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ORIGINAL ARTICLE

Improvements in breast cancer survival between 1995 and 2012 in Denmark: The importance of earlier diagnosis and adjuvant treatment

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ABSTRACT

Background Breast cancer mortality has declined from 1995 through 2012 which may be attributed to earlier diagnosis, changes in lifestyle risk factors, and improved treatments. To a large extent the relative contribution of these modalities are unknown. Mammography screening was introduced late in Denmark; in 1995 around 20% of the Danish female population aged 50–69 was covered by population-based screening, and this was in 2008 extended to the entire population. Breast conserving surgery gradually replaced mastectomy, and sentinel node biopsy was introduced. In the same period adjuvant treatment was extended considerable.

Methods A population-based study of 68 842 breast cancer patients registered in the clinical database of the Danish Breast Cancer Cooperative Group in 1995–2012. Comprehensive data on prognostic factors, comorbidity and treatment together with complete follow-up for survival were used to evaluate improvements in mortality and standardized mortality rate in successive time periods.

Results The results from this study demonstrated a significant improvement in prognosis in successive time periods covering 1995–2012. Apart from patients with a high Charlson Comorbidity Index (CCI) improvements were seen in all subgroups of patients. Prognostic factors were more favorable in the latest time period accordingly to the introduction of nationwide screening. In the study period adjuvant treatment was extended considerable.

Conclusion The impact of screening was by nature of limited magnitude. The modified treatment strategies implemented by the use of nationwide guidelines seemed to have a major impact on the substantial survival improvements.

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The incidence of breast cancer has steadily increased from 1000 patients per year in the early 1950s to around 5000 patients in 2010 corresponding to one of every nine Danish women (NORDCAN www.ancr.nu, [1]). However, breast cancer mortality has declined from 1995 through 2012 which may be attributed to earlier diagnosis, changes in lifestyle risk factors, and improved treatments. To a large extent the relative contribution of these modalities are unknown and it has not been clarified whether the improvements are similar in different subsets of women.

Mammography screening was introduced later in Denmark compared to Northern Europe in general. In 1995 around 20% of the Danish female population aged 50–69 was covered by population-based screening, and this was in 2008 extended to the entire population [2].

Women with breast cancer have successively been exposed to less extensive surgery. Breast conserving surgery (BCS) gradually replaced mastectomy as data emerged from randomized trials and was promoted at the NIH conference in 1991 [3,4]. Smaller margin has been adapted resulting in less tissue removed by BCS and axillary lymph node dissection has in clinically node negative cases been replaced by sentinel node biopsy [5,6]. Increased use of BCS has resulted in a similar increase in the use of radiotherapy, and in addition radiotherapy has increasingly been used in patients with node positive disease following mastectomy [7–10].

Women with early breast cancer are increasingly being exposed to adjuvant systemic therapies, which can safely be omitted in only a small subgroup of node negative patients aged 60 or older with estrogen receptor (ER) positive, HER2 negative, grade I tumors of 10 mm or less [11]. Endocrine treatment is the key component of the adjuvant therapy in patients with ER positive tumors and its duration has gradually been extended [12–14]. Human epidermal growth factor 2 (HER2) is overexpressed or amplified in 10–15% of breast cancers and HER2 positivity is associated with increased tumor aggressiveness, risk of recurrence and breast cancer mortality. Trastuzumab is a monoclonal antibody targeting the extracellular domain of HER2 and was introduced in the adjuvant setting in 2005 following the documentation of a beneficial

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effect [15,16]. Primarily trastuzumab was offered to patients with invasive cancers >1 cm who otherwise were allocated to chemotherapy, and from 2010 to all patients with a HER2-positive cancer.

Chemotherapy is well established as adjuvant therapy for early breast cancer and the recent overview from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) suggested that on average, chemotherapy reduces 10-year breast cancer mortality by about one third [17]. The proportional benefits were independent of age, nodal status, ER status and type of chemotherapy regimen. Consequently, adjuvant chemotherapy has been increasingly used and is now almost mandatory in patients with ER negative cancers. Chemotherapy has also been introduced to patients with ER positive cancers, but may safely be omitted in about one quarter of post-menopausal ER positive breast cancer patients who following optimal endocrine treatment are free of excess mortality [18].

The aim of the present study was to describe the changes in outcome for Danish breast cancer patients in the period 1995–2012 when mammography screening became nationwide, breast surgery became gentler, and the use of adjuvant systemic therapies was widened. Further to analyze the relative contribution of the changes in outcome attributable to earlier diagnosis and to treatment.

Methods

Since the establishment in 1977 the Danish Breast Cancer Cooperative Group (DBCG) has provided standard diagnostic and treatment algorithms for early breast cancer [19]. Data on diagnostic, therapeutic, and follow-up on newly diagnosed breast cancer patients have been collected prospectively in the DBCG Registry by the use of standardized forms. A population of all patients diagnosed in the period 1995–2012 were included in the present analysis. Data from the Danish National Patient Register (NPR) and the Central Population Register (CPR) were linked to the DBCG database using the unique personal identification number assigned to all Danish citizens by the CPR. The NPR has collected data on a nationwide basis on all somatic hospital admissions since 1977 and data on outpatients and emergency patients since 1995. NPR includes, on an individual level, information from all hospitalizations, including dates of admission and discharge and up to 20 discharge diagnoses per hospitalization. The CPR holds information on vital and emigration status on all Danish citizens. A complete follow-up for survival was achieved for 68 550 patients (99.6%) while 292 patients emigrated up to 18 years and 6 months after surgery. The estimated potential median observation time was 9 years and 9 months.

Comorbidity

Comorbidity was described according to Charlson Comorbidity Index (CCI) [20]. The CCI is a weighted index that takes into account both the number and the seriousness of 19 chronic conditions. The CCI in the present study was based on hospital contacts using International Classification of Diseases ICD-8 and ICD-10 data up to 10 years prior to the breast cancer diagnosis date.

Statistical analysis

Follow-up time was quantified in terms of a Kaplan-Meier estimate of potential follow-up. Time at risk was defined as time from diagnosis until date of death from any cause, emigration, or end of follow-up. Univariate and multivariate Poisson regression analysis for mortality and standardized mortality ratio (SMR) were used. The SMR, computed as the ratio of the observed to the expected number of deaths, served as an estimate of relative risk of death. The number of deaths expected was calculated by applying age- and calendar year-specific female mortality figures of the general Danish population and the corresponding person-years of follow-up for the respective cohort members. Ninety-five percent confidence intervals (CI) were computed based on the assumption that the observed number of deaths followed a Poisson distribution. The regression models were used to assess the relative risk (RR) within subgroups. Factors included in the multivariable analyzes were year of diagnosis, age, CCI, extension, tumor size, lymph node status, ER status, histological type and grade, and lymphovascular invasion. ER status was included with a time-dependent component. Interactions between covariates were investigated in separate models by applying the Wald test in the multivariate models.

Three outcome measures relating to year one, five and 10 after diagnosis have been calculated: absolute all-cause mortality rate per 100 person-years, absolute overall survival, and relative survival. All estimates were age-standardized according to the International Cancer Survival Standard (ICSS) 1 population. Absolute all-cause mortality rate (reported per 100 person-years) was calculated as the number of deaths divided by the sum of the patient-time at risk during the period concerned. Relative survival was estimated as the ratio of the observed survival of the patients (all deaths considered) to the expected survival. The expected survival was estimated from the general Danish female population, matched by age and calendar time. χ^2-test statistics were used to evaluate heterogeneity between the calendar periods. Statistical analyses were performed with the STATA v11.0 (StataCorp, College Station, TX, USA) and SAS v9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

The clinical DBCG database included 68 842 patients diagnosed with invasive breast cancer between 1995 and 2012 (Table 1). Overall, the disease was operable at diagnosis in 90% of patients, locally advanced in 1.4%, with distant metastasis in 1.9% and loco-regional extend was unknown in 7.8%.

Table 2 summarizes patient and tumor characteristics according to treatment period (1995–1999, 2000–2004, 2005–2009, and 2010–2012) in the 61 166 patients who initiated therapy with a curative intent and underwent surgery. Reflecting the increasing incidence the number of patients increased from 2578 in 1995 to 3760 in 2012. A peak in incidence was observed among women age 50–69 following the implementation of the national screening program in 2008. During the periods, substantial and statistical significant changes were observed in tumor characteristics including an increasing proportion of tumors sized 0–10 mm ($p < 0.0001$)

Table 1. Patient characteristics.

Year of inclusion			1995–1999		2000–2004		2005–2009		2010–2012		1995–2012	
Number of patients			15 753		18 039		21 308		13 742		68 842	
Median age			60		61		62		63		62	
			N	%	*N*	%	*N*	%	*N*	%	*N*	%
Age												
15–44			1688	11	1818	10	1890	9	1201	9	6597	10
45–54			3813	24	3936	22	3926	18	2688	20	14 363	21
55–64			3960	25	5017	28	6669	31	3743	27	19 389	28
65–74			3444	22	3739	21	5045	24	3611	26	15 839	23
≥75			2848	18	3529	20	3778	18	2499	18	12 654	18
Cancer extension												
Localized	Nodal status	Negative	7708	49	8214	46	9871	46	6958	51	32 751	48
		Positive	6343	40	7970	44	9139	43	5054	37	28 506	41
		Unknown	1298	8	1337	7	1500	7	1231	9	5366	8
Advanced	LABC		140	1	193	1	375	2	230	2	938	1
	DM		264	2	325	2	423	2	269	2	1281	2
CCI												
0			13 207	84	14 204	79	16 259	76	10 316	75	53 986	78
1			1467	9	2159	12	2821	13	1969	14	8416	12
2			735	5	1063	6	1293	6	863	6	3954	6
≥3			344	2	613	3	935	4	594	4	2486	4

CCI, Charlson Comorbidity Index; DM, distant metastatic; LABC, locally advanced breast cancer.

Table 2. Patient characteristics among patients with early breast cancer and known nodal status.

Year of inclusion	1995–1999		2000–2004		2005–2009		2010–2012		1995–2012
Number of patients	14 042		16 177		18 956		11 991		61 166
	N	%	*N*	%	*N*	%	*N*	%	*N*
Age									
<50	3184	23	3344	21	3323	18	2168	18	12 019
50–69	7559	54	8883	55	11 437	60	7145	60	35 024
≥70	3299	23	3950	24	4196	22	2678	22	14 123
CCI									
0	11 970	85	13 054	81	14 911	79	9261	77	49 196
1	1229	9	1818	11	2378	13	1633	14	7058
2	591	4	865	5	1035	5	681	6	3172
≥3	252	2	440	3	632	3	416	3	1740
Size, mm									
0–10	2105	15	2432	15	3378	18	2792	23	10 707
11–20	5569	40	6579	41	7872	42	5118	43	25 138
21–30	3515	25	4190	26	4686	25	2471	21	14 861
31–50	1935	14	2135	13	2232	12	1171	10	7473
51+	645	5	672	4	638	3	366	3	2321
Unknown	574	2	169	1	150	1	73	1	666
Positive lymphnodes									
0	7703	55	8212	51	9850	52	6951	58	32 716
1–3	3733	27	4963	31	6109	32	3684	31	18 489
4–9	1675	12	1738	11	1909	10	868	7	6190
10+	931	7	1264	8	1088	6	488	4	3771
Histological type									
Ductal	11 152	79	13 018	80	15 582	82	9573	80	49 325
Lobular	1657	12	1964	12	1879	10	1215	10	6715
Other	1030	7	1160	7	1363	7	1002	8	4555
Unknown	203	1	35	0	132	1	201	2	571
Grade (ductal and lobular)									
I	3658	29	4197	28	5535	32	3131	29	16 521
II	4714	37	6230	42	7597	44	4736	44	23 277
III	2449	19	3341	22	3885	22	2627	24	12 302
Unknown	1988	16	1214	8	444	3	294	3	3940
ER									
Negative (0–9%)	3267	23	3238	20	3221	17	1869	16	11 594
Positive (10–100%)	9310	66	12 744	79	15 614	82	10 018	84	47 686
Unknown	1465	10	195	1	121	1	104	1	1885
HER2									
Normal	476	3	2199	14	11 913	63	9957	83	24 545
Positive	160	1	885	5	2288	12	1581	13	4914
Unknown	13 406	95	13 093	81	4755	25	453	4	31 707
Lymphovascular invasion									
No	8998	64	13 373	83	16 190	85	10 204	85	48 765
Yes	1899	14	2482	15	2313	12	1223	10	7917
Unknown	3145	22	322	2	453	2	564	5	4484

CCI, Charlson Comorbidity Index; ER, estrogen receptor.

and a decreasing proportion with four or more positive nodes ($p < 0.0001$) (Table 2). The number of patients with ER negative tumors was constant through the time periods, whereas the ER unknown significantly decreased from the first period, and the number of patients with ER positive tumors increased steadily with a peak for 2008–2010 (Table 2, Figure 1).

Table 3 shows the number of patients who within each period received available loco-regional and systemic therapies. The predominant primary type of surgery switched completely from mastectomy (77%) to BCS (67%) during the study period.

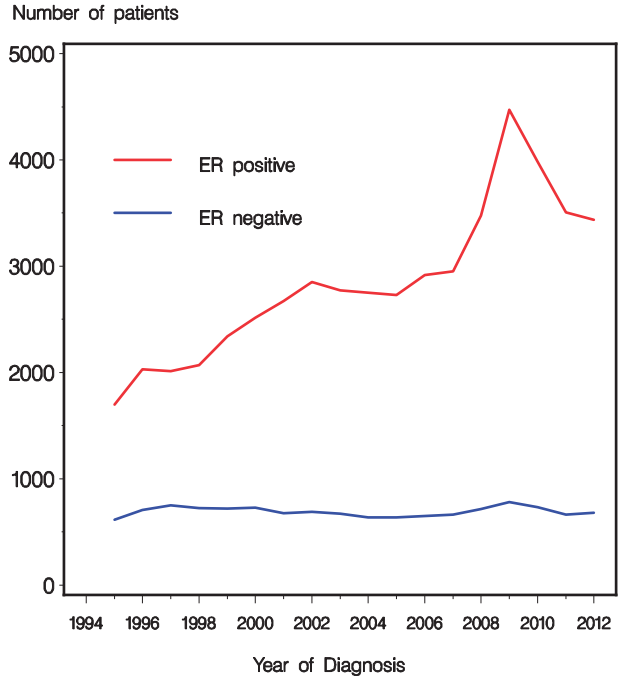

Figure 1. Number of patients diagnosed according to year and estrogen receptor (ER) status.

Among patients with mastectomy, the proportion receiving radiotherapy increased significantly in the second period, and then declined slowly. A similar pattern was seen regarding extending radiotherapy to regional nodes after lumpectomy. The use of systemic therapy increased significantly; the proportion of patients where systemic treatment were unknown dropped from 24% to 9%, and of the remaining patients, the proportion who did receive systemic therapy increased from 49% to 88%, comparing 1995–1999 with 2010–2012. An increase in the proportion of patients who received chemotherapy in addition to targeted therapy from 7% to 43% was seen. About half of those who received chemotherapy had a taxane-based regimen. In 80% of postmenopausal patients endocrine therapy included an aromatase inhibitor.

Using 1995–1999 as reference group, highly significant improvements were observed in the succeeding periods (Figure 2, Table 4, Supplementary Table 1–3) regarding mortality and SMR. The estimates for each time period improved adjusting for comorbidity at time of breast cancer diagnosis and further when also tumor extension was accounted (Figure 2A). Similar developments with even more distinct enhancements were seen when the results were restricted to the group of patients with early breast cancer (Figure 2B). The same pattern was seen for both mortality and SMR, although less pronounced for SMR (Figure 2C and D) reflecting the general improvements in survival in the Danish population. Adjustment for tumor characteristics slightly reduced the improvements ascribed time periods (Figure 2B and D).

Figure 3 shows the heterogeneity of improvement in mortality over time according to subgroups of age, CCI, ER status, and nodal status, respectively. Test for heterogeneity are shown. High age (Figure 3A) and high comorbidity score (Figure 3B) showed a less pronounced improvement, although still statistical significant ($p < 0.0001$). Also ER status and nodal status showed statistical significant heterogeneity for

Table 3. Treatment characteristics among patients with early breast cancer and known nodal status.

Year of inclusion			1995–1999		2000–20004		2005–2009		2010–2012		1995–2012
			N	%	*N*	%	*N*	%	*N*	%	*N*
Local regional treatment											
Mastectomy	RT	Yes	1505	11	3870	24	3258	17	1361	12	9994
		No	6165	44	3866	24	3680	17	1757	11	15 468
		Uknown[a]	3205	23	2510	16	890	5	241	2	6846
BCS	RT	Yes	2061	15	5117	32	9889	52	7308	61	24 375
		No[b]	20	0	325	2	307	2	207	2	859
		Uknown[a]	1086	8	483	3	703	4	562	5	2834
Neoadjuvant treatment			0	0	6	0	229	1	555	5	790
Adjuvant treatment											
CT	Yes		2463	18	4224	26	6028	32	4606	38	17 321
	No		8230	59	8408	52	10 570	56	6072	51	33 280
	Uknown[a]		3349	24	3545	22	2358	12	1313	11	10 565
ET	Yes		2924	21	7561	47	10 679	56	8277	69	29 441
	No		7717	55	5140	32	6349	33	2913	24	22 119
	Uknown[a]		3401	24	3476	21	1928	10	801	7	9606
HER2-targeted	Yes						1349	7	1285	11	
	No						14 003	74	9046	75	
	Uknown[a]						3604	19	1660	14	

BCS, breast conserving surgery; CT, chemotherapy; ET, endocrine treatment; RT, radiotherapy.
[a]Patients not enrolled into a treatment protocol (inclusion criteria not met) are not systematically registered with adjuvant treatment.
[b]Some of these patients may have had a subsequent mastectomy not reported.

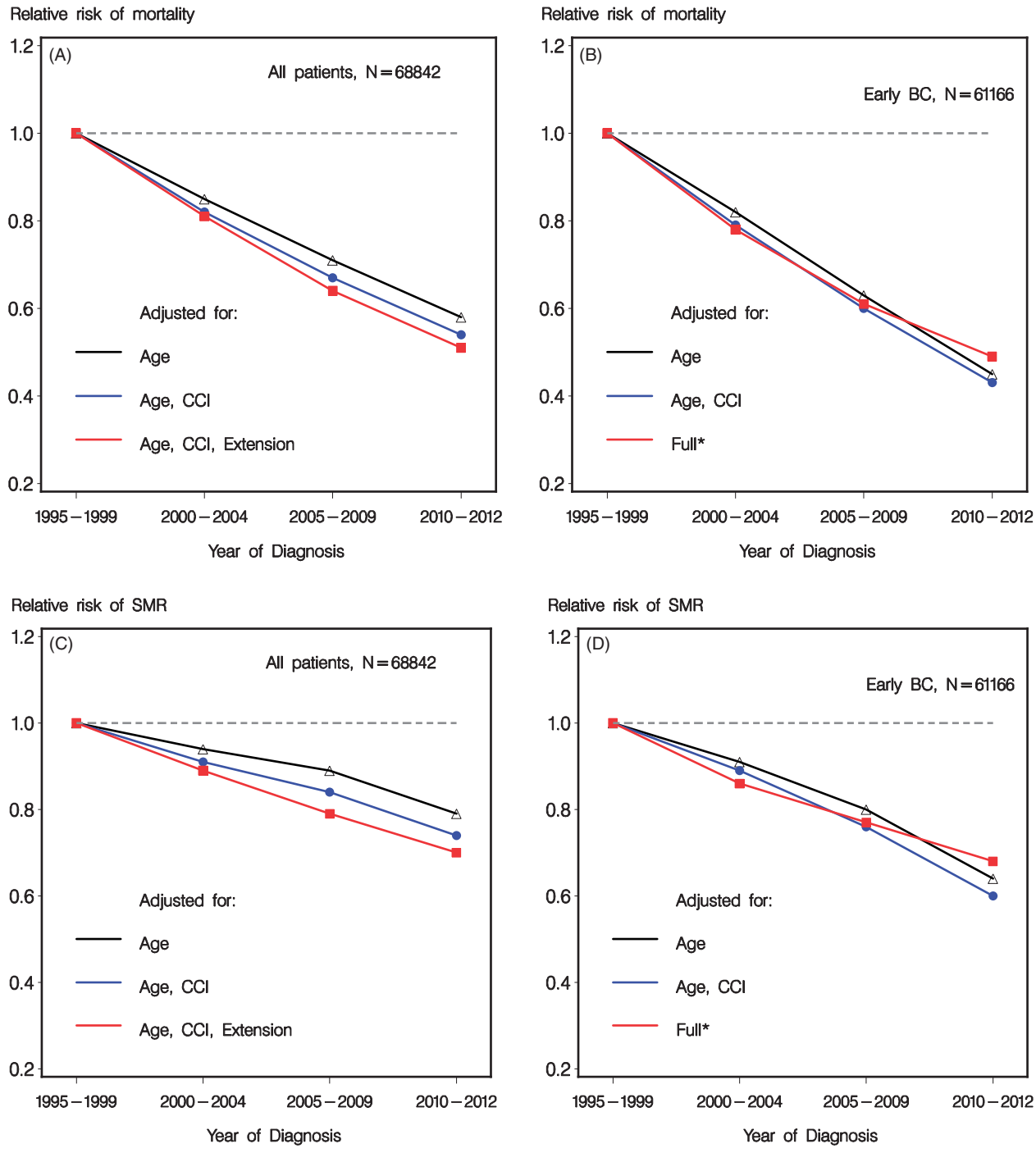

Figure 2. Relative risk of mortality (A and B) and SMR (C and D) according to calendar time, including all patients (A and C) and patients with early breast cancer and known nodal status (B and D). *Adjusted for age, CCI, tumor size, nodal status, histological type and grade, lymphovascular invasion and estrogen receptor status.

improvement over time (Figure 3C and D). No statistical significant heterogeneity according to tumor size (0–20 mm vs. 21 + mm) was seen ($p = 0.34$, data not shown). The analogous improvements in SMR over successive time periods are shown in Figure 4, where similar heterogeneity according to subgroups was seen. The improvement seen in mortality for the last time period and the youngest age group were modest (Figure 3A), translating to estimates of RR relating to SMR of 0.75 (95% CI 0.67; 0.84) for 2005–2009 and 0.80 (95% CI 0.66; 0.96) for 2010–2012, not being statistically different (Figure 4A). Patients with comorbidity score 3 + did not obtain a significant ($p = 0.58$) prognostic improvement (Figure 4B), although a trend of improvement was observed, with an estimate of 0.87 (95% CI 0.69; 1.10) for 2010–2012 compared to 1995–1999.

Discussion

The results presented show a significant improvement of the prognosis in breast cancer patients diagnosed in the period 1995–2012. Improvements were shown adjusted for of age, presence of comorbidities, and whether or not patients were considered operable at primary diagnosis. For patients with

Table 4. Overall survival (95% CI).

Year of inclusion				1995–1999	2000–2004	2005–2009	2010–2012	1995–2012
			Year					
			1	0.94 (0.94; 0.94)	0.95 (0.94; 0.95)	0.95 (0.95; 0.95)	0.96 (0.96; 0.96)	0.95 (0.95; 0.95)
			5	0.70 (0.69; 0.71)	0.74 (0.73; 0.74)	0.77 (0.76; 0.77)		0.75 (0.74; 0.75)
			10	0.51 (0.50; 0.52)	0.56 (0.55; 0.56)			
Age								
15–44			1	0.98 (0.98; 0.99)	0.98 (0.98; 0.98)	0.99 (0.99; 0.99)	0.99 (0.99; 0.99)	0.99 (0.99; 0.99)
			5	0.79 (0.78; 0.79)	0.87 (0.86; 0.87)	0.89 (0.88; 0.89)		0.86 (0.85; 0.86)
			10	0.68 (0.67; 0.68)	0.77 (0.76; 0.78)			
45–54			1	0.98 (0.97; 0.98)	0.98 (0.98; 0.98)	0.99 (0.98; 0.99)	0.99 (0.98; 0.99)	0.98 (0.98; 0.98)
			5	0.83 (0.83; 0.84)	0.87 (0.86; 0.87)	0.90 (0.90; 0.90)		0.87 (0.87; 0.88)
			10	0.73 (0.73; 0.74)	0.78 (0.78; 0.79)			
55–64			1	0.96 (0.96; 0.97)	0.97 (0.97; 0.97)	0.99 (0.98; 0.99)	0.99 (0.99; 0.99)	0.98 (0.98; 0.98)
			5	0.79 (0.79; 0.80)	0.83 (0.82; 0.83)	0.88 (0.88; 0.89)		0.85 (0.85; 0.85)
			10	0.65 (0.64; 0.65)	0.70 (0.70; 0.71)			
65–74			1	0.95 (0.94; 0.95)	0.96 (0.96; 0.96)	0.96 (0.96; 0.96)	0.97 (0.97; 0.98)	0.96 (0.96; 0.96)
			5	0.72 (0.71; 0.73)	0.77 (0.76; 0.77)	0.80 (0.79; 0.80)		0.78 (0.77; 0.78)
			10	0.52 (0.51; 0.53)	0.57 (0.56; 0.58)			
≥75			1	0.89 (0.88; 0.89)	0.89 (0.88; 0.89)	0.88 (0.88; 0.89)	0.91 (0.90; 0.91)	0.89 (0.89; 0.89)
			5	0.53 (0.52; 0.54)	0.55 (0.54; 0.56)	0.56 (0.55; 0.57)		0.55 (0.54; 0.55)
			10	0.25 (0.24; 0.26)	0.28 (0.27; 0.29)			
Cancer extension								
Localized	Nodal status	Negative	1	0.97 (0.97; 0.98)	0.98 (0.97; 0.98)	0.99 (0.98; 0.99)	0.99 (0.98; 0.99)	0.98 (0.98; 0.98)
			5	0.81 (0.80; 0.82)	0.84 (0.83; 0.85)	0.87 (0.86; 0.88)		0.85 (0.84; 0.85)
			10	0.63 (0.62; 0.64)	0.67 (0.66; 0.68)			
		Positive	1	0.93 (0.93; 0.94)	0.95 (0.94; 0.96)	0.96 (0.96; 0.97)	0.97 (0.96; 0.98)	0.95 (0.95; 0.96)
			5	0.62 (0.61; 0.63)	0.69 (0.68; 0.70)	0.75 (0.74; 0.76)		0.71 (0.70; 0.71)
			10	0.41 (0.40; 0.43)	0.49 (0.48; 0.50)			
		Unknown	1	0.84 (0.81; 0.87)	0.82 (0.78; 0.85)	0.84 (0.82; 0.87)	0.88 (0.86; 0.90)	0.85 (0.84; 0.87)
			5	0.52 (0.47; 0.56)	0.47 (0.43; 0.51)	0.54 (0.51; 0.57)		0.54 (0.52; 0.56)
			10	0.34 (0.30; 0.38)	0.30 (0.26; 0.34)			
Advanced		LABC	1	0.77 (0.71; 0.83)	0.74 (0.67; 0.80)	0.81 (0.77; 0.85)	0.86 (0.80; 0.90)	0.80 (0.77; 0.82)
			5	0.28 (0.22; 0.35)	0.28 (0.22; 0.35)	0.41 (0.36; 0.46)		0.35 (0.32; 0.39)
			10	0.17 (0.12; 0.23)	0.13 (0.09; 0.19)			
		DM	1	0.68 (0.64; 0.73)	0.60 (0.54; 0.66)	0.69 (0.65; 0.73)	0.77 (0.71; 0.82)	0.66 (0.63; 0.69)
			5	0.19 (0.16; 0.24)	0.21 (0.17; 0.26)	0.22 (0.18; 0.26)		0.22 (0.20; 0.25)
			10	0.09 (0.07; 0.13)	0.09 (0.06; 0.13)			
CCI								
0			1	0.95 (0.95; 0.96)	0.96 (0.95; 0.96)	0.96 (0.96; 0.97)	0.97 (0.97; 0.98)	0.96 (0.96; 0.96)
			5	0.73 (0.72; 0.74)	0.77 (0.76; 0.78)	0.81 (0.80; 0.81)		0.78 (0.77; 0.78)
			10	0.54 (0.53; 0.55)	0.59 (0.59; 0.60)			
1			1	0.92 (0.91; 0.93)	0.94 (0.93; 0.95)	0.94 (0.94; 0.95)	0.95 (0.94; 0.96)	0.94 (0.93; 0.94)
			5	0.63 (0.61; 0.66)	0.70 (0.68; 0.72)	0.73 (0.71; 0.74)		0.71 (0.70; 0.72)
			10	0.43 (0.41; 0.45)	0.50 (0.48; 0.52)			
2			1	0.89 (0.87; 0.91)	0.91 (0.89; 0.92)	0.93 (0.91; 0.94)	0.93 (0.91; 0.95)	0.92 (0.91; 0.93)
			5	0.57 (0.54; 0.61)	0.63 (0.60; 0.66)	0.68 (0.66; 0.71)		0.65 (0.63; 0.66)
			10	0.36 (0.33; 0.40)	0.44 (0.41; 0.47)			
≥3			1	0.85 (0.81; 0.88)	0.84 (0.81; 0.87)	0.87 (0.85; 0.89)	0.90 (0.87; 0.92)	0.86 (0.85; 0.88)
			5	0.50 (0.45; 0.55)	0.44 (0.40; 0.49)	0.51 (0.48; 0.54)		0.51 (0.49; 0.53)
			10	0.26 (0.22; 0.31)	0.25 (0.22; 0.29)			

CCI, Charlson Comorbidity Index; DM, distant metastatic; LABC, locally advanced breast cancer.

operable breast cancer improvements were shown irrespective of tumor size, lymph node status, and ER status. The improvement in SMR were 0.69 (95% CI 0.64; 0.74) comparing 2010–2012 with 1995–1999, and in the same period adjuvant treatment was extended considerable. Young age (≤35) was in 2002 included as an independent factor for allocation to systemic treatment, and gradually the low-risk group not having systemic treatment were raised and reached 60 years in 2010. For patients younger than 50 only a modest decrease in RR of mortality was obtained from 2005–2009 to 2010–2012 reflecting that treatment was not further improved beyond taxanes and trastuzumab. ER negative status was implemented as an independent factor for allocation to systemic treatment around 2000, and hereafter a marked improvement in outcome was seen compared to the previous period. The introduction of the sentinel node technique after 2001 resulted in stage migration with the potential of improved prognosis in both nodal groups.

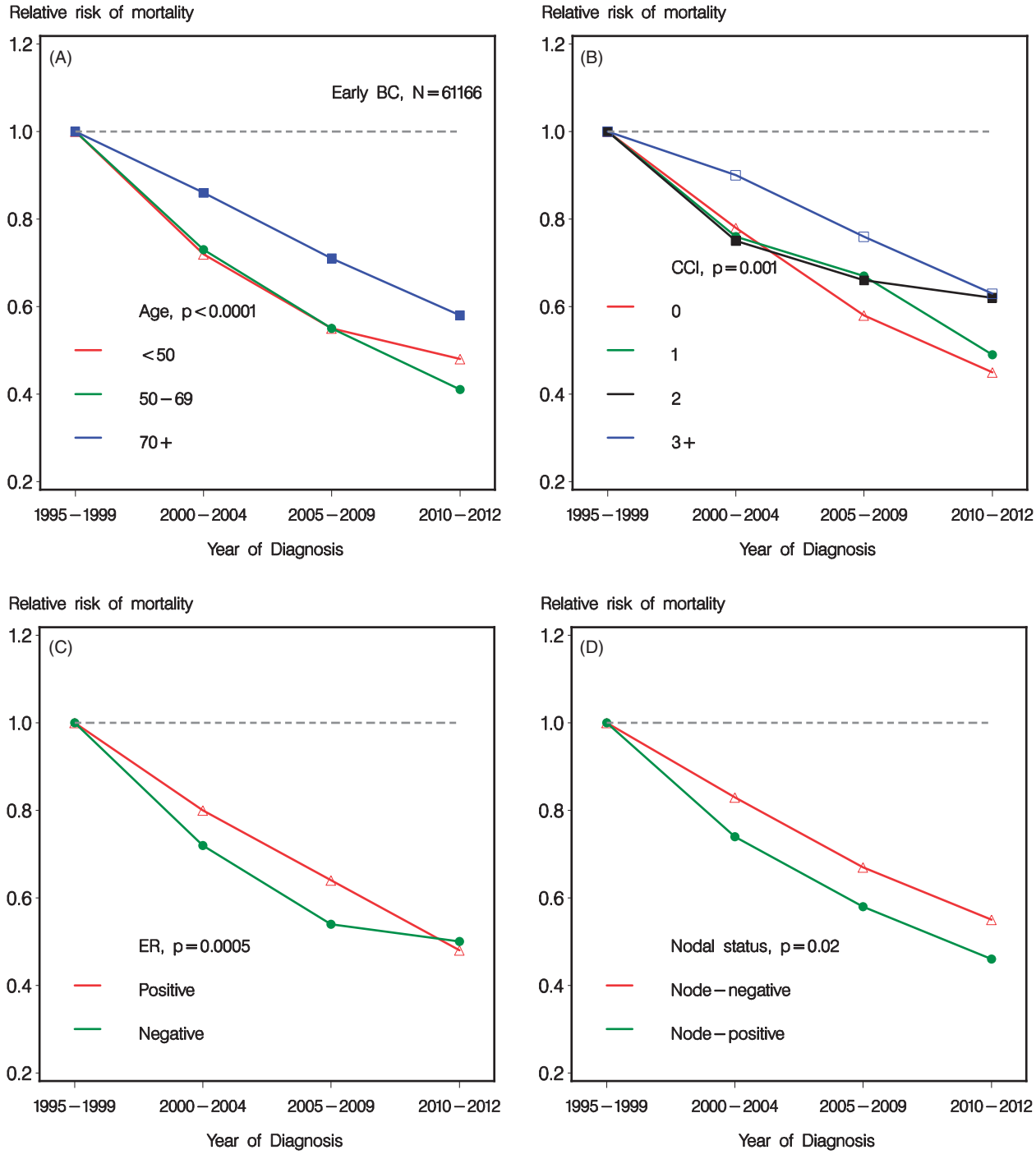

Figure 3. Relative risk of mortality according to calendar time and subgroups of age (A), CCI (B), estrogen receptor (ER) status (C), and nodal status (D), respectively. Including patients with early breast cancer and known nodal status and adjusted for age, CCI, tumor size, nodal status, histological type and grade, lymphovascular invasion and estrogen receptor status.

As a result of accumulating evidence and international consensus the use of adjuvant treatment increased significantly and the close linkage to the successive survival improvements, even with adjustment for changes in prognostic factors, supported a causal relationship.

Patients with a high comorbidity score did not achieve a statistical significant prognostic improvement, and this may in part be explained by reluctance towards adjuvant treatment in this group. Although improvements were observed in all age groups, patients 70 years and older obtained relatively less benefit which may have several explanations. Although the use of adjuvant treatment increased with time, patients 70 years or older were in contrast to younger patients not allocated to regional radiotherapy if node positive or to chemotherapy irrespective of other risk factors if ER negative in the 1990s and the beginning of the 2000s. The presence of comorbid conditions was significantly higher among older patients, and this may cause a restraint in applying optimal treatment regimens [21].

The proportion of patients with ER positive disease steadily increased during the study period [22]. In addition, the extension of screening covering the entire female population

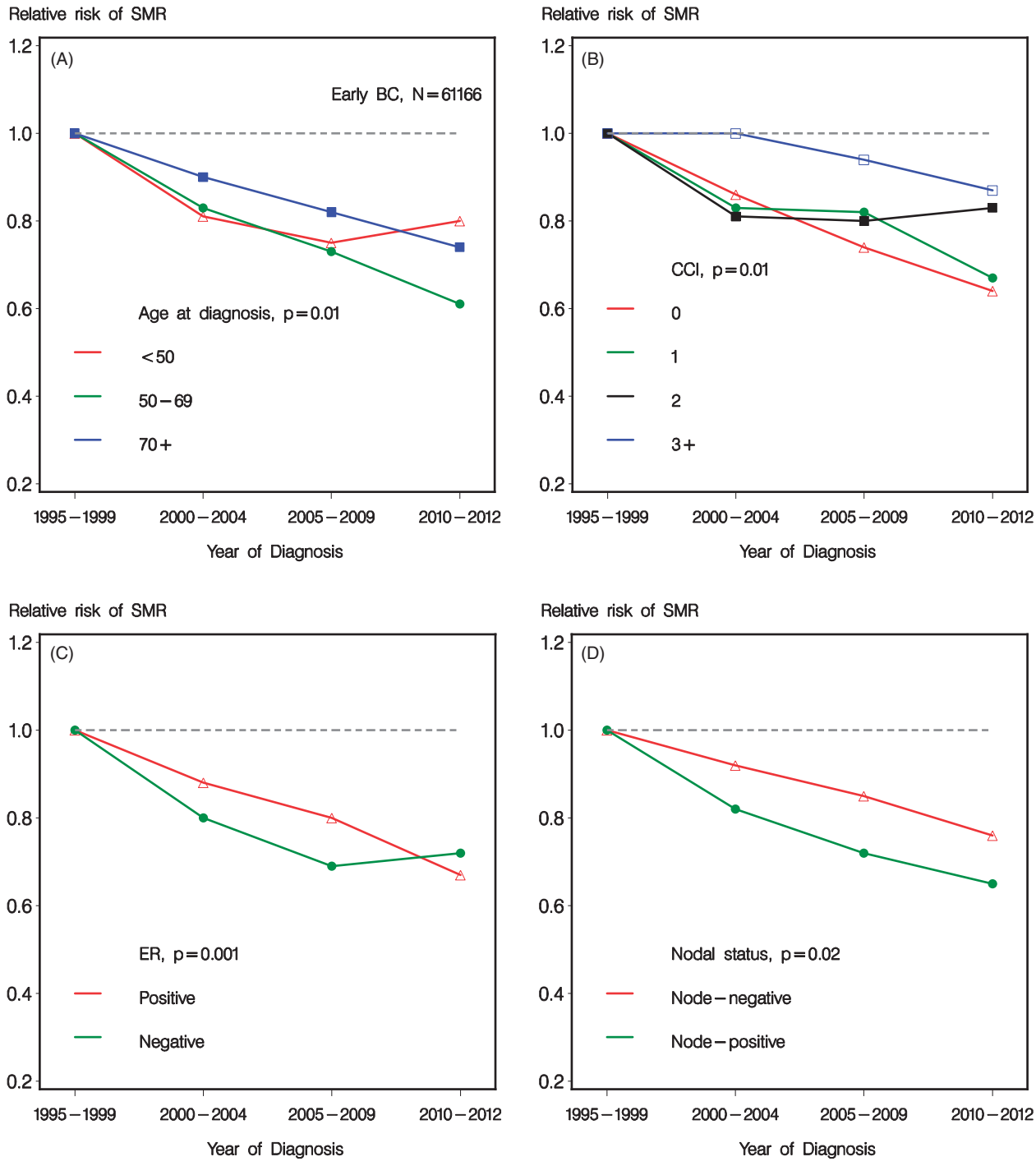

Figure 4. Relative risk of SMR according to calendar time and subgroups of age (A), CCI (B), estrogen receptor (ER) status (C), and nodal status (D), respectively. Including patients with early breast cancer and known nodal status and adjusted for age, CCI, tumor size, nodal status, histological type and grade, lymphovascular invasion and estrogen receptor status.

aged 50–69 years had an impact on prognostic factors, and especially a pronounced peak in incidence of ER positive cancer was seen. The improved prognosis was partly explained by these changes. This was apparent comparing estimates of improvements over time adjusted for age and CCI alone with estimates adjusted also for prognostic factors including tumor size, nodal status and hormone receptor status. The distinction was evident in the latest time period, when the changes in prognostic factors were observed. Thus, mammography screening had some influence on the observed survival improvements. Although the peak in ER positive patients observed with the introduction of nationwide screening partly explain the better prognosis overall, it does not solely explain a better outcome, as clear improvements were documented in the ER positive only subgroup. With this short time frame the impact of screening is limited to the age group 50–69, which constitutes just above half of the entire population.

The CISNET consortium reported the impact of screening and adjuvant treatment as modeled using SEER data by seven different research groups [23]. The models consistently showed that the observed mortality data could not be explained by

screening or adjuvant treatment alone. The relative improvements ascribed to screening and adjuvant treatment however varied considerable across models. Another limitation was that in the models the options for adjuvant treatment were restricted to tamoxifen and/or chemotherapy and the possible benefit of these treatments were prespecified according to age, year, stage and hormone receptor status. Two additional studies using SEER data attempted to analyze the relative contribution to improvement in breast cancer survival of screening and adjuvant treatment [24,25]. By evaluating secular trends in tumor size and ER status, these studies reversely concluded that the relative contribution of screening and adjuvant treatment were, respectively, the key component of the substantial improvements presented.

Several aspects should be considered when interpreting the present study. The large size and population-based design of our nationwide clinical database in an environment with free access to public healthcare minimized the potential risk of selection bias. Adjuvant treatment was registered in more than 90% of the patients in the last two periods but was unknown in a fourth of the patients in the first period. However, independent of time period the available data on adjuvant therapy are comprehensive and comparable to that of a clinical trial. Patients were included irrespective of availability of data on adjuvant treatment and linkage to the NPR and CPR registries ensured a complete follow-up for mortality and comorbidity in the entire population.

For the patient cohort presented in this study, the impact of screening was by nature very limited. Estimates for only one time period after the implementation of nationwide screening were available. The possibility of presenting data both before and after implementation of nationwide screening was a clear strength. The use of nationwide guidelines for treatment strategies together with a registration of the adherence hereof was obviously an advantage for the interpretation of the result presented. The results clearly demonstrated a significant improvement in prognosis in successive time periods covering 1995–2012. Apart from patients with a high CCI improvements were seen in all subgroups of patients. Except for CCI, prognostic factors were more favorable in the latest time period, and accordingly the impact of screening was obvious, although of limited magnitude. The successive modifications of treatment strategies implemented by the use of nationwide guidelines seemed to have a major impact.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary Table 1. Mortality per 100 person-years [95%CI].

Year of inclusion				1995–1999	2000–2004	2005–2009	2010–2012	1995–2012
			Year					
			0–1	6.20 [5.82;6.61]	5.64 [5.29;6.00]	5.19 [4.89;5.51]	4.06 [3.74;4.42]	5.28 [5.11;5.45]
			0–5	7.10 [6.90;7.31]	6.13 [5.96;6.31]	5.33 [5.18;5.48]		5.84 [5.75;5.94]
Age			0–10	6.84 [6.69;6.99]	5.91 [5.78;6.04]			
15–44			0–1	1.63 [0.39;6.85]	1.79 [0.48;6.69]	1.00 [0.18;5.52]	0.86 [0.08;8.94]	1.32 [0.60;2.93]
			0–5	4.75 [3.20;7.06]	2.83 [1.75;4.60]	2.40 [1.44;3.99]		3.02 [2.34;3.89]
			0–10	3.97 [2.87;5.48]	2.62 [1.81;3.79]			
45–54			0–1	2.38 [1.31;4.33]	1.85 [0.95;3.60]	1.39 [0.64;2.99]	0.94 [0.30;2.90]	1.69 [1.18;2.44]
			0–5	3.60 [2.87;4.51]	2.84 [2.22;3.64]	2.08 [1.55;2.77]		2.66 [2.32;3.06]
			0–10	3.14 [2.63;3.75]	2.49 [2.05;3.02]			
55–64			0–1	3.71 [2.64;5.21]	3.17 [2.29;4.40]	1.47 [0.97;2.22]	1.30 [0.72;2.34]	2.31 [1.90;2.81]
			0–5	4.66 [4.04;5.38]	3.81 [3.32;4.38]	2.48 [2.14;2.87]		3.23 [2.99;3.50]
			0–10	4.40 [3.94;4.90]	3.53 [3.17;3.93]			
65–74			0–1	5.28 [4.02;6.95]	3.97 [2.93;5.37]	3.89 [2.99;5.05]	2.75 [1.90;3.97]	3.97 [3.43;4.60]
			0–5	6.47 [5.75;7.28]	5.29 [4.67;5.98]	4.48 [3.99;5.03]		4.97 [4.65;5.30]
			0–10	6.45 [5.89;7.05]	5.54 [5.06;6.07]			
≥75			0–1	11.99 [9.79;14.69]	12.03 [10.02;14.43]	12.42 [10.44;14.77]	9.84 [7.76;12.48]	11.66 [10.58;12.86]
			0–5	12.59 [11.39;13.90]	12.00 [10.95;13.14]	11.70 [10.70;12.80]		11.83 [11.24;12.44]
			0–10	13.46 [12.44;14.57]	12.41 [11.55;13.34]			
Cancer Extension								
Localised	Nodal Status	Negative	0–1	2.60 [2.26;2.99]	2.23 [1.93;2.58]	1.46 [1.24;1.72]	1.44 [1.18;1.75]	1.90 [1.76;2.06]
			0–5	4.14 [3.94;4.36]	3.45 [3.26;3.64]	2.79 [2.64;2.95]		3.18 [3.09;3.28]
			0–10	4.58 [4.42;4.75]	3.93 [3.79;4.09]			
		Positive	0–1	6.85 [6.22;7.54]	5.11 [4.63;5.64]	3.66 [3.28;4.08]	2.88 [2.45;3.40]	4.60 [4.36;4.86]
			0–5	9.53 [9.16;9.92]	7.31 [7.03;7.61]	5.54 [5.31;5.78]		6.79 [6.64;6.94]
			0–10	8.99 [8.70;9.28]	7.07 [6.85;7.29]			
		Unknow	0–1	17.59 [15.34;20.18]	20.79 [18.35;23.56]	17.12 [15.06;19.46]	12.35 [10.47;14.56]	16.03 [14.94;17.19]
			0–5	13.94 [12.89;15.07]	16.30 [15.14;17.54]	12.88 [11.95;13.89]		13.20 [12.66;13.76]
			0–10	11.90 [11.13;12.73]	13.81 [12.95;14.73]			
Advanced	LABC		0–1	25.62 [16.93;38.79]	31.23 [23.69;41.17]	21.02 [16.63;26.57]	15.26 [10.81;21.53]	22.78 [19.75;26.28]
			0–5	26.75 [21.20;33.76]	26.81 [22.72;31.64]	18.65 [16.34;21.29]		21.46 [19.74;23.33]
			0–10	22.10 [17.79;27.45]	24.36 [20.95;28.32]			
	DM		0–1	40.08 [31.80;50.51]	52.69 [44.36;62.58]	38.44 [32.36;45.66]	27.79 [21.74;35.54]	43.27 [39.39;47.53]
			0–5	39.88 [34.56;46.03]	37.15 [32.89;41.96]	32.07 [28.77;35.75]		33.76 [31.66;36.00]
			0–10	34.96 [30.49;40.08]	33.50 [29.92;37.50]			
0			0–1	5.05 [4.67;5.45]	4.26 [3.93;4.61]	3.92 [3.62;4.24]	2.87 [2.56;3.22]	4.07 [3.90;4.24]
			0–5	6.24 [6.03;6.44]	5.18 [5.01;5.36]	4.27 [4.12;4.42]		4.93 [4.84;5.02]
			0–10	6.18 [6.03;6.34]	5.19 [5.05;5.32]			
1			0–1	8.28 [6.90;9.93]	6.65 [5.63;7.86]	6.21 [5.34;7.22]	4.77 [3.89;5.86]	6.30 [5.78;6.87]
			0–5	9.12 [8.38;9.93]	7.17 [6.64;7.74]	6.41 [5.97;6.88]		6.90 [6.62;7.19]
			0–10	8.65 [8.08;9.26]	7.01 [6.60;7.44]			
2			0–1	11.33 [9.07;14.14]	9.87 [8.11;12.01]	7.62 [6.23;9.32]	6.85 [5.28;8.89]	8.57 [7.68;9.56]
			0–5	11.26 [10.07;12.58]	9.33 [8.45;10.30]	7.74 [7.02;8.53]		8.80 [8.33;9.30]
			0–10	10.51 [9.60;11.51]	8.48 [7.83;9.20]			
≥3			0–1	16.26 [12.34;21.42]	18.08 [14.84;22.03]	13.91 [11.63;16.62]	11.12 [8.66;14.27]	14.67 [13.18;16.32]
			0–5	14.48 [12.46;16.82]	16.40 [14.73;18.27]	13.75 [12.54;15.08]		13.87 [13.07;14.71]
			0–10	13.77 [12.17;15.59]	14.74 [13.43;16.18]			

Abbreviations: CCI, Charlson Comorbidity Index. LABC, Locally Advanced Breast Cancer. DM, Distant Metastatic.

Supplementary Table 2. Relative Survival [95% CI].

Year of inclusion				1995–1999	2000–2004	2005–2009	2010–2012	1995–2012
			Year					
			1	0.97 [0.96;0.97]	0.97 [0.97;0.98]	0.97 [0.97;0.98]	0.98 [0.98;0.99]	0.97 [0.97;0.98]
			5	0.82 [0.81;0.83]	0.85 [0.84;0.86]	0.88 [0.87;0.88]		0.86 [0.85;0.86]
			10	0.72 [0.70;0.74]	0.77 [0.75;0.78]			
Age								
15–44			1	0.99 [0.98;0.99]	0.98 [0.98;0.98]	0.99 [0.99;0.99]	0.99 [0.99;0.99]	0.99 [0.99;0.99]
			5	0.79 [0.79;0.80]	0.87 [0.87;0.88]	0.89 [0.89;0.89]		0.86 [0.86;0.87]
			10	0.69 [0.68;0.70]	0.78 [0.78;0.79]			
45–54			1	0.98 [0.98;0.98]	0.99 [0.98;0.99]	0.99 [0.99;0.99]	0.99 [0.99;0.99]	0.99 [0.99;0.99]
			5	0.85 [0.85;0.86]	0.88 [0.88;0.89]	0.92 [0.91;0.92]		0.89 [0.89;0.89]
			10	0.77 [0.77;0.78]	0.82 [0.81;0.82]			
55–64			1	0.97 [0.97;0.98]	0.98 [0.97;0.98]	0.99 [0.99;0.99]	0.99 [0.99;1.00]	0.98 [0.98;0.99]
			5	0.84 [0.83;0.84]	0.86 [0.86;0.87]	0.92 [0.92;0.92]		0.89 [0.89;0.89]
			10	0.74 [0.73;0.75]	0.79 [0.78;0.79]			
65–74			1	0.97 [0.97;0.98]	0.98 [0.98;0.99]	0.98 [0.98;0.98]	0.99 [0.99;0.99]	0.98 [0.98;0.98]
			5	0.83 [0.82;0.84]	0.87 [0.86;0.87]	0.89 [0.88;0.89]		0.87 [0.87;0.88]
			10	0.73 [0.72;0.75]	0.77 [0.76;0.78]			
≥75			1	0.95 [0.95;0.96]	0.95 [0.95;0.96]	0.95 [0.94;0.95]	0.97 [0.96;0.97]	0.95 [0.95;0.96]
			5	0.80 [0.78;0.81]	0.81 [0.80;0.83]	0.81 [0.80;0.82]		0.81 [0.80;0.82]
			10	0.67 [0.65;0.70]	0.73 [0.71;0.76]			
Cancer Extension								
Localised	Nodal Status		Negative	1	1.00 [1.00;1.01]	1.01 [1.01;1.01]	1.01 [1.01;1.01]	1.01 [1.01;101]	1.01 [1.01;1.01]
				5	0.96 [0.94;0.97]	0.98 [0.96;0.99]	1.01 [1.00;1.02]		0.99 [0.98;0.99]
				10	0.92 [0.88;0.95]	0.95 [0.91;0.97]			
			Positive	1	0.96 [0.95;0.97]	0.98 [0.97;0.98]	0.99 [0.98;0.99]	0.99 [0.98;1.00]	0.98 [0.98;0.98]
				5	0.72 [0.70;0.74]	0.80 [0.78;0.81]	0.86 [0.85;0.88]		0.81 [0.80;0.82]
				10	0.58 [0.55;0.61]	0.67 [0.65;0.70]			
			Unknow	1	0.87 [0.83;0.90]	0.84 [0.81;0.87]	0.87 [0.84;0.89]	0.91 [0.88;0.93]	0.88 [0.87;0.89]
				5	0.62 [0.57;0.66]	0.56 [0.51;0.60]	0.61 [0.58;0.65]		0.63 [0.61;0.65]
				10	0.49 [0.43;0.54]	0.43 [0.38;0.48]			
Advanced		LABC		1	0.78 [0.71;0.84]	0.76 [0.69;0.82]	0.83 [0.79;0.87]	0.88 [0.82;0.92]	0.82 [0.79;0.85]
				5	0.30 [0.23;0.37]	0.30 [0.23;0.37]	0.46 [0.40;0.52]		0.40 [0.36;0.44]
				10	0.19 [0.13;0.26]	0.14 [0.09;0.21]			
		DM		1	0.69 [0.64;0.74]	0.62 [0.56;0.67]	0.71 [0.66;0.75]	0.78 [0.72;0.83]	0.68 [0.65;0.70]
				5	0.17 [0.13;0.21]	0.22 [0.17;0.27]	0.24 [0.20;0.29]		0.24 [0.22;0.27]
				10	0.09 [0.06;0.13]	0.09 [0.06;0.14]			
CCI								
0			1	0.98 [0.97;0.98]	0.99 [0.98;0.99]	0.99 [0.98;0.99]	1.00 [0.99;1.00]	0.99 [0.98;0.99]
			5	0.86 [0.85;0.87]	0.90 [0.89;0.91]	0.93 [0.92;0.94]		0.91 [0.90;0.91]
			10	0.78 [0.76;0.80]	0.84 [0.82;0.86]			
1			1	0.95 [0.93;0.96]	0.96 [0.95;0.97]	0.96 [0.95;0.97]	0.98 [0.97;0.99]	0.96 [0.96;0.97]
			5	0.73 [0.70;0.76]	0.81 [0.78;0.83]	0.82 [0.80;0.84]		0.81 [0.80;0.82]
			10	0.57 [0.53;0.61]	0.68 [0.64;0.71]			
2			1	0.92 [0.90;0.94]	0.93 [0.91;0.95]	0.95 [0.93;0.96]	0.96 [0.93;0.97]	0.94 [0.93;0.95]
			5	0.67 [0.62;0.71]	0.72 [0.69;0.75]	0.77 [0.74;0.80]		0.74 [0.72;0.76]
			10	0.50 [0.44;0.56]	0.59 [0.54;0.63]			
≥3			1	0.88 [0.83;0.91]	0.86 [0.83;0.89]	0.89 [0.87;0.91]	0.92 [0.89;0.94]	0.89 [0.87;0.90]
			5	0.57 [0.51;0.63]	0.51 [0.46;0.56]	0.57 [0.53;0.61]		0.57 [0.55;0.60]
			10	0.35 [0.28;0.41]	0.33 [0.28;0.38]			

Abbreviations: CCI, Charlson Comorbidity Index. LABC, Locally Advanced Breast Cancer. DM, Distant Metastatic.

Supplementary Table 3. Relative risk (95% CI) of mortality (A and B) and SMR (C and D) according to calendar time, including all patients (N = 68,842, A and C) and patients with early breast cancer and known nodal status (N = 61,166, B and D). See Figure 2.

Year of inclusion	1995–1999	2000–2004	2005–2009	2010–2012
Mortality				
A				
Age	Ref	0.85 (0.82;0.87)	0.71 (0.69;0.74)	0.58 (0.55;0.61)
Age, CCI	Ref	0.82 (0.79;0.84)	0.67 (0.65;0.70)	0.54 (0.51;0.57)
Age, CCI, Extension	Ref	0.81 (0.78;0.83)	0.64 (0.61;0.66)	0.51 (0.67;0.74)
B				
Age	Ref	0.82 (0.79;0.85)	0.63 (0.61;0.66)	0.45 (0.42;0.49)
Age, CCI	Ref	0.79 (0.77;0.82)	0.60 (0.58;0.40)	0.43 (0.40;0.46)
Full[1]	Ref	0.78 (0.75;0.81)	0.61 (0.59;0.64)	0.49 (0.46;0.52)
SMR				
C				
Age	Ref	0.94 (0.91;0.97)	0.89 (0.86;0.92)	0.79 (0.75;0.84)
Age, CCI	Ref	0.91 (0.88;0.94)	0.84 (0.81;0.87)	0.74 (0.70;0.78)
Age, CCI, Extension	Ref	0.89 (0.87;0.92)	0.79 (0.77;0.82)	0.70 (0.67;0.74)
D				
Age	Ref	0.91 (0.88;0.95)	0.80 (0.77;0.84)	0.64 (0.60;0.69)
Age, CCI	Ref	0.89 (0.86;0.92)	0.76 (0.73;0.80)	0.60 (0.56;0.65)
Full[1]	Ref	0.86 (0.83;0.89)	0.77 (0.74;0.80)	0.69 (0.64;0.74)

Abbreviations: CCI, Charlson Comorbidity Index. SMR, Standardised Mortality Rate. Ref, Reference group. [1]Adjusted for age, CCI, tumor size, nodal status, histological type and grade, lymphovascular invasion and estrogen receptor status.