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Does Stage at Diagnosis Explain the Difference in Survival after Breast Cancer in Denmark and Sweden?

Anni Ravnsbæk Jensen, Jens Peter Garne, Hans Henrik Storm, Gerda Engholm, Torgil Möller and Jens Overgaard

From the Centre for Cancer Documentation, Department of Experimental Clinical Oncology, Danish Cancer Society (A.R. Jensen, J. Overgaard), the Department of Surgery (J.P. Garne), Aarhus University Hospital, Denmark, the Department of Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark H. Hans, G. Engholm), and the South Swedish Regional Tumour Registry, Lund, Sweden (T. Möller)

Correspondence to: Anni R. Jensen, Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Nørrebrogade 44, Bldg 5, DK-8000 Aarhus C, Denmark. Tel: +45 89492629. Fax: +45 86197109. E-mail: anni@oncology.dk

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Breast cancer survival differs 9 percentage points between the neighbouring countries of Denmark and Sweden. The authors' aim was to analyse whether this was caused by early detection in Sweden. The extent of disease and outcome was compared in two population-based breast cancer cohorts in 1983–1989. Breast cancer management was decentralized in Denmark without mammography screening whereas treatment in Sweden was centralized and the population partly screened. Ten- and 15-year relative survival was 15% and 6% higher in Sweden ($p < 0.001$) with corresponding differences in crude and disease-specific survival. Stage distribution was significantly more favourable in the Swedish cohort. In multivariate analysis age, tumour size, extent of axillary surgery, and spread affected survival; however, the impact of region persisted ($p < 0.001$). Reanalysis without screening-detected patients only slightly affected the impact of region. It was concluded that early detection had significant impact on survival but other regional differences might be of importance.

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Survival comparisons for breast cancer in cancer registry data in the Nordic countries have revealed major differences in survival between Denmark and the other countries (1). In the 1960s survival was similar and breast cancer prognosis has since improved in all Nordic countries, but least in Denmark. Despite the similarity of healthcare systems and cancer registration in the Nordic countries, 5-year age-adjusted relative survival for breast cancer patients was 9 percentage points better in Sweden than in Denmark (2). The reasons for Denmark's poor performance are unknown and studies beyond register-based comparisons are necessary. If the difference is caused by dysfunctions in the Danish healthcare system, a considerable proportion of premature cancer deaths can potentially be prevented. This study compares in detail the extent of disease at diagnosis and outcome in population-based cohorts of breast cancer patients diagnosed during 1983–1989 in Aarhus County, Denmark and the city of Malmö Sweden. Survival differences in these areas were of the same magnitude as in the nationwide comparisons. The Danish county was characterized by a decentralized diagnostic and surgical organization without mammography screening, whereas the city of Malmö had a completely centralized organization and a partly screened population.

MATERIAL AND METHOD

The study design is a population-based historical follow-up study including all breast cancer patients in Aarhus County, Denmark and the city of Malmö, Sweden diagnosed between 1 January 1983 and 31 December 1989. Patients were identified in the national cancer registries (3, 4). Information on tumour size, histology, stage at diagnosis, extent of surgery performed, and cause of death was obtained from clinical records. Tumour stage was classified according to the UICC-TNM system (5). Patients with simultaneous bilateral breast cancer posed a special problem, and the breast with the largest tumour was chosen to be the primary. Date of death and data on the general population in the regions were provided from the National Population Registries.

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Patient population

A total of 2 000 patients with invasive breast carcinoma were included in the Danish and 1 148 patients in the Swedish cohort (Fig. 1). Clinical records from time of diagnosis were found for more than 99% of the Danish and for all the Swedish patients (3). We excluded patients with a previous history of invasive cancer, patients without histological/cytological verification or known from death certificates only. Patients were followed from the date of primary breast cancer diagnosis to 31 December 2000. Median survival time was 8.7 years in Denmark and 12.0 years in Sweden. The median potential follow-up time (time from entry date until date of assessment) was 14.4 years (range 11.0–18.0 years).

Healthcare organization

The organization of the healthcare systems in the two regions was similar with regard to free public services without a tradition of private healthcare services. However, diagnostic tools for breast cancer differed as mammography screening for early breast cancer took place in parts of Sweden. In Malmö, a randomized screening trial took place in 1976–1991 for females aged 45–69 with liberal access to mammography for those not allocated to screening. In a random sample in the control group 24% had at least one mammography screening performed during the trial period (6). In Denmark there was no organized mammography screening in the study period. Breast cancer treatment in Malmö was centralized in one hospital. In Aarhus breast cancer surgery was performed in 10 different surgical departments at local hospitals with one centre providing the oncological services.

Primary treatment

There were clinical trials for patients up to the age of 70/75 years, led by the South Sweden Breast Cancer Group and the Danish Breast Cancer Cooperative Group (7, 8). Trials differed with regard to surgical procedures and radiotherapy schedules as well as in adjuvant anti-oestrogenic and chemotherapy regimens (Table 1). In Denmark, treatment regimes remained unchanged in the study period, whereas in Malmö regimens changed in 1985. For patients not allocated clinical trials standard treatment in both countries was total mastectomy and possibly radiotherapy and/or anti-oestrogenic treatment.

Follow-up and statistical methods

The national cancer and population registries facilitated follow-up, which was done by the unique person ID number operating in each of the countries. Breast cancer was considered the cause of death or a contributing cause of death for patients dying with distant metastasis or loco-regional disease without complete remission. Comparisons between groups were done by the Mann–Whitney and Kruskal–Wallis tests. Overall and disease-specific survivals were estimated by the Kaplan–Meier method. Log-rank test was used for comparisons between groups and Cox proportional hazards model was used for estimating hazard ratios.

We used Cox regression analysis to examine whether residence was an independent risk factor after adjusting for potential confounding effects of known prognostic variables such as age, tumour size, and nodal status. Statistical analysis was performed by the likelihood-ratio test. For the continuous variables age and tumour size, test for linearity was done including log transformation and the

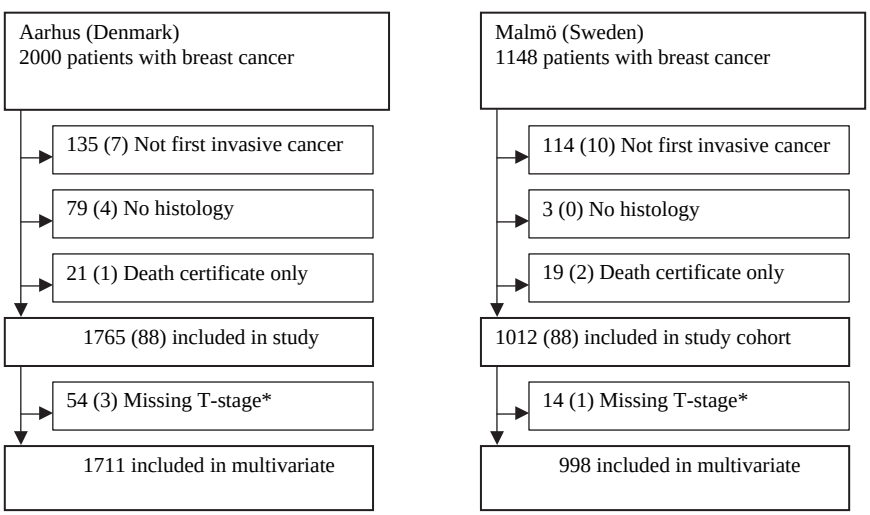

Fig. 1. Identification of final study cohorts after exclusion according to exclusion criteria. Percentages in parentheses. No significant changes in age-distribution were found between total cohorts and study cohorts. *For the multivariate analysis patients with unclassified T-stage were excluded. This group mainly consisted of old patients (age median 82.1) with unclassified nodal status. No difference between regions in age, nodal status and number of patients with distant metastasis.

Table 1

Treatment regimes in the two regions 1983–1989

Malmö, Sweden, patients ≤70 years, from June 1985 <75 years		
Tumour size <20 mm, N0	Local treatment Pre-menopausal January 1983 Local treatment +	 Post-menopausal January 1983 Local treatment +
N pos. or tumour size ≥20 mm	Randomization for I: radiotherapy II: radiotherapy+cyclophosphamide III: cyclophosphamide June 1985 to end of study period Local treatment (Radiotherapy for all N pos) + Randomization for I: tamoxifen 20 mg/day ×2 years II: no adjuvant treatment	Randomization for I: radiotherapy II: radiotherapy+tamoxifen 30 mg/day * III: tamoxifen 30 mg/day June 1985 to end of study period Local treatment (Radiotherapy for all N pos) + Randomization for I: tamoxifen 20 mg/day ×2 years II: tamoxifen 20 mg/day ×5 years
Aarhus, Denmark, patients <70 years		
Tumour size ≤50 mm, N0	Local treatment Pre-menopausal	 Post-menopausal
N pos. or tumour size >50 mm	Local treatment + Randomization for I: radiotherapy and CMF II: CMF III: CMF and tamoxifen 30 mg/day[1]	Local treatment + Randomization for I: radiotherapy and tamoxifen 30 mg/day[1] II: tamoxifen 30 mg/day[1] III: CMF and tamoxifen 30 mg/day[1]

Local treatment: Total mastectomy or breast conserving surgery+radiotherapy.
Radiotherapy: south Sweden: 48 Gy in 20 fractions, split-course 12/8 with 3-week break. Denmark: 50 Gy in 25 fractions, 5 fractions per week.
[1]Treatment one year.
South Sweden: Cyclophosphamide (130 mg/m^2) orally day 1–14 in 28-day cycles, 12 cycles.
Denmark: CMF; Cyclophosphamide 600 mg/m^2), methrotrexate (40 mg/m^2), fluorouracil (600 mg/m^2) intravenously every 4 weeks for 8 or 9 cycles.

squares of the values in the model. Both turned out to be highly significant indicating non-linearity. In the final models all values are treated as categorical values. T-stage was used as a combined measurement of tumour size and local tumour extension. The assumption of proportional hazards was tested and accepted for all variables except histopathological findings for which the analysis was stratified. Level of statistical significance was 5% and all p-values were two-tailed.

Age-specific incidence rate was calculated for 5-year age groups and standardized to the world population IARC (9). Level of significance was estimated by means of the log likelihood function of the rate ratio.

Relative survival

Relative survival is the ratio between the observed survival in a cohort and the expected survival for a group in the population with the same distribution as regards sex, age, and calendar time. The relative survival can be interpreted as the proportion of patients alive at the end of the interval if the disease investigated is the only cause of death (10). For calculation of relative survival we used SAS macros developed by the Mayo Clinic (11) and calculated expected survival as described by the Hakulinens cohort method (12). Since age distribution differed between Aarhus and Malmö an age adjustment was made using the age distribution of breast cancer patients in Denmark.

Statistical analysis was done with SPSS version 10.0 except relative survival, which was calculated with the SAS statistical package.

RESULTS

Main characteristics of the cohorts are summarized in Table 2.

Patients in Malmö were significantly older, median 65 year vs. 61 in Aarhus, due to a different age structure in the background population. Age-standardized incidence rates were similar. There were significant differences ($p = 0.001$) in tumour diameter, T-stage, and numbers of lymph nodes removed. A median 5 nodes were removed in Aarhus vs. 11 nodes in Malmö ($p = 0.001$). A positive correlation was found between total number of nodes examined and the proportion of node-positive patients ($p = 0.001$). More

Table 2

Patient characteristics, percentages in parentheses

	Full cohorts			Malmö (Sweden)	
	Aarhus (Denmark) n = 1 765	Malmö (Sweden) n = 1 012	p-value	Screening detected n = 200	Symptomatic n = 812
Age-standardized incidence/100 000 (world population)	600	640	NS		
Age (year)	61	65.1	p < 0.001	63.7	65.8
Median (range)	(25.5–94.7)	(24.1–97.3)		(4.34–78.5)	(24.1–97.3)
Age-group					
<45	300 (17)	94 (9)	p < 0.001	2 (1)	92 (11)
45–54	382 (22)	181 (18)		38 (19)	143 (18)
55–69	516 (29)	337 (33)		111 (56)	226 (28)
70+	567 (32)	400 (40)		49 (24)	351 (43)
Tumour size (mm)					
Median (range)	20 (2–200)	18 (1–100)	p < 0.001	11 (3–50)	19 (1–100)
Axillary nodes examined	5 (0–23)	11 (0–36)	p < 0.001	11 (0–31)	10 (0–36)
Median (range)					
Lymph nodes removed	183 (10)	542 (53)	p < 0.001	120 (60)	422 (52)
10 nodes +	792 (45)	287 (28)		69 (35)	218 (27)
5–9 nodes	372 (21)	17 (2)		3 (2)	14 (2)
3–4 nodes	170 (10)	10 (1)		1 (0)	9 (1)
1–2 nodes	231 (13)	69 (7)			69 (8)
0 nodes	17 (1.0)	87 (9)		7 (3)	80 (10)
Unknown					
Nodal status					
N-positive	654 (37)	323 (32)	p = 0.02	31 (16)	292 (36)
N-negative	863 (49)	533 (53)		162 (81)	371 (46)
Unclassified	248 (14)	156 (15)		7 (3)	149 (18)
Tumour-positive lymph nodes[1]			p = 0.006		
0 positive	863 (49)	553 (62)		162 (84)	371 (56)
1–3 positive	447 (25)	197 (23)		25 (13)	172 (26)
>3 positive	207 (12)	126 (15)		6 (3)	120 (18)
T-stage (UICC)					
$T_I \leq 10$ mm	255 (14)	178 (18)	p < 0.001	86 (43.0)	92 (11)
$T_I > 10$ mm	648 (37)	425 (42)		91 (45.5)	334 (41)
T_{II}	569 (32)	277 (27)		21 (10.5)	256 (32)
T_{III}	66 (4)	33 (3)		2 (1.0)	31 (4)
T_{IV}	173 (10)	85 (8)		0	85 (10)
Unclassified	54 (3)	14 (1)		0	14 (2)
Stage (UICC)					
I	569 (32)	415 (41)	p < 0.001	153 (77.7)	262 (32)
II	811 (46)	387 (38)		36 (18.3)	351 (43)
III	159 (9)	65 (6)		1 (0.5)	64 (8)
IV	128 (7)	98 (10)		7 (3.5)	91 (11)
Unclassified[2]	98 (6)	45 (5)		0	45 (6)
Histological type					
Ductal	1568 (89)	818 (81)	p < 0.001	166 (83)	653 (80)
Lobular	114 (7)	117 (12)		22 (11)	95 (12)
Others	86 (5)	76 (8)		12 (6)	64 (8)

For comparisons between groups Mann–Whitney and Kruskal–Wallis tests were used. The Malmö cohort was further split according to whether tumours were detected by mammography screening or clinically.
[1]Analysed only for patients with known nodal status.
[2]Stage unclassified due to unknown nodal status and T-stage one or two or unknown T-stage and N neg.

patients in the Aarhus cohort had lymph node metastases (p = 0.02) with corresponding differences in stage distribution.

There were slight differences in indication for adjuvant treatment between countries (see Table 1). Patients with negative nodal status and tumour diameters between 20 and

50 mm received adjuvant treatment according to protocol in South Sweden, whereas they did not in Denmark. Subgroup analysis in this patient group revealed no difference in survival between populations. To evaluate the impact of changes in treatment in Malmö in 1985 separate survival analyses were performed for pre- and post-menopausal women according to whether the diagnosis was made before or after the changes in 1985. There were no differences in overall or disease-specific survival in any of the groups.

Age-standardized relative survival, overall, and disease-specific survival analysis all resulted in significant differences between cohorts (Figs. 3 and 4). Relative survival was 15 percentage points higher in Malmö in 10 years and 6% in 15 years ($p < 0.001$). At the same time points differences in overall survival were 8% and 6% ($p < 0.001$) and in disease-specific survival 14% and 15% ($p < 0.001$).

To assess whether the risk of breast cancer death increased with time after diagnosis in the Swedish cohort compared with the Danish, we calculated hazard rates for 2-year periods. The excess in mortality Denmark compared with Sweden was evident up to 10 years after diagnosis (Fig. 2).

Univariate hazard rate overall survival in Aarhus/Malmö was 1.22 ([1.11–1.36]) and for disease-specific survival 1.59 ([1.39–1.81]). Results of multivariate analysis showed residence to bear a main effect after adjusting for potential confounders (Table 3).

In Malmö, 200 patients had tumours detected by mammography screening and these tumours were smaller, stage distribution more favourable, and patients younger. There was no difference in overall survival between the non-screening-detected group and the Aarhus cohort in univariate analysis, but the difference remained significant concerning disease-specific survival (see Fig. 4). Multivariate analysis in a subset of data without screening-detected tumours resulted in only a slight decrease in hazard rates for residence from 1.44 [1.2– —1.7] to 1.35 [1.2–1.6] in disease-specific survival and from 1.25 [1.1–1.4] to 1.20 [1.1–1.4] in overall survival.

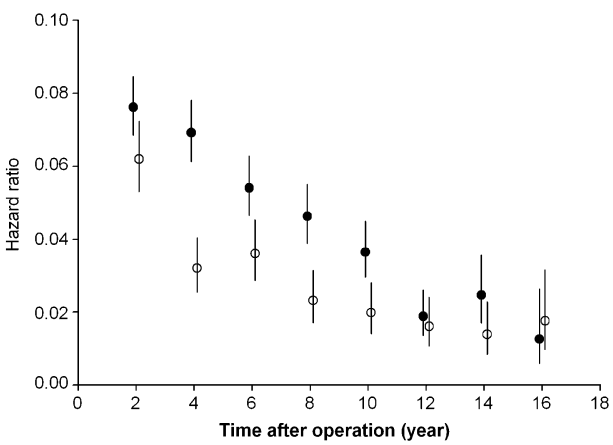

Fig. 2. Hazard ratio for 2-year periods (95% CI) of breast cancer mortality. ● Aarhus. ○ Malmö.

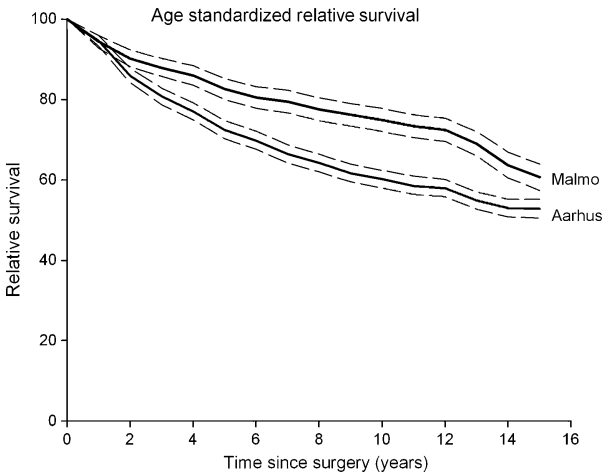

Fig. 3. Relative survival in the Aarhus and Malmö cohorts. Relative survival is an estimate of the risk of dying in breast cancer. Dashed lines represent 95% confidence intervals.

DISCUSSION

Tumour size is a major prognostic factor in breast cancer, as there is a strong correlation between tumour size, nodal involvement, and recurrence rate (13–15). The main effect of early detection is reducing tumour mass and stage at diagnosis, thereby improving survival (6). We found a substantial proportion of small tumours in the screened population. The open-door policy in the mammography clinics is reflected by the fact that patients beyond the age group 45–69 also had tumours detected by screening. However, stage distribution was also more favourable in the remaining part of the Malmö cohort, indication a general awareness of early detection.

Another major prognostic factor is axillary nodal status (16). The Danish programme recommended a minimum of 5 nodes removed, whereas the Swedish recommended 10 nodes. In general these guidelines were followed. Axillary dissection is considered both a staging procedure and a procedure to obtain loco-regional tumour control, thereby leading to improved survival (17–19). The risk of underestimating stage by removing only a few nodes is in the present study demonstrated by a correlation between extent of axillary dissection and the proportion of patients with positive nodal status. Our results indicate a higher risk of erroneous staging in the Danish cohort, underestimating the frequency of patients with positive nodal status (20). This does not explain the observed difference in survival between cohorts, but this bias introducing a differential misclassification will tend to overestimate the impact of region in multivariate analyses. Patients with unclassified nodal status had very high hazard rates and could represent

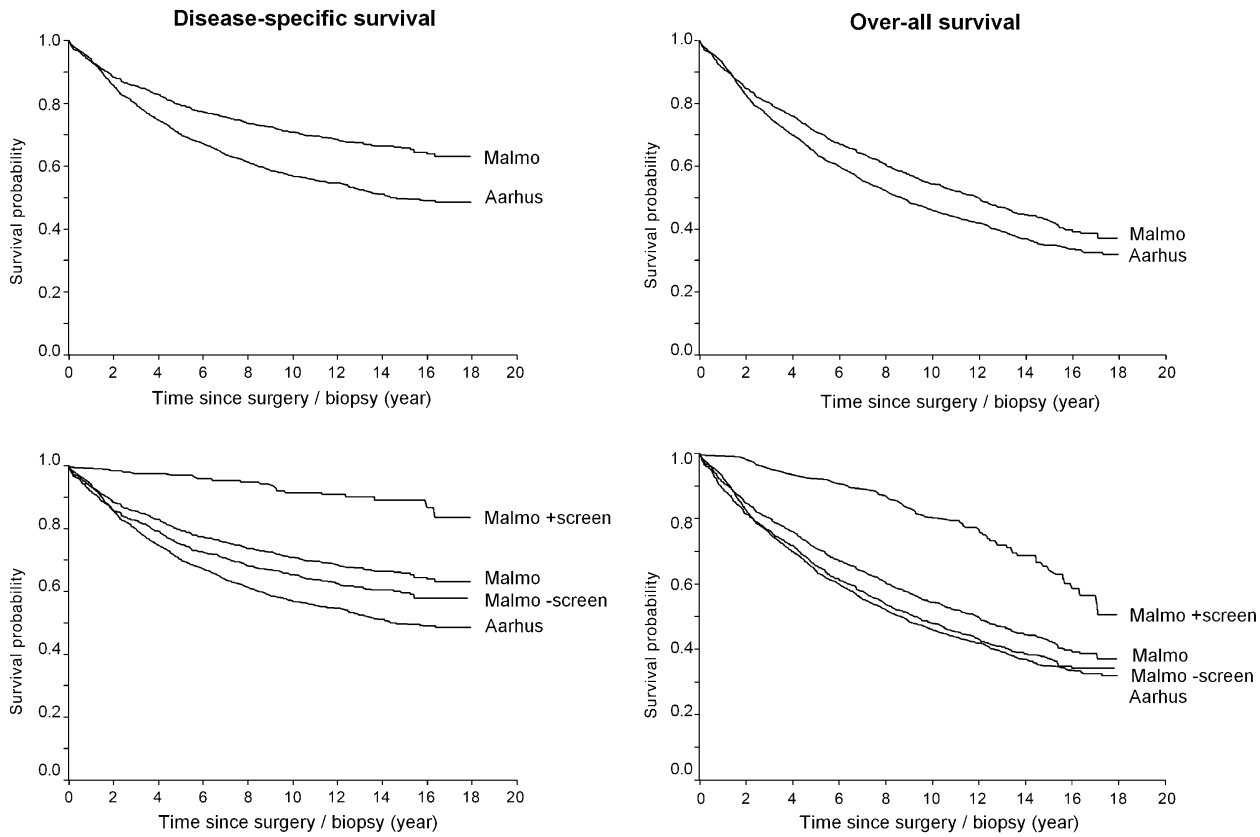

Fig. 4. Disease-specific and overall survival in accordance with region. The Malmö cohort was also analysed according to whether tumours were detected by mammography screening (Malmö+screen) or not (Malmö −screen).

a group with comorbidity, old age, or advanced disease. However, this group was equally distributed in the regions and a multivariate model excluding these patients did not assess the impact of residence.

In the model, T-stage, M-stage, and frequency of positive nodes were all independent predictors of outcome. Thus, early detection was shown to be an independent prognostic factor but region continued to be a significant predictor of outcome after adjusting for confounders.

The strategies for adjuvant treatment differed between regions and from 1985 post-menopausal patients stage II in Malmö were randomized to what turned out to be better treatment modalities than the Danish. However, we found no difference or even trends towards a difference in survival between Malmö patients allocated a protocol before or after June 1985, as we did not find any survival difference between regions for the small group of lymph node negative patients with tumours between 20 and 50 mm, who received only adjuvant treatment in south Sweden. Thus the differences in adjuvant treatment modalities cannot be regarded as severe confounders in this study.

Survival comparisons between screening-detected and symptom-detected cancers include a risk of selection, lead time, and length bias. The exact magnitude of these biases is difficult to estimate. In studies dealing with cancer detection at a preclinical level prolonging the interval between diagnosis and death, lead-time bias is inevitable whether or not early detection leads to more effective treatment. The effect of lead-time bias was in the Swedish two-county trial estimated at 3–4 years (21) and the great survival difference observed is therefore unlikely to be caused by lead time only.

Length bias is the risk of detecting early asymptomatic cancers, which would not be clinically detectable in the patient's lifetime. This bias is necessary to bear in mind though the incidence rate was not significantly higher in the partly screened population in Malmö. In this study selection bias was minimized by analysing population-based cohorts estimating the minimal efficacy expected from mammography screening. A recent report on breast cancer screening by WHO found in conclusion that mammography screening can reduce breast cancer mortality (22). We found a significant impact of early detection on both disease-specific and overall survival though it could not explain the observed survival differences between cohorts. This finding is in concordance with the results from a study comparing patients aged 50–79 and diagnosed in south Sweden and eastern Denmark in 1989 and 1994 (23).

Table 3

Cox uni- and multivariate regression analysis of the risk of breast cancer death or death from any cause

	Univariate analyses				Multivariate analyses			
	Disease specific		Overall		Disease specific		Overall	
	Hazard	p rate	Hazard	p rate	Hazard	p rate	Hazard	p rate
Area of residence		<0.001		<0.001		<0.001		<0.001
Malmö	1		1		1		1	
Aarhus	1.58 (1.4–1.8)		1.22 (1.1–1.3)		1.44 (1.2–1.7)		1.25 (1.1–1.4)	
Age		<0.001		<0.001		0.33		<0.001
<45	1		1		1		1	
45–54	0.96 (0.8–1.1)		1.07 (0.9–1.3)	0.50	1.05 (0.8–1.3)	0.68	1.09 (0.9–1.4)	0.45
55–69	1.13 (0.9–1.4)		1.41 (1.2–1.7)	<0.001	0.82 (0.6–1.2)	0.25	1.00 (0.7–1.3)	0.92
70+	1.76 (1.5–2.1)		3.45 (2.9–4.1)	<0.001	0.87 (0.6–1.2)	0.42	1.86 (1.4–2.5)	<0.001
Menopausal status		<0.001		<0.001		0.005		0.001
Pre-menopausal	1		1		1		1	
Post-menopausal	1.49 (1.3–1.7)		2.24 (2.1–2.5)		1.52 (1.1–2.0)		1.56 (1.2–2.0)	
T-stage (UICC)		<0.001		<0.001		<0.001		<0.001
T_I ($\leq$10 mm)	1		1		1		1	
T_I (>10 mm)	1.71 (1.3–2.2)	<0.001	1.41 (1.2–1.7)	<0.001	1.19 (1.2–1.9)	0.002	1.21 (1.0–1.4)	0.03
T_{II}	3.80 (3.0–4.9)	<0.001	2.61 (2.2–3.1)	<0.001	2.72 (2.1–3.5)	<0.001	1.93 (1.6–2.3)	<0.001
T_{III}	5.46 (3.9–7.7)	<0.001	3.11 (2.4–4.1)	<0.001	3.02 (2.1–4.3)	<0.001	2.02 (1.5–2.7)	<0.001
T_{IV}	12.86 (9.9–16.8)	<0.001	7.53 (6.2–9.2)	<0.001	3.88 (2.9–5.2)	<0.001	2.41 (1.9–3.0)	<0.001
Lymph nodes removed		<0.001		<0.001		<0.001		<0.001
10 nodes +	1		1		1		1	
5–9 nodes	1.13 (1.0–1.3)	0.15	1.02 (0.9–1.2)	0.75	1.18 (1.0–1.4)	0.08	1.07 (0.9–1.2)	0.34
3–4 nodes	1.39 (1.1–1.7)	0.002	1.12 (1.0–1.3)	0.16	1.51 (1.2–1.9)	0.001	1.15 (1.0–1.4)	0.14
1–2 nodes	1.80 (1.4–2.3)	<0.001	1.51 (1.2–1.9)	<0.001	2.12 (1.6–2.8)	<0.001	1.58 (1.3–2.0)	<0.001
0 nodes/unknown	4.87 (4.1–5.8)	<0.001	4.03 (3.5–4.7)	<0.001	5.86 (4.6–7.5)	<0.001	3.44 (2.8–4.1)	<0.001
Tumour-positive lymph nodes		<0.001		<0.001		<0.001		<0.001
0 positive	1		1		1		1	
1–3 positive	2.82 (2.4–3–3)	<0.001	1.99 (1.8–2.6)	<0.001	2.19 (1.9–2.6)	<0.001	1.71 (1.5–1.9)	<0.001
>3 positive	6.35 (5.3–7.6)	<0.001	3.91 (3.4–4.5)	<0.001	4.73 (3.9–5.7)	<0.001	3.11 (2.7–3.6)	<0.001
Distant metastasis		<0.001		<0.001		<0.001		<0.001
M0	1		1		1		1	
M1	6.35 (5.4–7.4)		4.29 (3.7–5.0)		3.14 (2.6–3.8)		2.47 (2.1–2.9)	

Hazard ratio represents the relative risk estimate. 95% CI in parentheses.
Multivariate analyses are stratified for type of histology (ductal, lobular, other).

Other factors of influence could be the centralized organization with dedicated breast cancer surgeons and pathologists in Malmö. There are other potential confounders, which was not the topic for the present study, such as tobacco smoking, alcohol, and fat intake, all with higher consumptions in Denmark (24), which are likely to influence the observed incidence rate but we cannot be sure that these can also affect survival (25).

Both incidence and mortality rates for breast cancer are high and can influence survival for the background population, thereby overestimating relative survival. However, they will not influence the observed differences in relative survival comparing populations.

CONCLUSION

The Danish breast cancer survival rates are below the Nordic average. Adjusted for variability in survival of the general populations the differences between the two regions in Denmark and Sweden remained substantial and call for further investigation. Patients in Malmö had smaller tumours and less spread to the axillary lymph nodes. The differences in overall and disease-specific survival could be attributed to the use of mammography screening and a general awareness of early detection in the Swedish population, but after adjusting for potential confounders significant benefits in survival to the Swedish cohort still persisted. An additional explanation could be centralization of breast cancer treatment in Malmö. Other yet unexplored factors remain, to understand the observed difference in survival and mortality. Recommendations for axillary dissection in Denmark are now equal to the south Swedish standards and a move towards centralization of breast cancer treatment is ongoing. If, furthermore, the same stage distribution as in Sweden can be achieved by earlier diagnosis, we can hope for a substantial reduction in premature breast cancer deaths in Denmark.

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