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Time trends and regional differences in registration, stage distribution, surgical management and survival of breast cancer in Denmark

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Abstract

The aim of this study was to analyse time trends, stage at diagnosis, survival and registration of population-based cohorts of breast cancer patients in selected Danish counties (in total 2504) in 1986 and 1996–1997. In 1986, no differences in the extent of disease were observed between the counties. Patients from one county (Funen) had centralised surgery, significantly more lymph nodes removed and a better survival in the multivariate analysis. In 1996–1997, mammographical screening had been implemented in Funen, leading to a significantly better stage distribution, whereas stage remained unchanged in the other counties. In Funen, survival was significantly better than in the other counties in univariate, but not in multivariate analysis. Survival increased significantly with time only in Funen. Inclusion in clinical trials increased over time and the coverage of the database in the Danish Breast Cancer Cooperative Group (DBCG) was high. However, patients not notified in DBCG had, beside older age, also worse stage of disease distribution and less extensive surgery. A difference in survival was observed between the counties. In 1986, this may be explained by a centralised surgical system in one county, whereas in 1996–1997 improvements could be due to an early diagnosis and other as yet unknown factors. The DBCG database cannot be considered as representative of the Danish population of breast cancer patients.

Keywords: Epidemiology; Breast cancer; Regional differences; Time trends

1. Introduction

Relative survival of breast cancer patients diagnosed between 1958 and 1991 was lower in Denmark than in the other Nordic countries [1]. This caused anxiety in the Danish population and initiated a debate on the potential reasons. All healthcare services are provided free of charge for all citizens and national guidelines on breast cancer management have been made by the Danish Breast Cancer Cooperative Group (DBCG) since 1977 [2,3]. However, previous studies found regional differences in the mortality rates from breast cancer, but did not include the extent of disease in the analyses [4–6]. Healthcare is organised by the local health authorities within each county and to analyse whether the lower survival probability in Denmark could be explained by regional differences in stage at diagnosis or were caused by differences in the quality of care, we analysed population-based cohorts of breast cancer patients from three counties, representing 30% of the Danish population. The county of Funen was chosen as it is a county where breast cancer surgery became centralised in the early 1980s and, since 1993, all female inhabitants in Funen between the ages of 50 and 70 years have been invited to mammographical screening every second year. The counties of Northern Jutland (NJ) and Aarhus were selected as two other provincial counties providing full oncological services, including

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radiotherapy, within the county. In both counties, breast cancer surgery was performed at all hospitals within the counties in the 1980s and, gradually, it has become more centralised during the 1990s. No organised mammographical screening programmes exist in either of these counties.

To analyse time trends, two time periods were selected with a time span of 10 years in between. National data on breast cancer patients are available from two independent registries in Denmark, the Danish Cancer Registry (DCR) and the clinical database of the Danish Breast Cancer Cooperative Group (DBCG). If a clinical database can be considered a population-based register with high quality data, much time spent on collecting additional information to the data in the cancer registry can be spared. We validated completeness and representativeness in the DBCG database compared with a corrected national dataset from the population-based cancer registry.

2. Patients and methods

2.1. Study design

The study was designed as a cross-sectional study in three counties in two time periods. The years 1996 and 1997 were the latest years with available data from the DCR and 1986 was selected as a period 10 years before this.

2.2. Data sources

2.2.1. The DCR

The DCR was founded in 1943 as a nationwide cancer registry. It is based on notifications from multiple sources and contains high quality incidence data [7], but information on the extent of disease and treatment for breast cancer can only be used with caution [8,9].

2.2.2. The DBCG

The DBCG was established in 1977 as an initiator and organiser of prospective adjuvant breast cancer treatment and management [2]. In addition, the group evaluates breast cancer treatment programmes and intends to collect prospective records also on patients who are treated outside of protocols. Data quality in the register has been found to be high [10]. The DBCG database holds detailed information on tumour size, histopathological characteristics, nodal involvement and surgical procedures.

2.3. Study populations

From the DCR, we identified all women with primary invasive breast cancer who were diagnosed in the counties of Funen, Aarhus and NJ in the years 1986, 1996 and 1997. Data from the DCR were merged with the database in DBCG by means of the unique personal identification number provided to all citizens in Denmark. Medical records from the hospitals/general practitioners were found for the patients who were not fully notified in the DBCG database. It was possible to find clinical information on all but 13 of the patients who were equally distributed between both time periods and the counties. We excluded patients with a previous history of invasive cancer, no histo-pathological verification of diagnosis and patients known by death certificate only (DCO). To examine the notification policy in the regions, we analysed differences in the tumour characteristics of those not allocated to trials, but fully notified versus those not notified or notified without clinical data. These analyses were restricted to the 1996–1997 cohort due to the small number of patients not notified in the 1986 cohort.

2.4. Follow-up

Survival was assessed on 15 March 2002. The potential median follow-up time (time from date of surgery/biopsy until the date of assessment) was 15.7 years (range 15.0–16.2 years) in the 1986 cohort and 5.2 years (range 4.3–6.2 years) in the 1996–1997 cohort. The National Population Registries provided data on the date of death.

2.5. Statistical analysis

Tumours were classified according to the International Union Against Cancer (UICC) TNM system [11]. Among patients with simultaneous bilateral breast cancer, the breast with the largest tumour was noted as the primary side, while the tumour on the other side was registered as a distant metastasis. T-stage was used as a combined measurement of tumour size and local tumour extension. Groups were compared by the Mann–Whitney and Kruskal–Wallis tests. The cumulative incidence rate was calculated as 5 times the sum of the 5-year age-specific incidence rates. The National Population Registries provided data on the general population in the regions that was needed for calculating the incidence rates.

Overall survival rates were 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 cohort. Cox regression analysis was used to compare risk estimates between counties, taking into account the different distribution of age and prognostic variables, the number of lymph nodes removed and the proportion of positive nodes in a stepwise model, as described by Gatta and colleagues [12]. The hazard ratios were used as estimators of the relative

risk. A statistical analysis was performed using the likelihood-ratio test. The level of significance was set at 5% and all P values were two-tailed.

3. Results

A total of 681 patients with primary invasive carcinoma of the breast were included in the 1986 cohort and 1823 in the 1996–1997 cohort (Fig. 1). The proportion of patients excluded was similar in all of the counties. Characteristics of the cohorts, differences between populations and times are summarised in Table 1.

3.1. The DBCG register

We found no difference in the proportion of patients included in the clinical trials or fulfilling the exclusion criteria between the three counties in either of the time periods (Table 2). There was a positive time trend with an increasing proportion of patients being included in trials. The highest percentage of patients not notified or notified without clinical data was observed in the county of Aarhus in both time periods. This percentage increased over time in the other two regions. We found significant differences between the groups for all variables except age (Table 3). The patients notified in the DBCG database had a more favourable mix of prognostic factors, more extensive surgery in terms of the lymph nodes removed and mastectomies versus biopsies. The survival analysis showed significant differences between those who were fully notified and those who were not notified ($P < 0.001$), but also a significant difference in overall survival between patients fully notified in DCBG and the whole cohort with 5-year overall survival rates of 77% (75–79%) and 72% (70–74%), respectively (Fig. 2).

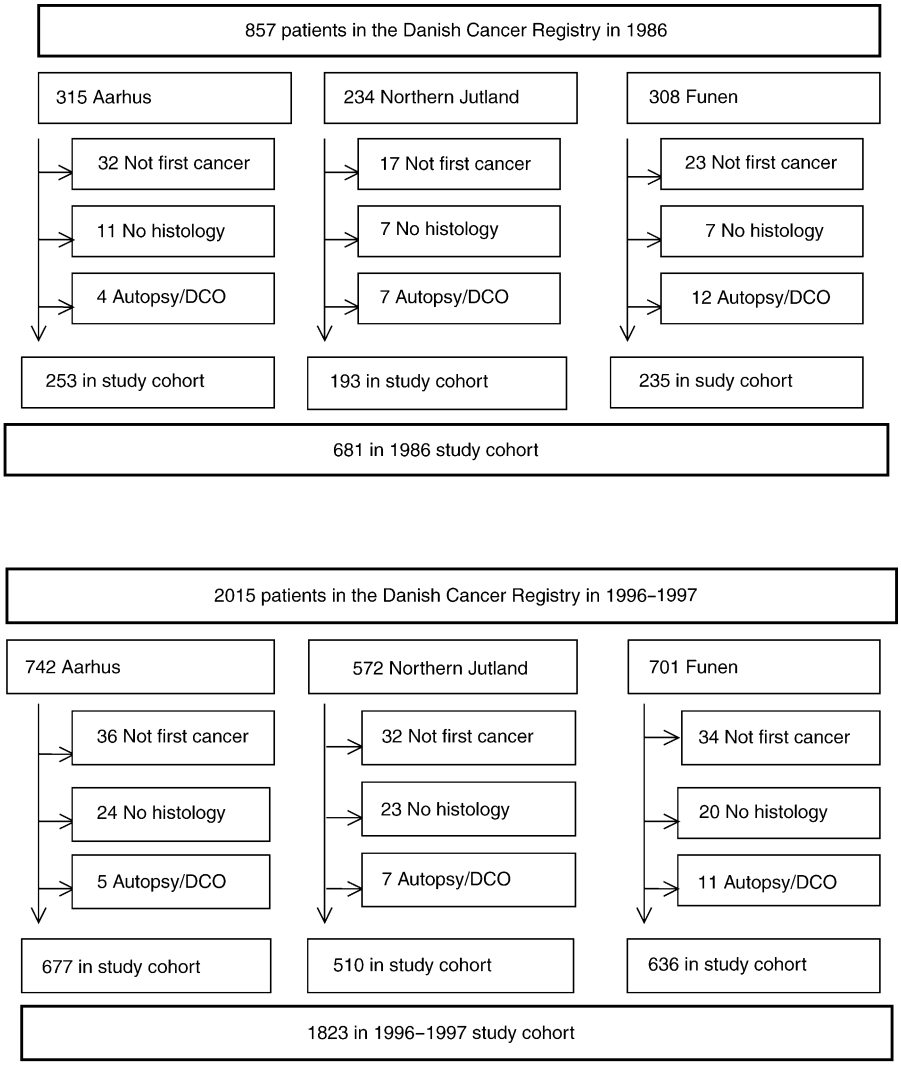

Fig. 1. Identification of final study cohorts after exclusions. No significant changes in age distribution were found between all breast cancer patients identified in the Danish Cancer Registry and the local study cohorts. DCO, death certification only.

Table 1
Basic patients' characteristics and comparisons according to the county and time period

	1986			Between counties P^* value	1996–1997			Between counties P^* value	Between time periods		
	Funen	Aarhus	NJ		Funen	Aarhus	NJ		Funen P' value	Aarhus P' value	NJ P' value
Number of patients	235	253	193		636	677	510				
Age (years)											
Median (range)	59.2 (28–94)	61.5 (31–92)	63.1 (30–94)	NS	61.1 (27–101)	59.3 (24–94)	61.5 (29–95)	0.03	NS	NS	NS
Cumulative incidence rate /100 000 woman years	9646	6762	7821	<0.05[a]	12 900	10 670	9916	<0.01[a]	<0.01	<0.01	<0.01
Tumour size (mm)											
Median (range)	22 (4–120)	20 (4–100)	20 (5–105)	NS	17 (1–80)	20 (1–130)	20 (1–120)	<0.001	<0.001	0.02	NS
Nodes removed											
Median (range)	8 (0–32)	5 (0–18)	7 (0–19)	<0.001	13 (0–40)	12 (0–40)	11 (0–38)	<0.001	<0.001	<0.001	<0.001
Nodes removed[b]											
According to guidelines	199 (85)	153 (60)	142 (74)	<0.001	490 (77)	564 (83)	359 (70)	0.001	0.02	<0.001	NS
Less than guidelines	36 (15)	100 (40)	51 (26)		146 (23)	113 (17)	151 (30)				
T-stage (UICC)				NS				0.01	<0.001	NS	NS
T_I ($\leqslant$10 mm)	25 (11)	30 (12)	19 (10)	NS	101 (16)	94 (14)	55 (11)	0.04	0.05	NS	NS
T_I (>10 mm)	74 (31)	88 (35)	82 (42)	0.06	262 (41)	249 (37)	202 (40)	NS	<0.01	NS	NS
T_{II}	103 (44)	99 (39)	75 (39)	NS	217 (34)	264 (39)	220 (43)	<0.01	<0.01	NS	NS
T_{III}	16 (7)	17 (7)	12 (6)	NS	13 (2)	34 (5)	19 (4)	NS	<0.01	NS	NS
T_{IV}	11 (5)	14 (6)	2 (1)	NS	31 (5)	30 (4)	12 (2)	NS	NS	NS	NS
Not classified	6 (3)	5 (2)	3 (2)		12 (2)	6 (1)	2 (<1)				
N-stage				NS				NS	0.05	NS	NS
N negative	110 (47)	137 (54)	109 (57)	0.08	330 (52)	327 (48)	224 (44)	NS	0.03	NS	NS
N positive	97 (41)	81 (32)	76 (59)	NS	210 (33)	255 (38)	188 (37)	0.03	NS	NS	<0.01
N_x	28 (12)	35 (14)	8 (4)		96 (15)	96 (14)	98 (19)				
Stage (UICC)				NS				0.03	<0.001	NS	NS
I	60 (26)	81 (32)	68 (35)	0.09	241 (38)	210 (31)	148 (29)	<0.01	<0.01	NS	NS
II	131 (56)	127 (50)	104 (54)	NS	304 (48)	342 (51)	270 (53)	NS	0.04	NS	NS
III	21 (9)	20 (8)	13 (7)	NS	30 (5)	45 (7)	24 (5)	NS	0.02	NS	NS
IV	14 (6)	15 (6)	3 (2)	0.05	28 (4)	58 (9)	35 (7)	0.01	NS	NS	<0.01
Not classified	9 (4)	10 (4)	5 (3)		33 (5)	22 (3)	33 (6)				
Histological type				NS				NS	NS	NS	NS
Ductal	182 (77)	204 (81)	133 (69)	0.01	486 (76)	516 (76)	389 (76)	NS	NS	NS	0.05
Lobular	22 (9)	16 (6)	29 (15)	<0.01	59 (9)	53 (8)	47 (9)	NS	NS	NS	0.03
Other	19 (8)	15 (6)	30 (16)	<0.01	50 (8)	66 (10)	48 (9)	NS	NS	0.09	0.02
Cytology only	12 (5)	18 (7)	1 (1)	<0.01	34 (5)	41 (6)	24 (5)	NS	NS	NS	<0.01
Unknown					7	1	2				
Malignacy grade (ductal only)				<0.001				NS	NS	NS	0.01
I	47 (26)	51 (27)	57 (45)	<0.01	149 (31)	140 (28)	134 (36)	<0.01	NS	NS	0.07
II	82 (46)	104 (56)	58 (46)	<0.01	226 (48)	252 (51)	166 (44)	NS	NS	NS	NS
III	49 (28)	31 (17)	12 (9)	<0.01	99 (21)	107 (21)	74 (20)	NS	NS	0.08	<0.01
Oestrogen receptor[c]								<0.001			
Positive					486 (76)	444 (65)	348 (68)	<0.001			
Negative					117 (18)	195 (29)	138 (27)	<0.001			
Unknown					33 (5)	42 (6)	24 (5)				
Type of surgery				0.04				<0.001	<0.001	<0.001	NS
Mastectomy	182 (77)	209 (83)	167 (87)	0.05	402 (63)	476 (70)	419 (82)	<0.001	<0.001	<0.001	NS
Lumpectomy	39 (17)	24 (9)	24 (12)	0.06	183 (29)	151 (22)	57 (11)	<0.001	<0.001	<0.001	NS
Biopsy only	14 (6)	20 (8)	2 (1)	<0.01	46 (7)	51 (8)	33 (6)	NS	NS	NS	<0.01
Unknown					5	1	1				

UICC, the International Union Against Cancer; NS, non-significant; NJ, Northern Jutland. P^* comparisons between counties by means of the Kruskal–Wallis test. P' comparisons between time periods within each county by means of the Mann–Whitney test. P values given when $P<0.1$.

[a] Differences between incidence rates analysed with Funen as reference.

[b] Axillary dissection was not recommended for patients with distant metastasis or inflammatory cancer, five nodes recommended in 1986 and 10 nodes in 1996–1997.

[c] Oestrogen receptor analysis was not routinely done in 1986.

Table 2
Number of patients and (%) allocated to a clinical trial and notified in DBCG according to county and period

	1986			1996–1997		
	Aarhus	Northern Jutland	Funen	Aarhus	Northern Jutland	Funen
In clinical trial	138 (55)	110 (57)	138 (59)	453 (67)	327 (64)	444 (70)
Not in clinical trial						
Fully notified in DBCG	77 (30)	75 (39)	87 (37)	148 (22)	135 (26)	138 (22)
No clinical data or not notified in DBCG	38 (15)	8 (4)	10 (4)	76 (11)	48 (9)	54 (8)
Not in trial, subtotal	115 (45)	83 (43)	97 (41)	224 (33)	183 (36)	192 (30)
Not in clinical trial, + exclusion criteria	89 (35)	69 (36)	87 (37)	182 (27)	146 (29)	159 (25)
Not in clinical trial, −no exclusion criteria stated	26 (10)	14 (7)	10 (4)	42 (6)	36 (7)	31 (5)
Unknown					1 (<1)	2 (<1)
Total	253 (100)	193 (100)	235 (100)	677 (100)	510 (100)	636 (100)
Carcinoma *in situ*, notified in DBCG	0	6	14	0	0	0

DBCG, Danish Breast Cooperative Group.
No significant differences were found between the counties in either of the time periods. Patients notified, but truly having carcinoma *in situ* cancer are not included in the study cohort.

Table 3
Tumour characteristics of patients not included in clinical trials in 1996–1997 according to whether they were notified in the DBCG

	Aarhus			Northern Jutland			Funen		
	Notified	Not notified	*P* value	Notified	Not notified	*P* value	Notified	Not notified	*P* value
Number of patients	148	76		135	48		138	54	
Age (years)									
Median	76.3	71.2	NS	76.7	72.3	NS	77.8	77.7	NS
(range)	(32–94)	(34–93)		(32–92)	(36–95)		(32–101)	(27–92)	
T-stage (UICC)			<0.001			<0.001			<0.001
T_I (⩽10 mm)	16 (11)	2 (3)		9 (7)	7 (15)		14 (11)	1 (2)	
T_I (>10 mm)	45 (30)	13 (19)		46 (34)	7 (15)		44 (33)	4 (9)	
T_{II}	76 (51)	19 (27)		69 (51)	18 (39)		65 (49)	11 (24)	
T_{III}	11 (7)	6 (9)		10 (7)	2 (4)		5 (4)	3 (7)	
T_{IV}	0	30 (43)		0	12 (26)		4 (3)	26 (58)	
N-stage			<0.001			<0.001			<0.001
N negative	55 (37)	5 (7)		30 (22)	5 (10)		41 (30)	3 (6)	
N positive	58 (39)	10 (13)		46 (34)	3 (6)		45 (33)	6 (11)	
N_x	35 (24)	61 (80)		58 (43)	40 (83)		50 (37)	45 (83)	
Lymph nodes removed			<0.001			<0.001			<0.001
Median (range)	11 (0–27)	0 (0–14)		3 (0–38)	0 (0–17)		6 (0–27)	0 (0–10)	
M-stage			<0.001			<0.001			<0.001
M_0	127 (86)	38 (51)		120 (90)	26 (55)		127 (93)	29 (60)	
M_1	21 (14)	37 (49)		14 (10)	21 (45)		9 (7)	19 (40)	
Stage (UICC)			<0.001			<0.001			<0.001
I	24 (18)	2 (3)		18 (17)	4 (10)		25 (22)	2 (5)	
II	80 (59)	9 (13)		68 (63)	7 (17)		72 (63)	7 (16)	
III	10 (7)	19 (28)		8 (7)	9 (22)		9 (8)	15 (35)	
IV	21 (16)	37 (55)		14 (13)	21 (51)		9 (8)	19 (44)	
Histological type			<0.001			<0.001			<0.001
Ductal	119 (80)	27 (38)		114 (85)	17 (37)		109 (80)	15 (33)	
Lobular	11 (7)	1 (1)		12 (9)	3 (7)		13 (10)	0	
Other	18 (12)	3 (4)		8 (6)	2 (4)		11 (8)	1 (2)	
Cytology only	0	41 (57)		0	24 (52)		3 (2)	30 (65)	
Type of surgery			<0.001			<0.001			<0.001
Mastectomy	122 (82)	19 (25)		125 (93)	7 (15)		111 (82)	5 (10)	
Tumorectomy	25 (17)	6 (8)		7 (5)	9 (19)		18 (13)	5 (10)	
Biopsy only	1 (1)	50 (67)		2 (1)	31 (66)		7 (5)	38 (79)	

Percentages in parentheses. Comparison between groups with the Mann–Whitney test.

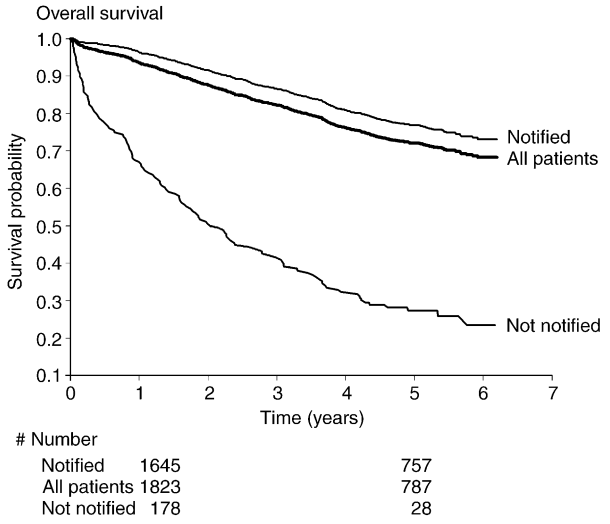

Fig. 2. Kaplan–Meier estimates of overall survival for the 1996–1997 cohort and among those notified/not notified to the Danish Breast Cancer Cooperative Group (DBCG) database. Log rank $P < 0.001$ for differences between those notified and not notified.

3.1.1. In 1986

Few differences were observed between the counties. In Funen, patients had significantly more lymph nodes removed and more lumpectomies were performed. The women tended to be younger at diagnosis and have slightly larger tumours in Funen than in the other two counties, but these differences were not significant. Compared with the other counties, there were very few patients in NJ with advanced disease, as only 5 patients had distant metastasis or locally advanced disease. In addition, only 1 patient had a biopsy as the only surgical procedure.

3.1.2. In 1996–1997

Patients from the county of Aarhus were significantly younger than in the other counties. In Funen, patients had significantly smaller tumours and a better T-stage and stage distribution. The most extensive axillary surgery was performed in this county, with a median of 13 nodes removed. Even though more lymph nodes were removed, the nodal status was significantly more favourable. Furthermore, among lymph node-positive patients, the number of positive nodes was smaller in Funen than the other counties. It seems the recommendations with regard to axillary dissection were followed most often in the county of Aarhus and less frequently in NJ. The percentage of patients offered breast-conserving surgery was highest in Funen.

3.1.3. Survival analysis

In 1986, there was no difference in overall survival between the counties until 8 years after diagnosis (Fig. 3). However, the long-term survival rate (8–16 years) was significantly higher in Funen than in the other counties. 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. An analysis including age (model 1) did not affect the risk estimates related to county (Table 4), but in the multivariate analysis taking prognostic variables into account, a large and significant survival advantage was seen in Funen (model 2). The risk estimates remained stable when the number of lymph nodes removed and frequency of positive nodes (model 3) were included, although the level of significance decreased.

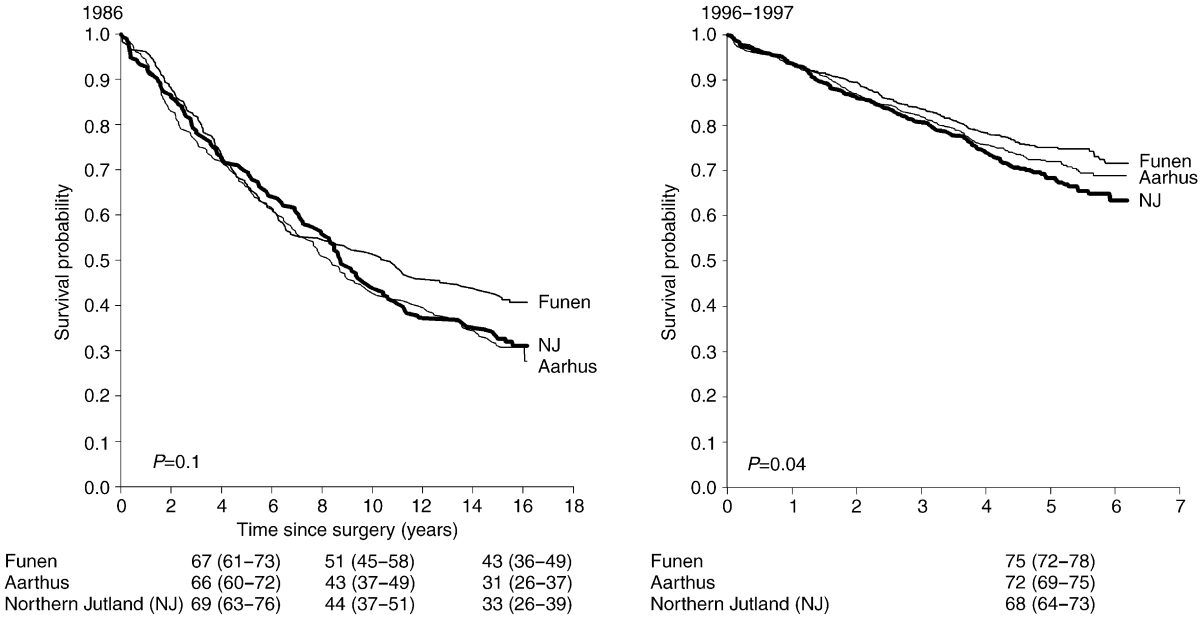

Fig. 3. Kaplan–Meier estimates of overall survival by county and year of diagnosis. Log-rank test for difference between groups. **Bold line**: Northern Jutland. Survival rated and 95% Confidence Intervals (CIs) at 5, 10 and 15 years are given below figure.

Table 4
Relative risk of death by county, age, prognostic factors, and determinants of lymph node stage. Patients diagnosed in 1986

	1986 cohort							
	Univariate analysis		Multivariate analysis[a]					
			Model 1		Model 2		Model 3	
	Hazard rate	*P* value	Hazard rate	*P* value	Hazard rate	*P* value	Hazard rate	*P* value
County		0.11		0.13		0.006		0.02
Funen	1		1		1		1	
Aarhus	1.26 (1.0–1.6)	0.04	1.24 (1.0–1.6)	0.06	1.39 (1.1–1.8)	0.009	1.37 (1.0–1.8)	0.02
NJ	1.21	NS	1.21	NS	1.48 (1.1–1.9)	0.003	1.41 (1.1–1.8)	0.01
Age (years)		<0.001		<0.001		<0.001		<0.001
<40	1		1		1		1	
40–49	0.86	NS	0.86	NS	0.75	NS	0.66	NS
50–59	1.15	NS	1.15	NS	0.95	NS	0.75	NS
60–69	1.54 (1.0–2.5)	0.07	1.52 (1.0–2.4)	0.08	1.22	NS	1.03	NS
70–79	2.48 (1.6–3.9)	<0.001	2.48 (1.6–4.0)	<0.001	1.86 (1.0–2.6)	0.07	1.66	NS
80+	4.11 (2.5–6.7)	<0.001	4.10 (2.5–6.7)	<0.001	3.59 (1.8–7.1)	<0.001	2.79 (1.4–5.7)	0.005
T-stage (UICC)		<0.001				<0.001		<0.001
T_I ($\leqslant$10 mm)	1				1		1	
T_I (>10 mm)	1.81 (1.2–2.7)	0.005			1.69 (1.1–2.7)	0.02	1.49 (0.9–2.4)	0.09
T_{II}	2.87 (1.9–4.3)	<0.001			2.36 (1.5–3.7)	<0.001	1.87 (1.2–3.0)	0.008
T_{III}	5.46 (3.3–8.9)	<0.001			4.47 (2.6–7.8)	<0.001	2.58 (1.4–4.6)	0.001
T_{IV}	13.25 (7.7–22.9)	<0.001			28.8 (10.3–80.3)	<0.001	15.13 (5.2–44.0)	<0.001
M stage		<0.001				<0.001		<0.001
M0	1				1		1	
M1	5.61 (3.9–8.1)				3.7 (2.2–6.4)		4.59 (2.6–8.1)	
Histology		0.16				0.22		0.47
Ductal	1				1		1	
Lobular	1.30 (1.0–1.7)	0.08			1.18	NS	1.11	NS
Other	0.91	NS			0.80	NS	0.84	NS
Malignacy grade[b]		0.003				0.18		0.20
I	1				1		1	
II	1.46 (1.1–1.9)	0.003			1.20 (0.9–1.6)	0.07	1.22	NS
III	1.67 (1.2–2.3)	0.002			1.38 (0.99–2.0)	<0.001	1.37 (1.0–1.9)	0.08
Menopausal status		<0.001				0.70		0.48
Premenopausal	1				1		1	
Postmenopausal	2.21 (1.8–2.7)				1.09 (0.7–1.7)		1.17 (0.8–1.8)	
Nodes removed		<0.001						0.001
10+	1						1	
5–9	1.07	NS					0.81	NS
3–4	1.05	NS					0.78	NS
1–2	1.44 (1.0–2.1)	0.06					0.64 (0.4–1.0)	0.08
0 nodes	4.07 (2.9–5.6)	<0.001					2.08 (1.2–3.6)	0.01
Positive nodes %		<0.001						<0.001
0 positive	1						1	
<33.3%	0.99	NS					0.89	NS
33.4–66.6%	1.83 (1.3–2.5)	<0.001					1.78 (1.3–2.5)	0.001
$\geqslant$66.7%	3.93 (3.0–5.1)	<0.001					3.53 (2.6–4.7)	<0.001

Univariate and multivariate Cox regression analysis. *P* values and 95% Confidence Intervals (in parentheses) given when $P<0.1$.
[a] Model 1 only includes county and age, model 2 county, age and prognostic factors, except lymph node status and the number of lymph nodes removed.
[b] Non ductal carcinoma analysed as grade II.

In 1997, the Kaplan–Meier plot showed significant differences between the counties (log rank $P=0.04$) with 5-year survival being 7% higher in Funen compared with NJ (Fig. 3). The risk estimates was not affected by age (model 1) (Table 5). However, in the multivariate analysis, this difference decreased due to a more favourable stage distribution in Funen (model 2). Including the number of lymph nodes removed and the frequency of positive nodes (model 3) tended to decrease these differences even more ($P=0.56$).

Table 5
Relative risk of death by county, age, prognostic factors and determinants of lymph node stage. Patients diagnosed in 1996 and 1997

	1996–1997 cohort							
	Univariate analysis		Multivariate analysis[a]					
			Model 1		Model 2		Model 3	
	Hazard rate	*P* value	Hazard rate	*P* value	Hazard rate	*P* value	Hazard rate	*P* value
County		0.04		0.045		0.14		0.56
Funen	1		1		1		1	
Aarhus	1.15	NS	1.21 (1.0–1.5)	0.08	0.97	NS	1.01	NS
NJ	1.32 (1.1–1.6)	0.01	1.31 (1.1–1.6)	0.02	1.22	NS	1.11	NS
Age (years)		<0.001		<0.001		<0.001		<0.001
<40	1		1		1		1	
40–49	0.70	NS	0.71	NS	0.73	NS	0.65	NS
50–59	0.87	NS	0.87	NS	0.60	NS	0.50 (0.3–0.98)	0.04
60–69	1.06	NS	1.07	NS	0.74	NS	0.64	NS
70–79	1.73 (1.1–2.6)	0.01	1.75 (1.2–2.7)	0.009	1.06	NS	0.89	NS
80+	2.99 (2.0–4.6)	<0.001	3.03 (2.0–4.6)	<0.001	3.40 (1.2–4.9)	0.02	1.23	NS
T-stage (UICC)		<0.001				<0.001		<0.001
T_I (⩽10 mm)	1				1		1	
T_I (>10 mm)	1.30	NS			1.07	NS	0.90	NS
T_{II}	3.17 (2.2–4.5)	<0.001			1.86 (1.2–2.8)	0.003	1.30	NS
T_{III}	6.08 (3.8-9.6)	<0.001			2.92 (1.7–5.0)	<0.001	1.75 (1.0–3.0)	0.04
T_{IV}	11.0 (7.2–17.0)	<0.001			6.69 (3.5–12.8)	<0.001	3.40 (1.7–6.6)	<0.001
M stage		<0.001				<0.001		<0.001
M0	1				1		1	
M1	6.68 (5.4–8.3)				5.06 (3.6–7.0)		4.22 (3.0–5.9)	
Histology		0.35				0.66		0.59
Ductal	1				1		1	
Lobular	0.78	NS			0.86	NS	0.90	NS
Other	0.94	NS			0.90	NS	1.20 (0.8–1.8)	0.01
Malignacy grade[b]		<0.001				0.003		0.009
I	1				1		1	
II	1.63 (1.3–2.1)	<0.001			1.53 (1.1–2.0)	0.004	1.38 (1.0–1.8)	0.03
III	2.73 (2.1–3.7)	<0.001			1.76 (1.2–2.4)	0.001	1.71 (1.2–2.4)	0.002
Oestrogen receptor		<0.001				<0.001		<0.001
Positive	1				1		1	
Negative	2.36 (2.0–2.8)				2.08 (1.7–2.6)		2.05 (1.6–2.6)	
Menopausal status		<0.001				0.06		0.01
Premenopausal	1				1		1	
Postmenopausal	1.83 (1.5–2.3)				1.64 (1.0–2.7)		1.92 (1.1–3.2)	
Nodes removed		<0.001						<0.001
10+	1						1	
5–9	1.33 (1.0–1.8)	0.06					1.06	NS
3–4	3.34 (1.8–6.3)	<0.001					1.10	NS
1–2	4.36 (2.6–7.3)	<0.001					1.70	NS
0 nodes	4.9 (4.0–5.9)	<0.001					3.41 (2.4–4.8)	<0.001
Positive nodes %		<0.001						<0.001
0 positive	1						1	
<33.3%	1.83 (1.4–2.4)	<0.001					2.01 (1.5–2.7)	<0.001
33.4–66.6%	4.39 (3.2–6.0)	<0.001					3.75 (2.7–5.3)	<0.001
⩾66.7%	6.93 (5.2–9.3)	<0.001					4.69 (3.4–6.5)	<0.001

Univariate and multivariate Cox regression analysis. *P* values and 95% Confidence Intervals (in parentheses) given when $P<0.1$.
[a] Model 1 only includes county and age, model 2 county, age and prognostic factors, except lymph node status and the number of lymph nodes removed.
[b] Non ductal carcinoma analysed as grade II.

3.1.4. Time trends

The cumulative incidence rates increased significantly in all of the cohorts and Funen maintained the highest rate (Table 1). However, the highest increase was observed in Aarhus ((10 670−6762)/10 670), corresponding to a 37% increase.

The main changes over time occurred in Funen, where tumours became smaller and the stage distribution more

favourable. In all three counties, we found a significant increase in the number of lymph nodes removed in the 10-year time period, but most nodes were still removed in Funen. In Aarhus, more patients were offered breast-conserving surgery, whereas the frequency remained unchanged in NJ. Few other changes occurred in Aarhus, but in NJ there were significantly more patients with lymph node metastasis and distant metastasis in the latest time period.

Survival analysis revealed a significant improvement in the overall survival rate over time in Funen from 67% in 1986 to 75% in 1996–1997 ($P=0.009$) and a non-significant improvement in Aarhus from 66% to 72% ($P=0.06$), whereas we found no change in survival in NJ, changing from 69% to 68% ($P=0.9$) within the study period (Fig. 3).

3.1.5. Histo-pathological characteristics

In 1986, there were differences in tumour morphology between NJ and the other counties, as fewer patients had a ductal carcinoma in NJ, but in 1996–1997, this difference had disappeared.

Ductal carcinomas were routinely graded into malignancy grade according to Bloom and Richardson [13,14] in both time periods, but especially in 1986, there were significantly more grade I tumours in NJ. The log rank test showed grade to separate prognostic groups also in NJ (data not shown). The oestrogen receptor status was not routinely assessed in 1986 and is therefore not included in the 1986 analysis. In the 1996–1997 cohort, we found a difference in the frequency of oestrogen-positive tumours between the counties with 76% (468/636) receptor-positive tumours in Funen and 66% (444/677) in Aarus and 68% (348/510) in NJ.

4. Discussion

Previous studies have found the quality of data in the DBCG database to be high [10,15,16]. In a recent study linking the DCR and the DBCG databases, the DBCG was found to be 82% complete in 1978–1994, increasing to 89% complete in 1992–1993 [17]. The present study confirmed these findings, with a completeness ranging from 87% to 96%. The purpose of the DBCG is to initialise and monitor randomised clinical trials. The present study demonstrated that 55–70% of patients were included in clinical trials. Inclusion required that patients were younger than 70 or 75 years, had early breast cancer and were otherwise healthy. Therefore, we would expect patients not included to have been older and have more advanced disease. However, it seemed that those not notified to the DBCG had more advanced disease and less extensive surgery than those notified, but not included in trials, while the age distribution of these two groups did not differ significantly. It is therefore likely that omission of notification is determined by the stage of disease rather than by the age of the patients. This is supported by the finding that patients not notified to the DBCG had a worse survival probability than those notified, but not included in trials. Beside the omission of a group with a bad prognosis, we also in one county found 6% non-invasive cancers notified as if they were invasive. The DBCG database has previously been used for comparing the quality of surgery and survival between one county and the remaining country [5,18]. The findings of the present study indicate that the DBCG database should be used, although its limitations should be acknowledged. These include a risk of selection bias and confounding by indication if the database is regarded as a complete population-based register. If an analysis of survival and surgical procedures is performed from the DBCG data only, a group of patients with the worst prognosis and less extensive surgery would be left out. Similar considerations are involved in comparing time trends or regional variations.

Adjuvant treatment in breast cancer is standardised nationwide in accordance with DBCG guidelines. The percentage of patients notified in the DBCG was equal in the counties in 1996–1997 and a former study including 1986 has shown that patients not included in the DBCG trials, but belonging to similar risk groups, received the same treatment and obtained equal survival probabilities [10]. It therefore seems unlikely that differences in adjuvant treatment can explain the observed difference in survival related to the county of residence.

In Funen, surgery was centralised to one hospital in both time periods. By contrast, in the other counties centralisation has gradually been implemented and this might be a contributing factor for the superior survival observed in Funen. A prolonged survival has been observed in patients treated by surgeons with a higher caseload [19] and the organisation of breast cancer surgery in Funen provides opportunities for breast clinics to adopt a multidisciplinary approach to breast cancer treatment. At present, axillary dissection is considered to be both a staging procedure and a procedure to obtain loco-regional tumour control, thereby potentially leading to improved survival [20–25]. To make a true nodal staging, a sufficient axillary dissection is needed. DBCG recommended a minimum of five nodes removed in 1986, whereas in 1996–1997 they recommended an axillary dissection with a minimum of 10 nodes removed. In 1986, significantly more nodes were removed from patients in the county of Funen and an earlier publication found survival for breast cancer patients to be significantly better in Funen than in the rest of Denmark during the 1980s [5]. The authors argued that this was due to the more extensive axillary surgery. However, the effects of age and extent of disease at diagnosis were not taken into account. Our

multivariate analysis confirm the superior overall survival found in the county of Funen prior to mammographical screening, in spite of larger tumours and more lymph node-positive patients in Funen (although these differences were not significant). The only explanatory factor remaining was the centralised surgical system and a significantly higher number of lymph nodes removed in Funen. In 1986, there was a risk of underestimating the percentage of patients with a positive nodal status by removing too few nodes, thereby leading to a stage migration and a higher risk of erroneous staging of patients in Aarhus and NJ [26]. Model 3 included the number of lymph nodes removed and the proportion of positive nodes. This further adjustment had only a slight impact on the risk estimates, but decisions on whether to give adjuvant treatment are closely related to the nodal status and the true impact of the lymph nodes removed cannot be determined from the present study. Although stage migration did not explain the observed differences in crude survival between the cohorts, it would tend to result in an overestimation of the impact of county in a multivariate analysis.

Dealing with the extent of axillary dissection also includes a risk of selection bias, as it might not be random whether a patient had many or only a few nodes removed. This is illustrated in Tables 4 and 5, where the risk estimates related to number of lymph nodes removed changed from the univariate to the multivariate analysis, after controlling for other potential confounders. Although most nodes were removed in Funen, the majority of patients in all of the cohorts received what is regarded as a sufficient axillary dissection, therefore stage migration and differential misclassification is not considered to be a major problem in the 1996–1997 cohort. Although recommendations with regard to axillary dissection were not followed for 30% of patients from NJ, a substantial proportion of these patients also had more lymph nodes removed than prescribed by the guidelines from 1986.

The significant changes over time in tumour size, stage distribution and survival were mainly seen in Funen, after the introduction of mammographical screening in 1993. Adjustment by the extent of disease reduced the difference between cohorts in the latest time period and the observed difference in crude survival between the counties can be explained by the more favourable stage distribution in patients from Funen. However, for breast cancer a follow-up time of 6.2 years is generally not sufficient. In particular, data concerning mammographical screening require a long follow-up time to ensure that it is not only lead time bias and sojourn time which is being measured [27,28]. Instead of improvements in survival or mortality rates, intermediate endpoints such as tumour size, T-stage or stage can be used as early and valid indicators of the effectiveness of screening and the results suggest that the improved survival observed in Funen in the 1996–1997 cohort will persist with a longer follow-up.

Regional differences in the incidence rates of breast cancer between the Danish counties, with only small variations in time trends, have previously been reported in Ref. [4]. In the current study, the cumulative incidence rate was highest in Funen in both time periods. In several studies, a higher incidence rate is reported in populations offered screening [29,30]. The incidence increased significantly in all three regions during the study period, but the largest increase was observed in Aarhus. This indicates that length time bias (detecting low malignant tumours that would never in a person's life-time become clinically detectable) is not a major problem in the current study.

In 1986, very few patients from NJ had advanced disease or a biopsy only and this might contribute to the rather beneficial survival rate observed in NJ in the first 8 years of observation, after which it declines to the rate observed in Aarhus. The increase in the frequency of patients with distant metastasis in NJ might explain why there is no improvement in 5-year survival in NJ over time.

Surprisingly, we found more malignancy grade I tumours in NJ, mainly in 1986 and, to examine if it was caused by interobserver variation between pathologists, we did a survival analysis according to malignancy grade and found grade to separate prognostic groups in the county of NJ. We cannot explain the observed difference, but if it is caused, to some extent, by different grading habits among the pathological departments, there is a risk of a differential misclassification in the multivariate analysis.

Overall survival rates are used for comparisons due to the rather small number of cases/small background populations within each county leading to large Confidence Intervals on the relative survival estimates. The expected life-times for women in Funen, Aarhus and NJ were almost equal, being 0.2 years higher in Aarhus (highest) versus NJ (lowest) in the time period from 1996 to 2000 (from statistics Denmark) and it is therefore unlikely that the observed survival probabilities can be explained by differences in the background populations. There is no evidence of differences in socio-economic factors between these provincial counties.

5. Conclusion

County of residence had a major impact on survival in 1986, a multivariate analysis confirmed a superior survival of breast cancer patients in a county with centralised surgery and accurate lymph-node staging. Due to stage migration, we may be over-estimating the impact of county. In the county with mammographical screening, patients had smaller tumours and less spread to the axillary lymph nodes. A more favourable stage

distribution explained the observed differences in survival between the counties which can be expected to persist with a longer follow-up time. In two counties, there was a positive time trend with increases in overall survival in the study period. This can partly be explained by a more favourable stage distribution and more extensive axillary surgery. Other as yet unexplored factors remain and further investigation is needed, but if all Danish breast cancer patients achieve the same beneficial stage distribution and a similar quality in surgery, a substantial proportion of premature breast cancer deaths will be prevented.

It is worth adding a cautionary note that the DBCG database cannot be considered to be representative of the entire Danish population of breast cancer patients, and estimates of the extent of disease or survival based on the clinical database will be too optimistic compared with population-based estimates.

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