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Age–period–cohort modelling of breast cancer incidence in the Nordic countries

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SUMMARY

The Nordic countries have experienced a steady increase in breast cancer incidence throughout the past 35 years. We analysed the incidence in Denmark, Finland, Norway and Sweden during the period 1958 to 1992 using age–period–cohort models and taking the systematic mammography screening into account. Assuming the age dependency of the incidence pattern in old age to be common for the Nordic countries, an internal comparison could be made among the four countries of the cohort effects and the period effects. The study indicated that the period effects have been of importance for the increase in breast cancer incidence seen in the Nordic countries. The widespread practice of neglecting the period effects in age–period–cohort analysis of time trends in breast cancer incidence therefore probably needs reconsideration. A key finding was that Danish women born in the 20th century seem to have been exposed to an increasing load of cohort borne breast cancer risk factors not experienced to the same extent by Norwegian women, whereas they were seemingly subjected to the same period effects. Copyright © 2001 John Wiley & Sons, Ltd.

INTRODUCTION

Breast cancer is the most common cancer in women. The incidence in Denmark, Finland and Sweden is at present 75–80 cases per 100 000 women in the World Standard Population per year and somewhat less in Norway. The current incidence level is a result of a steady increase over the past 35 years (see Figure 1). Only about 40 per cent of breast cancer cases in developed

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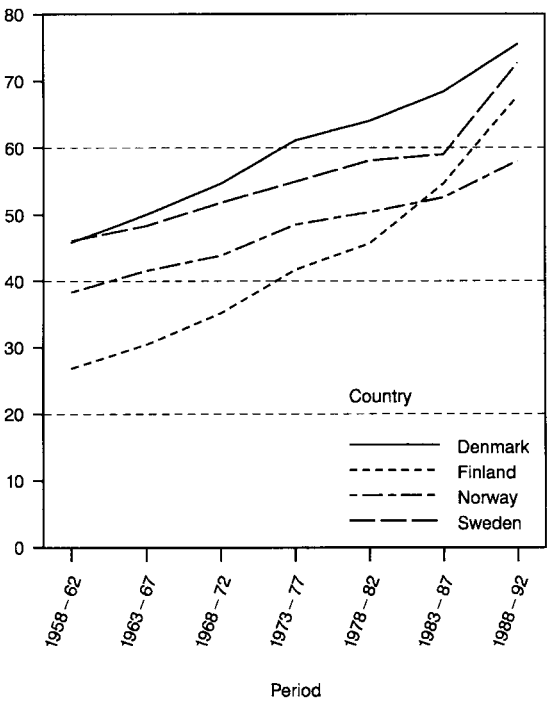

Figure 1. Breast cancer incidence in the Nordic countries 1958–1992. Age standardized rate per 100 000 (World Standard Population).

countries can be attributed to known risk factors [1, 2] and a better understanding of the aetiology is warranted. In the search for aetiological leads from routinely collected mortality and incidence data, age–period–cohort models are widely used. We applied these models to the long time series of breast cancer incidence data from the Nordic countries in order to disentangle the elements behind the increased incidence. We deliberately aimed for an open search without any *a priori* hypotheses and with a minimum of *a priori* assumptions in the modelling. In order to obtain valid inferences we had to include screening effects in the model too.

MATERIAL

Nationwide cancer registration started in Denmark in 1943, in Norway and Finland in 1953 and in Sweden in 1958 [3]. Cancer registration began in 1954 in Iceland, but these data were not included in the present analysis due to the relatively small population size. Breast cancer was defined as ICD-7:170, ICD-8:174 and ICD-9:174 (ICD = International Classification of Diseases and Causes of Death), and only the first breast cancer in a given woman was included in the analysis. Data on the risk populations in the Nordic countries were available recently from the population registers and previously from the censuses.

The analysis was restricted to the period 1958–1992 and to the age group 30–84 years. There are extremely few cases below age 30 years and the age group above 85 years is very heterogeneous. The number of breast cancer cases and incidence rates in Denmark were retrieved from the database of the national cancer register [4] for five-year age groups (30–34,...,80–84), and five-year calendar periods (1958–1962,1963–1967,...,1988–1992). Similar data from Norway, Sweden and Finland were retrieved from a Nordic database [3] in the five-year periods (1958–1962,1963–1967,...,1982–1987), and by personal communication from the cancer registers for 1988–1992. Raw data are given in Table I. The person-years at risk were derived as the number of breast cancer cases divided by the breast cancer incidence rate. The number of breast cancer cases and person-years at risk are given in Table II. Several sources [5–13] have documented the high completeness (of ascertainment) and accuracy of the registration of breast cancer in the Nordic cancer registries, convincing us that data quality concerns could safely be ignored in our analyses.

Information on breast cancer screening programmes in the Nordic countries was retrieved from several sources [14–20]. Systematic screening programmes started: in Sweden in some regions in the late 1970s and gradually spread to the vast majority of regions in the late 1980s; in Finland in half of the municipalities in 1987; and in Denmark in one region in 1991. In Denmark the age group covered was 50–69 years, in Finland it was 50–59 or 50–64 and in Sweden screening usually started either at age 40 or 50 and ended either at ages 64, 69 or 74.

METHODS

For each country the data can be represented by a two-way table where rows represent age categories and columns represent calendar periods. Each cell in the table gives the number of cases and the person-years at risk. Birth cohorts cannot be identified, but are substituted by the so-called synthetic birth cohorts made up from the diagonals of the table. With 5-year age and period groups the women contributing to such a cohort are born within a 10-year period, the same woman contributing to two adjacent synthetic birth cohorts.

The data from Denmark, Finland, Norway and Sweden were analysed separately. For each country, the breast cancer incidence rate in a given age-by-period group was described as a function of a number of predictors: age; birth cohort; time period, and (if relevant) screening programme. We used the standard log-linear Poisson regression technique, as described in Robertson and Boyle (Reference [21], p. 1306), to estimate the effects of the predictors. In this approach the logarithm of the breast cancer incidence rate is described as a sum of components reflecting the influence of each of the predictors:

$$\log(\text{rate}_{ap}) = \text{constant} + \text{screening}_{ap} + \text{age}_a + \delta(p - p_0) + \varepsilon(c - c_0) + \pi_p + \kappa_c$$

where a, p and c refer to age (coded as $30, 35, \ldots, 80$), period (coded as $58, 63, \ldots, 88$), and (synthetic) birth cohort (defined as $c = p - a$), respectively, and p_0 is the reference period and c_0 the reference cohort. Moreover, δ is the linear period effect (the period drift), ε is the linear cohort effect (the cohort drift), π_p are the residual period effects, κ_c are the residual cohort effects. The residual effects represent the non-linear part of the period and cohort effects. This type of modelling immediately provides estimates of rate ratios between various combinations of the values of the predictors.

Table I. Breast cancer incidence rates per 100 000 and number of incident breast cancer cases in Denmark, Finland, Norway and Sweden 1958–1992 by age and calender period.

Age	Period						
	1958–1962	1963–1967	1968–1972	1973–1977	1978–1982	1983–1987	1988–1992
(*a*) *Breast cancer incidence rates per 100 000*							
Denmark							
30–34	12.9	13.4	15.7	19.6	21.7	22.8	22.6
35–39	38.3	39.2	44.1	51.9	55.3	59.4	60.6
40–44	72.2	86.0	88.8	101.1	111.1	119.2	125.6
45–49	114.3	126.8	138.4	160.9	167.3	177.7	195.8
50–54	108.3	121.7	146.6	165.3	173.4	197.0	214.2
55–59	120.2	131.9	151.2	171.2	193.6	206.3	245.6
60–64	149.9	157.8	178.6	183.1	201.2	220.0	258.3
65–69	171.4	186.1	187.8	220.0	221.3	229.6	271.8
70–74	210.1	217.8	230.7	241.6	241.8	271.4	280.9
75–79	256.2	259.5	261.6	282.9	272.2	276.6	299.2
80–84	288.4	311.3	331.6	326.3	322.3	303.9	310.6
Finland							
30–34	8.6	13.9	12.7	15.4	19.3	18.4	20.1
35–39	20.9	26.5	31.6	38.4	40.3	47.0	51.4
40–44	51.0	46.6	61.6	72.8	76.8	94.7	101.9
45–49	72.1	79.2	87.6	105.4	122.8	149.7	178.4
50–54	66.8	75.1	88.5	108.5	115.8	157.3	234.1
55–59	76.1	89.5	98.3	116.5	128.7	161.8	239.0
60–64	90.7	99.9	121.6	131.9	144.7	161.1	207.4
65–69	101.0	117.8	124.8	151.2	161.4	186.0	218.2
70–74	105.2	128.0	145.4	168.8	182.6	204.6	231.9
75–79	105.9	121.8	160.9	192.2	201.4	241.3	270.0
80–84	105.1	135.8	173.8	202.9	237.9	268.1	274.5
Norway							
30–34	10.8	12.4	16.2	17.3	18.3	17.7	19.9
35–39	33.4	36.0	34.1	43.2	47.1	43.5	49.8
40–44	70.1	76.0	75.0	74.9	87.5	91.7	96.7
45–49	106.5	109.5	112.8	126.3	119.8	128.7	145.6
50–54	90.2	106.9	113.9	124.3	125.1	128.3	144.6
55–59	103.4	113.2	129.6	138.3	139.1	143.1	155.7
60–64	127.4	137.9	143.1	166.4	158.5	171.1	193.9
65–69	132.4	151.9	153.1	177.9	197.5	202.9	213.9
70–74	157.6	166.1	183.6	198.6	221.9	226.1	256.1
75–79	196.6	192.3	203.5	220.5	248.1	267.4	288.4
80–84	193.8	178.5	229.6	255.6	246.9	284.3	310.5
Sweden							
30–34	12.1	11.7	14.7	16.9	20.6	17.6	19.3
35–39	33.4	33.8	37.2	42.3	44.9	45.6	46.5
40–44	73.9	73.4	81.7	82.4	81.7	88.1	101.7
45–49	114.3	119.1	127.2	140.1	139.7	144.8	172.0
50–54	115.3	121.9	129.8	141.8	149.7	150.8	201.9
55–59	126.0	136.3	144.7	153.4	164.3	170.7	229.3
60–64	162.5	156.3	169.3	178.7	196.2	207.0	273.0
65–69	183.0	188.8	197.7	210.9	227.5	226.2	317.2
70–74	214.3	227.6	239.3	231.1	259.4	261.2	311.1
75–79	224.1	268.9	272.8	284.4	296.9	287.0	283.6
80–84	250.0	284.9	314.9	315.1	336.0	302.0	329.3

Table I. (Continued)

Age	Period						
	1958–1962	1963–1967	1968–1972	1973–1977	1978–1982	1983–1987	1988–1992
(*b*) *Number of incident breast cancer cases*							
Denmark							
30–34	94	94	117	179	216	208	206
35–39	300	284	309	388	504	590	553
40–44	552	669	639	704	824	1078	1242
45–49	880	957	1061	1143	1149	1302	1752
50–54	802	919	1084	1242	1206	1324	1539
55–59	801	947	1107	1227	1409	1389	1598
60–64	882	1004	1226	1281	1376	1526	1657
65–69	823	1010	1108	1408	1446	1464	1755
70–74	781	908	1098	1268	1385	1592	1606
75–79	649	745	868	1099	1187	1328	1476
80–84	393	503	637	763	906	976	1115
Finland							
30–34	66	97	92	124	201	184	189
35–39	159	199	219	277	321	490	512
40–44	358	350	455	501	549	751	1069
45–49	531	544	644	770	836	1062	1443
50–54	478	539	593	783	832	1057	1654
55–59	462	616	680	758	906	1139	1565
60–64	458	572	794	872	905	1096	1413
65–69	390	537	652	913	999	1097	1415
70–74	316	413	562	766	979	1139	1243
75–79	203	263	381	573	736	1064	1248
80–84	100	147	215	302	483	691	883
Norway							
30–34	60	61	81	108	138	132	154
35–39	213	199	168	217	294	328	375
40–44	447	481	412	368	439	572	728
45–49	646	691	708	689	585	642	931
50–54	511	639	708	770	674	619	721
55–59	545	627	758	842	844	755	729
60–64	601	699	765	940	934	1004	978
65–69	507	671	731	898	1056	1135	1181
70–74	465	563	725	854	1018	1106	1323
75–79	408	452	561	712	893	1045	1214
80–84	245	246	369	492	574	760	925
Sweden							
30–34	143	129	172	246	332	253	273
35–39	446	401	411	492	655	731	676
40–44	977	976	969	907	949	1278	1635
45–49	1518	1559	1681	1649	1529	1670	2488
50–54	1489	1593	1678	1847	1740	1631	2311
55–59	1470	1715	1849	1937	2095	1946	2443
60–64	1655	1749	2052	2204	2396	2558	3032
65–69	1563	1788	2075	2407	2654	2625	3742
70–74	1457	1705	2016	2181	2689	2791	3333
75–79	1037	1433	1642	1966	2348	2538	2622
80–84	649	855	1127	1332	1674	1785	2223

Table II. Number of breast cancer cases among women aged 30–84 years during the period 1958–1992 and number of person-years at risk in Denmark, Finland, Norway and Sweden.

Country	Number of cases	Person-years at risk (millions)
Denmark	73 837	49.2
Finland	49 875	46.7
Norway	47 659	38.6
Sweden	122 792	83.7

In its most general form the model above is overparameterized, since the mathematical relation between age, period and cohort allows the same model to be written in different ways. Hence the effects in the model cannot be uniquely identified. In particular, it is well known [22, 23] that only a single drift parameter is identifiable unless suitable constraints on the age, period or cohort parameters are introduced.

Normally, the non-identifiability problem is solved by imposing constraints on the period parameter [24–27], which is implicitly the case when fitting age–cohort models and interpreting the linear temporal trend as a true cohort effect only. In the present study, we were interested in the temporal effect and therefore we could not put constraints on the period and cohort effects. Curves representing second differences [23] of the age parameter estimates suggested that the accelerations were ignorable for old ages implying that the log(rate) was here a linear function of age. We therefore introduced constraints by assuming that the age dependence of the log(rate) was linear for ages above 60 and that these linear slopes were identical in the four Nordic countries. Note that the common slope, to be denoted α in the following, is non-identifiable if the model also includes both a period drift and a cohort drift, in which case exactly the same fit is obtained for all values of α. As long as α is unspecified no main effects are identifiable, only interaction effects, such as the relative cohort effect (country $\times$ cohort). In a comprehensive analysis of liver cirrhosis mortality in England, Wales and Scotland, Duffy and Latcham [28], also utilized an assumption of a common age structure to provide identifiability of interaction terms of interest.

The parameter α was set to zero when fitting these models. Note that we are not assuming α to be zero, but simply utilizing the non-identifiability to obtain a convenient way of analysing the data under the assumption of a common linear age slope for ages above 60 years. The estimated values of the parameters in the model equation will, in general, depend on the value of α. We avoided this problem by focusing on the relative period effects (the ratio of the period effects in one country to the analogous period effects in a reference country) and the relative cohort effects, defined in a similar way, since these quantities are independent of the value of α.

In practice we implemented the constraints by defining a new age variable, denoted age*, as equal to age for ages below 60 and zero otherwise. Replacing age with age* in the model equation leads to parameter estimates reflecting the effect of the predictors when the slope of the age parameter curve is zero for ages above 60. If needed, these estimates may easily be transformed to estimates of age, period and cohort parameters for any other value of the common linear slope for ages above 60. Details are given in the Appendix, together with definitions of relative period effects and relative cohort effects.

In Denmark, Finland and Sweden the age–period–cohort model did not fit particularly well due to an interaction between age and period, which we believe to be caused by organized screening

Table III. Percentage of person-years 'at risk' of being invited to their first mammography screening round* in Denmark, Finland and Sweden by age and period. Where not specified the percentage is 0.

Age	Denmark	Finland		Sweden				
	1988–1992	1983–1987	1988–1992	1968–1972	1973–1977	1978–1982	1983–1987	1988–1992
40–44	0	0	0	1.7	0.3	2.5	3.7	8.9
45–49	0	0	0	1.7	0.3	2.5	3.8	9.6
50–54	2.4	8.3	33.3	1.8	1.2	2.8	6.4	23.9
55–59	2.6	16.7	33.3	1.8	1.3	2.9	6.5	23.5
60–64	3.1	0	8.3	1.8	1.4	3.0	6.5	23.3
65–69	3.7	0	0	1.9	1.4	3.0	6.6	23.1
70–74	0	0	0	1.9	0	1.9	3.9	12.3

*For Sweden data were avaliable for each county on year of start of mammography screening, age groups invited and length of screening rounds [16]. We assumed the starting date to be 1 July in the designated year, and used the upper limit for the duration of screening rounds when an interval was given. The proportion of person-years in each county in each age group at any time relative to the country total were assumed to be similar to the proportion of inhabitants on 1 January 1989 [39]. In Denmark only one county offered mammography screening, starting 1 April 1991. The proportion of person-years were taken as the proportion of inhabitants on 1 January 1991 [40]. Mammography screening in Finland started at different points in time for different birth cohorts [17, 18]. We assumed that the person years for a given birth cohort were at risk during the first screening round offered to the cohort, each cohort contributing the same fraction of person-years at risk. Twelve one-year birth cohorts in a two-year screening round would make the fraction of the person-years at risk of screening sum to 1, so the fraction of Finnish person-years at risk of screening was scaled accordingly.

programmes. For example, when fitting an age–period–cohort model to the Swedish data, the deviance dropped from 291 on 45 degrees of freedom to 24 on 24 degrees of freedom when data for women aged 40–74 in the period 1978–1992 were excluded. We wanted to estimate the age, period and cohort effects undistorted by the effects of systematic screening. Similarly, an age–cohort model for the secular trend without screening has been constructed for the U.S. breast cancer incidence data [29].

The most important effect of screening appears in the first round of screening – the prevalence round – after which the incidence settles into a new steady state, not too different from the old. The predictor screening is the fraction of person-years 'at risk' of being invited to the first round of screening. Women were assumed to be at risk during the whole prevalence round. For Denmark and Sweden, these person-years were calculated for each county separately. For Finland we did not know the fraction of women living in municipalities with screening, so the covariate was scaled as if all municipalities participated. There was no organized screening programme in Norway [20]. Three out of 22 Swedish counties had 18 month screening intervals, all other counties and countries had 24 month screening intervals. Table III shows the scoring of the predictor screening, and details the calculation of the predictor.

For each country two series of analyses were performed. The first series of analyses took the full model with the unconstrained age variable as a starting point and the effect of different simplifications was assessed by referring the change in the deviance to the relevant chi-square distribution. The second series of analyses was based on models all assuming a common linear age slope for ages above 60. Again, the full model (the model above with age replaced by age*) was first fitted to the data and the effect of different simplifications was evaluated.

Table IV. Age–period–cohort analysis of breast cancer in the Nordic countries 1958–1992. Traditional approach without any assumptions. Deviance (dev.) and degrees of freedom (d.f.) for various models.

Model*	Country							
	Denmark		Finland		Norway		Sweden	
	d.f.	dev.	d.f.	dev.	d.f.	dev.	d.f.	dev.
A Constant + age + screen + drift + period + cohort	44	51	44	49	45	46	44	59
B Constant + age + screen + drift + cohort	49	104	49	58	50	55	49	124
C Constant + age + screen + drift + period	59	309	59	106	60	81	59	125
D Constant + age + screen + drift	64	341	64	116	65	90	64	185
E Constant + age + screen	65	1467	65	2859	66†	946†	65	548
F Constant + age	66	2015	66	4623	66	946	66	2725
G Constant	76	27 077	76	21 267	76	17 186	76	49 958

*Screen is the screening covariate, drift is the common drift, period is residual period effects, and cohort is the residual cohort effects. Screening is a serious confounder of temporal trends and is therefore included early in the model building to reveal the true significance of the temporal trends. The residual period effects become highly statistically significant in Finland if the screening covariate is removed. If screening is removed from the complete model, the drop in deviance is 15, 80 and 232, respectively, in Denmark, Finland and Sweden.

†Model F and E are identical in Norway, as there is no screening programme.

Table V. Age–period–cohort analysis of breast cancer incidence in the Nordic countries 1958–1992, assuming a common age dependence for ages above 60. Deviance (dev.) and degrees of freedom (d.f.) for various models.

Model†	Country							
	Denmark		Finland		Norway		Sweden	
	d.f.	dev.	d.f.	dev.	d.f.	dev.	d.f.	dev.
A* Constant + age* + screen + cd + pd + period + cohort	47	56	47	50	48	53	47	67
B* Constant + age* + screen + cd + pd + cohort	52	107	52	59	53	62	52	133
C* Constant + age* + screen + cd + pd + period	62	315	62	108	63	91	62	136
D* Constant + age* + screen + cd + pd	67	346	67	118	68	99	67	195

† screen is the screening covariate, cd is the cohort drift, pd is the period drift, period is residual period effects, and cohort is the residual cohort effects. Screening is a serious confounder of temporal trends and is therefore controlled for throughout.

RESULTS

Results from the first series of analyses are summarized in Table IV. Here the cohort drift and the period drift could not be separated and were combined in a single (linear) drift. Table V gives results from the second series of analyses, in which a common slope of the linear age dependence above age 60 was assumed.

In Table IV the first model represents the full age–period–cohort–screening model and the results allow the usual assessment of residual cohort effects, residual period effects and the contribution from the linear drift. For Denmark and Sweden, the separate contributions from each of the terms in the full model were statistically significant (that is, no simplification of the full model was possible). For Norway and Finland, the residual period effects were non-significant, indicating that a linear period effect was consistent with these data.

Table VI. Test of selected effects in models for breast cancer incidence in the Nordic countries. See Tables IV and V for definitions of models. Deviance and degrees of freedom (d.f.) for various tests.

	Country			
	Denmark	Finland	Norway	Sweden
A^* versus A: tests of non-linearity for ages above 60				
Deviance	5.42	1.34	6.49	8.54
D.f.	3	3	3	3
p-value	0.14	0.72	0.09	0.04
B^* versus A^*: tests for residual period effects				
Deviance	51.46	9.00	9.23	65.28
D.f.	5	5	5	5
p-value	<0.001	0.11	0.10	<0.001
C^* versus A^*: tests for residual cohort effects				
Deviance	259.55	57.74	38.04	68.60
D.f.	15	15	15	15
p-value	<0.001	<0.001	<0.001	<0.001

Similarly, in Table V the first model represents the full age*–period–cohort–screening model and the results presented in the table allow assessment of residual cohort effects and residual period effects both separately and simultaneously. These results also indicated that the period effect, but not the cohort effect, could be assumed linear for Norway and Finland, while no simplification of the initial model was possible for Denmark and Sweden.

For each country the assumption of a linear age effect for ages above 60 was assessed by comparing the goodness-of-fit of model A* and model A. None of the data sets showed a clear statistically significant non-linearity in the upper part of the age curve. It should be noted that this is not a test for a *common* linear slope, which is still an untestable assumption. These results are shown in Table VI which also includes selected comparisons derived from the results in Table V.

For all four countries, the incidence rates were adequately described by model A*, and the analysis therefore focused on the period effects and cohort effects estimated from this model. Figure 2 shows relative period effects estimated from the full age*–period–cohort–screening model (model A*). For each country, period effects (= period drift + residual period effects) were measured relative to the period effect in 1973–1977 and Norway was used as a reference for comparison between countries. Norway was chosen as the reference country because the period effects were fairly regular and because no organized screening took place. For Finland, the relative period effects showed a steady increase from 1958 to 1992. The almost linear trend was in accordance with the results in Table V, where the residual period effects were non-significant in both Finland and Norway, and the ratio between the period effects is therefore expected to be approximately linear in this range. The period effects in Denmark and Sweden were very similar to those in Norway until the last five years.

Figure 2 also shows relative cohort effects estimated from the full age*–period–cohort–screening model (model A*). For each country, cohort effects (= cohort drift + residual cohort effects) were measured relative to the cohort effect in the 1918–1927 birth cohort, and Norway was again used as a reference for comparison between countries. For the relative cohort effects, the patterns appear more complex, reflecting the fact that the residual cohort effects were highly statistically significant

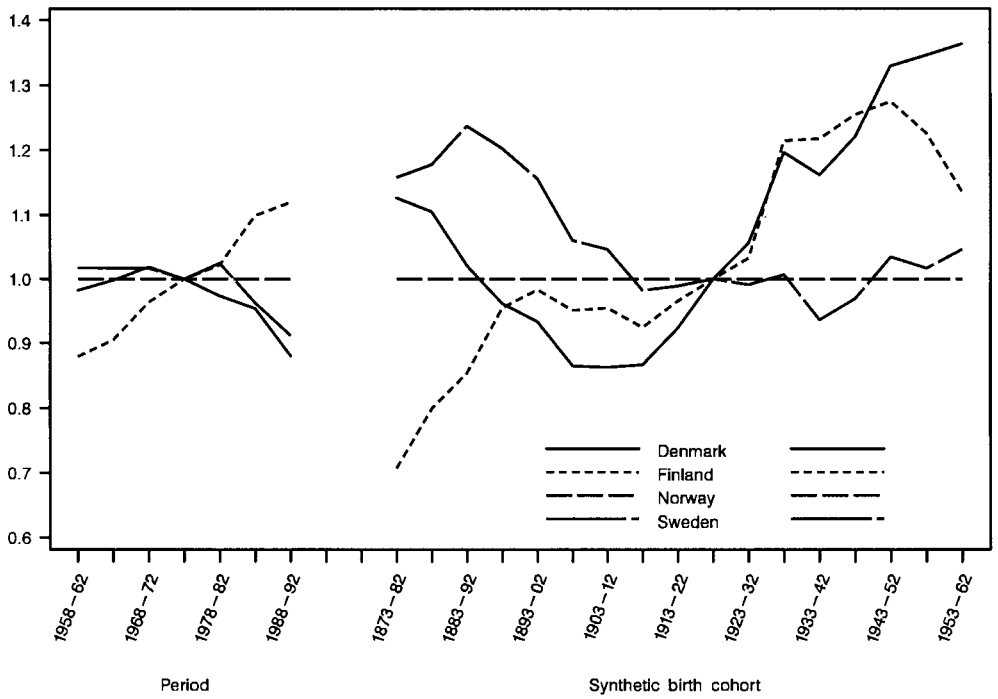

Figure 2. Breast cancer incidence in the Nordic countries 1958–1992. Relative period effect (left) and relative cohort effect (right). Rate ratios of effects relative to Norway. The standard error of the log of the relative period effect is around 0.03 for all periods and countries. The standard error of the log of the relative cohort effects is around 0.03 for the central cohorts, smoothly increasing in both directions to a maximum around 0.13 for the youngest cohorts in all countries.

for all countries. Note that the estimated effects at each end of the graph were based on small numbers. The Finnish cohort effects showed the largest deviations from the Norwegian with a ratio well below 1 for the oldest cohorts and above 1.2 for the youngest cohorts. In Denmark, cohort effects were substantially larger than the Norwegian in the youngest cohorts, but here the overall pattern was U-shaped. The Swedish cohort effects resembled the Norwegian ones for women born in the 20th century. Cohort effects have developed very similarly in Denmark and Finland for cohorts born in the 20th century. Comparing the two halves of Figure 2, it is clear that cohort effects showed a much larger variation between the Nordic countries than period effects.

Inspection of the fitted model B (data not shown) revealed that if the drift in Finland was exclusively a cohort effect, it would imply an almost ten-times increase in the incidence rate from the 1873–1982 cohort to the 1953–1962 cohort, which seems highly implausible. Moreover, inspection of the fitted models A^* and B^* (data not shown) strongly suggested that the period effects also contributed positively to the overall trend in Denmark, Norway and Sweden. The period trends in Denmark, Norway and Sweden were fairly similar until the very last five-year period. The data from Norway showed no residual period effect. Assuming that the Norwegian period effect had no contribution to the linear drift (corresponding to $\alpha = 0.0386$) implied that the rate ratio of the cohort effects in Denmark tripled in the 50 years from the 1898–1907 cohort to

the 1948–1957 cohort. This strongly suggests the presence of a significant positive period drift in these three countries as well.

An important feature of the analyses is the correction for the effects of the organized screening that has taken place in three of the four countries, because we wanted to estimate the age, period and cohort effects undistorted by the effect of systematic screening. The estimates of the screening parameters and their standard errors were 2.58(0.72), 0.91(0.10) and 1.64(0.10), respectively, for Denmark, Finland and Sweden in the A^* model. Owing to its large standard error, the estimate for Denmark could be assumed to be in line with the Swedish result. The low value for Finland is probably due to lower participation than anticipated in the scaling of the covariate.

DISCUSSION

During the last 35 years the incidence of breast cancer has almost doubled in the Nordic countries. We analysed the incidence data using age–period–cohort models while controlling for organized mammography screening and assuming that the age dependency of incidence above the age of 60 was similar in all the Nordic countries. We were then able to compare separately the cohort effects and the period effects between the Nordic countries.

Our analysis showed that the increase in the incidence of breast cancer in all the Nordic countries was most reasonably explained by a combination of period and cohort effects. The period effects were similar in Norway, Sweden and Denmark from 1958 to 1987, but varied in Finland from a level well below that of the other countries in the beginning of the period to a level far above at the end.

The cohort effects showed wide variations between the four countries. However, Norwegian and Swedish women born in the 20th century experienced a fairly similar development. In comparison with Norwegian women, Danish women experienced a peculiar development. The cohort trend was clearly stronger in Norway than in Denmark for women born in the 19th century, but the trends changed then, and the cohort trend for all Danish women born in the 20th century has been much stronger than that for the Norwegian women. Compared with the Norwegian women, almost all women born in Finland in the 20th century have experienced a stronger increase in their breast cancer incidence from one birth cohort to the next.

The period effects reflect changes that affect all ages equally at a given time, and the most likely candidates are therefore changes related to health service and breast cancer detection. In the time period covered by our study, all the Nordic countries had virtually free access to health service [30]. There has, however, been a very significant development in this service over time, for example, in 1966 the number of inhabitants per working physician ranged from 724–887 in Denmark, Norway and Sweden to 1371 in Finland, while in 1989 the same numbers were 332–408 in all countries [31, 32]. This reflects the fast economic growth in Finland in the 20th century. Spontaneous mammography screening is a likely cause for the stronger period effect in Norway in the last 5–10 years compared with Denmark and Sweden. The yearly number of mammograms taken outside organized programmes in Norway increased from 10 000 in 1983 to 220 000 in 1993, most of these among young urban women [33, 34], whereas in Denmark the numbers increased from 37 000 in 1983 to 50 000 in 1993 [19]. It seems conceivable that the observed period effects were health service related.

The cohort effects reflect changes that affect the breast cancer risk in a given birth cohort throughout their lifetime. Such changes could be living conditions in uterus and childhood and

during puberty, adolescence and childbearing. Our analysis indicated that a major part of the Norwegian and Swedish women had been subjected to the same living conditions, but both Danish and Finnish women born in the 20th century had experienced changes in their living conditions, increasing their breast cancer risk much more dramatically than that of Norwegian women.

We found few signs of recent changes in trends. Only the youngest two cohorts in Finland showed a declining trend. Otherwise the trends for cohorts and periods showed no sign of the recent declining trends reported, for example, for the U.S. [29].

Was the modelling technique suitable?

In the search for aetiological leads one would ideally want to be able to quantify period and cohort effects. Many claim to have found genuine solutions to the underlying identifiability problem, but in the real world these achievements are at best dubious, and the logical structure of the problem makes it unlikely that a satisfactory statistical solution will be found [23]. A theoretical solution would be to have the applied constraints based on a truly external data source. It could be based, for example, on a model of carcinogenesis linking the true age dependency of the incidence curve for individuals to some biologically measurable quantity, cell proliferation rate, say, but such a data source is not available.

There is thus no real alternative to age–period–cohort models applying sufficient constraints to ensure identifiability of quantities of interest. The untestable assumptions expressed through these constraints may in the end have a strong influence on the outcome of the analysis [24–27]. In the present study the common choice of putting constraints on the period effects could not be used because both the period and cohort effects were of interest. Instead we assumed a linear age dependency of the log(rate) above the age of 60 with common slopes in the four Nordic countries. The assumption of a partly common age dependency suffices to make the country by cohort and the country by period effects identifiable, while the assumption of linearity with slope α is motivated by convenience. The assumption also permitted the analysis to be performed as a set of separate analyses for each country. The same models could, however, be fitted to the combined data. The logarithm of the relative rate ratios would then reappear as a parameterization of the country by period and country by cohort interactions. The connection between the present approach and the one adopted by Duffy and Latcham [28] would then become clearer. Identifiability of main effects requires stronger assumptions, for example, a specific value for α. It should be remembered, however, that even minor differences in the true slopes could falsify some of our inferences and would cause visible changes in the graphs presented in Figure 2, see Appendix for formulae. We believe the true α's to be around 0.03, because this would ensure that both cohort and period effects overall contributed positively to the rising incidence trend in all the Nordic countries, and ensure a monotone increase in the incidence rate with age. If $\alpha_{\text{Finland}} - \alpha_{\text{Norway}} \approx 0.008$ then the period effects for Norway and Finland would coincide. If $\alpha_{\text{Denmark}} - \alpha_{\text{Sweden}} \approx 0.011$ then the cohort effects for Denmark and Sweden would coincide for women born in the 20th century. Thus the estimated relative rate ratios are only disturbed if α differs considerably from 0.03.

A constraint on the incidence pattern in older age seems to be reasonable from a biological point of view, if the risk of breast cancer is determined mainly by the cell kinetics of a pool of mutated cells built up before menopause [35–37]. This is the case with a Moolgavkar-type model of carcinogenesis, and the shape of the incidence curve by age complies with this model [35, 36]. It seems reasonable to assume the average cell kinetics to be similar across the Nordic populations.

Fitting a more detailed model for Denmark using 1-year age and period groups revealed that the factors based on 5-year groups for period, cohort and ages below 60 were inadequate as predictors, but a linear age slope in old ages was still compatible with the data. The linear slope of the age dependency in old ages might thus be a reasonable 'idealized' incidence pattern for breast cancer. It therefore seems a suitable place to put a one-parameter constraint that makes models comparable and identifiable. This one parameter, α in our case, is what Holford calls an alias parameter [38].

The good fit of our models indicates that the aetiological factors could be simple cohort or period effects. The good fit probably is due to the use of data only for women aged 30–84, thus excluding the young and old with the associated heterogeneity within cells, and to incorporation of the effect of organized screening in the modelling.

Conclusion

The study indicated the period effects to be of importance for the increase in breast cancer incidence in the Nordic countries throughout the past 35 years. The widespread practice of neglecting the period effects in age–period–cohort analysis of time trends in breast cancer incidence in developed countries therefore probably needs to be reconsidered.

A marked difference was found between Finland and the other countries in both the period and the cohort effects, reflecting the fast economic growth in Finland compared with the other countries. However, these differences are less interesting as aetiological leads because potential explanatory variables most likely will be highly correlated and thus hard to disentangle.

A key aetiological lead to be learned from the study is that Danish women born in the 20th century seem to have been exposed to an increasing load of cohort borne breast cancer risk factors not experienced to the same extent by women in Norway, whereas they were seemingly subjected to the same period effects. Future studies should explore the cohort differences between Danish and Norwegian women.

APPENDIX: RELATIVE RATE RATIOS (RELATIVE EFFECTS)

Let the true age parameters for country i be given by $\text{age}_{ai} = \text{age}^*_{ai} + \alpha_i(a - 60)$, that is, let α_i be the true slope of the age curve in old age for country i. Then

$$\log(\text{rate}_{api}) = \text{constant}_i + \text{screening}_{api} + \text{age}^*_{ai} + \Pi_{pi} + K_{ci}$$

that is, Π_p and K_c represent all period and all cohort effects, respectively, in the parameterization where $\alpha_i = 0$. Let RR_{pi} be the true rate ratio of the period effects for period p relative to period p_0 for country i. Then, using the same notation as above

$$\log(\text{RR}_{pi}) = \Pi_{pi} - \alpha_i(p - p_0)$$

From this it is easily seen that the relative rate ratio $\text{RR}_{pi}/\text{RR}_{pj}$ between countries i and j is independent of α_i and α_j provided $\alpha_i = \alpha_j$. We use this as a measure of relative period effects. Similarly for the cohort effects where

$$\log(\text{RR}_{ci}) = K_{ci} + \alpha_i(c - c_0)$$

From these expressions it can be seen that if $\alpha_i \neq \alpha_j$, then the rate ratio of the cohort effect in country i relative to j should be adjusted a factor $\exp(-(\alpha_i - \alpha_j)(c - c_0))$ and the rate ratio of

the period effect in country i relative to j should be adjusted a factor $\exp((\alpha_i - \alpha_j)(p - p_0))$ in Figure 2.

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