

ORIGINAL ARTICLE

Incidence and prognosis in early onset breast cancer

M. Sundquist,¹ S. Thorstenson,² L. Brudin, S. Wingren³ and B. Nordenskjöld³

¹Department of Surgery and ²Department of Pathology and Cytology, County Hospital, Kalmar;

³Department of Oncology, University Hospital, Linköping, Sweden

SUMMARY. The aim of this study was to assess the incidence and prognosis in early onset breast cancer. Age-adjusted incidence and death rate for the 5394 Swedish women diagnosed with breast cancer under the age of 40 between 1960 and 1996 was studied using data from the Swedish Cancer Registry and Swedish Death Cause Registry. A total of 107 consecutive young patients with invasive breast cancer undergoing surgery during 1980–1993 in the Southeast Swedish health care region were retrospectively followed up and their cancers reviewed and graded blindly. The median follow-up time was 11.2 years. The applicability of the Nottingham Prognostic Index (NPI) as a prognostic tool was investigated. Grade, age, node status, tumour size, S-phase fraction and steroid receptor content were related to survival univariately and multivariately in a Cox proportional hazard analysis.

The incidence of early onset breast cancer has increased moderately and the survival rate has not improved during the last 35 years. When young women are diagnosed with breast cancer their tumours are larger, their lymph nodes more often involved, and the median grade higher than in older with 64% having grade 3 tumours. Lymph node status was the strongest sole prognostic indicator but the use of NPI gave more accurate prognostic information than node status alone. © 2001 Harcourt Publishers Ltd

INTRODUCTION

The incidence of breast cancer is increasing in all industrialised countries. Changes in diet and reproductive patterns and altered exposure to endogenous and exogenous substances with hormonal activity have been suggested as contributing to this increase.^{1–6} One of the most obvious alterations of endocrine milieu has been the increase in postmenopausal use of hormone replacement therapy (HRT). Women diagnosed with breast cancer while on HRT have been shown to have tumours with favourable characteristics.^{7–12}

Whether or not young age at diagnosis of breast cancer is in itself a negative prognostic factor is a controversial issue. Many studies report a worse out-

come for women under 40 than older women diagnosed with tumours of the same size and nodal status.^{13–18} In recent years a number of trials have indicated that the higher mortality is attributable to an increased rate of tumours with high grade of malignancy.^{19–22}

The aim of this study was to assess the incidence and prognosis of early onset breast cancer in Sweden.

PATIENTS AND METHODS

Patients

All 5394 patients diagnosed with breast cancer under the age of 40 from 1960 to 1995 in Sweden were included in this epidemiological study.

To study the histopathological characteristics of early onset breast cancer, 107 women consecutively diagnosed with primary invasive breast cancer at a young age in the Southeast Swedish health care region 1980–1993 were investigated. Patients were 22–36 (mean 32.4) years old at the time of diagnosis. Approximately 75% of the patients had a modified radical mastectomy. Node-

Address correspondence to: Marie Sundquist, Unit of Surgical Oncology, Department of Surgery, Sahlgrenska University Hospital, S-431 80 Mölndal, Sweden.

E-mail: marie.sundqvist@mbox301.swipnet.se

Received: 10 January 2001

Revised: 16 May 2001

Accepted: 25 May 2001

Published online: 5 September 2001

positive patients had postoperative radiotherapy, as had women having breast-conservation surgery.

Women with metastatic axillary lymph nodes or tumour diameter of 2 cm or greater ($n=65$) had adjuvant chemotherapy; in the presence of steroid receptor positivity they also received tamoxifen and in some cases goserelin for 2 years within a clinical trial. Patient data were collected through Swedish Cancer and Death Cause Registries and hospital records. Three patients were lost to follow-up and the median follow-up time was 11.2 years (range 4–17.7 years).

Epidemiological methods

Data on incidence and mortality in breast cancer between 1960 and 1997 were acquired from the Swedish Cancer and Cause of Death Registries, Centre of Epidemiology, Social Board. To further explore the youngest age group, individual survival data for all the 5394 patients diagnosed with breast cancer under the age of 40 from 1960 to 1990 were extracted. Annual incidence was related to the mean number of women aged 20–40 years for each year. Five- and 10-year overall survivals were calculated.

The completeness of the cancer registry was very high, with approximately 1% missed diagnosis of invasive breast cancer during the period 1971–1991.²³ In two earlier periods (1961–63 and 1971–73), Rutquist and Wallgren had found 7% error in the registration from Stockholm, mainly due to over-reporting.²⁴ Up to 1980, a number of intraductal cancers had been registered as invasive cancers. The errors have thus been registration of too many cases in the beginning of the period with a successive improvement over time. After 1980 a small artefactual dip in the incidence curve was expected. The validity of the Cause of Death Registry for breast cancer patients in Malmö during 1964 to 1992 has been studied by Game.²⁵ A net over-registration of breast cancer as cause of death in 41 cases out of 2631 was found. The routine changed in 1981 concerning registration of contributing disease. From 1982 and onwards, under- and over-reporting were found to balance each other. If these results are extrapolated to the whole country it could be assumed that there is an over-registration of breast cancer mortality of approximately 2% up to 1981.

Histopathology

The cancer specimens were originally diagnosed at four different pathology laboratories in the Southeast Swedish health care region (Kalmar, Linköping, Jönköping and Norrköping). The tumour slides were reviewed blindly, classified and graded by one pathologist

(S.T.). When necessary, new slides were made from the paraffin blocks. Cancers <3 mm were excluded as proper grading according to the protocol was not possible. Only invasive carcinomas were included. All histologic types were graded and the classifications and definitions established by the Nottingham group were used.^{26,27} Grading was performed following a written protocol according to the method described by Elston et al.^{28,29} A set of photographic prints of different grades of nuclear atypia was also used as a visual calibration aid. All tumour slides of a particular case were assessed in order to evaluate the percentage of tubule formations. Considering only the invasive cancer component, nuclear atypia and mitotic frequency were evaluated in the most proliferative, atypical and non-necrotic areas. Mitoses were counted at a magnification of 400× using a Zeiss Axio-skop microscope (field diameter 0.43 mm) and the cut-off points of mitoses adjusted accordingly. A minimum of 20 high power fields (HPF) were counted. The maximum number of mitoses per series of 10 HPF was recorded. Each evaluated variable (tubule formation, nuclear atypia and maximum mitotic count) was scored as 1, 2 or 3 and the sum of the scores was used to ascribe the Nottingham histologic grade (NHG).

Statistics

Logistic regression was used to calculate incidence and mortality in the epidemiological study. Relative death rates and two-tailed tests of statistical significance of relationships in the histopathological investigation were calculated using Cox's proportional hazards methods in univariate and multivariate models.³⁰ Statistical analysis was performed using STATISTICA for windows.³¹ A probability level of $P<0.05$ was considered statistically significant.

RESULTS

Epidemiological study

Over the whole period investigated there was a statistically significant increase in age-adjusted incidence of breast cancer among women younger than 40 years (Fig. 1). The mean increase in incidence is 1.1% per year ($P<0.0000$). However, the incidence was stable over the period 1978–1996 whereas the increase in incidence was prominent from 1960 to 1977. The age-adjusted mortality rate from breast cancer in women under 40 years of age did not decrease during the investigated period ($P<0.01$, Fig. 2).

From 1960 to 1990, 5394 patients were diagnosed with breast cancer at the age of 39 or younger in

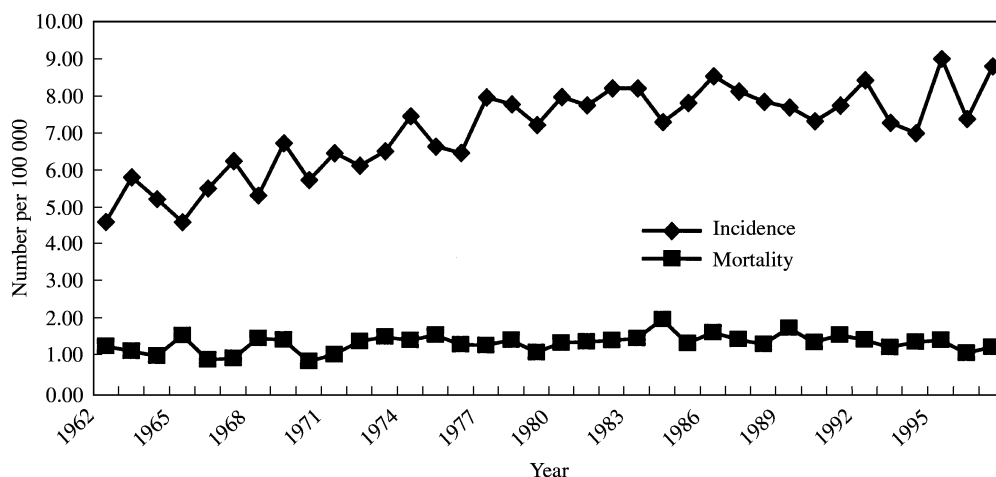


Fig. 1 Age-adjusted breast cancer incidence and mortality of women under 40 years of age at the time of diagnosis (1960–1997).

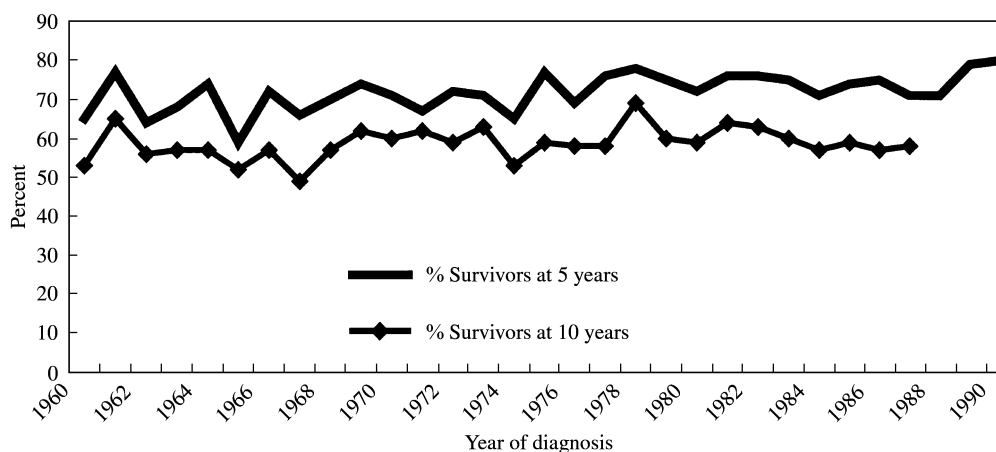


Fig. 2 Percentage of patients surviving at 5 and 10 years, respectively, after the diagnosis of breast cancer by year of diagnosis. Patients were <40 years of age at the time of diagnosis. The 5-year survival rate increases by a factor of 1.004/year ($P < 0.001$) between 1960 and 1990. There is no statistically significant change in 10-year survival between 1960 and 1987 ($P > 0.2$).

Sweden. Forty-five per cent have so far died of breast cancer after a follow-up period of 6–36 years (mean 18 years); 4.6% have died from other causes. Most deaths occur within in 5 years of diagnosis. Disease-specific deaths are, however, registered in the third and fourth decades after primary diagnosis. Also, of the patients diagnosed in 1961, 63% survived 10 or more years and 58% of those diagnosed in 1986 survived 10 or more years. Five-year survival was identical for patients diagnosed in 1961 and those diagnosed during 1989.

Histopathology study

We found that 78% of the carcinomas were of ductal non-specific type, 4.7% tubular variants, 6.5% lobular

carcinomas and 7.6% were of medullary type. A total of 64% of tumours were grade 3, 28% were grade 2 and only 7.5% were grade 1. Half of the patients had metastatic axillary nodes. In 13 cases node status was not known; 35% of patients had lymphovascular invasion. A total of 43% of patients with grade 3 tumours and 29% of grade 2 patients died from breast cancer. No patients with grade 1 tumours have died. Six patients with grade 3 and one with grade 2 tumours died from other causes.

In the univariate analysis, tumour size, node status, grade and lymphovascular invasion were all significantly associated with breast cancer mortality (Table 1). In the multivariate analysis of grade, node status, vascular invasion and size for the whole group of patients, node status was highly significant in

Table 1 Breast cancer specific death for the different values of the investigated parameters, grade, number of involved lymph nodes, tumour size and lymphovascular invasion.

Parameter	Breast cancer death			Univariate analysis			Multivariate analysis		
	<i>n</i>	<i>n</i>	Per cent	HR (95% conf. range)	<i>P</i>	<i>n</i>	HR (95% conf. range)	<i>p</i>	Induced parameters
Grade 1	8	0	0.0	1.00			1.00		
Grade 2	30	8	26.7	2.52 (1.25–5.1)			2.05 (0.95–4.4)		
Grade 3	69	28	40.6	6.34 (1.55–26)	0.01	92	4.19 (0.91–19.5)	0.07	
Node-	40	6	15.0	1.00			1.00		
Node 1–3+	31	15	48.4	2.66 (1.7–4.2)			2.58 (1.64–4.1)		
Node > 3+	21	13	61.9	7.06 (2.89–17.3)	<0.001	92	6.67 (2.7–16)	<0.001	
Size < 10 mm	9	2	22.2	1.00			1.00		1–3
Size 10–20 mm	40	9	22.5	2.36 (1.39–4.07)			1.38 (0.76–2.5)		
Size > 20 mm	52	23	44.2	5.59 (1.89–16.5)	0.002	90	1.91 (0.58–6.3)	0.3	
LVI Present	37	18	48.6	1.00			1.00		1–4
LVI Absent	65	18	27.7	0.48 (0.25–0.92)	0.03	87	0.85 (0.41–1.77)	0.7	
NPI < 3.4	13	2	15.4	1.00			1.00		2,5
NPI 3.4–5.39	49	12	24.5	4.41 (2.4–8.3)			3.13 (1.35–7.25)		
NPI ≥ 5.4	28	19	67.9	19.5 (5.5–69)	<0.001	90	9.80 (1.83–53)	<0.01	

Hazard ratios (HR) were calculated as $\exp(\beta)$, where β is the regression coefficients from the univariate and multivariate Cox analyses, respectively. Included parameters in the multivariate analysis are shown in the right column. LVI—lymphovascular invasion. When the Nottingham prognostic index (NPI) was compared to the nodal stage the latter lost its statistical significance ($P=0.25$) whereas the weighted index comprising tumour size, lymph node status and grade remained strongly significant.

predicting risk of breast cancer mortality, grade was just below significance, and size and vessel invasion were non-significant (Table 1).

Nodal stage was then compared to Nottingham Prognostic Index (NPI) values. In this context NPI was related significantly to mortality and node status alone was not. Thus, the combined, weighted assessments of the index provided additional information.

DISCUSSION

Despite the increased use of adjuvant local and systemic therapies, particularly in the younger age groups, and in the presence of the overall decrease in mortality from breast cancer in general, mortality in early onset breast cancer has not decreased over the last 36 years. This rather unexpected finding could have different explanations. More than half of the cancers in women 40–70 years of age are diagnosed by screening mammography. These tumours are less advanced and might be more curable. The steadily increasing incidence of breast cancer in women over 40³² has only a moderate correlate in younger women indicating that there are aetiological differences between these groups. The familial cancers more often associated with early age of onset might respond less well to therapy than the type of cancer seen in older women which might differ in their responsiveness to treatment, particularly hormonal manipulation. BRCA1 tumours have been associated with high-grade ductal cancers, as has BRCA2.³³ The frequencies of ductal NST carcinomas and medullary carcinomas are

increased and tubular and lobular tumours decreased as compared to the frequencies in patients of all age groups in our institute.³⁴ This is consistent with the reported increased frequency of high-grade NST ductal carcinomas and medullary cancers among BRCA1 and 2 carriers.^{35–37}

Early onset breast cancer is more often of high-grade and less hormone responsive than tumours diagnosed in older women. In a previous investigation we showed that the proportion of grade 3 tumours decreases with age. The proportion of grade 3 tumours in all patients diagnosed in our institutions between 1988 and 1991 was 38% whereas it was 64% among the youngest patients in this investigation.³⁸ Our study indicates that the type of breast cancer that is increasing in older age groups and is associated with a lower mortality might be a less aggressive disease than breast cancer developing in younger women. Trials showing that women on HRT have lower grade tumours when diagnosed support this.^{7,10,11} To further explore the characteristics of early onset breast cancer, its morphologic and genetic properties and how these differ from breast cancer in women over 40 may provide important insight in breast cancer aetiology. Young breast cancer patients present with large tumours and are more likely to have metastatic lymph nodes and vascular invasion. The overall and disease-specific mortality of this age group correlates with what would be expected according to their prognostic index.

We conclude that early onset breast cancer does not follow the trends seen in breast cancer in general, i.e. increasing incidence and decreasing mortality, indicating

diseases of different aetiology. Most young breast cancer patients have high-grade tumours but those with low-grade tumours have a good prognosis. The NPI is a valuable tool when counselling young breast cancer patients.

Acknowledgements

We are grateful to Kerstin Nordenskjöld (Linköping) and to the participating members of the Southeast Swedish Breast Cancer Group – Harald Bång (Motala) Eibert Einarsson, Eksjö-Nässjö, Åke Henning (Oskarshamn), Ann-Christin Källström (Norrköping) and Göran Tejler (Västervik). We are also greatly indebted to the staff at the Unit C Epidemiology, Swedish National Board of Health and Welfare for assistance. This investigation was supported by the Research Board of Southeast Sweden and the Swedish Cancer Society.

REFERENCES

- Millikan R, DeVoto E, Newman B, Savitz D. Studying environmental influences and breast cancer risk: suggestions for an integrated population-based approach. *Breast Cancer Res Treat* 1995; 35: 79–89.
- Wolff M S, Collman G W, Barrett J C, Huff J. Breast cancer and environmental risk factors: epidemiological and experimental findings. *Annu Rev Pharmacol Toxicol* 1996; 36: 573–596.
- O'Brien K, Caballero B. High bone mass as a marker for breast cancer risk. *Nutr Rev* 1997; 55: 284–286.
- Colditz G A, Frazier A L. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiol Biomarkers Prev* 1995; 4: 567–571.
- Weiss H A, Potischman N A, Brinton L A et al. Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 1997; 8: 181–187.
- Hansen J. Breast cancer risk among relatively young women employed in solvent-using industries. *Am J Ind Med* 1999; 36: 43–47.
- Bergkvist L, Adami H O, Persson I, Bergstrom R, Kruse U B. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy [see comments]. *Am J Epidemiol* 1989; 130: 221–228.
- Squitieri R, Tartter P I, Ahmed S, Brower S T, Theise N D. Carcinoma of the breast in postmenopausal hormone user and nonuser control groups. *J Am Coll Surg* 1994; 178: 167–170.
- Holli K, Isola J, Cuzick J. Hormone replacement therapy and biological aggressiveness of breast cancer [letter]. *Lancet* 1997; 350: 1704–1705.
- Bonnier P, Romain S, Giacalone P L, Laffargue F, Martin P M, Piana L. Clinical and biologic prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. *Obstet Gynecol* 1995; 85: 11–17.
- Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. *Breast Cancer Res Treat* 1996; 38: 325–334.
- Bonnier P, Bessenay F, Sasco A J et al. Impact of menopausal hormone-replacement therapy on clinical and laboratory characteristics of breast cancer. *Int J Cancer* 1998; 79: 278–282.
- Elkhuizen P H, van de Vijver M J, Hermans J et al. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Radiat Oncol Biol Phys* 1998; 40: 859–867.
- Kim S H, Simkovich-Heerdt A, Tran K N, Maclean B, Borgen P I. Women 35 years of age or younger have higher locoregional relapse rates after undergoing breast conservation therapy [see comments]. *J Am Coll Surg* 1998; 187: 1–8.
- Cowen D, Jacquemier J, Houvenaeghel G et al. Local and distant recurrence after conservative management of “very low-risk” breast cancer are dependent events: a 10-year follow-up. *Int J Radiat Oncol Biol Phys* 1998; 41: 801–807.
- Bertheau P, Steinberg S M, Cowan K, Merino M J. Breast cancer in young women: clinicopathologic correlation. *Semin Diagn Pathol* 1999; 16: 248–256.
- Chung M, Chang H R, Bland K I, Wanebo H J. Younger women with breast carcinoma have a poorer prognosis than older women. *Cancer* 1996; 77: 97–103.
- de la Rochefordiere A, Asselain B, Campana F et al. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993; 341: 1039–1043.
- Kollias J, Elston C W, Ellis I O, Robertson J F, Blamey R W. Early-onset breast cancer—histopathological and prognostic considerations. *Br J Cancer* 1997; 75: 1318–1323.
- Marcus J N, Watson P, Page D L, Lynch H T. Pathology and heredity of breast cancer in younger women. *J Natl Cancer Inst Monogr* 1994; 23–34.
- Walker R A, Lees E, Webb M B, Dearing S J. Breast carcinomas occurring in young women (<35 years) are different. *Br J Cancer* 1996; 74: 1796–1800.
- Bonnier P, Romain S, Charpin C et al. Age as a prognostic factor in breast cancer: relationship to pathologic and biologic features. *Int J Cancer* 1995; 62: 138–144.
- Garne J P, Aspegren K, Moller T. Validity of breast cancer registration from one hospital into the Swedish National Cancer Registry 1971–1991. *Acta Oncol* 1995; 34: 153–156.
- Rutqvist L E, Wallgren A. Inconsistencies in breast carcinoma registration. An investigation of 855 cases reported to the Swedish Cancer Registry. *Acta Radiol Oncol* 1983; 22: 109–112.
- Garne J P, Aspegren K, Balldin G. Breast cancer as cause of death—a study over the validity of the officially registered cause of death in 2631 breast cancer patients dying in Malmö, Sweden 1964–1992. *Acta Oncol* 1996; 35: 671–675.
- Pereira H, Pinder S E, Sibbering D M et al. Pathological prognostic factors in breast cancer. IV: Should you be a typer or a grader? A comparative study of two histological prognostic features in operable breast carcinoma. *Histopathology* 1995; 27: 219–226.
- Ellis I O, Galea M, Broughton N et al. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. *Histopathology* 1992; 20: 479–489.
- Elston C W. Grading of invasive carcinoma of the breast. In: Page D L and Anderson T J eds. *Diagnostic Histopathology of the Breast*. Edinburgh: Churchill Livingstone, 1987; 300–311.
- Elston C W, Ellis I O. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991; 19: 403–410.
- Cox D R. Regression models and life tables. *J R Stat Soc B* 1972; 34: 187–220.
- Stat Soft I. Computer program manual. Stat Soft, Inc, Tulsa, OK, USA 1995.
- Center of Epidemiology, Swedish National Board of Health and Welfare, Stockholm 1999. <http://www.sos.se/epc>
- Marcus J N, Watson P, Page D L et al. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer* 1996; 77: 697–709.
- Sundquist M. Prognostic factors in breast cancer. Faculty of Health Sciences, Linköping University Medical, Dissertations 2000; 632: 40pp.

35. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast Cancer Linkage Consortium. *Lancet* 1997; 349: 1505–1510.
36. Agnarsson B A, Jonasson J G, Bjornsdottir I B et al. Inherited BRCA2 mutation associated with high grade breast cancer. *Breast Cancer Res Treat* 1998; 47: 121–127.
37. Eisinger F, Jacquemier J, Charpin C et al. Mutations at BRCA1: the medullary breast carcinoma revisited. *Cancer Res* 1998; 58: 1588–1592.
38. Sundquist M, Thorstenson S, Brudin L, Nordenskjöld B. Applying the Nottingham Prognostic Index to a Swedish breast cancer population. *Breast Cancer Res Treat* 1999; 53: 1–8.