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GEOGRAPHIC VARIATIONS OF BREAST CARCINOMA INCIDENCE IN SWEDEN

Are the differences real?

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Abstract

The validity of the reported geographic variations of breast carcinoma incidence in Sweden was assessed by examination of two possible sources of bias: non-notification to the Cancer Registry of diagnosed carcinoma cases and 'biologically benign' breast carcinoma, i.e. with a low disease-specific lethality, e.g. detected accidentally at autopsy. No significant geographic differences in registration deficit were found even though non-notification tended to be slightly higher for old patients in low-incidence areas. Autopsy cases were estimated to account for less than one per cent of all cases and tended to be more frequent in high-incidence areas but the regional differences were generally small and not significant. An analysis of the relationship between 10-year relative survival and age-standardized incidence in 27 different regions revealed no significant correlation, whereas there was a significant positive correlation between age-standardized incidence and mortality. These findings indicate that non-lethal breast carcinoma cases do not explain the variations of incidence. In conclusion, no evidence was found suggesting that the geographic differences were artifactual. Registration deficit and autopsy cases, however, may have slightly increased the variations among elderly women.

Key words: Breast neoplasms; carcinoma, epidemiology, geographic variations.

In Sweden (pop. 8.3 million) breast carcinoma incidence rates vary between different regions to an extent which makes it unlikely that the variation is caused by chance alone (5, 9). The reported incidence in major urban areas is about 60 per cent higher than in low-risk areas which are mainly rural and located in the north and northwest (Fig. 1). Increased risks for women in high-incidence areas are found at all ages above 40 years (Fig. 2).

It might be questioned if regional differences in diet, reproductive behaviour or other life-style factors believed to be of etiologic significance, are great enough in Sweden to explain the reported variations of incidence. An alternative hypothesis is that the variations are artifactual, e.g. due to non-notification of diagnosed carcinoma cases in 'low-risk' regions or variations in diagnostic practices. The purpose of this paper was to investigate this alternative hypotheses.

In order to study the geographic pattern of non-notification of breast carcinoma to the Swedish Cancer Registry, we identified patients who died during 1978 with breast carcinoma mentioned on their death certificate, but who had previously not been reported to the Cancer Registry. Variations in diagnostic practices were assessed by an analysis of the relationship between incidence and survival and between incidence and mortality in different regions. It has been suggested that some breast carcinomas are 'biologically benign', i.e. even though they fulfil all histologic criteria of malignancy, they will not lead to serious consequences and early death within the patient's remaining life-time (3, 6). Some tumours of this type may be found accidentally at autopsy, but they may also be diagnosed clinically. The tumour may have a low growth rate and lack metastatic potential, and the patient may be old and thus have a limited life expectancy when the tumour becomes clinically detectable. Increased diagnostic efforts in 'high-risk' areas may have led to an increased diagnosis of such lesions and hence to an upward bias in the reported incidence. In such a case, a positive correlation is expected between incidence and survival, because the average disease-specific lethality should be lower in 'high-incidence' areas. Furthermore, according to this hypothesis, the age-standardized breast carcinoma mortality

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should show less geographic variation than the age-standardized incidence. This part of the investigation was supplemented with data on the geographic pattern of cases detected accidentally at autopsy.

Material and Methods

Completeness of registration. Data for 1978 were obtained from the Swedish Cancer Registry and Cause-of-Death Registry. Both registers cover the total population of Sweden and the coding is done according to internationally accepted rules (10, 12). A ten-digit identification number unique to all persons living in Sweden is used for identification of each recorded case. This number permits computerized record linkage of the 2 registers which is performed annually. The matching for 1978 identified a total of 1013 cancer cases diagnosed during 1958 through 1978, who were recorded with malignant disease in the Cause-of-Death Registry, but who had incorrectly not been reported to the Cancer Registry. This material was previously used by MATTSSON & WALLGREN (8) in a survey of the completeness of the Cancer Registry on a national scale and is described in more detail in their report. Of the mentioned 1013 cases, 35 were females with a death certificate diagnosis of breast carcinoma.

In the Cancer Registry files there were 1726 female breast carcinoma cases who died in 1978 with breast carcinoma mentioned on the death certificate. These patients were used as a control group in the analysis as they fulfilled the same criteria as the study group of non-notified cases, i.e. the same year of death, and breast cancer mentioned as underlying or contributory cause of death. The percentage deficit in the Cancer Registry was computed from the sum of already registered females who died of breast carcinoma in 1978, and the potentially registrable cases indicated by the death certificates.

The deficit was calculated for each of the 24 administrative districts of Sweden and for the 3 major urban areas of Stockholm, Gothenburg, and Malmö. However, due to small numbers these 27 regions were grouped according to age-standardized incidence for 1966–1973 (≥115%, 105–114%, 95–104%, 85–94% and ≤84% of national average, see Fig. 1) and a summary deficit was calculated for all regions in each of these 5 incidence categories.

Diagnostic practices. If geographic variations in incidence were due to more intense diagnostic efforts in high-incidence areas, the average disease-specific lethality would be lower in areas with high incidence than in those with low incidence, whereas the reported breast cancer mortality would show relatively little geographic variation.

To study this hypothesis, relative survival rates were calculated for cases diagnosed in each of the mentioned 27 regions during 1969–1973. The total number of reported female breast carcinoma cases during this period was

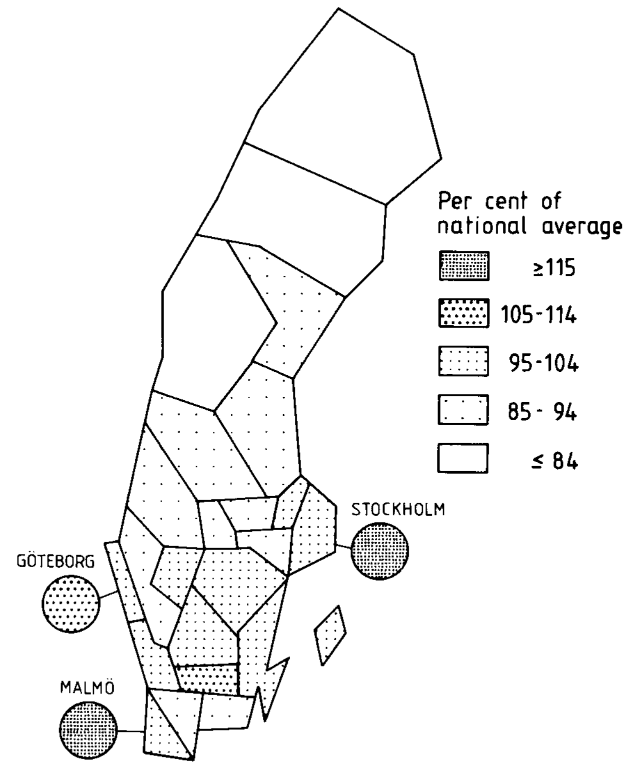

Fig. 1. Age-standardized incidence 1966–1973 of female breast carcinoma in the 24 administrative districts of Sweden. The incidence in the major urban areas of Stockholm, Gothenburg and Malmö is shown separately as indicated by the three rings. The incidence in each region is expressed in per cent of the national average. Age-standardization was performed with the direct method using the 1970 Swedish female census population as reference. (Source: The Swedish Cancer Registry.)

17698, 59 (0.3%) of which had to be excluded due to lack of complete identification number. The average number of cases in the regions was thus 653 with a range of 121 to 2416. Cases diagnosed before 1969 were not included because expected survival rates could not be computed due to lack of relevant age-specific death rates.

The relative survival is the ratio between the observed survival from all causes of death, and the expected survival of an age-matched general population (4). Follow-up data were obtained from the Cause-of-Death Registry. Data on deaths before December 31, 1981, were available. The observed survival was calculated with the life-table method. The expected survival was derived from age-specific death rates for each region which have been published for the periods 1969–1973 and 1974–1978 but not before 1969 (11). The standard error of the relative survival was calculated according to EDERER et coll. (4).

To assess a possible correlation between incidence and lethality the 10-year relative survival rates for cases in the 27 regions were compared with the age-standardized incidence rates for 1966–1973 (Fig. 1) and a conventional correlation coefficient was calculated. The relationship

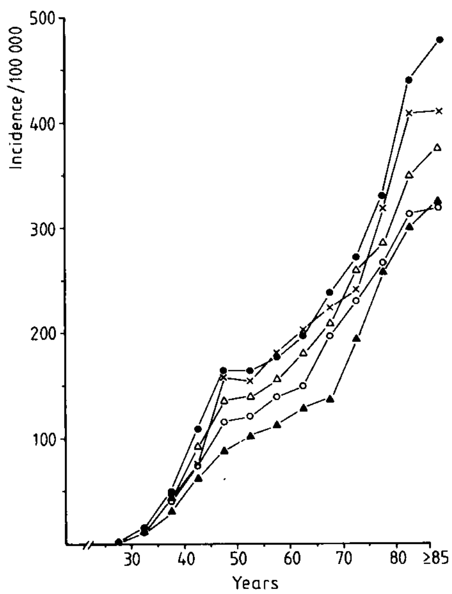

Fig. 2. Mean annual age-specific incidence 1966–1973 of female breast carcinoma in 27 Swedish regions grouped according to level of age-standardized incidence for the same period (Fig. 1). Percentages: ≥115 (●), 105–114 (×), 95–104 (△), 85–94 (○), ≤84 (▲). (Source: The Swedish Cancer Registry.)

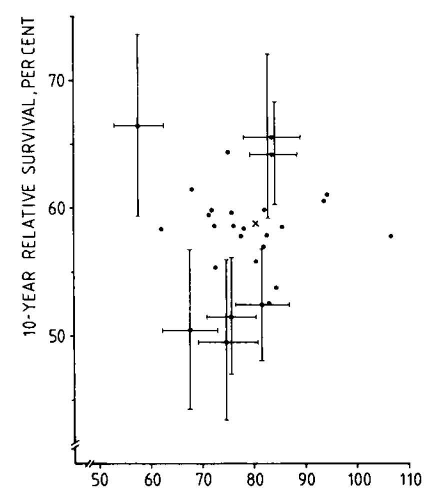

Fig. 3. The relationship between 10-year relative survival for breast carcinoma cases 1969–1973, and the mean annual age-standardized incidence 1966–1973 in 27 Swedish regions. The 95% confidence limits are indicated for those 3 regions with a 10-year relative survival which was significantly ($p < 0.05$) higher than the national average and for those 4 regions for which it was significantly lower. The × indicates national average.

between age-specific incidence and corresponding relative survival was also analysed by age (0–44 years, 45–54 years, 55–74 years and >74 years). Furthermore, the age-standardized incidence rates for 1966–1973 were compared with the age-standardized breast carcinoma mortality rates for 1974–1978.

Cases diagnosed accidentally at autopsy. An increased proportion of non-lethal tumours would not lead to a decreased average lethality if they were diagnosed first at autopsy. Such cases, which by definition have identical date of diagnosis and date of death, would instead tend to *increase* the average lethality as measured by the relative survival. The investigation was therefore supplemented with data on regional variations of such tumours. The Cancer Registry routinely records if a tumour was accidentally found at autopsy, but this information may have been inconsistently entered in the Registry files during the studied period and the completeness of registration may have varied from one region to another (B. Mattsson, personal communication). Due to the probably limited number of autopsy cases, even a small deficit may introduce a major bias in the estimated frequency of such cases. Therefore, instead of using the information in the registry files, we estimated the number of autopsy cases by selecting patients reported during 1969–1973 with identical date of diagnosis and date of death and for whom the underlying cause of death was not breast cancer. Due to small numbers, this estimate was calculated for the 27 regions grouped into 5 categories according to age-standardized incidence rate for 1966–1973.

Results

Table 1 shows the registration deficit by age in the 27 regions grouped according to level of age-standardized incidence 1966–1973. Among cases aged below 75 years at death, the deficit was only 0.6 per cent and it was similar in both high- and low-incidence areas. Among the older cases, the deficit was slightly lower in areas with an age-standardized incidence >104 per cent of national average (4.0%) than in areas with an incidence <95 per cent of average (8.1%) but this difference was not significant ($p > 0.05$, chi-squared test). The overall deficit was 2.0 per cent and was not significantly different in the two mentioned incidence categories, 1.5 and 2.7 per cent, respectively.

The estimated number of cases diagnosed accidentally at autopsy during 1969–1973 by age is given in Table 2. As in Table 1, the 27 regions are grouped according to reported incidence level. The estimated overall percentage of autopsy cases was 0.8. The percentage was significantly lower among cases aged below 75 years than among older cases (0.2; 3.3; $p<0.05$). There was a trend towards fewer autopsy cases in low incidence areas: such cases were estimated to 1.5 per cent in areas with incidence >104 per cent of national average as compared with 0.6 per cent in areas with incidence <95 per cent of average. This slight difference was not significant. The trend was apparent in both age-groups (≤74 years, >74 years) but was significant in neither.

Fig. 3 shows the relationship between the 10-year relative survival for cases diagnosed 1969–1973 and the age-

Table 1

Cancer register deficit of breast carcinoma cases who died in 1978 by age at death in 27 Swedish regions grouped according to level of age-standardized incidence 1966–1973 (Fig. 1)

Age-standardized incidence in per cent of national average (1966–1973)	Registered			Non-notified			Cancer register deficit (per cent)		
	≤74 years	>74 years	All ages	≤74 years	>74 years	All ages	≤74 years	>74 years	All ages
≥115	207	92	299	1	0	1	0.5 } 0.6	0 } 4.0	0.3 } 1.5
105–114	120	29	149	1	5	6	0.8 }	15.0 }	3.9 }
95–104	454	167	621	3	7	10	0.7	4.0	1.6
85–94	428	140	568	1	15	16	0.2 } 0.6	9.7 } 8.1	2.7 } 2.7
≤84	58	31	89	2	0	2	3.3 }	0 }	2.2 }
All regions	1 267	459	1 726	8	27	35	0.6	5.6	2.0

Table 2

Estimated frequency of breast carcinoma cases diagnosed accidentally at autopsy during 1969–1973 by age at diagnosis in 27 Swedish regions grouped according to level of age-standardized incidence 1966–1973 (Fig. 1)

Age-standardized incidence in per cent of national average (1966–1973)	Estimated frequency of cases detected first at autopsy 1969–1973 (%)		
	≤74 years	>74 years	All ages
≥115	13/2 445 (0.5)	40/757 (5.3)	53/3 202 (1.7)
105–114	4/1 181 (0.3)	13/343 (3.8)	17/1 524 (1.1)
95–104	9/5 567 (0.2)	31/833 (3.7)	40/6 400 (0.6)
85–94	9/4 338 (0.2)	23/1 193 (1.9)	32/5 531 (0.6)
≤84	0/760 (0)	4/222 (1.8)	4/982 (0.4)
All regions	35/14 291 (0.2)	111/3 348 (3.3)	146/17 639 (0.8)

standardized incidence 1966–1973 in each of the 27 regions. There was a considerable variation in relative survival, it ranged from 49±3 per cent (standard error) to 66±4 per cent with a national average of 59±1 per cent. There was no apparent positive correlation, however, between survival and incidence ($r = -0.05$, $p > 0.05$). The region with the lowest incidence (district of Norrbotten, 57/100 000) actually showed the highest 10-year relative survival (66±4%) and the region with the highest incidence (city of Malmö, 107/100 000) had a relative survival which was slightly lower (58±5%) than the national average. Fig. 4 shows the relationship between survival and incidence by age at diagnosis. Here too, there were considerable variations in both survival and incidence but there appeared to be no correlation.

The relationship between the age-standardized breast cancer mortality 1974–1978 and the age-standardized incidence 1966–1973 in the 27 regions is shown in Fig. 5. In order to illustrate the magnitude of variation, both the mortality and the incidence rates are expressed as percentages of the national averages. There was a considerable variation in mortality, it ranged from 71 to 146 per cent of average, i.e. the magnitude of variation was similar to that for incidence (which ranged from 71 to 132% of average). Furthermore, incidence and mortality showed a significant postive correlation ($r = 0.57$, $p < 0.01$).

Discussion

We did not find any significant regional differences in breast carcinoma registration deficit even though non-notification tended to be slightly higher in low-incidence regions among cases aged above 74 years (Table 1). This result should be viewed in relation to the fairly large variations of the reported incidence. As mentioned earlier, for women in high-incidence areas increased risks are reported at all ages above 40 years (Fig. 2). During 1966–1973, in areas with an age-standardized incidence ≥115 per cent of the national average, the age-specific risks in the interval 40–74 years were about 40 per cent higher than in areas with an age-standardized incidence ≤84 per cent of national average. For women aged above 74 years, the risk was about 30 per cent higher.

Due to methodologic reasons, the analysis of registration deficit was based on deceased cases with breast carcinoma mentioned on their death certificate. It might

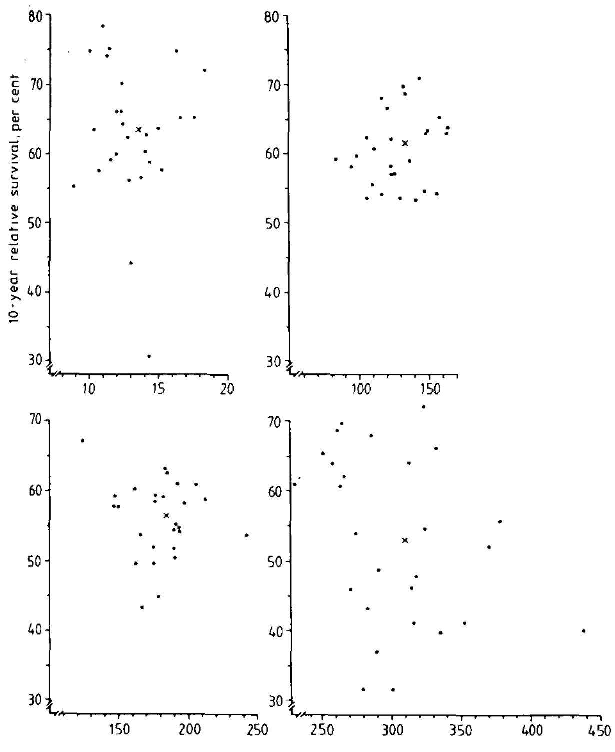

Fig. 4. The relationship between 10-year relative survival for breast carcinoma cases 1969–1973 by age, and the corresponding mean annual age-specific incidence 1966–1973 in 27 Swedish regions. The × indicates national average. Top left: 0–44 years. Top right: 45–54 years. Bottom left: 55–74 years. Bottom right: >74 years.

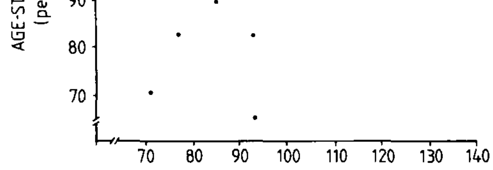

Fig. 5. The relationship between the age-standardized breast carcinoma mortality 1974–1978 and the age-standardized incidence 1966–1973 in 27 Swedish regions. Both measures are expressed as percentages of the national averages.

therefore be argued that the results are not relevant for all breast carcinoma cases. It has been suggested that non-notification is less frequent among those with recurrent disease than among 'non-lethal' cases (2). However, this hypothesis does not seem to hold good for cancer registration in Sweden. In a survey of non-notification in the district of Stockholm (pop. 1.5 million), the registration deficit was found to be similar both for 'lethal' and 'non-lethal' cases (7). We therefore conclude that regional differences in cancer registration cannot explain the reported variations of breast cancer incidence. Nor could the variations be explained by autopsy cases (Table 2) which were estimated to account for less than one per cent of all cases. There was a trend towards fewer autopsy cases in the low-incidence areas, especially among women aged above 74 years, but the differences were generally small and not significant. It should be noted, however, that for the age group >74 years, this trend coincided with the mentioned trend towards slightly higher frequency of non-notification in low-incidence areas. These factors may thus have accentuated the geographic incidence variations among old women.

The analysis of relative survival in the 27 regions showed a fairly large variation of the 10-year rate which ranged from 49 to 66 per cent (Fig. 3). The average disease specific lethality (the complement of the relative survival) was thus 51 per cent higher in the region with the lowest survival as compared with that with the highest. This variation did not, however, correlate with incidence. Furthermore, there *was* a significant positive correlation between incidence and mortality. These findings contradict the hypothesis that the variations of incidence are caused by non-lethal tumours.

The results presented do not all relate to cases diagnosed during the same period. Relative survival rates and autopsy cases, for instance, were estimated for cases diagnosed 1969–1973, whereas the registration deficit was analysed for cases who died in 1978. However, major bias due to this circumstance seems unlikely because the regional variations of incidence have remained fairly stable since the late 1950's. During 1959–1980 the age-standardized breast carcinoma incidence increased in all administrative districts and the rate of increase was similar in both high- and low-incidence areas (5, 9).

One possible explanation to the observed *survival* variation is differences in diagnostic practices with, on the average, earlier diagnosis in regions with high survival. However, the reasons for such diagnostic differences are unclear and merit further investigation. In this context it should be noted that large-scale screening programmes with mammography were not introduced in Sweden until the late 1970's and such can therefore not explain the observed survival pattern.

In conclusion, our results suggest that the reported variations of incidence are real even though registration deficit and autopsy cases may have contributed to the differences among older women. Factors which may have etiologic implications for breast cancer include dietary habits and reproductive behaviour (1, 3). An analysis of regional variations of such factors in Sweden thus seems worthwhile.

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