disease progression, as these treatment characteristics may be indicative of more aggressive disease.

In Denmark, nationwide guidelines for breast cancer diagnosis, treatment, and follow-up are established by the Danish Breast Cancer Group [24]. Patients with operable breast cancer are recommended to undergo follow-up exams to detect recurrent disease twice yearly in the first 5 years after diagnosis, and annually up to 10 years after diagnosis [25]. Despite these national guidelines, we cannot exclude the possibility that the low sensitivity of bone and visceral metastases in our study differs by demographic, clinical, and treatment characteristics, all of which may influence the frequency of hospital contact and detection of metastatic disease.

Studies suggest that the incidence of bone metastases in breast cancer patients has decreased over time [11, 21]. Our study adds to this evidence, given that we found a lower overall incidence of bone metastases than the previous Danish study [9]. This is also consistent with our finding of lower cumulative incidence of bone metastases in the more recent calendar periods of diagnosis compared with the earliest period. This decrease may reflect the implementation of a nationwide mammographic screening program in Denmark in 2007 [26], leading to increased incidence of tumors diagnosed at an early stage with a lower likelihood of metastases. It may also be attributable to the use of increasingly effective treatment [3]; for example, taxanes were integrated into breast cancer-directed chemotherapy in Denmark in 2007 [27] and correlate with survival benefit [28, 29]. Lower incidence of bone metastases also may be due to off-label use of bone-targeting therapies, such as bisphosphonates [30], which may be beneficial as adjuvant therapy in selected early stage breast cancer patients at increased risk of bone metastases [29]. Denosumab, a RANK ligand inhibitor, has also been shown to prevent fractures [31] and increase disease-free survival [32] in the adjuvant setting as reported in the ABCSG-18 trial, and a large trial (D-CARE) [33] will further examine its effect on bone metastases prevention and disease-free survival.

Our observed higher 5-year cumulative incidence of bone metastases among women with ER+ breast cancer compared with ER− disease is consistent with previous studies in Canada and Korea [34, 35], but contrasts to a UK-based study [11]. However, the UK-based study had substantial proportions of missing data—40% missingness for cancer stage, 40% for hormone receptor status, and almost 60% for HER2 status—which are likely to have impacted the study findings [36]. Bone is often the first metastatic site among patients with ER+ disease [34, 35].

Table 4 Crude and adjusted hazard ratios (HR) and associated 95% confidence intervals (95% CI) for breast cancer recurrence, bone metastases, and visceral metastases, and mortality among women in Denmark diagnosed with stage II and III, or regional stage breast cancer during 1999–2011 with follow-up through 2012

	Crude HR	95% CI	Adj HR[a,b]	95% CI
Bone metastases				
Age (vs. 50–59)				
<50	1.3	(1.1, 1.6)	1.3	(1.0, 1.7)
60–69	1.1	(0.89, 1.4)	1.2	(0.92, 1.5)
70+	0.85	(0.67, 1.1)	1.1	(0.83, 1.5)
Chemotherapy received (vs. no chemotherapy)	1.6	(1.3, 1.8)	1.4	(1.1, 1.8)
Endocrine therapy received (vs. no endocrine therapy)	1.0	(0.89, 1.2)	1.2	(0.95, 1.4)
ER+ status (vs. ER−)	0.81	(0.66, 0.99)	0.81	(0.63, 1.1)
Anti-HER2 therapy received	1.1	(0.8, 1.6)	0.82	(0.53, 1.3)
Radiotherapy received	1.5	(1.3, 1.7)	1.6	(1.3, 1.9)
Stage (vs. stage II)				
Stage III	4.1	(3.2, 5.1)	3.6	(2.8, 4.6)
Regional stage	3.2	(2.6, 3.9)	2.7	(2.1, 3.4)
Surgery type (vs. mastectomy)				
Breast-conserving surgery	0.53	(0.45, 0.63)	0.59	(0.49, 0.72)
Surgery type unknown	1.1	(0.7, 1.8)	0.95	(0.55, 1.6)
Charlson comorbidity index score (vs. CCI = 0)				
1	0.98	(0.76, 1.3)	1.2	(0.87, 1.5)
2	1.1	(0.71, 1.6)	1.1	(0.64, 1.7)
3+	0.58	(0.26, 1.3)	0.85	(0.38, 1.9)
Recurrence				
Age (vs. 50–59)				
<50	1.2	(1.1, 1.3)	1.1	(1.0, 1.2)
60–69	0.97	(0.9, 1.0)	1.1	(0.97, 1.2)
70+	1.0	(0.96, 1.1)	1.2	(1.1, 1.4)
Chemotherapy received (vs. no chemotherapy)	1.6	(1.5, 1.7)	1.3	(1.2, 1.5)
Endocrine therapy received (vs. no endocrine therapy)	0.89	(0.84, 0.94)	1.2	(1.1, 1.3)
ER+ status (vs. ER−)	0.53	(0.50, 0.57)	0.53	(0.48, 0.57)
Anti-HER2 therapy received	1.6	(1.4, 1.8)	1.1	(0.97, 1.3)
Radiotherapy received	0.9	(0.85, 0.95)	1.1	(1.0, 1.2)
Stage (vs. Stage II)				
Stage III	2.6	(2.4, 2.8)	2.1	(1.9, 2.3)
Regional stage	1.8	(1.7, 1.9)	1.8	(1.7, 2.0)
Surgery type (vs. mastectomy)				
Breast-conserving surgery	0.68	(0.64, 0.73)	0.79	(0.74, 0.85)
Surgery type unknown	1.8	(1.5, 2.1)	1.5	(1.3, 1.8)
Charlson comorbidity index score (vs. CCI = 0)				
1	0.94	(0.86, 1.0)	0.95	(0.85, 1.1)
2	1	(0.86, 1.2)	1.1	(0.92, 1.3)
3+	1.0	(0.84, 1.3)	1.1	(0.90, 1.5)
Visceral metastases				
Age (vs. 50–59)				
<50	1.2	(1.0, 1.4)	1.1	(0.96, 1.3)
60–69	0.86	(0.74, 0.98)	0.98	(0.84, 1.2)
70+	0.86	(0.75, 1.0)	1.1	(0.94, 1.4)
Chemotherapy received (vs. no chemotherapy)	1.8	(1.7, 2.0)	1.4	(1.2, 1.7)
Endocrine therapy received (vs. no endocrine therapy)	0.89	(0.81, 0.99)	1.3	(1.1, 1.5)

Table 4 continued

	Crude HR	95% CI	Adj HR[a,b]	95% CI
ER+ status (vs. ER−)	0.46	(0.41, 0.52)	0.48	(0.41, 0.56)
Anti-HER2 therapy received	2.1	(1.7, 2.5)	1.3	(1.0, 1.6)
Radiotherapy received	1.0	(0.94, 1.1)	1.2	(1.0, 1.3)
Stage (vs. stage II)				
Stage III	2.7	(2.4, 3.1)	2.2	(1.9, 2.6)
Regional stage	1.7	(1.5, 1.9)	1.6	(1.4, 1.9)
Surgery type (vs. mastectomy)				
Breast-conserving surgery	0.63	(0.56, 0.70)	0.69	(0.61, 0.78)
Surgery type unknown	1.2	(0.87, 1.6)	1.1	(0.77, 1.6)
Charlson comorbidity index score (vs. CCI = 0)				
1	0.93	(0.79, 1.1)	0.93	(0.76, 1.1)
2	0.92	(0.69, 1.2)	1.1	(0.77, 1.5)
3+	0.85	(0.56, 1.3)	0.96	(0.60, 1.5)
Mortality				
Age (vs. 50–59)				
<50	0.94	(0.86, 1.0)	1.1	(1.0, 1.2)
60–69	1.3	(1.2, 1.4)	1.5	(1.4, 1.7)
70+	3.3	(3.1, 3.5)	3.5	(3.1, 3.9)
Chemotherapy received (vs. no chemotherapy)	0.84	(0.80, 0.89)	1.2	(1.1, 1.4)
Endocrine therapy received (vs. no endocrine therapy)	0.98	(0.93, 1.0)	1.2	(1.1, 1.3)
ER+ status (vs. ER−)	0.58	(0.55, 0.62)	0.51	(0.47, 0.55)
Anti-HER2 therapy received	1.1	(0.96, 1.2)	1.1	(0.95, 1.3)
Radiotherapy received	0.67	(0.64, 0.71)	0.96	(0.90, 1.0)
Stage (vs. stage II)				
Stage III	2.4	(2.2, 2.6)	2.1	(1.9, 2.3)
Regional stage	1.9	(1.8, 2.0)	1.8	(1.7, 2.0)
Surgery type (vs. mastectomy)				
Breast-conserving surgery	0.42	(0.40, 0.45)	0.61	(0.57, 0.65)
Surgery type unknown	1.1	(0.96, 1.3)	1.1	(0.95, 1.3)
Charlson comorbidity index score (vs. CCI = 0)				
1	1.8	(1.7, 1.9)	1.5	(1.4, 1.6)
2	2.4	(2.2, 2.7)	1.8	(1.6, 2.1)
3+	3.8	(3.4, 4.3)	2.8	(2.4, 3.2)

[a]Model adjusted for all other predictors in the table

[b]Findings were similar when an adjustment was made for menopausal status (proxy ≥ 55 years) rather than age

Compared with ER− disease, ER+ disease correlates with higher disease-free survival rates in the first 5 years after breast cancer diagnosis, but the survival curves cross about 7 years post-diagnosis, and survival is subsequently higher in patients with ER− disease [35, 37]. Our study lacks sufficient follow-up time to detect this crossover. This may also contribute to the lower rates of bone metastases in our study compared with previous research [8–10].

A Canadian study by Yerushalmi et al. and a UK study by Harris et al. observed an increase in the ratio of non-bone to bone metastases over time [11, 21]. Our findings may support this, as we observed little change to the incidence of visceral metastases among patients diagnosed from 2004 onwards. This is cause for concern as survival is notoriously poor among patients with visceral metastases, especially when visceral metastases occur before bone metastases [11, 21].

In conclusion, our cohort study highlights the validity of the Danish registries at ascertaining data on breast cancer diagnoses and follow-up, and provides important information on the incidence of breast cancer recurrence, bone metastases, and visceral metastases in women diagnosed

with non-metastatic breast cancer. These findings should help to contextualize outcomes observed in breast cancer clinical trials, and to interpret the incidence rates of these events in a "real-world" population-based setting. Given the increasing population of breast cancer survivors, it is important to monitor continually the long-term health of these women [38].

Acknowledgements The authors thank Henriette Kristoffersen and Hanne M. Madsen for reviewing medical records.

Funding The study received financial support from Amgen Incorporated.

Authors' contribution DCF, AK, and MN have no disclosures. HTS has not received any personal grants; this study was partly supported by a grant to Clinical Institute, Aarhus University Hospital. JA was an employee and stock owner at Amgen at the time of completion of this study, and is currently employed and owns stock at GSK. AL and RKH are employees and own stock at Amgen, Inc.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by the Danish Data Protection Agency (J.nr. 2014-41-3250) and the Danish Health Board (J.nr. 3-3013-670/1/). Under Danish law, informed consent is not required for registry-based research.

Appendix

Breast cancer recurrence algorithm:

1. DNRP-registered or DCR-registered metastases code (ICD10: DC76–DC80) 180 or more days after first breast cancer surgery, and without a new primary cancer diagnosis registered in the DNRP or DCR between the date of the first breast cancer surgery and the date of the DNRP or DCR metastases code. Here and below, a new primary cancer was defined as a new cancer that is different from non-melanoma skin cancer (ICD10 C44).
2. Pathology Registry SNOMED combinations recorded 180 or more days after first breast cancer surgery, and without a new primary cancer diagnosis registered in the DNRP or DCR. Combinations were (1) T code (topography/location) in the breast (T04000-T09420) with morphology codes M8 or M9 with $\geq$3 in the fifth position (e.g., M8XXX3), (2) any T code with morphology codes M8 or M9 with the numbers 4, 6, or 7 in the fifth position.
3. A code specific for local breast cancer recurrence in the DNRP any time after primary diagnosis: DC509X (these codes have only been used in DNRP beginning in 2012). A code for "recurrence operation" (KHAF) in the DNRP any time after diagnosis.

We used the DC509X code to distinguish local from non-local recurrent disease.

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