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This is an electronic version of an article published in:

Patrik Johansson, Helena Fohlin, Lars-Gunnar Arnesson, Monika Dufmats, Kerstin Nordenskjöld, Bo Nordenskjöld and Olle Stål, Improved survival for women with stage I breast cancer in south-east Sweden: A comparison between two time periods before and after increased use of adjuvant systemic therapy, 2009, ACTA ONCOLOGICA, (48), 4, 504-513.

ACTA ONCOLOGICA is available online at informaworld™:

<http://dx.doi.org/10.1080/02841860902718754>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-18041>

**Improved survival for women with stage I breast cancer in South-east Sweden: A comparison between two time periods before and after increased use of adjuvant systemic therapy**

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**Running title:** Improved survival for women with stage I breast cancer

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## **Abstract**

*Purpose.* Continuous minor steps of improvement in the management of breast cancer have resulted in decreased mortality rates during the last decades. The aim of this study was to compare the clinical outcome of patients with stage I breast cancer diagnosed during two time periods that differed with respect to adjuvant systemic therapy.

*Material and methods.* The studied population consisted of all women <60 years of age, who were diagnosed breast cancer stage I between 1986 and 1999 in South-east Sweden, a total of 1407 cases. The cohort was divided into two groups based on the management programmes of 1986 and 1992, hereafter referred to as Period 1 and Period 2. Before 1992 the only adjuvant systemic therapy recommended was tamoxifen for hormone receptor (HR) positive patients aged 50 years or older. During Period 2 the use of adjuvant treatment was extended to younger patients at high risk, identified by a high tumour S-phase fraction, with either hormonal (HR+ patients) or cytotoxic (HR- patients) treatment.

*Results.* The estimated distant recurrence-free survival rate was significantly higher during Period 2 than during Period 1 ( $p=0.008$ ). Subgroup analysis showed that the most evident reduction of distant recurrence risk was among hormone receptor-negative patients (RR=0.58, 95% CI 0.31-1.09,  $p=0.09$ ) and among patients with a high tumour S-phase fraction (RR=0.53, 0.30-0.93,  $p=0.028$ ). The risk reduction between the periods was still statistically significant in multivariate analysis when adjusting for different tumour characteristics and treatment modalities, indicating an influence of other factors not controlled for. One such factor may be the duration of tamoxifen treatment, which likely was more frequently five years during Period 2 than during Period 1.

*Conclusions.* We conclude that the causes of the increase in distant recurrence free survival for women with breast cancer stage I are complex. The results support though that high-risk

subgroups of stage I breast cancer patients did benefit from increased use of systemic therapy as a consequence of an updated management programme.

## **Introduction**

Breast cancer incidence rates have increased among women in Europe and in the USA during the last decades and it is the most common type of cancer among women [1-3]. In Sweden, the yearly incidence and prevalence are high, however by international comparison, the Swedish breast cancer mortality rates have been low [4]. A recent population based study from South-east Sweden presented breast cancer specific ten-year survival rates of 90.9 % for stage I disease (T1N0M0) and 74.0 % for all stages [5]. A national screening schedule for women aged 40-74 years introduced in 1986, changes in surgery towards breast-conserving surgery in combination with adjuvant radiotherapy as opposed to mastectomy, more extensive use and tailoring of systemic adjuvant treatment for breast cancer stage I since the early 1990s might have been of importance for the high survival rates.

The prognosis of breast cancer patients is favourable if the disease is detected and adequately treated at an early stage [5, 6]. Estimation of recurrence risk for breast cancer stage I is based on malignancy grade, tumour proliferation activity, steroid hormone receptor status and tumour size [6]. A high S-phase fraction (SPF), or a high Nottingham histological grading (NHG) score indicate high risk of distant recurrence [6-11]. Tumour expression of oestrogen and/or progesterone receptors indicates a better short-term prognosis compared to tumours not expressing receptors, hereafter referred to as receptor positive and receptor negative tumours respectively. Patients with smaller tumours have better prognosis than those with larger ones [6, 12].

Since the mid 1980s, breast cancer patients in South-east Sweden have been treated and followed within the framework of a regional management programme with guidelines for systemic adjuvant therapy based on age and recurrence risk. The first regional management

programme that recommended systemic therapy for breast cancer stage I was issued in 1983 (Table 1a) [13]. The programme was updated in 1992 with recommendations for more extensive use of hormonal therapy, and with the introduction of cytotoxic therapy (Table 1b) [14]. The change in recommendation of adjuvant therapy in 1992 was based on clinical randomised trials that showed significantly reduced risk of recurrence and overall mortality for women with early breast cancer when given postoperative systemic therapy. Women with receptor positive tumours were shown to benefit from hormonal therapy and women with tumours with high proliferation markers benefited from cytotoxic therapy [15]. Initially, the regional management programme for South-east Sweden recommended two years hormonal therapy with tamoxifen for patients with receptor positive tumours [13, 14]. During 1995 the recommendation was changed to five years tamoxifen, since survival rates were shown to increase with longer duration of treatment [16]. The cytotoxic therapy for women with high S-phase fraction tumours initially combined cyclophosphamide, methotrexate and 5-fluoruracil (CMF), but methotrexate was gradually substituted with epirubicin (CEF) [6, 14] after a randomised trial between 1990 and 1998 [17]. Postoperative radiotherapy was only recommended after breast conserving surgery.

The results from the randomised trials of systemic adjuvant treatment versus no treatment seem indisputable, but there are few data confirming this outcome in clinical practice. The conditions for the general population of unselected patients could be different than those for patients selected in randomised clinical trials. Furthermore, in the present study the selection of patients who were recommended adjuvant systemic therapy was based on prognostic indicators. The survival rates for all stages of breast cancer in South-east Sweden have been reviewed [5], but the therapeutic benefits of the change in regional recommendations of systemic adjuvant therapy for stage I disease has not been studied. The main objective of this

*Table 1a. Breast cancer stage I. Recommendations for postoperative adjuvant systemic therapy according to the management programme of 1986 (Period 1).*

Patient age	Hormonal receptors	S-phase fraction	Tumour size	Systemic therapy
< 50 years	Positive	All	All	None
	Negative	All	All	None
≥ 50 years	Positive	All	11-20 mm	Hormonal
	Negative	All	All	None

*Table 1b. Breast cancer stage I. Recommendations for postoperative adjuvant systemic therapy according to the management programme of 1992 (Period 2).*

Patient age	Hormonal receptors	S-phase fraction	Tumour size	Systemic therapy
< 50 years	Positive	≥ 10%	11-20 mm	Hormonal
	Negative/Unknown	≥ 10%	11-20 mm	Cytotoxic
≥ 50 years <sup>1</sup>	Positive	All	11-20 mm	Hormonal
	Negative/Unknown	All	All	None

<sup>1</sup>The recommendations used for patients under 50 years of age could also be applied in the age group 50-60 years

study was to evaluate if there were any changes in distant recurrence free survival and overall survival among women treated for breast cancer stage I, after the regional management programme was updated in 1992. The secondary objective was to evaluate if any changes in distant recurrence free survival could be shown in subgroups of patients, based on S-phase fraction, hormone receptor status and tumour size.

## **Material and methods**

The study was designed as a retrospective cohort study based on data registered in the South-east Sweden regional database for breast cancer patients. Registration is compulsory, and the database holds information on surgery, lymph node involvement, tumour size, hormone receptor status, S-phase fraction, adjuvant therapy and clinical follow-up data. The studied

population consisted of all women <60 years of age, who were diagnosed breast cancer stage I between January 1986 and December 1999 in South-east Sweden, a total of 1407 cases. The study did not include women 60 years or older, since the recommendations for systemic adjuvant treatment in practice were limited to patients younger than 60 years. The cohort was divided into two primary groups based on the management programmes of 1983 and 1992, hereafter referred to as Period 1 and Period 2. Period 1 consisted of 519 women, diagnosed 1986 through 1991. Period 2 consisted of 888 women, diagnosed 1992 through 1999. In the analysis, Period 1 had the function of a historical control group for Period 2. Each group was further divided into secondary groups based on the prognostic parameters tumour size ( $\leq 10$  mm or 11-20 mm), steroid hormone receptor status (positive ( $\geq 30$  fmol/ $\mu$ g DNA) or negative) and S-phase fraction (high ( $\geq 10\%$ ) or low ( $< 10\%$ )). Oestrogen and progesterone receptor concentrations were measured with enzyme immuno assays (Abbott Laboratories, Chicago, USA) and the S-phase fraction was obtained from DNA flow cytometry analysis [18]. The primary groups were analysed for overall survival and distant recurrence free survival. The secondary groups were analysed for distant recurrence free survival.

The end date of follow-up was December 31, 2006. Fifty-six women had moved from the region or had data missing because of other reasons, and were controlled at the tax office for deaths. For seven women who had left Sweden, the date of migration was used as end date. For 14 women for whom the cause of death was breast cancer, there was no data of distant recurrence and for these patients the time of death has served as time for distant recurrence. Median duration of follow-up for recurrence free patients was 17.5 years in Period 1, and 10.3 years in Period 2.

In Period 2, the patient records for 115 women with high S-phase fraction tumours, and the records for 125 women with unknown or low S-phase fraction tumours were controlled for data on cytotoxic therapy and distant recurrence. The purpose of the control was to examine whether there were any cases with adjuvant therapy and/or distant recurrence not registered in the database. According to records, four patients with high S-phase fraction tumours and three patients with low S-phase fraction tumours had received cytotoxic therapy, which had not been registered in the regional database. Three patients with high S-phase fraction tumours and three patients with low S-phase fraction tumours had developed distant recurrence, which had not been registered. These findings were taken into account before analysis of data.

#### *Statistical methods*

Kaplan-Meier survival analysis [19] with log rank test [20] was used for analysing overall survival and distant recurrence free survival. Cox regression analysis [21] was used for analysing relative risk and for multivariate analysis. A two-sided p-value of  $<0.05$  was used as significance level. Relative risk, five-year and ten-year overall survival and distant recurrence free survival are stated with 95 % confidence interval (CI 95 %). The software used for the statistical tests was SPSS for Windows version 15.0. The figures were done with Stata/SE 10.0.

## Results

### *Patient age and tumour characteristics*

The patient median age was 50 years (range 24-59). The women in Period 2 were significantly older compared to Period 1 ( $p < 0.001$ ). Table 2 shows distribution of tumour characteristics divided by age and diagnosis period. S-phase fraction, receptor status, and tumour size did not differ significantly between the periods although there was a tendency towards a higher frequency of receptor positive tumours in Period 2 compared to Period 1 ( $p = 0.088$ ).

*Table 2. Patient and tumour data in the two cohorts, also divided by age*

Category	Group	Period 1 (1986-1991)				Period 2 (1992-1999)			
		<50 years		50-59 years		<50 years		50-59 years	
		N	%	N	%	N	%	N	%
	All patients	271	52.2	248	47.8	365	41.1	523	58.9
Tumour size	≤ 10 mm	102	38.2	94	38.4	140	39.1	202	39.1
	11-20 mm	165	61.8	151	61.6	218	60.9	315	60.9
	unknown	4		3		7		6	
Median tumour size (mm)		12		12		12		12	
Receptor status	Positive	140	75.3	135	77.6	205	81.7	261	80.6
	Negative	46	24.7	39	22.4	46	18.3	63	19.4
	unknown	85		74		114		199	
S-phase fraction	Low	93	75.0	94	75.2	140	71.4	191	74.6
	High	31	25.0	31	24.8	56	28.6	65	25.4
	unknown	147		123		169		267	
Surgical method	Mastectomy	109	40.1	114	46.2	126	34.6	141	27.0
	Breast-conserving	162	59.9	134	53.8	239	65.4	382	73.0
Adjuvant therapy	Radiotherapy	163	62.2	149	61.3	254	73.0	391	80.0
	Hormonal	24	8.9	127	51.2	90	24.7	227	43.4
	Cytotoxic	3	1.1	-	-	26	7.1	14	2.7
	None	101	37.3	46	18.5	77	21.1	63	12.0
Ten year follow-up	Dist. recurrence	42	15.5	32	12.9	38	10.4	44	8.4
	Mortality	40	14.8	36	14.5	30	8.2	60	11.5

### *Differences in treatment between Period 1 and Period 2*

Table 2 shows treatment for Period 1 and Period 2 divided by age. A significantly larger proportion of women ( $p < 0.001$ ) were operated with breast-conserving surgery in Period 2 (Table 2), the change being most notable for patients with tumours 11-20 mm (data not shown). The increased breast-conserving surgery paralleled an increase of patients given adjuvant radiotherapy, in agreement with regional guidelines [13, 14]. However, the number of women treated with radiotherapy did slightly exceed the number operated with breast-conserving surgery.

Table 3 shows frequency of hormonal and cytotoxic therapy divided by receptor status and S-phase fraction in Period 1 and 2. The frequency of patients who received hormonal therapy was significantly higher ( $p = 0.011$ ) in Period 2 compared to Period 1 (Tables 2 and 3).

However, it was only among women  $< 50$  years that hormonal therapy increased. In the age group 50-59 years, the frequency of patients who received hormonal therapy was lower in Period 2 compared to Period 1, the main reason being a lower frequency of women with receptor negative tumours being treated with tamoxifen. The frequency of patients who received cytotoxic therapy increased during Period 2 ( $P < 0.001$ ), especially among those  $< 50$  years (Tables 2 and 3). Overall, the increased use of systemic therapy was largely confined to patients with high SPF tumours, in accord with the management programme recommendations.

### *Overall survival*

There was a 28 % (HR= 0.72, CI 95% 0.53-0.98,  $p = 0.033$ ) reduction of ten-year overall mortality risk in Period 2 compared to Period 1 and the overall survival after ten years increased from 85.3% in Period 1 to 89.3% in Period 2 (Figure 1 A).

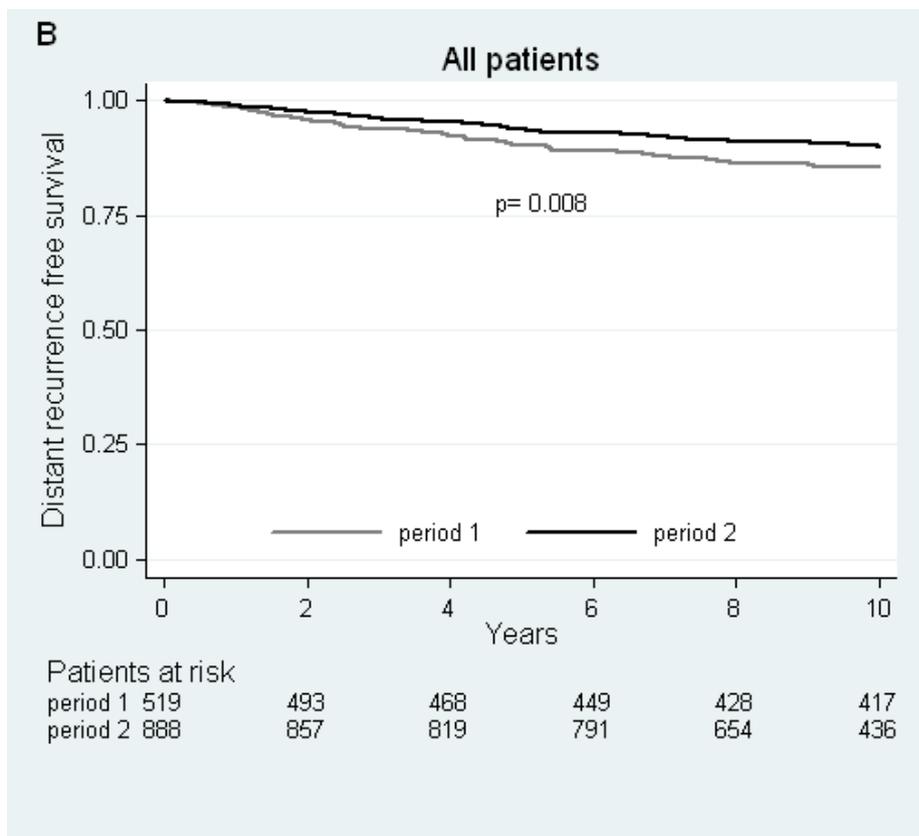
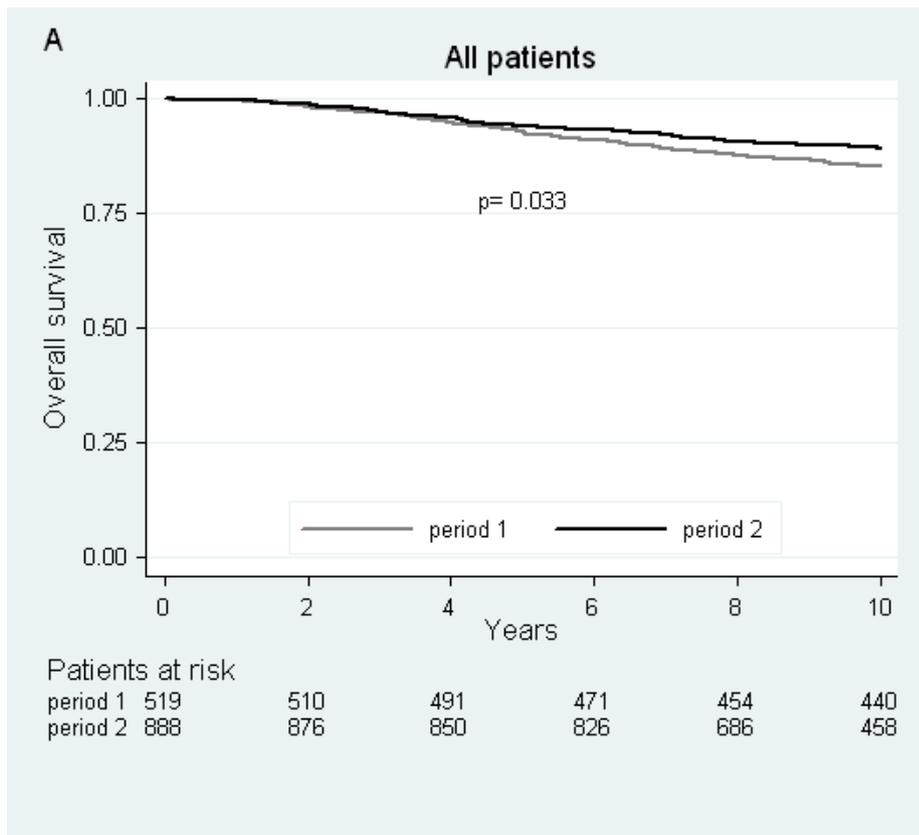
*Table 3. Frequency of adjuvant systemic treatment in Period 1 and 2, divided by receptor status and S-phase fraction.*

Receptor status	S-phase fraction	Period 1 (1986-1991)			Period 2 (1992-1999)		
		N	Hormonal therapy %	Cytotoxic therapy %	N	Hormonal therapy %	Cytotoxic therapy %
Positive	Low	161	44.7	-	282	46.8	1.1
	High	38	39.5	2.6	74	70.3	10.8
	Unknown	76	47.4	-	110	44.5	1.8
Negative	Low	24	8.3	-	31	3.2	12.9
	High	24	20.8	4.2	47	12.8	36.2
	Unknown	37	10.8	-	31	16.1	9.7
Unknown	Low	2	-	-	18	27.8	-
	High	0	-	-	0	-	-
	Unknown	157	10.8	0.6	295	22.7	1.0
All	All	519	29.1	0.6	888	35.7	4.5

#### *Distant recurrence free survival*

Five-year and ten-year differences in distant recurrence free survival are presented in Table 4. For all women, there was a 34 % (HR= 0.66, CI 95% 0.48-0.90, p=0.008) reduction of distant recurrence risk after ten years in Period 2 compared to Period 1 (Figure 1B). The estimated absolute increase in distant recurrence free survival after ten years was 4.6 % (Table 4).

Multivariate analysis of distant recurrence free survival, including period of diagnosis, tumour characteristics, treatment and patient age, showed that diagnosis period remained significant after adjustment for other factors (Table 5). Among other variables, S-phase fraction was the only factor that had significant influence on the outcome. Moreover, for patients who did not



*Figure 1. Overall survival (A) and distant recurrence free survival (B) for all patients.*

*Table 4. Five-year and ten-year distant recurrence free survival rates in Period 1 and 2, divided by tumour characteristics.*

Category	Diagnosis period	5 years (CI 95%)	10 years (CI 95%)
All patients	Period 1	90.2 ( $\pm$ 2.6)*	85.4 ( $\pm$ 3.1)*
	Period 2	93.8 ( $\pm$ 1.6)	90.0 ( $\pm$ 2.1)
T $\leq$ 10 mm	Period 1	93.8 ( $\pm$ 3.4)	89.6 ( $\pm$ 4.2)
	Period 2	95.5 ( $\pm$ 2.2)	93.5 ( $\pm$ 2.7)
T11-20 mm	Period 1	87.8 ( $\pm$ 3.6)*	82.5 ( $\pm$ 4.2)*
	Period 2	92.5 ( $\pm$ 2.3)	88.0 ( $\pm$ 2.9)
Receptor positive	Period 1	91.5 ( $\pm$ 3.3)	85.1 ( $\pm$ 4.3)
	Period 2	92.7 ( $\pm$ 2.4)	88.3 ( $\pm$ 3.1)
Receptor negative	Period 1	79.9 ( $\pm$ 8.6)	73.8 ( $\pm$ 9.4)
	Period 2	87.0 ( $\pm$ 6.4)	83.8 ( $\pm$ 7.1)
Low S-phase fraction	Period 1	94.0 ( $\pm$ 3.4)	87.8 ( $\pm$ 4.8)
	Period 2	95.3 ( $\pm$ 2.3)	90.4 ( $\pm$ 3.4)
High S-phase fraction	Period 1	72.4 ( $\pm$ 11.2)	62.2 ( $\pm$ 12.2)*
	Period 2	80.7 ( $\pm$ 7.1)	78.8 ( $\pm$ 7.4)
Receptor positive, low S-phase	Period 1	94.3 ( $\pm$ 3.6)	87.8 ( $\pm$ 5.2)
	Period 2	96.0 ( $\pm$ 2.3)	91.2 ( $\pm$ 3.5)
Receptor positive, high S-phase	Period 1	73.3 ( $\pm$ 14.2)	62.2 ( $\pm$ 15.7)
	Period 2	78.2 ( $\pm$ 9.5)	76.4 ( $\pm$ 9.9)
Receptor negative, low S-phase	Period 1	91.5 ( $\pm$ 11.3)	87.1 ( $\pm$ 13.6)
	Period 2	87.1 ( $\pm$ 11.8)	82.0 ( $\pm$ 14.8)
Receptor negative, high S-phase	Period 1	70.8 ( $\pm$ 18.2)	62.2 ( $\pm$ 19.5)*
	Period 2	84.7 ( $\pm$ 10.4)	82.4 ( $\pm$ 11.1)

\* log rank p-value < 0.05

receive any systemic adjuvant treatment, S-phase fraction was a strong indicator (HR= 3.25, CI 95% 1.90-5.57, p<0.001) of distant recurrence (Figure 2).

When specifically controlled for tumour size, the difference in distant recurrence risk between Period 1 and 2 was not statistically significant (HR= 0.62, CI 95% 0.34-1.15, p=0.12) for patients with tumours  $\leq$ 10 mm (Figure 3). For patients with tumours 11-20 mm there was a 35

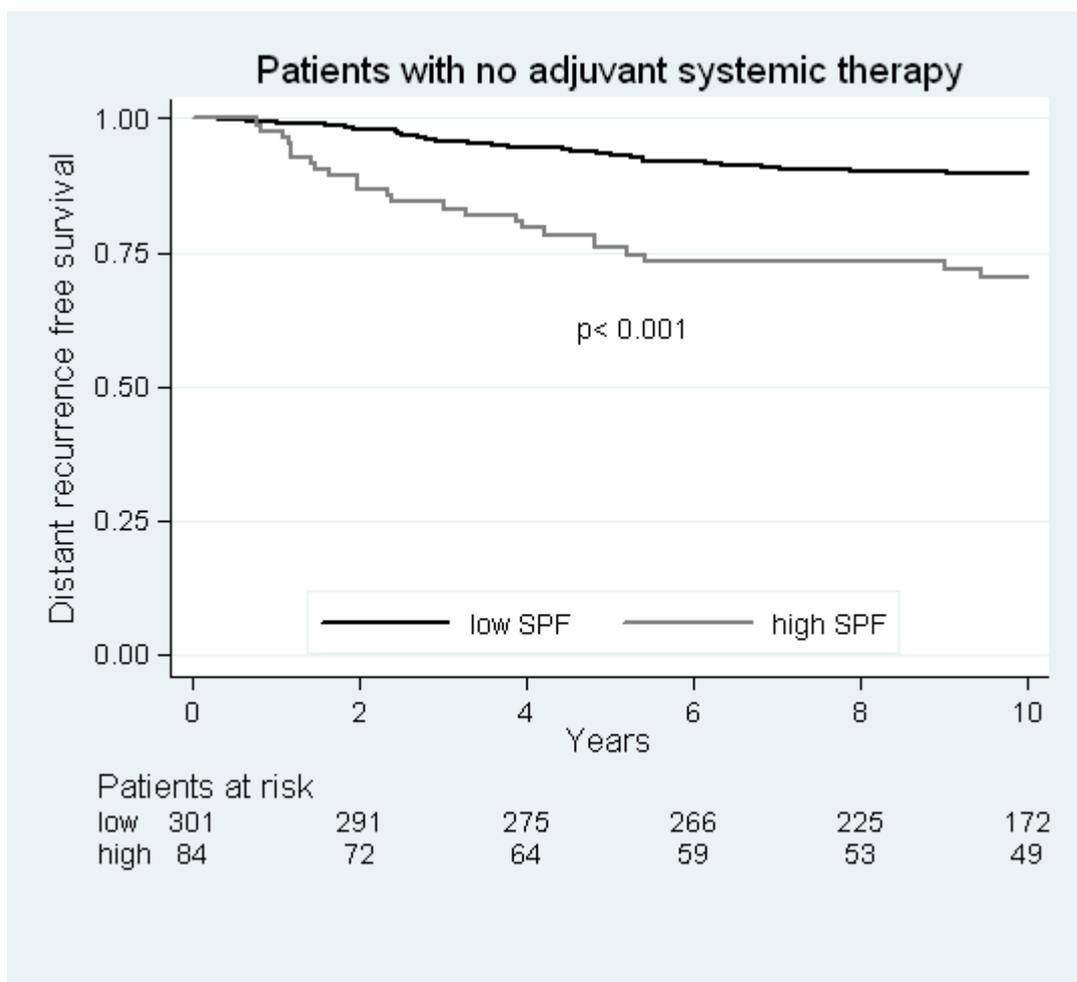
*Table 5. Multivariate analysis of distant recurrence rates with Cox proportional hazard method including diagnosis period, tumour characteristics, treatment and patient's age.*

Category	Group	RR <sup>1</sup>	CI 95 %	P-value
Diagnosis period	Period 1	1.00		
	Period 2	0.61	0.40-0.93	0.021
Tumour size	≤10 mm	1.00		
	11-20 mm	1.45	0.87-2.41	0.15
Receptor status	Negative	1.00		
	Positive	1.08	0.62-1.88	0.80
S-phase fraction	Low	1.00		
	High	2.67	1.73-4.13	<0.001
Surgical method	Mastectomy	1.00		
	Breast-conserving	0.81	0.54-1.22	0.31
Hormonal therapy	No	1.00		
	Yes	0.84	0.52-1.36	0.48
Cytotoxic therapy	No	1.00		
	Yes	1.77	0.85-3.72	0.13
Age	<50 years	1.00		
	50-59 years	1.01	0.65-1.58	0.96

<sup>1</sup>Distant recurrence rate ratio

% (HR= 0.65, CI 95% 0.45-0.94, p=0.020) reduction of distant recurrence risk in Period 2 compared to Period 1 (Figure 3) and an estimated 5.5 % absolute increase in distant recurrence free survival after ten years (Table 4).

For patients with receptor positive tumours there was no statistically significant difference in distant recurrence free survival between the two periods (HR= 0.77, CI 95% 0.51-1.17, p=0.22), while there was a 42 % reduction of distant recurrence risk (HR=0.58, CI 95% 0.31-1.09, p=0.090) for patients with receptor negative tumours (Table 4). Furthermore, the reduction in distant recurrence rate between the periods appeared to be larger for patients with



*Figure 2. Distant recurrence-free survival in relation to S-phase fraction for patients given no adjuvant systemic therapy.*

high S-phase tumours (HR=0.53, CI 95% 0.30-0.93, p=0.028) than for those showing a low SPF (HR=0.77, CI 95% 0.44-1.33, p=0.34). The estimated absolute increase in distant recurrence free survival after 10 years was 16.6% and 2.6%, respectively (Table 4). Analysis of hormone receptor status and S-phase fraction in combination revealed that the most evident difference between the periods was seen among receptor negative patients with high SPF tumours (Table 4, Figure 4).

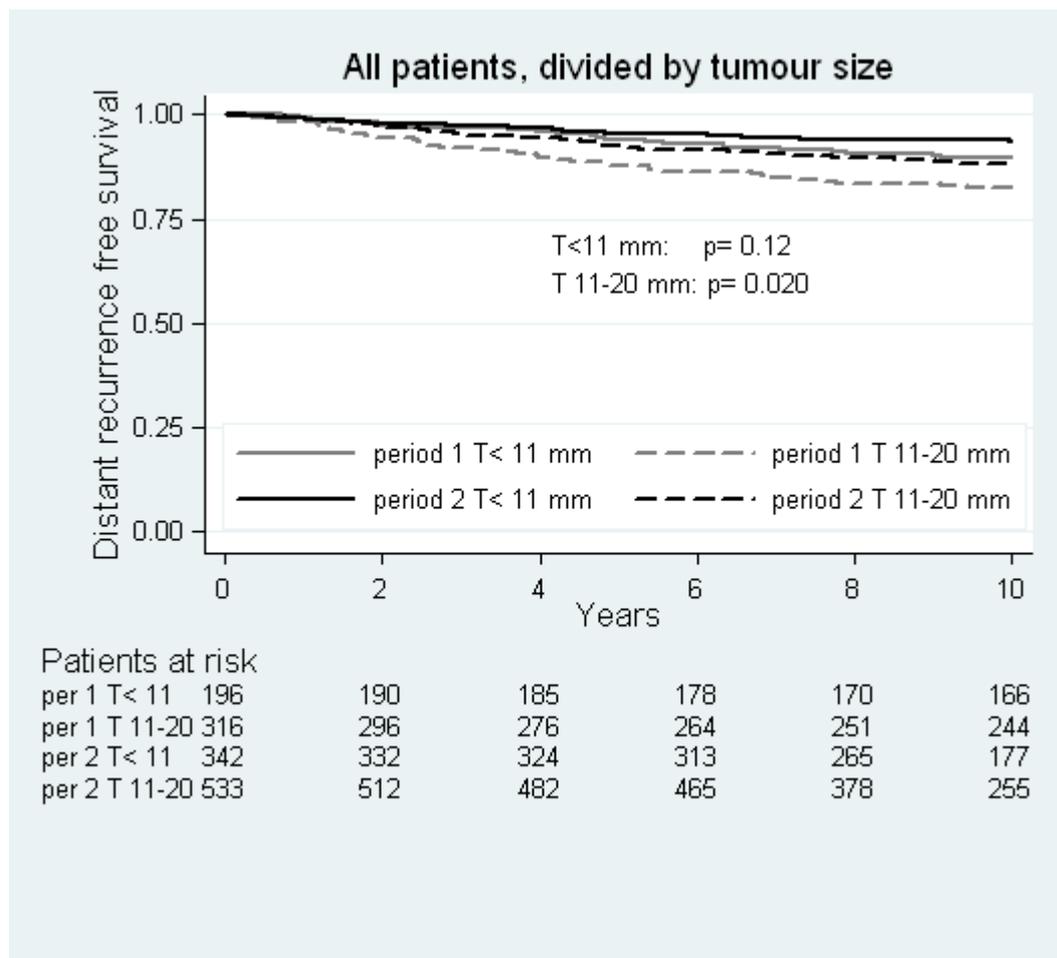


Figure 3. Distant recurrence free survival for the two periods divided by tumour size.

## Discussion

In this study we identified all patients <60 years of age, who were registered for breast cancer stage I between 1986 and 1999 in the South-east Sweden regional breast cancer database. The tumour characteristics in the studied population were comparable, and the only significant difference between the studied time periods was the significantly higher frequency of women 50-59 years in Period 2 compared to Period 1. A possible contributing factor could be the increasing use of hormonal replacement therapy (HRT) among menopausal women during the 1990s. The HRT-frequency increased from <10 % during the 1980s, to >40 % in the 1990s [22-24], and has been shown to increase the risk of breast cancer [25].

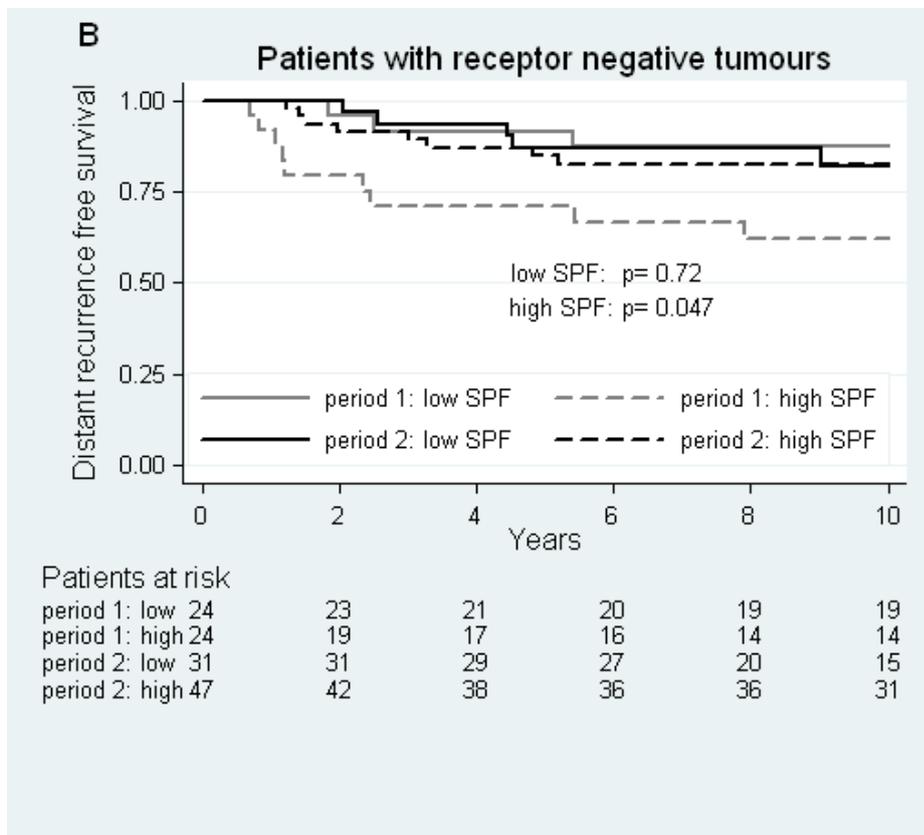
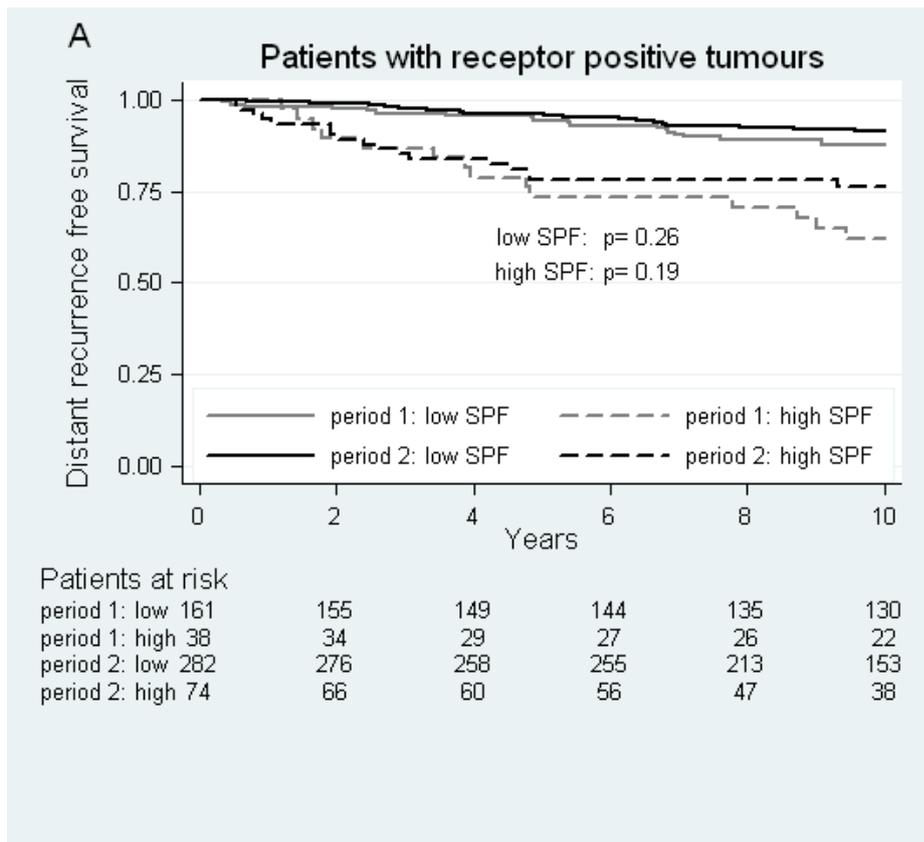


Figure 4. Distant recurrence free survival for the two periods divided by hormone receptor status and S-phase fraction. (A) Receptor positive patients. (B) Receptor negative patients.

The beneficial effect of adjuvant hormonal and cytotoxic therapy for early stages of breast cancer is known [15]. By analogy with the intentions of the recommended extended use of systemic adjuvant therapy in the South-east Sweden regional management programme of 1992 [14], our study has shown that for women diagnosed breast cancer stage I in Period 2, both overall survival and distant recurrence free survival have increased significantly. In agreement with the programme of 1992, the women with high S-phase tumours in Period 2 more frequently received hormonal therapy and cytotoxic therapy compared to the women in Period 1. However, the compliance to the recommendations was moderate and more patients could have received chemotherapy. The women 50-59 years of age did receive less hormonal therapy in Period 2, but since this mainly was due to a more selective approach depending on receptor status, it should not have affected distant recurrence rates negatively.

Survival analysis of the secondary groups divided by tumour characteristics showed that for patients with tumour size 11-20 mm, and for patients with receptor negative tumours and high S-phase fraction, there was a statistically significant decrease in distant recurrences. Tumour size and high S-phase fraction are both markers for high risk of distant recurrence, and in the programme of 1992 both of these variables were indicators for systemic therapy (Table 1a and 1b). With this taken into account, it seems probable that the extended use of systemic therapy based on the identification of high-risk groups in Period 2 influenced distant recurrence free survival rates. For approximately half of the patients information on S-phase fraction was missing due to the fact that tumour material sometimes was unavailable for analysis and that DNA analysis not always is informative as regards the SPF. Although most patients with missing information had small tumours ( $\leq 10$  mm), many other patients could have been recommended systemic therapy if the marker used had been informative. Therefore it might

be important to evaluate proliferation markers with other techniques of high applicability, such as immunohistochemistry.

For patients with receptor positive tumours and low S-phase fraction there was a minor, statistically non-significant, increase in distant recurrence free survival. For this group of patients there was no change in recommendations of postoperative management between the periods, and neither did the use of systemic therapy increase significantly. However, from 1995 and onwards, the recommended duration of hormonal therapy was changed from two to five years, which means that this group of patients also had longer duration of treatment. In agreement with the extended recommendations of the management programme, patients with receptor positive tumours and high S-phase fraction received a higher frequency of hormonal therapy in Period 2. However, for this group of patients, there was no significant change in distant recurrence free survival. This was an unexpected result since it has been shown that patients with receptor positive tumours benefit from hormonal therapy [15] and that distant recurrence free survival increases with longer duration of hormonal therapy [16, 26]. Neither has it been shown that high S-phase fraction should affect the beneficial effect of hormonal therapy negatively among receptor positive patients [8, 26]. No specific analysis of the relationship between distant recurrence free survival and duration of hormonal therapy was possible, due to lack of data.

The multivariate analysis showed that diagnosis period in itself had statistical significance for higher distant recurrence free survival, which implies that one or more factors not controlled for in the study were of importance for the prognosis. This result stayed true when the entire cohort was made analysable by replacing missing values for receptor status and SPF with corresponding mean values (data not shown). As mentioned above, we did not adjust for the

duration of tamoxifen treatment and it is likely that the more frequent use of 5 years of treatment during Period 2 did contribute to the increase in recurrence-free survival. Since it has been shown that screened populations have higher survival rates [27-28], one such possible factor is the screening schedule for breast cancer. Screening began in 1986, but it was not until the 1990s that there was a large screened population. Postoperative radiotherapy and systemic therapy have an additive effect for reducing distant recurrence risk [29-30]. Since both of these regimens increased in Period 2, it might have influenced diagnosis period as a prognostic marker, although one should keep in mind that the effects of different regimens of radiotherapy used after mastectomy and breast conserving surgery, respectively, may not be equivalent. Yet another factor that might have affected the prognosis is the possible increase in the number of breast cancers linked to HRT during the studied time periods [31].

Although data are not shown in results, there was a significant increase in distant recurrence free survival among patients not given systemic therapy in Period 2, compared to the corresponding group in Period 1 (36 % lower recurrence risk,  $p=0.027$ ). The most likely reason for this is that during Period 2, the identification of high-risk and low-risk patients was more pronounced. When controlled for risk factors, the patients who did not receive any systemic adjuvant therapy had a higher frequency of tumours that were receptor positive, had a low S-phase fraction, and size  $\leq 10$  mm. On the other hand, the patients who did receive systemic therapy in Period 2 had as a group a higher frequency of high risk factors. This group had a slight tendency ( $p=0.11$ ) for lower recurrence risk in Period 2 compared to systemically treated patients in Period 1, despite the prognostic handicap. These results strengthen the hypothesis that the identification and selection of patients who would or would not benefit from systemic therapy was well grounded. It also illustrates that over-treatment

would be a substantial problem if all the patients were given adjuvant chemotherapy. Given the ten-year distant recurrence-free survival rate in the first period of 85.4% (Table 4) and a 30% risk reduction with adjuvant chemotherapy the estimated number needed to treat (NNT) would be over 20. On the other hand, for receptor negative patients with high S-phase tumours the NNT would be less than 10.

The multivariate analysis also showed that the S-phase fraction is a strong prognostic factor in stage I breast cancer. The use of gene-expression profiling to better identify patients at increased risk of recurrence has revealed that signatures related to cell proliferation might be the most important [32-34]. We were not able to analyse tumour grade since data on grade was not continuously registered in the past. The NHG score is a simple and an important prognostic marker, however maybe not the optimal one, since tumours of intermediate grade can be separated into gene expression profiles representing a good or poor prognosis [35].

When controlled, cases were discovered in which data was missing regarding cytotoxic therapy and distant recurrence, cases where cause of death was breast cancer but without any registration of distant recurrence, and cases with lack of follow-up because of patients who had moved from the region. This might illustrate some of the possible problems with studies based on historical databases, and highlights the probable need for at least some level of review of such data before analysis.

The survival rate of breast cancer is high among women diagnosed and treated in South-east Sweden. This accounts especially for stage I disease, for which the breast cancer specific ten-year survival rate for all patients diagnosed 1986 through 1999 was estimated to 90.9 % [5]. Our study has shown that the overall survival rate after ten years for patients <60 years

diagnosed 1986-1991 and 1992-1999 was 85.3 % compared to 89.3 % respectively, and the corresponding distant recurrence free survival rate was 85.4 % compared to 90.0 %. The conclusions are that the causes of the increase in overall survival and distant recurrence free survival for women with breast cancer stage I are complex. The continuous development of local and systemic treatment, together with changes in the regional management programme, has been beneficial. It is likely that women with high-risk stage I tumours have benefited from the extended systemic adjuvant therapy. Women with low-risk tumours seem to have a favourable prognosis even without systemic therapy. The continuing identification of risk groups and tailoring of treatment is of importance for overall survival and distant recurrence free survival for women with breast cancer stage I.

## References

1. Levi F, Lucchini F, Negri E, La Vecchia C. The decline in cancer mortality in the European Union, 1988-1996. *Eur J Cancer* 2000; 36: 1965-1968.
2. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25 % in year 2000 at ages 20-69 years. *Lancet* 2000; 335: 1822.
3. Mouridsen HT, Bjerre KD, Christiansen P, Jensen M-B, Møller S. Improvement of prognosis in breast cancer in Denmark 1977-2006, based on the nationwide reporting to the DBCG Registry. *Acta Oncologica* 2008; 47: 525-536.
4. Felay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Annals of Oncology* 2007; 18: 581-592.
5. Tejler G, Norberg B, Nordenskjöld B on behalf of the South East Sweden Breast Cancer Group. Survival after treatment for breast cancer in a geographically defined population. *Br J Surg* 2004; 91: 1307-1312.
6. Svenska bröstcancergruppen. Nationella riktlinjer för behandling av bröstcancer. <http://www.swebcg.roc.se/natriktlinjbrca2007.htm>
7. Stål O, Hatschek T, Carstensen J, Nordenskjöld B. DNA Analysis in the Management of Breast Cancer. *Diagn Oncol* 1991; 1: 140-154.
8. Stål O, Dufmats M, Hatschek T, Carstensen J, Klintenberg C, Rutqvist LE, et al. S-Phase Fraction is a Prognostic Factor in Stage I Breast Carcinoma. *J Clin Oncol* 1993; 9: 1717-1722.
9. Remvikos Y, Mosseri V, Asselain B, Fourquet A, Durand JC, Pouillart P, et al. S-Phase Fractions of Breast Cancer Predict overall and Post-relapse Survival. *Eur J Cancer* 1997; 4: 581-586.

10. Daidone MG, Silvestrini R. Prognostic and Predictive Value of Proliferation Indices in Adjuvant Therapy of Breast Cancer. *J Natl Cancer Inst* 2001; 30: 27-35.
11. Latinovic L, Heinze G, Birner P, Samonigg H, Hausmaninger H, Kubista E, et al; Austrian Breast and Colorectal Cancer Study Group. Prognostic relevance of three histological grading methods in breast cancer. *Int J Oncol* 2001; 6: 1271-1277.
12. Rosen PP, Groschen S, Saigo PE, Kinne DW, Hellman S. A long term, follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol* 1989; 7: 355-366.
13. Sydöstra bröstcancergruppen. Vårdprogram för bröstcancer stadium I. Onkologiskt Centrum för Sydöstra Sjukvårdsregionen, Regionsjukhuset i Linköping, 1983.
14. Sydöstsvenska bröstcancergruppen. Vårdprogram för bröstcancer. Sydöstsvenska Bröstcancergruppen och Onkologiskt Centrum för Sydöstra Sjukvårdsregionen, Universitetssjukhuset i Linköping, 1992.
15. Early Breast Cancer Trialist's Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687-1717.
16. Swedish Breast Cancer Cooperative Group (SBCCG). Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. *J Natl Cancer Inst* 1996; 88: 1543-1549.
17. Ejlertsen B, Mouridsen HT, Jensen M, Andersen J. et al. Improved outcome from substituting methotrexate with epirubicin: Results from a randomised comparison of CMF versus CEF in patients with primary breast cancer. *European Journal of Cancer* 2007; 43: 877-884.
18. Fernö M, Stål O, Baldetorp B, Hatschek T, Källström A-C, Malmström P, et al. South Sweden Breast Cancer Group, and South-East Sweden Breast Cancer Group. Results

- of two or five years of adjuvant tamoxifen correlated to steroid receptor and S-phase levels. *Breast Cancer Res Treat* 2000; 59: 69-76.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; 53: 457-481.
  20. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: Wiley. 1980.
  21. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B* 1972; 34: 187-220.
  22. Hammar M, Brynhildsen J, Dabrosin L, Frisk J, Lindgren R, Nedstrand E, et al. Hormonal replacement therapy and previous use of oral contraceptives among Swedish women. *Maturitas* 1996; 25: 193-199.
  23. Brynhildsen J, Björs E, Skarsgård C, Hammar M. Is Hormone Replacement Therapy a Risk Factor for Low Back Pain Among Postmenopausal Women? *SPINE* 1998; 7: 809-813.
  24. Ekblad S, Bergendahl A, Enler P, Ledin T, Möllen C, Hammar M. Disturbances in postural balance are common in postmenopausal women with vasomotor symptoms. *Climacteric* 2000; 3: 192-198.
  25. Olsson HL, Ingvar C, Bladström A. Hormone Replacement Therapy Containing Progestins and Given Continuously Increases Breast Carcinoma Risk in Sweden. *Cancer* 2003; 6: 1387-1392.
  26. Fernö M, Baldetorp B, Bendahl PO, Borg A, Ewers SB, Olsson H, et al. Recurrence-free survival in breast cancer improved by adjuvant tamoxifen – especially for progesterone receptor positive tumours with a high proliferation. *Breast Cancer Res Treat* 1995; 36: 23-34.

27. Goldhirsch A, Colleoni M, Domenighetti G, Gelber RD. Systemic treatments for women with breast cancer: outcome with relation to screening for the disease. *Ann Oncol* 2003; 14: 1212-1214.
28. Jatoi I, Miller AB. Why is breast-cancer mortality declining? *Lancet Oncology* 2003; 4: 251-254.
29. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *NEJM* 1997; 337: 949-955
30. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen. *Lancet* 1999; 353: 1641-1648.
31. Schuetz F, Diel IJ, Poeschel M, von Holst T, Solomayer EF, Lange S, et al. Reduced incidence of distant metastasis and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. *Am J Obstet Gynecol* 2007; 196: 342.e1-9.
32. Desmedt C, Sotiriou C. Proliferation: the most prominent predictor of clinical outcome in breast cancer. *Cell Cycle* 2006; 5: 2198-202.
33. Dai H, van't Veer L, Lamb J, He YD, Mao M, Fine BM, et al. A cell proliferation signature is a marker of extremely poor outcome in a subpopulation of breast cancer patients. *Cancer Res* 2005; 65: 4059-66.
34. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res* 2006 ;8 :R25.

35. Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J, et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. *J Natl Cancer Inst* 2006; 98: 262-72.