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Breast cancer survival trends in different stages and age groups – a population-based study 1989–2013

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ABSTRACT

Background: During the recent decades, breast cancer survival has gradually improved but there is limited knowledge on the improvement in population-based studies of patients diagnosed with different stages of the disease and in different age groups.

Patients and methods: In two Swedish health care regions a total of 42,220 female breast cancer patients below 90 years of age were diagnosed between 1989 and 2013. They were treated and followed according to national and regional guidelines and formed a population-based cohort.

Results: Using patients diagnosed in 1989–1993 as a reference to the relative risk, 5-year mortality decreased with 49% for patients diagnosed at the end of the observation period (CI 95% 45–58). The mortality tended to decrease for patients with all stages of breast cancer and test for trend resulted in a statistically significant improvement over time in 5-year relative survival in stage III and IV and in 10-year survival in stage I and III. For each operable stage of disease, patients aged below 40 years or more than 70 years when diagnosed tended to have less favorable survival than patients diagnosed between 40–69 years of age. Test for trend resulted in statistically significant improvements over time for patients diagnosed at ages below 40, 40–54 and 54–69, but less marked improvements for patients older than 70 when diagnosed.

Conclusions: During the period 1989–2013 the relative risk of 5-year mortality decreased with 49%. Improvements were seen in all age groups but were unevenly distributed between stages and age groups pointing to the need for further improvements for younger and elderly patients.

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Introduction

During the last decades, there has been a marked improvement in the survival of patients diagnosed with breast cancer [1]. In the United States, the five-year relative survival rates for women with breast cancer have improved from 75% in 1975–1977 to 90% in 2003–2009 [2]. In the period 1995–1999, England and Denmark had modest five-years breast cancer survival rates of 74% and 76% but are closing the international gap and for 2005–2009 reported survival rates of 81% and 82%. Sweden, Australia and Canada have reported less marked increases from 84% to 86% during the same time periods [3]. Early diagnosis and more effective therapy have contributed. There is limited information from population-based studies on the distribution of stages at diagnosis over time and quantifications of the improvement of survival in different stages of disease and in different age groups. However, studies of patients diagnosed with metastatic disease show little or no improved survival [4] and patients younger than 35 years at diagnosis seem to have worse prognosis [5]. Fredholm et al. have shown that young women have a high risk of distant recurrence even when diagnosed in an early stage and that the risk of relapse is most pronounced with Luminal B tumors. With these tumors, low age is an independent unfavorable prognostic factor of distant disease-free survival and loco-regional recurrence-free survival [5].

In Sweden, breast cancer constitutes about 30% of all female cancers and all incident cancers are registered in the Swedish Cancer register with a high completeness [6]. After publication of the results of the first randomized trials investigating population-based mammography screening [7], Sweden introduced a nationwide screening for women 50–69 years old in the 1980s. Population-based screening was gradually introduced in the two regions starting 1978 in Östergötland (Southeastern region) as part of the WE trial and in 1982 in the western region with the Gothenburg trial [8]. By 1988 screening was introduced in all parts of the regions. In the entire southeastern region and in parts of the western region women 40–74 were invited but in most parts

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of the western region women 50–74 were screened. The patients studied in the present report were diagnosed after the introduction of the public mammography-screening program. The national guidelines in Sweden for the treatment of breast cancer, follow the St Gallen guidelines [9] and the differences in treatment between regions are small.

The aim of this study was to analyze the development of the stage-specific and the age groups specific survival during the last 25 years in a population with public mammography screening and homogenous treatment principles.

Material and methods

Cancer registration

In Sweden, cancer care for the 10 million inhabitants is organized in six healthcare regions. In each region, there is a regional cancer center responsible for cancer registration and cancer management programs. In Sweden, it has been compulsory since 1958 for both the treating physician and the pathologist/cytologist to independently notify the Swedish cancer register (SCR) of all new incidences of cancer. The SCR receives reports containing the ICD code of the malignancy, the histological systematized nomenclature of medicine (SNOMED) code, the TNM stage of the disease, the date of diagnosis, the date of birth for the patient and the personal identification number unique to each individual in Sweden. The completeness of the national register is about 96% [6]. Majority of the patients are also regionally registered in clinical cancer registers. These registers contain more detailed information about incident tumor characteristics and primary treatment. For breast cancer, >95% of the patients are treated according to a national management program and registered in the clinical cancer register databases associated with the program [10].

The cohort

This study includes all patients ($n = 42{,}220$) below 90 years of age with their first breast cancer diagnosed in the southeastern and the western regions of Sweden (2.5 million inhabitants) between 1989–2013.

Ethical approval

The present study was approved by the Gothenburg Regional Ethical Review Board. (Dnr 248-17)

Patient management routines

The vast majority of patients with breast cancer in both the southeast and the western regions have been treated and followed up according to the common guidelines developed and updated by the national Swedish Breast Cancer Group. This includes yearly mammograms. Investigations for distant recurrence were only performed in the presence of symptoms. The breast cancer treatments have been in accordance with the up-dated St Gallen guidelines [9].

Statistical methods

Relative survival was computed using the Ederer II method [11]. Age standardization was applied according to International Cancer Survival Standard 1 (ICSS 1) with the weights 0.04, 0.15, 0.37 and 0.44 for the age groups <40, 40–55, 55–69 and ≥70, respectively. The weights 0.44, 0.22, 0.17, 0.14 and 0.03 were used for the stage standardization for stage I, II N0, II N+, III and IV, respectively. Mortality data for the general population in Sweden was used to estimate expected survival rates for the study populations. The mortality data comprised the probability of death for single-year age groups in 1-year calendar periods. Survival time was calculated from date of diagnosis to 31 December 2014 or to date of death if it occurred before that date. For each stage, excess mortality rate ratio between different calendar periods was estimated using Poisson regression, including the categorical variables year of diagnosis (in groups of five calendar years each) and *age group*.

In Figure 2 and Figure 3, in order to increase the number of patients in each calendar period, the years of diagnosis were grouped into variables containing three calendar years, so that year 1990 represents the years of diagnosis 1989–1991 and year 1993 represents the years 1992–1994 and so on.

In order to investigate for which stage(s) the relative survival has/have improved most over time, we applied a linear regression model including stage, the continuous variable year of diagnosis and an interaction term between these two variables. The statistical significance of the interaction term was examined using the likelihood ratio test. A p value of <.05 was considered to be statistically significant. All statistical analyses were performed with Stata/SE 13.1.

Results

Stage distribution

During the period 1989–2013 the number of patients diagnosed with breast cancer per year gradually increased, from 1480 in 1989 to 2069 in 2013, an increase of 40%. The disease of all patients were staged according to the 2009 version of the WHO classification [12]. Of all 42,220 patients, 44% had stage I disease, 22% stage II N0 and 18% Stage II with lymph node involvement; 14% had stage III disease, while 3% diagnosed with stage IV disease did not have surgery with curative intention. For 6% of the patients, stage was not registered (Table 1). The proportion of patients diagnosed in different stages of disease was relatively stable during the period, however patients in stage I were slightly more common during the second half of the period and the changes in stage distribution are statistically significant over time. ($p < .001$). Among patients aged less than 40 years at diagnosis, 29% had stage I disease as compared to 52% for those diagnosed between 55–69 and 44% for the entire cohort (Table 2).

Table 1. Number of patients per stage and percent per stage at indicated time periods.

	Stage (%)						
Year of diagnosis	I	II N0	II N+	III	IV	Unknown	Total
1989–1993	2831 (42)	1586 (24)	1102 (16)	983 (15)	224 (3)	428	7154
1994–1998	3164 (44)	1663 (23)	1098 (15)	1014 (14)	200 (3)	537	7676
1999–2003	3531 (44)	1859 (23)	1363 (17)	1173 (14)	185 (2)	601	8712
2004–2008	3825 (44)	1790 (21)	1691 (19)	1179 (14)	223 (3)	344	9052
2009–2013	4132 (45)	1925 (21)	1718 (19)	1120 (12)	260 (3)	471	9626
Total	17483 (44)	8823 (22)	6972 (18)	5469 (14)	1092 (3)	2381	42220

Table 2. Number of patients per stage and percent per stage in indicated age groups.

	Stage (%)						
Age	I	II N0	II N+	III	IV	Unknown	Total
<40	442 (29)	337 (22)	358 (23)	368 (24)	39 (3)	85	1629
40–54	4553 (44)	1982 (19)	2035 (20)	1607 (15)	196 (2)	554	10927
55–69	7950 (52)	2590 (17)	2597 (17)	1708 (11)	330 (2)	718	15893
70–89	4538 (36)	3914 (31)	1982 (16)	1786 (14)	527 (4)	1024	13771
Total	17483 (44)	8823 (22)	6972 (18)	5469 (14)	1092 (3)	2381	42220

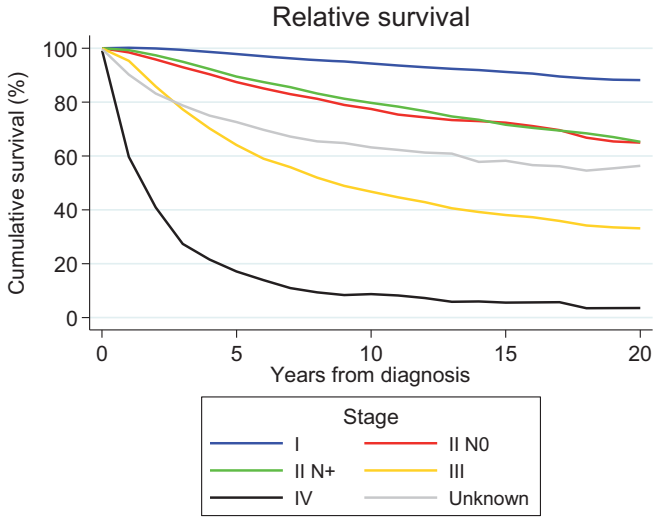


Figure 1. Survival of breast cancer patients diagnosed 1989–2013 with different stages of the disease.

Survival by stage

Figure 1 and Table 3 illustrate survival by stage. Interestingly, the survival for stage II patients with nodal involvement was very similar to that of stage II patients without nodal involvement.

Changes in excess mortality rate

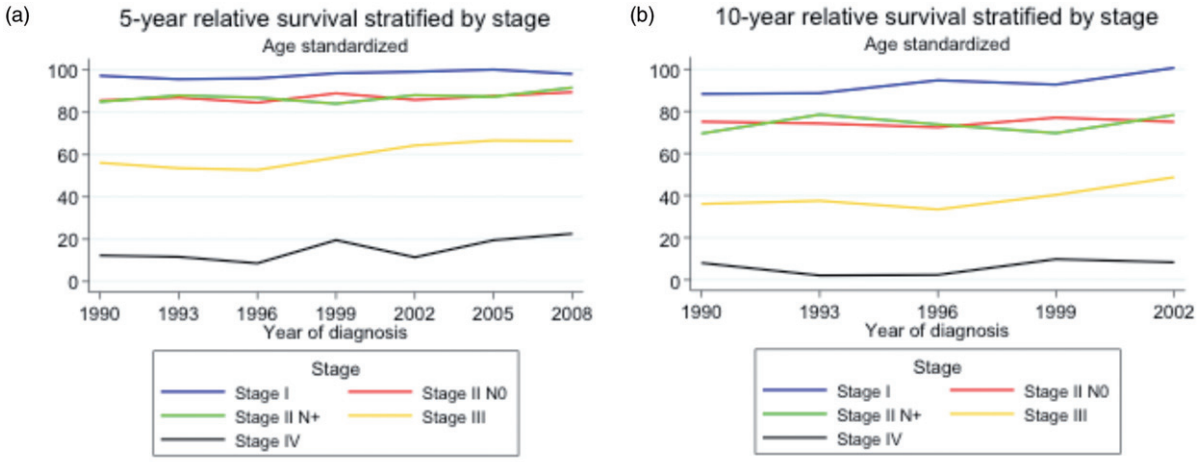
Using all patients diagnosed between 1989–1993 as reference, the 5- and 10-years excess mortality rate ratio subsequently diminished in patients treated 1994–1998, 1999–2003, 2004–2008, 2009–2013 (Table 4). For patients treated 2009–2013 the excess mortality rate up to five years of follow-up was 0.51(CI 95% 0.45–0.58) and in patients treated 2004–2008 the 10 years excess mortality rate 0.60(CI 95% 0.55–0.66) in comparison to patients treated 1989–1993 (Table 4).

Table 3. Survival at indicated years for patients diagnosed 1989–2013 with different stages of the disease.

Stage	Endpoint (years)	Survival% (95 % CI)
I	5	97.8 (97.4–98.4)
	10	94.3 (93.5–95.2)
	15	91.2 (89.9–92.5)
	20	88.2 (86.1–90.2)
IIN0	5	87.4 (86.3–88.5)
	10	77.5 (75.8–79.1)
	15	72.4 (70.2–74.6)
	20	65.0 (61.8–68.2)
IIN+	5	89.5 (88.4–90.5)
	10	79.8 (78.2–81.3)
	15	71.6 (69.4–73.8)
	20	65.3 (62.1–68.4)
III	5	64.1 (62.6–65.6)
	10	46.8 (45.0–48.6)
	15	38.1 (36.0–40.3)
	20	33.2 (30.5–35.9)
IV	5	17.1 (14.6–19.8)
	10	8.7 (6.6–11.3)
	15	5.6 (3.4–8.6)
	20	3.6 (1.4–7.6)

Table 4. Five respectively ten-year excess mortality ratio (EMR) in the indicated stages and time periods.

Stage	Year of diagnosis	5-year EMR (95 % CI)	*p* value	10-year EMR (95 % CI)	*p* value
I	1989–1993	1.00		1.00	
	1994–1998	1.37 (0.91–2.07)	.13	0.88 (0.66–1.18)	.40
	1999–2003	0.65 (0.40–1.08)	.10	0.72 (0.53–0.97)	.03
	2004–2008	0.59 (0.36–0.99)	.04	0.55 (0.39–0.78)	.001
	2009–2013	0.39 (0.16–0.92)	.03		
II N0	1989–1993	1.00		1.00	
	1994–1998	1.05 (0.81–1.34)	.72	1.01 (0.83–1.23)	.90
	1999–2003	0.78 (0.60–1.03)	.08	0.75 (0.60–0.92)	.006
	2004–2008	0.79 (0.61–1.04)	.09	0.70 (0.56–0.87)	.001
	2009–2013	0.80 (0.60–1.09)	.16		
II N+	1989–1993	1.00		1.00	
	1994–1998	0.83 (0.62–1.10)	.20	0.95 (0.77–1.18)	.001
	1999–2003	0.70 (0.53–0.93)	.02	0.68 (0.55–0.85)	<.001
	2004–2008	0.58 (0.43–0.77)	<.001	0.56 (0.44–0.70)	<.001
	2009–2013	0.44 (0.30–0.65)	<.001		
III	1989–1993	1.00		1.00	
	1994–1998	0.99 (0.86–1.15)	.92	0.96 (0.85–1.10)	.59
	1999–2003	0.75 (0.64–0.87)	<.001	0.74 (0.65–0.84)	<.001
	2004–2008	0.65 (0.56–0.77)	<.001	0.64 (0.56–0.73)	<.001
	2009–2013	0.52 (0.43–0.63)	<.001		
IV	1989–1993	1.00			
	1994–1998	0.98 (0.79–1.21)	.87		
	1999–2003	0.91 (0.73–1.13)	.40		
	2004–2008	0.83 (0.67–1.03)	.08		
	2009–2013	0.69 (0.55–0.86)	.001		
Total	1989–1993	1.00		1.00	
	1994–1998	0.94 (0.85–1.03)	.19	0.90 (0.83–0.98)	.02
	1999–2003	0.69 (0.62–0.77)	<.001	0.69 (0.63–0.75)	<.001
	2004–2008	0.62 (0.56–0.69)	<.001	0.60 (0.55–0.66)	<.001
	2009–2013	0.51 (0.45–0.58)	<.001		



	Coefficient for linear trend (95 % CI)			
Stage	5-year	P value	10-year	P value
I	0.0016 (-0.000048 – 0.0033)	0.06	0.0096 (0.0042 – 0.015)	0.002
II N0	0.0017 (-0.00037 – 0.0037)	0.10	0.00057 (-0.0038 – 0.0049)	0.78
II N+	0.0026 (-0.00028 – 0.0054)	0.07	0.0030 (-0.0048 – 0.011)	0.42
III	0.0080 (0.0044 – 0.012)	< 0.001	0.0089 (0.0012 – 0.017)	0.03
IV	0.0051 (0.00065 – 0.0095)	0.03	0.0023 (-0.0055 – 0.010)	0.52

Figure 2. Development of 5 and 10 years relative survival in patients with different stages of breast cancer, 1989–2013.

Changes in excess mortality rate by stage

Table 4 shows a gradual decrease of the five-year excess mortality rate for patients diagnosed with all stages but the decrease was most pronounced and statistically significant for patients with stages I, II N + and III. Also, the ten-year excess mortality rate decreased for patients diagnosed with stages I, II N0, II N + and III.

For stage IV patients the three-year excess mortality rate ratio shows a significant decrease of approximately 30% between 1989–1993 and 2009–2013.

We also performed tests for interaction to investigate whether the improvement of mortality was significantly different between the stages. The relative improvement for stage I patients was used as base for comparisons. As compared to stage I patients, five years excess mortality rate was significantly more improved for patients with stage III. However, we found no statistically significant differences in the relative improvements of ten-year excess mortality between patients with stage I disease and patients with stages II N+, III or IV disease.

Relative survival rates

Between 1989–1991 and 2007–2009, the five years survival rates for stage I increased from 97% to 98% while between 1989–1991 and 2001–2003 ten years survival increased from 88% to 100% as shown in Figure 2.

Interestingly the survival rate increased more for Stage II N + patients as compared to stage II N0 patients. Between 1989–1991 and 2007–2009 five year rates increased from 86% (N0) and 85%(N+) to 90%(N0) respectively 92%(N+) while between 1990 and 2002, 10 years survival increased from 75%(N0) and 69%(N+) to 75%(N0) respectively 78%(N+), though with overlapping 95% confidence intervals.

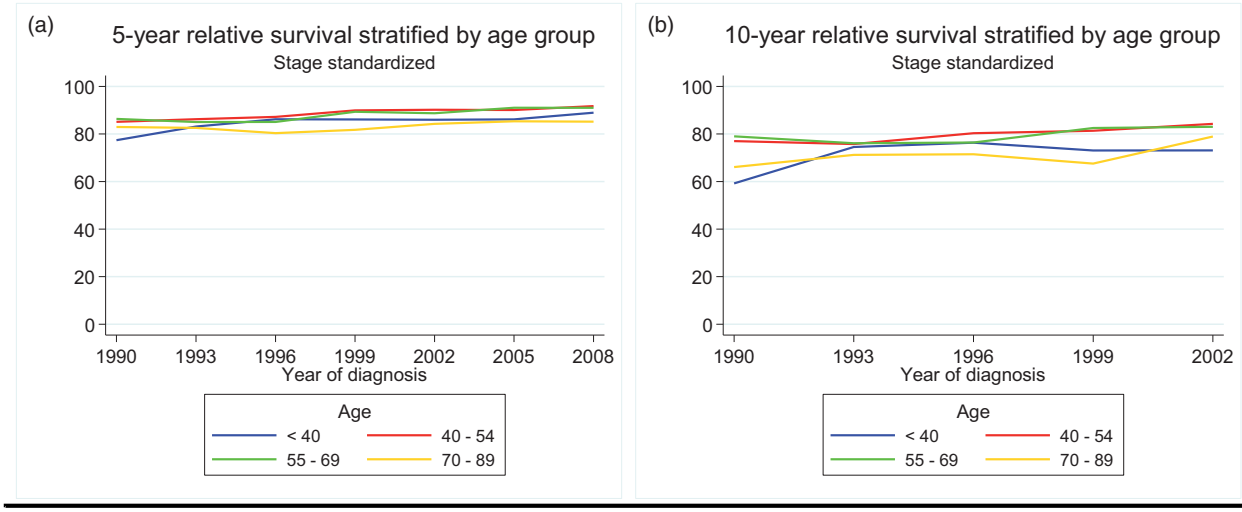
Between 1989–1991 and 2007–2009 five years survival for stage III patients increased from 56% to 66% while between 1989–1991 and 2001–2003 ten years survival increased from 36% to 49%. Thus the improvement for stage III patients was more marked than that observed for patients with other stages of the disease.

Between 1989–1991 and 2007–2009 five years survival for stage IV patients increased from 12% to 23% while between 1989–1991 and 2001–2003 ten years survival remained below 10%.

The changes in 5- and 10-year relative survival rates and statistical analyses of tests for trend in different stages over the observation period are illustrated in Figure 2. For stage III and IV, the test for trend demonstrates a statistically significant improvement in 5-year survival over the observation period and 10-year survival was significantly improved for patients with stage I and III (Figure 2).

Changes in mortality rate in different age-groups

Patients less than 40 or older than 70 years at diagnosis tended to have more unfavorable prognosis as compared to



	Coefficient for linear trend (95 % CI)			
Age	5-year	P value	10-year	P value
< 40	0.0058 (-0.000032 – 0.012)	0.05	0.0098 (0.0011 – 0.018)	0.03
40 – 54	0.0038 (0.0027 – 0.0050)	< 0.001	0.0071 (0.0035 – 0.011)	0.001
55 - 69	0.0036 (0.0023 – 0.0048)	< 0.001	0.0048 (0.0013 – 0.0083)	0.01
70 - 89	0.0016 (-0.00022 – 0.0035)	0.08	0.0070 (-0.00022 – 0.014)	0.06

Figure 3. Development of 5 and 10 years relative survival in patients diagnosed 1989–2013 and stratified by age group.

patients 40–69 (Figure 3). In Figure 3 the changes in 5- and 10-year survival in the different age groups, standardized for stage, are shown. The test for trend indicates statistically significant improvements of 5- and 10-year excess mortality for the age groups below 40, 40–54 and 55–69 at diagnosis (Figure 3). For the age group 70–89 at diagnosis, we registered less improvement.

Discussion

It was more common for patients aged 55–69 to be diagnosed with stage I disease as compared to younger or older patients. This can be explained by their high attendance in the mammography screening and the fact that mammography is known to be an effective diagnostic tool in this age group.

In this Swedish population-based prospective cohort study the main finding is the 49% relative decrease in five-year mortality in patients diagnosed 2009–2013 compared to those diagnosed 1989–1993. Positive changes in survival rates were seen for patients with all stages of disease but test for interaction demonstrated that improvements in five-year survival were significantly more marked for stage I, II N+, III and stage IV disease. Chen et al [13] were able to show that in the US from 1992 to 2006, the improvements were more marked for stage III and IV patients. As discussed below, changes in treatment probably contributed to the prolonged survival but as pointed out by Andersson et al. lead-time bias may also have influenced the result since the attendance to mammography screening has become higher and the mammography technique improved during the study period [14].

During the period 1989–2013, treatment was given according to national guidelines and best international practice but standards were gradually changed and it reasonable to believe that some of these changes have influenced survival. Important changes were the prolongation of adjuvant tamoxifen therapy to five years in 1996 and subsequently the introduction of aromatase inhibitors. Also, adjuvant chemotherapy has been much improved by the introduction of anthracyclines, taxanes and potent antiemetics and after its initial use for premenopausal patients with metastatic axillary nodes its use has been expanded to include postmenopausal patients and many stage I patients. More frequently used chemotherapy in stage II N+than in stage II N0 may explain the slightly better outcome seen in the former group. Also, the introduction of trastuzumab around the year 2000 has influenced survival of patients with HER 2 positive disease.

As pointed out by Fredholm et al. [5], newer and more intense treatments with chemotherapy and trastuzumab were first offered to young women while adjuvant tamoxifen was first introduced for postmenopausal women. These differences probably influenced age-related survival differences.

Sheridan et al [15] investigated whether the poor prognosis for young patients remains after the introduction of

modern adjuvant therapies and found that age less than 40 predicted inferior survival despite modern therapies. We confirm the pattern with less favorable outcome for patients under 40 but we observed a gradual improvement in survival for the young patients. Fredholm et al. [5] were able to show that the unfavorable outcome for young patients was more significant for those with luminal B tumors. As compared to older patients, there were much fewer patients younger than 40, therefore that the improvement in survival among young patients was statistically less significant must be interpreted with caution. In fact, Kvåle et. al. [16] showed that women under 50 years had a more profound drop in mortality than older patients.

Notably, we observed a 40% increase in breast cancer diagnoses between 1989 and 2013. Part of this might be explained by the aging society, as increasing age is a major risk factor for breast cancer. Gradually increased participation in mammography screening introduction of digital mammography with excellent detection rate and increased use of ultrasound and MR for breast examinations may also have contributed to the increased detection rate.

During the two decades of patient recruitment, there has been a gradual development of CT-scanning, MR and PET technology facilitating the detection of distant metastasis possibly resulting in an increased rate of patients with stage IV disease. However, this rate remained low around 2.6% during the entire period. Therefore, we think that improved treatment rather than stage migration explains the improved five-year outcome.

Moreover, the stage distribution during the time period was relatively stable, which contradicts stage migration as an explanation for the improved relative survival. The proportion of patients with stage II N + disease markedly increased with time possibly reflecting the improved pathological and radiological techniques available to detect lymph node metastases.

For women, over 70 years of age, the relative survival is lower than in the other age groups and there was little improvement during the study period. Partly, this result may be explained by a limited use of chemotherapy for this age group, but it is somewhat disappointing that the improved knowledge about the delivery of endocrine therapy has not resulted in more markedly increased survival in this group. However, our data should be interpreted with caution since relative survival is difficult to estimate for old patients with a high rate of competing mortality. Also, Manjer et. al. found that elderly patients had a more severe prognosis [17]. However, our data contrast to a population-based study from the Netherlands, which shows marked survival gains for the elderly [18] and findings from the US by Park et al. who demonstrated improved five-year survival for elderly and correlated this to tumor size and ER status [19]. In Estonia, breast cancer survival has since 1995, from relatively low levels, markedly increased for patients diagnosed with all stages of disease, also for patients below 50 and above 70 years of age [20]. We think that our data indicates that elderly patients have been undertreated and that patients with ER-positive disease should be encouraged to accept endocrine therapy of adequate duration and that for an increased proportion of the patients aged more than 70 chemotherapy should be considered.

Disclosure statement

No potential conflict of interest was reported by the authors.

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