

# Comorbidity and survival of Danish breast cancer patients from 2000–2011: a population-based cohort study

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**Objective:** Previous studies have suggested that breast cancer survival in Denmark has improved, primarily in cancer patients without comorbidity. We therefore conducted a population-based cohort study to examine recent temporal changes in survival and mortality among breast cancer patients with different extents of comorbidity.

**Methods:** We used population-based medical and administrative registries to identify breast cancer patients diagnosed between 2000 and 2011 in the Central Denmark Region. We defined comorbid diseases according to the Charlson Comorbidity Index (CCI), including a history of hospitalization for comorbid disease up to 10 years before breast cancer diagnosis. We studied the impact of comorbidities on overall 1- and 5-year survival in different calendar time periods, using a hybrid analysis for survival prediction in the most recent calendar periods.

**Results:** We included 9,329 breast cancer patients. The proportion of patients within different comorbidity categories remained stable from 2000 to 2011. One-year survival improved from 91% in 2000–2002 to 95% in 2009–2011, while 5-year survival improved from 72% to a predicted 78%. During the entire study period, comorbidity was a strong predictor of the survival of breast cancer patients. However, we observed improvements over time in 1- and 5-year survival for all comorbidity groups. During the 12-year study period, the estimated 5-year survival for patients with a high comorbidity disease burden (CCI score  $\geq 3$ ) increased from 25% to a predicted 50%, and their 5-year age-adjusted mortality hazard ratio (HR) fell from 4.0 (95% confidence interval [CI]: 3.0, 5.4) to 2.7 (95% CI: 2.0, 3.6), respectively, compared with patients with no comorbid disease.

**Conclusion:** Survival of breast cancer patients diagnosed in the Central Denmark Region improved from 2000 to 2011, regardless of the extent of comorbid disease.

**Keywords:** breast neoplasm, survival, mortality, comorbidity, prognosis

## Introduction

Denmark currently has the second-highest breast cancer incidence and the highest mortality from breast cancer in Europe.<sup>1</sup> Breast cancer risk increases with age, so breast cancer patients often have comorbid disease at the time of their breast cancer diagnosis.<sup>2–4</sup> In Denmark, this amounts to about 20% of all breast cancer patients.<sup>5</sup> Several studies have documented that comorbid diseases negatively affect survival after breast cancer.<sup>6,7</sup> Mortality in these patients may often be related to the comorbidities rather than to the breast cancer,<sup>8,9</sup> in particular among patients with extensive comorbidity.<sup>10–12</sup>

Survival after breast cancer has improved in Denmark<sup>13</sup> but, according to a recent Danish population-based study, the 5-year survival of breast cancer patients

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with a Charlson Comorbidity Index (CCI) score of  $\geq 3$  has only increased from 42.0% in 1990–1994 to 43.5% in 2000–2004.<sup>14</sup> Another previous Danish population-based study reported slightly poorer survival over time among breast cancer patients with severe comorbidity between 1995 and 2005.<sup>5</sup> The aim of this paper was to study temporal changes in mortality in a cohort of breast cancer patients diagnosed between 2000 and 2011 by extent of comorbid diseases, as defined by the CCI.<sup>15</sup>

## Materials and methods

### Study population

This population-based cohort study was based in the Central Denmark Region, which has approximately 1.2 million inhabitants. The Danish National Health service provides universal, tax-supported health care, guaranteeing unfettered access to all general practitioners and hospitals. Accurate and unambiguous linkage of all registries at the individual level is possible in Denmark by means of the unique civil personal registration (CPR) number assigned to each Danish inhabitant at birth or immigration.<sup>16</sup>

### Identification of patients with breast cancer

The Danish National Registry of Patients (NRP) contains information on all discharges from nonpsychiatric hospitals in Denmark since 1977 and from emergency room and outpatient visits at hospitals since 1995.<sup>17</sup> Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th edition (ICD-8) until the end of 1993, and ICD-10 thereafter. Using the NRP, we identified all female patients with an invasive breast cancer diagnosis (ICD-10 code C50) from January 1, 2000 to December 31, 2011. Patients with breast cancer diagnosed between 1977 and 1999 were excluded.

### Comorbid diseases at breast cancer diagnosis

To assess patient comorbidity, the CCI score was computed at date of breast cancer diagnosis for each patient based on NRP records up to 10 years preceding the date of the breast cancer diagnosis (Table S1).<sup>15</sup> The CCI has been adapted and validated for use with hospital discharge data for the prediction of short- and long-term mortality.<sup>15,18</sup> The following disease categories are included: liver diseases; myocardial infarction; congestive heart failure; peripheral vascular disease; chronic pulmonary disease; cerebrovascular disease; hemiplegia;

dementia; connective tissue disease; ulcer disease; diabetes; renal disease; cancer; and HIV/AIDS. Breast cancer diagnoses were excluded when we computed the CCI score. Furthermore, cancer diagnoses within 60 days before the breast cancer diagnosis were excluded from the calculations, in order to eliminate possible nonspecific cancer diagnoses related to the breast cancer diagnosis. We categorized comorbidities as none (CCI score = 0), medium (CCI score = 1–2), or high (CCI score  $\geq 3$ ).

### Vital status

Members of the study cohort were linked via their CPR number to the Danish Civil Registration System to obtain information on vital status.<sup>16</sup> This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates. The outcome was overall mortality defined as death from any cause. Follow-up was through patient date of death, emigration, or December 31, 2011, whichever occurred first.

### Statistical analysis

The prevalence of comorbidity was computed in study patients during four 3-year calendar time periods (2000–2002, 2003–2005, 2006–2008, and 2009–2011). For each comorbidity category, we constructed Kaplan–Meier survival curves for the different calendar time periods. Next, we used Cox proportional hazards regression to compute 1- and 5-year crude and age-adjusted hazard ratios as a measure of relative overall mortality to assess the association of comorbidity with mortality using a CCI score = 0 as the reference category in each calendar time period. In the latter periods, we predicted 1- and 5-year survival using a hybrid analysis in which survival was estimated using the survival experience of patients in the previous calendar time periods.<sup>19</sup> Breast cancer stage and grade were considered to be causal intermediates in the association between comorbidity and mortality, thus not included in the analyses. The proportional hazards assumption was assessed graphically and found to be appropriate. All analyses were performed using SAS software (v 9.2; SAS Institute Inc, Cary, NC, USA). The Danish Data Protection Agency approved the study (record number 2009-41-3866).

## Results

The study included 9,329 women diagnosed with breast cancer between 2000 and 2011. As shown in Tables 1 and S2, the proportion of patients across different CCI score categories and individual comorbid diseases was relatively

**Table 1** Distribution of breast cancer patients diagnosed between 2000 and 2011 by CCI score in four calendar time periods

	2000–2002	2003–2005	2006–2008	2009–2011
Patients, n (%)	1,980 (21)	1,994 (21)	2,410 (26)	2,945 (32)
Median age in years (IQR)	62 (53, 74)	61 (52, 72)	63 (54, 71)	63 (54, 70)
Age group, n (%)				
15–49 years	380 (19)	416 (21)	395 (16)	459 (16)
50–74 years	1,134 (57)	1,156 (58)	1,569 (65)	1,996 (68)
≥75 years	466 (24)	422 (21)	446 (19)	490 (17)
CCI score, n (%)				
0	1,567 (79)	1,557 (78)	1,862 (77)	2,290 (78)
1–2	344 (17)	349 (18)	445 (18)	536 (18)
≥3	69 (3)	88 (4)	103 (4)	119 (4)
Median age in years (IQR) by CCI score				
0	60 (51, 71)	59 (50, 69)	61 (53, 68)	62 (53, 68)
1–2	71 (60, 80)	71 (60, 80)	68 (61, 78)	68 (61, 78)
≥3	74 (65, 81)	75 (63, 81)	71 (63, 79)	71 (65, 79)

**Abbreviations:** CCI, Charlson Comorbidity Index; IQR, interquartile range.

constant over the 4 calendar time periods. The number of breast cancer patient diagnoses increased markedly between 2000 and 2011, almost doubling for patients aged between 50 and 74 years. The proportion of patients aged 50 to 74 years increased markedly in each time period from 57% in 2000–2002 to 68% in 2009–2011. In contrast, the proportion of patients aged 75+ years fell from 24% to 17%.

## Survival

Table 2 presents survival and relative mortality across calendar periods and age groups. Overall, the 1-year survival improved between 2000–2002 and 2009–2011, from 91% to 95%, while 5-year survival improved from 72% to 78%. The 1- and 5-year survival remained rather constant over time among patients aged 15–49 years and for patients aged ≥75 years, but increased from 93% to 97% and from 77% to 84%, respectively, for patients aged between 50 and 74 (Table 2).

Figure 1 shows the Kaplan–Meier survival curves for breast cancer patients in the four calendar time periods stratified by CCI score. For patients with a CCI score of ≥3, survival improved markedly after the period 2000–2002.

Table 3 shows that patients with high CCI scores had higher 1- and 5-year mortality compared with those with low CCI scores, regardless of calendar period. However, 1-year survival improved over time for all three CCI categories. Most of the 1-year survival improvement in all CCI categories seemed to happen early in the study period, ie, between 2000–2002 and 2003–2005, in particular for the CCI score ≥3 patients. 5-year survival also improved over time

**Table 2** One- and 5-year survival and relative mortality stratified by four calendar time periods and age group of breast cancer diagnosis

	Year of diagnosis			
	2000–2002	2003–2005	2006–2008	2009–2011
1 year				
Survival	91% (90%–93%)	94% (93%–95%)	94% (93%–95%)	95% (94%–96%)
Adjusted MRR <sup>a</sup>	1 (reference)	0.66 (0.52–0.83)	0.73 (0.59–0.91)	0.59 (0.47–0.74)
5 years				
Survival	72% (70%–74%)	75% (73%–77%)	75% (74%–77%) <sup>b</sup>	78% (76%–80%) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.87 (0.77–0.98)	0.87 (0.77–0.98) <sup>b</sup>	0.78 (0.69–0.87) <sup>b</sup>
Age group				
15–49 years				
1-year survival	97% (95%–98%)	99% (97%–99%)	99% (97%–99%)	97% (95%–98%)
5-year survival	85% (81%–88%)	86% (82%–89%)	89% (86%–92%) <sup>b</sup>	87% (84%–90%) <sup>b</sup>
50–74 years				
1-year survival	93% (92%–95%)	96% (94%–97%)	95% (94%–96%)	97% (96%–98%)
5-year survival	77% (74%–79%)	80% (78%–82%)	80% (78%–82%) <sup>b</sup>	84% (82%–85%) <sup>b</sup>
≥75 years				
1-year survival	82% (78%–85%)	85% (82%–88%)	83% (79%–86%)	84% (80%–87%)
5-year survival	50% (45%–54%)	50% (45%–54%)	48% (43%–52%) <sup>b</sup>	48% (43%–52%) <sup>b</sup>

**Notes:** 95% confidence intervals are presented in brackets. <sup>a</sup>Adjusted for differences in age and comorbidity; <sup>b</sup>predicted values.

**Abbreviation:** MRR, mortality rate ratio.

in all CCI categories, with most pronounced improvements seen among CCI score ≥3 patients – from 25% in 2000–2002 to a predicted 50% in 2009–2011 (Table 3).

## Mortality

The mortality across calendar periods was rather constant from 2003–2005 (Table 3). Compared with 1-year mortality in patients with no recorded comorbidity, the adjusted 1-year mortality hazard ratio (HR) for patients with a CCI score of 1–2 remained similar over time, ie, HR = 1.8 (95% confidence interval [CI]: 1.3, 2.6) in 2000–2002 and HR = 1.9 (95% CI: 1.2, 2.8) in 2009–2011. The corresponding 5-year mortality HRs were 1.4 (95% CI: 1.1, 1.7) in 2000–2002 and 1.8 (95% CI: 1.5, 2.2) in 2009–2011. For patients with a CCI score of ≥3, the adjusted 1-year mortality HRs compared with patients with no recorded comorbidity were 5.4 (3.5, 8.5) in 2000–2002 and 5.7 (3.6, 9.2) in 2009–2011. The 5-year mortality HRs were 4.0 (95% CI: 3.0, 5.4) in 2000–2002 and 2.7 (95% CI: 2.0, 3.6) in 2009–2011, compared with patients without comorbidity.

**Table 3** One- and 5-year survival and relative mortality for patients diagnosed with breast cancer in four calendar time periods stratified by Charlson Comorbidity Index score

Year of diagnosis	Charlson comorbidity index score		
	0	1–2	≥3
<b>2000–2002</b>			
1 year			
Survival	94% (93%–95%)	86% (82%–89%)	62% (50%–73%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.8 (1.3–2.6)	5.4 (3.5–8.5)
5 years			
Survival	76% (74%–78%)	63% (57%–68%)	25% (15%–35%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.4 (1.1–1.7)	4.0 (3.0–5.4)
<b>2003–2005</b>			
1 year			
Survival	96% (95%–97%)	90% (87%–93%)	77% (67%–85%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.6 (1.1–2.5)	3.49 (2.1–5.9)
5 years			
Survival	80% (78%–82%)	61% (56%–66%)	43% (33%–53%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.7 (1.3–2.0)	2.5 (1.9–3.4)
<b>2006–2008</b>			
1 year			
Survival	95% (94%–96%)	91% (88%–93%)	75% (65%–82%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.4 (0.9–2.0)	3.8 (2.4–6.0)
5 years			
Survival	80% (78%–82%) <sup>b</sup>	62% (58%–67%) <sup>b</sup>	47% (37%–56%) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	1.6 (1.3–1.9) <sup>b</sup>	2.4 (1.8–3.3) <sup>b</sup>
<b>2009–2011</b>			
1 year			
Survival	97% (96%–98%)	92% (89%–94%)	74% (64%–81%)
Adjusted MRR <sup>a</sup>	1 (reference)	1.9 (1.2–2.8)	5.7 (3.6–9.2)
5 years			
Survival	83% (81%–84%) <sup>b</sup>	64% (59%–68%) <sup>b</sup>	50% (40%–59%) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	1.8 (1.5–2.2) <sup>b</sup>	2.7 (2.0–3.6) <sup>b</sup>

**Notes:** 95% confidence intervals are presented in brackets. <sup>a</sup>Adjusted for differences in age; <sup>b</sup>predicted values.

**Abbreviation:** MRR, mortality rate ratio.

## Discussion

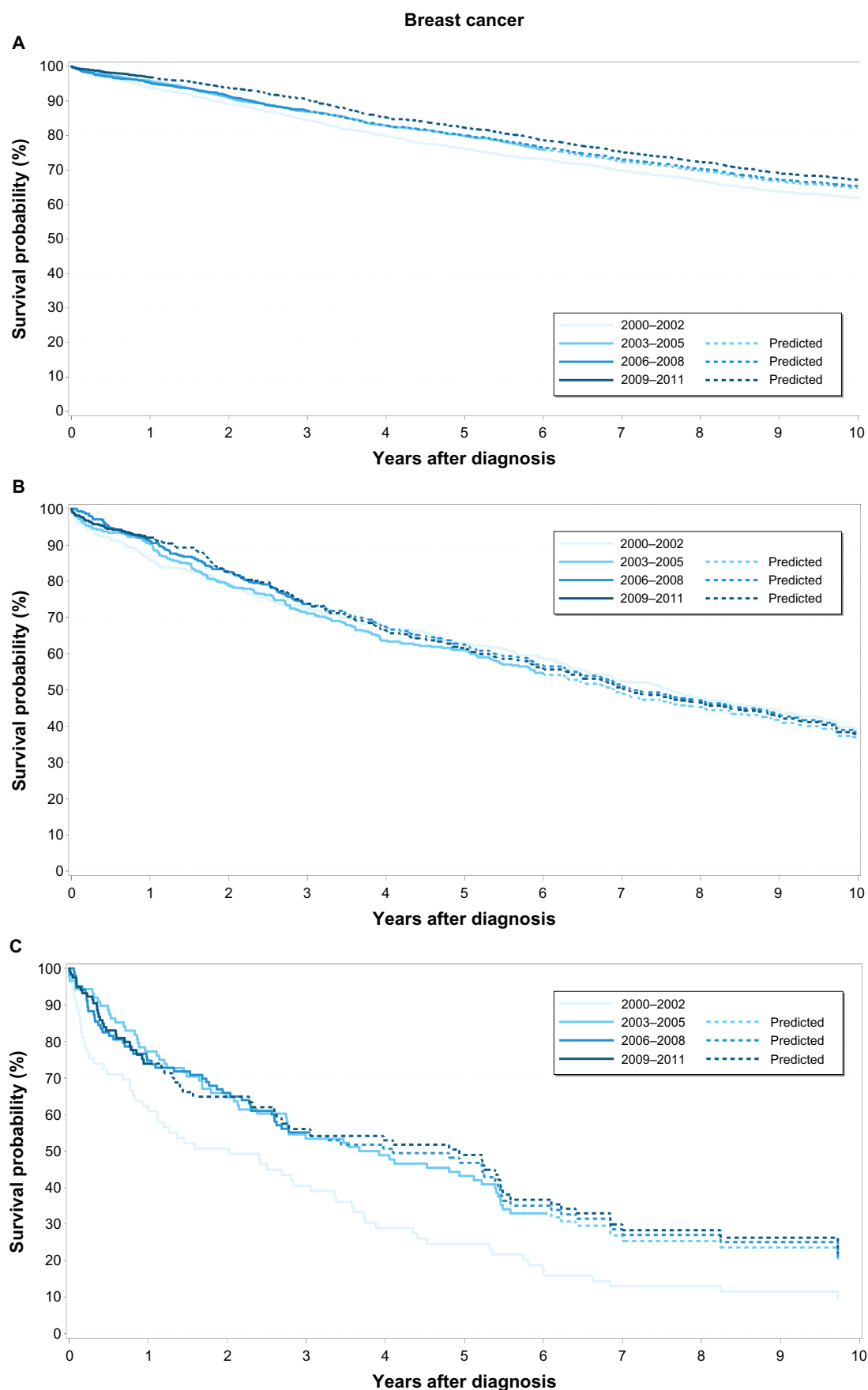
This large, population-based study showed improved 1- and 5-year survival of breast cancer patients diagnosed in the Central Denmark Region from 2000 through 2011. Comorbidity was a strong predictor of breast cancer survival. Nonetheless, we observed marked improvements in survival for all comorbidity groups. This survival improvement over time was even seen among patients with the highest comorbidity burden (CCI scores ≥3), and corresponded to a decreased 5-year mortality HR compared with patients with no comorbid diseases (CCI score = 0).

Our study has both strengths and weaknesses. We used nationwide administrative and medical registries with prospectively collected data to identify breast cancer patients, comorbid diseases, and vital status, thereby avoiding selection bias and loss to follow-up. We obtained our information on breast cancer diagnoses from the NRP, which is regularly updated, allowing us to include the newest available data on breast cancer cases in Denmark. Moreover, the validity of breast cancer diagnoses recorded in the NRP is high.<sup>20</sup>

We used the CCI as a measure of the comorbidity burden. This index has been validated as a predictor of mortality in breast cancer patients and is often used in breast cancer research, allowing for comparison of our results with previous studies. The positive predictive values of diseases included in the CCI collected from the NRP have been shown to be high.<sup>21</sup> However, as outpatient diagnoses were first added to the NRP in 1995, our study may be prone to nondifferential misclassification of the CCI score. Such misclassification would result if the inclusion of outpatient diagnoses increases the recorded comorbidity in the NRP and the measured comorbidity burden over time. Outpatient diagnoses are likely to be less severe than inpatient diagnoses, which may have contributed to the improvement in survival among patients with severe comorbidity. On the other hand, the effect of including outpatient diagnoses since 1995 should have resulted in a survival improvement before 2011, which was not the case.<sup>5,14</sup> Furthermore, we lacked information on lifestyle-related risk factors (such as body mass index, smoking habits, and alcohol consumption), breast cancer stage, cancer treatment, and medication prescribed for the comorbid diseases, which could all affect the mortality rate.

We note relatively few patients with a CCI score ≥3, and estimates were therefore imprecise. Nonetheless, our findings are consistent with previous studies, which have indicated higher mortality among breast cancer patients with comorbidity compared with those without comorbidity.<sup>5,14</sup> There are several plausible explanations for this survival disparity. First, severe comorbidity could increase mortality independent of breast cancer, which in itself has a good prognosis. Second, women with extensive comorbid disease may have their cancer diagnosed at a later stage because comorbidity may mask any evidence of an underlying cancer.<sup>22</sup> On the other hand, other studies have found a higher prevalence of comorbidity in earlier stages of breast cancer, probably because patients with comorbidity often require frequent medical care.<sup>23,24</sup> Third, treatment options may be restricted in patients with severe comorbidity, who may not tolerate aggressive cancer treatment.<sup>25,26</sup>

Yet, in contrast to a recent Danish 5-year follow-up of breast cancer patients diagnosed from 1990 to 2004, which did



**Figure 1** Kaplan–Meier survival curves for breast cancer patients in four calendar time periods stratified by Charlson Comorbidity Index score.

**Notes:** (A) Charlson score = 0; (B) Charlson score = 1–2; (C) Charlson score  $\geq 3$ .



not indicate any improvement in 5-year survival for patients with a CCI score of  $\geq 3$ ,<sup>14</sup> we observed a marked improvement in predicted 5-year survival for patients with a CCI score of  $\geq 3$  during the calendar period from 2000–2011. However, this may be due to chance, because the survival of the 69 patients diagnosed in the reference period (2000–2002) was relatively poor compared with the following calendar time periods, so it is difficult to make any conclusions on these findings. Introduction of the national Danish mammography screening program for women 50–69 years of age in 2007 is expected to result in an increased number of patients in this age group, which is consistent with our findings, as well as more patients diagnosed with early-stage breast cancer and thereby in need of less extensive treatment, since less extensive treatment is well tolerated regardless of comorbidity level. This may decrease the survival gap related to comorbidity.

Although comorbidity is associated with a poorer prognosis in breast cancer, we observed a modest improvement in survival, which may suggest improved management of breast cancer patients with comorbidity over time.

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## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary tables

**Table S1** Specification of Charlson diseases, International Classification of Diseases (ICD)-8 and ICD-10 codes, and the Charlson weight

Charlson comorbidity index variable	ICD-8	ICD-10	Charlson weight
Myocardial infarction	410	I21, I22, I23	1
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2	1
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77	1
Cerebrovascular disease	430–438	I60–I69, G45, G46	1
Dementia	290.09–290.19, 293.09	F00–F03, F05.1, G30	1
Chronic 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	1
Connective tissue disease	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	1
Ulcer disease	530.91, 530.98, 531–534	K22.1, K25–K28	1
Mild liver disease	571, 573.01, 573.04	B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0	1
Diabetes type 1	249.00, 249.06, 249.07, 249.09	E10.0, E10.1, E10.9	1
Diabetes type 2	250.00, 250.06, 250.07, 250.09	E11.0, E11.1, E11.9	1
Hemiplegia	344	G81, G82	2
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	2
Diabetes with end organ damage			2
Type 1	249.01–249.05, 249.08	E10.2–E10.8	
Type 2	250.01–250.05, 250.08	E11.2–E11.8	
Any tumor	140–194	C00–C75	2
Leukemia	204–207	C91–C95	2
Lymphoma	200–203, 275.59	C81–C85, C88, C90, C96	2
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	3
Metastatic solid tumor	195–198, 199	C76–C80	6
AIDS	079.83	B21–B24	6

**Table S2** Distribution of breast cancer patients diagnosed between 2000 and 2011 by individual Charlson disease in four calendar time periods

	Calendar time period								All	
	2000–2002		2003–2005		2006–2008		2009–2011		N	%
	N	%	N	%	N	%	N	%		
Myocardial infarction	28	1.4	36	1.8	38	1.6	32	1.1	134	1.4
Congestive heart failure	43	2.2	57	2.9	49	2.0	47	1.6	196	2.1
Peripheral vascular disease	52	2.6	54	2.7	47	2.0	69	2.3	222	2.4
Cerebrovascular disease	79	4.0	91	4.6	102	4.2	116	3.9	388	4.2
Dementia	6	0.3	9	0.5	14	0.6	16	0.5	45	0.5
Chronic pulmonary disease	91	4.6	105	5.3	134	5.6	145	4.9	475	5.1
Connective tissue disease	52	2.6	37	1.9	58	2.4	75	2.5	222	2.4
Ulcer disease	39	2.0	36	1.8	54	2.2	49	1.7	178	1.9
Mild liver disease	8	0.4	4	0.2	18	0.7	23	0.8	53	0.6
Diabetes I and II	37	1.9	40	2.0	49	2.0	73	2.5	199	2.1
Hemiplegia	7	0.4	5	0.3	4	0.2	4	0.1	20	0.2
Moderate to severe renal disease	6	0.3	15	0.8	27	1.1	23	0.8	71	0.8
Diabetes with end organ damage	21	1.1	41	2.1	40	1.7	38	1.3	140	1.5
Any tumor	80	4.0	62	3.1	90	3.7	130	4.4	362	3.9
Leukemia	2	0.1	1	0.1	0	0	4	0.1	7	0.1
Lymphoma	6	0.3	3	0.2	12	0.5	9	0.3	30	0.3
Moderate-to-severe liver disease	3	0.2	3	0.2	5	0.2	3	0.1	14	0.2
Metastatic solid tumor	7	0.4	16	0.8	22	0.9	22	0.7	67	0.7
AIDS	0	0	0	0	0	0	0	0	0	
Total	1,980	100	1,994	100	2,410	100	2,945	100	9,329	100

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