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Can the survival difference between breast cancer patients in Denmark and Sweden 1989 and 1994 be explained by patho-anatomical variables?—A population-based study

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Abstract

Analyses of data from cancer registries have shown a 10% unit difference in 5-year relative survival between Danish and Swedish patients with breast cancer. This study investigates the effect of age and patho-anatomic variables on this survival difference. Hospital records were collected for women over 40 years of age diagnosed in 1989 or 1994 in east Denmark and south Sweden; patho-anatomical variables and survival were compared between 2289 Danish and 1715 Swedish women. Tumours were smaller, node-negative axillae more frequent and well-differentiated tumours almost 10% more frequent in Sweden. A superior 5-year relative survival in Sweden was found in the 50- to 79-year age group. The adjusted hazard rate ratio between countries was 1.7 in 1989 and 1.3 in 1994. Conditional survival after surviving the first 5 years was similar for the two countries. Adjusting for patho-anatomical variables reduced but did not eliminate the higher risk of death among the Danish patients. Higher population death rates could explain some but not all of the residual elevated risk for Danish women.

Keywords: Breast cancer; Cancer registry; Epidemiology; Patho-anatomical variables; Population-based, relative survival; Survival

1. Introduction

Breast cancer is the most common type of cancer among women in the Nordic countries, with an age-adjusted incidence rate (world) in 1993–1997 of 74 per 100 000 person-years [1]. Incidence rates have increased since 1958–1962, and a continued increase is predicted up to 2022 [1]. In 1999, breast cancer was the most common cancer in both Danish and Swedish women, comprising almost 30% of all female cancers [2,3]. In Denmark, 3776 new cases and 1353 deaths were reported in 1999 [2]. The corresponding figures for Sweden were 6317 new cases and 1485 deaths [3].

Whereas mortality rates for breast cancer have remained stable in all Nordic countries [4], relative survival has improved [5]. However, in spite of an overall improvement in the age-adjusted 5-year relative survival for all the Nordic countries since 1960, Denmark continues to have the lowest and Sweden the highest survival-rate ratio [5]. According to the Eurocare II study, which compares the relative survival of different tumour types among the countries of Europe between 1985 and 1989, the proportion ratio for 5-year relative survival was 70.6% in Denmark and 80.6% in Sweden [6].

The management of breast cancer has been standardised in both countries, with uniform guidelines (care programmes) for diagnosis, treatment, care and follow-up being established in the late 1970s. In Sweden, the Southern Swedish Breast Cancer Study Group was established in 1976 (T. Möller, Regional Tumour Registry of Southern Sweden, Lund, Sweden), and in Denmark the Danish Breast Cancer Cooperative Group was established in 1977 [7]. Mammographic screening was introduced on a limited scale (randomised study) in

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Malmö in 1976, and reached nationwide coverage for women between 50 and 70 years of age in 1991 [8]. Before 1994 the screening age had been extended to 74 years for the region (T. Möller, Regional Tumour Registry of Southern Sweden, Lund, Sweden). In Denmark, mammographic screening was not introduced in the municipality of Copenhagen until 1991 [9], in 1993 in the county of Funen, and in 1994 in the municipality of Frederiksberg. Some 18% of Danish women aged 50-69 years are currently offered screening [9].

Age at diagnosis affects breast cancer survival adversely [6]. Recognised prognostic adverse patho-anatomical variables for survival include involvement of the axillary lymph nodes [10,11], large tumour size [12], poor differentiation [13] and negative oestrogen-receptor status [14]. Registry-based studies comparing relative survival in the Nordic countries have not considered prognostic variables [5,6]. The aim of the present study was therefore to compare the survival of patients diagnosed with breast cancer in 1989 and 1994 in east Denmark and south Sweden, taking the prognostic patho-anatomical variables and age into account.

2. Patients and methods

2.1. Patient selection

Women with a diagnosis of invasive carcinoma of the breast in 1989 or 1994 in east Denmark and in south Sweden were identified from the Danish Cancer Registry and the Regional Tumour Registry of Southern Sweden. Residency in east Denmark included the counties of Copenhagen, Frederiksborg, Roskilde, Vestsjælland, and Storstrøm and the municipality of Copenhagen, but excluded the municipality of Frederiksberg and Bornholm county. Residency in south Sweden included the counties of Kronoberg, Blekinge, Kristianstad, Malmöhus, the municipality of Malmö, and the southern part of the county of Halland. Patients known from death certificates only, from findings at death or at autopsy were excluded, in accordance with the practice of the Eurocare II study [6]. Also excluded were patients for whom the diagnosis of breast cancer could not be microscopically verified, *in situ* cancers and sarcomas, patients under 40 years of age at diagnosis, patients with a previous history of cancer (except non-melanoma skin cancer), and patients for whom data were not available (Table 1).

The female population in both 1989 and 1994 was 1.1 million in east Denmark (2.6 million in Denmark) and in south Sweden 0.7 million (4.4 million in Sweden) [4]. The two regions are alike with regard to socioeconomic factors such as education, employment and income [15], and the incidence of breast cancer is similar [2–4]. The age-adjusted (world) incidence rates of breast cancer in 1989 and 1994 for east Denmark were 79.5 and 77.6 per 100 000 women (in Denmark 74.2 and 78.8 per 100 000, respectively) and for south Sweden 72.8 and 83.5 per 100 000 women (in Sweden 70.4 and 78.6 per 100 000, respectively) [4]. Similarly, the survival of patients with breast cancer in the two regions did not differ from the survival in the respective countries (P.W. Dickman, Department of Medical Epidemiology, Karolinska Institutet, Box 281, 17177 Stockholm, Sweden).

2.2. Data collection and management

Information on the diagnosis and treatment of the breast cancers was retrieved from clinical and pathology hospital records (28 hospitals in Denmark and 15 in Sweden). In this study we used age at diagnosis, the

Table 1
Women with a breast cancer diagnosis in the cancer registers in 1989 and 1994 in east Denmark and south Sweden and the distribution of exclusion/inclusion criteria

	East Denmark				South Sweden			
	1989	(%)	1994	(%)	1989	(%)	1994	(%)
Breast cancer cases diagnosed age 40 years	77		59		32		49	
Breast cancer patients 40+ years identified in cancer registers	1333	(100)	1349	(100)	997	(100)	1141	(100)
Exclusions based on register information								
Death certificate only (DK) or diagnosis registered at death (SE)	3		8		1		3	
Previous cancer diagnosis	73		82		79		133	
Diagnosis '*in situ*' or morphology = 80 109, 90 203, 99 903, 99 993	70		90		81		87	
Hospital records to be sought	1187	(89)	1169	(87)	836	(84)	918	(80)
Exclusions based on hospital records								
Autopsy information only	7		2		3		3	
Previous cancer diagnosis	6		1		7		5	
Diagnosis '*in situ*' or morphology not included	11		9		6		7	
No hospital records	2		7		4		1	
Diagnosis or treatment outside area	2		0		1		2	
In analysis	1139	(85)	1150	(85)	815	(82)	900	(79)

occurrence of distant metastases at diagnosis, tumour size (measured by the pathologist or, if this information was missing, measured clinically), the number of axillary lymph nodes and tumour-involved nodes removed, oestrogen-receptor status, and histological differentiation. If any data were missing, information was sought from the records of private specialists or general practitioners, and from the files of the Danish Breast Cancer Cooperative Group [7] or the South Sweden Breast Cancer Group registry in Lund. Follow-up information for death or emigration by the end of 2000 was retrieved from the Central Population Register of Denmark and the Cancer Register of Sweden, respectively.

All registration forms were scanned with the 'eyes and hands' scanning system with built-in quality control (page-wise verification of all individual data and mass verification of all ciphers per page). The data were saved in SAS databases.

Data were further cleaned, especially checking the sequence of dates and the internal consistency of the variables.

2.3. Definitions used

The tumours were classified into well-differentiated or poorly differentiated types according to the guidelines of the International Typing of Breast Tumours, World Health Organisation [16]. Grading of ductal carcinomas followed the guidelines of Bloom and Richardson [17]; grading of non-ductal carcinomas was in accordance with the suggestions outlined by Tabar and colleagues [18]. Malmö, Sweden, used a grading system introduced by Linell in 1980, which is slightly different from the Bloom and Richardson grading [19]. The tumours from Malmö (18% of all Swedish tumours) were reclassified according to the Bloom and Richardson grading and were included in the analyses.

2.4. Statistical methods

The homogeneity of the distribution of the prognostic factors in east Denmark and south Sweden for each of the years studied was assessed using the χ^2 test. Proportion ratios for relative survival were estimated in order to compare our data with previous registry-based analyses [5,6]. Relative survival was computed for groups of patients as the ratio between the observed and the expected survival proportion for the group, using the population mortalities in Denmark and Sweden. Female population mortality in the regions was very similar to the respective national female mortalities (not shown). The relative survival was estimated using SAS 'macros' developed by the Mayo Clinic [20], and the method used for the calculation of the expected survival was based on Hakulinen's cohort method [21]. Using relative survival to some extent controls for differences in non-breast cancer mortality rates between the two countries.

Relative survival was age standardised in 10-year groups using the age distribution of the breast cancer patients included in 1994. For the age groups 50–79 years the possible influence on the hazard rate of death in the 5 years following diagnosis by age and the prognostic patho-anatomical variables (nodal status (number of lymph nodes examined and number of positive nodes), tumour size, histological differentiation of tumour, and oestrogen-receptor status), in combination with country, was analysed by Cox regression [22], using the PHREG procedure in *SAS 8.1* (SAS institute, inc., Cary, North Carolina, USA). Women diagnosed with breast cancer in 1989 who then survived the first 5 years were followed up through 2000 and the conditional hazard rate of death was also modelled by Cox regression. Patients with distant metastases at diagnosis were omitted from all analyses, as were women with no nodes examined and/or unknown tumour size.

The Cox model did not take account of the known higher total mortality in Denmark as opposed to Sweden. To study the influence of the differing mortalities, we tried to fit both multiplicative relative-risk models and relative excess-risk models.

The relative-risk models used Poisson regression of the observed number of deaths, with the logarithm of the expected number of deaths as an offset variable, a constant, in the regression. The expected number of deaths was calculated as the sum of the products of observed time under risk for the patient population and the country, age and calendar time-specific mortality rates. The relative excess-risk model was the Hakulinen and Tenkanen relative-survival model for grouped life-table data [23]. The expected survival was calculated as described for relative survival above. Both models were fitted using the *GENMOD* procedure in *SAS 8.1*.

3. Results

3.1. Sample characteristics

As shown in Table 1, 1333 and 1349 women aged 40 years or older were diagnosed with breast cancer in 1989 and 1994 in east Denmark, of whom 146 (11%) and 180 (13%) were excluded before the search for hospital information. In south Sweden, out of 997 and 1141 women with incident breast cancer, 161 (16%) in 1989 and 223 (20%) in 1994 were excluded. After the collection of information from hospital records, an additional 48 (4%) and 19 (1%) in east Denmark and 21 (2%) and 18 (2%) in south Sweden were excluded, leaving 1139 and 1150 Danish women and 815 and 900 Swedish women with hospital information for analysis in 1989 and 1994, respectively.

3.2. Distribution of variables

In Table 2, the distribution of age and prognostic patho-anatomical variables is shown for each of the four cohorts defined by country and year. In general, a preponderance of worse prognostic signs was seen in Denmark. Age at diagnosis differed between the two countries, with significantly more women in the younger age groups in Denmark. Distant metastases at diagnosis were equally present in both cohorts. The number of axillary lymph nodes examined was lower in Denmark in 1989, but higher in Denmark than in Sweden in 1994. Irrespective of this, node-negative patients were more frequent in Sweden in 1994. Tumour sizes tended to be larger in Denmark than in Sweden in both periods; however, they were only significant for the cohorts from 1994. Well-differentiated tumours were significantly more frequent in Sweden than in Denmark in both years. The percentage of women for whom data on oestrogen-receptor status were missing was high in both countries in 1989, and in Sweden in 1994. In 1994 most of the Danish women had been tested for oestrogen-receptor status.

3.3. Relative survival

The 5-year age-standardised relative survival was significantly lower in Denmark than in Sweden in both

Table 2
Characteristics of the study population of breast cancer patients in 1989 and 1994 in east Denmark and south Sweden

Risk factors	1989			1994		
	East Denmark ($n=1139$) %	South Sweden ($n=815$) %	Test for homogeneity P	East Denmark ($n=1150$) %	South Sweden ($n=900$) %	Test for homogeneity P
Age at diagnosis (years)			<0.01			<0.01
40–49	20	17		19	20	
50–59	24	18		24	21	
60–69	25	28		26	22	
70–79	20	20		21	22	
80+	11	16		10	15	
Distant metastases			0.15			0.15
No	96	97		97	96	
Yes	4	3		3	4	
Number of nodes examined			<0.01			<0.01
0	16	16		12	16	
1–4	23	12		5	7	
5–9	41	34		31	35	
10+	20	38		52	42	
Number of positive nodes			0.17			<0.01
None examined	16	16		12	16	
0	46	47		46	53	
1–3	24	22		23	19	
4–6	6	9		8	5	
7+	7	6		10	7	
Tumour size (mm)[a]			0.07			<0.01
1–10	13	17		14	21	
11–20	38	38		38	39	
21–30	24	23		23	21	
31–50	14	12		16	11	
51+	8	7		7	5	
Multiple or unknown	2	4		3	4	
Histology			<0.01			<0.01
Well differentiated	25	33		28	37	
Poorly differentiated	69	67		70	63	
Not applicable	6	0		2	0	
Oestrogen receptor			<0.01			<0.01
Positive	45	56		67	50	
Negative	13	12		27	19	
Missing	42	31		5	31	

[a] Distribution of tumour size as a continuous variable in the four cohorts: 10% percentile 10,9, 10, and 8; medians 20, 20, 20, and 18; 90% percentile 50, 45, 50, and 40; means 27, 24, 27, and 22.

years. In 1989 it was 73.2% (95% confidence interval (CI) 70.5–75.9) in east Denmark and 81.6% (78.6–84.5) in south Sweden. In 1994 the corresponding percentages were 80.4% (77.8–83.0) and 87.0% (84.4–89.6). The relative survival was similar between countries and years for patients aged 40–49 years, and was not statistically different for patients in the 80+ years age group (Fig. 1). Further analysis was therefore restricted to ages 50–79 years. A significantly lower survival was seen for Danish women in this age span, but with a varying survival difference pattern between age groups 50–59, 60–69 and 70–79 (Fig. 1).

The differences in age-standardised, 5-year relative survival between Denmark and Sweden were largest for women in the age group 50–79 years with no nodes examined or with positive axillary nodes, large tumours (30 mm or more), or poor tumour differentiation (Table 3). Of those women who had no nodes examined ($P = 208$) the majority belonged to the age group 70–79 years, more so in Denmark (70%) than in Sweden (50%). Many women in Sweden with no nodes examined had small tumours (1–10 mm) (24% and 41% in 1989 and 1994, respectively). In Denmark the same values were 11% and 6% in 1989 and 1994, respectively.

3.4. Cox analyses

The distribution of the risk factors varied between countries and years of diagnosis (Table 2). To assess the hazard rate ratio or relative risk (RR) of death following breast cancer for east Denmark relative to south Sweden and to adjust for the possible confounding effect of the risk factors on the RR, whether caused by a different distribution of the factors between countries or a different effect of the factors from different treatments in the two countries, we modelled the risk of death by Cox regression with the factor 'country' alone, in two-factor models with 'country' and each single risk factor, and in multiple regressions with all factors included.

Tables 4 and 5 show estimates of the risk of death in the first 5 years following diagnosis in 1989 and in 1994, respectively; Table 6 shows estimates of the risk of death conditional on surviving the first 5 years for the women diagnosed in 1989 and followed through 2000. The number of positive lymph nodes had the highest influence on the risk of death in all analyses, with substantial differences between the different numbers of positive lymph nodes. The effect of the factors was as expected (i.e. a higher RR with the higher-risk group) in the first 5 years for both the 1989 and the 1994 cohorts.

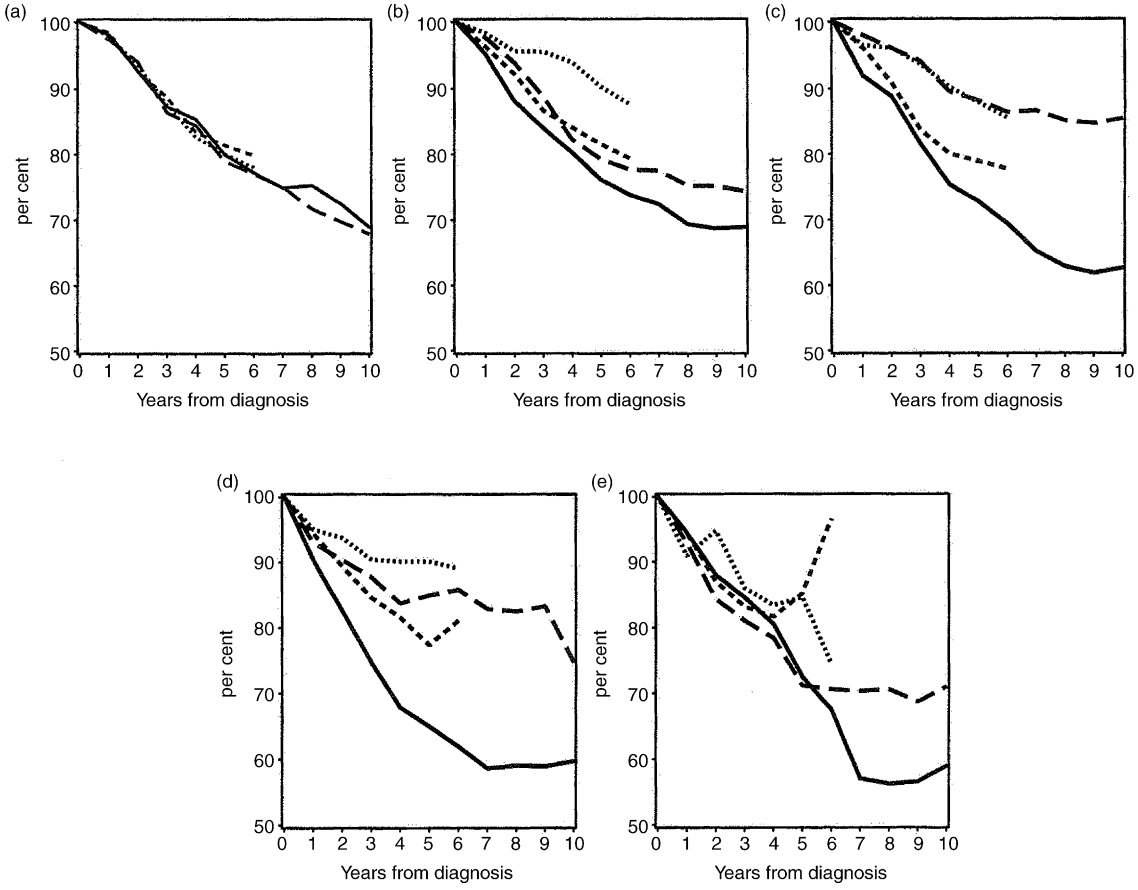

Fig. 1. Relative survival after breast cancer by age at diagnosis, east Denmark and south Sweden in 1989 and 1994: (a) age 40–49 years; (b) age 50–59 years; (c) age 60–69 years; (d) age 70–79 years; (e) age 80+ years.—Denmark 1989; – – – – Sweden 1989; - - - - - - - - Denmark 1994; ·····Sweden 1994.

The unadjusted RR in the first 5 years for Denmark relative to Sweden was 1.8 (95% CI: 1.4–2.3), irrespective of whether the patient had been diagnosed in 1989 or 1994. Adjusting for tumour size or histology in the1989 cohorts reduced the RR to 1.7, while adjustment for age, number of examined lymph nodes or number of positive nodes increased the RR to 1.9. Adjusting for all factors in the1989 cohorts left the RR for Denmark at 1.7 (95% CI: 1.3–2.2) (see Table 4).

For the 1994 cohorts, adjustment for number of positive lymph nodes, tumour size or oestrogen-receptor status reduced the risk to 1.4 or 1.5, while adjustment for all the factors reduced the RR for Denmark to a borderline statistical significant value of 1.3 (95% CI: 1.0–1.8) (see Table 5).

The conditional RR of death after surviving 5 years for the cohorts diagnosed in 1989 is shown in Table 6. The difference in RR between Denmark and Sweden was statistically insignificant at 1.1 (95% CI: 0.8–1.4) and remained insignificant when adjusting for all factors. Only age and number of positive lymph nodes had a significant influence on the risk of death after 5 years' survival.

We also checked for interactions between country and the other risk factors and found that none was statistically significant, thus indicating no effect modification on country by the other factors (data not shown).

We attempted to adjust for the known higher population mortality in Denmark. Multiplicative modelling of the ratio observed:expected mortality rate did not produce sensible estimates, whereas the more appropriate relative excess-risk models could be fitted but were rather unstable. Results from the relative excess-risk models indicated that the risk was still significantly higher for Danish patients from 1989 and of borderline significance for 1994 patients (data not shown).

4. Discussion

The southern part of Sweden was part of Denmark until 1658. The two geographical areas studied here are separated by only a narrow sound, and the populations, both of which enjoy a high standard of living, although with some differences in lifestyle, are considered very similar in relation to demographic and socioeconomic

Table 3
Age-standardized relative survival (95% confidence interval; CI) for women with a breast cancer diagnosis at age 50–79 years in east Denmark and south Sweden in 1989 and 1994 in relation to nodal stage, tumour size, histology and oestrogen-receptor status (women with distant metastases were excluded)

5-year relative survival	1989				1994			
	Denmark		Sweden		Denmark		Sweden	
	Survival	(95% CI)	Survival	(95% CI)	Survival	(95% CI)	Survival	(95% CI)
All	75.1	(71.8–78.4)	87.0	(83.4–90.5)	82.1	(79.0–85.2)	92.1	(89.1–95.1)
Number of nodes examined								
0	45.2	(30.9–59.6)	81.3	(70.2–92.4)	44.0	(25.8–62.3)	79.2	(64.1–94.3)
1–4	71.4	(64.6–78.3)	89.0	(79.9–98.1)	90.4	(77.2–103.5)	89.0	(78.1–99.9)
5–9	80.2	(75.2–85.3)	89.9	(84.4–95.3)	85.5	(80.2–90.8)	96.9	(92.8–101.0)
10+	69.1	(61.0–77.2)	88.1	(82.7–93.5)	83.4	(79.4–87.5)	89.7	(85.0–94.4)
Number of positive nodes								
0	89.1	(84.6–93.5)	98.7	(95.0–102.3)	98.6	(95.4–101.8)	102.8	(100.4–105.3)
1–3	73.1	(66.4–79.9)	88.0	(80.3–95.6)	84.0	(77.7–90.3)	82.3	(74.6–90.0)
4–6	34.1	(21.9–46.9)	55.6	(41.4–69.8)	57.9	(45.4–70.3)	85.5	(70.9–100.1)
7+	32.3	(19.4–45.3)	49.5	(31.6–67.4)	36.9	(27.1–46.6)	40.5	(24.7–56.3)
Tumour size in mm								
1–10	89.1	(80.6–97.6)	98.5	(92.0–105.1)	93.4	(86.1–100.7)	103.7	(100.1–103.7)
11–20	84.6	(79.7–89.6)	95.2	(90.4–100.0)	94.0	(89.9–98.1)	96.1	(91.9–100.4)
21–30	74.7	(67.8–81.6)	78.7	(70.2–87.1)	80.0	(73.6-86.4)	81.5	(74.3–88.7)
31–50	56.9	(47.7–66.1)	72.7	(60.1–85.3)	65.0	(56.0–74.1)	78.7	(64.3–93.0)
51+	37.2	(24.3–50.1)	48.3	(28.5–68.1)	33.2	(18.8–47.6)	43.8	(19.4–68.2)
Histology								
Well differentiated	89.1	(83.5–94.7)	97.2	(92.7–101.7)	96.0	(91.5–100.6)	100.2	(96.8–103.7)
Poorly differentiated	70.0	(65.9–74.0)	81.9	(77.2–86.6)	76.2	(72.3–80.1)	86.7	(82.5–91.0)
Oestrogen receptor								
Positive	81.7	(77.3–86.1)	88.5	(84.1–92.9)	88.3	(84.9–91.6)	93.7	(89.7–97.6)
Negative	60.9	(50.5–71.4)	65.6	(52.5–78.6)	66.4	(59.6–73.3)	76.1	(67.0–85.2)
Missing	70.7	(65.2–76.3)	91.6	(85.3–97.8)	82.5	(67.5–97.4)	98.2	(93.7–102.7)

factors [15]; both sets of factors are known to affect survival [24]. The completeness and accuracy of the Danish and the Swedish Cancer registers are generally considered to be very high [1]. The year 1989 was selected in order to relate to the published survival data [5], whereas 1994 was the most recent year of tabulation of the Danish Cancer Register at the start of the study. Patients under 40 years of age were not included in the study. Breast cancer in this age group is rare; also, it is often hereditary [25]. In Denmark it constituted 5.5% of all breast cancer cases in 1989 and 4.2% in 1994, and in Sweden the figures were 3.1% in 1989 and 4.1% in 1994. The municipality of Frederiksberg in Denmark (female population 47 000) was excluded because mammographic screening had been introduced there in 1994 and the sudden increase in breast cancer cases induced by screening might have biased the survival estimates [9].

The incidence of breast cancer is similar in the two countries and has been so for the past 40 years [2–4], whereas in this period the 5-year relative survival was 10% units higher in Sweden than in Denmark [5,6]. Differences in the estimates for age-adjusted 5-year relative-survival for breast cancer cohorts in east Denmark and south Sweden from 1989 were similar to previously found differences between the two countries [5,6], and the two population fractions used in this study are therefore regarded as representative for elucidating differences causing this survival gap. It is also reassuring that the effect on mortality in the Cox analyses was as expected for the different patho-anatomical variables for the first 5 years in both nations (Tables 4 and 5).

The diagnosis and care of women with breast cancer has been somewhat different for the two populations. Mammographic screening was introduced in Malmö,

Table 4
Cox regression analyses of death in the first 5 years after diagnosis: women with a breast cancer diagnosis aged 50–79 years in 1989 in east Denmark and south Sweden (193 deaths among 623 breast cancer patients from east Denmark and 90 deaths among 482 patients from south Sweden); women with distant metastases and missing values for any of the variables except oestrogen-receptor status were excluded

1989 cohorts	One- or two-factor models[a]					Multiple regression[b]		
Risk factor	Denmark/Sweden				Factor test			
	RR (95% CI)[a]		RR (95% CI)		*P*	RR (95% CI)		*P*
Country					<0.01			<0.01
Sweden			1			1		
Denmark			1.8	(1.4–2.3)		1.7	(1.3–2.2)	
Age at diagnosis (years)	1.9	(1.5–2.5)			<0.01			<0.01
50–59			1			1		
60–69			1.0	(0.8–1.4)		1.2	(0.9–1.6)	
70-79			1.9	(1.5–2.6)		1.8	(1.3–2.4)	
Lymph nodes examined	1.9	(1.4–2.4)			0.07			<0.01
1–4			1.3	(1.0–1.8)		1.6	(1.2–2.1)	
5–9			1			1		
10+			1.3	(1.0–1.7)		1.1	(0.8–1.4)	
Positive lymph nodes	1.9	(1.5–2.5)			<0.01			<0.01
0			1			1		
1–3			1.9	(1.4–2.6)		1.7	(1.3–2.4)	
4–6			5.5	(4.0–7.8)		4.6	(3.2–6.6)	
7+			6.6	(4.7–9.3)		5.0	(3.4–7.4)	
Tumour size (mm)	1.7	(1.3–2.1)			<0.01			<0.01
1–10			0.7	(0.5–1.2)		0.8	(0.5–1.3)	
11–20			1			1		
21–30			1.8	(1.3–2.4)		1.4	(1.0–1.9)	
31–50			2.9	(2.1–4.0)		1.7	(1.2–2.4)	
51+			4.4	(2.9–6.5)		2.2	(1.4–3.2)	
Histology (differentiation)	1.7	(1.3–2.2)			<0.01			<0.01
Well differentiated			0.5	(0.4–0.6)		0.7	(0.5–0.9)	
Poorly differentiated			1			1		
Oestrogen-receptor status	1.8	(1.4–2.3)			<0.01			<0.01
Positive			1			1		
Negative			2.1	(1.5–2.9)		1.8	(1.3–2.5)	
Missing			1.1	(0.8–1.4)		1.5	(1.1–1.9	

RR, hazard rate ratio; CI, confidence interval.
[a] Models included country and the specific factor.
[b] Model included country, age, lymph nodes examined, positive lymph nodes, tumour size, histology, and oestrogen-receptor status.

Sweden, as early as 1976 [26], and covered the southern part of Sweden by 1991 [8]. In contrast, Denmark did not begin mammographic screening until 1991, and at present only 18% of the female population in the relevant age groups is offered screening [9], corresponding to 25.6% of the female population in east Denmark in 1994.

Most patho-anatomical prognostic variables, such as lymph-node status, tumour size, clinical stage, histological grade and oestrogen/progesterone-receptor status, are expected to be more favourable when the tumours are detected early, as with mammographic screening [18,26]. We found a slightly higher percentage of well-differentiated tumours and tumours of 1–10 mm in Sweden, and the better survival of Swedish women in the extended-screening population group in 1994 (i.e. women aged 50–74 years), in which small tumours are detectable, supports this view. However, a direct link between small tumour size and improved survival in Sweden could not be explained by our Cox models (Tables 4, 5), probably because the potential for a tumour to metastasise, which is an important prognostic indicator independent of tumour size, may differ from one tumour to another, and the survival outcome in women diagnosed with breast cancer is also dependent on the biology of each individual tumour [18,27].

As our data were population based, the results are probably very complete and precise. The intensity of investigation for distant metastases is not believed to differ between the two regions, and the preponderance of poor prognostic factors in Denmark can hardly be explained by anything but delayed diagnosis. In spite of there being fewer axillary operations in Denmark in 1989 a similar number of positive nodes was found in the two countries, and in 1994, when axillary surgery was more common in Denmark, positive lymph nodes were also more common. In addition, tumours detectable on self-examination, i.e. larger than 20 mm, were more common in Denmark during both years.

The difference in relative survival between Denmark and Sweden was considerable for women who had had

Table 5
Cox regression analyses of death in the first 5 years after diagnosis: women with a breast cancer diagnosis at age 50–79 years in 1994 in east Denmark and south Sweden (176 deaths among 718 breast cancer patients from east Denmark and 76 deaths among 518 patients from south Sweden); women with distant metastases and missing values for any of the variables except oestrogen-receptor status were excluded

1994 cohorts	One- or two-factor models[a]					Multiple regression[b]		
Risk factor	Denmark/Sweden RR (95% CI)		RR (95% CI)		Factor test *P*	RR (95% CI)		Factor test *P*
Country					<0.01			0.05
Sweden			1			1		
Denmark			1.8	(1.4–2.3)		1.3	(1.0–1.8)	
Age at diagnosis (years)	1.8	(1.4–2.4)			<0.01			<0.01
50–59			1			1		
60–69			1.3	(1.0–1.8)		1.3	(0.9–1.7)	
70–79			1.8	(1.3–2.5)		2.0	(1.5–2.8)	
Lymph nodes examined	1.8	(1.4–2.3)			0.41			0.06
1–4			1.3	(0.8–2.3)		1.2	(0.7–2.1)	
5–9			1			1		
10+			1.2	(0.9–1.5)		0.7	(0.6–1.0)	
Positive lymph nodes	1.4	(1.1–1.9)			<0.01			<0.01
0			1			1		
1–3			2.9	(2.1–4.1)		2.5	(1.8–3.6)	
4–6			5.4	(3.6–8.2)		4.3	(2.8–6.6)	
7+			12.1	(8.7–16.9)		8.8	(6.0–13.0)	
Tumour size (mm)	1.5	(1.1–2.0)			<0.01			0.02
1–10			0.5	(0.3–0.9)		0.8	(0.5–1.3)	
11–20			1			1		
21–30			2.1	(1.5–2.9)		1.3	(0.9–1.7)	
31–50			2.9	(2.0–4.1)		1.4	(1.0–2.1)	
51+			7.5	(4.9–11.5)		2.0	(1.3–3.2)	
Histology	1.7	(1.3–2.2)			<0.01			<0.01
Well differentiated			0.4	(0.3–0.5)		0.6	(0.4–0.8)	
Poorly differentiated			1			1		
Oestrogen-receptor status	1.4	(1.1–1.9)			<0.01			<0.01
Positive			1			1		
Negative			2.3	(1.8–3.0)		2.0	(1.5–2.6)	
Missing			0.5	(0.3–0.9)		0.8	(0.4–1.4)	

RR, hazard rate ratio; CI, confidence interval.

[a] Models included country and the specific factor.

[b] Model included country, age, lymph nodes examined, positive lymph nodes, tumour size, histology, and oestrogen-receptor status.

Table 6
Cox regression analyses of death conditional on having survived the first 5 years after diagnosis and followed to the end of 2000: women with a breast cancer diagnosis at age 50–79 years in 1989 in east Denmark and south Sweden (107 deaths among 430 breast cancer patients from east Denmark and 97 deaths among 392 patients from south Sweden); women with distant metastases and missing values for any of the variables except oestrogen-receptor status were excluded

1989 cohorts	One- or two-factor models[a]					Multiple regression[b]		
Risk factor	Denmark/Sweden RR (95% CI)		RR (95% CI)		Factor test *P*	RR (95% CI)		Factor test
Country					0.75			0.14
Sweden			1			1		
Denmark			1.1	(0.8–1.4)		1.3	(0.9–1.7)	
Age at diagnosis (years)	1.2	(0.9–1.6)			<0.01			<0.01
50–59			1			1		
60–69			1.7	(1.2–2.5)		1.8	(1.2–2.7)	
70–79			3.8	(2.6–5.5)		3.8	(2.6–5.7)	
Lymph nodes examined	1.0	(0.8–1.3)			0.50			0.28
1–4			1.2	(0.8–1.7)		1.1	(0.8–1.6)	
5–9			1			1		
10+			0.9	(0.7–1.3)		0.8	(0.6–1.1)	
Positive lymph nodes	1.1	(0.8–1.4)			<0.01			<0.01
0			1			1		
1–3			1.7	(1.3–2.3)		1.6	(1.2–2.2)	
4–6			2.3	(1.3–3.9)		2.4	(1.4-4.2)	
7+			5.1	(3.1–8.4)		6.8	(3.6–11.6)	
Tumour size (mm)	1.0	(0.8–1.3)			0.05			0.91
1–10			0.8	(0.6–1.3)		1.2	(0.8–1.9)	
11–20			1			1		
21–30			1.3	(0.9–1.8)		1.1	(0.8–1.6)	
31–50			1.2	(0.8–2.0)		1.0	(0.6–1.6)	
51+			2.3	(1.3–4.3)		1.0	(0.5–2.0)	
Histology	1.1	(0.8–1.4)			0.48			0.33
Well differentiated			1.1	(0.8–1.5)		1.2	(0.9–1.6)	
Poorly differentiated			1	–		1		
Oestrogen-receptor status	1.1	(0.8–1.4)			0.04			0.14
Positive			1			1		
Negative			0.9	(0.6–1.5)		1.0	(0.6–1.7)	
Missing			0.7	(0.5–0.9)		0.7	(0.5–1.0)	

RR, hazard rate ratio; CI, confidence interval.
[a] Models included country and the specific factor.
[b] Model included country, age, lymph nodes examined, positive lymph nodes, tumour size, histology, and oestrogen-receptor status.

no axillary surgery (Table 3). This group was found mainly in the age group 70–79 years and more often in Denmark, whereas women in Sweden more often had small tumours (1–10 mm). An explanation could be that for a period some hospitals in south Sweden omitted axillary surgery in cases with small tumours (T. Möller, personal communication).

Our findings are similar to those from Estonia, which in comparison with Finland had a 10% lower 5-year relative survival for breast cancer (55.9% versus 67.3%), a difference that was caused by higher clinical stages especially among older Estonian patients [29].

Histological differentiation is considered a strong prognostic indicator independent of size and nodal status [13]. Provided that a tumour retains the same histological grade from the time it is detectable by mammography until it is palpable as a lump, the fraction of poorly differentiated tumours would be expected to be the same in both countries. This was not the case. Well-differentiated tumours were 10% units more common in Sweden than in Denmark in both 1989 and 1994, suggesting a reduction in histological differentiation with increasing tumour size. However, it cannot be excluded that Swedish pathologists may have a greater tendency than Danish pathologists to diagnose a tumour as well differentiated [30].

It has been suggested that the improved survival of women whose tumours were diagnosed by mammographic screening is caused by lead-time bias [28]. An almost 10% unit difference in relative survival among breast cancer patients between Denmark and Sweden has existed for the past 40 years [5], far longer than time

at which mammographic screening was begun in either country. It is therefore unlikely that screening or lead-time could be the sole explanation for the survival difference between the two countries.

We found a statistically significant difference in the age distribution of breast cancer between Denmark and Sweden in both years (Table 2). This difference was expected as the age distribution of the background population is slightly different in the two study populations, with more elderly women in Sweden [4], and a lower mortality from all causes in Sweden than in Denmark. Our analyses of relative survival were stratified by age, yielding the main survival difference in women of the extended screening population (50–79 years) (Table 3; Fig. 1). According to our conditional Cox analyses, only age and lymph-node status had an influence on mortality after 5 years' survival (Table 5). Mortality differences between countries could not be demonstrated after survivals of 5 years.

Do differences in patho-anatomical variables and the higher population mortality in Denmark explain the survival differences between Denmark and Sweden? Not entirely: in the age group invited to screening an elevated risk still prevailed after adjustment for these variables, higher in 1989 than in 1994. Further studies on the treatment given, any delays in diagnosis and therapy, or lifestyle factors will be needed to clarify the nature of other variables contributing to the nearly 10% unit difference in relative survival for patients with breast cancer between Denmark and Sweden.

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6. Ethics

The study was approved by the scientific ethical committee of greater Copenhagen and the Danish Register Council as well as the research ethics committee of Lund University, Sweden.

7. Conflict of interest statement

No conflict of interest is found for any of the authors.

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