Comparison of breast carcinomas diagnosed in the 1980s with those diagnosed in the 1940s to 1960s

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Abstract

Objective—To find out if breast carcinomas diagnosed in the 1980s differ from those diagnosed a few decades ago.

Design—Retrospective comparative cohort study.

Setting—City of Turku, south western Finland.

Patients—439 patients with breast carcinoma diagnosed in 1945-65 with a median follow up of 27 years (95% of all those histologically diagnosed in Turku); and 370 patients with breast carcinoma diagnosed in 1980-4 with a median follow up of 6 years (94% of all those histologically diagnosed in Turku).

Main outcome measures—Breast cancer incidence, mortality from breast cancer, age at diagnosis, stage of cancer, seven histological factors, DNA ploidy.

Results—Age adjusted incidence of breast cancer increased from 30.8/100 000 person years in 1953-7 to 62.2/100 000 in 1983-7; mortality in breast cancer increased from 16.7 to 17.2/100 000 person years. Survival of patients with stages II to IV (but not with stage I) improved. The mean age at diagnosis increased from 55.5 years in 1945-55 to 62.5 years in 1980-4 ($p<0.0001$); the proportion of patients with T0-1 carcinomas increased from 13% to 41% ($p<0.0001$) and with pN0 carcinomas from 43% to 55% ($p=0.003$) from 1945-65 to 1980-4. There was no change in histological type or DNA ploidy of breast cancer, but in the 1980-4 cohort carcinomas were more often well differentiated, had lower mitotic counts and less nuclear pleomorphism, more often had a well defined tumour margin, and had less tumour necrosis. There was, however, no difference between the two cohorts in these histological characteristics except for tumour necrosis when they were compared in a multivariate log linear model at a given size of primary tumour.

Conclusion—Improved survival with breast cancer can at least partially be explained by detection of increased numbers of small carcinomas with favourable histological characteristics.

Introduction

The incidence of breast cancer is increasing in all countries with available statistics.^{1,2} Despite this increasing incidence mortality from breast cancer has remained stable or increased only slightly.^{2,3} Improved survival rates may be explained by earlier detection of breast cancer and improved treatment results, but less aggressive biological behaviour of breast cancer has not been ruled out as an alternative or additional factor.⁴

We compared clinical presentation, histology, and DNA ploidy in two cohorts of women with breast cancer and with different follow up time to find out trends in these prognostic factors.

Patients and methods

PATIENTS

From 1945 to 1965, 461 women (of 48 000 in 1945 and 75 000 in 1965) in the city of Turku in south western Finland were histologically diagnosed as having breast cancer. The patients' names were collected from the files of the department of pathology, University of Turku; the Turku University Central Hospital; the City Hospital of Turku; and the Finnish Cancer Registry, which was founded in 1952. Twenty two patients were treated outside Turku, were lost from follow up, or had insufficient clinicopathological data, leaving 439 patients (95%) in this series, which has been described in greater detail elsewhere.^{5,6} The median follow up time was 27 (range 22-42) years.

In 1980-4, according to data from the Finnish Cancer Registry, 404 women (of 87 000 in Turku) were diagnosed as having breast cancer. Histological review showed that nine had either benign tumours or some other type of cancer than breast carcinoma. In two no biopsy sample had been taken and in one the sample was taken at necropsy; in 22 either an adequate histological sample or clinical data were lacking. This left 370 patients for analysis, which is 94% of all those in the area histologically diagnosed as having breast cancer. The median follow up was 6 (4-9) years. The hospital records and necropsy details were reviewed, and follow up information was available for all 809 patients in the study.

Clinical staging was done according to the International Union against Cancer's TNM classification.⁷ Patients aged more than 49 at diagnosis were considered to be postmenopausal. In 1945-65 and 1980-4, respectively, 245 (56%) and 186 (50%) patients had radical mastectomy, 94 (21%) and 140 (38%) had mastectomy and axillary evacuation, 72 (16%) and 39 (11%) had a mastectomy, 23 (5%) and 2 (1%) had a partial mastectomy, and 5 (1%) and 2 (1%) had a biopsy. Postoperative orthovoltage radiotherapy was given to 305 (69%) patients in 1945-65 and megavoltage therapy to 198 (54%) in 1980-4. Adjuvant therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) was given to 10 (3%) patients and adjuvant tamoxifen to 29 (8%) in 1980-4.

HISTOLOGY

New haematoxylin-eosin and van Gieson stained slides were prepared from each tissue block and the original slides were reviewed. The histological typing and grading were done, slightly modifying the WHO classification,⁸ by one pathologist (ST), and the tumours were classified into four types: infiltrating ductal carcinoma not otherwise specified (including apocrine, mixed mucinous, and atypical medullary types); infiltrating lobular carcinoma with variants; other special types (including tubular, medullary, cribriform, papillary, metaplastic, and pure mucinous carcinomas); and intraductal carcinoma. Other histo-

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pathological features were evaluated semiquantitatively as described in detail earlier^{5,6} and shown in table I.

ANALYSIS OF DNA

Processing of tissue embedded in paraffin, DNA staining, flow cytometry, and histogram classification into diploid and non-diploid types were done as described earlier.^{6,9} The mean coefficient of variation of diploid peaks was 7.6% (SD 2.0%) in the 1945-65 series and 6.0% (1.2%) in the 1980-4 series. Ploidy was not determined in 55 cases (13%) in the 1945-65 series and in 34 cases (9%) in the 1980-4 series because of lack of tissue, poor quality of DNA histogram, or uncertainty in histogram classification.

STATISTICS

Frequency tables were analysed with the χ^2 test. The χ^2 test for trend was used for ordinal variables. Comparison of age distributions was done with the Mann-Whitney U test. Cumulative survival was estimated with the product limit method, and comparison of cumulative survival between groups was performed with the log rank test. Interactions between the cohorts and the various histological characteristics when adjusted to primary tumour size were analysed with a log linear model.¹⁰ Survival corrected for intercurrent deaths was used in statistical calculations, and women

TABLE I—Comparison of survival corrected for intercurrent deaths by year of diagnosis

	Diagnosed 1945-65		Diagnosed 1980-4		p Value
	No	No (%) survived for 5 years	No	No (%) survived for 5 years	
Age at diagnosis:					
≤49	152	91 (60)	74	54 (73)	0.008
>49	287	152 (53)	296	228 (77)	<0.0001
Primary tumour size:*					
pT1 (≤2 cm)	56	52 (93)	149	133 (89)	0.43
pT2 (2-5 cm)	244	151 (62)	160	114 (71)	0.03
pT3 (>5 cm)	73	19 (26)	19	9 (47)	0.10
pT4	58	11 (19)	35	18 (51)	0.001
Axillary nodal state:†					
pN0	147	125 (85)	177	163 (92)	0.09
pN1-3	192	58 (30)	144	82 (57)	<0.0001
Presence of distant metastases at diagnosis:‡					
M0	408	318 (78)	345	321 (93)	<0.0001
M1	31	2 (6)	22	12 (55)	0.02
Stage:†					
I	41	40 (98)	96	94 (98)	0.68
II	194	120 (62)	168	128 (76)	0.001
III	81	20 (25)	41	20 (49)	0.02
IV‡	18	1 (6)	13	8 (62)	0.001
Histological grade:					
1	111	101 (91)	126	122 (97)	0.004
2	173	99 (57)	142	101 (71)	0.005
3	155	43 (28)	102	58 (57)	<0.0001

*Not known in two cases; intraductal cancers (eight in 1945-65 and five in 1980-4) are not shown.

†Given only for patients who had axillary nodal evacuation.

‡Two year survival figures; data missing in three cases.

TABLE II—Comparison of clinicopathological factors of women with breast carcinoma by year of diagnosis. Figures are numbers (percentages) unless otherwise stated

	Diagnosed 1945-65	Diagnosed 1980-4	p Value
Age at diagnosis (years):			
Mean (95% CI)	55.5 (54.4 to 56.6)	62.5 (61.1 to 64.0)	<0.0001
Median (range)	55.0 (28-89)	64.0 (29-97)	
Percentage >49	65	80	<0.0001
Size of primary tumour:			
pT1 (≤2 cm)	56 (13)	149 (41)	
pT2 (2-5 cm)	244 (57)	160 (44)	
pT3 (>5 cm)	73 (17)	19 (5)	
pT4	58 (14)	35 (10)	<0.0001
Axillary nodal status:*			
pN0	147 (43)	177 (55)	
pN1-3	192 (57)	144 (45)	0.003
Presence of distant metastases at diagnosis:			
M0	408 (93)	345 (94)	
M1	31 (7)	22 (6)	0.54
Stage:*			
I	41 (12)	96 (30)	
II	194 (58)	168 (53)	
III	81 (24)	41 (13)	
IV	18 (5)	13 (4)	<0.0001

*Given only for patients who had axillary nodal evacuation.

FIG 1—Age adjusted incidence of breast cancer and mortality from breast cancer in Finland. Data supplied by Finnish Cancer Registry

FIG 2—Survival corrected for intercurrent deaths of patients diagnosed with breast cancer 1945-65 (---; 370 patients) and 1980-4 (—; 436 patients). Numbers of patients at risk given in parentheses; bars are 95% confidence intervals

who died from other causes than breast cancer were withdrawn from the analysis at the date of death. Women who died with disseminated breast cancer based on clinical or necropsy evidence were considered to have died from breast cancer. All p values are two tailed. Statistical analyses were done with the biomedical data program (BMDP statistical software, department of biomathematics, University of California, Los Angeles, California).

The breast cancer rates shown in figure 1 are average annual rates per 100 000 women with the Finnish female population at risk in the period as denominator, age standardised to the world population by the direct method.¹¹

Results

INCIDENCE AND MORTALITY

The age adjusted incidence of breast cancer in Finnish women is available from the Finnish Cancer Registry from 1953 onwards. The incidence increased from 30.8 to 62.2 per 100 000 person years as calculated in each five year period from 1953-7 to 1983-7 whereas mortality from breast cancer remained almost stable, 16.7 and 17.2 per 100 000 person years in 1953-7 to 1983-7 (fig 1).

The five year survival corrected for intercurrent deaths improved 21% (95% confidence interval 12% to 30%) from 55% in 1945-65 to 76% in 1980-4 ($p<0.0001$; fig 2). Survival improved in premenopausal and postmenopausal patients; in pT2, pT4, pN+, M0, and M1 carcinomas; in stages II, III, and IV; and in all histological grades but not in pT1 or pN0 carcinomas nor in stage I carcinomas (table I).

CLINICOPATHOLOGICAL FACTORS AND DNA CONTENT

The mean age at diagnosis was 55.5 years in 1945-65 and 62.5 years in 1980-4 ($p<0.0001$, table II). The

FIG 3—Age at diagnosis by year of diagnosis of breast cancer

proportion of postmenopausal patients increased from 65% to 80%. Figure 3 shows age distributions at the time of the diagnosis.

Carcinomas classified as pT1 increased from 13% to 41% ($p<0.0001$) and those classified as pN0 from 43% to 55% ($p=0.003$), but there was no change in the frequency of M1 cancer (table II). Compared with pT2-4 cancers, pT1 cancers were more often well differentiated (grade 1 49% v 23%, grade 2 34% v 40%, grade 3 17% v 37%; $p<0.0001$) and had lower mitotic counts in a high power field (rare 63% v 37%, 2-3 24% v 35%, >3 13% v 28%; $p<0.0001$) and less tumour necrosis (none 82% v 62%; spotty, moderate, or severe 18% v 38%, respectively; $p<0.0001$). Distribution by histological type or DNA ploidy of carcinomas did not differ between the two cohorts, but cancers found in 1980-4 were more often well differentiated, had lower mitotic counts and less nuclear pleomorphism, more commonly had a well defined tumour margin, and had less tumour necrosis (table III).

Comparison of histological factors between the two cohorts at a given level of primary tumour size (pT1-pT4) by a multivariate log linear analysis model showed a significant association with cohort only for tumour necrosis ($p=0.01$). Spotty or more severe tumour necrosis was more often present in pT4 tumours diagnosed in 1945-65 than in 1980-4 (59% v 34%).

Discussion

Little information is available on how breast carcinomas diagnosed a few decades ago differ from those seen today, yet such information is of importance when evaluating the results of treatment for breast cancer. Although the incidence of breast cancer more than doubled from the 1950s to the 1980s, mortality from breast cancer changed little (fig 1). Plausible explanations for such a large improvement in survival are major advances in treatment, an increase in the mean age of the patients together with a higher survival rate in the elderly, a change in the biological behaviour of breast cancer, improved early detection of cancer, or a combination of these factors.

Improved prognosis of pT2-4, pN+, and M1 carcinomas suggests advances in treatment, but improved surgical or oncological treatment alone is unlikely to explain the greatly improved survival rates. Surgical techniques were no more radical in the 1980s than in 1945-65, postmastectomy radiotherapy does not seem to have a major effect on survival,¹² and adjuvant chemotherapy and tamoxifen improve survival rates only slightly¹³ and were given to only a few patients. The increase of five year survival from 6% to 55% in M1 cancer is impressive, but patients with disseminated breast cancer still have a median survival of only about 18 months and ultimately die from the

disease,¹⁴ and distant metastases may have been detected at an earlier stage of the disease in the 1980s than in 1945-65.

The increase in the number of postmenopausal patients is also unlikely to explain the improved survival figures because there was no difference in survival corrected for intercurrent causes between premenopausal and postmenopausal patients in the present series ($p=0.56$) and no other significant cut off level for age at the time of the diagnosis could be found.

There was little difference in histological factors or DNA ploidy between the two cohorts after adjustment to the size of the primary tumour. However, the frequency of pT1 cancers increased greatly (from 13% to 41%), and we found that pT1 cancers were more often well differentiated and had lower mitotic counts and less tumour necrosis than pT2-4 carcinomas. pT1 cancers were associated with a 90% five year survival rate. Hence early detection of small cancers with favourable histological features seems to be a major factor contributing to the improved survival rate in the 1980s.

Postmortem studies have shown that a considerable proportion of women in the general population may have in situ carcinoma of the breast and a few may even have undiagnosed invasive cancer.¹⁵ It is probable that in conditions where doctors are few and women are not aware of the symptoms and signs of breast cancer the carcinomas are larger when found, and some of the less aggressive ones may remain undiagnosed. A total of 54 cancers (15%) diagnosed in 1980-4 were incidental findings made by physicians and nurses. In addition, 42 (11%) cancers were found in conjunction with screening for cervical cancer when the breasts were investigated by palpation. It is not known how many of the cancers diagnosed in 1945-65 were found incidentally.

The minimum follow up time of the women in the 1945-65 cohort was 22 years, and in this cohort 72% of all breast cancer deaths took place within five years of the diagnosis.⁵ The five year survival rate corrected for intercurrent deaths in the 1980-4 cohort was 76%, and if mortality from breast cancer after the first five years of follow up is as low in the 1980-4 cohort as in the

TABLE III—Comparison of histological factors and DNA ploidy of breast carcinoma by year of diagnosis. Figures are numbers (percentages) of biopsy samples

	Diagnosed in 1945-65 (n=370)	Diagnosed in 1980-4 (n=439)	p Value
Tumour necrosis:			
None	269 (61)	277 (75)	<0.0001
Spotty, moderate, or severe	170 (39)	93 (25)	
Mitotic count in high power field:			
Rare	166 (38)	183 (49)	0.001
2-3	155 (35)	111 (30)	
>3	118 (27)	76 (21)	
Histological grade:			
1	111 (25)	126 (34)	0.003
2	173 (39)	142 (38)	
3	155 (35)	102 (28)	
Tumour margin circumscription:			
Definite	63 (14)	72 (19)	0.02
Questionable	114 (26)	106 (29)	
None	262 (60)	192 (52)	
Nuclear pleomorphism:			
Slight	73 (17)	86 (23)	0.03
Moderate	253 (58)	202 (55)	
Severe	113 (26)	82 (22)	
Tubule formation:			
Extensive	15 (3)	9 (2)	0.38
Moderate	118 (27)	119 (32)	
Slight/none	306 (70)	242 (65)	
DNA ploidy:			
Diploid*	123 (32)	115 (34)	0.53
Non-diploid	261 (68)	221 (66)	
Histological type:			
Ductal invasive	313 (71)	254 (69)	0.55
Lobular	65 (15)	61 (16)	
Other special types	46 (10)	43 (12)	
Intraductal cancer	15 (3)	12 (3)	

*Includes DNA histograms with a "shoulder" in the G0/G1 peak.

1945-65 cohort then most of the women in the 1980-4 cohort will die from causes other than breast cancer.

We conclude that breast carcinomas diagnosed in the 1980s have a smaller primary tumour size, fewer axillary metastases, and more favourable histological features and are associated with better prognosis than cancers diagnosed a few decades ago. Improved survival with breast cancer can at least partially be explained by detection of increased numbers of small carcinomas with favourable histological characteristics.

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Insulin dependent diabetes in childhood and material deprivation in northern England, 1977-86

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Abstract

Objective—To determine the incidence of insulin dependent diabetes in the Northern region of England in children less than 16 years old in the period 1977 to 1986 and to relate the incidence data to an index of deprivation.

Design—Retrospective analysis of hospital case records identified from the regional health authority's computer; validation of the primary source with hospital clinic registers and community paediatric registers.

Setting—Northern region, excluding South Cumbria District Health Authority (659 300 children under 16 in 1981).

Patients—All children diagnosed with insulin dependent diabetes before the age of 16 and resident in the region at time of diagnosis.

Main outcome measures—Incidence rates for the 10 year period and analysis of incidence rates within categories of deprivation.

Results—919 incident cases were identified. The validation procedure covered 54% of all cases identified and gave 95% completeness of ascertainment. The average annual incidence over the 10 year period was 14.8/100 000 for girls and 13.4/100 000 for boys. The annual incidence for the most and least deprived areas of the region was 18.7/100 000 (95% confidence interval 16.2 to 21.5) for boys and 7/100 000 (5.6 to 8.8) for girls. There was a highly significant trend ($p < 0.001$) of decreasing incidence with decreasing level of deprivation.

Conclusions—In the north of England the incidence of childhood diabetes is related to material deprivation.

Introduction

Evidence for the role of environmental factors in the aetiology of insulin dependent diabetes¹ has stimulated interest in epidemiological studies of the disease, and these have shown variations in incidence between

countries and over time.^{2,3} If environmental factors are of aetiological significance an analysis of incidence and a measure of socioeconomic category could be relevant. Previous studies have not found the incidence of diabetes to be significantly related to socioeconomic status^{4,5} or social class,⁶ but these studies can be criticised because of the proxy used for social status. We analysed incidence data with respect to a composite index of material deprivation that has been shown to vary significantly with an index of health state in the Northern region.⁷

Patients and methods

The Northern region covers a population of 3.1 million and is well contained with respect to medical services. Because of poor reporting rates South Cumbria District Health Authority was excluded from the present analysis.

Patients diagnosed with diabetes and treated with insulin before their 16th birthday and resident within the region at the time of diagnosis were eligible for inclusion. Patients in whom diabetes was associated with other disease states were excluded.

It was assumed that all individuals fulfilling the inclusion criteria would have been admitted to hospital at initial diagnosis of their disease. A regional health authority computer printout of all admissions with the code for diabetes mellitus (in the appropriate age group and time period) was used to identify all newly diagnosed diabetic patients. All case records were then checked to determine patients' eligibility for inclusion, and information was collected concerning date of birth, date of diagnosis, and address at time of diagnosis.

Validation of the primary data source was needed to test the assumption that all newly diagnosed diabetic patients were admitted to hospital and included on the printout. Questionnaires were sent to all consultant paediatricians in the region to determine their policy with respect to the admission to hospital of children

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