

ORIGINAL ARTICLE

Trends in breast cancer during three decades in Denmark: Stage at diagnosis, surgical management and survival

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Abstract

Background. Diagnostic and treatment of breast cancer has steadily improved in the last decades; mammography-screening, more aggressive axillary surgery and finally sentinel lymph node biopsies. This study analyses the impact of time trends in diagnostic and surgical procedures on stage at diagnosis and survival in three Danish counties in three decades. **Methods.** We compare extent of disease and outcome in three complete population-based patient cohorts with primary invasive breast cancer, diagnosed in 1986, 1996–1997 and 2002–2003; 3 385 patients, thereby comparing populations with and without centralised breast cancer management, mammography-screening, sentinel lymph node biopsies and the effect of time-period. **Results.** The 5-year over-all survival increased significantly ($p < 0.001$) from 74% (70–78) in 1986 to 84% (82–86) in 2002–2003 with a corresponding increase in 10-year relative survival from 63% (58–68) in 1986 to 74% (71–77) in 1996–1997. In 1986 patients from Funen had median 10 lymph-nodes removed vs. median 5 and 7 in the other counties ($p < 0.001$), and significantly more patients had positive lymph-nodes. In 1996–1997 the number of lymph-nodes removed increased significantly in all counties (median 12,13,14). In Funen, mammography-screening was implemented and patients had more favourable stage distribution ($p < 0.001$). This was associated with significantly better over-all survival in univariate- but not in multivariate analysis. In 2002–2003 we found smaller tumors and more favourable stage-distribution in patients from Funen ($p < 0.001$), and the 5-year relative survival increased to 90% (86–93). With increasing attention to the axilla more patients were found with positive nodal status, least in Funen (45% vs. 51% and 53%) ($p < 0.001$). We found no significant differences in over-all survival according to county. **Conclusion.** During these three decades over-all survival of breast cancer improved. In the earlier periods we found survival differences according to residence, but in the late cohort there were no difference despite better stage distribution in the county with mammography-screening.

Management of early breast cancer has changed during the last three decades with the introduction of mammography screening, sentinel lymph node biopsies and a steadily more intensive adjuvant treatment. In Denmark, mammography screening and sentinel lymph node biopsies (SLNB) have not been implemented in all counties at the same time, whereas the adjuvant treatment has been similar in all counties since 1977 and prescribed according to national guidelines from the Danish Breast Cancer Cooperative group (DBCG) [1,2]. Other studies have described differences in stage at diagnosis and survival between Danish counties [3,4] both before and after the introduction of screening. These differences could also to some extent be explained by different degree of centralisation and approach to axillary surgery, and with the introduction

of SLNB more patients are expected to be diagnosed with positive lymph nodes [5]. We aimed to make a population-based cross-sectional study in three time periods in three counties, analysing stage distribution and over-all survival, and thereby describe three decades from before centralisation of breast cancer surgery, before the introduction of mammography screening till the implementation of screening in one county and further till the implementation of SLNB techniques in two counties.

Material and methods

We compared three time periods (1986, 1996–1997, and 2002–2003) in three Danish counties, selected because of different approaches to axillary surgery in

the 1980's, introduction of screening in the 1990's and finally SLNB in this century. The counties under study were Funen, Aarhus and the County of Northern Jutland (NJ). On January 1, 2003 the number of inhabitants in the three counties were 473 471, 649 177 and 495 625 respectively [6]. The county of Funen had early centralisation of breast cancer surgery [7], and since 1993 mammography screening was offered biannually to all women between age 50 and 70. In the other counties breast cancer surgery has gradually been centralised during the nineties, but no organised mammography screening has yet been implemented. In 2002 SLNB was fully implemented in Funen and Aarhus. A summary of the diagnostic and surgical approaches in the three counties in the three time periods is shown in Table I.

From the Danish cancer Registry [8,9], we extracted records on all women diagnosed with primary invasive breast cancer in the three time periods and living in the selected counties. Data were merged with the DBCG registry by means of the unique personal identification number provided to all citizens in Denmark. The DBCG hosts a database with high quality clinicopathological data [10]. Clinical records were traced for patients not fully notified in the DBCG-database. We excluded patients older than 70 years, patients with a previous history of invasive cancer, no histopathological verification of diagnosis, and patients known by death certificate only. Data on dead was provided from the National Population Registries, and assessment of survival was on the first of September 2007. The potential follow-up time (time from surgery until the date of assessment) was 21.2 years median (range 20.7–21.8) in the 1986 cohort, 10.7 years median (range 9.7–11.7) in the 1996–1997 cohort and 4.6 years median (range 3.5–5.7) in the 2002–2003 cohort.

Statistical analysis

Tumors were classified according to the UICC TNM system [11]. Among patients with simulta-

neous bilateral breast cancer, the breast with the largest tumor was chosen to be the primary side. T-stage was used as a combined measurement of tumor size and local tumor extension. Groups were compared by the Mann-Whitney and the Kruskal-Wallis tests. Overall survival was estimated by the Kaplan-Meier method. Log-rank tests were used for comparisons between groups. The assumption of proportional hazards was tested and accepted for all variables except county in the 1986 cohorts. Due to the lack of proportional hazards, we performed a Cox regression analysis with time dependent covariates and found no significant effect of the interaction term of time and county. The build up from the full to the final model was done in backward stepwise manner. In the final model, all previous variables with p-values <0.1 were evaluated once more. The hazard ratios were used as estimators of the relative risk. Statistical analysis was performed by the likelihood-ratio test. Level of significance was 5% and all p-values were two-tailed.

The relative survival is the ratio of the observed survival of the patients to the expected survival of a comparable group from the general population with the same distribution of age and calendar time. The relative survival has been interpreted as the proportion of patients alive at the end of the interval if the disease investigated is the only cause of death [12].

The statistical software package SPSS, version 13.0 was used except for the analysis of relative survival, which was done with the SAS statistical package version 9.1.

Results

The analysis included 3 385 patients from three different counties in three time periods. Patient characteristics are summarized in Table II.

The 1986 cohort

Few differences were observed between counties. In Funen, patients had significantly more lymph nodes

Table I. Treatment strategies in the three counties according to time period.

	1986	1996–1997	2002–2003
NJ	No Mammography screening No SLNB	No Mammography screening No SLNB	No Mammography screening No SLNB
Aarhus	No Mammography screening No SLNB	No Mammography screening No SLNB	No Mammography screening + SLNB
Funen	No Mammography screening No SLNB	+ Mammography screening No SLNB	+ Mammography screening + SLNB

Table II. Basic patient characteristics according to county and time period.

	1986				1996–1997				2002–2003			
	Funen	Aarhus	N J		Funen	Aarhus	N J		Funen	Aarhus	N J	
N	172	181	135	p	463	507	354	p	527	599	447	p
Age (year) Median (range)	53.4 (28–70)	54.5 (31–70)	55.9 (29–70)	ns	55.2 (26–70)	54 (24–70)	55 (28–70)	ns	57 (28–70)	55 (21–70)	56 (28–70)	0.03
Tumor size Median (range)	20 (4–120)	20 (4–100)	20 (5–91)	ns	16 (1–80)	19 (1–130)	20 (1–120)	0.001	15 (1–150)	20 (1–100)	20 (1–120)	0.001
Nodes removed Median (range)	10 (0–32)	5 (0–18)	7 (2–19)	0.001	14 (0–40)	13 (0–40)	12 (0–38)	0.001	18* (0–40)	14* (0–35)	18* (0–47)	0.001
T-stage (UICC)				ns				0.004				0.001
T ₁	81 (48)	89 (50)	78 (58)		298 (65)	286 (57)	186 (53)		350 (68)	290 (52)	233 (54)	
T ₂	67 (40)	71 (40)	48 (35)		140 (30)	177 (35)	152 (43)		140 (27)	242 (43)	177 (41)	
T ₃	14 (8)	10 (6)	9 (7)		7 (2)	22 (4)	10 (3)		20 (4)	25 (4)	16 (4)	
T ₄	7 (4)	7 (4)	0		15 (3)	17 (3)	5 (1)		3 (1)	1 (0)	5 (1)	
N-stage				0.009				0.03				0.001
N neg	80 (47)	107 (61)	77 (57)		269 (58)	266 (52)	175 (49)		276 (52)	243 (41)	199 (45)	
N pos	77 (45)	61 (34)	58 (43)		169 (37)	206 (41)	155 (44)		238 (45)	318 (53)	231 (51)	
N x	15 (8)	9 (5)	0		25 (5)	35 (7)	24 (7)		13 (3)	38 (6)	17 (4)	
Stage (UICC)				ns				0.001				0.001
I	54 (32)	65 (37)	53 (39)		204 (44)	182 (36)	118 (33)		224 (43)	166 (29)	126 (29)	
II	88 (51)	91 (52)	71 (53)		220 (48)	251 (50)	196 (56)		265 (51)	364 (63)	277 (64)	
III	16 (9)	11 (6)	8 (6)		13 (3)	27 (5)	10 (3)		23 (4)	26 (5)	19 (4)	
IV	13 (8)	9 (5)	3 (2)		21 (5)	44 (9)	26 (7)		6 (1)	18 (1)	10 (2)	
Surgery				0.002				0.001				0.001
mastectomy	130 (76)	158 (87)	120 (89)		280 (61)	343 (68)	291 (82)		307 (58)	243 (41)	125 (28)	
lumpectomy	31 (18)	16 (9)	15 (11)		161 (35)	134 (27)	46 (13)		219 (42)	356 (59)	318 (71)	
sentinel lymph node procedure									278 (53)	299 (50)	55 (12)	0.001
Histology				ns				ns				0.001
ductal	142 (83)	158 (87)	100 (74)		383 (83)	421 (83)	284 (80)		419 (79)	445 (75)	343 (77)	
lobular	17 (10)	11 (6)	16 (12)		46 (10)	37 (7)	35 (10)		51 (10)	79 (14)	46 (11)	
other	12 (7)	12 (7)	19 (14)		31 (7)	46 (9)	35 (10)		44 (8)	39 (7)	50 (11)	
Malignancy grade				0.001				0.04				0.001
I	40 (25)	38 (22)	32 (24)		119 (27)	112 (23)	96 (29)		140 (27)	118 (21)	65 (15)	
II	58 (36)	84 (49)	43 (33)		183 (41)	198 (41)	112 (33)		170 (33)	180 (32)	168 (39)	
III	38 (24)	28 (16)	44 (33)		85 (9)	103 (21)	63 (9)		102 (20)	138 (25)	98 (23)	
Non-ductal	26 (16)	21 (12)	32 (24)		56 (13)	70 (15)	65 (19)		95 (19)	118 (21)	96 (22)	
Estrogen receptor [^]								0.001				ns
Negative					97 (22)	165 (34)	105 (31)		93 (18)	124 (22)	92 (21)	
positive					345 (78)	316 (66)	238 (69)		418 (82)	435 (78)	348 (79)	

* Not including patients with sentinel lymph node biopsies. ^ Estrogen receptor status was not routinely analysed in 1986. Percentages in parentheses.

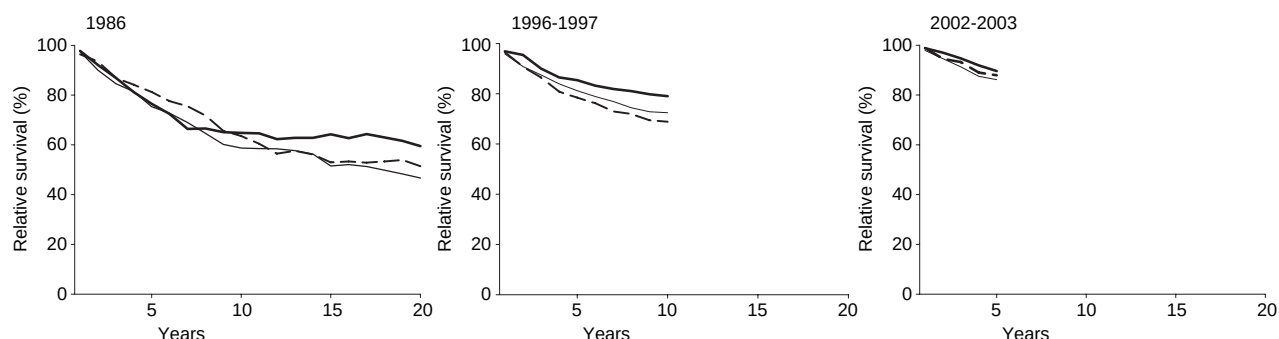


Figure 1. Estimate of Relative Survival proportion ratios by year of diagnosis and county. Thick line: Funen, Thin line: Aarhus, Dot line: Northern Jutland.

removed, more patients had positive lymph nodes and more breast conserving surgery was performed. Figure 1 shows that there was no difference in relative survival between counties until 8 years after diagnosis. The long time crude and relative survival rates (20 years) were significantly higher in Funen than in the other counties (Table III). This difference was also found in the multivariate analysis with significantly higher hazard rates in Aarhus 1.36 (1.03–1.80) and NJ 1.46 (1.08–1.96) compared to Funen (Table IV).

The 1996–1997 cohort

There were significant differences in all prognostic parameters except age and histology; all differences in favour of Funen, where mammography screening was implemented. The univariate over-all survival analysis showed significant differences between counties ($p=0.04$) and the 5-year survival rate was 6% higher in Funen versus NJ and 9% at 10 years (Table III). However, in the multivariate analysis this difference disappeared due to the more favourable stage distribution in the patients from Funen (Table IV). The differences in 5-year relative survival between counties were 7% and 10% (Figure 1).

The 2002–2003 cohort

Also in these cohorts there were significant differences in the distribution of prognostic parameters

according to county of residence. The only parameter which did not differ significantly was estrogen receptor status, and even here there was a tendency towards more favourable distribution in Funen. Analysed together, significantly more patients were diagnosed with positive lymph nodes, which is due to a significant increase in patients with positive nodes in Funen and Aarhus (Tables II and V). The differences between cohorts was only translated into small differences in 5-year over-all survival, best in Funen (86%) and worst in Aarhus (83%) (Table III). No survival difference was found in neither uni- nor multivariate analysis concerning county at diagnosis (Table IV).

Time trends

Within a time frame of 27 years, several positive changes are seen (Table V). Tumors became smaller, primary due to screening in Funen (Table II), and more patients had estrogen receptor positive tumors. More patients had breast conserving surgery, significantly more lymph nodes were removed, the sentinel lymph node biopsies were introduced and especially in the years 2002–2003 more patients were found with tumor positive lymph nodes.

A 10% improvement in 5-year over-all survival was seen during this time period. The 5-year survival probability was 74% (70–78) in 1986, 78% (76–80) in 1996–1997 and finally 84% (82–86) in 2002–2003 ($p<0.001$). Corresponding 10-year over-all

Table III. Crude and relative survival according to year at diagnosis. 95% CI in parentheses.

Year of diagnosis	Crude over-all survival (%)			Relative survival (%)		
	1986	1996–1997	2002–2003	1986	1996–1997	2002–2003
5 year	73.8 (70–78)	78.2 (76–80)	84.1 (82–86)	77.4 (73–81)	81.9 (80–84)	87.8 (86–90)
10 year	55.1 (51–60)	66.2 (64–69)		62.2 (57–67)	73.8 (71–77)	
15 year	45.1 (41–49)			56.4 (51–65)		
20 year	36.5 (32–41)			52.6 (47–59)		

Table IV. Multivariate Cox regression analysis of prognostic factors for death of all causes. 95% confidence intervals in parentheses.

	1986		1996–1997		2002–2003		All Patients	
	Hazard rate ratios	p	Hazard rate ratios	p	Hazard rate ratios	p	Hazard rate ratios	p
County		0.03		0.30		0.75		0.01
Funen	1		1		1		1	
Aarhus	1.36 (1.0–1.8)	0.03	0.97 (0.8–1.2)	0.77	0.87 (0.6–1.2)	0.46	1.14 (1.0–1.3)	0.93
NJ	1.46 (1.1–2.0)	0.01	1.16 (0.9–1.5)	0.26	0.90 (0.6–1.3)	0.59	1.29 (1.1–1.5)	0.03
Age (year)		<0.001		<0.001		0.14		<0.001
<40	1		1		1		1	
40–49	0.73 (0.4–1.2)	0.22	0.65 (0.4–1.0)	0.05	1.30 (0.6–2.7)	0.48	0.77 (0.6–1.0)	0.09
50–59	0.97 (0.6–1.6)	0.89	0.74 (0.5–1.1)	0.15	1.83 (0.9–3.7)	0.09	0.92 (0.7–1.2)	0.54
>59	1.52 (0.9–2.4)	0.78	1.27 (0.9–1.9)	0.24	1.80 (0.9–3.6)	0.10	1.30 (1.0–1.7)	0.05
T-stage		<0.001		<0.001		<0.001	0.31 (0.2–0.4)	<0.001
T _I	1		1		1		1	<0.001
T _{II}	1.54 (1.2–2.0)	<0.001	1.44 (1.2–1.8)	0.001	1.81 (1.3–2.5)	<0.001	1.63 (1.4–1.9)	
T _{III}	2.64 (1.7–4.1)	<0.001	1.70 (1.1–2.7)	0.02	3.00 (1.8–5.1)	<0.001	2.33 (1.8–3.0)	<0.001
T _{IV}	6.59 (1.9–2.3)	0.003	3.17 (1.7–6.0)	<0.001	6.16 (2.2–18)	<0.001	4.76 (3.0–7.5)	<0.001
N-stage		<0.001		<0.001		<0.001		<0.001
N-neg	1		1		1		1	
N-pos	1.57 (1.2–2.0)	<0.001	2.36 (1.9–2.9)	<0.001	2.72 (1.9–3.9)	<0.001	2.04 (1.8–2.4)	<0.001
Nx	1.56 (0.5–4.9)	0.44	3.27 (2.0–5.3)	<0.001	3.54 (0.8–15)	<0.001	2.43 (1.6–3.6)	<0.001
M-stage		<0.001		<0.001		<0.001		<0.001
M ₀	1		1		1		1	
M _I	2.91 (1.7–5.1)		3.90 (2.8–5.6)		4.67 (2.2–9.8)		3.30 (2.5–4.3)	
Malignancy grade		0.003		0.003		0.18		<0.001
I	1		1		1		1	
II, III	1.57 (1.2–2.1)		1.51 (1.2–2.0)		1.41 (0.9–2.3)		1.73 (1.4–2.1)	
Estrogen receptor				<0.001		<0.001		
negative			1		1			
positive			0.52 (0.4–0.6)		0.41 (0.3–0.6)			
Sentinel lymph node biopsy						0.003		
no					1			
yes					0.58 (0.4–0.8)			
Year at diagnosis								<0.001
1986							1	
1996–97							0.71 (0.6–0.8)	<0.001
2002–03							0.50 (0.4–0.6)	<0.001

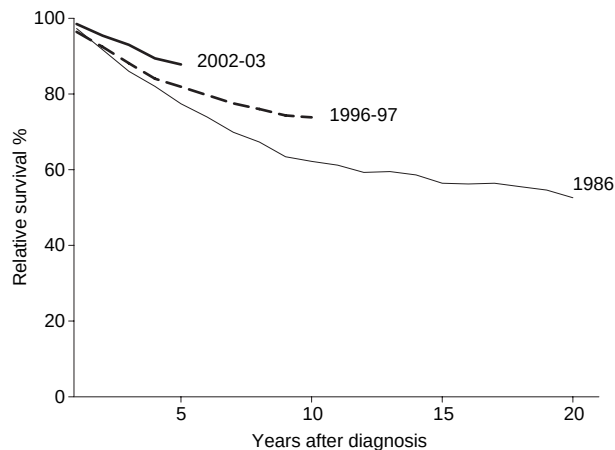


Figure 2. Estimates of Relative Survival proportion ratios by year of diagnosis.

survival probabilities were 55% (51–60) for patients diagnosed in 1986 and 66% (64–69) for patients from 1996–1997. In multivariate analysis, year at diagnosis remained a significant predictive factor (Table IV). The relative survival increased in all counties, in Funen the 5-year relative survival rate for patients diagnosed in 2002–2003 was 90% (86–93) indicating that the risk of dying of breast cancer within the first five years after diagnosis was around 10% (Figure 2).

Discussion

There were significant differences in stage at diagnosis according to county of residence. Differences, which remained present during the study period, and

Table V. Time trends for all counties and within each county.

	All Counties					Funen		Aarhus		NJ	
	1986	1996–97	2002–03	86/96–97	96–97/02–03	86/96–97	96–97/02–03	86/96–97	96–97/02–03	86/96–97	96–97/02–03
	488	1324	1573	p	p	p	p	p	p	p	p
Age (year) Median (range)	54 (28–70)	54 (24–70)	56 (21–70)	ns	ns	0.03	ns	ns	ns	ns	ns
Tumor size Median (range)	20 (4–120)	18 (1–130)	19 (1–150)	0.001	0.06	0.001	ns	0.01	0.02	ns	ns
Nodes removed Median (range)	7 (0–32)	13 (0–40)	16* (0–47)	0.001	0.001	0.001	0.001	0.001	0.009	0.001	0.001
T-stage (UICC)				0.003	ns	0.001	ns	ns	ns	ns	ns
T ₁	250 (52)	770 (59)	873 (58)								
T ₂	188 (39)	469 (36)	559 (37)								
T ₃	33 (7)	39 (3)	61 (4)								
T ₄	14 (3)	37 (3)	9 (1)								
N-stage				ns	0.001	0.007	0.03	0.05	0.001	0.04	ns
N neg	267 (55)	710 (54)	718 (46)								
N pos	197 (40)	530 (40)	787 (50)								
N x	24 (5)	84 (6)	68 (4)								
Stage (UICC)				ns	ns	0.001	ns	ns	ns	ns	ns
I	174 (36)	504 (38)	516 (34)								
II	252 (52)	667 (51)	906 (59)								
III	37 (7)	50 (4)	68 (5)								
IV	25 (5)	91 (7)	34 (2)								
Surgery				0.001	0.001	0.001	ns	0.001	0.001	0.05	0.001
Mastectomy	408 (84)	914 (69)	675 (43)								
Lumpectomy	62 (13)	341 (26)	893 (57)								
Histology				ns	0.001	ns	ns	ns	0.001	ns	ns
Ductal	400 (82)	1088 (82)	1207 (77)								
Lobular	44 (9)	118 (9)	176 (11)								
Other	43 (9)	112 (9)	133 (9)								
Malignancy grade				0.001	0.01	ns	ns	ns	ns	ns	0.001
I	121 (26)	327 (26)	323 (22)								
II	186 (40)	493 (39)	518 (34)								
III	79 (17)	251 (20)	338 (22)								
Non-ductal	79 (17)	191 (15)	309 (21)								
Estrogen receptor ^					0.001		ns		0.001		0.001
Negative		367 (29)	309 (20)								
Positive		899 (71)	1201 (80)								

* Not including patients with sentinel lymph node biopsies. ^Estrogen receptor status was not routinely analysed in 1986. Percentages in parentheses.

probably reflected different diagnostic activities. With the introduction of the SLNB, the sentinel lymph nodes are examined with extensive histopathological techniques and more patients are expected to be found with positive lymph nodes [13,14], including patients with only micro metastasis. This can cause stage migration [15], and complicate the interpretation of analysis with different patient populations and in might reduce the influence of county in multivariate analysis in the 2002–2003 cohorts. However, also in the county of NJ, where SLNB was not implemented, there were more patients with positive lymph nodes, indicating an improvement in the histopathological examination of the lymph nodes as well as a higher quality of the axillary surgery where median 18 lymph nodes were removed, which also might lead to stage migration. Having a SLNB seems to be a prognostic favourable factor in itself, indication confounding by indication, as this procedure is mainly offered to patients with small tumors and no clinical macro metastasis prior to surgery.

As reported in other populations [16,17] we found an significant increase in over-all survival during the last three decades. There was an improvement in all counties, also the county of Funen, which had early centralisation of breast cancer surgery, early focus on lymph node staging, implementation of population based mammography screening and finally SLNB. In 1986 county of residence had a major impact on survival in univariate as well as in multivariate analysis. These differences have gradually disappeared, as we only found a difference in the univariate analysis in the 1996–1997 cohorts, indication that the early diagnosis in Funen could explain the difference. In the latest cohorts from 2002–2003 there were no differences in survival according to county, though we still find a significant more favourable stage distribution in the county of Funen and a non-significant trend towards better survival. A Swedish study found regional differences in breast cancer survival despite common guidelines, but they also found that differences decreased with time after complete implementation of the guidelines [18]. The DBCG guidelines on adjuvant treatment are followed in all Danish counties [19]. Within the time frame of this study more prognostic factors have been regarded “high risk factors” and more patients receive adjuvant treatment, which also has changed and steadily becomes more effective [20–23]. A substantial part of the patients are prescribed endocrine therapy for 5 years and was still receiving treatment at end of follow-up. It might be due to the intensive adjuvant treatment, that there is no significant difference in 5 year survival probabilities

between the 2002–2003 cohorts despite differences in distribution of prognostic factors.

The strength of our study is the population-based data-source, with complete coverage and availability of reliable information on diagnostic activities and tumor characteristics.

Conclusion

During these three decades there has been a 10% improvement in over-all and relative survival of breast cancer. Much attention has been drawn to the axillary surgery and correct lymph-node staging, resulting in an increasing number of patients with positive lymph-nodes. In the 1986 and 1996–1997 cohorts we found significant differences in over-all survival related to county of residence, but in the late cohort there were no difference despite better stage distribution in the county with mammography-screening.

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