Breast cancer incidence and survival

registry-based studies of long-term trends and determinants

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Zing, vecht, huil, bid, lach, werk en bewonder

Voor mijn vader

Contents

CHAPTER 1

INTRODUCTION

1

Introduction

1.1 Background

Breast cancer is the most frequent cancer among women in the Netherlands, and it is the most important cause of cancer death. Between age 35 and 55 about 20% of all deaths among women is due to breast cancer.[1] The age-standardised incidence rate is among the highest in Europe,[2] and incidence rates have been increasing since 1960.[3] The mortality from breast cancer has been fairly stable for many years, but decreased somewhat in the last decade (figure 1).

The detection of (early) breast cancer has been facilitated by the introduction and increased use of mammography and cytology since the 1980s. The implementation of the mass breast cancer screening programme between 1991 and 1996 further increased the incidence of breast cancer, also because of an increased awareness in the population. However, any increase associated with early detection would be temporary. Some of the screen-detected tumours would never have been diagnosed without a mass screening programme, so some of the increase is likely to be artificial.

It has been suggested that the increased breast cancer risk is largely due to a growing number of breast tumours with lower malignant potential or more early stage disease.

On the other hand, the increased incidence might be the result of a change in the risk factors for breast cancer many years ago. Many known risk factors are related to endogenous hormones: young age at menarche, higher age at menopause, high age at birth of first child, lower parity, shorter lactation.[4] These factors have changed in an adverse way over the past decades and have probably contributed to the increased breast cancer incidence. Nutrition (in particular obesity),[5] physical activity[6] and alcohol consumption[5] may also have played a role.

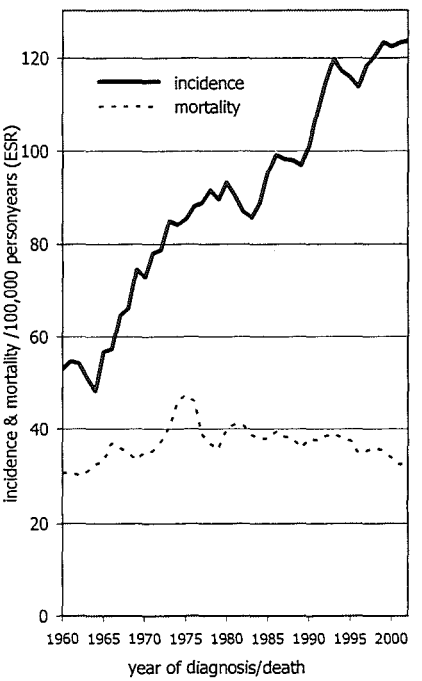

Figure 1 Trends in breast cancer incidence and mortality in southeastern Netherlands 1960-2002

Survival from breast cancer has improved for several decades, both for women younger (figure 2) and older than 70 at diagnosis. In the 1970s 5-year relative survival was less than 50%, of the patients diagnosed in 2000-2002 about 80% will survive at least five years.

Several factors are thought to be responsible for this better survival. Firstly, treatment (and staging) has considerably improved. In the early 1980s chemotherapy was introduced, but also the administration and dosage of radiotherapy became more accurate. Chemotherapy was estimated to explain 7-50% of the improved survival of breast cancer.[7, 8] Also early detection played a role in improved survival. The introduction of the mass screening programme is estimated to contribute 30%[7] to 50%[8] to improved survival rates. Early detection resulting in a more favourable stage distribution also allows for better and less mutilating therapeutic regimens. Finally, part of the improved survival is due to bias, lead time bias (as a result of early detection the time between diagnosis and death is by definition longer) and length bias (some screen detected tumours would never have progressed to metastasis or death if they had remained undiagnosed).

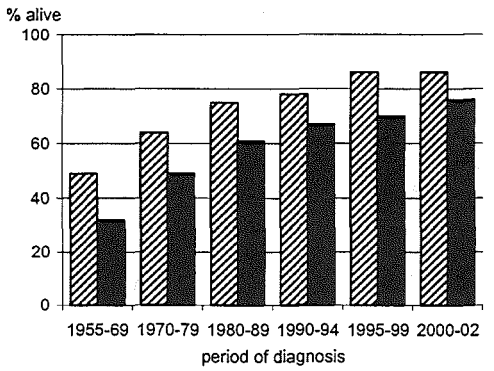

Figure 2 Trend in relative 5- and 10-year survival of breast cancer patients younger than 70 diagnosed in southeastern Netherlands

More than half of the breast cancer patients in the Netherlands is aged 60 years or older,[9] and the proportion of elderly patients in the Dutch population will increase substantially in the next decades (figure 3). With increasing age, the prevalence of coexistent diseases increases,[10] and previously already 50% of all breast cancer patients over 60 years were found to have serious concomitant disease at the time of breast cancer diagnosis. These patients with co-morbidity require special care, treatment guidelines are or cannot always followed and short-term survival was lower independent from age and stage of disease.[11]

Another subgroup of vulnerable patients is represented by women from lower socioeconomic backgrounds. Co-morbidity was more prevalent among these patients,[12] and they had worse stage distribution at diagnosis and experienced lower survival in the 1980s.[13]

The demand for care within the Dutch health care system is likely to increase over the coming decades. With an increasing age of the population, the number of new patients will also rise, of whom a large proportion requires specific care due to concomitant diseases. Because treatment guidelines since 2000 tend towards more adjuvant systemic therapy, an increase of about 50% in the number of patients receiving such treatment was expected in Dutch hospitals.[14]

Since survival rates have been improving, the number of prevalent cases is also expected to increase considerably. In 2005 there were about 119,000 (ex-) breast cancer patients in the Netherlands, who in 2015 might have increased to about 194,000. About 80% of these women still require some form of health care, either for diagnosis and treatment, surveillance during follow-up, or because of recurrences, metastases or new primary malignancies.[15]

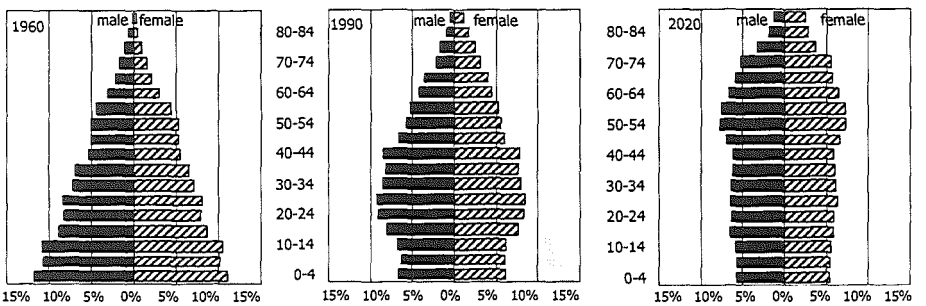

Figure 3 Age-distribution of the population in the area of the Eindhoven Cancer Registry

1.2 Outline

The objectives of the studies described in this thesis were:

1. *To explore the trends in incidence and survival of breast cancer in a large population-based setting*
2. *To investigate determinants of survival as available in the registry, but also focussing on a standardised indicator of severity*
3. *To explore clinical issues arising during the course of disease and long-term follow-up*

Preceding the mass breast cancer screening programme, incidence rose markedly. We investigated whether this increase consisted predominantly from tumours with low malignant potential, which would be the case if the increase was largely due to earlier and improved detection. The mitotic activity index (MAI) was used as it is a standardised and powerful measure of breast cancer aggressiveness and the time trend according to MAI is described in **chapter 2.1**. The long-term trends in incidence of and survival from breast cancer in the population-based Eindhoven Cancer Registry since 1975 are described in **chapter 2.2**. Using the data from all Dutch cancer registries combined, the trends in occurrence and outcome of uncommon histological types of breast cancer were studied and also the impact of histological type on survival (**chapter 2.3**).

In **chapter 3.1** the value of the mitotic activity index in predicting long-term prognosis was studied for patients with early breast cancer who did not receive systemic therapy. The impact of co-morbidity at the time of diagnosis on prognosis was investigated, to explore their effects on treatment chosen and also breast cancer survival up to 9 years after diagnosis (**chapter 3.2**). In the 1980s a negative association between socio-economic status and breast cancer survival was observed. We investigated among breast cancer patients aged 50-69 years the variation in survival according to socio-economic status, before, during and after the implementation of the mass mammography screening programme (**chapter 3.3**).

During the course of the disease, at least six months after initial treatment and diagnosis, many breast cancer patients are (again) treated with radiotherapy. We studied the quantity of radiotherapy use by following a cohort of breast cancer patients for 4-10 years since diagnosis (**chapter 4.1**). The occurrence of new primary tumours during the long-term follow-up (up to 30 years) of women diagnosed with breast cancer is described in **chapter 4.2**. We also explored shifts in the pattern of causes of death of patients who survived at least 10 years after diagnosis when life expectancy almost normalizes. This is described in **chapter 4.3**.

This thesis ends with an overview of studies on long-term survivors of breast cancer and the prognostic factors (**chapter 5.1**). In the general discussion (**chapter 5.2**) the main results and future perspectives for research and clinical management are considered.

1.3 Methods, population and patients

Cancer Registry and population

The Eindhoven Cancer Registry (ECR) was started in 1955 as part of a programme for nation-wide cancer registration in the area of southeastern North Brabant. Data on all new cancer patients were collected directly from pathology reports and patients medical records. The registry was started in three hospitals in Eindhoven and gradually expanded to include the southeastern part of the Dutch province of North-Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of North-Brabant since 1986 (except the small most western part).

Other regional registries had discontinued their activities, until a successful nation-wide programme was re-established since 1984. Since 1989 the whole Dutch population is covered by one of nine regional cancer registries, which established the National Cancer Registry.

The area of the population-based Eindhoven Cancer Registry is now served by 10 general hospitals at 16 locations and two large radiotherapy institutes. The area does not contain university or specialised cancer hospitals.

There are six pathology laboratories, all participating in the nationwide PALGA network, which also notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed cases on a regular basis from the pathology departments. In addition the medical records departments of the hospitals provide lists of outpatients and hospitalised cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumours) are collected and trained tumour registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records.

Figure 4 The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

Patients who live in the catchment area of the Eindhoven cancer Registry, but are diagnosed in hospitals elsewhere in the Netherlands, are regularly retrieved from all other Dutch cancer Registries since 1989. Before this year it was done directly through retrievals at all the cancer centres.

The region is characterised by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres.

In the area of the Eindhoven Cancer Registry, a biannual breast cancer mammography screening programme for women aged 50-69 was started in 1991 and fully implemented in 1996. The attendance rate was about 80%.[16] Since 1998 women aged 70-74 were also invited.

The population in the area is increasingly ageing (figure 3), with an increased proportion of elderly women, and since 1965 a decreasing number of children.

Staging

Stage of the solid tumours was categorised according to the TNM-classification IUCC[17] for all patients diagnosed until 2002. From 2003 onwards, a new classification became effective with some adjustments in the classification of axillary lymph nodes.[18]

Patients with more than 3 positive lymph nodes were previously coded N1, and are now classified as N2 (4-9 positive nodes) or N3 (more than 10). This resulted in a shift from stage II to stage III breast cancer.

In case of a sentinel node biopsy the pathological N status was based on the examination of the sentinel node only: N0 if no sentinel lymph node metastasis was found, N1 if a positive sentinel node was found.

Before 2003 the node status could only be categorised when at least 6 lymph nodes were examined, so in case of a negative sentinel node a NX was assigned.

Table 1 Stage distribution according to TNM-classification IUCC

Stage	T	N	M
0	is	0/X	0/X
I	1*	0/X	0/X
IIA	2	0/X	0/X
	0,1*	1	0/X
IIB	3	0/X	0/X
	2	1	0/X
IIIA	0,1*-2,X	2	0/X
	3	1-2	0/X
IIIB	4	all	0/X
	all	3	0/X
IV	all	all	1
unknown	X	1/X	0/X

* T1 including T1mic

Histological classification

Breast tumours were classified based on topography and histology, according to the WHO International Classification of Diseases for Oncology (ICD-O).[19] Codes were grouped according to the classification in table 2.

Table 2 Classification of histology according to the WHO ICD-O

Histological group	Morphology code according to ICD-O[19]
Ductal (not otherwise specified)	8010-8021,8140-8141,8190,8230-8231,8310-8441,8500-8502,8508,8514,8521,8523,8530,8550
Lobular	8145,8520,8524
Mixed ducto-lobular	8522
Mucinous	8480,8481,8482
Medullary	8510-8513
Tubular	8211
Papillary	8050,8260,8450,8503,8504,8507
Metaplastic	8031-8035, 8560,8570-8573,8575,8801,8980, 9180,9183,9220
Squamous cell (SCC)	8070-8074
Adenocystic	8200
Cribriform	8201
Carcinoid	8240-8246,8574,8249,9091
Signet ring cell	8490
Paget disease	8540-8543
Sarcoma	8800,8810-8921,8931,8935,8990,8991,9040-9044, 9131-9179, 9184-9219, 9221-9230, 9232-9342,9364-9372, 9473,9540-9559, 9561-9581
Hemangiosarcoma	9120-9130
Phyllodes	9020
Lymphoma*	9590-9729,9850
Other	all other codes, including patients without pathological verification

Mitotic activity index (MAI)

MAI was measured according to a strict protocol[20] in a special collaboration with the department of pathology from the Free University in Amsterdam. The participating regional pathology laboratories retrieved paraffin-embedded blocks from the archives; 4µm sections were cut from neutral formaldehyde-fixed paraffin-embedded tissue blocks that contained the least differentiated areas of the tumour. The most cellular area in the periphery of the tumour of hematoxylin-eosin stained sections was selected. Mitotic figures were counted in 10 neighbouring high power fields defined at x400 magnification with a x40 objective (numerical aperture, 0.75; field diameter, 450 µm). The MAI was defined as the total number of sharply defined mitoses in these 10 high power fields (total area 1.6 mm^2).[20]

Co-morbidity

Since 1993 the registry also recorded comorbidity according to a slight adaptation of the list of serious diseases drawn up by Charlson and colleagues.[21] In short, the following important conditions were recorded (table 3): chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Connective tissue diseases, rheumatoid arthritis, kidney,bowel, and liver diseases, dementia, tuberculosis and other chronic infections were also recorded.[22]

Table 3 Classification of co-morbidity, modified version of the list of Charlson et al. [21]

Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease: myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft (CABG)
Peripheral arterial disease: intermittent claudication, abdominal aneurysm, surgical intervention
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell skin carcinoma)
Hypertension
Diabetes mellitus
Other:
Autoimmune diseases: sarcoidosis, Wegener's disease, systemic lupus erythematosis (SLE)
Rheumatoid arthritis (only severe)
Kidney diseases: glomerulonephritis, pyelonephritis
Gastrointestinal: stomach ulcer and resection, colitis
Liver diseases: cirrhosis, hepatitis
Dementia
Chronic infections

Socioeconomic status

An indicator of socioeconomic status developed by Statistics Netherlands was used.[23] At the six-position level of postal code, data on household income and the economical value of the house are available from fiscal data from the year 2000. Within

each postal code there are about 17 households, so this aggregate measure counts for a very small geographic area, which enhances the reliability. Furthermore, the use of routinely collected income tax data (no questionnaires or interviews) gives reliable estimates of household income. Socioeconomic status was categorized according to quintiles raging from 1 (low) to 5 (high), with a separate class for postal codes with a care providing institution (such as a nursing home). This measure is assumed to be valid 10 years before and after the set year (2000), so for patients diagnosed before 1990 we used a measure which was also based on postal code of residence, but socio-economic status (5 categories) was assigned based on data from a marketing agency.[24]

Socio-economic differences based on neighbourhood data have proven to be a fairly good reflection of socio-economic differences at an individual level [25-27].

Data-analyses

Incidence and mortality

Because the age-distribution varies over time, and to enable international comparisons, age-adjustment was performed by direct standardisation according to the European Standard Population (European Standardised Rates, ESR).

Annual incidence and mortality rates were calculated as 3-year moving averages.

Trends in incidence and mortality were estimated by calculating the estimated annual percentage change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as regressor variable, i.e., $y=mx + b$ where $y=\ln(\text{rate})$ and $x=$calendar year. Then $EAPC=100x (e^m -1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Age, drift, period and birth cohort effects were investigated with the incidence data using the age-period-cohort modelling as described by Clayton and Schifflers methods.[28, 29]

Drift is a term which was introduced to describe models for which age-period and age-cohort parameters fit the data equally well. The model implies the same linear change in the logarithm of the rates over time in each age group. Such a model thus serves as an estimate of the rate of change of a regular trend.

Survival

Information on the vital status of all patients diagnosed until December 31st 2002 was obtained initially from the municipal registries and since 1998 the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens. Patients who moved outside the Netherlands were lost to follow-up; the estimated proportion was 0.2%. Follow-up lasted until January 1st 2005.

Crude survival analyses were performed. Cox regression models were used to compute multivariate rates.

Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival

in a background population with the same age structure.[30] Expected survival rates were calculated from life tables for regional female populations with the same 5-year age distribution. Generalised linear models with a Poisson error structure were used, based on collapsed data and exact survival times.[31]

References

1. CBS. Statline, 2006.
2. Ferlay J, Bray F, Sankila R, Parkin DM. EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union 1998, ed. 5.0 Lyon: IARC, 1999.
3. Nab HW, Voogd AC, Crommelin MA, Kluck HM, vd Heijden LH, Coebergh JW. Breast cancer in the southeastern Netherlands, 1960-1989: trends in incidence and mortality. *Eur J Cancer* 1993;29A:1557-9.
4. Breast cancer. In: Adami HO, Hunter D, D T, eds. Textbook of Cancer Epidemiology Oxford: Oxford Univeristy Press, 2002:301-39.
5. SignaleringscommissieKanker, De rol van voeding bij het ontstaan van kanker. KWF Kankerbestrijding, 2004.
6. SignaleringscommissieKanker, De rol van lichaamsbeweging bij preventie van kanker. KWF Kankerbestrijding, 2005.
7. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. *Br J Cancer* 2004;91:242-7.
8. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005;353:1784-92.
9. NederlandseKankerRegistratie. http://www.ikcnet.nl/page.php?id=1865&nav_id=41, 2005.
10. Havlik RJ, Yancik R, Long S, Ries L, Edwards B. The National Institute on Aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. *Cancer* 1994;74:2101-6.
11. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994;120:104-10.
12. Schrijvers CT, Coebergh JW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer* 1997;80:1482-8.
13. Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic status and breast cancer survival in the southeastern Netherlands, 1980-1989. *Eur J Cancer* 1995;31A:1660-4.
14. Voogd AC, Louwman WJ, Coebergh JW, Vreugdenhil G. [Impact of the new guidelines for adjuvant systemic treatment of breast cancer at hospital level]. *Ned Tijdschr Geneeskd* 2000;144:1572-4.
15. SignaleringscommissieKanker, Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. KWF Kankerbestrijding, 2004.
16. Verbeek AL, Broeders MJ. Evaluation of The Netherlands breast cancer screening programme. *Ann Oncol* 2003;14:1203-5.
17. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 5th Geneva, Switzerland: Wiley-Liss, 1997:227.
18. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 6th Geneva, Switzerland: Wiley-Liss, 2002:239.
19. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International Classification of Diseases for Oncology, ed. 3rd Geneva: World Health Organization, 2000.
20. van Diest PJ, Baak JPA, Matze-Cok P, Wisse-Brekelmans ECM, van Galen CM, Kurver PHJ, et al. Reproducibility of mitosis counting in 2,469 breast cancer specimens: results from the Multicenter Morphometric Mammary Carcinoma Project [see comments]. *Hum. Pathol.* 1992;23:603-07.

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
22. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993-1996. *J Clin Epidemiol* 1999;52:1131-6.
23. van Duijn C, Keij I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de bevolking* 2002;50:32-35.
24. Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 1995;75:2946-53.
25. Bos V, Kunst AE, Mackenbach JP, Nationale gegevens over sociaal-economische sterfteverschillen op basis van informatie over kleine geografische eenheden. Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, 2000.
26. Bos V, Kunst AE, Mackenbach JP. De omvang van sociaal-economische sterfteverschillen gemeten op buurtniveau: vergelijking met schattingen op basis van informatie op individueel niveau. In: Stronks K, ed. Sociaal-economische gezonheidsverschillen: Van verklaren naar verkleinen, vol. 5 Den Haag: Zon/MW, 2001:8-20.
27. Smits J, Keij I, Westert G. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte. *Mndstat bevolking* 2001;11:4-10.
28. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. *Stat Med* 1987;6:449-67.
29. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. *Stat Med* 1987;6:469-81.
30. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comput. Programs Biomed.* 1985;19:197-207.
31. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;23:51-64.

CHAPTER 2

LONG-TERM TRENDS IN INCIDENCE, MORTALITY AND SURVIVAL

2.1

Trends in breast cancer aggressiveness before the introduction of mass screening in Southeastern Netherlands 1975-1989

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Abstract

Objective: The increased incidence of breast cancer in the Southeastern Netherlands was accompanied by markedly improved relative survival and stable mortality. We investigated whether the average aggressiveness of tumours changed over time in a population-based study, before the introduction of mass screening.

Methods: The mitotic activity index (MAI) was determined retrospectively for 1051 consecutive patients diagnosed with invasive, non-metastatic breast cancer in 1975, 1981, 1988, and 1989. Trends over time, and effects of age, tumour size and lymph node status were examined by univariate and multivariate regressions. Results: Age-adjusted incidence of low MAI tumours changed from 35/100,000 in 1975 to 45/100,000 in 1988-89, an increase of 30% (P = 0.01), the incidence of tumours with a high MAI increased about 20% (P = 0.28), from 25 to 29/100,000. For small tumours (T1) the odds for a high MAI was lower in 1981 (OR 0.80, 95%CI 0.37-1.73) and 1988-89 (OR 0.66, 95%CI 0.35-1.23) compared to 1975. Among T3 and T4 tumours the odds increased to 2.03 (95%CI 0.71-5.86) in 1981 and 2.16 (0.76-6.18) in 1988-89.

Conclusion: Although the incidence of tumours with low aggressive potential increased, the incidence of high MAI tumours also increased. Stable breast cancer mortality rates in the face of increasing incidence rates during the period 1975-89 cannot be attributed solely to changes in tumour aggressiveness; early diagnosis and better treatment may also have contributed.

Introduction

A regular breast cancer screening program in the southeastern Netherlands was started in 1992. Even before its introduction the age-adjusted incidence of primary breast cancer doubled since 1960[1] (Figure 1) to become one of the highest in Europe [2]. Mortality has only increased for women of 75 years and over.[1,3] 10-year relative survival for women under 70 years of age at diagnosis increased from 32% for patients diagnosed in 1955-1969 to 63% for patients diagnosed in 1980-1986.[1,3] Improved survival is likely to be caused by earlier detection, better staging and advances in treatment. Earlier detection cannot explain a fairly continuous increase in incidence, because its effects would largely be temporary.[4] Furthermore, 10-year relative survival for patients with stage I tumours improved from 73 % for patients diagnosed in 1970-1974 to 85% for those diagnosed in 1980-1984.[3] Tumour aggressiveness may have decreased, most likely in relation to certain risk factors.[5]

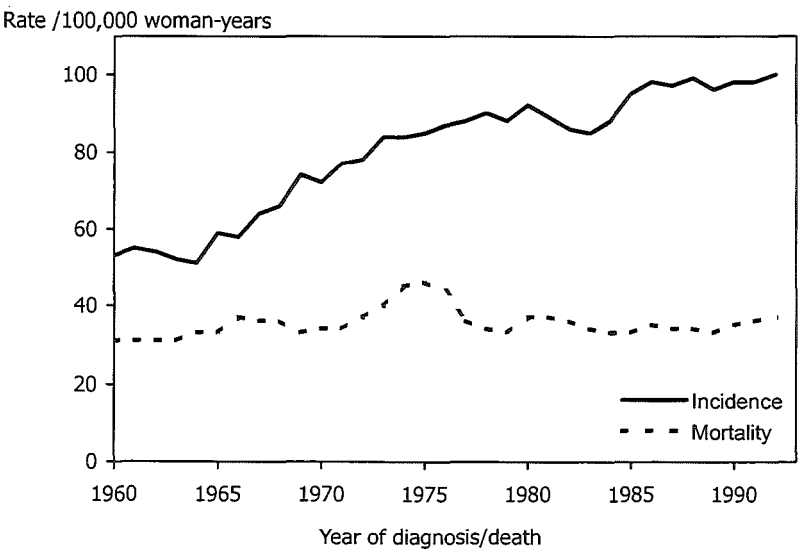

Figure 1 Age-adjusted incidence and mortality rates (European standardized rates) of female breast cancer (3-year moving averages), since 1960 per 100,000 woman years.

We therefore decided to study the time trends in tumour aggressiveness. Many publications have shown that tumour cell proliferation is a good indicator for this. [6] The prognostic value of the mitotic activity index (MAI) has been repeatedly demonstrated.[7-9]. Furthermore, MAI can be easily assessed and is highly reproducible (mean correlation coefficient 0.91) if a protocol with quality control is followed.[10]

We retrospectively assessed trends in the distribution of MAI in tumour specimens from three cohorts of unselected patients with localized breast cancer diagnosed in 1975, 1981, and 1988-1989. We investigated whether incidence rates according to tumour

proliferation changed over time. Furthermore, we studied if the proportion of patients with a low MAI increased over the years, taking into account tumour size as well.

Methods

Patients

Data on diagnosis, stage of disease, and treatment were obtained from the population-based Eindhoven Cancer Registry, which has collected data on new cancer patients since 1955 according to international guidelines.[2] The registry covers an area of 2,500 km^2 in Southeastern Netherlands with a population of almost one million inhabitants. The data were derived, after notification by pathologists, from the pathology reports, the patient's medical hospital records, and from the regional Radiotherapy Institute.

Table 1 Number of unselected patients diagnosed with invasive breast cancer in Southeastern Netherlands in 1975, 1981 and 1988-89; reasons for exclusion from study and included cases by department of pathology

	Year of diagnosis			
	1975	1981	1988-89	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Total number of patients diagnosed	228	364	803	1395
Excluded cases				
Metastasis at time of diagnosis	12 (5.3)	21 (5.8)	42 (5.2)	75 (5.4)
No surgery as primary treatment	11 (4.8)	19 (5.2)	64 (8.0)	94 (6.7)
Histological type				
Mucinous, medullary, papillary	9 (3.9)	8 (2.2)	17 (2.1)	34 (2.4)
Sarcoma	1 (0.4)	0	5 (0.6)	6 (0.4)
M. Paget	1 (0.4)	0	5 (0.6)	6 (0.4)
DCIS	4 (1.8)	15 (4.1)	14 (1.7)	33 (2.4)
No carcinoma	4 (1.8)	0	0	4 (0.3)
Histological specimen inadequate	1 (0.4)	6 (1.6)	16 (2.0)	23 (1.6)
Specimen could not be traced	19 (8.3)	24 (6.6)	26 (3.2)	69 (4.6)
Total	62 (27)	93 (26)	189 (24)	344 (25)
Included cases				
Department of pathology				
Helmond	0[a]	29 (11)	58 (9)	87 (8)
Venlo	47 (28)	82 (30)	180[b] (29)	309 (29)
PAMM Eindhoven	119 (72)	160 (59)	376[c] (61)	655 (62)
Total	166 (100)	271 (100)	614 (100)	1051 (100)

[a] archive not available

[b] 139 had already been assessed for a study on reproducibility[10]

[c] 263 had already been assessed for a study on reproducibility[10]

All 1056 consecutive patients diagnosed with invasive breast cancer in 1975, 1981 and 1988 were eligible to be included in the present study. Their tumour specimens were stored at three participating pathological laboratories, each of them serving 2-4 general hospitals. Since two laboratories had previously contributed to a study on reproducibility

of MAI values in breast cancer patients diagnosed in 1988 and 1989,[10] the 374 patients diagnosed in 1989 at these laboratories were also included. Assessment of MAI for 35 patients diagnosed in 1975 was not possible in one laboratory. 1051 patients remained for assessment after excluding 344 (25%) for reasons given in Table 1.

Diagnosis of breast cancer was facilitated by the gradual introduction of mammography in the region between 1975, when it was available in 2 of the 10 hospitals, and 1979 when mammography was carried out in all 10 hospitals. Cytology became more common between 1979 and 1987.[11]

Treatment of the patients depended on the size of the tumour and the presence of positive axillary nodes.[12] Axillary dissection, already performed in the 1970s, became more common during the 1980s, and nodal status became increasingly reliable. Since the mid-1970s adjuvant therapy was introduced only for axillary node-positive patients. The cancer registry has recorded endocrine therapy separately since 1984; in the prior years it was recorded as chemotherapy.

Mitotic activity index (MAI)

MAI was measured according to the strict protocol as used in a previous study.[10] In short, the pathology laboratories retrieved paraffin-embedded blocks from the archives; 4µm sections were cut from neutral formaldehyde-fixed paraffin-embedded tissue blocks that contained the least differentiated areas of the tumour. The most cellular area in the periphery of the tumour of hematoxylin-eosin stained sections was selected. Mitotic figures were counted in 10 neighbouring high power fields defined at x400 magnification with a x40 objective (numerical aperture, 0.75; field diameter, 450 µm). The MAI was defined as the total number of sharply defined mitoses in these 10 high power fields.[10]

MAI values had already been assessed for 402 patients included in a previous study.[10] MAI was divided in two categories: < 10 and ≥ 10 mitoses per 10 high power fields.

Quality control

To ensure the accuracy of the MAI, the pathologists from the three participating laboratories followed instructions from the Department of Pathology, Free University Hospital, Amsterdam, and sent slides for review to this reference laboratory. Each laboratory had to send in the first 10 counted slides. On the basis of the difference between the counts recorded by the participating laboratory and the reference laboratory, the number of slides subsequently to be reviewed was determined as follows: 2 points per slide if the difference between the two MAI values was less than the square root of the value determined at the participating laboratory; one point if the difference was between one and two times the square root, and no points if it exceeded twice the square root of the MAI. The total number of points for the 10 samples (maximum 20) determined the number of samples to be sent in for control. In the case of 16 points or

more every 10th sample would have to be reviewed by the reference laboratory, if the total number of points was between 11 and 16 every 5th sample, and if the score was ≤ 10 every second sample would have to be reviewed. After another 10 samples had been reviewed (based on 100, 50, or 20 patients, respectively) a new score was calculated and the frequency of sending samples for control was redetermined. MAI values from the reproducibility study[10] were not reviewed again. The proportion reviewed centrally was highest for 1975 (64%), because the laboratories began reviewing the 1975 cases first, so the first 30 samples were all from that year. Consequently, the proportion reviewed for 1975 (9%) was comparable to review rates for 1981 and 1988-89 (11% and 15%, respectively).

A total of 103 slides were reviewed (Table 2). Although no points could be assigned for 23 slides (22%), only two major discrepancies (2%) occurred, i.e. a patient shifted from one diagnostic category to another (MAI < 10 and MAI ≥ 10, respectively).

Table 2 Results of quality control of MAI assessment; number of slides reviewed by the reference laboratory according to year of diagnosis

	Year of diagnosis			
	1975	1981	1988-89	Total
	No.	No.	No.	No.
Score per slide[a]				
2	25	15	20	60
1	9	5	6	20
0	8	10	5	23
Diagnostic category[b]				
same	42	29	30	101
other	0	1	1	2
Total number reviewed	42	30	31[c]	103

[a] 2 points if the difference between the 2 MAI values was <√MAI determined at the participating laboratory; 1 point if the difference was between once and twice √MAI, and no points if it was >2√MAI

[b] two diagnostic categories were distinguished, i.e., MAI < 10 and MAI ≥ 10

[c] specimens already assessed in a previous study (n=402) were not reviewed[10]

To confirm the discriminatory prognostic value of MAI, survival of patients with a low MAI (<10) and those with a high MAI (≥ 10) was compared. Prognosis was estimated as relative survival, which is the crude survival divided by expected survival using the method of Ederer II; the computer program of the Finnish cancer registry was applied.[13, 14] The 10-year relative survival was 78% for patients with a low MAI compared to 66% for those with a high MAI ($P < 0.001$).

Statistical analysis

Pearson's chi-square test or Fisher's exact test was used to compare frequencies among groups. The Mantel-Haenzel test for trend was applied.

Incidence rates by MAI category were standardized using the European standard population.[15] The number of patients whose specimen could not be traced decreased over the years, whereas 5-year survival in this group improved from 62% in 1975 to 71% in 1988-89. Thus, the proportion of patients with high MAI was probably underestimated in 1975 and to a lesser extent in 1981. We attributed the excess of unknown cases (in comparison with 1988/89) to the high MAI group: in 1975 100% (n = 12) and in 1981 66% (n = 8).

Logistic regression analysis was used to assess the determinants of MAI, especially year of diagnosis. We stratified according to tumour size, because of a differential effect of year of diagnosis on MAI.

All tests of statistical significance were two sided.

Table 3 Clinical characteristics of non-metastatic breast cancer patients by year of diagnosis

	Year of diagnosis			
	1975	1981	1988-89	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Age (years)				
≤50	50 (30)	74 (27)	179 (29)	303 (29)
50-69	84 (51)	125 (46)	303 (49)	512 (49)
≥70	32 (19)	72 (27)	132 (21)	236 (22)
Tumour size (cm)				
≤2.0	51 (31)	64 (24)	287 (47)	402 (38)
2.1-5.0	57 (34)	119 (44)	243 (40)	419 (40)
> 5.0 or direct extension to chest wall or skin	22 (13)	72 (27)	79 (13)	173 (16)
unknown	36 (22)	16 (6)	5 (1)	57 (5)
Axillary lymph nodes				
negative	79 (48)	131 (48)	347 (57)	557 (53)
positive	55 (33)	110 (41)	261 (43)	426 (41)
unknown	32 (19)	30 (11)	6 (1)	68 (6)
Therapy				
surgery alone	73 (44)	73 (27)	124 (20)	270 (26)
surgery + radiotherapy	93 (56)	158 (58)	286 (47)	537 (51)
surgery ± radiotherapy + chemotherapy[a]		040 (15)	75 (12)	115 (11)
surgery ± radiotherapy + endocrine therapy	-	-	129 (21)	129 (12)
Total	166 (100)	271 (100)	614 (100)	1051 (100)

[a] no distinction between adjuvant chemotherapy and endocrine treatment in 1975 and 1981

Results

Clinical characteristics of the study population are presented in Table 3. Age distribution and mean age (57, 60, and 59 years, respectively) were rather similar in the three periods of diagnosis. Almost 40% of the tumours were smaller than 2 cm and about the same proportion were between 2.1 and 5.0 cm at diagnosis. About 50% of the patients had negative lymph nodes. Treatment consisted of surgery and/or radiotherapy in 1975; after the introduction of systemic therapy over 30% was treated with chemotherapy or hormonal treatment in 1988-89.

Table 4. Odds ratio of MAI ≥ 10 in unselected non-metastatic breast cancer patients diagnosed in southeastern Netherlands in 1975, 1981, and 1988-89

	Odds Ratio	95% Confidence Interval	
Univariate analysis			
Age (years)			$P < 0.01$
< 50	1.78	(1.25 - 2.55)	
50-69	1.52	(1.09 - 2.11)	
≥ 70	1.00		
Tumour size (cm)			$P < 0.01$
≤ 2.0	1.00		
2.1-5.0	1.68	(1.27 - 2.23)	
> 5.0 or direct extension to chest wall or skin	1.39	(0.96 - 2.01)	
unknown	1.02	(0.57 - 1.84)	
Axillary lymph nodes			$P = 0.18$
negative		1.00	
positive	1.21	(0.93 - 1.56)	
unknown	0.80	(0.47 - 1.36)	
Year of diagnosis			$P = 0.33$
1975	1.00		
1981	1.26	(0.84 - 1.87)	
1988-89	1.02	(0.71 - 1.45)	
Multivariate analysis[a]			
Year of diagnosis			$P = 0.24$
1975	1.00		
1981	1.30	(0.88 - 1.94)	
1988-89	1.03	(0.72 - 1.47)	
Stratified according to tumour size			
≤ 2.0 cm			
Year of diagnosis			$P = 0.38$
1975	1.00		
1981	0.80	(0.37 - 1.73)	
1988-89	0.66	(0.35 - 1.23)	
2.1-5.0 cm			
Year of diagnosis			$P = 0.56$
1975	1.00		
1981	1.37	(0.72 - 2.61)	
1988-89	1.14	(0.63 - 2.04)	
> 5.0 cm or direct extension to chest wall or skin			
Year of diagnosis			$P = 0.34$
1975	1.00		
1981	2.03	(0.71 - 5.86)	
1988-89	2.16	(0.76 - 6.18)	

[a] adjusted for age

Changes in MAI according to tumour size and year of diagnosis are shown in Figure 2. For small tumours (≤ 2 cm) a modest increase in the proportion of patients with a lower MAI was observed over time (from 59 to 69 %). Among the larger and more advanced tumours (T3 and T4) the proportion of patients with a lower MAI decreased from 73% to 57%. However, none of the differences in the distribution of MAI by year of diagnosis was statistically significant, nor were any of the observed trends. Within age groups proportional distribution of MAI remained stable over time (data not shown).

Univariate logistic regression analysis did not reveal an association between MAI and year of diagnosis (Table 4). However, lower MAI values were more often observed in patients with small tumours ($P = 0.01$) and it was inversely related to age ($P = 0.01$). After adjustment for age the odds of a MAI value ≥ 10 declined in the small tumours (≤ 2 cm) (P=0.38) and the odds increased in large and advanced tumours (T3 & T4) (P=0.34). Addition of lymph node status to the model did not affect odds ratios substantially (data not shown).

Age-adjusted incidence rates increased in both MAI categories (Table 5), being largest in the low MAI category (around 30 %, $P = 0.01$), but also present in the high MAI group (around 20 %, $P = 0.28$).

Table 5 Age-standardized incidence rates (per 100,000) of unselected non-metastatic breast cancer patients by MAI category and year of diagnosis

	MAI < 10		MAI ≥ 10	
	ESR[a]	WSR[b]	ESR[a]	WSR[b]
1975	35	25.5	24.5	18
1981	39	28.1	30.3	22.3
1988-89	45.3	33.1	29.4	22.1
Increase	29.40%	29.70%	19.90%	22.80%
	$P = 0.01$	$P = 0.01$	$P = 0.28$	$P = 0.20$

[a] European Standardized Rate
[b] World Standardized Rate

Discussion

In the present study MAI was assessed in unselected breast cancer patients diagnosed in 1975, 1981, and 1988-89 before the introduction of mass screening. The major findings were increases of incidence both of low MAI and high MAI, albeit only significantly for the former ($P = 0.01$). Age-adjusted incidence of low MAI tumours increased 30% between 1975 and 1988-89, while the incidence of high MAI increased about 20%. For small tumours (T1) the odds for a high MAI decreased over time, whereas for T3 and T4 tumours the odds increased.

We used the MAI as an indicator of tumour aggressiveness. The MAI is a quantitative index made out of the mitotic frequency in the most active part of the tumour. Quantitative features, such as the MAI, discriminate very well less aggressive tumours from more aggressive ones.[7-9, 16, 17] Also in our material an increasing MAI was indicative of a less favourable prognosis. Other measures of proliferation are often more time-consuming or fairly subjective. Furthermore, our quality control procedure confirmed the accuracy of the MAI values.

Only a few studies investigated time trends in tumour proliferation. In Southwestern Finland a trend towards lower mitotic counts was observed over a period of 40 years,[18]. but this disappeared after adjustment for tumour size. Using the more complex ^{3}H-thymidine labelling index (TLI) an increase in tumour aggressiveness from 1972 up to the mid-1980s was found for node negative breast cancers diagnosed in a large cancer institute in Northern Italy.[19] However, selection of patients cannot be excluded here.

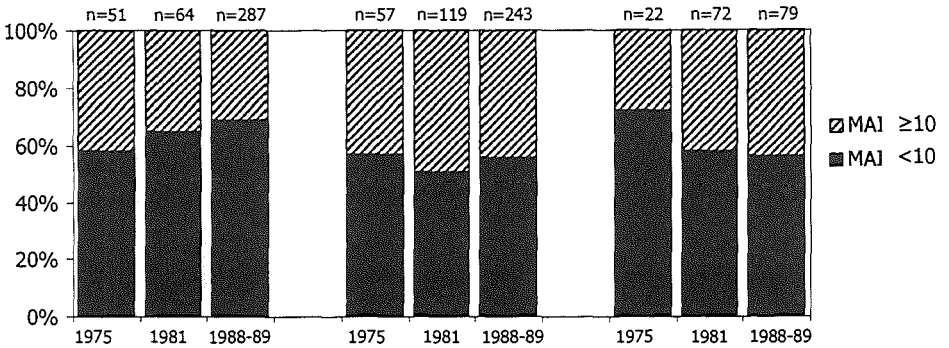

Figure 2. Distribution of unselected, non-metastatic breast cancer patients diagnosed in 1975, 1981, and 1988-89 by MAI category, year of diagnosis and tumour size. A. ≤ 2 cm (T1); B. 2-5 cm (T2); C. > 5 cm or direct extension to chest wall or skin (T3 & T4)

We found a non-significant trend towards more tumours with a high MAI among the larger and more advanced tumours, which is probably due to earlier detection. In the past, a substantial proportion of large and advanced tumours may also have grown slowly, whereas they would already have been detected earlier nowadays with the increased breast awareness and availability of mammography. This would also explain why survival rates for the patients with large and more advanced tumours did not increase despite better treatment.[3, 20]

It has been suggested that the rise in the incidence of breast cancer in developed countries is not necessarily alarming, since it may also reflect a change over time in the boundaries of what is called cancer.[21, 22] The increase in incidence of less aggressive tumours (MAI < 10) was about 1.5 times as large as the increase of high MAI (≥ 10) tumours in our study. If the increased detection of low MAI tumours hardly affected mortality, that is certainly not the case for patients with high MAI tumours whose prognosis is fatal within 10 years in about 45% of the cases.[17] Thus the combination of a 20% rise in the incidence of high MAI tumours and stable breast cancer mortality must somehow be the consequence of better management. This involves earlier detection and better staging which allows for more appropriate treatment. Furthermore, the introduction of megavoltage radiotherapy since 1972, systemic therapy and better supportive care may have played a part in improved management of the disease.

Conclusion: two phenomena may have happened simultaneously in the occurrence of breast cancer over time in our area; an increase of tumours with low malignant potential and a more modest increase of tumours with high malignant potential.

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References

1. Nab HW, Voogd AC, Crommelin MA, Kluck HM, vd Heijden LH, Coebergh JW. Breast cancer in the southeastern Netherlands, 1960-1989: trends in incidence and mortality. Eur J Cancer 1993;29A:1557-9.
2. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents., vol. VII Lyon: IARC Scientific Publications, 1997.
3. Nab HW, Hop WC, Crommelin MA, Kluck HM, Coebergh JW. Improved prognosis of breast cancer since 1970 in south-eastern Netherlands. Br J Cancer 1994;70:285-8.
4. Miller AB. Fundamental issues in screening for cancer. In: Schottenfield D, Fraumeni JF. Cancer Epidemiology and preventioned. Oxford: Oxford University Press, 1996:1433-52.
5. Adami HO, Sparen P, Bergstrom R, Holmberg L, Krusemo UB, Ponten J. Increasing survival trend after cancer diagnosis in Sweden: 1960-1984. J Natl Cancer Inst 1989;81:1640-7.
6. Simpson JF, Wilkinson EJ. Malignant neoplasia of the breast: infiltrating carcinomas. In: Bland KI, Copeland EMI. The breast: Comprehensive management of benign and malignant diseasesed. Philadelphia: Saunders, 1998:285-95.
7. Baak JPA, van Dop H, Kurver PHJ, Hermans J. The value of morphometry to classic prognosticators in breast cancer. Cancer 1985;56:374-82.
8. Clayton F. Pathologic correlates of survival in 378 lymph node-negative infiltrating ductal breast carcinomas. Mitotic count is the best single predictor. Cancer 1991;68:1309-17.
9. Eskelinen M, Lipponen P, Papinaho S, Aaltomaa S, Kosma VM, Klemi P, Syrjanen K. DNA flow cytometry, nuclear morphometry, mitotic indices and steroid receptors as independent prognostic factors in female breast cancer. Int. J. Cancer 1992;51:555-61.
10. van Diest PJ, Baak JPA, Matze-Cok P, Wisse-Brekelmans ECM, van Galen CM, Kurver PHJ, Bellot SM, Fijnheer J, van Gorp LH, Kwee WS, Los J, Peterse JL, et al. Reproducibility of mitosis counting in 2,469 breast cancer specimens: results from the Multicenter Morphometric Mammary Carcinoma Project [see comments]. Hum. Pathol. 1992;23:603-7.
11. Coebergh JW, Crommelin MA, Kluck HM, van Beek M, van der Horst F, Verhagen-Teulings MT. [Breast cancer in southeast North Brabant and in North Limburg; trends in incidence and earlier diagnosis in an unscreened female population, 1975-1986]. Ned Tijdschr Geneeskd 1990;134:760-5.
12. Voogd AC, van Beek MW, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JW. Management of early breast cancer in southeast Netherlands since 1984. A population-based study. Regional Breast Cancer Study Group. Acta Oncol 1994;33:753-7.
13. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. Comput. Programs Biomed. 1985;19:197-207.
14. Hakulinen T, Tenkanen L, Abeywickrama K, Päivärinta L. Testing equality of relative survival patterns based on aggregated data. Biometrics 1987;43:313-25.
15. Esteve J, Benhamou E, Raymond L. Statistical methods in cancer researched., vol. IV. Lyon: IARC Scientific Publications, 1994.
16. Biesterfeld S, Noll I, Noll E, Wohltmann D, Bocking A. Mitotic frequency as a prognostic factor in breast cancer [see comments]. Hum. Pathol. 1995;26:47-52.
17. Uyterlinde AM, Baak JP, Schipper NW, Peterse H, Matze E, Meijer CJ. Further evaluation of the prognostic value of morphometric and flow cytometric parameters in breast-cancer patients with long follow-up. Int J Cancer 1990;45:1-7.
18. Joensuu H, Toikkanen S. Comparison of breast carcinomas diagnosed in the 1980s with those diagnosed in the 1940s to 1960s [see comments]. Brit. med. J. 1991;303:155-8.
19. Silvestrini R, Daidone MG, Luisi A, Mastore M, Leutner M, Salvadori B. Cell proliferation in 3,800 node-negative breast cancers: consistency over time of biological and clinical information provided by 3H- thymidine labelling index. Int. J. Cancer 1997;74:122-7.
20. Nab HW, Hop WC, Crommelin MA, Kluck HM, van der Heijden LH, Coebergh JW. Changes in long term prognosis for breast cancer in a Dutch cancer registry. Bmj 1994;309:83-6.
21. Fox MS. On the diagnosis and treatment of breast cancer. Jama 1979;241:489-94.
22. Bailar JC, 3rd. Diagnostic drift in the reporting of cancer incidence [letter; comment]. J. natl. Cancer. Inst. 1998;90:863-4.

2.2

On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004

a long-term population-based study in southeastern Netherlands

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Abstract

Background: Much progress has been made in the early diagnosis and treatment of breast cancer. We have assessed the changing burden of this disease, by means of a comprehensive description of trends in incidence, survival and mortality.

Methods: Data on breast cancer patients diagnosed between 1975 and 2004 (n=26,464) registered in the population-based Eindhoven Cancer Registry were investigated.

Results: Incidence for patients aged below 40 and 40-49 has increased by 2.1% and 2.4% annually since 1995 (p=0.08 and p=0.001, respectively). Mortality decreased in all age groups, but most markedly among women aged 50-69 (-1.5% yearly since 1985, p=0.14). The proportion of stage I tumours increased from 25% to 39%, that of advanced stages (III & IV) decreased from 30% (1975-1984) to 13% in 1995-2004, and the proportion in situ tumours increased from 1.5% to 10%. Adjuvant systemic treatment was administered to 15% of patients in 1975-1984 vs 49% in 1995-2004. Relative 10-year survival rates for women aged 50-69 (period analysis) increased from 53% to 75% between 1975-2004. The best prognosis was observed for women aged 45-54. Women younger than 35 had a particularly poor prognosis.

Conclusion: The observed improvement in survival of breast cancer patients during the last three decades is impressive. The peak in breast cancer incidence is not yet in sight considering the recent trends in exposure to known risk factors. The combination of increasing incidence and improved survival rates implies that the number of prevalent cases will continue to increase considerably in the next ten years.

Introduction

Breast cancer is a major health burden. Worldwide, over 1.1 million cases of breast cancer are diagnosed each year.[1] In Europe, the number of breast cancer cases was estimated to be 350,000 for the year 2000.[2] A large variation in breast cancer incidence has been observed between countries, also within the European Union, ranging from about 68/100,000 in Spain and Greece to over 110/100,000 in Denmark, Sweden, Belgium and the Netherlands.[3, 4] In the Netherlands, over 11,500 new cases of female breast cancer were diagnosed in 2003. Standardised for age (European Standardised Rate, ESR) this amounted to 124 cases per 100,000 women per year.[5]

Large increases in breast cancer incidence have been observed in most industrialised countries as well as developing countries. This has been ascribed to adverse changes in risk factors, in particular the patterns in childbearing and breastfeeding (lower parity and shorter or no lactation), hormonal intake and dietary factors, since the 1950s.[6] In southeastern Netherlands, the incidence of breast cancer among females had already doubled from 1960 to 1990.[7, 8] This increase applied for both aggressive and less aggressive tumours.[9] Also, the proportion of small and node-negative tumours increased.[10]

Breast cancer mortality decreased in some countries and has been fairly stable in others.[11] The number of breast cancer deaths in Europe was about 130,000 in the year 2000.[2] Both earlier diagnosis due to screening and better treatment may have played a role in the declining mortality in some European countries.

To fully assess how the breast cancer burden has changed and to understand implications for preventive strategies and health care planning, the trends in incidence, survival and mortality should be analysed and interpreted together.[12]

In the current paper such a comprehensive description of these trends in incidence and mortality as well as the prognosis for invasive breast cancer is given, based on data from the large population-based Eindhoven Cancer Registry, which is among the oldest in Europe.

Methods

Study population

Data on incident cases were obtained from the population-based Eindhoven Cancer Registry.[10] The Eindhoven Cancer Registry serves more than 12 general hospitals which are covered by six pathology laboratories, all participating in the nationwide PALGA network which notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed cases on a regular basis from the pathology departments. In addition the medical records departments of the hospitals provide lists of outpatients and hospitalised cancer patients. Following this notification, the medical files of newly diagnosed patients (and tumours) are collected and trained tumour registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records, and records are assumed to be complete.[13]

Table 1 Characteristics of the study population: unselected patients with invasive breast cancer diagnosed in southeastern Netherlands between 1975 and 2004

	1975-1984		1985-1994		1995-2004		Total	
	n	%	n	%	n	%	n	%
Age								
<40	321	9	698	8	932	7	1951	7
40-59	718	21	1702	19	2748	19	5168	20
50-69	1570	46	4081	47	6667	47	12318	47
70+	835	24	2264	26	3928	28	7027	27
Stage at diagnosis								
I	855	25	2762	32	5608	39	9225	35
II	1149	33	3980	46	6352	44	11481	43
III	812	24	1133	13	1303	9	3248	12
IV	208	6	460	5	611	4	1279	5
unknown	420	12	410	5	401	3	1231	5
Treatment								
Surgery alone (S)	902	26	1896	22	2600	18	5394	20
S+ radiotherapy (RT)	1777	52	3394	39	4091	29	9262	35
S+RT+ Systemic therapy*	360	10	1790	20	4267	30	6417	24
S+ Systemic therapy	141	4	807	9	2135	15	3083	12
Systemic therapy alone	48	1	456	5	596	4	1100	4
Other/N	214	6	221	3	264	2	699	3
Unknown	2	0	185	2	322	2	509	2
Total	3444	100	8745	100	14275	100	26464	100

*Systemic therapy includes both chemotherapy and hormonal treatment, before 1984 these were not separated in the Cancer Registry Database

During the study period 1975-2004, the population of the Eindhoven Cancer Registry catchment area increased from almost 600,000 to 2,400,000, mainly due to expansion of the registry area, related to the adherence area served by the radiotherapy institutes.[10] Since 1989, the total Dutch population is covered by 9 regional cancer registries. Patients who live in the area of the Eindhoven Cancer Registry, but are diagnosed in hospitals elsewhere in the Netherlands, have regularly been retrieved from all other Dutch Cancer Registries since 1989. This procedure is complete up to 2002, so incidence rates for 2003 and 2004 may be underestimated by about 3% (unselected patients). Statistics Netherlands (CBS) provided mortality data.

Information on the vital status of all patients diagnosed up to December 31st 2002 was obtained initially from the municipal registries and since 1998 from the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens. Patients who moved outside the Netherlands were lost to follow-up; the estimated proportion was 0.2%. Follow-up lasted until January 1st 2005.

Stage and treatment

Stage was categorised according to the TNM-classification IUCC for all patients diagnosed before 1989.[14] Patients diagnosed between 1989 and 2003 were categorized according to the newer classifications,[15, 16] which resulted in a shift from stage I to stage

II because patients with a positive lymph node which contained micrometastases (pN1a) were considered stage I until 1989, but any pN1 (either pN1a or pN1b) is considered stage II since that time. From 2003 onwards, the latest classification became effective.[17] Patients with more than 3 positive lymph nodes were previously included in stage II and are now considered stage III, so this caused a shift between stage II and III breast cancer.

Patients were treated according to regional guidelines. Before 1981 standard treatment was mastectomy, with radiotherapy depending on the localisation and stage of the initial tumour. Adjuvant chemotherapy was introduced in the 1970s for premenopausal axillary lymph node-positive patients. Breast-conserving therapy was introduced in 1981 for patients with tumours ≤ 2cm across; this was increased to ≤ 3 cm in 1984. Adjuvant endocrine therapy (tamoxifen) was introduced for post-menopausal node-positive patients with oestrogen receptor-positive tumours in the early 1980s.[18] In 1998, the indications for adjuvant systemic therapy were extended to node-negative patients with unfavourable tumour characteristics (intermediately or poorly differentiated tumours ≥ 2cm).[19]

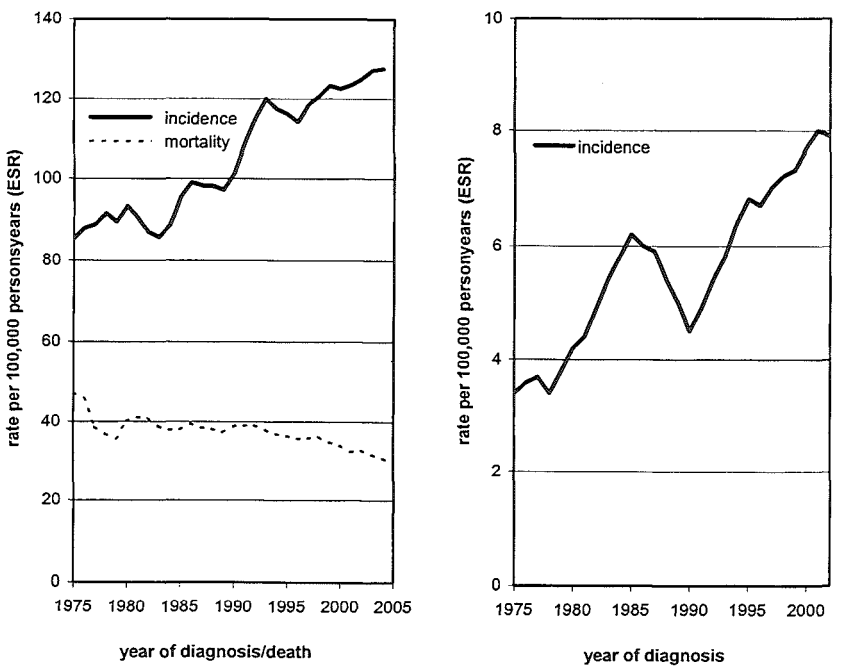

Figure 1 Trend in incidence and mortality of breast cancer in southeastern Netherlands 1975-2004 (a), and the incidence of contralateral breast cancer (b)

Statistical analyses

Analyses are presented for all women combined or according to age group (<40, 40-49, 50-69, and 70+). The cut-off points were based on the age limits for mass mammography screening (introduced between 1991 and 1996 for women aged 50-69, and since 1998 for women up to 74 years old), and the importance of showing the results for young women (<40) separately.

Incidence and mortality rates were age-adjusted by direct standardisation according to the European Standard Population (European Standardised Rates, ESR). Annual rates were calculated as 3-year moving averages. Trends in incidence and mortality were estimated by calculating the estimated annual percentage change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as regressor variable, i.e. $y=mx + b$ where $y=\ln(\text{rate})$ and $x=$calendar year. Then $EAPC=100x (e^m -1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Age, drift, period and birth cohort effects were investigated with the incidence data using the established age-period-cohort modelling[20] and were calculated for the two youngest as well as the two oldest groups combined (<50, 50+).

Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a background population with the same age structure [21]. Expected survival rates were calculated from life tables for the regional female population with the same 5-year age distribution. We used period-analysis to calculate the relative survival rates, which provides the most up-to-date survival rates.[22, 23]

Results

Between 1975 and 2004 26,464 women were diagnosed with invasive breast cancer (Table 1). The patients diagnosed between 1975 and 1984 were slightly younger (median age 58) than those diagnosed in the more recent periods (median age 59 in both periods).

Incidence and mortality

The incidence increased from about 85/100,000 (European Standardised Rate, ESR) in 1975 to almost 130/100,000 women in 2004 (Figure 1). After an initial drop, mortality was rather stable around 40/100,000 in the 80s. Since the mid 1990s mortality has decreased (EAPC -2.0% since 1995, p=0.8)

The incidence of breast cancer for patients aged below 40 and 40-49 has increased by 2.1% and 2.4% annually since 1995 (p=0.08 and p=0.001, respectively) (Figure 2). The incidence among patients aged 50-69 increased markedly in the early 90s, then dropped, but has increased again since 2000. The incidence among women older than 70 increased steadily, with a marked increase around the year 2000 followed

by a decrease. Age-specific mortality rates decreased most markedly among women aged 50-69, already since 1985 (EAPC: -1.5%, p=0.14).

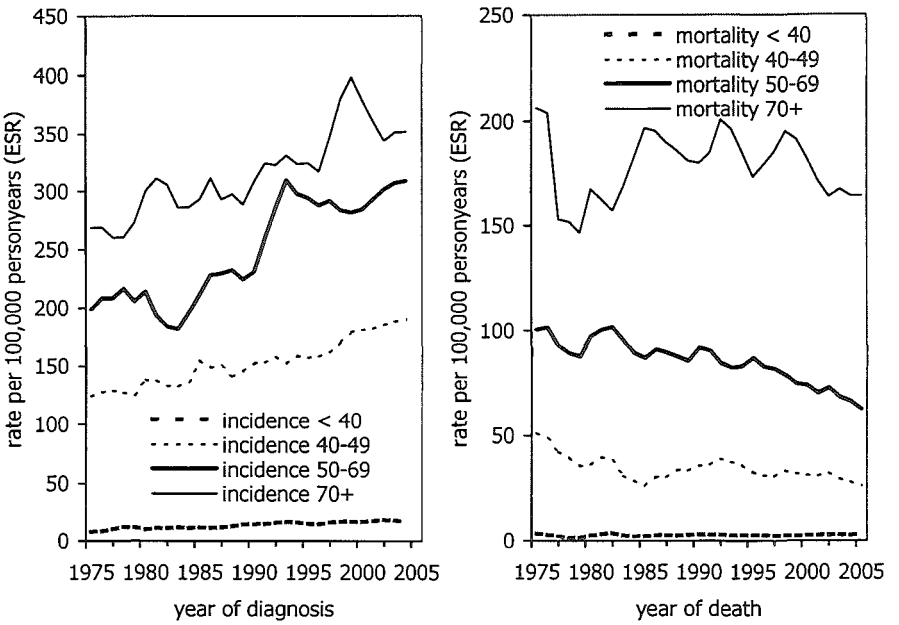

Figure 2 Age-specific trend in incidence and mortality of breast cancer in southeastern Netherlands in 1975-2004

Age-period-cohort analyses resulted in an age-period-drift model as the best fitting model for women younger than 50, as well as for those older than 50. Generally, an increased risk was observed for the more recent periods, risk estimates were higher for women older than 50 (figure 3).

Stage and treatment

Stage distribution became more favourable over time. The proportion of stage I and II tumours increased from 61% in 1975-79 to 77% in 2000-04, whereas the proportion of advanced stages (III & IV) decreased from almost 40% to 13%. (Figure 4). The proportion of in situ tumours increased from 1.5% in 1975-79 to 10% in recent years. Age-standardised incidence of patients with stage I tumours steadily increased (EAPC 4.2%,p <0.0001). Until 2002 the incidence of stage II increased and the incidence of stage III tumours decreased. However, due to the introduction of the new TNM coding the trends were reversed from 2002 onwards. The incidence of stage IV tumours remained around the same level during the study period, although it seems to have decreased a little in recent years to about 5/100,000 in 2004.

The proportion of patients receiving adjuvant systemic therapy increased for all stages combined and for patients both younger and older than 70. In 1975-79 about

20% of patients with stage II or III received systemic therapy and in 2000-04 this proportion had increased to 60%.

Radiotherapy was administered to 50% of the stage I patients in 1975-79 and 65% of these patients in 2000-04.

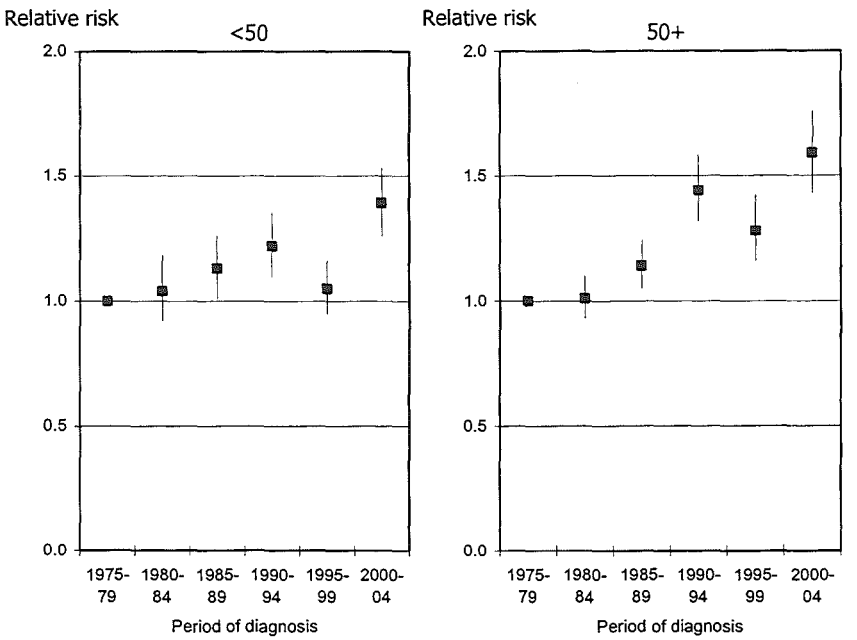

Figure 3 Period effect among women with breast cancer according to age in southeastern Netherlands during 1975-2004

Relative survival

Improvements in relative survival were observed for all age-groups. For women aged 50-69 relative 10-year survival increased from 53% for patients diagnosed in 1975-79 to 75% for patients diagnosed in 1995-02 (Figure 5). Ten-year relative survival rates were 65%, 72% and 62% respectively for patients diagnosed before age 40, between age 40-49, and older than 70, respectively.

A comparison of stage-specific relative survival between the period 1990-1994 and 1995-2002 showed that the rates improved for stage I, II, and III disease (Figure 6), but only marginally for patients with metastasis at diagnosis (stage IV).

The most favourable 3 to 20-year survival rates were observed for patients diagnosed at the age of 45-54 (Figure 7). Prognosis was worse for women older than 80 and particularly poor for women diagnosed before age 35.

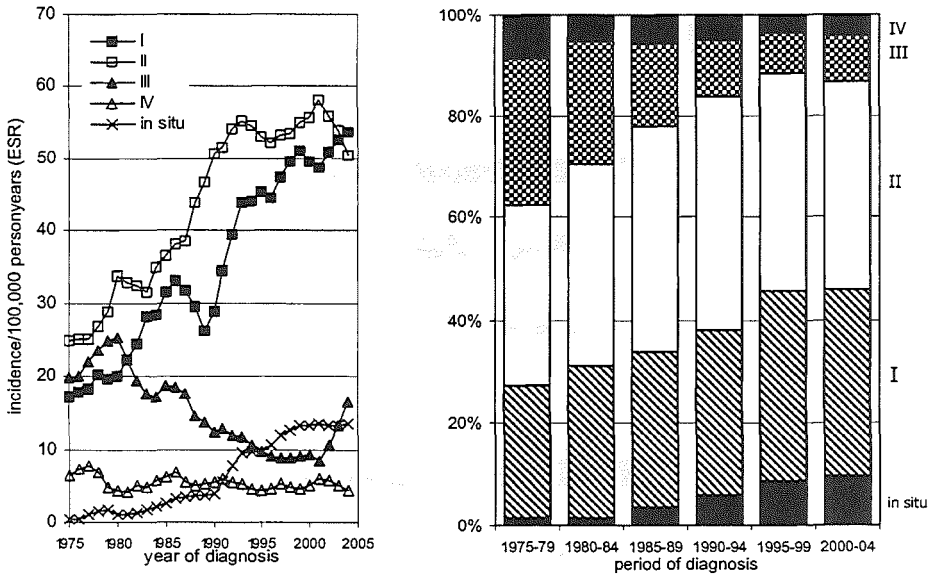

Figure 4 Trend in breast cancer incidence according to stage (a) and stage distribution (b) in southeastern Netherlands in 1975-2004.

Discussion

There has been a sharp increase in breast cancer incidence since 1975. For women younger than 50, the risk was most notably increased in recent periods. Mortality rates were stable for decades but have decreased since the early 1990s, especially for women younger than 70. Stage distribution became more favourable after 1975 but has shown no further improvement since 1995. Treatment increasingly involved a combination of modalities including systemic therapy. Relative 5- and 10-year survival rates improved for each stage and for each age group. The best prognosis at every point in time since diagnosis was observed for patients diagnosed between ages 40 and 50.

Early detection has played a major role in the increase in breast cancer incidence since 1975. The diagnosis of (early) breast cancer has been facilitated by the introduction and increased use of mammography and cytology since the 1980s. In developed countries, recent increases in breast cancer incidence have been partly attributed to (organised) screening activities and increased awareness. However, some of the screen-detected tumours would probably never have been diagnosed without a mass screening programme, so some of the increase is likely to be artificial.

The introduction of mass screening seems to be the most likely explanation for the increase in early stage breast cancer,[24] also in our data, and the decline in the incidence of advanced stage in women aged 50-69.[25] We had already found similar trends, although they started before the introduction of mass screening[7, 8] and involved both aggressive and less aggressive tumours.[9]

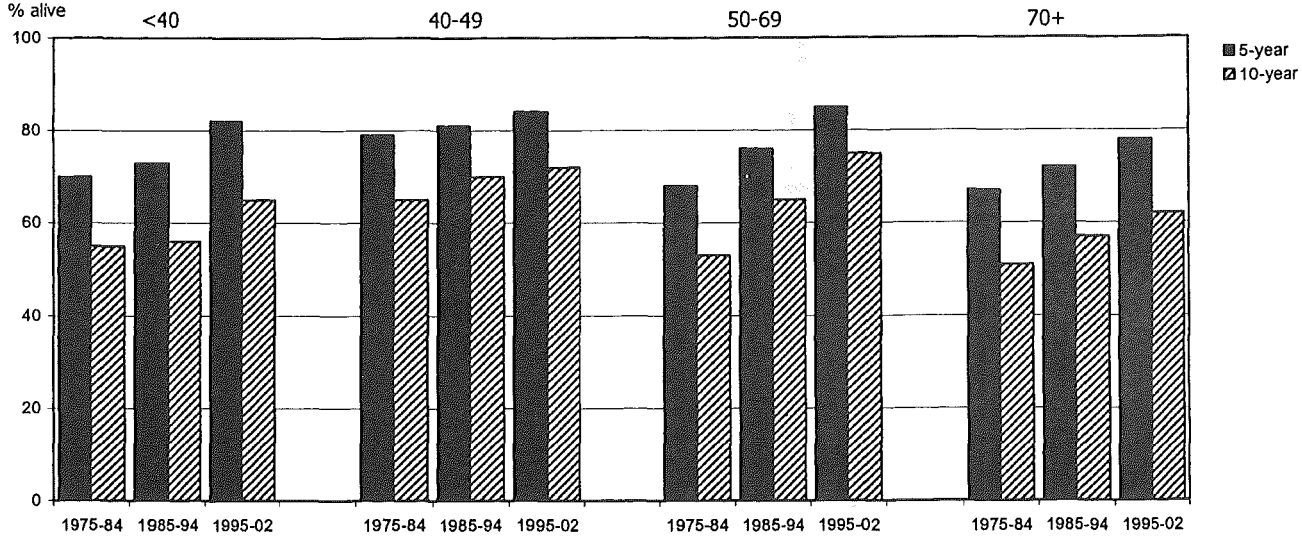

Figure 5 Trend in 5- and 10-year relative survival of breast cancer patients diagnosed between 1975 and 2002 in southeastern Netherlands

This implies that increased exposure to risk factors for breast cancer is likely to have contributed to the observed incidence trends. Moreover most increase associated with early detection could only be temporary. Many known risk factors are in some way related to endogenous hormones: young age at menarche, older age at menopause, older age at birth of first child, lower parity, shorter lactation.[26, 27] These factors have generally changed in an adverse way over the past decades and have probably contributed substantially to the increase. Furthermore, nutrition and in particular obesity,[28] diminishing physical activity[29] and increased alcohol consumption[28] are likely to have had a negative impact on the occurrence of breast cancer.

Among women below age 50 the rising incidence may also be attributed partly to the more vigorous search for families with inheritable breast cancers since 1995. This is in line with the period effect found for this age group. Among women older than 50 the age-period model that fitted the data can be explained by the gradual introduction of mass mammography screening between 1991 and 1996. The period directly following the introduction of screening shows a slight decrease (slowly growing tumours were detected in a previous screening round) followed by an increased risk for the most recent period. The rising risk for periods preceding the population screening programme is probably caused by the subsequent introduction of better diagnostic techniques since the early 1980s and increased awareness since the mid 1980s.

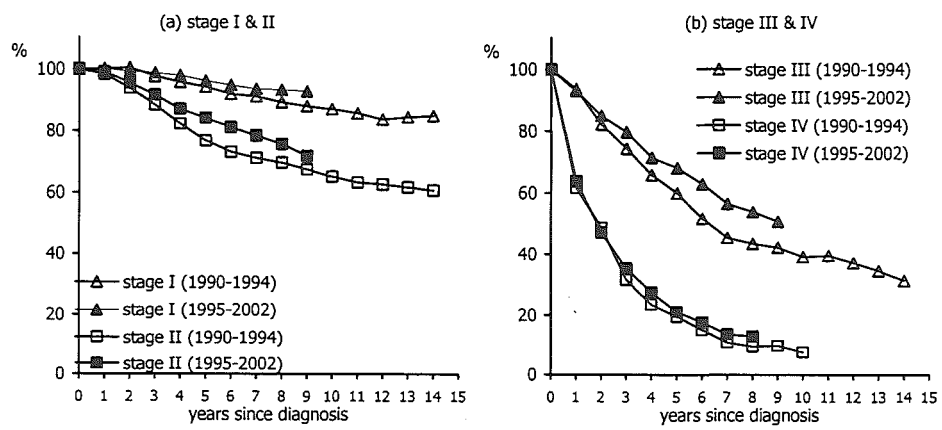

Figure 6 Relative survival of women with invasive breast cancer diagnosed in 1990-2002 in Southeastern Netherlands according to stage of the disease at diagnosis (a) stage I & II (b) stage III and IV

In Europe breast cancer mortality has increased since 1960 to 21.6/100,000 in 1990, but has since decreased to about 20/100,000 (WSR) in 1999, despite the continuing increase in breast cancer incidence. The annual decline in the period 1990-2000 was 1.4%.[30,31]

In the Netherlands, breast cancer mortality had been stable for decades and started to decline in the late 1980s.[11] The ESR has dropped from 39 per 100,000 woman years in 1989 to 32 in 2003 (WSR from 27 to 22/100,000). In addition to a change in the

natural history of the disease, there are two possible explanations for this decline: earlier diagnosis and better treatment.

Although population screening and thus earlier diagnosis is likely to be responsible for the recent decline in mortality,[32] a decrease in mortality as a result of population screening is not expected to become visible until about 10 years after the introduction of screening.[33] Moreover, in Southeastern Netherlands the prognosis had already started to improve after 1970.[7, 8] Generally, changes in survival rates for solid tumours over time in the USA reflect changing patterns of diagnosis rather than true progress in treatment of the disease.[34] The contribution of the introduction of mass mammography screening to the improved survival rates was estimated to be 30% to 50%.[35, 36] Part of the improvement in survival is due to lead time bias (as a result of early detection the time between diagnosis and death is by definition longer) and length bias (some screen-detected tumours would never have progressed to metastasis or death if they had remained undiagnosed).

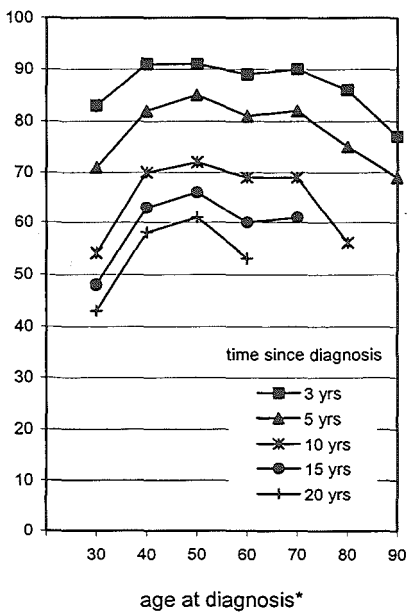

Figure 7 Relative survival of breast cancer patients diagnosed between 1990 and 2002 in southeastern Netherlands, according to age (*midpoint of 10 year age interval) at diagnosis and time since diagnosis

The treatment of breast cancer has changed substantially during the last decades and may have accounted for at least part of the decrease in mortality.[35, 37, 38] Chemotherapy was introduced in the late 1970s, first to node-positive patients and since 1998 also to a subgroup of node-negative patients. The use of adjuvant systemic therapy increased from 15% for patients diagnosed in 1975-1984 to 49% of those diagnosed in

1995-2004. Similar trends have been observed worldwide, following the more pronounced role of systemic therapy in international guidelines.[39, 40] Chemotherapy was estimated to explain 7-50% of the improvement in the breast cancer survival rates.[35, 36] One should note, however, that survival already started to improve in the seventies.[7, 8]

The administration and dosage of radiotherapy became more accurate and the use of megavoltage was introduced in 1974. The increased use of radiotherapy is also related to the increased use of breast-conserving treatment.[41]

Stage-specific survival improved for each tumour stage, as described before,[42] which can partly be explained by stage migration:[43] many patients who previously would have been classified in a "good" stage were assigned to a "bad" stage due to improved diagnostic possibilities. Because the prognosis for those who migrated, although worse than that for other members of the good-stage group, was better than that for other members of the bad-stage group, survival rates rose in each group without any change in individual outcomes. To see whether this played an important role in our study, we also calculated relative survival according to tumour size (T), instead of according to stage (figure 4), the survival rates were fairly similar (data not shown). Moreover the proportion of patients with positive lymph nodes given a certain tumour size did not increase dramatically over the years (among T1 patients it increased from 22% in 1975-1984 to 26% in 1995-2004, among T2 patients from 48% to 50%). So it seems unlikely that stage migration was responsible for the improved stage-specific survival rates

The variation in relative survival according to age and time since diagnosis for patients diagnosed in 1975-1989 was similar to that found in Sweden during the 1980s,[44] although our relative survival rates were somewhat higher. Highest survival was found for women aged 45-54, as was reported by others before the introduction of screening.[44-46] A more favourable distribution of prognostic factors, such as tumour stage, cell differentiation and cell growth rate, was responsible for better survival in this age group in a Finnish study.[47] The particularly poor survival for women diagnosed before age 35 was confirmed in another more recent study.[48] Despite diagnostic and therapeutic advances, the prognosis for women younger than 35 continued to be poor after 1990.

In conclusion, impressive progress appeared in prolonging survival of breast cancer patients, at least partly related to the improved diagnostic possibilities which lead to the detection of smaller lesions. Incidence rates continue to increase and exposure to adverse hormonal and lifestyle factors is not expected to level off or decrease in the near future. Thus the peak in breast cancer incidence is not expected to occur soon. Currently the cumulative risk of developing breast cancer before age 75 is 10%.[10] The combination of increasing incidence and improving survival rates implies that the number of prevalent breast cancer cases will continue to rise. In 2005 there was an estimated number of 119,000 (ex-) breast cancer patients in the Netherlands. In 2015, this number might increase to about 194,000.[49] About 80% of these women will still require some form of health care, either for diagnosis and treatment, surveillance during follow-up, or because of recurrences, metastases or new primary malignancies. This will result in a heavy

burden for health care services. In the long run prevention would be the most useful public health intervention to decrease this burden.

Acknowledgment

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References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide, ed. 5.2 Lyon: IARC Press, 2002.
2. Tyczynski JE, Plesko I, Aareleid T, Primic-Zakelj M, Dalmas M, Kurtinaitis J, Stengrevics A, Parkin DM. Breast cancer mortality patterns and time trends in 10 new EU member states: mortality declining in young women, but still increasing in the elderly. Int J Cancer 2004;112:1056-64.
3. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002;38:99-166.
4. Ferlay J, Bray F, Sankila R, Parkin DM. EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union 1998, ed. 5.0 Lyon: IARC, 1999.
5. NetherlandsCancerRegistry. http://www.ikcnet.nl/page.php?id=1865&nav_id=41, 2005.
6. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004;6:229-39.
7. Nab HW, Hop WC, Crommelin MA, Kluck HM, van der Heijden LH, Coebergh JW. Changes in long term prognosis for breast cancer in a Dutch cancer registry. Bmj 1994;309:83-6.
8. Nab HW, Hop WC, Crommelin MA, Kluck HM, Coebergh JW. Improved prognosis of breast cancer since 1970 in south-eastern Netherlands. Br J Cancer 1994;70:285-8.
9. Louwman WJ, van Diest PJ, van Beek MW, Schapers RF, Nolthenius-Puylaert TM, Baak JP, Coeberg JW. Trends in breast cancer aggressiveness before the introduction of mass screening in southeastern Netherlands 1975-1989. Breast Cancer Res Treat 2002;73:199-206.
10. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW. Results of 50 years cancer registry in the South of the Netherlands: 1955-2004 (in Dutch) Eindhoven: Eindhoven Cancer Registry, 2005.
11. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. Eur J Cancer 2003;39:1718-29.
12. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Should we use incidence, survival or mortality to assess breast cancer trends in European women? Nat Clin Pract Oncol 2006;3:228-9.
13. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents., vol. VIII Lyon: IARC Scientific Publications, 2002.
14. Harmer MH. TNM classification of malignant tumors, 3rd ed. Geneva: IUCC, 1978.
15. Hermanek P, Sobin L. TNM classification of malignant tumors, 4th, 2nd rev. ed. Berlin: Springer-Verlag, 1992.
16. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 5th Geneva, Switzerland: Wiley-Liss, 1997:227.
17. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 6th Geneva, Switzerland: Wiley-Liss, 2002:239.
18. Voogd AC, van Beek MW, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JW. Management of early breast cancer in southeast Netherlands since 1984. A population-based study. Regional Breast Cancer Study Group. Acta Oncol 1994;33:753-7.
19. Rutgers EJ, Nortier JW, Tuut MK, van Tienhoven G, Struikmans H, Bontenbal M, von Meyenfeldt MF, Vreugdenhil G, Benraadt T, Garssen B, Peterse JL. [Dutch Institute for Healthcare Improvement guideline, "Treatment of breast cancer"]. Ned Tijdschr Geneeskd 2002;146:2144-51.

20. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. Stat Med 1987;6:449-67.
21. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. Comput. Programs Biomed. 1985;19:197-207.
22. Houterman S, Janssen-Heijnen ML, van de Poll-Franse LV, Brenner H, Coebergh JW. Higher long-term cancer survival rates in southeastern Netherlands using up-to-date period analysis. Ann Oncol 2006;17:709-12.
23. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996;78:2004-10.
24. van Dijck JA, Hendriks JH, Holland R, Schouten LJ, Verbeek AL. [Alterations of stage distribution for breast cancer since the implementation of national screening program in the Netherlands during 1989-1995]. Ned Tijdschr Geneeskd 2000;144:1119-24.
25. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. Br J Cancer 2004;91:861-7.
26. Hankinson S, D H. Breast cancer. In: Adami HO, Hunter D, D T. Textbook of Cancer Epidemiologyed. Oxford: Oxford Univeristy Press, 2002:301-39.
27. Macmahon B. Epidemiology and the causes of breast cancer. Int J Cancer 2006;118:2373-8.
28. SignaleringscommissieKanker, De rol van voeding bij het ontstaan van kanker. KWF Kankerbestrijding, 2004.
29. SignaleringscommissieKanker, De rol van lichaamsbeweging bij preventie van kanker. KWF Kankerbestrijding, 2005.
30. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Cancer mortality in Europe, 1995-1999, and an overview of trends since 1960. Int J Cancer 2004;110:155-69.
31. Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from major cancers in the European Union, including acceding countries, in 2004. Cancer 2004;101:2843-50.
32. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, Verbeek AL, de Koning HJ. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-7.
33. Jatoi I, Miller AB. Why is breast-cancer mortality declining? Lancet Oncol 2003;4:251-4.
34. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? Jama 2000;283:2975-8.
35. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. Br J Cancer 2004;91:242-7.
36. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.
37. Thomson CS, Brewster DH, Dewar JA, Twelves CJ. Improvements in survival for women with breast cancer in Scotland between 1987 and 1993: impact of earlier diagnosis and changes in treatment. Eur J Cancer 2004;40:743-53.
38. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
39. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005;16:1569-83.
40. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357-65.
41. Siesling S, van de Poll-Franse LV, Jobsen JJ, Repelaer van Driel OJ, Voogd AC. [Trends and variation in breast conserving surgery in the southeast and east of the Netherlands over the period 1990-2002]. Ned Tijdschr Geneeskd 2005;149:1941-6.
42. Visser O, van Leeuwen FE. Stage-specific survival of epithelial cancers in North-Holland/Flevoland, The Netherlands. Eur J Cancer 2005;41:2321-30.
43. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604-8.

44. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. N Engl J Med 1986;315:559-63.
45. Sant M, Capocaccia R, Verdecchia A, Esteve J, Gatta G, Micheli A, Coleman MP, Berrino F. Survival of women with breast cancer in Europe: variation with age, year of diagnosis and country. The EUROCARE Working Group. Int J Cancer 1998;77:679-83.
46. Mohle-Boetani J, Grosser S, Malec M, Whittemore AS. Survival advantage among patients with breast cancer diagnosed at 45 to 49 years of age. N Engl J Med 1986;315:587.
47. Holli K, Isola J. Effect of age on the survival of breast cancer patients. Eur J Cancer 1997;33:425-8.
48. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. Bmj 2000;320:474-8.
49. SignaleringscommissieKanker, Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. KWF Kankerbestrijding, 2004.

2.3

Uncommon breast cancer in perspective: incidence, treatment and survival in the Netherlands

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Abstract

The relatively small group of patients with breast tumours other than the ductal, lobular or mixed ducto-lobular types, has reached non-negligible numbers due to the ongoing increase in the incidence of breast cancer.

We investigated stage and grade distribution of uncommon breast tumours using the nation-wide Netherlands Cancer Registry (population 16.5 million) and incidence patterns, treatment and long-term survival (up to 19 yrs) using the regional Eindhoven Cancer Registry (population 2.4 million).

Incidence of all uncommon breast tumours together was 9.2/100,000 personyears (age-standardised, ESR). The proportion of stage I tumours was 70% among patients with tubular (n=3456) and 40% to 50% for mucinous (n=3482), papillary (n=1078), cribriform (n=503), and neuroendocrine (n=76) tumours, contrasting to 27%, 28% and 36%, respectively among patients with Signet ring cell cancer (n=75), Paget's disease (n=818) and the common invasive ductal carcinomas (n=121,656).

A better age-, stage-, and grade-adjusted prognosis was observed for patients with lobular (death risk ratio 0.8, 95%CI: 0.7-0.9), mucinous (0.5, 0.3-0.9), medullary (0.5, 0.3-0.9) and tubular (0.4, 0.2-0.6) carcinoma or phyllodes tumour (0.02, 0.0-0.2), compared with invasive ductal carcinomas. For patients with papillary (0.6, 0.2-1.6) and cribriform (0.1, 0.0-5.1) tumours better prognosis was not statistically significant.

In conclusion, histologic type was an essential determinant of survival for about 10% of all newly diagnosed women with invasive breast cancer. Because patients with mucinous, tubular, medullary and phyllodes tumours have such a good prognosis, less aggressive treatment should be considered in some cases whereby specific guidelines are becoming increasingly desirable. Communication to patients with these specific histological types should reflect this.

Introduction

The large majority of breast cancer patients is diagnosed with an invasive ductal (about 65-75%) or lobular (15%) carcinoma.[1] An increasing proportion of up to 7% is diagnosed with a mixed ducto-lobular tumour (two-fold increase between 1987-1999 in the USA).[2] The remaining 10% of newly diagnosed breast cancers with another histology have been the subject of only a limited number of studies.

Previously, the substantial variation found in age-specific incidence between different histological subtypes in large population-based studies,[3, 4] suggested different aetiologies. Patients with a papillary or mucinous tumour are 5 to 10 years older than those with a ductal carcinoma, while patients with a medullary tumour tend to be about 10 years younger.[3, 5] Survival according to morphology has been reported in a few studies, but these described small series of patients,[6-9] only one or two specific subtypes,[6, 9, 10] on patients diagnosed and treated before 1995[6, 8, 11], or without complete information on treatment.[12, 13] In these studies prognosis for mucinous[10, 12, 13] , tubular[7, 10, 13] medullary[13] or papillary[13] carcinoma was significantly better than that of patients with an invasive ductal carcinoma.

Within the increasing incidence of breast cancer the incidence and the number of patients with an uncommon tumour may increase more. Therefore, more knowledge about the frequency and natural history of these tumours is desirable. A large population is necessary to obtain a sufficient number of patients with these relatively rare tumours in a reasonable time span.

The Netherlands Cancer Registry (NCR), in operation since 1989 and covering the whole country with a current population of 16.5 million people, provides a unique opportunity to investigate the occurrence and characteristics of these uncommon breast tumours. In addition, we will study details regarding treatment and long-term survival in a part of the NCR, the Eindhoven Cancer Registry (ECR) that was started in 1955.

Patients and methods

We used data from the nation-wide Netherlands Cancer Registry (www.ikcnet.nl), which consists of nine regional cancer registries since 1989. The cancer registries receive lists of newly diagnosed cases on a regular basis from the pathology departments, all participating in a nation-wide pathology network (PALGA). In addition the medical records departments of hospitals provide lists of diagnoses of outpatients and hospitalised cancer patients. Following this notification, trained tumour registration clerks abstract information according to a minimum data set, including patient characteristics (gender, birth date), tumour information (topography, histology, stage, date of diagnosis) and treatment.

Topography and histology were coded according to the International Classification of Diseases for Oncology (ICD-O).[14] We grouped the histology codes according to the classification in table 1.

We included all patients diagnosed with a first histological type of malignant breast tumour between January 1989 and December 2003 (n=158,353). In addition 493 patients with a second primary breast tumour other than invasive ductal, lobular, mixed ducto-lobular or other/NOS were included in the analyses, resulting in 158,846 tumours for analyses of which 13,666 (8.6%) uncommon histological types.

Table 1 Classification of morphology of consecutive patients diagnosed with malignant breast tumours in the Netherlands (1989-2003) and Southeastern Netherlands (1973-2004)

		Netherlands Cancer Registry		Eindhoven Cancer Registry	
Histological group	Morphology code according to ICD-O[14]	n	%	n	%
Invasive ductal (not otherwise specified)	8010-8021,8140-8141,8190,8230-8231,8310-8441,8500-8502,8508, 8514,8521,8523,8530,8550	121,656	77	22,160	78
Lobular	8145,8520,8524	17,293	11	3,105	11
Mixed ducto-lobular	8522	6,231	3.9	961	3.4
Mucinous	8480,8481,8482	3,482	2.2	473	1.7
Medullary	8510-8513	1,677	1.1	271	1.0
Tubular	8211	3,456	2.2	533	1.9
Papillary	8050,8260,8450,8503,8504,8507	1,078	0.7	124	0.4
Metaplastic	8031-8035, 8560,8570-8573, 8575, 8801,8980, 9180,9183,9220	312	0.2	33	0.1
Squamous cell (SCC)	8070-8074	44	0.0	12	0.0
Adenoid cystic	8200	98	0.1	9	0.0
Cribriform	8201	503	0.3	63	0.2
Neuroendocrine (carcinoid)	8240-8246,8574,8249,9091	76	0.0	5	0.0
Signet ring cell	8490	75	0.0	5	0.0
Paget disease	8540-8543	818	0.5	127	0.4
Sarcoma	8800,8810-8921,8931,8935,8990, 8991,9040-9044, 9131-9179, 9184-9219, 9221-9230, 9232-9342,9364-9372, 9473,9540-9559, 9561-9581	79	0.0	15	0.1
Hemangiosarcoma	9120-9130	70	0.0	12	0.0
Phyllodes	9020	427	0.3	83	0.3
Lymphoma*	9590-9729,9850	98	0.1	24	0.1
Other	all other codes, including patients without pathological verification	1,373	0.9	344	1.2
Subtotal uncommon		*13,6*	*8.6*	*2,133*	*7.5*
Total		158,846	100	28,359	100

* Only patients with invasive lymphoma of the breast stage I^E (Ann Arbor)

These data were used to analyse the age at diagnosis and the stage and grade distribution according to histological group.

Age was presented as median, with 25% and 75% percentiles (Q1-Q3) and the 1%-99% range.

Stage of the solid tumours was categorized according to the IUCC TNM-classification[15] for all patients diagnosed until 2002. From 2003 onwards, when a new

classification became effective,[16] patients with more than 3 positive lymph nodes, previously included in stage II , are now considered stage III. Stage could not be classified according to the TNM system for patients with (hemangio)sarcomas, phyllodes tumours, and those with other/NOS tumours (the latter groups comprised 403 patients (0.25%) with a clinical diagnosis only). For patients with a lymphoma the Ann Arbor classification was used. We selected only patients with Ann Arbor stage IE, i.e. the patients with only one extranodal tumour site, i.e. the breast[17] (n=98, 0.6% of all lymphomas in women, 4% of all extranodal lymphomas).

Grade was categorised in 4 classes: well (1), moderately (2), or poorly (3) differentiated or undifferentiated/anaplastic (4). Strict criteria for assigning stage were only followed since the most recent decade, so the value of the tumour grade before that time is somewhat limited.

In addition we used data from the Eindhoven Cancer Registry (ECR) in the south of the Netherlands (population 0.9 million between 1975 and 1985, over 2 million since 1988 after an expansion of the registration area, comprising 15% of the Dutch population in 2004). This population-based cancer registry was started in 1955 and is the oldest cancer registry in the Netherlands and among the oldest in Europe. Data on patients who lived in the catchment area of the Eindhoven Cancer Registry, but who were diagnosed in hospitals elsewhere in the Netherlands, were retrieved on a routine basis from all other Dutch Cancer Registries since 1989. This has been completed up to 2002, so incidence rates for 2003 and 2004 may be underestimated by about 3% (unselected patients).

From the ECR, all breast cancer patients diagnosed between 1973 and 2004 (n=28,359) were used to study time trends in incidence. Age-adjustment was performed by direct standardisation according to the European Standard Population (European Standardised Rates, ESR). Annual incidence rates were calculated as 3-year moving averages.

Trends in incidence were estimated by calculating the estimated annual percentage change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as regressor variable, i.e., $y=mx + b$ where $y=\ln(\text{rate})$ and x=calendar year. Then $EAPC=100x (em -1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

We used information on type of treatment (surgery, radiotherapy, systemic therapy) for patients diagnosed in 1985-2004 (n=24,217); these results are presented separately for patients younger and older than 70 years at diagnosis separately.

For a subgroup of patients (n=16,797) diagnosed in the eastern part of the ECR region and those diagnosed since 1994 in the western part (all until 2002), we obtained complete information on vital status up to 1-1-2005 from the Central Bureau for Genealogy (CBG). This registry provides virtually complete coverage of all deceased Dutch citizens.

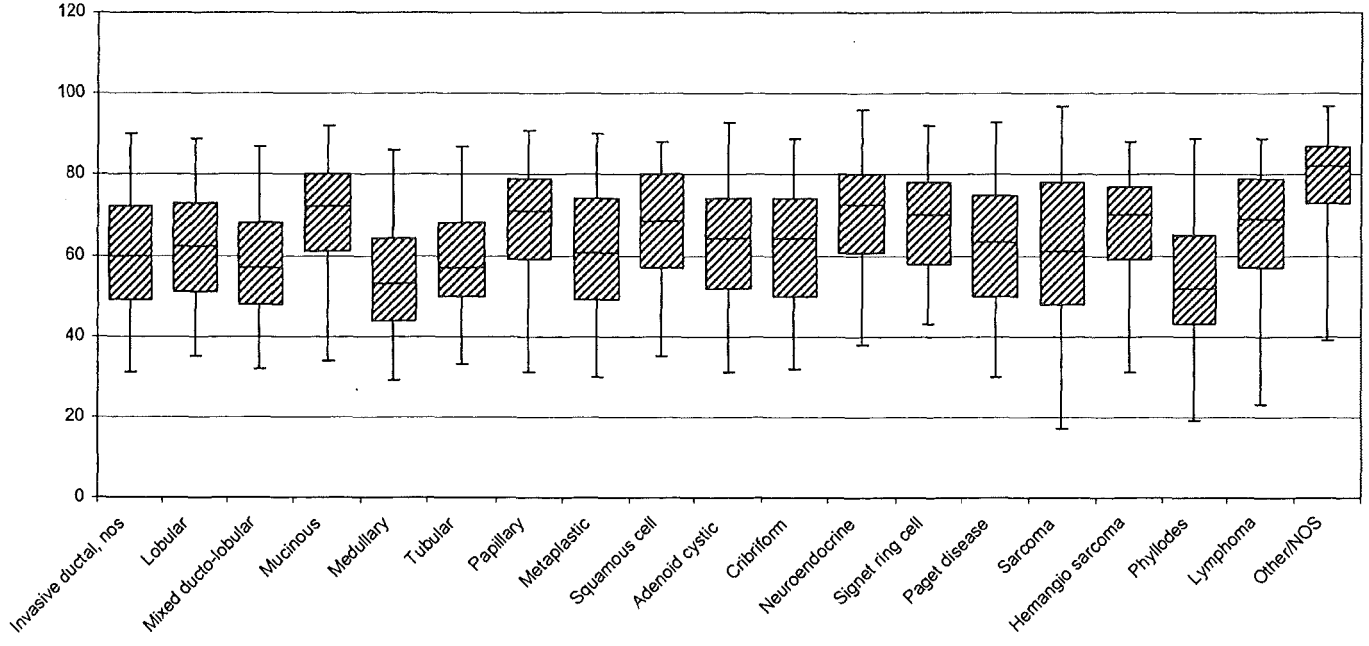

Figure 1 Age distribution of consecutive patients diagnosed with invasive breast cancer in the Netherlands 1989-2003 (median, Q1, Q3, P1,P99)

Relative survival (the ratio of the observed to the expected survival rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a reference population with the same age structure [18]. Expected survival rates were calculated from life tables for the female population of the ECR catchment area with the same 5-year age distribution. We used generalised linear models with a Poisson error structure, based on collapsed data and exact survival times.[19] When the number of patients effectively at risk in a particular category became too small for a reliable estimation of relative survival (i.e. <10), the results are not shown.

All statistical analyses were performed with SAS (SAS System version 9.1, Cary, CA, USA).

Results

The incidence of all uncommon breast cancers combined (i.e. all breast cancers other than invasive ductal, lobular, or mixed ducto-lobular) was 9.2/100,000 personyears (ESR) over the period 1989-2003, in total more than 13,500 new patients in the Netherlands (8.6% of all breast cancers).

The median age varied according to histological type (figure 1). The median age of patients with a ductal carcinoma at diagnosis was 60 years (Q1-Q3: 49-72). Patients with a phyllodes tumour or medullary, or tubular carcinoma were younger (median age 52, 53, and 57 years, respectively). Those with other histological types were older; patients with a histology classified as other/NOS were the oldest at diagnosis (median 82 (73-87)).

Stage distribution was most favourable for patients with mucinous, tubular, papillary, cribriform and neuro-endocrine tumours (table 2). For example, the proportion of patients with a stage I tumour was 42%, 70%, 45%, 52% and 42%, respectively, in comparison to 36% of patients with an invasive ductal carcinoma. A less favourable stage distribution with only 27% and 28% stage I tumours was observed for patients with Signet ring cell cancer and Paget's disease, respectively. Although tumour grade was unknown for a relatively large proportion of patients (44%) the proportion with a grade 1 tumour was high among patients with mucinous, tubular, papillary, cribriform and phyllodes tumours, compared to those with an invasive ductal carcinoma.

The incidence of invasive ductal carcinoma varied between 75 and 85/100,000 personyears (ESR) during the 70s and 80s, but has increased markedly since the early 1990s (figure 2). In the mid 1990s during the start of the mass screening programme for women of 50-69 years (since 1998 extended to women of 70-74 years) a small decline was observed. But thereafter the incidence increased markedly again, to about 110/100,000. The incidence of lobular breast tumours increased markedly until 1985 upto about 12/100,000, thereafter it increased more modestly to about 15/100,000 in 2003, the mixed-ductolobular tumours increased from 1985 onwards and has been to about 5/100,000 since 1995.

Table 2 Characteristics of patients with malignant breast tumours diagnosed 1989-2003 in the Netherlands according to histological group

	Invasive ductal, nos		Lobular		Mixed ducto-lobular		Mucinous		Medullary		Tubular		Papillary		Metaplastic		Squamous cell		Adenoid cystic	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age at diagnosis																				
<50 years	34074	28	4103	24	2061	33	458	13	728	43	1001	29	159	15	91	29	7	16	20	20
50-69	51275	42	7565	44	2743	44	971	28	676	40	1777	51	356	33	112	36	16	36	43	44
70+ years	36307	30	5625	33	1427	23	2053	59	273	16	678	20	563	52	109	35	21	48	35	36
Stage at diagnosis																				
I	43744	36	5433	31	2206	35	1468	42	583	35	2415	70	488	45	51	16	8	18	49	50
II	57817	48	8318	48	3200	51	1672	48	1002	60	893	26	478	44	145	46	29	66	43	44
III	10785	9	2191	13	521	8	176	5	65	4	75	2	48	4	25	8	5	11	1	1
IV	7287	6	1002	6	179	3	100	3	18	1	31	1	27	3	12	4	1	2	2	2
NA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	73	23	0	0	0	0
unknown	2023	2	349	2	125	2	66	2	9	1	42	1	37	3	6	2	1	2	3	3
Grade																				
1	9735	8	943	5	546	9	531	15	9	1	1097	32	186	17	8	3	3	7	8	8
2	30356	25	2971	17	1533	25	539	15	76	5	267	8	161	15	26	8	13	30	8	8
3	34054	28	1494	9	1069	17	198	6	537	32	94	3	90	8	117	38	12	27	2	2
4	562	0	42	0	6	0	2	0	17	1	3	0	2	0	2	1	1	2	0	0
unknown	46949	39	11843	68	3077	49	2212	64	1038	62	1995	58	639	59	159	51	15	34	80	82
Total	121656		17293		6231		3482		1677		3456		1078		312		44		98	

	Cribriform		Neuro endocrine		Signet ring cell		Paget disease		Sarcoma		Hemangio sarcoma		Phyllodes		Lymphoma		Other/NOS		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age at diagnosis																				
<50 years	127	25	8	11	12	16	205	25	24	30	9	13	193	45	14	14	57	4	43351	27
50-69	193	38	26	34	24	32	313	38	28	35	25	36	154	36	37	38	207	15	66541	42
70+ years	183	36	42	55	39	52	300	37	27	34	36	51	80	19	47	48	1109	81	48954	31
Stage at diagnosis																				
I	263	52	32	42	20	27	233	28	0	0	0	0	0	0	0	0	4	0	56997	36
II	215	43	30	39	28	37	316	39	0	0	0	0	0	0	0	0	2	0	74188	47
III	15	3	5	7	11	15	142	17	0	0	0	0	0	0	0	0	1	0	14066	9
IV	5	1	4	5	14	19	27	3	0	0	0	0	0	0	0	0	3	0	8712	5
NA	0	0	0	0	0	0	0	0	79	100	70	100	427	100	98	100	1363	99	2110	1
unknown	5	1	5	7	2	3	100	12	0	0	0	0	0	0	0	0	0	0	2773	2
Grade																				
1	97	19	9	12	1	1	11	1	6	8	6	9	84	20	0	0	2	0	13282	8
2	108	21	12	16	8	11	115	14	8	10	4	6	1	0	0	0	0	0	36206	23
3	48	10	13	17	23	31	275	34	8	10	8	11	12	3	0	0	4	0	38058	24
4	0	0	1	1	2	3	1	0	1	1	1	1	1	0	0	0	5	0	649	0
unknown	250	50	41	54	41	55	416	51	56	71	51	73	329	77	23	23	1362	99	70576	44
Total	503		76		75		818		79		70		427		98		1373		158846	100

NA=not applicable

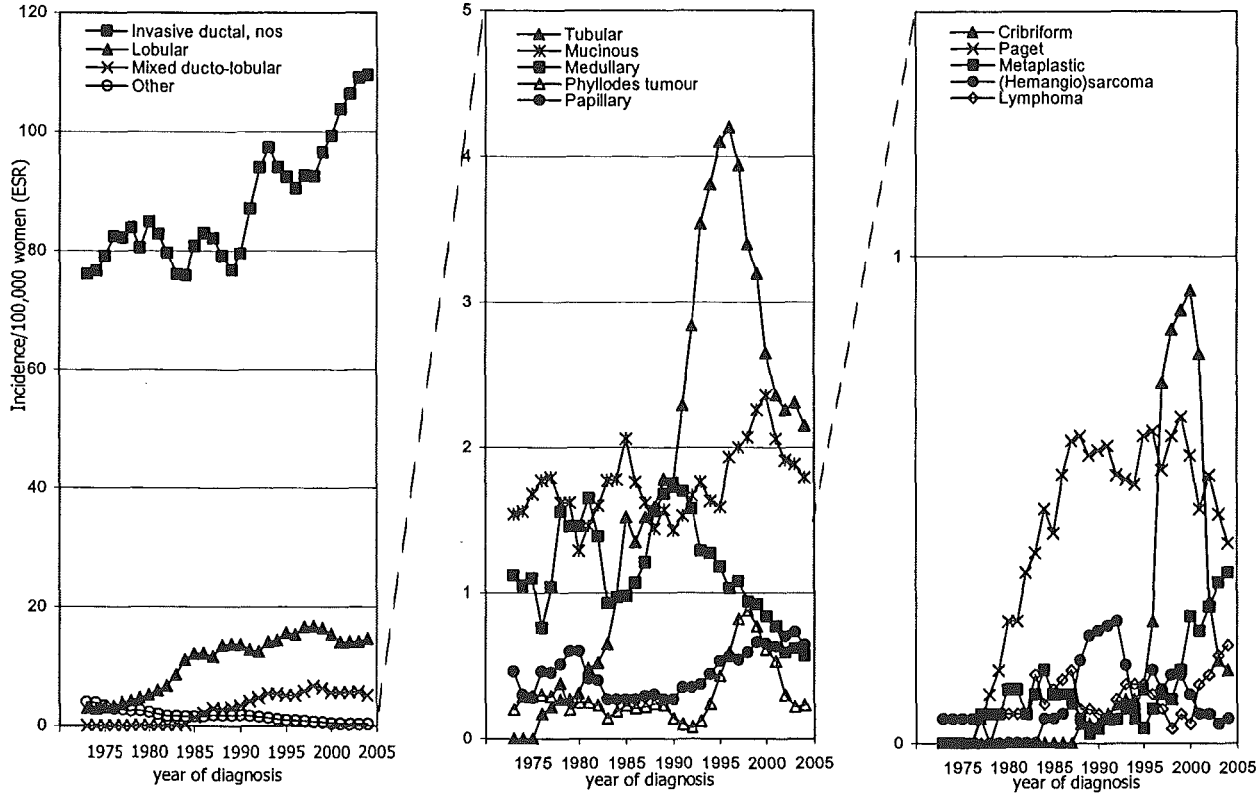

Figure 2 Trend in incidence (3-year moving averages) according to histology for consecutive patients diagnosed with invasive breast cancer in southeastern Netherlands 1973-2004

Table 3 Treatment of patients with malignant breast cancer diagnosed in the southeast of the Netherlands 1985-2004 according to histological group and age at diagnosis

Age		Invasive ductal, nos		Lobular		Mixed ducto-lobular		Mucinous		Medullary		Tubular		Papillary		Metaplastic		Squamous cell		Adenoid cystic	
<70	Treatment	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	S alone	2418	18	374	19	154	21	37	21	39	23	90	21	18	31	2	13	2	33	1	17
	S+RT	4924	36	703	35	212	29	92	51	66	38	239	57	26	45	4	25	1	17	5	83
	S+RT+ST	4075	30	586	29	246	33	26	15	48	28	56	13	6	10	7	44	1	17	0	0
	S+ST	1609	12	242	12	95	13	15	8	15	9	23	5	6	10	2	13	1	17	0	0
	ST alone	242	2	39	2	4	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0
	Unknown	298	2	31	2	23	3	4	2	2	1	13	3	2	3	1	6	1	17	0	0
	Other/N	226	2	30	2	8	1	5	3	1	1	0	0	0	0	0	0	0	0	0	0
Total		13792		2005		742		179		172		422		58		16		6		6	

		Cribriform		Neuro endocrine		Signet ring cell		Paget disease		Sarcoma		Hemangio sarcoma		Phyllodes		Lymphoma		Other/NOS		Total	
	Treatment	n	%	n	%	n	%	n	%	n	%			n	%	n	%	n	%	n	%
	S alone	8	19	0	0	1	33	31	42	4	44	4	57	59	92	1	7	1	2	3244	18
	S+RT	14	33	1	100	0	0	16	22	5	56	0	0	4	6	0	0	3	6	6315	36
	S+RT+ST	10	24	0	0	1	33	16	22	0	0	0	0	0	0	1	7	0	0	5079	29
	S+ST	7	17	0	0	1	33	9	12	0	0	2	29	0	0	3	20	0	0	2030	11
	ST alon	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	7	22	43	310	2
	Unknown	3	7	0	0	0	0	1	1	0	0	1	14	1	2	0	0	4	8	385	2
	Other/N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	60	21	41	300	2
Total		42		1		3		73		9		7		64		15		51		17663	100

Age		Invasive ductal, nos		Lobular		Mixed ducto-lobular		Mucinous		Medullary		Tubular		Papillary		Metaplastic		Squamous cell		Adenoid cystic	
70+	Treatment	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	S alone	1124	24	196	23	62	28	76	34	12	29	24	25	14	29	7	47	3	75	2	67
	S+RT	1060	22	199	23	52	24	58	26	14	33	38	40	20	42	4	27	0	0	1	33
	S+RT+ST	907	19	175	20	53	24	19	9	5	12	17	18	6	13	0	0	0	0	0	0
	S+ST	861	18	156	18	43	20	43	19	6	14	14	15	6	13	2	13	0	0	0	0
	ST alon	544	11	98	11	2	1	13	6	2	5	1	1	1	2	0	0	1	25	0	0
	Other/N	166	3	21	2	2	1	6	3	0	0	2	2	0	0	2	13	0	0	0	0
	Unknown	104	2	14	2	4	2	6	3	3	7	0	0	1	2	0	0	0	0	0	0
Total		4766		859		218		221		42		96		48		15		4		3	

		Cribriform		Neuro endocrine		Signet ring cell		Paget disease		Sarcoma		Hemangio sarcoma		Phyllodes		Lymphoma		NOS		Total	
	Treatment	n	%	n	%	n	%	n	%	n	%			n	%	n	%	n	%	n	%
	S alone	12	57	3	75	0	0	21	46	3	60	5	100	6	86	2	25	1	1	1573	24
	S+RT	3	14	1	25	0	0	7	15	1	20	0	0	0	0	1	13	0	0	1459	22
	S+RT+ST	3	14	0	0	1	50	8	17	0	0	0	0	0	0	0	0	0	0	1194	18
	S+ST	1	5	0	0	0	0	8	17	0	0	0	0	0	0	0	0	2	1	1142	17
	ST alon	0	0	0	0	1	50	1	2	1	20	0	0	1	14	0	0	138	75	804	12
	Unknown	2	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	3	139	2
	Other/N	0	0	0	0	0	0	1	2	0	0	0	0	0	0	5	63	38	21	243	4
Total		21		4		2		46		5		5		7		8		184		6554	100

In 2004 these two groups together comprised about 15% of all invasive breast cancers. The incidence of all uncommon tumours combined was generally low (3 to 5/100,000/year) during the 1970s and 1980s, but increased over time to 12/100,000 in 1998; it subsequently decreased to about 7/100,000 in 2004. A markedly increased incidence in the mid 1990s followed by a decline was observed for patients with tubular, phyllodes and cribriform tumours. This trend was also observed for (hemangio)sarcoma, but about 5 years earlier. The incidence of patients with a medullary tumour has decreased since the early 1990s from 1.8 to 0.6/100,000 in 2004 (EAPC: -9.4%, p=0.001). A steady increase, also in recent years, was observed for papillary (EAPC: +7.5%, p=0.001) and metaplastic (EAPC: +10%, p=0.05) tumours and lymphomas (EAPC: +6%, p=0.2).

The large majority of patients underwent surgery, especially those younger than 70 (94%) (table 3). Treatment of patients below age 70 with mucinous, tubular, papillary, cribriform, Paget or (hemangio) sarcomas was generally less aggressive; the proportion receiving adjuvant systemic therapy in addition to surgery and radiotherapy was significantly lower (respectively 15%, 13%, 24%, 22%, 0%) in comparison with patients with invasive ductal carcinomas (30%). Similar tendencies were observed for patients older than 70 years at diagnosis. Systemic therapy (mostly hormonal therapy) was administered to 48% of patients with an invasive ductal carcinoma, these proportions were 34%, 34%, 28%, and 19%, respectively, for patients with mucinous, tubular, papillary, and cribriform carcinoma.

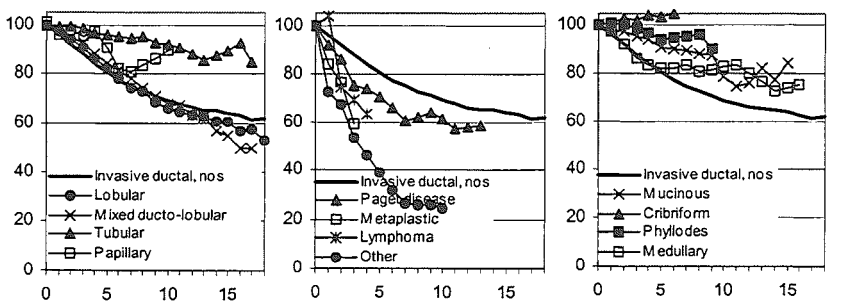

Figure 2 Relative survival according to histology for consecutive patients diagnosed with invasive breast cancer in the southeastern Netherlands

Relative 5-year survival rates for patients with lobular (82%) or mixed ducto-lobular (84%) carcinomas were slightly more favourable than those for patients with an invasive ductal carcinoma (81%) (figure 3). Prognosis was significantly worse for those with Paget's disease, metaplastic tumours, breast lymphoma or other/NOS tumours, with 3-year survival rates of 75%, 59%, 69% and 54%, respectively. All other histological groups exhibited significantly better survival rates compared to invasive ductal carcinoma, especially patients with tubular carcinoma or phyllodes tumour, with 5-yr relative survival rates of 97% and 94%, almost similar to that of women without breast cancer. Survival of

patients with cribriform tumours was comparable to that for women never diagnosed with breast cancer (5-year relative survival 104%).

Multivariate analyses of relative survival (table 4) showed a significantly better prognosis for patients with lobular (Relative Excess Risk of death (RER) 0.82, 95%CI: 0.7-0.9), mucinous (0.53, 0.3-0.9), medullary (0.52, 0.3-0.9), tubular (0.39, 0.2-0.6) carcinoma or phyllodes tumour (0.02, 0.0-0.2), independent of age at diagnosis, stage, and grade. Prognosis for patients with papillary (RER 0.57, 95%CI: 0.2-1.6), and cribriform (0.11, 0.0-5.1) tumours was also better than that for patients with invasive ductal carcinoma, though not statistically significant.

Table 4 Multivariate regression analysis of relative survival rates of consecutive patients with malignant breast tumours in southeastern Netherlands, 1985-2002

		RER	95% CI
Histolgical group	Invasive ductal, nos	1.00	
	Lobular	0.82	0.7 - 0.9
	Mixed ducto-lobular	0.95	0.8 - 1.1
	Mucinous	0.53	0.3 - 0.9
	Medullary	0.52	0.3 - 0.9
	Tubular	0.39	0.2 - 0.6
	Papillary	0.57	0.2 - 1.6
	Metaplastic*		
	Squamous cell carcinoma (SCC)*		
	Adenoid cystic*		
	Cribriform	0.11	0.0 - 5.1
	Neuroendocrine*		
	Signet ring cell*		
	Paget disease	0.76	0.4 - 1.3
	Sarcoma*		
	Hemangiosarcoma*		
	Phyllodes	0.02	0.0 - 0.2
	Lymphoma*		
	Other	0.97	0.6 - 1.6
Age at diagnosis	<50 years	1.00	
	50-69 years	1.04	1.0 - 1.1
	70+ years	1.36	1.2 - 1.5
Stage at diagnosis	I	1.00	
	II	2.43	2.2 - 2.7
	III	5.10	4.5 - 5.8
	IV	19.8	18 - 22
	NA	10.1	6.1 - 17
	unknown	2.59	1.9 - 3.5
Grade	1	1.00	
	2	1.61	1.2 - 2.2
	3	2.31	1.7 - 3.1
	4	2.35	1.4 - 4.0
	unknown	1.97	1.5 - 2.6

* Number of patients at risk too small for calculation of RER

NA=not applicable

Discussion

The number of patients with uncommon tumours in the Netherlands has increased markedly since 1989, with about 700-800 new patients every year; for this largely heterogeneous group the incidence lies between those of cervical and ovarian cancer.

The less frequent histological types of breast cancer were clearly other entities than ductal carcinoma, as shown by differences in age at diagnosis, stage, and grade distribution. The pattern of incidence rates over time was different from that of ductal carcinoma and relative survival rates also differed for the uncommon tumours, with very good survival rates for patients with cribriform or tubular cancer or phyllodes tumour, and poor survival for the lymphomas and metaplastic tumours.

Use of data from the large nation-wide Netherlands Cancer Registry allowed analyses of rare tumours which otherwise could not have been studied at a population-based level due to insufficient numbers. A potential drawback might be the involvement of a large number of pathologists who diagnosed the breast tumours, which may have led to some morphology misclassification, although it seems unlikely that this resulted in over- or under representation of specific histolgical types. This is also supported by the similarity of histological distribution of the Dutch (NCR) and the Eindhoven Cancer Registry. Also, the distribution according to age, stage, and grade between the two populations was very similar (data not shown). Furthermore, the pathology diagnoses became more accurate over time, the number of pathologists increased, especially since the 1980s and they became increasingly aware of differences in histological types. This increased awareness is probably related to a decrease in the incidence of breast cancers with unknown histology. Simultaneously with this decrease, the incidence of all specific histological groups (including invasive ductal NOS, lobular and mixed ducto-lobular) increased and the total incidence of unknown histologies was lower than the incidence of all uncommon tumours combined. Thus, it seems unlikely that the majority of uncommon tumours were previously diagnosed with unknown histology.

The median ages at diagnosis for the different histological types were similar to the population-based SEER data on patients diagnosed in the 1990s[4] and also to other histological type-specific studies in industrialized countries.[7, 9, 20, 21] Patients with medullary breast cancer are generally younger, possibly because this type of tumour might be hereditary, occuring at a younger age than sporadic breast tumours.[22]

The stage and grade distribution showed the less aggressive nature of mucinous, tubular, papillary and cribriform carcinoma and phyllodes tumours, as also found in earlier studies.[4, 7, 9, 10, 12]

Table 5 Overview of studies on survival of patients with uncommon tumours of the breast

Authors	Study population	Histological types	No. of patients	Survival rates*	Risk ratio#	Median survival	Remarks
Sullivan[7]	Massachusets General Hospital 1980-2002	tubular	73			90.5 mths	
Allemani[8]	population-based cancer registries of Estonia, France, Italy, Spain, Netherlands, UK 1990-1992	medullary	62	5-yr: 86% (76-96)	1.19 (0.49-2.85)		relative survival, RER, adjusted for age, stage, hormone receptor status
		special types (i.e. tubular, apocrine, cribriform, papillary, mucinous, signet ring cell)	211	5-yr: 95% (90-100)	0.35 (0.12-0.99)		
Ellis[47]	Nottingham City Hospital 1974-1987	tubular	38	10-yr: 90%			
		cribriform	13	10-yr: 91%			
		mucinous	14	10-yr: 80%			
		medullary	44	10-yr: 51%			
Komenaka[9]	Columbia University-Presbyterian Medical Center 1980-1998	mucinous	65	5-yr: 93.6% 10-yr: 72.8%			
Kuper-Hommel[45]	2 regional population-based cancer registries in the Netherlands 1981-1999	lymphomas	38	2-yr: 63%		38 mths	
Li[13]	SEER 1974-1998	mucinous	3923		0.80 (0.86-0.91)		only patients 50-79 yrs
		medullary	2902		0.82 (0.78-0.87)		HR, adjusted for age, yr of diagnosis, stage, SEER registry, surgery, RT
		tubular	2260		0.66 (0.60-0.73)		
		papillary	1049		0.81 (0.73-0.90)		
Fu[20]	Providence Hospital & Medical Centers 1980-1999	Paget	41			42 mths	

Diab[10]	San Antonio, TX, breast cancer databases	tubular mucinous	444 1221	5-yr: 88% (p<0.001) 5-yr: 80% (p=0.088)			p for comparison with ductal carcinomas nos
Ha[46]	University of Texas M.D. Anderson Cancer Center Lymphoma database 1972-1994	lymphoma	23	5-yr: 74%			
Northridge[12]	SEER 1973-1990	mucinous	4082		0.38 (0.34-0.42)		HR, adjusted for age, stage, yr of diagnosis, race, grade
Gamel[11]	SEER 1973-1991	medullary	2908			2.8-3.9 yr	
Berg[40]	SEER 1973-1987	medullary mucinous paget papillary tubular	4486 3553 1775 1395 1092	5-yr: 82% 5-yr: 95% 5-yr: 79% 5-yr: 95% 5-yr: 96%			relative survival
Pedersen[6]	Danish Breast Cancer Cooperative group 1977-1987	medullary	235	5-yr: 82% 10-yr: 77%			read from the graphs
Venable[42]	George Washington Univeristy Medical Center 1971-1975, 1981-1986	cribriform	32	5-yr: 100%			12 patients with pure cribriform, 20 with at least 50% cribriform component
Wargotz[43, 48]	Armed Forces Institute of Pathology Washington DC before 1983	metaplastic: matrix-producing spindle cell	 26 100	 5-yr: 68% 5-yr: 64%			
Lattes[44]	1970s	lymphoma	33	5-yr: 9%			

* crude survival rate unless otherwise stated
\# compared to invasive ductal carcinoma, nos

Women diagnosed with tubular carcinoma are more likely to be detected at screening.[23] Our results also suggest this, because the incidence of tubular carcinoma increased markedly in the mid 1990s followed by a decline a few years later. This is in accordance with the introduction of population screening for women aged 50-69 in the area of the Eindhoven Cancer Registry in 1991 which was fully implemented in 1996. This temporary rise in incidence was also observed for phyllodes tumours and cribriform carcinoma. A few years earlier, an increase followed by a decrease was observed for (hemangio)sarcomas, which are related to previous radiotherapy to the breast.[24, 25] In our study 28 patients (40%) with an hemangiosarcoma had suffered a prior breast cancer. The increasing incidence rates for lobular and mixed ducto-lobular carcinoma might be related to the use of hormone replacement therapy,[2, 26-28] although this use remained relatively modest in the Netherlands (10-16%[29-31] compared to over 50% in the USA[32]).

Treatment of uncommon breast tumours has rarely been studied, because it is difficult to obtain sufficient numbers of patients in each category. In an average hospital one observes most of these categories of patients only once every 5 to 10 years. So, it is not illogical that in the Dutch guidelines for breast cancer treatment, no specifications according to histological type are shown (although it is stated that axillary treatment of patient with tubular carcinomas smaller than 1 cm is not necessary),[33] nor were they an issue at the international expert consensus meeting in St Gallen (Switzerland).[34] Therefore treatment decisions were probably based on the same criteria as for invasive ductal carcinoma: stage, grade, menopausal status, and hormone receptor status. Unfortunately, we do not have information about the latter in our database. We observed less aggressive treatment of patients with mucinous, tubular, papillary, and cribriform tumours in accordance with the favourable stage and grade distribution. However, for older patients comorbidity may also have played a role.[35] Treatment recommendations for patients with some rare tumours, e.g. adenoid cystic[36], tubular,[37] and phyllodes,[38] advise excision, in some cases combined with radiotherapy but without adjuvant chemotherapy. Patients with metaplastic tumours should be treated as invasive ductal carcinomas,[39] and those with lymphoma of the breast should be treated as all extranodal lymphoma patients, based on appropriate staging and histopathology.

Like previous studies (table 5), we found a very good prognosis for patients with tubular,[7, 10, 13, 40] and mucinous[9, 10, 12, 13, 40] carcinoma. Relative 5-yr survival of patients with medullary cancer was about equal to that found in a study which combined data over 1990-92 from six European cancer registries.[8] Due to the limited number of cases, only a few studies have reported on the survival of patients with cribriform carcinoma.[41, 42] In our relatively recent series of patients the prognosis was even better than for women in general. The very good prognosis for patients with papillary carcinoma has been reported before from the SEER database.[13, 40]

The poor survival rates for patients with metaplastic tumours is probably affected by the heterogeneity of the group; previous studies consisted of small series of cases and

5-year survival rates ranged from 40%[1] to 68% for the matrix-producing subtype.[43] Survival of patients with breast lymphomas has been reported to be very poor,[44, 45] but survival might improve for more recent patients through modern staging and therapy.[46]

Relative excess risks of death (RER) were calculated for most histological types, if a sufficient number of patients was available. Only one previous study reported RERs according to histology[8] but could not distinguish the various histologic subtypes, nor could it adjust for grade. We found that histology significantly predicted survival after adjustment for age, stage, and grade. Treatment, which varied over the years and is largely related to stage and grade, was also added to the model, but this did not change the RERs significantly (data not shown).

In conclusion, in about 10% of all newly diagnosed breast cancer patients specific histology has implications for the detection, diagnosis, stage (and thus also treatment) and survival. Despite a less aggressive treatment, the survival for certain histological types appeared to be very high, even comparable to that of women without breast cancer. Furthermore, after adjustment for age, stage and grade, patients with mucinous, tubular, and medullary carcinoma or phyllodes tumours exhibited such a low risk of death that in some cases even less aggressive treatment should be considered. Communication to patients with these specific histological types should reflect this relatively favourable prognosis.

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References

1. Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the Breast, ed. 3 Philadelphia: Lippincott Williams & Wilkins, 2004.
2. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. Jama 2003;289:1421-4.
3. Anderson WF, Chu KC, Chang S, Sherman ME. Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 2004;13:1128-35.
4. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer 2005;93:1046-52.
5. Stalsberg H, Thomas DB. Age distribution of histologic types of breast carcinoma. Int J Cancer 1993;54:1-7.
6. Pedersen L, Zedeler K, Holck S, Schiodt T, Mouridsen HT. Medullary carcinoma of the breast. Prevalence and prognostic importance of classical risk factors in breast cancer. Eur J Cancer 1995;31A:2289-95.

7. Sullivan T, Raad RA, Goldberg S, Assaad SI, Gadd M, Smith BL, Powell SN, Taghian AG. Tubular carcinoma of the breast: a retrospective analysis and review of the literature. Breast Cancer Res Treat 2005;93:199-205.
8. Allemani C, Sant M, Berrino F, Aareleid T, Chaplain G, Coebergh JW, Colonna M, Contiero P, Danzon A, Federico M, Gafa L, Grosclaude P, et al. Prognostic value of morphology and hormone receptor status in breast cancer - a population-based study. Br J Cancer 2004;91:1263-8.
9. Komenaka IK, El-Tamer MB, Troxel A, Hamele-Bena D, Joseph KA, Horowitz E, Ditkoff BA, Schnabel FR. Pure mucinous carcinoma of the breast. Am J Surg 2004;187:528-32.
10. Diab SG, Clark GM, Osborne CK, Libby A, Allred DC, Elledge RM. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol 1999;17:1442-8.
11. Gamel JW, Meyer JS, Feuer E, Miller BA. The impact of stage and histology on the long-term clinical course of 163,808 patients with breast carcinoma. Cancer 1996;77:1459-64.
12. Northridge ME, Rhoads GG, Wartenberg D, Koffman D. The importance of histologic type on breast cancer survival. J Clin Epidemiol 1997;50:283-90.
13. Li CI, Moe RE, Daling JR. Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. Arch Intern Med 2003;163:2149-53.
14. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S. International Classification of Diseases for Oncology, ed. 3rd Geneva: World Health Organization, 2000.
15. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 5th Geneva, Switzerland: Wiley-Liss, 1997:227.
16. Sobin LH, Wittekind C. UICC International Union against Cancer. TNM Classification of malignant tumours., ed. 6th Geneva, Switzerland: Wiley-Liss, 2002:239.
17. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1.
18. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. Comput. Programs Biomed. 1985;19:197-207.
19. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23:51-64.
20. Fu W, Mittel VK, Young SC. Paget disease of the breast: analysis of 41 patients. Am J Clin Oncol 2001;24:397-400.
21. Galobardes B, Morabia A, Bernstein MS. Diet and socioeconomic position: does the use of different indicators matter? Int J Epidemiol 2001;30:334-40.
22. Armes JE, Venter DJ. The pathology of inherited breast cancer. Pathology 2002;34:309-14.
23. Newcomer LM, Newcomb PA, Trentham-Dietz A, Storer BE, Yasui Y, Daling JR, Potter JD. Detection method and breast carcinoma histology. Cancer 2002;95:470-7.
24. Yap J, Chuba PJ, Thomas R, Aref A, Lucas D, Severson RK, Hamre M. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys 2002;52:1231-7.
25. Vorburger SA, Xing Y, Hunt KK, Lakin GE, Benjamin RS, Feig BW, Pisters PW, Ballo MT, Chen L, Trent J, 3rd, Burgess M, Patel S, et al. Angiosarcoma of the breast. Cancer 2005;104:2682-8.
26. Verkooijen HM, Fioretta G, Vlastos G, Morabia A, Schubert H, Sappino AP, Pelte MF, Schafer P, Kurtz J, Bouchardy C. Important increase of invasive lobular breast cancer incidence in Geneva, Switzerland. Int J Cancer 2003;104:778-81.
27. Rosenberg LU, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman PW. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. Breast Cancer Res 2006;8:R11.
28. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, Marchbanks PA, Norman SA, Weiss LK, Ursin G, Berlin JA, Burkman RT, et al. Relation of regimens of combined

hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer 2002;95:2455-64.

29. van Duijnhoven FJ, van Gils CH, Bezemer ID, Peeters PH, van der Schouw YT, Grobbee DE. Use of hormones in the menopausal transition period in the Netherlands between 1993 and 1997. Maturitas 2006;53:462-75.
30. Westendorp IC, in't Veld BA, Grobbee DE, Pols HA, Meijer WT, Hofman A, Witteman JC. Hormone replacement therapy and peripheral arterial disease: the Rotterdam study. Arch Intern Med 2000;160:2498-502.
31. Tobi H, van den Berg PB, Brouwers JR, de Jong-van den Berg LT. [Hormone replacement therapy in the peri-menopausal and post menopausal period: more than half of the women were treated for more than one year]. Ned Tijdschr Geneeskd 2003;147:1853-5.
32. Brett KM, Madans JH. Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. Am J Epidemiol 1997;145:536-45.
33. NABON_Nationaal_Borstkanker_Overleg_Nederland. http://www.oncoline.nl [Breast cancer treatment: National guideline] in Dutch Utrecht: Vereniging van Integrale Kankercentra, 2005:158.
34. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005;16:1569-83.
35. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. Eur J Cancer 2005;41:779-85.
36. Sanders ME, Kasami M, Means-Powell J, Page DL. Adenoid cystic carcinoma of the breast. In: Raghavan D, Brecher ML, Johnson DH, Meropol NJ, Moots PL, Rose PG. Textbook of uncommon cancer, 3rd ed. Chichester, England: John Wiley & Sons, Ltd, 2006:187-93.
37. Sanders ME, Mayer IA, Page DL. Tubular carcinoma. In: Raghavan D, Brecher ML, Johnson DH, Meropol NJ, Moots PL, Rose PG. Textbook of uncommon cancer, 3rd ed. Chichester, England: John Wiley & Sons, Ltd, 2006:230-5.
38. Ellis I, Sawyer EJ, Rampaul R, Pineda CG. Phyllodes tumor of the breast. In: Raghavan D, Brecher ML, Johnson DH, Meropol NJ, Moots PL, Rose PG. Textbook of uncommon cancer, 3rd ed. Chichester, England: John Wiley & Sons, Ltd, 2006:209-17.
39. Gobbi H, Mayer IA, Chakravarthy AB. Metaplastic breast carcinoma. In: Raghavan D, Brecher ML, Johnson DH, Meropol NJ, Moots PL, Rose PG. Textbook of uncommon cancer, 3rd ed. Chichester, England: John Wiley & Sons, Ltd, 2006:181-6.
40. Berg JW, Hutter RV. Breast cancer. Cancer 1995;75:257-69.
41. Dawson PJ, Karrison T, Ferguson DJ. Histologic features associated with long-term survival in breast cancer. Hum Pathol 1986;17:1015-21.
42. Venable JG, Schwartz AM, Silverberg SG. Infiltrating cribriform carcinoma of the breast: a distinctive clinicopathologic entity. Hum Pathol 1990;21:333-8.
43. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. I. Matrix-producing carcinoma. Hum Pathol 1989;20:628-35.
44. Lattes R. Sarcomas of the breast. Int J Radiat Oncol Biol Phys 1978;4:705-8.
45. Kuper-Hommel MJ, Snijder S, Janssen-Heijnen ML, Vrints LW, Kluin-Nelemans JC, Coebergh JW, Noordijk EM, Vreugdenhil G. Treatment and survival of 38 female breast lymphomas: a population-based study with clinical and pathological reviews. Ann Hematol 2003;82:397-404.
46. Ha CS, Dubey P, Goyal LK, Hess M, Cabanillas F, Cox JD. Localized primary non-Hodgkin lymphoma of the breast. Am J Clin Oncol 1998;21:376-80.

CHAPTER 3

DETERMINANTS OF SURVIVAL

3.1

Long-term survival of T1 and T2 lymph node-negative breast cancer patients according to mitotic activity index:
a population-based study

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Abstract

Node-negative breast cancer patients have a relatively good prognosis, but eventually one-third will die of the disease. Thus, prognostic factors to identify the high-risk group among these patients are needed. We retrospectively determined the Mitotic Activity Index (MAI) for a large series of node-negative breast cancer patients (n=468) with tumours smaller than 5 cm who only received locoregional treatment. Patients were followed for up to 29 years; crude and relative survival were calculated, both univariate and multivariate. Relative survival differed significantly according to MAI (p=0.05), the difference occurred in the first 5 years after diagnosis and remained constant thereafter. After adjustment, MAI still significantly affected relative survival (RER 1.9, 95%CI: 1.1-3.5). Tumour size also increased the risk, but this was not statistically significant (RER 1.5, 95%CI: 0.8-2.7). Survival of patients with a T1 tumour and MAI < 10 was similar to that for the general population in the first 5 years after diagnosis.

In conclusion, MAI significantly predicted long-term survival for T1/T2N0 breast cancer. Adjuvant systemic therapy appears to have little benefit for node-negative breast cancer patients with a T1 tumour, regardless of the MAI. For those with a T2 tumour and a MAI ≥ 10 systemic therapy might have reduced mortality. The need for close surveillance of node-negative breast cancer patients with a T1 tumour and MAI < 10 seems limited.

Introduction

Adjuvant chemotherapy and hormonal treatment have been shown to improve survival for patients with breast cancer but have potentially serious side-effects, and are costly. Therefore, adjuvant treatment should only be given to high-risk patients, which requires reliable prognostic factors to indicate high risk.[1]

Patients with node-negative disease have a relatively good prognosis, but approximately one-third will eventually die of their disease.[2-4]

At the St Gallen meeting in 2001,[5] updated in 2003,[6] it was agreed to select high-risk node-negative patients for adjuvant systemic therapy on the basis of tumour size, age, hormone receptor status and histological grade.

Several studies have shown that the Mitotic Activity Index (MAI) is the most important constituent of the histological grade.[7, 8] In previous studies the prognostic value has been demonstrated, independent of tumour size and node status. [9-12]

MAI can be assessed easily and is highly reproducible (mean correlation coefficient 0.91) if a protocol with quality control is used.[13]

In the Dutch guidelines which became effective in the year 2000 it was decided to use either the MAI or the histological grade, in combination with tumour size, to select node-negative patients for adjuvant systemic therapy.[14]

Few studies have investigated long-term survival based on MAI in large series of breast cancer patients with negative axillary nodes,[10, 15-19] however, none of them population-based. In most studies, part of the population received systemic therapy, thus making it impossible to evaluate the pure prognostic value of this variable.

In a study on tumour aggressiveness we retrospectively assessed MAI values for breast cancer patients diagnosed in the years 1975, 1981, 1988 and 1989.[20] These patients were followed for vital status until January 2004, so a follow-up of 15 to 29 years was attained.

The aim of the present study was to evaluate the pure prognostic value of MAI in an adequate series of patients with node-negative breast cancer treated with locoregional therapy alone. We calculated crude and relative survival, taking into account deaths from causes other than breast cancer, both univariate and multivariate.

Methods

Patients

Data were derived from the population-based Eindhoven Cancer Registry, which has collected data on all new cancer cases in southeastern Netherlands since 1955. The registry covers a population of 2.3 million inhabitants and is embedded in the Comprehensive Cancer Centre South, where cancer patients are discussed in multi-disciplinary meetings. The area offers good access to specialised medical care supplied in 12 general hospitals and two large radiotherapy institutes. Trained registry personnel actively collect data on diagnosis, staging, and treatment from the medical records after

notification by pathologists and medical registration offices. Information on tumour grade was not available for patients diagnosed before 1983 and hormone receptor status was not routinely collected for breast cancer patients diagnosed in the period under investigation (1975-89) in our cancer registry. Therefore, these two parameters were not included in our analysis.

Table 1 Characteristics of consecutive patients diagnosed with T1 or T2 node-negative breast cancer in the Southeast Netherlands

	MAI[a] < 10	MAI ≥ 10	Total
	N (%)	N (%)	N (%)
Age (years)			
< 50	78 (27)	67 (38)	145 (31)
50-69	147 (50)	81 (46)	228 (49)
70+	68 (23)	27 (15)	95 (20)
Tumour size (cm)			
≤ 2.0	180 (61)	86 (49)	266 (57)
2.1-5.0	113 (39)	89 (51)	202 (43)
Morphology			
ductal	230 (78)	166 (95)	396 (85)
lobular	59 (20)	7 (4)	66 (14)
other/unknown	4 (1)	2 (0)	6 (1)
Therapy			
surgery alone	114 (39)	61 (35)	175 (37)
surgery + radiotherapy	179 (61)	114 (65)	293 (63)
Year of diagnosis			
1975	35 (12)	25 (14)	60 (13)
1981	60 (20)	43 (25)	103 (22)
1988-1989	198 (68)	107 (61)	325 (65)
Total	293 (63)	175 (37)	468 (100)

[a] MAI: Mitotic Activity Index

A detailed description of the study population can be found elsewhere.[20] In short, all 1430 consecutive breast cancer patients diagnosed in 1975, 1981, 1988, and 1989 in the eastern part of the region (population 1.1 million) were selected. We excluded patients with distant metastasis at the time of diagnosis (n=75), patients who did not undergo surgery (n=94), those with one of the following histological types (mucinous, medullary, pappilary, sarcoma, M. Paget, or DCIS, n=89) or those whose histological specimen was inadequate, could not be traced or appeared to be no carcinoma (n=131) . For the remaining 1051 patients MAI values were determined retrospectively according to the strict protocol used in a previous study, being defined as the total number of sharply defined mitoses in 10 high-power fields (total area 1.6 mm^2).[13] We used a cut-off point of 10 mitoses/10 high power fields, which corresponds to the cut-off of 12 mitoses/ 2 mm^2 that is used in the Dutch treatment guidelines.[14] To ensure the accuracy of the MAI, a quality control system with review of tumour specimens by a reference laboratory was set up; 98% of reviewed slides were in the same diagnostic category.[20]

For the present study we selected lymph node-negative patients only, with tumours smaller than 5 cm (T1 & T2), n=492.

According to treatment guidelines at that time, these patients were treated either by surgery alone or by surgery and radiotherapy. As a result of trial participation 24 patients also received adjuvant systemic therapy. These patients were excluded, so 468 remained for analysis.

Follow-up

Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 from the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens. Patients lost to follow-up (n=22) were checked again by reviewing the hospital records. In this way additional information on vital status was obtained for 14 patients, so only 8 (1.7%) were lost to follow-up. Follow-up lasted until January 1st 2004.

Statistical analysis

Differences in distribution between patients with MAI <10 and MAI ≥10 were tested with the chi-square test.

Crude survival analyses were performed. The log-rank test was used to evaluate significant differences between survival curves in univariate analyses. We used Cox regression models to compute multivariate rates. The independent prognostic effect of MAI (categorised and as a continuous variable) was investigated, adjusting for age (<50, 50-69, 70+ years), tumour size (<2 cm, 2-5 cm), morphology (ductal or lobular/other), treatment and year of diagnosis (1975, 1981, 1988-89).

Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in the general population with the same age structure.[21] Expected survival rates were calculated from life tables for regional male and female populations with the same 5-year age distribution. We used generalised linear models with a Poisson error structure based on collapsed data and exact survival times.[22] If the number of patients at risk in a particular category became to small to calculate a reliable estimate of relative survival (i.e. SE >10%), results were not shown.

All statistical analyses were performed with SAS (the SAS System, Cary CA, USA).

Results

Characteristics of the study population are given in Table 1. The proportion of patients younger than 50 was highest in the high MAI group, 38% compared to 27% of the low MAI group (p=0.01). Patients with high MAI had larger tumours (p=0.01) which were more often ductal carcinomas (p=<0.0001). Treatment and year of diagnosis did not differ significantly between MAI categories.

Crude survival rates according to MAI are presented in Figure 1. The difference between low and high MAI occurred about 2 years after diagnosis and is largest about 7 years after diagnosis (MAI<10: 84%, MAI≥10: 73%, p=0.007). Thereafter the survival

curves came closer together, and the overall effect of MAI on crude 30-year survival was not statistically significant (p=0.6).

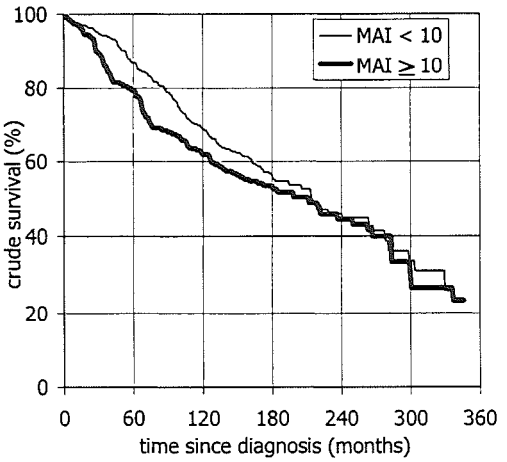

Figure 1 Crude survival for node-negative T1 & T2 breast cancer patients according to Mitotic Activity Index (MAI)

Multivariate analysis of crude survival revealed the effect of MAI not to be statistically significant (HR 1.2, 95%CI: 0.9-1.5). Age and tumour size significantly affected survival (Table 2). Patients aged 50-69 years had a HR of 2.0 (95%CI: 1.4-2.9) and those aged 70+ even 5.3 (95%CI: 3.6-7.9). The risk of death was about 40% higher among patients with tumours 2-5 cm compared with those with smaller tumours (HR 1.4, 95%CI: 1.1-1.8).

Relative survival was significantly different on the basis of MAI (p=0.05) (Figure 2). In multivariate analyses of relative survival (Table 2) MAI showed a significant effect on survival (RER 1.9, 95%CI: 1.1-3.5). Age at diagnosis no longer predicted survival, whereas tumour size revealed an elevated risk (RER 1.5, 95%CI: 0.8-2.7).

Relative survival according to tumour size showed that a low MAI resulted in better survival for patients with T1 (Figure 3a) as well as those with T2 tumours (Figure 3b); however this was not statistically significant (p=0.07 and p=0.4, respectively). Survival of patients with a small (T1) tumour and low MAI was similar to that of the general population the first 5 years after diagnosis (Figure 3a).

Discussion

In this large series of node-negative breast cancer patients diagnosed 1975-1988 we found that MAI significantly predicted relative survival in multivariate analyses up to almost 30 years after diagnosis.

Previous studies also found that MAI is an independent prognostic factor, even for node-negative patients.[23-25]

Table 2 Multivariate regression analyses of crude and relative survival rates of consecutive patients diagnosed with T1 or T2 node-negative breast cancer in the Southeast Netherlands

	Crude Survival Cox regression		Relative survival Poisson Regression	
	HR	(95% CI)	RER	(95% CI)
MAI[a]				
<10	1.0		1.0	
≥ 10	1.2	(0.9-1.5)	1.9	(1.1-3.5)
Age (years)				
< 50	1.0		1.0	
50-69	2.0	(1.4-2.9)	1.2	(0.7-2.2)
70+	5.3	(3.6-7.9)	0.0	-
Tumour size (cm)				
≤ 2.0	1.0		1.0	
2.1-5.0	1.4	(1.1-1.8)	1.5	(0.8-2.7)
Morphology				
ductal	1.0		1.0	
lobular/other/unknown	1.1	(0.8-1.6)	1.3	(0.1-16)
Therapy				
surgery alone	1.0		1.0	
surgery + radiotherapy	0.8	(0.6-1.1)	0.9	(0.5-1.8)
Year of diagnosis				
1975	0.9	(0.6-1.4)	0.5	(0.2-1.6)
1981	1.2	(0.8-1.6)	0.9	(0.5-1.9)
1988-1989	1.0		1.0	

[a] MAI: Mitotic Activity Index

Studies on large series of node-negative breast cancer patients are scarce.[10, 15-17] However, for evaluating the pure prognostic value only patients who have not received systemic therapy should be studied. This was previously studied in a patient population in Italy,[18, 19] where mitotic activity significantly predicted 6-year overall crude survival. In our study MAI also remained significant for relative survival in multivariate analyses. The present study provides new information with respect to that of other investigators in that it evaluated the clinical impact of MAI on long-term survival before the introduction of adjuvant systemic therapy for node-negative breast cancer patients. To assess the pure prognostic relevance of the marker, we studied a large series of node-negative breast cancer patients receiving locoregional therapy alone from a population-based cancer registry, with follow-up of up to 30 years.

The MAI is made up of the mitotic frequency in the most active part of the tumour. Quantitative features, such as the MAI, clearly discriminate less aggressive tumours from more aggressive ones.[9, 10, 26, 27] Although there are well-known problems about the reproducibility of grading in the absence of strict protocols,[28-30] the MAI is highly reproducible (mean correlation coefficient 0.91) if a protocol with quality control is used.[13] Our quality control procedure also confirmed the accuracy of the MAI values.[20]

Unfortunately, information on hormone receptor status and tumour grade was not available in our study. A previous studies showed the prognostic value of MAI after adjustment for both estrogen and progesterone status.[19] Several studies investigated the

prognostic value of MAI and compared it with histological grade.[9, 19, 31-34] They all conclude that the MAI is the best prognostic factor, so the additional value of histological grade would be limited.

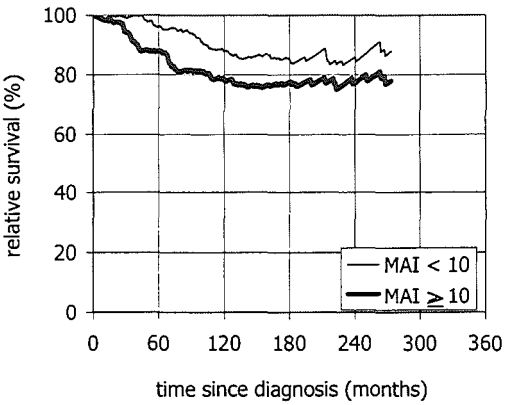

Figure 2 Relative survival for node-negative T1 & T2 breast cancer patients according to Mitotic Activity Index (MAI)

The crude survival rates for patients with low MAI and patients with high MAI come closer together as time goes by, because eventually every person dies. The relative survival rates, which reflect the disease-specific survival, do not come closer. Relative survival of patients with a high MAI remains worse than the survival of those with a low MAI even after 25 years of follow-up. Because we selected patients from 3 diagnostic periods, the longest follow-up (29 years) can only be attained by patients diagnosed in 1975, patients diagnosed in 1981 or 1988-89 have only reached a maximum follow-up of 23 or 15 years, respectively. The number of cases after 15 years of follow-up is thus limited, but population-based studies with follow-up beyond 15 years after diagnosis are scarce.

After the first 5 years of follow-up the difference in relative survival for MAI<10 and MAI ≥ 10 remained stable. Thus, although MAI is still a prognostic factor, the largest value occurs in the first five years after diagnosis. Previous studies on the effect of chemotherapy for node-negative breast cancer also showed that the effects mainly occur in the first five years after diagnosis.[35, 36] The Dutch guidelines suggested adjuvant systemic therapy for node-negative breast cancer patients only when expected (crude) 10-year survival was below 80%.[14] The relative survival of patients with T1 tumours was relatively good (figure 3a), so the benefit of adjuvant systemic treatment for these patients is likely to be limited. Administration of chemotherapy to patients with T1 N0 and MAI ≥ 10 breast cancer might have resulted in minimal survival benefit and considerable over-treatment.[37] Survival of patients with a T2 tumour (figure 3b) and a high MAI (≥ 10) was considerably lower, so these patients might have benefited more from adjuvant therapy, especially endocrine treatment when positive hormonal receptors were present

in their tumours. In addition, hormonal therapy reduces the risk of contralateral breast cancer and is less toxic than chemotherapy.[38] This is true for all ages, above 60 years chemotherapy is less effective.

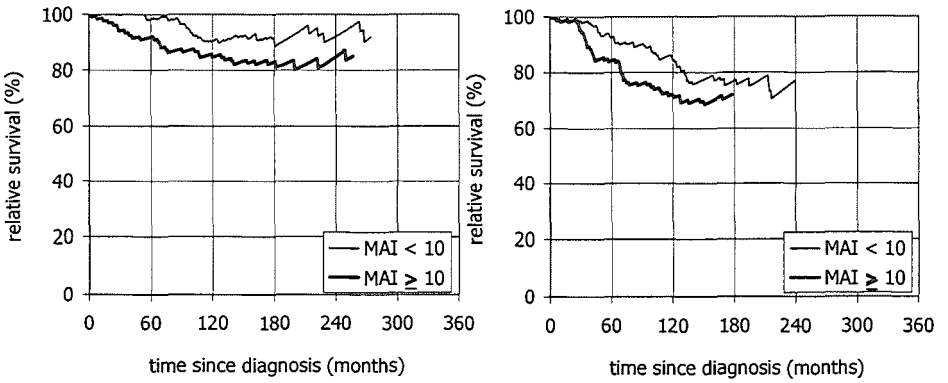

Figure 3 Relative survival for node-negative breast cancer patients according to Mitotic Activity Index (MAI): a) T1, b) T2

Ten years after diagnosis the relative survival curves for both the low MAI group and the high MAI group became horizontal, implying that patients who have survived the first 10 years do not have a worse prognosis than women in the general population, regardless of their MAI. This is in accordance with a previous study that found that the risk of recurrence was negligible 10 years after diagnosis.[39] Previous studies that did not focus only on node-negative patients reported that the limit of breast cancer dormancy is about 20 to 25 years, and the mortality rate at this time was similar to that for the general population.[40] A recent study by Schairer and colleagues[41] showed that the probability of death from breast cancer after almost 30 years is similar to the probability of death from other causes for white breast cancer patients diagnosed with localised disease before age 50. For older patients the probability of dying from other causes is much larger compared to the risk of dying from breast cancer. Previously, we found that although there is excess mortality from breast cancer 20 years after diagnosis, the life expectancy is similar to that for the general population.[42]

In conclusion, these findings indicate that MAI is an important prognostic factor in early stage breast cancer. Adjuvant systemic therapy should not be given to node-negative breast cancer patients with a T1 tumour, because these patients already have a relatively good prognosis and the adverse effects of chemotherapy may not outweigh the limited gain in survival. For those with a T2 tumour and a MAI $\geq$ 10 systemic therapy might be helpful in reducing mortality. The need for close surveillance of node-negative breast cancer patients with tumours smaller than 2 cm (T1) and a low MAI (<10) who have been treated with either surgery alone or a combination of surgery and radiotherapy is limited.

Acknowledgement

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References

1. van Diest PJ, van der Wall E, Baak JP. Prognostic value of proliferation in invasive breast cancer: a review. J Clin Pathol 2004;57:675-81.
2. Bonadonna G, Valagussa P. Systemic therapy in resectable breast cancer. Hematol Oncol Clin North Am 1989;3:727-42.
3. Pritchard KI. Systemic adjuvant therapy for node-negative breast cancer: proven or premature? Ann Intern Med 1989;111:1-4.
4. Harris JR, Morrow M, Norton L. Malignant tumors of the breast. In: De Vita VT, Hellman S, Rosenberg SA. Cancer. Principles and practice of oncology.ed. Philadelphia: Lippincott-Raven, 1997:1557-616.
5. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer. J Clin Oncol 2001;19:3817-27.
6. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357-65.
7. Le Doussal V, Tubiana-Hulin M, Friedman S, Hacene K, Spyratos F, Brunet M. Prognostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR). An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer 1989;64:1914-21.
8. Genestie C, Zafrani B, Asselain B, Fourquet A, Rozan S, Validire P, Vincent-Salomon A, Sastre-Garau X. Comparison of the prognostic value of Scarff-Bloom-Richardson and Nottingham histological grades in a series of 825 cases of breast cancer: major importance of the mitotic count as a component of both grading systems. Anticancer Res 1998;18:571-6.
9. Baak JPA, van Dop H, Kurver PHJ, Hermans J. The value of morphometry to classic prognosticators in breast cancer. Cancer 1985;56:374-82.
10. Clayton F. Pathologic correlates of survival in 378 lymph node-negative infiltrating ductal breast carcinomas. Mitotic count is the best single predictor. Cancer 1991;68:1309-17.
11. Kato T, Kameoka S, Kimura T, Tanaka S, Nishikawa T, Kobayashi M. p53, mitosis, apoptosis and necrosis as prognostic indicators of long-term survival in breast cancer. Anticancer Res 2002;22:1105-12.
12. Kronqvist P, Kuopio T, Collan Y. Morphometric grading in breast cancer: thresholds for mitotic counts. Hum Pathol 1998;29:1462-8.
13. van Diest PJ, Baak JPA, Matze-Cok P, Wisse-Brekelmans ECM, van Galen CM, Kurver PHJ, Bellot SM, Fijnheer J, van Gorp LH, Kwee WS, Los J, Peterse JL, et al. Reproducibility of mitosis counting in 2,469 breast cancer specimens: results from the Multicenter Morphometric Mammary Carcinoma Project [see comments]. Hum. Pathol. 1992;23:603-7.
14. Bontenbal M, Nortier JW, Beex LV, Bakker P, Hupperets PS, Nooij MA, van Veelen H, Vreugdenhil G, Richel DJ, Blijham GH. [Adjuvant systemic therapy for patients with resectable breast cancer: guideline from the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology]. Ned Tijdschr Geneeskd 2000;144:984-9.
15. Page DL, Gray R, Allred DC, Dressler LG, Hatfield AK, Martino S, Robert NJ, Wood WC. Prediction of node-negative breast cancer outcome by histologic grading and S-phase

analysis by flow cytometry: an Eastern Cooperative Oncology Group Study (2192). Am J Clin Oncol 2001;24:10-8.

16. Mandard AM, Denoux Y, Herlin P, Duigou F, van De Vijver MJ, Clahsen PC, van Den Broek L, Sahmoud TM, Henry-Amar M, van De Velde CJ. Prognostic value of DNA cytometry in 281 premenopausal patients with lymph node negative breast carcinoma randomized in a control trial: multivariate analysis with Ki-67 index, mitotic count, and microvessel density. Cancer 2000;89:1748-57.
17. Clahsen PC, van de Velde CJ, Duval C, Pallud C, Mandard AM, Delobelle-Deroide A, van den Broek L, van de Vijver MJ. The utility of mitotic index, oestrogen receptor and Ki-67 measurements in the creation of novel prognostic indices for node-negative breast cancer. Eur J Surg Oncol 1999;25:356-63.
18. Medri L, Volpi A, Nanni O, Vecci AM, Mangia A, Schittulli F, Padovani F, Giunchi DC, Vito A, Amadori D, Paradiso A, Silvestrini R. Prognostic relevance of mitotic activity in patients with node-negative breast cancer. Mod Pathol 2003;16:1067-75.
19. Volpi A, Bacci F, Paradiso A, Saragoni L, Scarpi E, Ricci M, Aldi M, Bianchi S, Muretto P, Nuzzo F, Simone G, Mangia A, et al. Prognostic relevance of histological grade and its components in node-negative breast cancer patients. Mod Pathol 2004;17:1038-44.
20. Louwman WJ, van Diest PJ, van Beek MW, Schapers RF, Nolthenius-Puylaert TM, Baak JP, Coeberg JW. Trends in breast cancer aggressiveness before the introduction of mass screening in southeastern Netherlands 1975-1989. Breast Cancer Res Treat 2002;73:199-206.
21. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. Comput. Programs Biomed. 1985;19:197-207.
22. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23:51-64.
23. van Diest PJ, Baak JP. The morphometric prognostic index is the strongest prognosticator in premenopausal lymph node-negative and lymph node-positive breast cancer patients. Hum Pathol 1991;22:326-30.
24. Uyterlinde AM, Baak JP, Schipper NW, Peterse HJ, Meijer JW, Vooys PG, Matze E. Prognostic value of morphometry and DNA flow-cytometry features of invasive breast cancers detected by population screening: comparison with control group of hospital patients. Int J Cancer 1991;48:173-81.
25. van der Linden JC, Baak JP, Lindeman J, Hermans J, Meyer CJ. Prospective evaluation of prognostic value of morphometry in patients with primary breast cancer. J Clin Pathol 1987;40:302-6.
26. Eskelinen M, Lipponen P, Papinaho S, Aaltomaa S, Kosma VM, Klemi P, Syrjanen K. DNA flow cytometry, nuclear morphometry, mitotic indices and steroid receptors as independent prognostic factors in female breast cancer. Int. J. Cancer 1992;51:555-61.
27. Biesterfeld S, Noll I, Noll E, Wohltmann D, Bocking A. Mitotic frequency as a prognostic factor in breast cancer [see comments]. Hum. Pathol. 1995;26:47-52.
28. Dalton LW, Page DL, Dupont WD. Histologic grading of breast carcinoma. A reproducibility study. Cancer 1994;73:2765-70.
29. Boiesen P, Bendahl PO, Anagnostaki L, Domanski H, Holm E, Idvall I, Johansson S, Ljungberg O, Ringberg A, Ostberg G, Ferno M. Histologic grading in breast cancer--reproducibility between seven pathologic departments. South Sweden Breast Cancer Group. Acta Oncol 2000;39:41-5.
30. Frierson HF, Jr., Wolber RA, Berean KW, Franquemont DW, Gaffey MJ, Boyd JC, Wilbur DC. Interobserver reproducibility of the Nottingham modification of the Bloom and Richardson histologic grading scheme for infiltrating ductal carcinoma. Am J Clin Pathol 1995;103:195-8.

31. Uyterlinde AM, Schipper NW, Baak JP, Peterse H, Matze E. Limited prognostic value of cellular DNA content to classical and morphometrical parameters in invasive ductal breast cancer. Am J Clin Pathol 1988;89:301-7.
32. Manders P, Bult P, Sweep CG, Tjan-Heijnen VC, Beex LV. The prognostic value of the mitotic activity index in patients with primary breast cancer who were not treated with adjuvant systemic therapy. Breast Cancer Res Treat 2003;77:77-84.
33. de Jong JS, van Diest PJ, Baak JP. Hot spot microvessel density and the mitotic activity index are strong additional prognostic indicators in invasive breast cancer. Histopathology 2000;36:306-12.
34. de Jong JS, van Diest PJ, Baak JP. Number of apoptotic cells as a prognostic marker in invasive breast cancer. Br J Cancer 2000;82:368-73.
35. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992;339:71-85.
36. Retsky MW, Swartzendruber DE, Bame PD, Wardwell RH. A new paradigm for breast cancer. Recent Results Cancer Res 1993;127:13-22.
37. Boyages J, Chua B, Taylor R, Bilous M, Salisbury E, Wilcken N, Ung O. Use of the St Gallen classification for patients with node-negative breast cancer may lead to overuse of adjuvant chemotherapy. Br J Surg 2002;89:789-96.
38. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451-67.
39. Nab HW, Kluck HM, Rutgers EJ, Coebergh JW, Hop WC. Long-term prognosis of breast cancer: an analysis of 462 patients in a general hospital in south east Netherlands. Eur J Surg Oncol 1995;21:42-6.
40. Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy. J Natl Cancer Inst 1999;91:80-5.
41. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 2004;96:1311-21.
42. Louwman WJ, Klokman WJ, Coebergh JW. Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal. Br J Cancer 2001;84:700-3.

3.2

Less extensive treatment and inferior prognosis for breast cancer patients with comorbidity: a population-based study

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Eur J Cancer 2005; 41: 779-785

Abstract

Background: The prevalence of coexistent diseases in addition to breast cancer becomes increasingly important in an ageing population. However, clinical implications are unclear.

Patients and methods: Age-specific prevalence of serious comorbidity among all new breast cancer patients diagnosed 1995-2001 (n=8966) in the South of the Netherlands was analysed in relation to age, stage and treatment. Independent prognostic effects of age and comorbidity were evaluated (follow-up until 1 January 2004).

Results: The prevalence of comorbidity increased from 9% for those <50 years to 56% for patients 80+. The most frequent conditions were cardiovascular disease (7%), diabetes mellitus (7%), and previous cancer (6%). In the presence of comorbidity fewer patients received radiotherapy (51% vs. 66%, P<0.0001) and fewer patients who underwent breast conserving surgery also had axillary dissection (P<0.0001). Relative 5-year survival rates for patients without comorbidity (87%) were significantly higher (P<0.01) than those for patients with previous cancer (77%), diabetes mellitus (78%), and for patients with 2+ coexistent diseases (59%). Relative survival of patients without comorbidity increased with age to 93% for patients older than 70. Comorbidity negatively affected prognosis, independent of age, stage of disease, and treatment (HR=1.3, P=0.0001 for one coexistent disease and HR=1.4, P=0.0001 for 2+ coexistent diseases). The most important effects were found for previous cancer (HR=1.4, P=0.003), cerebrovascular disease (HR=1.6, P<0.004) or dementia (HR=2.3, P<0.0001).

Conclusion: Elderly breast cancer patients can be divided in those without other diseases, who have a relatively good prognosis, and those who have at least one other serious coexistent disease and significantly poorer prognosis.

Introduction

Breast cancer is the most common type of cancer among women in the Netherlands, as in many other western countries [1], and 51% of all new patients are 60 years or older [2]. With increasing age, the prevalence of coexistent diseases increases [3]. Previously we found that about 50% of all breast cancer patients aged 60 years and older have one or more serious coexistent diseases [4]. Clinical trials that focus on treatment evaluation often exclude older patients and those with pre-existing serious diseases, so that optimal treatment for these patients is still uncertain. Elderly patients often do not receive any treatment and are less likely to undergo a combination of therapeutic modalities [5]. Often, patients with comorbidity are not treated according to guidelines [6, 7], although this may be the effect of advanced age instead of comorbidity. In addition to the influence on treatment, comorbidity has also been demonstrated to lower 3-year survival rates, independent of age, stage of disease, and type of treatment [8].

Since 1993 the Eindhoven Cancer Registry has routinely collected data on serious coexistent diseases in all newly diagnosed cancer patients in the southeastern part of the Netherlands [9]. This provides us with the unique opportunity to study its prognostic implications in a population-based setting.

In an increasingly ageing population comorbid conditions will become to play an even more important role in clinical decision-making and outcome. The presence of these coexistent diseases warrants care programmes with adapted treatment guidelines.

In the present study we describe the prevalence of serious comorbidity for all consecutive breast cancer patients since 1995 with follow-up until 1-1-2004. We investigated the impact of comorbidity on treatment and its effect on prognosis, independent from age and stage of the disease.

Patients and methods

Data were derived from the population-based Eindhoven Cancer Registry, which collects data on all new cancer cases in southeastern Netherlands since 1955. The registry covers a population of about 2.3 million inhabitants and is embedded in the Comprehensive Cancer Centre South, where all cancer patients are discussed in multi-disciplinary meetings. The area offers good access to specialised medical care supplied in 12 general hospitals and two large radiotherapy institutes. Trained registry personnel actively collect data on diagnosis, staging, and treatment from the medical records after notification by pathologists and medical registration offices. Data on type of treatment (surgery, radiotherapy, chemotherapy or hormonal therapy) were recorded as well as details on the type of surgical procedure (such as breast conserving surgery, mastectomy, axillary dissection).

Since 1993 the registry also records comorbidity according to a slight adaptation of the list of serious diseases drawn up by Charlson et al. [10]. In short, the following important conditions were recorded: chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell

carcinoma of the skin), and diabetes mellitus. Connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis and other chronic infections were also recorded [9].

Between 1995 and 2001 a total of 9123 patients with invasive breast cancer were diagnosed. A previous malignancy was diagnosed in 658 patients, for which the localisation could be traced in 71% of the cases. Patients who had been diagnosed with breast cancer (invasive or in-situ) before 1995 and developed a second breast tumour during 1995-2001, were excluded from the analyses (n=164). After the exclusion, the most frequent previous tumours were gynaecological tumours (25%), and colorectal cancer (23%).

Table 1 Number of serious concomitant conditions and type of comorbidity by age of consecutive breast cancer patients diagnosed 1995-2001 in southeastern Netherlands

	age at diagnosis (years)				
	<50	50-69	70-79	≥80	all ages
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of concomitant conditions					
0	1816 (79)	2804 (67)	826 (50)	283 (35)	5729 (64)
1	184 (8)	686 (16)	458 (27)	268 (34)	1596 (18)
≥ 2	23 (1)	174 (4)	228 (14)	175 (22)	600 (7)
unknown	290 (13)	521 (12)	156 (9)	74 (9)	1041 (12)
Type of concomitant condition*					
Previous cancer	52 (2)	212 (5)	136 (8)	93 (12)	493 (6)
Cardiovascular disease	17 (1)	197 (5)	240 (14)	170 (21)	624 (7)
COPD	57 (2)	174 (4)	114 (7)	58 (7)	403 (4)
Diabetes mellitus	18 (1)	245 (6)	241 (14)	133 (17)	637 (7)
Cerebrovascular	10 (0)	54 (1)	81 (5)	62 (8)	207 (2)
Tuberculosis	8 (0)	36 (1)	37 (2)	19 (2)	100 (1)
Dementia	0 (0)	3 (0)	24 (1)	43 (5)	70 (1)
Digestive tract	27 (1)	50 (1)	34 (2)	32 (4)	143 (2)
Other†	33 (1)	54 (1)	31 (2)	20 (3)	138 (2)
Total	2313	4185	1668	800	8966

* Patients may suffer from more than one concomitant condition
† Connective tissue diseases, rheumatoid arthritis, kidney diseases

Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens. Patients who moved outside the Netherlands were lost to follow-up; the estimated proportion was 0.2%. Follow-up lasted until January 1st 2004.

The prevalence of comorbidity was analysed according to age (<50, 50-69, 70-79, and ≥80); sometimes combining the patients 70-79 and 80+ because of the small numbers. Differences in treatment between patients with and without comorbidity were analysed according to age group, and tested with the chi-square test. Crude survival

analyses were performed separately for the first year of follow-up and for the following period, and were stratified according to age at diagnosis. The log rank test was performed to evaluate significant differences between survival curves in univariate analyses. We used Cox regression models to compute multivariate rates. The independent prognostic effect of comorbidity (in general and specific diseases) was investigated, adjusting for age, stage of disease, and treatment of the patient.

Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a background population with the same age structure [11]. Expected survival rates were calculated from life tables for regional male and female populations with the same 5-year age distribution.

Results

The proportion of patients with one or more serious coexistent disease at the time of diagnosis of breast cancer increased from 9% for patients younger than 50 to 55% for patients aged 80 years and older (table 1).

The most frequent coexistent diseases were cardiovascular disease (7%), diabetes mellitus (7%), and previous cancer (6%), for all age groups (table 1).

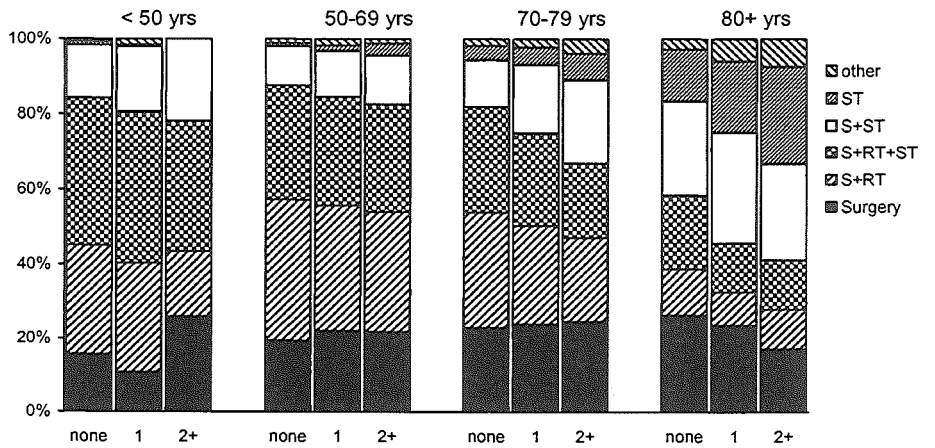

Figure 1 Primary treatment (%) of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995-2001, according to age and number of comorbid conditions
S=surgery, RT=radiotherapy, ST=systemic therapy. ST was mainly chemotherapy (93%) in age <50 y, and mainly hormonal treatment (78%, 96% and 100%) in age groups 50-69, 70-79 and 80+, respectively
* $p \leq 0.01$

Treatment of patients without comorbidity was less extensive in the older age groups (Figure 1). The presence of comorbidity affected treatment in all age groups, but these effects were much smaller before age 70.

Table 2 Overall survival (% and SE) of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995-2001, according to age and concomitant disease.

age	<50 y			50-69 y			≥ 70 y			All ages combined
	Survival			survival			survival			survival
	crude		relative	crude		relative	crude		relative	relative
time since diagnosis	1 yr	5 yr	5yr	1 yr	5 yr	5yr	1 yr	5 yr	5yr	5yr
No comorbidity	98 (0.3)	84 (1.0)	84 (1.0)	98 (0.3)	84 (0.7)	87 (0.8)	93 (0.8)	68 (1.6)	93 (2.1)	87 (0.6)
One concomitant disease:										
Previous cancer	96 (2.9)	77 (7.2)	78 (7.2)	**92 (2.2)**	**73 (3.8)**	**76 (3.9)**	89 (2.8)	59 (4.9)	78 (6.5)	**77 (3.2)**
Cardiovascular disease	100 (0.0)	-	-	98 (1.2)	83 (4.0)	88 (4.1)	**93 (2.0)**	**56 (4.4)**	**77 (6.0)**	83 (3.8)
COPD	100 (0.0)	74 (6.9)	75 (7.0)	98 (1.4)	84 (3.7)	88 (3.9)	94 (2.9)	62 (6.8)	88 (10)	84 (3.5)
Diabetes mellitus	93 (6.9)	-	-	96 (1.5)	84 (3.1)	88 (3.3)	**87 (2.6)**	**53 (4.4)**	**69 (5.8)**	**78 (3.2)**
Cerebrovascular	-	-	-	94 (6.1)	-	-	**80 (4.8)**	**48 (6.6)**	75 (10)	76 (8.4)
Tuberculosis	-	-	-	100 (0.0)	87 (6.9)	91 (7.2)	96 (3.6)	-	-	84 (7.1)
Dementia	-	-	-	-	-	-	**83 (6.2)**	**27 (8.8)**	-	-
Digestive tract	96 (4.2)	83 (9.5)	-	95 (3.7)	87 (6.1)	91 (6.3)	89 (5.9)	60 (10)	-	94 (6.2)
Other	96 (3.5)	81 (7.9)	81 (8.0)	97 (3.1)	84 (7.8)	86 (8.0)	**84 (7.3)**	**54 (10)**	-	85 (6.4)
Two or more concomitant diseases	96 (4.3)	72 (9.6)	73 (9.7)	**92 (2.1)**	**65 (4.3)**	**68 (4.4)**	**81 (2.0)**	**35 (2.8)**	**53 (4.2)**	**59 (3.1)**

*) - = number of patients at risk too small for reliable survival estimate (SE > 10%)
Bold: Survival significantly different from patients without comorbidity ($P<0.01$)

Patients with at least one serious coexistent disease received less radiotherapy (51% vs. 66%, P<0.0001) and more systemic therapy (tamoxifen 44% vs. 30%, P<0.0001) compared to those without comorbidity (all ages combined). The effect of comorbidity on treatment was most clear for patients aged 80 years and older, when the proportion treated with surgery alone was lower for those with comorbidity (21% vs. 26%, P=0.09), and treatment with only tamoxifen was higher (21% vs. 14%, P=0.01). Surgical procedures were less extensive for patients with comorbidity. The standard breast conserving treatment consists of lumpectomy, axillary dissection and radiotherapy. Among all patients who underwent lumpectomy (n=3138), axillary dissection was performed in 78% of the patients with at least two other serious diseases, compared to 97% of those without comorbidity (P<0.0001) (Figure 2). Radiotherapy was administered to 94% of the patients without comorbidity who underwent lumpectomy, compared to 87% of patients with one coexistent disease and 78% of patients with 2 or more comorbid conditions (p<0.0001). This effect was strongest among patients aged over 80 years at diagnosis. The proportion who underwent axillary dissection combined with lumpectomy decreased from 70% in those without coexistent disease to 46% and 40% in those with one and 2 or more coexistent diseases, respectively (P=0.009). The proportion that received radiotherapy in this patient group decreased from 70% in those without comorbidity to 54% and 50% of patients with one and 2 or more coexistent diseases, respectively (P=0.12) (Figure 2).

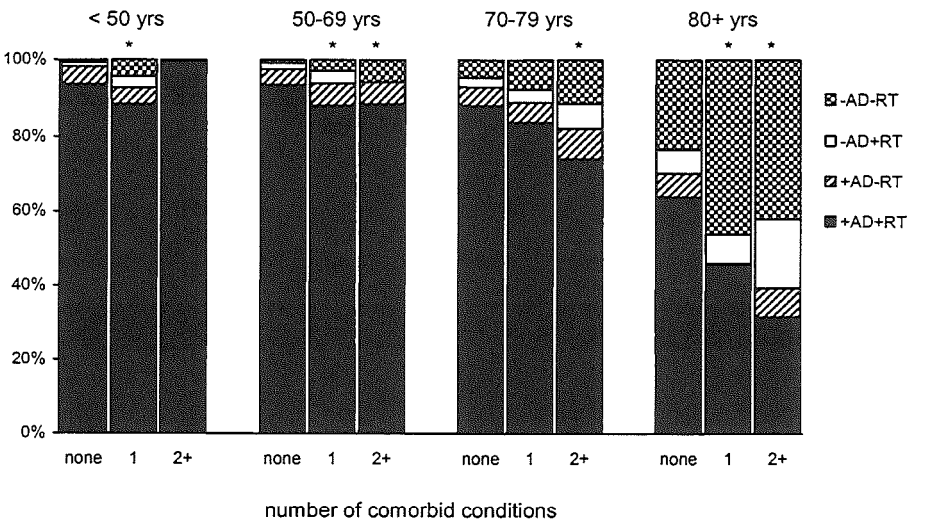

Figure 2 Proportion axillary dissection and radiotherapy among breast cancer patients who underwent lumpectomy in southeastern Netherlands, 1995-2001, according to age and number of comorbid conditions AD= axillary dissection, RT=Radiotherapy * p≤ 0.01

Crude five-year survival rates for patients who suffered from comorbidity were significantly lower than for patients without coexistent diseases (table 2). Among patients aged 50-69 years both 1-yr and 5-yr survival rates were significantly lower in the

presence of previous cancer (P<0.01). Crude survival of 70+ patients with a cardiovascular disease, diabetes mellitus, cerebrovascular disease, dementia or other comorbidity cancer was significantly lower (P<0.01). Survival adjusted for background mortality (relative survival) yielded similar results (table 2).

Table 3 Multivariate survival of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995-2001

	n	(%)	HR	(95% CI)	*P* value
Concomitant disease					
No comorbidity	5729	(64)	1.00		
One concomitant disease:					
Previous cancer	493	(6)	1.37	(1.2-1.7)	0.003
Cardiovascular disease	624	(7)	1.34	(1.1-1.7)	0.009
COPD	403	(4)	1.13	(0.9-1.5)	0.4
Diabetes mellitus	637	(7)	1.33	(1.1-1.6)	0.004
Cerebrovascular	207	(2)	1.63	(1.2-2.3)	0.004
Tuberculosis	100	(1)	1.02	(0.6-1.7)	1.0
Dementia	70	(1)	2.34	(1.6-3.5)	0.0001
Digestive tract	143	(2)	1.18	(0.8-1.8)	0.5
Other	138	(2)	1.27	(0.8-1.9)	0.2
Two or more concomitant diseases	600	(7)	1.44	(1.3-1.5)	0.0001
Stage					
I	2490	(28)	1.00		
II	3680	(41)	1.93	(1.6-2.3)	0.0001
III/IV	1105	(12)	3.82	(3.2-4.6)	0.0001
unknown*	1691	(19)	1.82	(1.5-2.2)	0.0001
Treatment					
S	1850	(21)	1.00		
S+RT	2733	(30)	0.70	(0.6-0.8)	0.0001
S+RT+ST	2656	(30)	1.05	(0.9-1.2)	0.5
S+ST	1245	(14)	1.29	(1.1-1.5)	0.001
ST	310	(3)	2.99	(2.5-3.6)	0.0001
other	172	(2)	3.62	(2.9-4.6)	0.0001
Age (years)					
< 50	2313	(26)	1.00		
50-69	4185	(47)	0.97	(0.9-1.1)	0.7
70-79	1668	(19)	1.47	(1.3-1.7)	0.0001
80+	800	(9)	2.42	(2.1-2.8)	0.0001

*) Patients with a negative sentinel node without complete axillary clearance were coded as stage unknown by the cancer registry

Relative 5-year survival for patients without comorbidity (all ages combined) was 87% (95%CI: 86-88), which was significantly higher than that for patients with a previous cancer (77% (95%CI: 71-83)), or diabetes mellitus (78% (95%CI: 72-84)). Patients with only one comorbid condition experienced 80% 5-year relative survival, patients with 2 or more conditions only 59% (95%CI: 53-65). Comparing patients without comorbidity by age group showed that patients without coexistent disease above

age 70 had higher relative 5-year survival rates than those below age 50 (93% (95%CI: 89-97) vs 84% (95%CI: 82-86)).

In a multivariate survival analysis the presence of any comorbidity yielded a prognostic effect, after adjustment for age, stage of disease, and treatment (HR=1.3, P=0.0001 for one coexistent disease and HR=1.4, P=0.0001 for 2+ coexistent diseases) (table 3). The most important effects on survival were found for previous cancer (HR=1.4, P=0.003), cerebrovascular disease (HR=1.6, P<0.004), and dementia (HR=2.3, P<0.0001).

Discussion

Primary treatment of breast cancer patients with serious comorbidity was less extensive than treatment of those without comorbidity. Adjuvant radiotherapy was administered less often, being replaced by either another surgical procedure (mastectomy instead of breast-conserving surgery) or adjuvant hormonal treatment. Axillary dissection was omitted in a large portion of the (older) patients with serious comorbidity. Independent of age, stage and treatment, survival was significantly worse for breast cancer patients who suffered from a previous cancer, cardiovascular disease, diabetes mellitus, cerebrovascular disease, or dementia, compared to those without these coexistent diseases. The discrepancy in survival between those patients with only breast cancer and those who also suffered from other chronic diseases increased.

Charlson's list was used to score prognostic comorbidity in the present study, without subdivision according to severity, because this was too complex for the registrars. Misclassification of comorbidity is limited, because the comorbid diseases are recorded routinely by trained registry personnel and data is collected directly from the medical records of the patients. A validation study among breast cancer patients showed some underregistration, mainly for cardiovascular diseases [12]. This means that the real effects of comorbidity on treatment choice and survival are probably even stronger than those described here.

Other studies also reported less extensive treatment of older breast cancer patients [13, 14], although they could not attribute this to either advanced age or the presence of comorbidity. We found that treatment was affected much more among the patients aged 70 and older than in the younger patients. About 10% of elderly patients were not treated according to guidelines [6, 7, 14]. More specifically, elderly patients did not receive radiotherapy [6, 13] and surgical procedures were less extensive [7, 13], especially with respect to axillary lymph node dissection [7]. In the western part of the Netherlands, the proportion receiving non-standard treatment was higher among patient aged 75 years and older, the highest for patients with severe comorbidity [6]. We also found that older patients received less radiotherapy and less extensive surgery. The presence of comorbid conditions clearly altered the therapeutic regimen, independent from age and stage.

The question is whether this is good clinical practice. Treatment of patients with coexistent conditions according to current guidelines may cause more complications and thus lower survival rates. But, these patients could also be in fact 'understaged' and/or 'undertreated'. The omission of radiotherapy has been shown to have adverse effects on recurrence rates and overall mortality [15-17]. Furthermore, axillary node dissection contributes to prolonged survival [18]. In contrast, we found no relation between the number of post-surgical complications and severity of comorbidity in a random sample of about 500 patients, but we did find an increase of the severity of comorbidity with age [19]. This could explain the increased contrast in survival between patients with and without comorbidity in the older age groups.

Obviously, breast cancer patients are at risk of dying from breast cancer as well as from other causes. However, it seems likely that serious comorbidity affects survival, either due to mortality as a result of the comorbid disease or because of 'undertreatment'. Recently, Yancik et al. [7] showed that diabetes and previous cancer predicted early mortality. The death of only about 50% of the patients who died within 30 months after diagnosis was due to breast cancer. Schairer et al. [20] found that white patients older than 70 with localised, regional or unknown stage at diagnosis had a higher probability of dying from other causes than breast cancer 5 years after diagnosis. The probability of death from other causes at the end of follow-up (27.9 y) exceeded that from breast cancer for patients with localised disease aged >50, and patients with regional disease aged >60. Unfortunately, we do not have individual data on cause of death, so we used relative survival to estimate disease-specific survival (this means we adjusted for survival for the background population with the same age structure). This showed significantly lower 5-year survival rates for most of the recorded coexistent diseases, with rates up to 50% lower. Furthermore, hazard ratios were still significantly elevated after adjustment for age, stage and treatment. Thus an independent effect of the presence of comorbidity on survival was demonstrated.

We also observed an independent prognostic effect of age. This implies that other prognostic factors may play a role, such as an inferior performance status, decreased organ reserves, a diminished mental condition, and unfavourable social factors [21, 22].

To our knowledge, this is the first time that the effect of comorbidity in breast cancer patients has been investigated in a population-based setting with a population of this size and such a long follow-up period. We could disentangle the prognostic effect of the coexistent disease itself from the effect of the altered treatment of patients with comorbidity.

In an increasingly ageing population comorbid conditions will play an even more important role in clinical decision-making and outcome. We demonstrated that elderly breast cancer patients can be divided in those without other diseases, with a relatively good prognosis, and those who have at least one other serious coexistent disease with a significantly poorer prognosis. The presence of these coexistent diseases warrants care programmes with adapted treatment guidelines.

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References

1. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents., vol. VIII Lyon: IARC Scientific Publications, 2002.
2. Visser O, Siesling S, van Dijck JA. Incidence of cancer in the Netherlands 1999/2000 Utrecht: Vereniging van Integrale Kankercentra, 2003.
3. Havlik RJ, Yancik R, Long S, Ries L, Edwards B. The National Institute on Aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. *Cancer* 1994;74:2101-6.
4. Coebergh JWW, Janssen-Heijnen MLG, Louwman WJ, Voogd AC. Cancer incidence, care and survival in the south of the Netherlands, 1955-1999: a report from the Eindhoven Cancer Registry (IKZ) with cross-border implications. Eindhoven: Comprehensive Cancer Centre South (IKZ), 2001.
5. de Rijke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA. Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol* 1996;7:677-85.
6. Bergman L, Dekker G, van Kerkhoff EH, Peterse HL, van Dongen JA, van Leeuwen FE. Influence of age and comorbidity on treatment choice and survival in elderly patients with breast cancer. *Breast Cancer Res Treat* 1991;18:189-98.
7. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *Jama* 2001;285:885-92.
8. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994;120:104-10.
9. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993-1996. *J Clin Epidemiol* 1999;52:1131-6.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
11. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comput. Programs Biomed.* 1985;19:197-207.
12. Houterman S, Verheij CDGW, Janssen-Heijnen MLG, Coebergh JWW, Validation study on co-morbidity in women with breast cancer diagnosed between 1995 and 1999. Eindhoven Cancer Registry, 2003.
13. Bergman L, Kluck HM, van Leeuwen FE, Crommelin MA, Dekker G, Hart AA, et al. The influence of age on treatment choice and survival of elderly breast cancer patients in south-eastern Netherlands: a population-based study. *Eur J Cancer* 1992;28A:1475-80.
14. Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-Caspar I, Schafer P, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol* 2003;21:3580-7.

15. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2000;355:1757-70.
16. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;96:115-21.
17. Vinh-Hung V, Voordeckers M, Van de Steene J, Soete G, Lamote J, Storme G. Omission of radiotherapy after breast-conserving surgery: survival impact and time trends. *Radiother Oncol* 2003;67:147-58.
18. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival--a Bayesian meta-analysis. *Ann Surg Oncol* 1999;6:109-16.
19. Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *Br J Cancer* 2004;90:2332-7.
20. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. *J Natl Cancer Inst* 2004;96:1311-21.
21. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998;16:1582-7.
22. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an italian group for geriatric oncology study. *J Clin Oncol* 2002;20:494-502.

3.3

Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival

a population-based study

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Abstract

Background: After a systematic mass mammography breast cancer screening programme was implemented between 1991 and 1996 (attendance 80%), we evaluated its impact on survival according to socioeconomic status (SES).

Methods: We studied survival rates up to 1-1-2005 for all consecutive breast cancer patients aged 50-69 and diagnosed in the period 1983-2002 in the area of the Eindhoven Cancer Registry (n= 4939). Multivariate analyses were performed using Cox regression analysis.

Results: The proportion of breast cancer patients with a low SES decreased from 22% in 1983-1990 to 14% in 1997-2002 when attendance was 85%. The proportion of newly diagnosed patients with stage III or IV disease in 1997-2002 was only 10% compared to 14% in 1991-1996 and 26% in 1983-1989 ($p<0.0001$). Stage distribution improved for all socio-economic groups ($p=0.01$). Survival was similar for all socio-economic groups in 1983-1990, but after the introduction of the screening programme women with low SES had lower age- and stage-adjusted survival rates (HR 2.0, 95%CI: 1.3-3.0). Survival was better for patients diagnosed in 1997-2002 compared to 1983-1990 for all socioeconomic strata; it was substantially better for the high SES group (HR 0.36, 0.2-0.5) compared to the lowest SES (HR 0.77, 0.6-1.1).

Conclusion: Although survival improved for women from each of the socio-economic strata, related to the high participation rate of the screening programme, women from lower socio-economic strata clearly benefited less from the breast cancer screening programme. That is also related to the higher prevalence of comorbidity and possibly suboptimal treatment.

Introduction

Mammography screening aims at early detection of breast cancer so that adequate treatment will eventually lower breast cancer mortality. In a mass screening programme, it is therefore especially important to reach women who have the highest chance of being diagnosed with advanced stage or have the lowest survival rates.

Women from lower socio-economic strata are less likely to attend population screening programmes[1-4] and are also more likely to present with unfavourable stage at diagnosis,[1, 5, 6] although not all studies confirm this.[7-9] Lower breast cancer survival rates among the disadvantaged are usually attributed to advanced stage at presentation, but also to suboptimal access to adequate treatment. A recent population-based study in Switzerland found social class to be an independent prognostic factor.[10]

The mass breast cancer screening programme was introduced in 1991 for women of 50 to 69 years and became fully implemented in 1996 in the south of the Netherlands covered by the population-based Eindhoven Cancer Registry, with a continuous high participation rate. Based on previous work[11] and a new postcode-based indicator of socio-economic status (SES) introduced by Statistics Netherlands[12] we were able to investigate survival according to SES for a sufficient period of time after introduction.

We studied whether survival according to SES was affected differentially by the implementation of the screening programme.

Methods

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the south-eastern part of the Netherlands, an area with now 2.4 million inhabitants (about 15% of the Dutch population) and only general hospitals. Trained registry personnel actively collect data on diagnosis, staging, and treatment from the medical records after notification by pathologists and medical registration offices.

In the area of the Eindhoven Cancer Registry, a biennial breast cancer screening programme for women aged 50-69 years was started in 1991 and fully implemented in 1996. The attendance rate was more than 80%.[13]

For our analyses we included all patients age 50-69 years diagnosed in 1983-2002 with invasive breast cancer in the eastern part of the registration area (about 1 million inhabitants). This population has been followed-up for vital status up to 1-1-2005. Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 from the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens.

An indicator of socioeconomic status was developed by Statistics Netherlands[12] being based on individual fiscal data from the year 2000 on the economic value of the home and household income and provided at aggregated level for each postal code (average of 17 households). Socioeconomic status was categorized according to quintiles ranging from 1 (low) to 5 (high), with a separate class for postal codes with a care-providing institution (such as a nursing home). This measure is assumed to be valid 10

years before and after the basic year (2000), so for patients diagnosed before 1990 we used a measure which was also based on postal code of residence, but socio-economic status (5 categories) was based on data from a marketing agency (self-reported occupation and education define 45 social classes, collapsed into a 5-level indicator based on average number of years of education), as described before.[11] We also used both SES indicators for the whole study period (1983-2002) to make sure any effect of diagnostic period was not attributable to the indicator we used.

We calculated distribution of age and stage of disease according to period of diagnosis.

Table 1 Characteristics of all women age 50-69 years diagnosed with invasive breast cancer between 1983-2002 in Southeastern Netherlands

	1983-1990		1991-1996		1997-2002		Total	
	n	%	n	%	n	%	n	%
TNM								
I	465	30	642	41	838	45	1945	39
II	638	42	665	43	805	44	2108	43
III	278	18	152	10	115	6.2	545	11
IV	115	7.5	68	4.4	65	3.5	248	5.0
unknown	38	2.5	31	2.0	24	1.3	93	1.9
Treatment*								
S alone	271	18	341	22	249	13	861	17
S+RT	766	50	628	40	658	36	2052	42
S+RT+ST	305	20	422	27	673	36	1400	28
S+ST	108	7	123	8	231	13	462	9.4
ST alone	26	1.7	23	1.5	23	1.3	72	1.5
Other	58	3.8	21	1.4	13	0.7	92	1.9
Socio-economic status								
1 (low)	336	22	285	18	262	14	883	18
2	325	21	319	20	342	19	986	20
3	308	20	279	18	355	19	942	19
4	154	10	274	18	358	19	786	16
5 (high)	302	20	315	20	414	22	1031	21
institution#	0	0.0	23	1.5	33	1.8	56	1.1
unknown	109	7.1	63	4.0	83	4.5	255	5.2
Total	1534		1558		1847		4939	100

* S=Surgery, RT=Radiotherapy, ST=Systemic therapy
\# institution= care-providing institution such as a nursing home

Stage was categorized according to the TNM classification.[14] Patients with either positive lymph nodes or metastases were considered to have advanced disease.

Chi-square test was performed of changes in the distribution across the three diagnostic periods. T-tests were performed of differences between two groups.

Crude survival analyses were performed. The log-rank test was used to evaluate significant differences between survival curves in univariate analyses. We used Cox

regression models to compute multivariate rates. The proportional hazard assumption of the predictor was evaluated by applying Kaplan-Meier Curves. The predictor satisfied the assumption of proportionality as the graphs of the survival function versus the survival time resulted in graphs with parallel curves as did the graphs of the log(-log(survival)) versus log of survival time. The independent prognostic effect of SES was investigated, adjusting for age and stage of disease, and stratified according to period of diagnosis (1983-1990, 1991-1996, 1997-2002). We also calculated the age and stage-adjusted effect of period of diagnosis stratified according to SES.

Results

Median age was similar for all 3 periods of diagnosis (59, 60, and 59 years, respectively).

Patients diagnosed between 1997 and 2002 had a significantly more favourable stage at diagnosis than patients diagnosed in earlier periods ($p<0.0001$): the proportion diagnosed with stage I (tumour smaller than 2 cm, no axillary lymph nodes involved) increased from 30% in 1983-1990 to 41% in 1991-1996 and 45% in more recent years (table 1). The proportion with advanced disease, i.e. stage III or IV, was significantly lower in the most recent period (9.7%) compared to 1991-1996 (14%) and 1983-1989 (26%, $p<0.0001$). Treatment varied over time, with a large proportion receiving systemic therapy in recent years (50%, vs. 36% and 29%).

The proportion of patients from the lowest socio-economic class decreased from 22% in 1983-90 to 18% in 1991-96 and 14% in 1997-2002 ($p<0.0001$), whereas the proportion from in the higher social classes increased

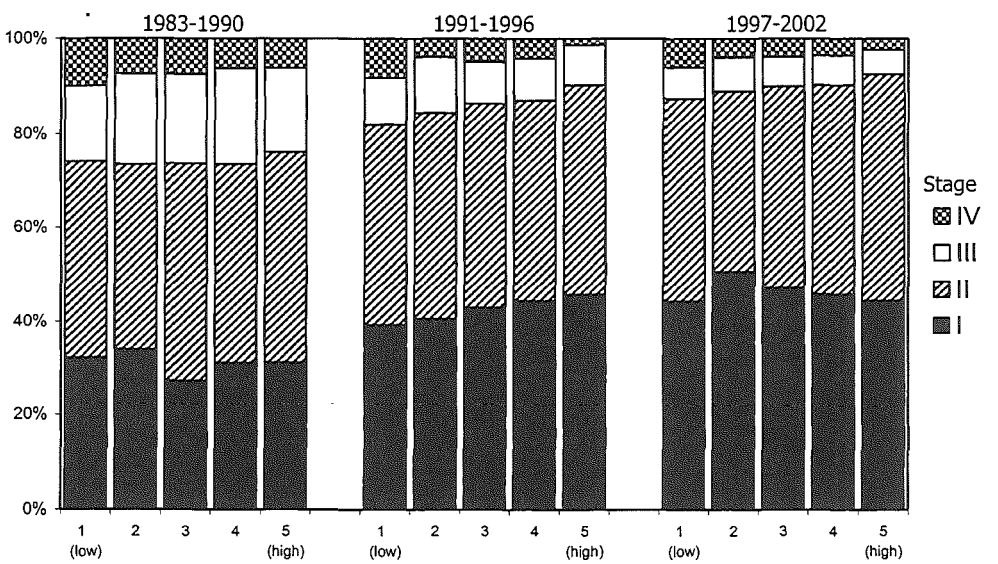

Figure 1 Stage distribution according to socio-economic status and period of diagnosis of patients age 50-69 years with invasive breast cancer in Southeastern Netherlands

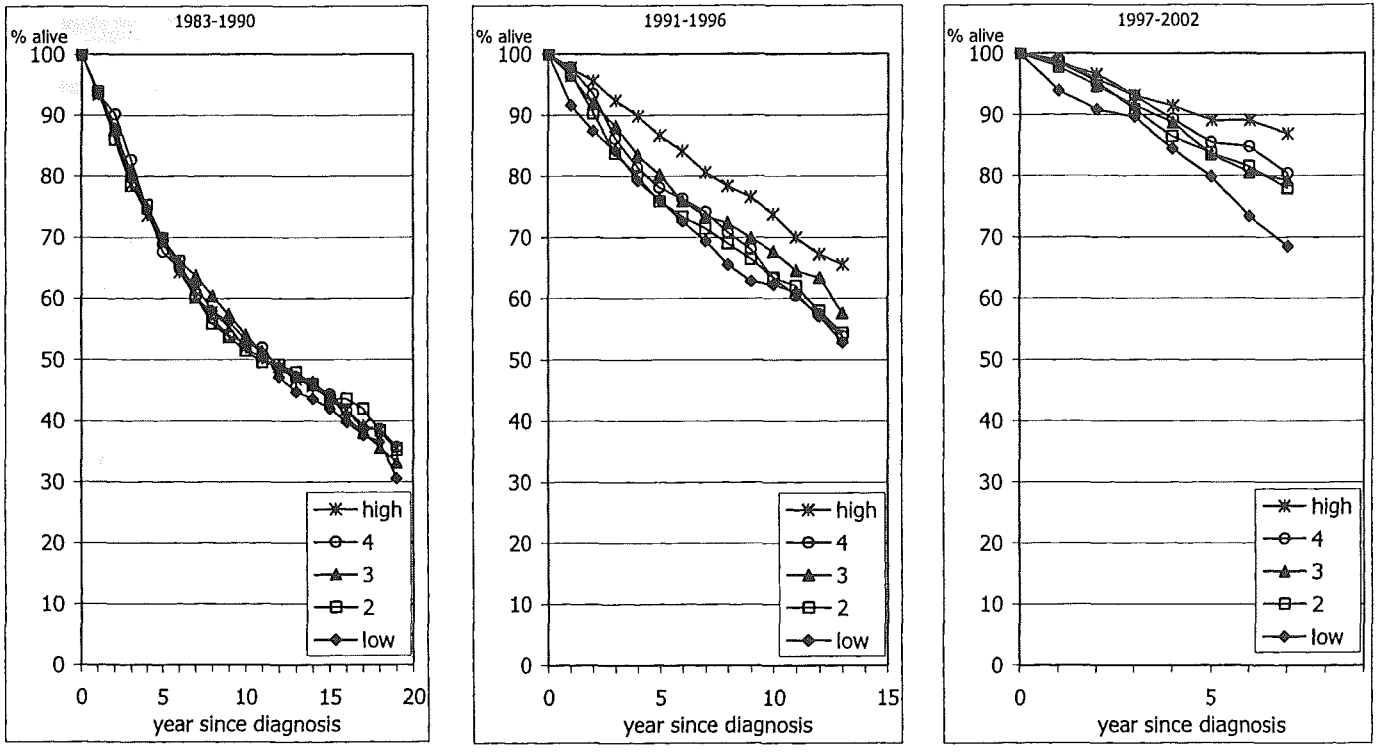

Figure 2 Trend in survival according to socio-economic status for all women age 50-69 years diagnosed with invasive breast cancer in Southeastern Netherlands

Stage distribution improved significantly over time for each social class (p<0.01). It was similar for all SES groups in 1983-90 (p=0.7, figure 1), although the proportion with stage IV was somewhat lower in the highest classes. The stage distribution was marginally more favourable for high SES compared to the lowest SES group in both 1991-96 and 1997-2002 (p=0.06 both periods), although the overall effect of SES on stage was not significant in the last period of time (p=0.4).

Survival improved for all socio-economic strata over time (figure 2). Survival rates did not differ among patients from each of the socio-economic classes diagnosed 1983-1990 in the period (p=0.9), 5-year survival rates being 70%, 70%, 70%, 68% and 69% for patients from the lowest to the highest social class, respectively. For patients diagnosed in 1991-1996, survival of patients with a high SES was better than that of all other socio-economic strata (p=0.01), 5-year survival rates being 76%, 76%, 80%, 78, and 87%, respectively. For patients diagnosed in 1997-2002 an increasing gradient in survival was observed (p=0.002) ranging from the lowest rates for the lowest SES group to the highest for the higher classes (80%, 84%, 83%, 85%, and 89%, respectively).

Table 2 Multivariate regression analysis of survival of breast cancer patients age 50-69 years according to period of diagnosis, Southeastern Netherlands

	1983-1990		1991-1996		1997-2002	
	HR*[a]	95% CI	HR*[a]	95% CI	HR*[a]	95% CI
Age (continuous)	1.03	1.0 - 1.0	1.04	1.0 - 1.1	1.01	1.0 - 1.0
Socio-economic status						
1 (low)	1.01	0.8 - 1.2	1.29	1.0 - 1.7	2.01	1.3 - 3.0
2	1.03	0.8 - 1.3	1.28	1.0 - 1.7	1.54	1.0 - 2.3
3	0.95	0.8 - 1.2	1.18	0.9 - 1.6	1.53	1.0 - 2.3
4	0.99	0.8 - 1.3	1.39	1.0 - 1.8	1.33	0.9 - 2.0
5 (high)[b]	1.00		1.00		1.00	
X^2 trend	*0.58 (p=0.97)*		*5.9 (p=0.21)*		*11.4 (p=0.02)*	
TNM stage						
I[b]	1.00		1.00		1.00	
II	1.75	1.5 - 2.1	2.33	1.9 - 2.9	2.00	1.4 - 2.8
III	3.11	2.5 - 3.8	4.67	3.5 - 6.2	5.39	3.6 - 8.1
IV	9.85	7.6 - 13	16.0	12 - 22	16.5	11 - 24
unknown	2.25	1.4 - 3.5	2.56	1.4 - 4.6	4.81	2.3 - 10

* HR=Hazard Ratio, CI=Confidence Interval
a Adjusted for all variables listed
b Reference

Multivariate analysis (table 2) showed that patients diagnosed since 1990 from the lower social classes had a 29% higher risk of death compared to the highest socio-economic group, after adjusting for age and stage at diagnosis (HR for the lowest vs. the highest SES group: 1.29, 95%CI: 1.0-1.7). The risk of death for low SES patients diagnosed since 1997 was twice as high as that for the highest SES group (HR: 2.01, 95%CI: 1.3-3.0). The overall effect of socio-economic status was significant in the last

period (p=0.02). Additional adjustment for treatment did not change risk estimates more than 5% (data not shown).

Age and stage-adjusted survival improved over time for all socioeconomic strata (table 3), the largest improvements were found for the highest social classes.

Discussion

We found that the proportion of breast cancer patients with a low SES has decreased since the introduction of a mass biennial mammography screening programme with high response rates. Although stage distribution improved for all socio-economic groups, the proportion with advanced disease decreased the most in the highest socio-economic group. In the 1980s survival was similar for all socio-economic groups, but since the introduction of screening the survival of women with a high SES has improved more than that for low socio-economic classes, also after adjustment for age and stage.

We used an indicator of socio-economic status based on the postal code of a residential area. This aggregate covers a relatively small geographical area, and thus represents a reliable approximation of individual socio-economic status. Furthermore, routinely collected income tax data (no questionnaires or interviews) have been found to provide reliable estimates of household income. Previous studies have proven that socio-economic differences based on neighbourhood data tend to reflect socio-economic differences well at the individual level [15-17]. Furthermore, this objective measure of SES is also applicable for older women (born before 1955), whose occupation or education does not always properly reflect their social class.[18] We also repeated the analyses comparing both SES indicators if they were applied for the whole study period (1983-2002) to ensure any that effect of diagnostic period was not attributable to the indicator we used, and it was not.

The lower proportion of patients with a low SES since the introduction of screening is not likely to reflect the higher attendance rate of women from a higher social class because of the very high participation rate, although this is not known according to social class. Studies from other countries have shown that SES does play a role in participation in the screening programme,[2] sometimes[3] but not always[4] due to the costs of a screening mammogram. However, the costs for the mass screening programme in the Netherlands are completely covered by public funds. Furthermore, the mean attendance rate in the Netherlands has always been rather high (about 80%),[13] and in our study area even higher than the national mean (85% in 2005).[19]

Foreign-born women are more likely to be non-attenders in the Netherlands,[20] as well as in Sweden,[21] Australia,[3] and the US,[22] for a variety of reasons. However the incidence of breast cancer among these groups of migrants is relatively low in the Netherlands and the stage distribution is comparable to that of women born in the Netherlands.[20] So this is unlikely to have affected survival rates in our study.

Table 3 Multivariate regression analysis of survival according to socio-economic status (SES) of breast cancer patients age 50-69 years in Southeastern Netherlands

SES	1 (low)		2		3		4		5 (high)	
	HR*[a]	95% CI	HR*[a]	95% CI	HR*[a]	95% CI	HR*[a]	95% CI	HR*[a]	95% CI
Period of diagnosis										
1983-1990[b]	1.00		1.00		1.00		1.00		1.00	
1991-1996	0.87	0.7 - 1.1	0.72	0.6 - 0.9	0.80	0.6 - 1.0	0.84	0.6 - 1.1	0.60	0.5 - 0.8
1997-2002	0.77	0.6 - 1.1	0.49	0.4 - 0.7	0.61	0.4 - 0.8	0.49	0.3 - 0.7	0.36	0.2 - 0.5
X^2 trend	*3.21 (p=0.21)*		*20.9 (p<0.001)*		*9.2 (p=0.01)*		*14.1 (p<0.001)*		*35.6 (p<0.001)*	

* HR=Hazard Ratio, CI=Confidence Interval
a Adjusted for age at diagnosis and stage of disease
b Reference

A lower attendance rate of low social classes will result in a more advanced disease stages at presentation.[23] Before the start of the mammography screening programme, we found that the stage distribution for breast cancers diagnosed in 1980-1989 was slightly more favourable for the highest socio-economic group.[24] We have now shown that this was also true after the introduction of screening, although the differences were small. In fact, we found that, although stage distribution became more favourable for all socio-economic groups, the proportion with advanced disease decreased less in the lower socio-economic group. This differential stage distribution was also described in a recent Danish study,[6] although our differences were smaller.

The variation in survival according to SES may also be related to differences in treatment, which depends on the disease stage and varies over time. The use of surgery and radiotherapy was similar across SES groups. However, we found that the administration of adjuvant chemotherapy varied across the social strata among stage II patients (8% of the lowest SES group vs. 17% of the highest SES group, $p<0.001$). Patients with a higher SES seem to have benefited more from the general trend towards more adjuvant chemotherapy independent of the disease stage. This may explain, at least in part, the diverging trend in survival rates.

Another explanation for differential survival could be socio-economic variations in lifestyle. Smoking has become relatively more prevalent among low SES groups. [25, 26] This may have had an adverse effect on survival due to a poor general health while undergoing breast cancer treatment or to smoking related diseases (such as chronic obstructive pulmonary diseases (COPD) or cardiovascular disease).

Also related to an unhealthy lifestyle is obesity, which has become an increasingly important problem in the last decade,[27, 28] especially among women from the lower social classes.[29]

Serious concomitant diseases besides breast cancer also affect survival rates,[30] which may explain differences in survival if comorbidity occurs more frequently in low SES groups.

Since the Eindhoven Cancer Registry has recorded comorbidity for all newly diagnosed patients since 1993, we checked whether the prevalence varied across socioeconomic strata. Indeed, the proportion of patients with comorbidity was higher among those with a lower SES (70% of patients in the lowest SES group had one or more concomitant conditions compared to 60% of the high SES group). In particular, the prevalence of diabetes and cardiovascular disease was highest in the low SES groups (diabetes in 10% with low SES and 4% with high SES, cardiovascular disease 7% and 4%, respectively).

Several studies have reported increased survival rates after the introduction of breast cancer screening.[31-35] As far as we know, no studies describe a differential effect of the introduction of screening on survival rates for socio-economic strata. However, socioeconomic inequalities in mortality have been widening in recent decades in western European countries.[36] In fact, socio-economic differences in breast cancer mortality

increased between 1983 and 1993 among women in Finland and Italy (Turin), but remained stable in Denmark and decreased somewhat in Norway where a mass screening programme was only introduced later.[36, 37]

In conclusion, despite a very high participation rate women from lower socio-economic strata clearly benefited less from the introduction of the breast cancer screening programme than those with a lower SES, probably due to a higher prevalence of comorbidity and suboptimal treatment (for both the cancer and the concomitant disease).

References

1. Bradley CJ, Given CW, Roberts C. Disparities in cancer diagnosis and survival. *Cancer* 2001;91:178-88.
2. Zackrisson S, Andersson I, Manjer J, Janzon L. Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma. *Int J Cancer* 2004;108:754-60.
3. O'Byrne AM, Kavanagh AM, Ugoni A, Diver F. Predictors of non-attendance for second round mammography in an Australian mammographic screening programme. *J Med Screen* 2000;7:190-4.
4. Olsson S, Andersson I, Karlberg I, Bjurstam N, Frodis E, Hakansson S. Implementation of service screening with mammography in Sweden: from pilot study to nationwide programme. *J Med Screen* 2000;7:14-8.
5. Schrijvers CT, Mackenbach JP, Lutz JM, Quinn MJ, Coleman MP. Deprivation and survival from breast cancer. *Br J Cancer* 1995;72:738-43.
6. Dalton SO, During M, Ross L, Carlsen K, Mortensen PB, Lynch J, et al. The relation between socioeconomic and demographic factors and tumour stage in women diagnosed with breast cancer in Denmark, 1983-1999. *Br J Cancer* 2006;95:653-9.
7. Brewster DH, Thomson CS, Hole DJ, Black RJ, Stroner PL, Gillis CR. Relation between socioeconomic status and tumour stage in patients with breast, colorectal, ovarian, and lung cancer: results from four national, population based studies. *Bmj* 2001;322:830-1.
8. Carnon AG, Ssemwogerere A, Lamont DW, Hole DJ, Mallon EA, George WD, et al. Relation between socioeconomic deprivation and pathological prognostic factors in women with breast cancer. *Bmj* 1994;309:1054-7.
9. Liu MJ, Hawk H, Gershman ST, Smith SM, Karacek R, Woodford ML, et al. The effects of a National Breast and Cervical Cancer Early Detection Program on social disparities in breast cancer diagnosis and treatment in Massachusetts. *Cancer Causes Control* 2005;16:27-33.
10. Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. *Int J Cancer* 2006;119:1145-51.
11. Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 1995;75:2946-53.
12. van Duijn C, Keij I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de bevolking* 2002;50:32-35.
13. Verbeek AL, Broeders MJ. Evaluation of The Netherlands breast cancer screening programme. *Ann Oncol* 2003;14:1203-5.
14. Sobin L, Wittekind C. TNM classification of malignant tumors, ed. 5th. New York, NY: Wiley, 1997.

15. Bos V, Kunst AE, Mackenbach JP, Nationale gegevens over sociaal-economische sterfteverschillen op basis van informatie over kleine geografische eenheden. Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, 2000.
16. Bos V, Kunst AE, Mackenbach JP. De omvang van sociaal-economische sterfteverschillen gemeten op buurtniveau: vergelijking met schattingen op basis van informatie op individueel niveau. In: Stronks K, ed. Sociaal-economische gezonheidsverschillen: Van verklaren naar verkleinen, vol. 5 Den Haag: Zon/MW, 2001:8-20.
17. Smits J, Keij I, Westert G. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte. *Mndstat bevolking* 2001;11:4-10.
18. Berkman LF, Macintyre S. The measurement of social class in health studies: old measures and new formulations. *IARC Sci Publ* 1997:51-64.
19. [Annual report 2005] in Dutch. Stichting Bevolkingsonderzoek Borstkanker Zuid, 2006.
20. Visser O, van der Kooy K, van Peppen AM, Ory FG, van Leeuwen FE. Breast cancer risk among first-generation migrants in the Netherlands. *Br J Cancer* 2004;90:2135-7.
21. Lagerlund M, Maxwell AE, Bastani R, Thurfjell E, Ekbom A, Lambe M. Sociodemographic predictors of non-attendance at invitational mammography screening--a population-based register study (Sweden). *Cancer Causes Control* 2002;13:73-82.
22. Rimer BK, Keintz MK, Kessler HB, Engstrom PF, Rosan JR. Why women resist screening mammography: patient-related barriers. *Radiology* 1989;172:243-6.
23. Adams J, White M, Forman D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *Bmj* 2004.
24. Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic status and breast cancer survival in the southeastern Netherlands, 1980-1989. *Eur J Cancer* 1995;31A:1660-4.
25. Stronks K, van de Mheen HD, Looman CW, Mackenbach JP. Cultural, material, and psychosocial correlates of the socioeconomic gradient in smoking behavior among adults. *Prev Med* 1997;26:754-66.
26. Lahelma E, Rahkonen O, Berg MA, Helakorp S, Prattala R, Puska P, et al. Changes in health status and health behavior among Finnish adults 1978-1993. *Scand J Work Environ Health* 1997;23 Suppl 3:85-90.
27. Gast GC, Frenken FJ, van Leest LA, Wendel-Vos GC, Bemelmans WJ. Intra-national variation in trends in overweight and leisure time physical activities in The Netherlands since 1980: stratification according to sex, age and urbanisation degree. *Int J Obes (Lond)* 2006.
28. Visscher TL, Kromhout D, Seidell JC. Long-term and recent time trends in the prevalence of obesity among Dutch men and women. *Int J Obes Relat Metab Disord* 2002;26:1218-24.
29. Hulshof KF, Brussaard JH, Kruizinga AG, Telman J, Lowik MR. Socio-economic status, dietary intake and 10 y trends: the Dutch National Food Consumption Survey. *Eur J Clin Nutr* 2003;57:128-37.
30. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *Eur J Cancer* 2005;41:779-85.
31. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003;361:1411-7.
32. Blanks RG, Moss SM, McGahan CE, Quinn MJ, Babb PJ. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *Bmj* 2000;321:665-9.

33. Hakama M, Pukkala E, Heikkila M, Kallio M. Effectiveness of the public health policy for breast cancer screening in Finland: population based cohort study. *Bmj* 1997;314:864-7.
34. Barchielli A, Paci E. Trends in breast cancer mortality, incidence, and survival, and mammographic screening in Tuscany, Italy. *Cancer Causes Control* 2001;12:249-55.
35. Duffy SW, Tabar L, Chen HH, Holmqvist M, Yen MF, Abdsalah S, et al. The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties. *Cancer* 2002;95:458-69.
36. Mackenbach JP, Bos V, Andersen O, Cardano M, Costa G, Harding S, et al. Widening socioeconomic inequalities in mortality in six Western European countries. *Int J Epidemiol* 2003;32:830-7.
37. Zahl PH, Strand BH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. *Bmj* 2004;328:921-4.

CHAPTER 4

COURSE OF THE DISEASE

4.1

A population-based study of radiotherapy in a cohort of patients with breast cancer diagnosed between 1996 and 2000

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Abstract

Purpose: To study the use of radiotherapy (RT) in a cohort of 6561 patients with invasive breast cancer diagnosed between 1996-2000.

Patients and Methods: Radiation given or planned within 6 months of diagnosis was considered part of primary treatment (PRT). RT given 6 months or later after diagnosis or after PRT was considered delayed or secondary RT (SRT). The odds for receiving SRT were studied by logistic regression analysis, taking into account age, co-morbidity, socioeconomic status, stage, second breast tumour, RT department (2 departments, each serving general hospitals only), primary surgical treatment and prior PRT. The retreat-rate and the cumulative use of RT at any time were calculated.

Results: Of all patients, 67% received RT, 3554 (54%) only PRT, 323 (5%) only SRT and 503 (8%) both. The cumulative use of SRT at 100 months was 17%. The 826 patients receiving SRT underwent 1846 courses 0-105 months (median 36) after primary diagnosis; the retreat-rate was 35%. Patients older than 50 received SRT significantly less often ($OR_{age\ 50\text{-}69}$=0.7, 95%CI=0.6-0.8 and $OR_{age\ \geq 70}$=0.4, 95%CI=0.3-0.5). The following factors increased the chance for SRT: patients from the eastern region (OR=1.3, 95% CI=1.1-1.6); patients who received PRT (OR=1.3, 95%CI=1.0-1.5) and patients who underwent mastectomy including axillary node dissection as well as unresected patients (OR=1.9, 95%CI=1.5-2.4, OR=2.6, 95%CI=1.7-3.9, respectively).

Conclusions: Thirteen percent of all patients with breast cancer received SRT, with a large variation in age and between the 2 RT departments in the region.

Introduction

The incidence of breast cancer amounted to 120 per 100,000 women in 2000. Radiotherapy (RT) is an essential part of breast cancer treatment, either as part of the primary treatment within the framework of breast-conserving treatment or mastectomy[1-3], or for palliation of recurrent or metastasized breast cancer [4, 5]. Therefore patients with breast cancer constitute a large proportion of the patients treated in a RT department.

Of all cancer patients about 50% are assumed to receive radiotherapy (RT) during the course of their disease[6, 7]. This percentage is not derived from population-based studies but is nevertheless often used in the process of decision-making for estimation of the future capacity of RT equipment and personnel needed. The overall percentage usually consists of a mixture of primary RT (PRT) as part of the initial treatment and secondary RT (SRT) in the case of recurrent disease or metastases without taking into account whether patients had already received primary RT[6, 8]. In a population-based study of patients treated with RT as part of their primary treatment we found that 30% of all cancer patients received PRT[9, 10]. For patients diagnosed with breast cancer in 1998-2002 this amounted to 55%[9]. SRT has been studied in our region for all cancer patients diagnosed between 1975 and 1989: 5% of previously non-irradiated patients received RT for recurrent disease or metastases, and about 40% of all irradiated patients had RT again[11]. Recent studies used an evidence-based approach to determine the use of RT as part of primary treatment and for treatment of recurrences or metastases. They estimated that 66% to 83% of all breast cancer patients received RT during the course of their illness[12, 13].

Since we had already performed several studies on the use of primary RT we wanted to estimate the percentage of patients receiving RT during their illness, which can also be relevant for planning purposes. We determined, in a population-based setting in a region with 2 large RT departments, the proportion of patients with breast cancer who received RT as part of their primary treatment and as SRT. We explored the influence of patient and tumour characteristics on SRT and variations in referral for SRT.

Methods

We studied a cohort of patients with a first invasive breast cancer, diagnosed between 1-1-1996 and 31-12-2000 and followed until 1-1-2005. Data were derived from the population-based Eindhoven Cancer Registry (ECR), which has recorded data on all patients newly diagnosed with cancer since 1955. The registry covers a large part of South Netherlands with approximately 2.4 million inhabitants in 2004. The medical infrastructure consists of six Pathology departments, hospital medical records offices in 10 general hospitals and two large RT departments (one in the western (Tilburg) and one in the eastern (Eindhoven) part of the region). Patients never have to travel more than one hour to a RT department.

Table 1 Characteristics of patients with breast cancer diagnosed between 1996 and 2000(n=6561) receiving primary radiotherapy in South Netherlands

Patient characteristics	Primary radiotherapy		
	No (n=2504) n (%)	Yes (n=4057) n (%)	Total (n=6561) n (%)
Age at diagnosis			
≤ 49 years	554 (22)	1142 (28)	1696 (26)
50 t/m 69	1002 (40)	2059 (51)	3061 (47)
≥70+	948 (38)	856 (21)	1804 (28)
Number of concomitant diseases			
None	1188 (47)	2441 (60)	3629 (55)
One	580 (23)	889 (22)	1469 (22)
2+	387 (16)	372 (9)	759 (12)
Unknown	349 (14)	355 (9)	704 (11)
Socioeconomic status			
Low	687 (28)	977 (24)	1664 (25)
Middle	927 (37)	1669 (41)	2596 (40)
High	660 (26)	1249 (31)	1909 (29)
Institution[a]	195 (8)	131 (3)	326 (5)
Unknown	35 (1)	31 (1)	66 (1)
Stage at diagnosis			
I	897 (36)	1713 (42)	2610 (40)
II	1135 (45)	1815 (45)	2950 (45)
III	133 (5)	390 (10)	523 (8)
IV	176 (7)	105 (3)	281 (4)
unknown	163 (7)	34 (1)	197 (3)
Second breast tumour			
No	2377 (95)	3847 (95)	6224 (95)
Yes	127 (5)	210 (5)	337 (5)
Vital status 1-1-2005			
Alive	1664(66)	3068 (76)	4732 (72)
Deceased	840 (34)	989(24)	1829 (28)
Surgery[b] (western region)			
BCS + AC	432 (3)	1227 (67)	1269 (39)
BCS	62 (4)	32 (2)	94 (3)
MRM + AC	1074 (76)	510 (28)	1584 (49)
MRM	63 (4)	25 (1)	88 (3)
No surgery	176 (12)	41 (2)	217 (7)
Surgery (eastern region)			
BCS + AC	53 (5)	1632 (73)	1685 (51)
BCS	51 (5)	35 (2)	86 (3)
MRM + AC	840 (77)	502 (23)	1342(41)
MRM	28 (3)	18 (1)	46 (1)
No surgery	115 (11)	35 (2)	150 (5)
Radiotherapy Department			
Western region	1417 (57)	1835 (45)	3252 (50)
Eastern region	1087(43)	2222 (55)	3309 (50)
Secondary Radiotherapy			
No	2181 (87)	3554 (88)	5735 (87)
Yes	323 (13)	503 (12)	826 (13)

a) institution: patients living in an institution (i.e. nursing home)
b) BCS=Breast conserving surgery, AC=axillary clearance, MRM=modified radical mastectomy

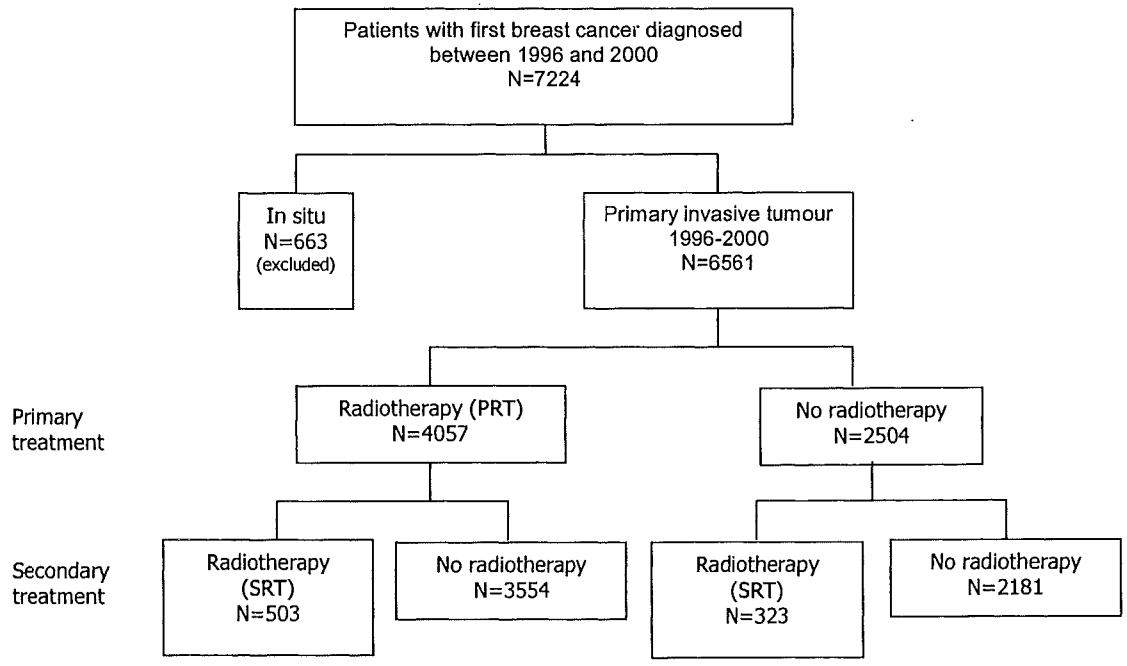

Figure 1 Flow chart of the study-population: breast cancer patients diagnosed between 1996 and 2000 in South Netherlands (PTR=primary radiotherapy, SRT=secondary radiotherapy)

Trained registry personnel from the ECR actively collect data on diagnosis, staging, co-morbidity and primary treatment, given or planned within 6 months of diagnosis, from the hospital charts after notification of newly diagnosed cases by the regional Departments of Pathology, Haematology and Radiotherapy as well as the national Registry of Hospital Discharge Diagnoses. An indicator of socioeconomic status (SES) was developed by Statistics Netherlands based on individual fiscal data (economic value of the home and household income) and provided at aggregated levels for each postal code (average of 17 households). Socioeconomic status was categorized 1 (low) to 3 (high), with a separate class for postal codes with a care-providing institution (such as a nursing home).

Cancer registries in The Netherlands usually cover over 95% of all cases, thanks to the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used[14]. In both RT Departments each course of RT is recorded with date of onset, patient characteristics and treatment protocol number indicating the kind of radiation treatment given. Data on all patients with breast cancer who received RT between 1-1-1996 and 1-1-2005 at the two RT Departments were combined with the above- mentioned data from the ECR.

Between 1996 and 2000, a total of 7224 patients was first diagnosed with breast cancer, including sarcomas (n=55) and unknown morphology (n=38). Patients with carcinoma in situ (n=663) were excluded. We only considered RT given for the first tumour. Eventually we included 6561 patients with invasive breast cancer in our analysis (Figure 1).

Radiation given or planned within 6 months of diagnosis was considered PRT[15]. This includes patients irradiated within 6 months of diagnosis only for metastases as planned primary treatment (n=64). We also included patients who were irradiated as part of primary treatment later than 6 months after diagnosis (in case of prolonged chemotherapy) (n=86). RT given 6 months or later after diagnosis (other than the above) or RT given after a previous course of radiation for breast cancer (even within 6 months) was considered as delayed or SRT. Patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment, were also considered to have received SRT (n=57). When data from the RT institutes were compared with data from the ECR we found that PRT was not registered in the ECR in 136 cases (2% of the total cohort). We included them in our analysis as part of the PRT group. RT registered in the ECR for 2 patients who were treated later than 6 months (25 and 51 months) after diagnosis was considered to be SRT.

Twenty-one patients were treated with a combination of hyperthermia and external RT for recurrent breast cancer, all administered in the RT department at the Western region, which is a top level reference department for superficial hyperthermia[16]. Eleven of these patients received previous PRT at the same department, and 9 in the other; 1 had previous SRT for recurrent breast cancer in the same institute.

The retreat-rate is defined as the number of radiation courses given after the first course divided by the number of all first courses either as PRT or as SRT (=number of patients irradiated).

Table 2 Odds of receiving secondary radiotherapy for patients with breast cancer diagnosed between 1996 and 2000 (n=6561) in South Netherlands, each variable adjusted for all others

	Odds-ratio	95% CI	P-value
Age at diagnosis			
≤ 49 years	1		
50 t/m 69	0.7	0.6-0.8	<0.0001
≥70	0.4	0.3-0.5	<0.0001
Number of concomitant diseases			
None	1		
One	0.9	0.8-1.1	0.5
2+	0.8	0.6-1.1	0.1
Unknown	1	0.7-1.2	0.7
Socioeconomic status			
Low	1		
Middle	1	0.9-1.3	0.7
High	1.1	0.9-1.4	0.4
Institution[a]	0.8	0.5-1.3	0.4
Unknown	1.4	0.7-2.9	0.4
Stage at diagnosis			
I	1		
II	2.2	1.8-2.7	<0.0001
III	2.9	2.1-3.9	<0.0001
IV	8	5.5-11.5	<0.0001
Unknown	0.9	0.5-1.7	0.8
Radiotherapy Department			
Western region	1		
Eastern region	1.3	1.1-1.6	0.0003
Primary Radiotherapy			
No	1		
Yes	1.3	1.0-1.5	0.02
Second breast tumour			
No	1		
Yes	1	0.7-1.5	0.8
Surgery[b]			
BCS + AC	1		
BCS	1.6	0.9-2.8	0.09
MRM + AC	1.9	1.5-2.4	<0.0001
MRM	1.7	1.0-3.0	0.07
No surgery	2.6	1.7-3.9	<0.0001

[a]Institution: patients living in an institution (i.e. nursing home)
[b]BCS=Breast conserving surgery, AC=axillary clearance, MRM=modified radical mastectomy

Characteristics of patients who did or did not receive PRT are listed in table 1. For surgery we distinguished between patients from the western and the eastern region. We used logistic regression analysis to estimate the chance of receiving SRT adjusting for age, number of concomitant conditions, socioeconomic status, stage, second breast

tumour, RT institute, primary surgical treatment and prior PRT. We assessed the number of patients receiving SRT, and the number and type of secondary radiation treatments (for recurrent or for metastasized disease) they received.

The cumulative use of any RT (PRT or SRT) over time was calculated according to the Life Table Method[17], starting on the date of diagnosis and ending on the date of start of RT, or censored on the date of death or 1-1-2005 whichever occurred first. In total 1543 patients were censored on 1-1-2005. The cumulative use of SRT was calculated by means of the same method: follow-up for patients who received PRT (n=4057) started on the last day of primary RT (according to the definition, these patients were at risk for SRT after having received PRT); follow-up for patients who received no PRT (n=2385, 119 patients died within 6 months of diagnosis) started 6 months after diagnosis (by definition patients without PRT were at risk for SRT 6 months after diagnosis). Follow-up of both groups ended on the date of initiating SRT, date of death or 1-1-2005, whichever occurred first. These 2 groups were compared by means of the log-rank test.

Results

In our cohort of 6561 patients with breast cancer diagnosed between 1996 and 2000, (median follow-up 66 months), 4380 (67%) patients received RT between 1-1-1996 and 1-1-2005: 3554 (54%) only PRT, 323 (5%) only SRT and 503 (8%) both (Figure 1). Five-hundred-three patients who received PRT and 120 patients who received only SRT were irradiated twice or more. The retreat-rate was 35% (1523/4380). The patient characteristics are listed in table 1. About half of all patients underwent breast-conserving surgery and half mastectomy. In the eastern region a higher percentage received breast-conserving surgery and was referred for PRT. Five percent of the patients (n=337) developed a second breast tumour between 1-1-1996 and 1-1-2005, 146 (43%) of whom received PRT for the second tumour. Six patients developed a second tumour in the ipsilateral breast, but with other morphology or at another sub localisation, 331 in the contralateral breast. For 105 patients the second tumour was diagnosed within 1 month of the first, for 82 of these patients on the same day. In this study we only considered RT given for the first tumour (n=57). The odds for receiving SRT are shown in table 2. Patients aged 50 years or older received SRT significantly less often (OR =0.7, 95% CI=0.6-0.8 and OR=0.4, 95%CI=0.3-0.5 for patients 50-69 years and 70 years or older, respectively). Patients with an initial tumour stage higher than stage I received SRT significantly more often (stage II: OR=2.2, 95%CI=1.8-2.7, stage III: OR=2.9, 95%CI=2.1-3.9, stage IV: OR=8, 95%CI=5.5-11.6). Patients from the eastern region were referred more often for SRT (OR=1.3, 95% CI=1.1-1.6). Patients who received PRT had a slightly higher chance of receiving SRT (OR=1.3, 95%CI=1.0-1.5). Patients who underwent mastectomy including axillary node dissection and patients who did not undergo surgery had SRT significantly more often (OR=1.9, 95%CI=1.5-2.4, OR=2.6, 95%CI=1.7-3.9, respectively).

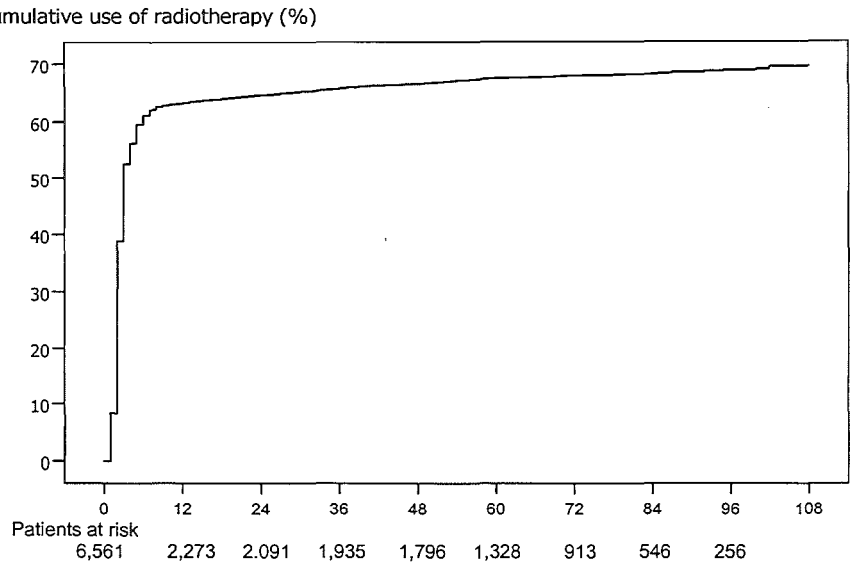

Figure 2 Cumulative use of radiotherapy (primary or secondary) in a cohort of breast cancer patients (n=6561) diagnosed between 1996 and 2000 in South Netherlands (RT=radiotherapy).

Of 826 patients receiving SRT, 138 (17%) had the first course of SRT for a recurrence and 688 for metastases; they underwent 1846 courses in total, with a range of 0 - 101 months (median 36 months) after primary diagnosis: 174 courses for relapsed breast tumours and 1672 courses for metastases. Seventy-four percent of these patients had more than one secondary treatment (median=3) (table 3).

Figure 2 shows the cumulative use of RT, either PRT or SRT. Of all patients at risk, 4035 (61%) had RT within the first 6 months of diagnosis. After 101 months 4380 patients had received RT, or 67% of the patients at risk. In figure 3 the cumulative use of SRT is shown separately for patients who did or did not receive previous PRT. The total cumulative use of SRT was 17% 100 months after start of follow-up. The cumulative chance to have SRT was slightly higher for patients who did not receive prior PRT (p=0.2).

Discussion

We studied the percentage of patients with breast cancer in a cohort diagnosed between 1-1-1996 and 31-12-2000 in our region who received either primary or secondary RT. With a median follow-up of 66 months, 67% of all breast cancer patients received RT at some point in the course of their illness. This is similar to an evidence-based estimation for optimal RT utilization in Canada, while an evidence-based study in

Australia calculated a higher level[12, 13]. However, reported actual RT utilization rates were much lower (25-50%)[18, 19], except in the state of New South Wales, Australia (71%) which was the only study that included patients who had their first RT late during the course of their disease[20].

Table 3 Number of secondary radiation courses (range:0*-105 months after primary diagnosis) per patient in a cohort of breast cancer patients diagnosed between 1996-2000 (n=6561) in South Netherlands

Number of secondary radiotherapy courses	Number of patients (%)	Total number of secondary radiotherapy courses	Cumulative number of secondary radiotherapy courses
1	438 (53)	438	438
2	166 (20)	332	770
3	76 (9.2)	228	998
4	47 (5.7)	188	1186
5	44 (5.3)	220	1406
6	14 (1.7)	84	1490
7	13 (1.6)	91	1581
8	11 (1.3)	88	1669
9	5 (0.6)	45	1714
10	4 (0.5)	40	1754
11	6 (0.7)	66	1820
12	0 (0)	0	1820
13	2 (0.2)	26	1846
Total	826 (100)	1846	1846

*0 months after diagnosis: patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment.

We found that patients older than 50 years of age had a significantly lower chance to receive SRT than younger patients. Manders and colleagues described the clinical management of women with metastatic breast cancer, demonstrating that patients aged 70 years or older were less likely to receive both chemotherapy or RT[21]. Elderly patients were also treated less often with primary irradiation, sometimes related to co-morbidity[22, 23].

Socioeconomic status did not affect the chance to receive SRT in our cohort (Table 2), while in the USA large treatment disparities were found[24]. However, socio-economic disparities in the Netherlands are relatively small and medical insurance covers cancer treatment for 99% of the population[25].

The chance to receive RT for an invasive carcinoma may have been influenced by a previous carcinoma in situ (CIS). According to the national guidelines duct carcinoma in situ (DCIS) should be treated with breast-conserving surgery, including RT, or alternatively with a simple mastectomy on indication [26]. Currently 49% of patients with DCIS are irradiated but in 1996 this was only 20% [27]. After breast-conserving therapy, including irradiation for a previous DCIS, no standard RT is possible for a new invasive tumour in the same breast. As a result patients with an invasive carcinoma after earlier

treatment for DCIS are more likely to undergo a mastectomy without irradiation. DCIS forms 8% (in 1996) to 10% (in 2003) of all new breast tumours[28].

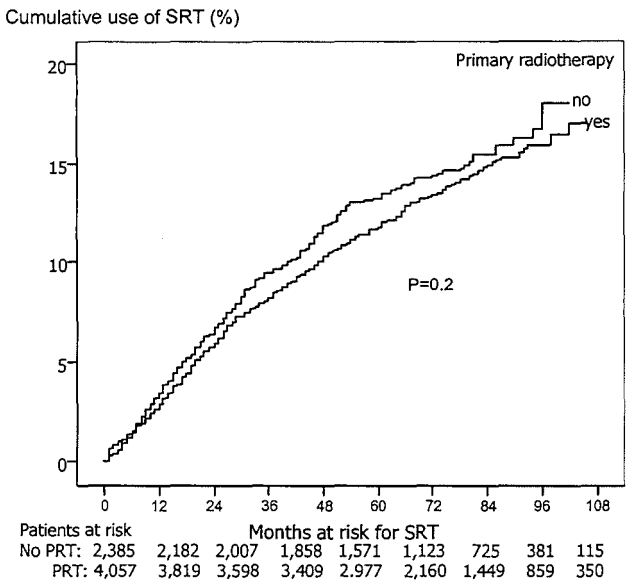

Figure 3 Cumulative use of secondary radiotherapy for patients who did or did not receive primary radiotherapy in a cohort of breast cancer patients (n=6561) diagnosed between 1996 and 2000 in South Netherlands (PTR=primary radiotherapy, SRT=secondary radiotherapy).

In our cohort 337 (5%) patients developed a second breast tumour between 1-1-1996 and 1-1-2005. This percentage was also found in another population-based study[29]. Because we only considered RT given for the first tumour, we excluded these second tumours, 43% of which received PRT, from our cohort. If these patients received SRT, we distinguished for which tumour on the basis of data from the RT departments. Only SRT for the first tumour was included in our study. A second breast tumour did not influence the chance to receive SRT for the first tumour.

When a local recurrence occurs after mastectomy (66% of patients primarily undergoing a mastectomy received no PRT), the recurrent tumour can often be treated with SRT. Patients with a recurrence after breast conserving-treatment (97% of whom received PRT) are usually not suited for RT for their recurrence. Therefore a mastectomy will commonly be the first treatment of choice. Some of these patients are eligible for regional lymph node irradiation. Superficially located recurrent breast cancer in a previously irradiated area can be treated with RT in an adapted fractionation schedule combined with hyperthermia as radiosensitizer[16].

In the eastern region a higher percentage of patients were treated with breast-conserving surgery, which leads to a higher percentage of patients receiving PRT in that region. This can be explained by variations in surgical management, which are larger in the western region than in the eastern region[30, 31]. This variation in referral for radiotherapy was observed not only for PRT but also for SRT.

Patients with a higher stage, usually treated with mastectomy including axillary node dissection, have a higher risk for metastases amenable to RT. Patients who did not have any surgery at all had a significantly higher chance of receiving SRT, probably because almost 50% of them had a stage IV tumour at diagnosis, thus a higher risk for symptomatic metastases amenable to RT. Eventually, skeletal metastases occur in 20-40% of patients with breast cancer[32, 33]. RT relieves pain in most cases, is effective in spinal cord decompression and can prevent a pathological fracture in the case of lytic lesions of the bone cortex [34-36]. It also improves quality of life and may prolong median survival for most patients with symptomatic brain metastases which occur in 10-20% of women with metastasized breast cancer[37].

The cumulative use for SRT was slightly higher for patients who did not receive prior PRT (Figure 3), but after adjustment, the chance of receiving SRT was 30% higher for patients with prior PRT in comparison with patients without prior PRT (OR=1.3, Table 2). This can partly be explained by the differences in stage distribution and variations in surgical procedures.

A potential drawback of our study is the median follow-up time for our cohort (66 months, range 0-107), which is not very long for a population of breast cancer patients. However, we were unable to study an earlier cohort, because data was incomplete before 1996. Although the development of loco-regional recurrences after 5 years is not uncommon[38], the majority of recurrences and distant relapses occur in the first 5 years[39-41]. Generally, breast cancer often behaves as a chronic disease for many patients, resulting in prolonged survival with metastases[41, 42]. Patients with metastasized disease may be referred for the first SRT many years after the first appearance of the disease and can be treated with irradiation on different localizations until their death. Only 28% of patients in our cohort had died on 1-1-2005. So, whereas the majority of SRT for recurrent breast cancer will occur within our study period, illustrated by the levelling off of the total referral rate (PRT and SRT) after the first year of follow-up (Figure 2), the cumulative use of SRT (17% at 100 months after the start of follow-up) will undoubtedly continue to increase slowly over subsequent years.

Conclusions

The required capacity for RT for breast cancer is likely to be higher than the cumulative rates calculated now, requirements also need to be based on RT for DCIS (now 10% of all breast cancers, 50% of whom receive RT), and the RT for second primary breast cancer. Furthermore, there was a relatively low rate of breast-conserving surgery (and thus PRT) attributable to several referring specialists[30, 31] and there was also some undertreatment of elderly patients[22, 23]. This approach to the investigation of

radiotherapy consumption stimulates discussion on optimal treatment and clinical justification of treatment variations. Therefore continued monitoring and discussion with referring specialists is highly warranted.

References

1. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000;18:1220-9.
2. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;96:115-21.
3. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2000;355:1757-70.
4. van der Sangen MJ, Coebergh JW, Roumen RM, Rutten HJ, Vreugdenhil G, Voogd AC. Detection, treatment, and outcome of isolated supraclavicular recurrence in 42 patients with invasive breast carcinoma. *Cancer* 2003;98:11-7.
5. McQuay HJ, Carroll D, Moore RA. Radiotherapy for painful bone metastases: a systematic review. *Clin Oncol (R Coll Radiol)* 1997;9:150-4.
6. van Daal WA, Bos MA. Infrastructure for radiotherapy in The Netherlands: development from 1970 to 2010. *Int J Radiat Oncol Biol Phys* 1997;37:411-5.
7. Porter A, Aref A, Chodounsky Z, Elzawawy A, Manatrakul N, Ngoma T, et al. A global strategy for radiotherapy: a WHO consultation. *Clin Oncol (R Coll Radiol)* 1999;11:368-70.
8. Moller TR, Brorsson B, Ceberg J, Frodin JE, Lindholm C, Nylen U, et al. A prospective survey of radiotherapy practice 2001 in Sweden. *Acta Oncol* 2003;42:387-410.
9. Vulto A, Louwman M, Rodrigus P, Coebergh JW. Referral rates and trends in radiotherapy as part of primary treatment of cancer in South Netherlands, 1988-2002. *Radiother Oncol* 2006;78:131-7.
10. Lybeert ML, Louwman M, Coebergh JW. Stable overall referral rates of primary radiotherapy for newly diagnosed cancer patients in the ageing population of South-Eastern Netherlands, 1975-1998. *Radiother Oncol* 2004;73:101-8.
11. de Jong B, Crommelin M, van der Heijden LH, Coebergh JW. Patterns of radiotherapy for cancer patients in south-eastern Netherlands, 1975-1989. *Radiother Oncol* 1994;31:213-21.
12. Foroudi F, Tyldesley S, Walker H, Mackillop WJ. An evidence-based estimate of appropriate radiotherapy utilization rate for breast cancer. *Int J Radiat Oncol Biol Phys* 2002;53:1240-53.
13. Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for breast carcinoma: a review of the evidence. *Cancer* 2003;98:1977-86.
14. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993;22:369-76.
15. Vulto JCM, Louwman MW, Poortmans P, Lybeert ML, Rutten HJ, Coebergh J. A population-based study of radiotherapy in a cohort of patients with rectal cancer diagnosed between 1996 and 2000. Eur J Surg Oncol 2007.
16. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer:

results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* 1996;35:731-44.

17. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis* 1958;8:699-712.
18. Hill DJ, White VM, Giles GG, Collins JP, Kitchen PR. Changes in the investigation and management of primary operable breast cancer in Victoria. *Med J Aust* 1994;161:110-1, 14, 18 passim.
19. Luke C, Chapman P, Priest K, Roder D. Use of radiotherapy in the primary treatment of cancer in South Australia. *Australas Radiol* 2003;47:161-7.
20. NSW radiotherapy management information system report 2000. Sydney: New South Wales Health Department, 2001. *Statewise Services Development Branch* 2001.
21. Manders K, van de Poll-Franse LV, Creemers GJ, Vreugdenhil G, van der Sangen MJ, Nieuwenhuijzen GA, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer* 2006;6:179.
22. Vulto AJ, Lemmens VE, Louwman MW, Janssen-Heijnen ML, Poortmans PH, Lybeert ML, et al. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. *Cancer* 2006;106:2734-42.
23. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *Eur J Cancer* 2005;41:779-85.
24. Voti L, Richardson LC, Reis I, Fleming LE, Mackinnon J, Coebergh JW. The effect of race/ethnicity and insurance in the administration of standard therapy for local breast cancer in Florida. *Breast Cancer Res Treat* 2006;95:89-95.
25. <http://www.minvws.nl/dossiers/>zorgverzekering/onverzekerden/default.asp. 2007.
26. <http://www.oncoline.nl> 2006.
27. Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien JP, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006;24:3381-7.
28. www.ikcnet.nl. 2006.
29. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. *Int J Radiat Oncol Biol Phys* 2003;56:1038-45.
30. Vulto JC, Louwman WJ, Poortmans PM, Coebergh JW. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999. *Eur J Cancer* 2005;41:2722-7.
31. Siesling S, van de Poll-Franse LV, Jobsen JJ, Repelaer van Driel OJ, Voogd AC. [Trends and variation in breast conserving surgery in the southeast and east of the Netherlands over the period 1990-2002]. *Ned Tijdschr Geneeskd* 2005;149:1941-6.
32. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987;55:61-6.
33. Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastases. *Bone* 1991;12 Suppl 1:S9-10.
34. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol* 1991;9:509-24.
35. van der Linden YM, Steenland E, van Houwelingen HC, Post WJ, Oei B, Marijnen CA, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol* 2006;78:245-53.

36. Rades D, Veninga T, Stalpers LJ, Schulte R, Hoskin PJ, Poortmans P, et al. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2006;64:182-8.
37. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004;22:3608-17.
38. van der Sangen MJ, van de Poll-Franse LV, Roumen RM, Rutten HJ, Coebergh JW, Vreugdenhil G, et al. The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. *Eur J Surg Oncol* 2006;32:34-8.
39. van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 1999;35:32-8.
40. Holzel D, Engel J, Schmidt M, Sauer H. [A model for primary and secondary metastasis in breast cancer and the clinical consequences]. *Strahlenther Onkol* 2001;177:10-24.
41. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist* 2003;8:514-20.
42. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat* 2000;59:271-8.

4.2

Primary malignancy after primary female breast cancer in the south of the Netherlands, 1972-2001

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Abstract

A cohort of 9919 breast cancer patients registered in the population-based Eindhoven registry was followed for vital status and development of second cancer. Person-year analysis was applied to determine the risk of second primary breast or urogenital cancer among breast cancer patients and to assess its relationship to age, treatment and time since the first breast cancer diagnosis. Women with previous breast cancer have an elevated risk of overall second breast or urogenital cancer. The largest relative risk was observed for second breast cancer (SIR [Standardised Incidence Ratio]: 3.5; 95%CI: 3.2-3.8) and second ovarian cancer (SIR: 1.7; 95%CI: 1.2-2.3). The absolute excess rate was highest for second breast cancer (64/10,000 patients per year). On the other hand, breast cancer has an inverse relationship to risk of cervical cancer. Changes in behavioural risk factors are important for lowering the risk of second cancer after breast cancer.

Introduction

A history of breast cancer is a risk indicator for second primary cancer among women, especially for second primary breast and genital cancer. Higher risks of second breast cancer,[1, 2] subsequent ovarian cancer[2] and uterine cancer [3, 4] after primary breast cancer [5] have been found. However, the association with cervical cancer and cancer of the vagina-vulva has not been well studied in detailed.[2] Only a few studies have shown an increased risk of second primary kidney and bladder cancer among breast cancer patients.[6, 7]

Examination of the association between breast cancer and second primary cancer may contribute to the development of preventive interventions. Understanding these issues may also help identify the treatment that carries the lowest risk of second cancer for breast cancer patients. In addition, it may also contribute to early detection of second cancer. Common risk factors, such as dietary habits, reproductive characteristics, exogenous oestrogen exposure and genetic factors play an important role in the aetiology of second female cancers, particularly breast, uterine and ovarian cancer.[8] Breast cancer treatments, such as radiotherapy, systemic chemotherapy[6, 9] and hormonal therapy, may be associated with a higher risk of certain second primary cancers among breast cancer patients. In addition, hormonal therapy with tamoxifen has been found to increase the risk of cancer of the uterine, in particular mixed mullerian tumours.[10-12]

The effect of factors such as latency time, cancer treatment and the age at diagnosis, on the risk of second female cancer remains unknown. Our cohort comprises the most recent data, with a long follow-up time and a large number of cases. This enables us to assess the role of important risk factors in the development of second primary cancer. The aim of this population-based cohort study was to determine the incidence of second primary breast and urogenital cancers among breast cancer patients in the south of the Netherlands, compared to the incidence expected in the general population, and to relate this incidence to the initial breast cancer treatment, follow-up time, and age at breast cancer diagnosis.

Patients and methods

Patients

Breast cancer patients were obtained from the Eindhoven Cancer Registry in the south of the Netherlands. This is a population-based cancer registry, which covered almost 2.3 million individuals in 2004. A detailed description of the data collection has been reported elsewhere.[13]

We excluded patients with less than 1 year of follow-up time (n=1458), patients with in situ primary breast cancer (n=458), patients with other malignancies diagnosed before breast cancer as well as patients with a second cancer that appeared to be a metastasis (n=44). For the calculation of risks of second ovarian cancer, patients who

were oophorectomised as treatment for breast cancer were not included in the analyses (n=9). As a result, in the period 1972-2000, 9919 breast cancer patients older than 25 years were available for analysis.

Analyses were stratified according to age at diagnosis of the initial tumour (categories: premenopause [age < 50 years] and postmenopause [age ≥ 50] years); initial treatment combination of breast cancer (categories: Surgery [S], radiotherapy ± S, chemotherapy ± S, hormonal therapy ± S, radiotherapy and chemotherapy ± S, radiotherapy and hormonal therapy ± S; and other treatments [chemotherapy and hormonal therapy ± S, radio- and chemo- and hormonal therapy ± S, no treatment and unknown treatment); and follow-up time after diagnosis (categories: 1-4 years, 5-9 years, 10-14 years and longer than 15 years).

Methods

The risk of developing a second cancer was investigated by means of person-years analysis, corrected for age and calendar-year period to the date of death, date of last follow-up, date of diagnosis of the second cancer or end of the study (December 31, 2001) which ever came first.[14] We compared the incidence of second primary tumours among patients with a diagnosis of breast cancer (the observed incidence) with the incidence for the same tumours in the general population (the expected incidence), which is expressed as the Standardised Incidence Ratio (SIR). Calculation of the expected subsequent primary cancer was derived from the same population, using EUROCIM 4.2. The statistical significance and 95% confidence intervals were determined by means of exact Poisson probability.[15] The Absolute Excess Risk (AER) was calculated by subtracting the expected number from the observed number and then dividing the difference by person-years at risk (per 10,000 breast cancer patients/year).[8] All statistical analyses were performed using SPSS 11.5 for Windows (Statistical Products and Service Solution, Inc, Chicago, USA).

Results

Our cohort yielded 65,938 person-years. General characteristics at the time of primary breast cancer diagnosis are shown in table 1. The average age at breast cancer diagnosis was 58.8 years, the average follow-up time was 6.6 years, and the median follow-up time was 4.9 years. Overall, 725 breast cancer patients developed second breast and urogenital cancer, compared to the expected 266 patients in the population (SIR: 2.7; 95%CI: 2.5-2.9) (table 2.). The relative risk of developing second urogenital cancer after excluding all second breast cancers was higher among breast cancer patients than in the general population (SIR: 1.9; 95%CI: 1.6-2.3).

Table 1 Relative (SIR)[a] and absolute risks (AER)[b] of second cancer among breast cancer patients in the south of the Netherlands

	All Patients				Pre-menopause[c]			Post-menopause[d]		
Num. of patients	9919				2950			6969		
Num. of personyrs	65,938				22,546			43,392		
Site of 2nd cancer	Obs[e]	SIR	95% CI[f]	AER	Obs	SIR	AER	Obs	SIR	AER
All second cancers	1298	2.4[g]	2.3-2.5	115.0	415	4.5[g]	143.0	883	2.0[g]	100.5
Mouth and pharynx	12	1.7	0.9-3.1	0.8	4	2.9	1.2	8	1.4	0.6
Salivary glands	4	4.6[g]	1.2-12.5	0.5	3	18.9[g]	1.3	1	1.4	0.1
Pharynx	3	2.0	0.4-6.4	0.2	0	E 0.4[h]	-0.2	3	2.7	0.4
Digestive tract	196	1.3[g]	1.1-1.5	7.2	27	1.9[g]	5.8	169	1.3[g]	8.0
Oesophagus	7	1.5	0.6-3.3	0.4	1	2.1	0.2	6	1.5	0.4
Stomach	33	1.3	0.9-1.8	1.1	8	4.4[g]	2.7	25	1.1	0.3
Colon	90	1.5[g]	1.1-1.5	4.5	10	1.8	2.0	80	1.5[g]	5.9
Rectum	36	1.3	1.0-2.0	1.1	7	2.0	1.5	29	1.2	0.9
Gall bladder	12	1.1	0.6-2.0	0.2	0	E 0.6[h]	-0.3	12	1.2	-0.4
Pancreas	16	1.1	0.6-1.8	0.2	1	0.7	-0.2	15	1.1	0.5
Respiratory tract	36	1.2	0.9-1.7	1.0	12	2.0	2.6	24	1.0	0.1
Lung	34	1.3	0.9-1.8	1.1	11	2.0	2.5	23	1.1	0.4
Pleura	2	3.5	0.4-14.4	0.2	1	10.9	0.4	1	2.1	0.1
Bone	2	3.2	0.4-13.5	0.2	2	21.6[g]	0.8	0	E 0.5[h]	-0.1
Connective Tissue	6	3.2[g]	1.2-7.3	0.6	2	4.3	0.7	4	2.8	0.6
Melanoma	21	1.8[g]	1.1-2.7	1.4	12	3.2[g]	3.7	9	1.1	0.2
Breast	588	3.5[g]	3.2-3.8	63.9	255	6.3[g]	95.2	333	2.6[g]	47.6
Urogenital tract	137	1.5[g]	1.2-1.7	6.6	40	2.5[g]	10.6	97	1.3	4.5
Cervix uteri	9	0.9	0.4-1.7	-0.2	5	1.8	1.0	4	0.5	-0.8
Corpus uteri	40	1.4	1.0-1.9	1.8	8	1.6	1.4	32	1.4	2.0
Ovarium	43	1.7[g]	1.3-2.4	2.8	21	3.9[g]	6.9	22	1.1	0.6
Vagina Vulva	6	1.3	0.4-2.6	0.1	1	2.6	0.3	5	1.0	0
Kidney	17	1.2	0.7-2.0	0.5	2	1.1	0.1	15	1.2	0.7
Bladder	22	1.9[g]	1.2-2.9	1.6	3	3.5	0.9	19	1.8[g]	1.9
Brain	6	1.2	0.5-3.2	0.2	3	2.6	0.8	3	0.8	-0.2
Thyroid	2	0.8	0.1-3.3	-0.1	2	2.9	0.6	0	E 2.3[h]	-0.5
Non-Hodgkin's lymphoma	12	0.8	0.4-1.4	-0.5	3	1.3	0.3	9	0.7	-1.0
Myeloma	4	0.5	0.1-1.4	-0.6	1	1.4	0.1	3	0.4	-1.0
Leukaemia	15	1.3	0.9-2.6	0.8	1	0.8	-0.1	14	1.7	1.3

[a] SIR: standardised incidence ratio
[b] AER: Absolute excess risk per 10,000 person per year
[c] Obs: Observed numbers of second primary cancers diagnosed in 1972-2001
[d] 95% CI: 95 % confidence interval
[e] Age at primary breast cancer diagnosis less than 50 years old
[f] Age at primary breast cancer diagnosis more than or equal to 50 years old
[g] 95 % Confidence interval excludes 1
[h] E: Expected numbers of second primary cancers in the south of Netherlands

Markedly increased risks of second breast cancer (SIR: 3.5; 95%CI: 3.2-3.8) and ovarian cancer (SIR: 1.7; 95%CI: 1.2-2.3) were also observed among these patients. The absolute excess risk (AER) was highest for second breast cancer (64/10000 person years).

Age

In general, the increased risk of overall second urogenital cancer (SIR: 2.1; 95%CI: 1.9-2.3), second breast cancer (SIR: 2.6; 95%CI: 2.4-2.9) and second ovarian cancer (SIR: 1.1; 95%CI: 0.7-1.7) was more marked among patients who were diagnosed with breast cancer before menopause (table 3). In contrast, no differences in the SIR were observed between patients diagnosed before and after menopause for second uterine, cervix, vagina-vulva, kidney and bladder cancer. A higher incidence rate and absolute excess of second breast and ovarian cancer were observed among women diagnosed before menopause.

Treatment

The risk of second breast cancer was elevated for breast cancer patients receiving any treatment, compared to those undergoing surgical treatment (SIR: 3.4; 95%CI: 2.9-4.0). Treatment was not associated with the elevated risks of cervix, endometrial, vagina-vulva, kidney or bladder cancer compared to patients treated surgically (table 4).

Furthermore, we assessed whether the excess risk of second breast and endometrial cancer among women aged 50 years and older receiving hormonal treatment ± radiotherapy was higher than the excess risk among women undergoing surgical treatment (data are not shown). We observed a significantly lower SIR for second breast cancer among women who received hormonal treatment ± radiotherapy (SIR: 1.6 95%CI: 1.2-2.2) than those who were treated surgically (SIR: 2.8; 95%CI: 2.3-3.4). In contrast, we observed a higher SIR for second endometrial cancer (SIR: 1.7; 95%CI: 0.7-3.4) among patients receiving hormonal treatment ± radiotherapy than among those undergoing surgical therapy (SIR: 0.7 95%CI: 0.2-1.8).

Follow-up time

The SIR for second breast cancer was 4.6 (95%CI: 4.0-5.1) during the first 4 years of follow-up then it decreased steadily to 14 years of follow-up and then increased again after 15 years (SIR: 4.7; 95%CI: 3.5-6.1) (figure 1). The SIR for ovarian cancer increased after 5-9 years of follow-up (SIR: 2.2 95%CI: 1.2-3.7) and again after 15 years of follow-up (SIR: 5.5 95%CI: 2.7-10.4). The SIR for cervical, endometrial, vagina-vulva, kidney, and bladder cancer did not vary according to follow-up time. However, after 5 years of observation, the SIR for cervical cancer remained below 1.

Discussion

Our results suggest that women diagnosed with a primary breast cancer are at increased risk of developing a second breast and ovarian cancer. This is in line with previous studies.[1, 4-6, 16, 17] Elevated risks were particularly marked among pre-menopausal women. In the south of the Netherlands (area of Eindhoven Cancer Registry), every year, 11 of every 1000 breast cancer patients develop second a cancer (I. Soerjomataram, Netherlands Institute of Health Sciences), half of which are second primary breast cancers. Common risk profiles, side-effects of the initial breast cancer treatment and

genetic factors have been proposed to cause the elevated risk of second female cancer in breast cancer patients.

Age at first breast cancer diagnosis is an important determinant of the incidence of second breast and ovarian cancers: the risk for women diagnosed before the age of 50 was significantly higher than that observed for those diagnosed at older ages, as reported in previous studies.[6, 18] This highlights the importance of female hormones in the pathogenesis of second breast and ovarian cancer. Nonetheless, other common risk factors, which initially induced the breast cancer, may also be involved in the aetiology of the second breast cancer, including genetic factors. BRCA1 and BRCA2 mutation would explain 5-10 % of breast and ovarian cancer cases.[19, 20]

Age at breast cancer diagnosis was closely related to the treatment choice. A higher risk of second uterine cancer in post-menopausal breast cancer patients taking on hormonal therapy was found, as has been reported by other authors.[11, 17] Tamoxifen, a hormonal therapy, which has been widely used since the late 80's for post-menopausal women, has been suggested to cause the increase in uterine cancer in breast cancer patients, although controversy exists.[4, 10] In our study we found a decreased risk of second endometrial cancer after 15 years of follow-up, which might suggest a latency period of less than 15 years for tamoxifen to induce second endometrial cancer.

However, the risk of second breast cancer among post-menopausal breast cancer patients who received tamoxifen was lower in comparison to that for women who underwent surgical treatment (SIR: 1.6 vs. 2.8). In addition to the side-effects of tamoxifen in inducing cancer of the uterine, some potential beneficial effects in post-menopausal breast cancer patients are now being examined: for example, the anti-oestrogenic role of tamoxifen in mammary cells was found to protect against second breast cancer.[9, 21]

We found an elevated risk of second breast cancer during the total follow-up period. It has been reported that after radiation there is a latency period of at least 10 years.[22] During the last decades, both radiotherapy and chemotherapy for breast cancer treatment have improved. This includes lower radiation dose, better protection of the normal tissue and more effective polychemotherapy regimens. These changes have diminished some side-effects of radiotherapy in breast cancer patients.[22] Our result supported this fact by showing no difference in second breast cancer risk between women who underwent surgical or radiotherapy.

We observed declining risks of cervical cancer during the follow-up period, which reached 0 in the last follow-up period. This may be related to the human papilloma virus's (HPV) latency period of ± 17 years (the time needed from infection to formation of invasive cancer),[23] suggesting sexual behaviour changes among breast cancer women. Some authors have also noticed the lowered risk of cervical cancer among breast cancer patients.[2, 5, 18, 24] In contrast to cervical cancer, breast cancer is observed more often among women with a higher socio-economic position and among women who had their

first child at an older age.[25, 26] This may also relate to the lower risk of cervical cancer in breast cancer patients.

During 28 years of follow-up only 6 patients developed carcinoma of the vagina and vulva. These cancers are rare and represent only 7-8 % of gynaecological cancers.[25] Consequently, we could not draw any conclusion on the association between breast cancer and cancer of the vagina and vulva. However, vagina and vulva cancer have been related to HPV infection. The risk of second vagina and vulva cancer became 0 after a follow-up of more than 15 years, as found for second cervical cancer in our study. This suggests a possible inverse relationship between breast cancer and second vagina-vulva cancer. Breast cancer patients may change their lifestyle towards a healthier one that protects against vagina and vulva cancer.

We could not find an excess risk for second primary kidney or bladder cancer after breast cancer. A few studies found a slightly increased risk of second kidney and bladder cancer among breast cancer patients.[6, 7] Elevated kidney and bladder cancer risk was found for women receiving high radiation exposure in the pelvic area such as radiotherapy for cervical cancer.[27] The bladder is one of the organs that receives a considerable amount of scattered radiation during radiotherapy for breast cancer treatment.[28] However, this seems to be insufficient to induce bladder or kidney cancer.

We could not collect information for some of the main risk factors such as reproductive characteristics or lifestyles of the patients and did not adjust for potential confounders or effect modifiers. Also, there may be some bias caused by metastases of the primary breast cancer. We expect this bias to be minimal because trained personnel from the cancer registry checked each patient's medical record.

In conclusion, our results show that breast cancer patients are at increased risk of developing second breast and ovarian cancer. Initial breast cancer treatment plays a limited role in causing second breast cancer, this suggesting a bigger role for common risk factors that induce both primary and second primary breast cancer. This stresses the importance of behaviour modification among breast cancer patients, in addition monitoring in order to prevent increased morbidity and mortality caused by second breast cancer. As for second ovarian cancer, women diagnosed with breast cancer before menopause may benefit from a longer follow-up directed to the early detection of second ovarian cancer. As our understanding of the relationship between risk factors and the occurrence of a second cancer develops, more questions will arise. Thus, extensive studies on multiple cancers will continue to play an important role in the medical sciences. Such studies may serve as a foundation for understanding the environmental and genetic determinants of cancer.

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References

1. Murakami R, Hiyama T, Hanai A, Fujimoto I. Second primary cancers following female breast cancer in Osaka, Japan--a population-based cohort study. Jpn J Clin Oncol 1987, 17, 293-302.
2. Brenner H, Siegle S, Stegmaier C, Ziegler H. Second primary neoplasms following breast cancer in Saarland, Germany, 1968-1987. Eur J Cancer 1993, 29A, 1410-1414.
3. Levi F, Te V-C, Randimbison L, La Vecchia C. Cancer risk in women with previous breast cancer. Ann Oncol 2003, 14, 71-73.
4. Adami HO, Bergstrom R, Weiderpass E et al. Risk for endometrial cancer following breast cancer: a prospective study in Sweden. Cancer Causes Control 1997, 8, 821-827.
5. Levi F, Randimbison TV, La Vecchia C. Second primary cancers in breast cancer patients in Vaud, Switzerland. Cancer Causes Control 1997, 8, 764-770.
6. Rubino C, de Vathaire F, Diallo I, Shamsaldin A, Le MG. Increased risk of second cancers following breast cancer: role of the initial treatment. Breast Cancer Res Treat 2000, 61, 183-195.
7. Teppo L, Pukkala E, Saxen E. Multiple cancer--an epidemiologic exercise in Finland. J Natl Cancer Inst 1985, 75, 207-217.
8. van Leeuwen FE. Second Cancers. In de Vita VT, Hellman S, Rosenberg AS, eds. Cancer: principles & practice of oncology. Philadelphia, Lippcott-Raven Publishers, 1997, 2773-2793.
9. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001, 344, 1997-2008.
10. Bergman L, Beelen ML, Gallee MP et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 2000, 356, 881-887.
11. Cook LS, Weiss NS, Potts MS. Second cancers after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 1997, 89, 657-659.
12. Sasco AJ, Raffi F, Satge D et al. Endometrial mullerian carcinosarcoma after cessation of tamoxifen therapy for breast cancer. Int J Gynaecol Obstet 1995, 48, 307-310.
13. Coebergh, JWW, Janssen-Heijnen, MLG, Louwman, WJ, and Voogds, AC. Cancer incidence, care and survival in the South of Netherlands, 1955-1999: a report of the Eindhoven Cancer Registry with cross-border implications. Eindhoven, the Netherlands, Comprehensive Cancer Centre South (IKZ), 2001.
14. van Leeuwen FE, Klokman WJ, Hagenbeek A et al. Second cancer risk following Hodgkin's disease: a 20-year follow up study. J Clin Oncol 1994, 12, 312-325.
15. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ 1987, 1-406.
16. Ewertz M, Storm HH. Multiple primary cancers of the breast, endometrium and ovary. Eur J Cancer Clin Oncol 1989, 25, 1927-1932.
17. Volk N, Pompe-Kirn V. Second primary cancers in breast cancer patients in Slovenia. Cancer Causes Control 1997, 8, 764-770.
18. Adami HO, Bergkvist L, Krusemo U, Persson I. Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. J Natl Cancer Inst 1984, 73, 1049-1055.
19. Arver B, Du Q, Chen J, Luo L, Lindblom A. Hereditary breast cancer: a review. Semin Cancer Biol 2000, 10, 271-288.
20. Hemminki K, Vaittinen P, Easton D. Familial cancer risks to offspring from mothers with 2 primary breast cancers: leads to cancer syndromes. Int J Cancer 2000, 88, 87-91.

21. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998, 351, 1451-1467.
22. Boice JD, Jr., Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992, 326, 781-785.
23. Schiffman M, Krüger Kjaer S. Chapter 2: Natural History of Anogenital Human Papillomavirus Infection and Neoplasia. J Natl Cancer Inst Monogr 2003, 31, 14-19.
24. Ewertz M, Mouridsen HT. Second cancer following cancer of the female breast in Denmark, 1943-80. Natl Cancer Inst Monogr 1985, 68, 325-329.
25. Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina and vulva. In de Vita VT, Hellman S, Rosenberg AS, eds. Cancer: principles & practice of oncology. Philadephia, Lippincott-Raven Publishers, 1997, 1433-1478.
26. Harris J, Morrow M, Norton L. Malignant tumors of the breast. In deVita VT, Hellman S, Rosenberg AS, eds. Cancer: principles & practice of oncology. Philadelphia, Lippicott-Raven Publishers, 1997, 1557-1616.
27. Hall EJ. Etiology of cancer: physical factors. In DeVita VT, Hellman S, Rosenberg AS, eds. Cancer: principles & practice of oncology. Philadelphia, Lippincott-Raven Publishers, 1997, 203-218.
28. Mattsson A, Hall P, Ruden BI, Rutqvist LE. Incidence of primary malignancies other than breast cancer among women treated with radiation therapy for benign breast disease. Radiat Res 1997, 148, 152-160.

4.3

Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal

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Abstract

The number of long-term survivors with breast cancer is increasing for demographic and epidemiologic reasons. Several studies have shown that life expectancy of breast cancer patients has become similar to the general female population 20 years after diagnosis, but little is known about the pattern of causes of death in these patients. In this population-based study causes of death have been traced for 418 deceased breast cancer patients diagnosed in 1960-1979 who survived at least 10 years after diagnosis. The pattern of causes of death in these patients has been compared with the general female population by calculation of standardised mortality ratios (SMRs). Of all 418 patients surviving at least 10 years, 196 (47%) died from breast cancer and 50 (12%) died from another cancer. The SMR for breast cancer was 15.8 (95%CI: 13.1-18.8) 10-14 years after diagnosis; it was still 4.7 (95%CI: 2.6-7.8) after 20 years. Overall mortality was higher than expected 10-14 years after diagnosis (SMR: 1.3; 95%CI: 1.1-1.5), but lower after more than 20 years (SMR: 0.6; 95%CI: 0.4-0.7). Despite a normal (or even improved) life expectancy for breast cancer patients 20 years after diagnosis the risk of dying from this disease remains elevated.

Introduction

Prognosis for breast cancer patients has improved over the last decades; relative 10-year survival rates increased from 47% for patients diagnosed in 1970-1974 to 61% for patients diagnosed in 1980-1984.[1] In studies carried out in the UK, Sweden, New Zealand, and The Netherlands it was found that about 20 years after diagnosis, the life expectancy of patients with breast cancer resembles that of the average population,[2-6] suggesting that patients can then be considered cured. However, breast cancer recurrences or metastases may develop decades after initial diagnosis and treatment[4, 5] and a higher death rate due to breast cancer has been reported up to 40 years after diagnosis.[6]

Since the age-adjusted incidence rate in Southeast Netherlands, as in many other western countries, has doubled since 1960[7] and prognosis has improved, the number of long-term survivors of breast cancer has increased markedly. However, it remains unclear whether these patients should still be considered at increased risk of being affected by breast cancer, even though this is important for follow-up surveillance and learning the natural history of breast cancer.

In the present population-based study we traced causes of death of deceased breast cancer patients who survived at least 10 years after diagnosis. Causes of death were compared with the general population by calculating standardised mortality ratios (SMRs). Furthermore, we investigated whether initial tumour characteristics were related to late death from breast cancer.

Methods

Data on diagnosis, stage of disease, and treatment were obtained from the population-based Eindhoven Cancer Registry, which has collected data on new cancer patients since 1955 according to international guidelines.[8] The registry covers an area of 2,500 km^2 in Southeast Netherlands with a population of almost one million inhabitants. The data on first and second primary breast tumours were obtained, after notification by pathologists, from pathology reports, hospital records, and the regional Radiotherapy Institute. Access to specialised care was good during the whole period.

Medical registration of causes of death in the Netherlands is similar to that in other countries, according to WHO-guidelines. The attending physician must report the underlying cause of death. Statistics Netherlands assigns a code for the underlying cause of death according to the International Classification of Diseases, ninth revision (ICD-9).[9] If any other medically relevant information is mentioned on the death certificate, the secondary cause of death is also recorded. The anonymous cause-of-death register, maintained by Statistics Netherlands, is listed per municipality according to sex and age (derived from date of birth and date of death).

Patients were tracked by the Central Bureau of Genealogy in order to obtain the unique death certificate number. Statistics Netherlands was provided with a list,

according to municipality of death, the date of birth, date of death and death certificate number (when available). The data were obtained at an aggregate level fit for data analysis.

All 1460 patients diagnosed with breast cancer in 1960 through 1979 who survived at least 10 years after initial diagnosis were selected for the present study. Follow-up was completed until 1-1-1994, when 487 long-term survivors had deceased. The cause of death of those patients who survived at least 10 years but died in 1970-1979 (n=47) was not traced, because of the high costs per year and the low yield. For 22 patients the cause of death could not be traced. Thus, observed causes of death are presented only for 418 patients.

In the analysis intervals of follow-up (10-14, 15-19 and 20 years or more) were distinguished.

Table 1 Characteristics of 418 deceased breast cancer patients diagnosed in 1960-1979 who survived at least 10 years

	period of diagnosis		
	1960-1969 n (%)	1970-1979 n (%)	Total n (%)
Age at diagnosis (yrs)			
< 40	6 (7.8)	16 (4.7)	22 (5.3)
40-49	21 (27)	58 (17)	79 (19)
50-59	21 (27)	83 (24)	104 (25)
60-69	21 (27)	117 (34)	138 (33)
≥ 70	8 (10)	67 (20)	75 (18)
Tumor stage			
local	42 (55)	168 (49)	210 (50)
regional	34 (44)	121 (36)	155 (37)
distant	0 (0)	4 (1.2)	4 (1.0)
unknown	1 (1.3)	48 (14)	49 (12)
Histological type			
ductal	49 (64)	300 (88)	349 (84)
lobular	2 (2.6)	12 (3.5)	14 (3.3)
mucinous	1 (1.3)	9 (2.6)	10 (2.4)
medullar	2 (2.6)	6 (1.8)	8 (1.9)
sarcoma	1 (1.3)	0 (0)	1 (0.2)
not otherwise specified	22 (29)	14 (4.1)	36 (8.6)
Radiotherapy			
no	17 (22)	144 (42)	161 (39)
yes	60 (78)	197 (58)	257 (62)
Total (% of study population)	77 (13)	341 (87)	418 (100)

Causes of death have been grouped together according to major disease categories. SMRs were calculated for comparison of causes of death in the study population with the general female population. In this person-years type of analysis, the ratio of the observed (O) and expected (E) numbers of deaths was determined. Time at risk began at the date of diagnosis and ended at the date of death or the end of the

follow-up period (1-1-1994), whichever occurred first. Taking into account the person-years of observation in the cohort (by age and calendar period), E numbers of death were computed with the use of age-, and calendar-period-specific cancer death rates from the area of the Eindhoven Cancer Registry. The confidence limits of SMR were obtained with the use of the Poisson distribution of O numbers.[10] SMRs were calculated for all patients together and separately by follow-up interval.

Results

Clinical characteristics are presented in Table 1 according to period of diagnosis. Adjuvant primary radiotherapy was administered to 53% of patients with localised tumours and 84% of those with regional or distant disease. Only 11 patients received adjuvant systemic therapy, 9 of who had regional or distant disease at the time of diagnosis, one had a T4 tumour and in one patient tumour stage was unknown.

Of all 418 patients surviving for at least ten years after diagnosis 196 (47%) died from breast cancer and 50 (12%) from another cancer (Table 2). In another 13 cases breast cancer was recorded as secondary cause of death.

Table 2 Causes of death in breast cancer patients surviving for more than 10 years after diagnosis in 1960-1979 for different intervals of follow-up

Cause of death	10-14 yrs n (%)	15-19 yrs n (%)	≥ 20 yrs n (%)	Total n (%)
Breast cancer	126 (54)	56 (42)	14 (27)	196 (47)
Other cancer	23 (9.7)	17 (13)	10 (20)	50 (12)
Cardiovascular disease	53 (22)	36 (27)	17 (33)	106 (25)
Respiratory disease	7 (3.0)	3 (2.2)	4 (7.8)	14 (3.3)
Disease of the digestive system	4 (1.7)	3 (2.2)	3 (1.3)	10 (2.4)
External causes*	6 (2.5)	4 (3.1)	-	10 (2.4)
Other causes	16 (6.8)	13 (10)	3 (1.3)	32 (7.6)
Total (% of study population)	235 (56)	132 (31)	51 (12)	418 (100)

* Includes accidents, murder, suicide

Among those who survived 10-14 years after initial diagnosis the observed number of total deaths was higher than expected (SMR: 1.3; 95% CI: 1.1-1.5) (Table 3). The risk of dying from breast cancer was almost 16 times higher than expected (13.1-18.8). In the patients who survived 15-19 years the SMR for all causes of death was 1.0, with an excess risk of dying from breast cancer (SMR: 11.0; 95% CI: 8.3-14.3). For those patients surviving more than 20 years the observed number of total deaths was lower than expected (SMR: 0.6; 95% CI: 0.4-0.7), but the risk of dying from breast cancer was still almost 5 times higher than expected (95% CI: 2.6-7.8).

The distribution of patients dying from cancer other than breast cancer is revealed in Table 4. High, but not statistically significant SMRs were observed for small bowel and brain tumours and low SMRs for cancer of the stomach, larynx and lung. Another cancer was the secondary cause of death for another 9 patients, of whom 4 had female genital cancer.

Table 3 Number of observed (O) and expected (E) causes of death, standardised mortality ratios (SMRs) and 95% CI in breast cancer patients for different intervals of follow-up

	10-14 years				15-19 years				≥ 20 years			
Cause of death	O	E	SMR	(95% CI)	O	E	SMR	(95% CI)	O	E	SMR	(95% CI)
Breast cancer	126	8.0	15.8	(13.1-18.8)	56	5.1	11	(8.3-14.3)	14	3	4.7	(2.6-7.8)
Other cancer	23	32.2	0.7	(0.5-.1.1)	17	21.6	0.8	(0.5-1.3)	10	13.4	0.7	(0.4-1.4)
Cardiovascular disease	53	89.2	0.6	(0.4-0.8)	36	64.6	0.6	(0.4-0.8)	17	44.2	0.4	(0.2-0.6)
Respiratory disease	7	11.7	0.6	(0.2-1.2)	3	9.7	0.3	(0.1-0.9)	4	7.3	0.5	(0.1-1.4)
Other causes	26	39.5	0.7	(0.4-1.0)	20	32.2	0.6	(0.4-1.0)	6	24	0.3	(0.1-0.5)
Total	235	180.7	1.3	(1.1-1.5)	132	133.1	1	(0.8-1.2)	51	91.9	0.6	(0.4-0.7)

Table 4 Number observed (O) and expected (E), standardised mortality ratios (SMR), and 95% CI for breast cancer patients who survived ≥ 10 years and died from cancer other than breast cancer

Tumor site (ICD-codes)	O	E	SMR	(95%CI)
Head, Neck, Oesophagus (140-150)	1	1.6	0.6	(0.0-3.5)
Stomach (151)	3	7.3	0.4	(0.1-1.2)
Small bowel (152)	2	0.3	6.1	(0.8-24)
Colon, Rectum (153, 154)	10	14.2	0.7	(0.3-1.3)
Liver, Biliary tract, Pancreas (155-157)	5	8.2	0.6	(0.2-1.4)
Larynx, Lung (161, 162)	2	5.2	0.4	(0.0-1.4)
Cervix uteri (180)	1	1.2	0.8	(0.0-4.6)
Corpus uteri (182)	1	1.6	0.6	(0.0-3.5)
Ovary (183)	6	4.6	1.3	(0.5-2.8)
Urinary tract (188, 189)	4	4.2	0.9	(0.3-2.4)
Brain (191)	2	0.7	2.7	(0.3-10)
Haemopoietic (200-208)	6	6.7	0.9	(0.3-2.0)
Other malignancies	8	11.4	0.7	(0.3-1.4)
Total	50	67.3	0.7	(0.6-1.0)

Patients who died from breast cancer after 10 years were generally younger at diagnosis and at death than those who died from other causes (Table 5). Among patients with localised disease the proportion who died from breast cancer equalised to the proportion dying from other causes, until 20 years after diagnosis. Patients diagnosed with regional disease were more likely to die from breast cancer 10-14 years after diagnosis, whereas the proportion dying from other causes became higher thereafter.

A second primary breast tumour was present in 131 of the 1460 patients (9%). For 76 women with a second breast tumour the cause of death was unknown because the patients were still alive at 1-1-94 (n=67), died between 1970 and 1979 (n=5), or the cause of death could not be traced (n=4). For 55 patients with a second breast tumour the cause of death was known: 39 (71%) died from breast cancer and 16 died from other causes.

Discussion

Breast cancer patients who have survived 20 years or more after diagnosis and are presumed to have a normal life expectancy were still at a 5-fold increased risk of dying from breast cancer. Mortality from other causes was lower, except for other cancers and respiratory disease.

Registration of cause of death in the Netherlands is similar to that in other countries, according to WHO guidelines. Could overreporting of breast cancer as underlying cause of death explain the excess death risk? We think that this tendency, if present, rather declines with the duration of follow-up. Breast cancer would only be reported if there was clear progression in the disease or a second breast cancer had occurred. We found that in 39 (71%) of the 55 of the patients who had developed a second primary breast tumour the cause of death was attributed to breast cancer.

Fentiman et al.[3] found that 10% of patients surviving more than 20 years since diagnosis of the first tumour died from metastases from contralateral cancer and late deaths from breast cancer were due to new tumours rather than a late manifestation of slow growing metastases. Of the 51 such patients in our study 11 (22%) developed a second breast tumour, 7 of whom died from the disease. A total of 14 long-term survivors died from breast cancer (Table 2). So if the 7 deaths in those with a second primary tumour were caused by this second tumour, the other 7 deaths due to breast cancer (50%) resulted from progression of the initial disease.

Table 5 Age and stage of breast cancer patients who survived at least 10 years after diagnosis at different intervals of follow-up. Patients who died from breast cancer are compared with patients who died from other causes

	10-14 yrs		15-19 yrs		≥ 20 years	
	breast cancer	other cause	breast cancer	other cause	breast cancer	other cause
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mean age (yrs) at diagnosis (SD)	56 (12)	65 (10)	54 (11)	62 (10)	50 (11)	56 (10)
Mean age (yrs) at death (SD)	69 (12)	77 (10)	71 (11)	79 (10)	72 (11)	80 (9)
Age at diagnosis (yrs)						
< 50	43 (81)	10 (19)	21 (65)	11 (35)	6 (38)	10 (63)
50-69	68 (51)	65 (49)	31 (41)	45 (59)	8 (24)	25 (76)
≥ 07	15 (31)	34 (69)	4 (16)	20 (84)	0	2 (100)
Tumor stage						
local	58 (48)	63 (52)	31 (52)	29 (48)	9 (31)	20 (69)
regional	54 (64)	30 (36)	20 (37)	34 (63)	4 (24)	13 (76)
distant	2 (67)	1 (33)	0	1 (100)	0	0
unknown	13 (46)	15 (54)	5 (25)	12 (75)	1 (20)	4 (80)
Total	126 (54)	109 (46)	56 (42)	76 (58)	14 (27)	37 (73)

Irrespective of whether late death from breast cancer was due to metastasis from the initial tumour or from a second primary, the question remains whether excess death from breast cancer can be prevented by longer regular surveillance or better treatment. Routine follow-up by physical examination and an annual or biannual mammography would be sufficient to detect recurrences or a second primary tumour [11]. More importantly, overall mortality in patients who survived over 20 years after initial diagnosis became lower than in the general population. Even if those deceased patients of whom the cause of death was not traced (n=69) were added to the observed number of deaths the SMRs for overall mortality remained roughly the same (SMR: 1.5, 1.1, and 0.7 for those surviving 10-14 years, 15-19, and ≥ 20 years, respectively).

Patients diagnosed before the age of 50 were more likely to die from breast cancer than from other causes. Proportional mortality from breast cancer is clearly related to the age at death.[12] At younger ages women are less likely to die from other causes, therefore the proportion dying from breast cancer is relatively high. We accounted for this by calculating standardised mortality rates, but breast cancer mortality remained higher than expected. We also checked whether misclassification of cause of

death in the oldest elderly may have affected the high death rates from breast cancer. However, we found that the percent of patients who died from breast cancer was actually lower in the 85+ group than in the total study-population.

The pattern of death due to cancer other than breast cancer was not very surprising. The increased observed/expected ratio for small bowel cancer could also be a random finding. Increased risks after breast cancer, regularly reported for cancer of the colon-rectum, ovary, and uterus[13-17] are partly explained by a common aetiology or pathogenesis (e.g., hormonal exposure or susceptibility). The decreased risk for tobacco-related cancers in the lung and head and neck area could also be related to the high socio-economic status of breast cancer patients,[18] greater health awareness could also play a role.

Previously, excess mortality from breast cancer despite a normal life-expectancy was also observed in British diagnosed between 1947 and 1950 who survived more than 20 years.[2, 19] The present study indicates that these findings are still valid for patients diagnosed in later decades (1960-1979). Despite a normal (or even improved) life expectancy for breast cancer patients 20 years after diagnosis, the risk of dying from this disease remained elevated.

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References

1. Nab HW, Hop WC, Crommelin MA, Kluck HM, Coebergh JW. Improved prognosis of breast cancer since 1970 in south-eastern Netherlands. Br J Cancer 1994;70:285-8.
2. Brinkley D, Haybrittle JL. The curability of breast cancer. Lancet 1975;2:95-7.
3. Fentiman IS, Cuzick J, Millis RR, Hayward JL. Which patients are cured of breast cancer? Br Med J (Clin Res Ed) 1984;289:1108-11.
4. Hibberd AD, Horwood LJ, Wells JE. Long term prognosis of women with breast cancer in New Zealand: study of survival to 30 years. Br Med J (Clin Res Ed) 1983;286:1777-9.
5. Nab HW, Hop WC, Crommelin MA, Kluck HM, van der Heijden LH, Coebergh JW. Changes in long term prognosis for breast cancer in a Dutch cancer registry. Bmj 1994;309:83-6.
6. Rutqvist LE, Wallgren A. Long-term survival of 458 young breast cancer patients. Cancer 1985;55:658-65.
7. Nab HW, Voogd AC, Crommelin MA, Kluck HM, vd Heijden LH, Coebergh JW. Breast cancer in the southeastern Netherlands, 1960-1989: trends in incidence and mortality. Eur J Cancer 1993;29A:1557-9.

8. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents., vol. VII Lyon: IARC Scientific Publications, 1997.
9. WHO WHO. International Classification of Diseases, injuries an causes of death, 9th revision. ed. Geneva, Switserland: World Health Organization, 1977.
10. Pearson E, Hartley H. Biometrika tables for statiticians, 3 ed. London, UK: Biometrika Trust, 1976.
11. Rutgers EJ, van Slooten EA, Kluck HM. Follow-up after treatment of primary breast cancer. Br J Surg 1989;76:187-90.
12. Phillips KA, Glendon G, Knight JA. Putting the risk of breast cancer in perspective. N Engl J Med 1999;340:141-4.
13. Harvey EB, Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935-82. Natl Cancer Inst Monogr 1985;68:99-112.
14. Teppo L, Pukkala E, Saxen E. Multiple cancer--an epidemiologic exercise in Finland. J Natl Cancer Inst 1985;75:207-17.
15. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. J Natl Cancer Inst 1995;87:645-51.
16. Schenker JG, Levinsky R, Ohel G. Multiple primary malignant neoplasms in breast cancer patients in Israel. Cancer 1984;54:145-50.
17. Ewertz M, Mouridsen HT. Second cancer following cancer of the female breast in Denmark, 1943-80. Natl Cancer Inst Monogr 1985;68:325-9.
18. Schrijvers CT, Coebergh JW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer 1997;80:1482-8.
19. Brinkley D, Haybittle JL. Long-term survival of women with breast cancer. Lancet 1984;1:1118.

CHAPTER 5

OVERVIEW AND DISCUSSION

5.1

An overview of prognostic factors for long-term survivors of breast cancer

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Abstract

Background: Numerous studies have examined prognostic factors for survival of breast cancer patients, but relatively few have dealt specifically with 10+-year survivors.

Methods: A review of the PubMed database from 1995 to 2006 was undertaken with the following inclusion criteria: median/mean follow-up time at least 10 years; overall survival and/or disease-specific survival known; and relative risk and statistical probability values reported. In addition, we used data from the long-standing Eindhoven cancer registry to illustrate survival probability as indicated by various prognostic factors.

Results: 10-year breast cancer survivors showed 90% 5-year relative survival. Tumor size, nodal status and grade remained the most important prognostic factors for long-term survival, although their role decreased over time. Most studies agreed on the long-term prognostic values of MI (mitotic index), LVI (lymphovascular invasion), Her2-positivity, gene profiling and comorbidity for either all or a subgroup of breast cancer patients (node-positive or negative). The roles of age, socioeconomic status, histological type, BRCA and p53 mutation were mixed, often decreasing after correction for stronger prognosticators, thus limiting their clinical value. Local and regional recurrence, metastases and second cancer may substantially impair long-term survival. Healthy lifestyle was consistently related to lower overall mortality.

Conclusions: Effects of traditional prognostic factors persist in the long term and more recent factors need further follow-up. The prognosis for breast cancer patients who have survived at least 10 years is favorable and increases over time. Improved long-term survival can be achieved by earlier detection, more effective modern therapy and healthier lifestyle.

Introduction

Breast cancer (BC) is the most common cancer among women, with a lifetime risk of up to 12% and a risk of death of up to 5%.[1] Its incidence has been increasing but after a period of continuous rise in many industrialized countries BC mortality has been stable or has even decreased in the last 10-15 years.[2, 3] The introduction of mass mammographic screening programmes also resulted in earlier detection and diagnosis of small and less aggressive tumours. This, in combination with therapeutic improvements, has led to a substantial increase in breast cancer survivors over the last few decades (figure 1). A long-term survivor is commonly defined as a person who is still alive 5 years after cancer diagnosis.[4] For breast cancer, the relative survival at five and ten years after diagnosis is 88% and 77%, respectively, both substantially higher than the 5-year relative survival of all cancers together (64%).[4] Thus, it seems logical to consider factors known to play an important role in predicting 5-year survival of BC patients and to question their importance in survival 10 years after diagnosis and even longer. Furthermore, in recent years major advances in the prognostic value of several molecular markers have been achieved, hence the need to incorporate this data into our current knowledge. Therefore, we have summarized available knowledge on the determinants of survival 10 years or more after breast cancer diagnosis. We supported our analyses and considerations with data from the population-based, long-standing Eindhoven cancer registry in the Netherlands.

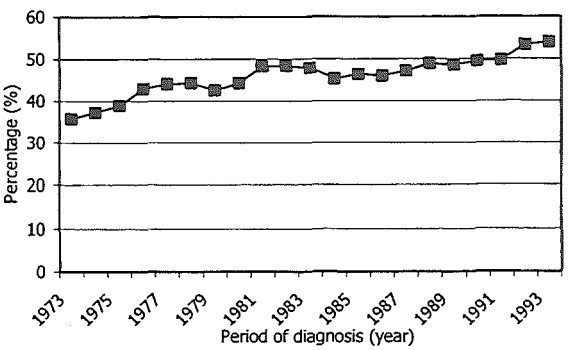

Figure 1 Proportion of breast cancer patients (3-year moving average) diagnosed between 1973-2003 who survived 10 years or longer in Southeastern Netherlands

Methods

We initially searched PubMed, using the search MESH term for 'breast neoplasms' AND 'prognoses' AND 'long-term'. Only papers published in English between 1995 and 2006 (September) which researched female adults (19+ years) were included. We retrieved 528 articles and studied the abstracts (sometimes also the methods section). We selected only articles that assess or show the results for those surviving 10 years or longer with cohorts having a mean/median follow-up of 10 years or longer. If mean/median follow-up time was not reported, we examined the proportion of patients

who survived 10 years after diagnosis, and this ought to be larger than 50%. If, for a specific topic of interest, no relevant studies with a follow-up of at least 10 years were found (such as BRCA mutation or gene profiling, which have been studied only during the last decade), then studies with the longest available follow-up were chosen. Furthermore, the following inclusion criteria were used: overall and/or breast cancer-specific survival was reported; relative risk or hazard rate and statistical probability values were given; at least 250 BC patients included at the beginning of study. We also searched the reference lists collected by this search strategy and selected those that were relevant to both our study question and inclusion criteria. Reviews and books that gave general overviews were also included in the reference list.

We present data from the Eindhoven Cancer Registry (ECR) to illustrate the role of factors such as age, stage, tumour size, lymph node involvement, grade and time since diagnosis. Within the Netherlands, ECR is unique because it has collected follow-up data since 1970, including clinical aspects of cancer patients. This is a population-based cancer registry covering a population of almost 2.4 million people in 2004.[5] Cumulative survival proportion was calculated using the Kaplan Meier method. Relative survival was calculated by comparing the survival of breast cancer patients to the general population.

Throughout the text the term long-term and/or survival will frequently be mentioned; this corresponds to at least 10-year survival unless otherwise indicated.

Results and discussions

Patient characteristics

Age at diagnosis

Very young women, i.e. younger than 30/35 years,[6, 7] exhibited a particularly poor survival as do those older than 70 (figure 2).[8, 9] Young BC patients were more likely to have a more negative clinical presentation, such as affected lymph nodes, negative for oestrogen receptors, and have large tumour with a high fraction of p53 nuclei and overexpression of c-erb-2 oncoprotein.[6, 10, 11] However, current adjuvant treatment seems to diminish the poor prognostic value of young age;[6] young women who did not receive adjuvant treatment had a significantly increased risk of dying; those diagnosed at 35-39 years and <35 years had a 1.4 and 2.2 higher risk of death, respectively, compared to those of 45-49 years.[6] Older patients exhibited higher mortality rates,[12] probably because of less extensive treatment (either related to advanced age itself or the presence of serious concomitant diseases (comorbidity)).[13]

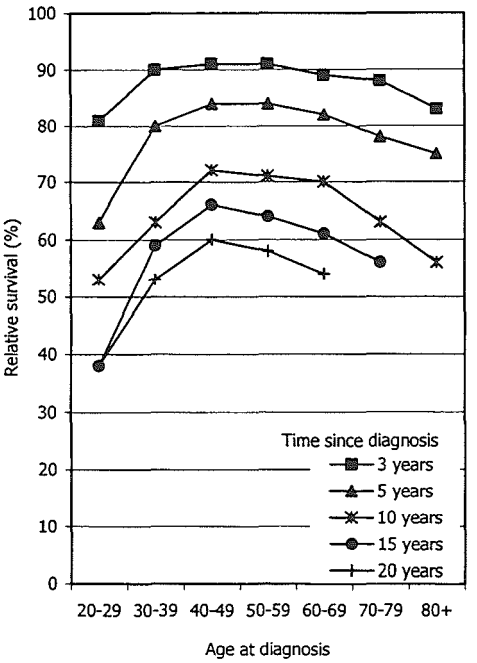

Figure 2 Relative survival of breast cancer patients (n: 13,279) diagnosed in 1990-2002 and followed until 2004, according to age at diagnosis and time since diagnosis in southeastern Netherlands.

Comorbidity

Concurrent health conditions (comorbidity) at the time of BC diagnosis have a significant impact on early[13] as well as long-term survival of BC patients.[12] The most prevalent conditions were cardiovascular disease (7%), previous cancer (7%) and diabetes mellitus (6%), all becoming more common with increasing age.[13] Compared to those without comorbidity whose 5-year relative survival was 87%, those with diabetes mellitus or cardiovascular disease represented 78% and 83% of the respective survival estimates.[13] Patients with severe comorbidity exhibited a 2.7-3.4 higher risk of death in 10 years compared to those without comorbidity.[12, 14]

Period of diagnosis

Access to care and treatment of BC has improved over time in most industrialized countries, which is reflected in the higher long-term survival of BC cases across all age groups and the tumour characteristics of those diagnosed more recently.[15-18] In Finland, relative survival 10 years after diagnosis among patients younger than 50 years increased from 49% for those diagnosed in 1953-1959 to 68% for the 1983-1989 cohort.[15] Furthermore, 60% of node-positive BC patients diagnosed in 1978–1979 in Italy survived 10 years or longer compared to the 50% probability 10-year survival for those diagnosed

in 1968–1969.[17] In addition, changes in BC diagnosis, e.g. screening[19, 20] and better staging[17], may partly be responsible for the observed increase in the proportion of survivors.

Time after diagnosis

The longer a woman survives BC the more the prognosis improves, illustrated by conditional survival.[16, 21] Probably the subgroup of patients who survived longer had less aggressive tumours due to a different genetic make-up or better life-style. In Australia, 79% of women with localized BC survived 10 years after diagnosis, yet among those still alive 5 years after diagnosis 84% had a 10-year survival.[16] The respective values for regional vs. advanced BC were 53% and 68%.[16] Unlike other cancers, relative conditional survival remained stable below 100% after 12 years of survival and decreased again after about 19 years (figure 3).[5] This may be a consequence of late recurrences and metastases, second cancers or late side-effects of treatment.[22]

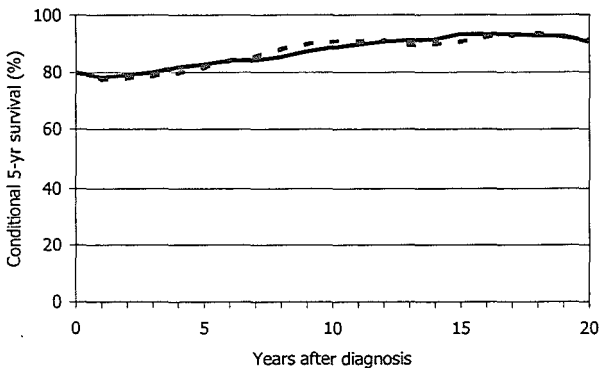

Figure 3 Conditional 5-year relative survival (calculated using period analysis[118]) of breast cancer patients diagnosed in southern Netherlands in 1985-2002 and followed until 2004, according to age. Dashed line: diagnosed at 25-49 years, solid line: diagnosed at 50-74 years

Socioeconomic status (SES) and race

A population-based study of breast cancer patients diagnosed in 1968-1999 in France showed a diminishing role of SES on excess mortality among women with BC over these periods.[23] Long-term follow-up studies reported that women with BC from low social classes had a 20-50% poorer survival compared to patients from higher social classes,[24, 25] although others contradicted this.[26] Low SES patients were more likely to be diagnosed at a later stage, had more aggressive tumour characteristics and might have received sub-optimal treatment. However, differences in these prognostic factors did not fully explain the variation in survival according to social class.[24] This is also the case when breast cancer survival is studied according to race/ethnicity. Ten years after treatment 58% of African Americans were still alive compared to 66% of the white Americans. After adjusting for other prognostic factors, 41% excess mortality from all causes was still

observed among African Americans compared to caucasians.[27] This suggests other residual factors such as lifestyle (higher body weight was observed among African Americans), comorbidity,[14] genetics or variation in the delivery of treatment, which influence outcome beyond variation in tumour aggressiveness.[28]

Tumour-related characteristics

Tumour size

Tumour size is one of the strongest prognostic indicators (figure 4),[7, 29] even after 20 years of follow-up.[8, 30] A larger tumour has been related to more positive lymph nodes,[31] thus their interaction further influences the survival from BC. Nonetheless, the independence of survival by node status is shown by the lower 10-year overall survival rate found for node-negative patients with a tumour of 2-5 cm compared to those with a tumour smaller than 1 cm, 66% vs. 79%, respectively.[32]

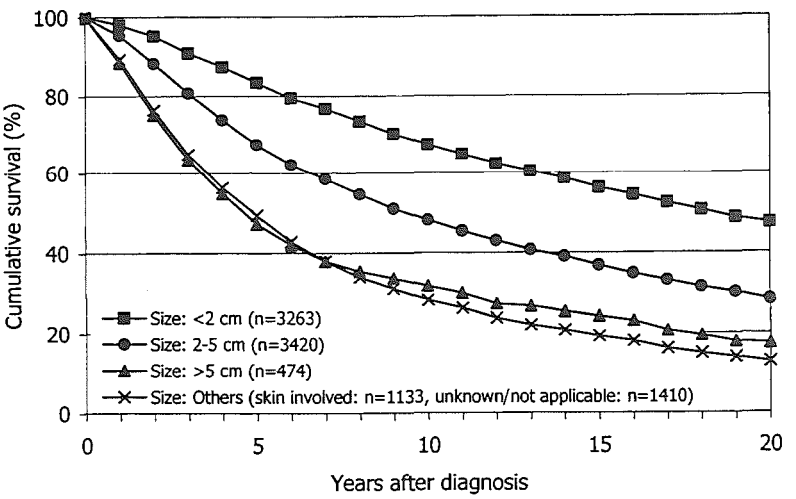

Figure 4 Cumulative survival of proportion of breast cancer patients diagnosed in southern Netherlands in 1970-1994 and followed until 2004, according to tumour size (based on pathological diagnosis)

Histological type

The prognostic value of histological type can be grouped into four: excellent, good, poor and very poor prognosis.[33] BC with an excellent prognosis, such as invasive cribriform, tubular[34], tubulo-lobular and mucinous [35, 36] showed >80% survival at 10 years.[9] Tubular mixed, mixed ductal with special type, atypical medullary[37] and alveolar lobular carcinoma have a good prognosis with a 60-80% 10-year survival. Those with invasive papillary, classic lobular and medullary cancers have a worse prognosis. Finally, 10-year survival among those with ductal, solid lobular, mixed ductal and lobular carcinoma is below 50%.[33] In most populations infiltrating ductal carcinoma covers about

70% of all diagnoses.[35, 38] Inflammatory BC has a particularly poor prognosis: about 30% survived 10 years.[39]

Histological grade

The most widely used grading systems are Scarff-Bloom-Richardson classification, Fisher grading nuclear system and Nottingham Combined Histologic Grade (NCHG).[40] The validity of grading has been subjected to inter-observer reproducibility and subjectivity.[41] However, higher grades have been quite consistently associated with lower long-term survival.[7, 8, 30, 42-44] Depending on other prognostic factors, such as nodal status or tumour size,[45, 46] cumulative survival among patients with the lowest score was 90-94% 10 years after diagnosis and 30-78% among those with the highest score.[36, 47]

Regional lymph node involvement

Lymph node involvement is a valuable indicator of long-term survival (figure 5).[8, 31] Node- positive patients have about a 4-8 times higher mortality than those without nodal involvement.[8, 9, 48] The more nodes involved the worse the prognosis. Prognosis for patients with 10 or more involved axillary nodes showed 70% more deaths at 10 years than for those with 1-3 involved nodes.[31] The survival of node-positive patients improved due to better staging procedures and application of systemic treatment.[7, 30, 49]

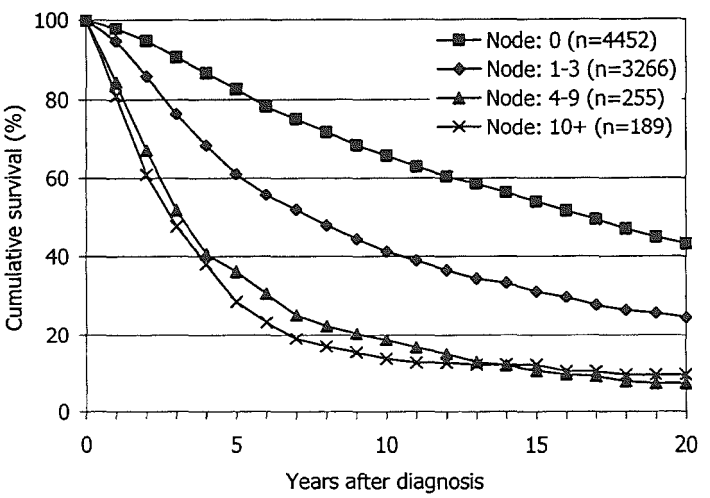

Figure 5 Cumulative survival proportion of breast cancer patients diagnosed in southern Netherlands in 1970-1994 and followed until 2004, according to nodal status (based on pathological diagnosis)

Lymphovascular invasion (LVI) and molecular markers of tumours angiogenesis

At the St. Gallen meeting in 2005, LVI was added to the prognostics for node-negative patients.[50] Compared to patients having no LVI, a 60% higher breast cancer mortality was observed for node-negative BC patients having positive LVI,[51, 52] although

others did not observe the independent role of LVI.[45, 49] In this line of research, studies have also focused on the value of microvessel density,[43] blood invasion (BVI)[53] and markers of angiogenesis (VEGFR (vascular endothelial growth factor receptor), CD105, Tie-2)[54, 55] in predicting long-term survival of BC patients, although the results are still conflicting.

Grouped prognostic factors

Some of the prognostic factors have been combined into a prognostic index, such as the TNM classification, as shown by the data of the ECR (figure 6), and also the more current Nottingham Prognostic Index (NPI), both highly predictive for estimating long-term survival.[40] TNM staging consists of information on primary tumour size, involvement of the regional lymph node and the presence of distant metastasis. Only 53% of patients with regional or locally advanced BC had survived 10 years after diagnosis compared to79% of those with localised BC[16]. Patients with metastasis (stage: M1) at diagnosis exhibited very poor 10-year survival (3.4%).[56]

Tumour size, grade and lymph node status make up the NPI.[11, 45, 48] In a large series of 2879 BC patients, 10-year survival proportion was 85% for those with the lowest NPI score and 19% for those with the highest score.[11]

Recurrence, metastasis and second cancer

Patients with recurrent, metastasized or second cancer generally exhibited lower long-term survival than those without.[9, 21, 57-60] Ten years after surgery, the probability for survival for another 10 years, thus 20 years after diagnosis, for node-negative patients aged ≥45 years, tumour ≤1 cm, grade 1 and without a recurrence or metastasis was 0.89. If a recurrence occurred, the probability of being alive at 20 years dropped to 0.72. If a metastasis was observed the probability of survival was only 0.18.[21] The prognosis decreases with larger primary tumour size, nodal involvement,[61] higher grade,[21] early recurrence (within 5 years of surgery)[62], location of recurrence (regional rather than local ipsilateral)[58] and inadequate primary cancer treatment.[9, 63] In the dataset of the ECR, overall survival was better for women without second primary tumours than for women who developed a new primary cancer (figure 6). Only 68% of early BC patients with second malignancies had survived 10 years of follow-up compared to 78% of those without multiple cancers.[64] Younger breast cancer patients are reported to have poorer survival and a higher risk of second cancer.[58] Corrected for race and grade, women in the 20–29 year old category who had a second breast cancer had a probability of 10-year survival probability of only 23% compared to 57% for those without multiple cancers.

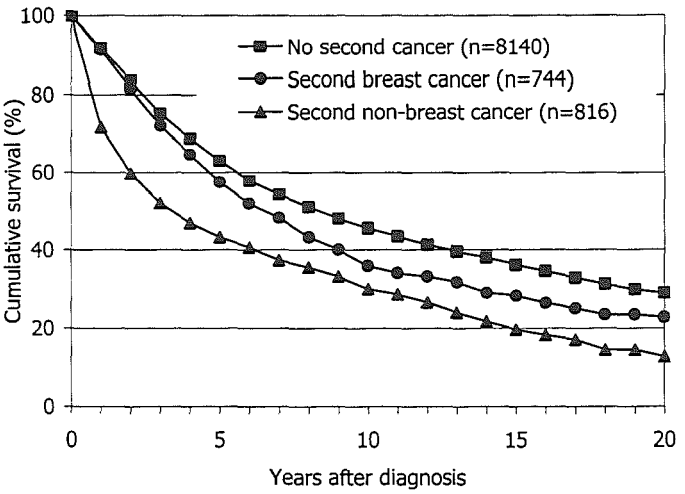

Figure 6 Cumulative survival of breast cancer patients diagnosed in southern Netherlands in 1970-1994 and followed-up until 2004, according to second cancer. Follow-up for patients with second cancer begins at the date of second cancer diagnosis.

Other tumour markers

Hormone Receptors

The presence of hormone receptors such as oestrogen (ER) and progesterone (PR) receptors predicts the long-term outcome of hormonal therapy,[65] thus they have been more commonly used as a predictive marker rather than as a prognostic marker. Thus given a particular treatment, e.g. tamoxifen, ER-positive patients have a considerably better prognosis than ER-negative patients. The prognostic value is weak[29, 42] or negligible,[36] particularly in the early years after diagnosis.[66]

HER-2 expression

Node-positive patients with BC cells showing amplification of the gene for human epidermal growth factor receptor type 2 (HER2), and/or overexpression of its product had a lower 10-year overall survival proportion, 50% versus 65% for those without HER2 amplification.[17, 67] After 10 years the difference in survival persisted, although it became somewhat smaller.[17] Tumours that overexpress HER2 are more likely to contain p53 abnormalities, to be hormone receptor- and bcl-2-negative and to have lymphoid infiltration and a high mitotic index, all known to be markers of poor prognosis for breast cancer.[17, 68, 69] As for patients with node- negative tumours, HER2 did not seem to affect long-term survival significantly.[17, 36, 68] HER-2 expression has been valuable in predicting treatment responses to trastuzumab, certain endocrine therapies and chemotherapy, adding to it's role as a predictive marker.[67]

MAI (Mitotic Activity Index)

MAI is an indicator of tumour proliferative activity that represents the mitotic activity in a given area of the tumour. Combined with another prognostic factor (NCHG), MAI has proven to be an accurate tool for assessment of long-term survival.[47] In a population-based study women with node-negative tumours < 5 cm and a MAI ≥ 10 exhibited 80% survival at 10 years compared to 90% for an MAI <10.[70]

Gene expression profile

A very promising new finding is the microarrays method, in which a set of intrinsic genes is clustered and segregated into major subgroups; BC with a good and poor prognosis profile is correlated to the probability of distant metastases[71] or a tumour with basal or luminal characteristics which are strongly associated with ER status.[72] In a study of 295 patients diagnosed with stage I or II breast cancer, those classified as having a good prognosis profile had a 95% overall 10-year survival rate compared to 55% for those with a poor profile.[73] This classification predicted outcome regardless of the nodal status, implying that more accurate criteria have become available for administering adjuvant systemic treatment.

Various molecular markers

BRCA1 & 2 mutations were first identified in 1994 and are BC risk factors for some specific groups.[74] Their role as prognostic indicator for long-term (more than 10-year) survival has not yet been established. A study of 496 women (median follow-up: 116 months), 56 of whom (11%) carried a BRCA1/BRCA2 mutation, showed worse breast cancer-specific survival for women with BRCA1 mutations than for those without (62% at 10 years versus 86%; P < 0.0001), but not for women with the BRCA2 mutation.[75] However, another study which compared patients from BRCA1, BRCA2 and non-BRCA1/2 families as well as sporadic cases did not confirm the prognostic role of BRCA1/2.[76]

Long-term follow-up studies have not demonstrated an independent effect of p53 mutations on long-term survival. The P53 mutation was related to a poor clinical profile for patients, hence in multivariate analysis its role on survival diminished.[10, 68, 77, 78]

A high level of tissue urokinase-type plasminogen activator (uPA) and its inhibitors has been correlated with poor outcome for node-negative and node-positive patients. Those having the highest level of uPA have a 5 times greater risk of dying from breast cancer compared to those with the lowest level.[68] Other factors such as Ki67 (MIB-1), cathepsin-D, DNA ploidy and S-phase have been suggested as prognosticators of survival, with conflicting results, particularly among long-term survivors. Their use in general clinical settings is therefore not recommended.[79, 80]

Table 1 Overview of studies reporting long-term prognostic factors for breast cancer (BC) patients

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
1	Haerslev & Jacobsen 1995[69] *	490	10.6	MS, T, N, Htyp, MI, G, PR, Her2	All patients: N & PR. In N+: MI & PR. In N-: MS & G.	Her2	Overall survival was measured. P53 was related to absence of tubular formation, high G, ER-negative, high PCNA (proliferating cell nuclear antigen) score.
2	Pietilainen 1995[10]	392	11.1	P53, N, T, Htyp, tubular formation, intraductal growth, margin formation, necrosis, DNA ploidy, S-phase fraction	All patients: N, T, MI In N+: T, MI In N-: T, p53, G		Overall survival was measured. P53 is related to younger age, MI, AI, G, nuclear pleomorphism
3	Haerslev 1995[78] *	490	11	PCNA	T, G, PR	Her2 & PCNA (Proliferating cell nuclear antigen)	Overall survival was measured. PR was only an independent factor in N-positive pts. Her2 & PCNA were related to more positive N, higher G, ER-/PR-negative.
4	Gamel 1996[38]	163,808	NR. Range 1mos-19yrs.	Histological type by stage (localized & regional BC)			Breast cancer specific survival was measured.
5	West 1996[12]	1196	NR. Diagnosed: 1973-1986. End FU: 1994.	Comorbidity	Level of comorbidity	Adjusted for age, race, stage, N, therapy. Values for these factors were not shown	Overall survival was measured. Charlson comorbidity index was used. There is no difference in the significance of comorbidity on survival of Caucasians and African American (AA)
6	Haerslev 1996[112] *	487	>10	Ki-67, PCNA	T, G, PR	KI-67 & PCNA.	Overall survival was measured. PR only an independent factor for N+ patients. Ki-67 was related to T, MI, G.
7	Northridge 1997[35]	Mucinous BC: 4082. Infiltrating duct BC: 139,154	NR. Diagnosed: 1973-1990.		HTyp, period of diagnosis, Stage, G	Age	Breast cancer specific survival was measured.
8	Kollias 1997[11] *	2879 age≤70, T<5cm	>10	Age<35, NPI	T, G, N	Age	Overall survival was measured. Younger than 35 yrs had higher grade, more LVI and worse NPI group. After 10yrs NPI did not change OS.

Table 1 *(continued)*

9	Zahl & Tretli 1997[95]	8802 age< 70	Diagnosed: 1965-74. End FU: 1991	Survival categorized by age, stage and follow-up time			Excess hazard from breast cancer was measured. After 8 yrs being younger than 35 does not influence survival. Stage was an important prognosticator up to 20 years.
10	Pinder 1998[46]	465	12	N by grade, Treatment by grade			Overall survival was measured. The study aimed to confirm value of Nottingham grading system for survival. N+G3 patients benefited from prolonged chemotherapy.
11	Gaffney 1998[113]	BRCA1: 30. BRCA2: 20 Control: 18278 BC pts	BRCA1: 9.8 BRCA2: 7.5 Control: NR			BRCA1 vs. BRCA2 vs. control	Overall survival was measured. Case and control were matched for date of birth, date of diagnosis and tumour size. Patients with BRCA+ were younger. Patients with BRCA1 had higher grade.
12	Wojcik 1998[27]	6577 patients. Whites: 5879. African American (AA): 698	At 10 years 59-67% patients were alive	Race, G, N, T, stage, waiting time, smoking, being a widow, having other family as dependent	Race, age, stage	UV: alcohol, family history	Overall survival was measured. AA is more likely to be younger at diagnosis, have larger tumour, higher stage and more lymph nodes.
13	Mansi 1999[114]	350	12.5	Bone marrow micrometastases	N, T	Bone marrow micrometastases, LVI	Overall and breast cancer-specific survival was measured. Bone marrow metastases may be useful as prognostic factor for BC pts without information on T and N.
14	Kollias 1999[45] *	319 T≤1cm	>10	G, N, LVI, NPI	G, N	LVI	Overall survival was measured.
15	Tabar 1999[44]	2468	NR. Diagnosed: 1977-85. End FU: 1996	T, N, G, detection mode, HTyp	TXN, age*N, Htyp*N, T*N*G.		Overall survival was measured. Screening arrests disease progression. Tumour progression is more rapid in BC patients <50yrs. OS of T1a(1-5mm) vs. T1b(6-10mm) NS.

Table 1 *(continued)*

16	Nomura 1999[57]	1857 <80yrs stage I-III	12	Second cancer and recurrence	Age, ER, N, recurrence, second cancer		Overall survival was measured. Recurrence is related to higher stage, younger age at diagnosis, Htyp, and therapy. Second cancer is related to younger age. Death related to recurrence and second cancer is increased 12 yrs after diagnosis.
17	Reed 1999[36]	613 T1-2N0	15.5	Age >50, T, G	G, T, treatment	UV: treatment, ER, PR, Her2, P53	Overall survival was measured. Her2 was related to PR-, ER-negative, P53, G. P53 was related to PR-. Treatment was ovarian & locoregional irradiation that had lower mortality rate
18	Aebi 2000[7]	3700 pre- & perimenopausal	12	Age <35 vs. ≥35	N, T, G, age<35*ER+	Age, ER	Overall survival was measured. Younger patients with ER+ who were not amenorrhoea had a significantly shorter survival.
19	Ferrero 2000[77]	297 N-	11	T, ER, P53	T, ER	Age, PR, G	Breast cancer-specific survival was measured. P53 was related to grade, T, ER-negative. P53 was continuous variable
20	Kroman 2000[6]	10,356 age<50	NR. Diagnosed: 1978-96.		Age, T, N, G	Period of treatment and surgery	Relative survival was measured for excess mortality due to BC. When chemotherapy was given BC at young age does have worse prognosis.
21	Ferrero-Pous 2000[68]	488	10	ER, uPA, G, N, PR, P53 by Her2	All patients: uPA, N, T, Her2, age. In N-: uPA, T. In N+: N: uPA, T, age, Her2.		Overall survival was measured. For patients who received chemotherapy uPA, T & N determined OS. For patients who received hormonal therapy uPA, Her2 & N determined OS.
22	Kato 2001[43] *	377	10	T, N, G	AMC, T, N, G	Necrosis	Overall survival was measured. AMC is a good prognostic factor for N- and T2-3 patients.
23	Liu 2001[96]	791	16.3	T, N, G, ER, Her2, p53, MIB-1, MAI, AI	All patients: N, T, G, ER, Her-2. In N-: G. In N+: N, age, ER, Her2	UV: age. MV All patients: AI, MI, MIB-1, ER, G MV in N- & N+: AI, MI, ER, G.	Breast cancer-specific mortality was measured. When patient FU was truncated at 5 years, MI was prognostic factor for N+ and N-.

Table 1 *(continued)*

24	Page 2001[115]	311 no adjuvant therapy.	11.6	High risk group (ER- or T≥3cm) vs. low risk (ER+ and T<2cm)	T, risk group (high vs. low)	G, MI	Overall survival was measured. MI was only significant when FU was truncated at 5 years. Grade was significant prognostic factor for short- and long-term survival.
25	Frkovic-Grazio & Bracko 2001[47]	270 T1N0M0	12.5	G, Tubular score, MI	Tubular score and MI		Breast cancer-specific survival was measured. This study confirmed the use of Nottingham grading system in their cohort.
26	D'Eredita 2001[48]	402	≥16	T, N, Htyp, G, LVI, NPI	T, N, G	UV: Age, MS, ER, type of surgery. MV: LVI & Htyp	Overall survival was measured. NPI gives similar survival prognosis as T, N, G.
27	Thomson 2001[25]	23786	At 10 years about 50% patients were alive	Age stratified by SES	Intermediate vs. high SES group corrected for age, ER, N, T, stage	Deprived vs. high SES group corrected for age, ER, N, T, stage	Deprived women have more ER- tumours. ER distribution and treatment method accounted for 20% of disparities in survival.
28	Vorgias 2001[29]	269 stage II	12	NR	T, N, age, ER/PR	MS, therapy	Overall survival was measured.
29	Vincent-Salomon 2001[42]	685 T≤3 cm	10.8	G, N, ER, necrosis	N, necrosis, G	UV: Vascular density, LVI, age, PR	Overall survival was measured. Intratumoral vascular density was related to larger tumour size and higher grade.
30	Eerola 2001[76]	Familial BC: 359. Sporadic BC: 59517.	NR. Diagnosed: 1953-1995. End FU: 1997	-	Stage, age, period of BC diagnosis, FU time (after 2 and 3 yrs of diagnosis)	BRCA1, BRCA2	5-year relative survival was measured for excess mortality due to BC.
31	Kitchen 2001[34]	9520	12		Tubular BC type vs. other type, by nodal status and chemotherapy		Overall survival was measured. Tubular BC type had better prognosis than other type. This type was more likely to have low G & ER+.
32	Kato 2002[49] *	422	10	P53, MI, necrosis, T, N, LVI	MI, T, N	UV: AI	Overall survival was measured. In MV P53 & MI were independent prognostic factors for N- patients only. P53 was related to MI, AI, necrosis, G, T, N, ER/PR

Table 1 *(continued)*

33	Kato 2002[53] *	398	10	BVI, T, N, G, chemotherapy	BVI, T, N, G, chemotherapy	UV: necrosis	Overall survival was measured.
34	Costa 2002[66]	670	11.4	N, T, age, ER/PR	N, T, age	MS, ER/PR	Breast cancer-specific survival was measured. After 5 years of FU ER and PR were not independent prognostic factors.
35	Menard 2002[17]	1928	Diagnosed in 1968-69 and 1978-79.	Her2, N, T, MS, lymphoid infiltration, PR-	G, T, N, lymphoid infiltration		Overall survival was measured. HER-2 was related to large tumours, higher G, lymphoid infiltration, higher mitotic index, PR-.
36	Van de Vijver 2002[73]	295 age<53, stage I-II	6.7	Gene profile (Good vs. bad prognosis) for all patients, N+, N-	Gene profile, T, N, chemotherapy	VI, G, age, hormonal therapy	Overall survival was measured.
37	Van't veer 2002[71]	117 age <55	NR.				Better classification of patients with high risk of metastasis and in need of chemotherapy.
38	Hatteville 2002[21]	3180	15.8		OS<5yr: N, G, recurrence or metastasis OS≥5 yr: G and recurrence or metastasis	Age, T	If patient remains without recurrence or metastasis, effect of prognostic factors decreases over time. With metastases, this effect increases.
39	Sotiriou 2003[72]	99	6.1	Gene profile (luminal 1-3 vs. basal 1-2 & Her2 type)			Luminal-like 1-3 was predominantly ER+. Basal-like 1-2 and Her2 was predominantly ER-
40	Olivotto 2003[56]	620 stage IIIB-M1	>20	Supraclavicular BC, Stage IIIB and M1			Overall and breast cancer specific survival were measured. Patients with supraclavicular metastases had significantly better survival than patients with M1. Survival of these patients resembles that of BC stage IIB. (FU for living patients 20 yrs, for all patients 4.5 yrs)
41	Weiss 2003[31]	905 N+ Chemotherapy+	22.6	N+ (N1-3 vs. N4-9 vs. N>10), also by treatment and follow-up time	N, T, MS	MV: NXT, MSXT, additional vincristine and prednison	Overall survival was measured. N was related to T. MS was related to receptor status.

Table 1 *(continued)*

42	Taylor 2003[16]	54,228	At 10 years 65% patients were alive	Period of diagnosis, stage by age, FU time by stage			Relative survival was measured for excess mortality due to BC. The longer the survival the better the prognosis. Improvement in relative survival for all patients and all stages since 1972.
43	Dales 2004[55]	905 aged 25-81	11.7	In N- : CD105+ vessels. In all pts: CD31, Tie-2/Tek	In all pts: G, CD105 vessels, ER. In N-: G, CD105 vessels, PR.	In all pts: T, Htyp, CD31, PR, age. In N-: T, CD31 vessels, ER, age.	Overall survival was measured. MV: Tie-2/Tek showed significant role for predicting OS in all patients and N- patients.
44	Brenner & Hakulinen 2004[15]	18,578 age< 50	NR. Diagnosed: 1953-1999.	Period of diagnosis, stage, stage*period, time after diagnosis			Improvement of prognosis for BC patients younger than 50 over the past decades. Relative survival remains lowered even 40 yrs after diagnosis.
45	Robson 2004[75]	584 Ashkenazi Jewish	116	BRCA1, T, N, ER, age, chemotherapy	BRCA1, T, N, Age	Tamoksifen, BRCA2	Breast cancer-specific survival was measured. No effect of BRCA on non-BC death. BRCA1 only predicted BC death in patients without chemotherapy
46	Chia 2004[32]	1187 LVI-, N-, Adjuvant systemic therapy-	10.4	T, G	TXG		Overall and breast cancer specific survival were measured. Patients with higher grade and size have greater chance to die from other & those with low risk disease greater chance of death from BC.
47	Yoshimoto 2004[18]	15,416	NR. Diagnosed 1946-2001.	Period of diagnosis.			Over the decades, there were less extensive surgery and lymph node examination, less radiotherapy, more chemo- and hormonal therapy.
48	Houterman 2004[116]	527 age≥40	4.7	Comorbidity, N, Therapy, age≥70, comorbidity*N	In age<70: comorbidity, N In age≥70: comorbidity, age	In age <70: therapy In pts age≥70: N, therapy	Relative survival was measured for excess mortality due to BC. Older patients with comorbidity were not treated differently but had a worse prognosis.
49	Schoppmann 2004[52]	374	22.4	LVI, G, N, Therapy	LVI, G, N	LMVD (Lymphatic Microvessel Density), T, Htyp, ER, age, MS	Overall survival was measured. LVI is related to young premenopausal BC, lower G, N+
50	Warwick 2004[30]	2299	>10	G, N, T, Metastases	G, N, T, Metastases		Breast cancer specific survival was measured. All studied factors predicted long-term survival, but their value decreased over time.

Table 1 *(continued)*

51	Robsahm & Tretli 2005[26]	5042	NR. Diagnosed: 1964-92. End FU: 1992	NR	Location of home, age at first child, physical activity at work	MV corrected for: age, period of diagnosis, birth cohort, educational level	Breast cancer-specific survival was measured. Incidence of BC increases with higher educational level, and case fatality decreases by increasing education level.
52	Vu-Nishino 2005[37]	1490 received with breast-conserving treatment	13.9			Medullary BC vs other BC type	Overall survival was measured. Medullary BC type had better prognosis than other type. This type was more likely to have ER+, PR+ & less BRCA1/2 mutation. Medullary type was only a prognostic factor for the first 5 years.
53	Galper 2005[62]	2102 stage I-II, 314 with local recurrence (LR)	13.1	NR	No LR treatment, Invasive LR, time (yrs) to local recurrence, age at initial BC diagnosis	T, detection method, number of nodes sampled, ER/PR, histological type, G, LVI, margins	Measure of survival: distant failure, second malignancy, or death. Patients with a longer time to recurrence have prolonged survival.
54	Voogd 2005[61]	266 BC with LR	11.2 after LR for living pts	NR	Location of LR, size of LR, skin involvement of LR, N+ for primary tumour		Overall survival was measured. Early detection of local recurrence may improve the treatment outcome.
55	Louwman 2005[13]	8966	Diagnosed 1995-2001. End FU: 2004	2 or more comorbidities, diabetes mellitus and previous cancer	Previous cancer, CVD, DM, cerebrovascular disease, dementia, 2 or more comorbidities, stage, treatment (RT, ST, age)		Overall as well as relative survival was measured for excess mortality due to BC. Primary treatment of BC patients with serious comorbidity was less extensive than treatment of those without comorbidity.
56	Tammemagi 2005[14]	906	10	Number of severe comorbidities, race, type of comorbidity	All patients: 3 or more comorbidities adjusted for stage, age, ER, surgery, chemotherapy, radiotherapy		Overall survival was measured. AA had more diabetes and hypertension. After adjustment for these 2 comorbidities disparity disappeared.

Table 1 *(continued)*

57	Meunier-Carpentier 2005[54]	909/918 age: 25-81	11.3	Tie2	-	UV: VEGFR-2, VEGFR-2	Overall survival was measured. VEGFR-1 and Tie2 were reported as independent prognostic factors corrected for T, G, Htyp, in all patients and N-. However no estimates were given.
58	Tai 2005[39]	6184 Inflammatory BC	NR. Diagnosed 1973-1995. End FU: 2000.	Period of diagnosis			Breast cancer-specific survival was measured. Prognosis has improved over the decades due to more aggressive therapy.
59	Louwman 2005[70]	492 T1-2 N0	>10 yrs	MAI	OS: age, T BCS: MAI	OS: HTyp, therapy, period of diagnosis. BCS: therapy, period of diagnosis, age, T, Htyp	Overall (OS) as well as relative survival (BCS) was measured for excess mortality due to BC. Higher MAI was a significant prognostic factor for N- and N+, but only during the first 10 yrs of FU.
60	Arrigada 2006[8]	2410 T≤7cm N1-2	19	T, skin fixation, muscle fixation, G, N, age.	Total FU: T, N, G, age<35, age≥55. FU 0-5yrs: T, N, G, age≥55. FU 5-10yrs: N, G, age <35, age≥55. FU 10-15yrs: N>10, age>55. FU 15-20yrs: age≥65.		Overall survival was measured. Long-term effect of prognostic factors vanishing.
61	Newman 2006[28]	90,124. White American: 76,111. AA: 14,013			Age, stage, SES		Meta-analysis. African American is an independent predictor of poor outcome for overall survival and breast cancer specific mortality
62	Menvielle 2006[23]	407,435 women followed for BC death (N:1408)	Women who died of BC in 1968-96.	Level of education by period of diagnosis			Breast cancer death among women with the highest education compared to women with the lowest education in 1968-74 was 0.43; and in 1990-96: 1.17 (NS)

Table 1 *(continued)*

63	Bouchardy 2006[24]	3920 age<70	NR. Diagnosed in 1980-2000.	SES	SES corrected for age, period of diagnosis, marital status, country of birth, Htyp, ER, detection method, stage, sector of care, therapy		Overall survival was measured. Lowest SES had less frequently screen-detected cancers, less stage I, less lobular BC, less BCT, less lymph node dissection.
64	Siegelmann-Danieli 2006[117]	992, age≥70	6.9	Being in wheelchair, renal insufficiency, dementia, CHF, cardiac arrhythmia, DM, IHD, osteoporosis, PVD, cerebrovascular disease, COPD, Parkinson's disease, valvular heart disease.	In stage 1A-2A: age, CHF, DM, PVD, stage, cardiac arrhythmia, Parkinson's disease, renal insufficiency. In stage 2B-4: G, stage, N, wheelchair-bound, renal insufficiency, COPD, age, DM	Systemic therapy	Overall survival was measured. CHF: Cardiac Heart Failure. DM: Diabetes Mellitus. IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary Disease. Role of comorbidity varies by age.
65	Pritchard 2006[67]	639 premenopausal N+	10	Her2 amplification	Her2 corrected for age, N, ER, type of surgery		Overall survival was measured. Those with amplified Her2 have improved survival with CEF.
66	Lee 2006[51]	(A) Adjuvant therapy - : 990. (B) Adjuvant treatment + : 1765	Group A: 13. Group B: 6.8.	LVI	Group A: T, G, LVI, Htyp. Group B: T, G, LVI, chemotherapy, hormonal therapy	B: ER, age, Htyp	Breast cancer-specific survival was measured. For patients without adjuvant treatment, role of G in survival was higher in the first 5 years. Role of Htyp was not significant for the first 5 years of FU.

indicates the overlapping patients used by the same author to answer another research question Yrs: years; UV: Univariate analysis. MV: Multivariate analysis. MS: Menopausal Status; T: Tumour size; N: Nodal involvement; Htyp: Histological type; MI: Mitotic Index; G: Grade; PR: Progesterone Receptor status; ER: Oestrogen Receptor status; PCNA: proliferating cell nuclear antigen; mos: months; NR: Not Reported; AA: African American; age: is in year and indicate age at primary breast cancer unless otherwise state; NPI: Nottingham Prognostic Index; LVI: Lymphovascular Invasion; (Prognostic factor)(Prognostic factor): interaction between 2 factors; AMC: Average Microvessel Count; MAI: Mitotic Activity Index; AI: Apoptosis Index; FU: Follow-up; SES: Socioeconomic Status; BVI: Blood vessel Invasion; LMVD: Lymphatic Microvessel Density; LR: local recurrence; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; RT: radiotherapy; ST: Systemic therapy; VEGFR: Vascular Endothelial Growth Factor Receptor; OS: Overall survival; BCS: Breast Cancer Specific Survival; NS: not significant; CHF: Cardiac Heart Failure; IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary. CEF: cyclophosphamide, epirubicin and fluorouracil

Miscellaneous

Lifestyle

Generally, increased death rates due to BC (13-20%), other causes (49-86%) and all causes (14-70%) have been observed among obese patients.[81-84] Normal body weight tended be more beneficial in death from other causes than from BC:[82, 83] 9.5% of obese patients died from non breast cancer causes compared to 6.4% and 5.8%, respectively, of the normal or intermediate groups.[81] Obesity was also related to a 2-fold increased risk of postmenopausal contralateral BC and a 60% higher occurrence of second other cancers.[83] Therefore, normal weight may reduce the risk of second post-menopausal BC, second other cancers and overall mortality.[82, 83, 85]

Compared with women who engaged in less than 9 MET (metabolic equivalent task)-hours per week of activity, women who engaged in 9 or more MET-hours per week had a 40% lower risk of death from all causes, translating into a 6% absolute (unadjusted) reduction in mortality,[86] which emphasizes the need to advise physical activity.

So far, although studies have not convincingly shown the positive influence of eating fruit, vegetables and soy bean on long-term BC survival,[84, 87] diets high in fruits, vegetables, legumes, poultry, and fish and a low intake of red meat, desserts and high fat dairy products are likely to protect against mortality from non-BC causes.[88]

Modification of BC's prognostic factors

Various studies have questioned the role of breast cancer risk factors in determining the biological tumour features as mentioned above. Indeed, breast cancer risk factors seem to differ according to histological type, grade, size, nodal status and ER/PR receptor status.[89-92] For example, excessive alcohol intake and obesity increased the risk for the development of ER-positive tumours.[91, 92] As for late age at first full-term birth and obesity are related to an increased risk of large tumours.[90] Hence, risk factors for breast cancer may also affect breast biology and clinical behaviour, thus also BC prognosis.

Changing importance of prognostic factors over time after diagnosis

Commonly, the value of prognostic factors decreases depending on the length of the follow-up period.[30, 93] Survival curves according to prognostic factors usually show a large drop in survival for all stages during the first 5 years; afterwards the curve stabilizes. Studies agreed on the long-lasting influence of tumour size at diagnosis on survival, albeit attenuating over time.[30, 93, 94] Grade, nodal status and metastases were also valuable in predicting survival up to 20 years after diagnosis.[30, 94] Although, others have reported that 10 years after diagnosis only tumour size[93] or nodal status[8] or old age[8] remained as an independent predictor of long-term survival. Similarly, ER/PR status and MAI only had a significant prognostic role in the first 5-10 years after diagnosis.[66, 70, 95] Because even 10 years after BC diagnosis the probability of survival for BC patients does not seem to reach that of the general population, the role of other

prognostic factors in determining survival for long-term survivors still needs to be determined.

The role of early detection

Increased awareness among women and improvement in diagnostic procedures have enabled earlier and better detection of BC. Trials on population screening have reported 21%-29% reduction in BC mortality for women invited for screening within 14-16 years of follow-up.[19, 96] Screening identified tumours at an early stage consequently, survival improved.[97, 98] Screening also identified patients with slowly growing tumours who might receive unnecessarily aggressive cancer treatment. Thus, Joensuu et al[99] examined recurrence rates among patients detected by screening compared to those detected outside screening. After adjusting for tumour aggressiveness (tumour size, nodal status, grade, age, treatment, PR status, HER-2), hence eliminating bias towards detection of indolent cancers (length bias), the benefit of screening for the prognosis for BC patients remained evident.[99] This suggests that other factors explain the indolent behaviour of BC detected by screening. Hence, until this factor is established, detection mode should probably be considered as a prognostic factor and thus be taken into account in patient management.

The role of treatment

Improvement in BC treatment has undoubtedly also increased the long-term survival of BC patients,[100] as reflected by the improved overall survival across all BC stages.[16] Using historical data from population-based studies in periods when effective treatment was not available, it was estimated that without treatment only 4% of BC patients would survive 10 years or longer.[101] BC treatment guidelines have been modified continuously in the last 28 years, tailored to most of the prognosticators mentioned earlier.[50] Effectiveness of various treatment modalities has been summarized by others who conclude that radiation, chemotherapy and hormonal therapy may reduce long-term mortality by up to 57%.[65, 102-104] Emerging new therapeutic approaches using a monoclonal antibody directed against HER-2 have yielded improved short-term survival for advanced stage[105] as well as operable BC patients.[106] Quality of treatment as indicated by loco-regional failure[107], surgeon workload[108] or hospital volume[109], may affect survival although its role on long-term survival still needs confirmation. In conclusion, on the one hand we have observed a shift in stage towards less aggressive cancers; on the other hand, better and more (systemic) treatment has become available, leading to improved survival for breast cancer patients.

Table 2 Prognostic role of lifestyle on 10-year survival of breast cancer patients

No.	Author, year	No. of patients	Follow-up	Univariate (UV)	Multivariate (MV)	Outcome measure	Remark
1	Daling et al, 2001[84]	1177	NR	BMI ≤ 21: 21% BMI ≥ 26: 34%	HR: Highest vs lowest 25% percentile: 1.7	UV: proportion mortality at 10 years MV: 5-yr all cause mortality	Breast cancer younger than 45 yrs BMI 1 yr before dx MV: T, N, PR, ER, c-erb B-2, BCL-2, p53, p27
2	Dignam et al, 2005[83]	4077	NR		BM: BMI 25-29: 1.18 ns BM: BMI 30-34: 1.02 ns BM: BMI ≥ 35: 1.13 OM: BMI 25-29: 0.89 ns OM: BMI 30-34: 1.11 ns OM: BMI ≥ 35: 1.86	BM: HR breast cancer mortality OM: HR other death	Breast cancer with lymph node and ER negative. MV: Treatment, T, age, race, ER level, PR level. BMI ≤ 24 was reference 56% of patients were overweight.
3	Dignam et al, 2003[82]	3385	166 mos		BM: BMI ≤ 18.5: 1.08 ns BM: BMI 25-29: 1.02 ns BM: BMI ≥ 30: 1.20 ns OM: BMI ≤ 18.5: 3.5 OM: BMI 30-34: 1.19 ns OM: BMI ≥ 35: 1.49	BM: HR death following recurrence or second breast cancer OM: HR other death	Breast cancer with lymph node negative and ER positive. MV: Treatment, T, age, MS, race, ER level, PR level. BMI 18.5-24 was reference 50% of patients were overweight.
4	Berclaz et al, 2004[81]	6792	14 yrs	BMI < 25: 55% BMI 25-29: 57% BMI ≥ 30: 61%	BMI 25-29: 1.07ns BMI ≥ 30: 1.14	UV: proportion survival at 10 years, estimates from graph. MV: 10-year mortality from all cause	MV: MS, T, N, LVI, G, ER, PR, treatment BMI 18.5-24 was reference.

Table 2 *(continued)*

5	Holmes et al, 1999[85]	1982	157 mos		BMI 21-22: 0.91 ns BMI 23-24: 0.8 ns BMI 25-28: 1.1 ns BMI ≥ 30: 1.7 Protein intake after diagnosis 2st quintile: 0.90 ns 3st quintile: 0.55 4st quintile: 0.64 5st quintile: 0.65 Protein intake prior diagnosis 2st quintile: 1.02 ns 3st quintile: 0.7 ns 4st quintile: 0.62 5st quintile: 0.7 ns	All cause mortality	MV for BMI: age, family history of BC, diet interval, calender, OC, MS, HRT, smoking, age at menarche and first birth, N, T, G, ER, PR MV for protein intake: BMI and factors above without family history of BC BMI <21 was reference. 1st quintile was reference Trend test for protein intake prior to BC diagnosis was significant (0.2). Significant trend of higher mortality from lowest to highest quintiles of fiber, lutein & zeaxanthin, calcium & protein intake, with 13-35% lower mortality in the lowest quintile. Alcohol ns effect.
6	Holmes et al, 2005[87]	2987	96 mos		BC: MET 3-8: 0.8 ns BC: MET 9-14: 0.5 BC: MET 15-23: 0.56 BC: MET ≥ 30: 0.6 TM: MET 3-8: 0.7 TM: MET 9-14: 0.59 TM: MET 15-23: 0.56 TM: MET ≥ 30: 0.65	BC: breast cancer mortality TM: total mortality	Physical activity at a median of 38 mos after diagnosis MV: age, interval between diagnosis and physical activity assessment, smoking, BMI, MS, HRT, age at first birth, parity, energy intake, stage, treatment

NR: not reported, cumulative survival proportion at 10 years larger than 50%.
Mos: months, yrs: years
BMI: body mass index
HR: Hazard ratio
ns: not significant
BC: breast cancer
MET: metabolic equivalent task hours per week. T: Tumour size, N: Lymph node status, PR: progesterone receptor, ER: estrogen receptor, MS: Menopausal status, OC: oral contraceptive use, HRT: postmenopausal hormone use, LVI: lymphovascular invasion, G: grade

Table 3 Selected prognostic factors for long-term overall mortality of breast cancer (BC) patients

Patient groups based	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis	**Morphology based**	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis	**Molecular based**	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis
Age at diagnosis [8]	HR:	Lymph node status [30]	HR:	HER2[68]	HR:
<35 vs. 35-44	1.4 (p: 0.07)	N≥1 vs. N0 [b]	2.4 (1.9-3.9)	> 500 vs. ≤ 500	1.82 (1.1-2.9)
45-54 vs. 35-44	1.1 (ns)				Only in node-positive patients
55-64 vs. 35-44	2.0 (p: 0.000)	Metastases vs. N0	22.73 (16.1-32.2)		
65-75 vs. 35-44	2.5 (p: 0.000)				
Period of diagnosis [16]	Relative Survival [a]:	Tumour size (mm) [30]	HR:	Cell proliferation index	HR:
1972-1976	59%	T10-14 vs. T1-9	1.2 (0.8-1.9)	(MAI)	
1977-1986	64%	T15-19 vs. T1-9	1.7 (1.1-2.6)	>10 vs. ≤10 [10]	1.02 (1.00-1.03)
1987-1991	70%	T20-29 vs. T1-9	2.5 (1.6-3.9)		Only in node-positive patients
		T30-49 vs. T1-9	3.8 (2.4-6.0)		
		T≥50 vs. T1-9	4.6 (2.9-7.6)		
Time after diagnosis [16]	Relative Survival:	Tumour grade [43]	HR:	Gene expression profile[73]	
0 vs. 5 yrs after diagnosis		II vs. I	2.5 (1.0-6.1)	Poor vs. good signature [e]	S:
Regional BC	79% vs. 84%	III vs. I	5.7 (2.6-12.4)		55% vs. 95%
Locally advanced BC	53% vs. 68%				
Socioeconomic status [25]	HR:	Tumour type[33]	S:	ER/PR status [29]	HR:
Intermediate vs. affluent	1.2 (1.0-1.4)	Poor vs. excellent [c,d]	<50% vs. >80%	Positive vs. negative	0.38 (0.02-1.06)
Deprived vs. affluent	1.2 (0.99-1.53)				

HR: Hazard ratio calculated within multivariate analysis of breast cancer patients followed for a median/mean of 10 years or longer

a Estimates taken from graph

b becomes larger as numbers of involved lymph nodes increases [8]

c Excellent prognosis: tubular, invasive cribriform, mucinous, tubulolobular. Poor prognosis: mixed lobular, solid lobular, ductal and mixed ductal lobular.

d unadjusted estimates

Conclusion

The prognosis of breast cancer has become relatively good, with current 10-year relative survival about 70% in most western populations,[16, 110] especially if up-to-date statistical method such as the period analyses is used.[110] Even better, the longer patients survive their breast cancer the higher their survival chance.[16] Our review shows conventional prognostic factors of survival, such as tumour size, lymph node status and grade, remain the most important determinants of 10-year survival for BC patients (table 2). Most studies agreed on the value of MAI and LVI for prediction of long-term survival. The influence of host factors including age, race/ethnicity or socio-economic factors and tumor-related factors such as histological type and angiogenesis diminishes after correction for other factors. For most recent markers such as Her2, gene profiling, p53 mutation and uPA level longer follow-up is needed. Recurrence, metastases and a second cancer double the burden of disease thus increase risk of mortality. Similarly, co-occurrence with other diseases is in no doubt decrease survival.

Healthier lifestyle generally increases long-term survival. Modifiable risk factors (such as alcohol consumption and obesity) not only affect incidence but also tumour' clinical behaviour and thus survival.

Although a lot is known about the prognosis for breast cancer patients, effect of traditional prognostic factors appears to attenuate over time, leaving room for studies on the role of other and newer factors for long-term survival.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. Ann Oncol 2003;14 Suppl 5:v61-118.
3. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. Eur J Cancer 2003;39:1718-29.
4. ACS, Cancer facts and figures 2005., 2005.
5. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW. Van meten naar weten. 50 jaar kankerregistratie. Eindhoven: Integraal Kankercentrum Zuid (IKZ), 2005:104.
6. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. Bmj 2000;320:474-8.
7. Aebi S, Gelber S, Castiglione-Gertsch M, Gelber RD, Collins J, Thurlimann B, Rudenstam CM, Lindtner J, Crivellari D, Cortes-Funes H, Simoncini E, Werner ID, et al. Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? Lancet 2000;355:1869-74.
8. Arriagada R, Le MG, Dunant A, Tubiana M, Contesso G. Twenty-five years of follow-up in patients with operable breast carcinoma: correlation between clinicopathologic factors and the risk of death in each 5-year period. Cancer 2006;106:743-50.

9. Fisher ER, Anderson S, Tan-Chiu E, Fisher B, Eaton L, Wolmark N. Fifteen-year prognostic discriminants for invasive breast carcinoma: National Surgical Adjuvant Breast and Bowel Project Protocol-06. Cancer 2001;91:1679-87.
10. Pietilainen T, Lipponen P, Aaltomaa S, Eskelinen M, Kosma VM, Syrjanen K. Expression of p53 protein has no independent prognostic value in breast cancer. J Pathol 1995;177:225-32.
11. Kollias J, Elston CW, Ellis IO, Robertson JF, Blamey RW. Early-onset breast cancer--histopathological and prognostic considerations. Br J Cancer 1997;75:1318-23.
12. West DW, Satariano WA, Ragland DR, Hiatt RA. Comorbidity and breast cancer survival: a comparison between black and white women. Ann Epidemiol 1996;6:413-9.
13. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 2005;41:779-85.
14. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. Jama 2005;294:1765-72.
15. Brenner H, Hakulinen T. Are patients diagnosed with breast cancer before age 50 years ever cured? J Clin Oncol 2004;22:432-8.
16. Taylor R, Davis P, Boyages J. Long-term survival of women with breast cancer in New South Wales. Eur J Cancer 2003;39:215-22.
17. Menard S, Balsari A, Casalini P, Tagliabue E, Campiglio M, Bufalino R, Cascinelli N. HER-2-positive breast carcinomas as a particular subset with peculiar clinical behaviors. Clin Cancer Res 2002;8:520-5.
18. Yoshimoto M, Tada K, Hori H, Morota A, Tanabe M, Nishimura S, Takahashi K, Makita M, Iwase T, Kasumi F, Takahashi S, Ito Y, et al. Improvement in the prognosis of Japanese breast cancer patients from 1946 to 2001--an institutional review. Jpn J Clin Oncol 2004;34:457-62.
19. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909-19.
20. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, Verbeek AL, de Koning HJ. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411-7.
21. Hatteville L, Mahe C, Hill C. Prediction of the long-term survival in breast cancer patients according to the present oncological status. Stat Med 2002;21:2345-54.
22. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. Int J Radiat Oncol Biol Phys 2006;64:1081-91.
23. Menvielle G, Leclerc A, Chastang JF, Luce D. Social inequalities in breast cancer mortality among French women: disappearing educational disparities from 1968 to 1996. Br J Cancer 2006;94:152-5.
24. Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. Int J Cancer 2006.
25. Thomson CS, Hole DJ, Twelves CJ, Brewster DH, Black RJ. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. J Epidemiol Community Health 2001;55:308-15.
26. Robsahm TE, Tretli S. Weak associations between sociodemographic factors and breast cancer: possible effects of early detection. Eur J Cancer Prev 2005;14:7-12.
27. Wojcik BE, Spinks MK, Optenberg SA. Breast carcinoma survival analysis for African American and white women in an equal-access health care system. Cancer 1998;82:1310-8.
28. Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. J Clin Oncol 2006;24:1342-9.

29. Vorgias G, Koukouras D, Paleogianni V, Tzoracoeleftherakis E. Prognostic significance of factors affecting disease free interval and overall survival for Stage II breast cancer in Greece. A multivariate cohort study. Eur J Obstet Gynecol Reprod Biol 2001;95:100-4.
30. Warwick J, Tabar L, Vitak B, Duffy SW. Time-dependent effects on survival in breast carcinoma: results of 20 years of follow-up from the Swedish Two-County Study. Cancer 2004;100:1331-6.
31. Weiss RB, Woolf SH, Demakos E, Holland JF, Berry DA, Falkson G, Cirrincione CT, Robbins A, Bothun S, Henderson IC, Norton L. Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: a study by the Cancer and Leukemia Group B. J Clin Oncol 2003;21:1825-35.
32. Chia SK, Speers CH, Bryce CJ, Hayes MM, Olivotto IA. Ten-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion-negative early breast cancers without adjuvant systemic therapies. J Clin Oncol 2004;22:1630-7.
33. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Res Treat 1992;22:207-19.
34. Kitchen PR, Smith TH, Henderson MA, Goldhirsch A, Castiglione-Gertsch M, Coates AS, Gusterson B, Brown RW, Gelber RD, Collins JP. Tubular carcinoma of the breast: prognosis and response to adjuvant systemic therapy. ANZ J Surg 2001;71:27-31.
35. Northridge ME, Rhoads GG, Wartenberg D, Koffman D. The importance of histologic type on breast cancer survival. J Clin Epidemiol 1997;50:283-90.
36. Reed W, Hannisdal E, Boehler PJ, Gundersen S, Host H, Marthin J. The prognostic value of p53 and c-erb B-2 immunostaining is overrated for patients with lymph node negative breast carcinoma: a multivariate analysis of prognostic factors in 613 patients with a follow-up of 14-30 years. Cancer 2000;88:804-13.
37. Vu-Nishino H, Tavassoli FA, Ahrens WA, Haffty BG. Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (BCT). Int J Radiat Oncol Biol Phys 2005;62:1040-7.
38. Gamel JW, Meyer JS, Feuer E, Miller BA. The impact of stage and histology on the long-term clinical course of 163,808 patients with breast carcinoma. Cancer 1996;77:1459-64.
39. Tai P, Yu E, Shiels R, Pacella J, Jones K, Sadikov E, Mahmood S. Short- and long-term cause-specific survival of patients with inflammatory breast cancer. BMC Cancer 2005;5:137.
40. Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the breast, 3 ed. Philadelphia: Lippincott Williams & Wilkins, 2004.
41. Gilchrist KW, Kalish L, Gould VE, Hirschl S, Imbriglia JE, Levy WM, Patchefsky AS, Penner DW, Pickren J, Roth JA, et al. Interobserver reproducibility of histopathological features in stage II breast cancer. An ECOG study. Breast Cancer Res Treat 1985;5:3-10.
42. Vincent-Salomon A, Carton M, Zafrani B, Freneaux P, Nicolas A, Massemin B, Fourquet A, Clough K, Pouillart P, Sastre-Garau X. Long term outcome of small size invasive breast carcinomas independent from angiogenesis in a series of 685 cases. Cancer 2001;92:249-56.
43. Kato T, Kameoka S, Kimura T, Soga N, Abe Y, Nishikawa T, Kobayashi M. Angiogenesis as a predictor of long-term survival for 377 Japanese patients with breast cancer. Breast Cancer Res Treat 2001;70:65-74.
44. Tabar L, Duffy SW, Vitak B, Chen HH, Prevost TC. The natural history of breast carcinoma: what have we learned from screening? Cancer 1999;86:449-62.
45. Kollias J, Murphy CA, Elston CW, Ellis IO, Robertson JF, Blamey RW. The prognosis of small primary breast cancers. Eur J Cancer 1999;35:908-12.
46. Pinder SE, Murray S, Ellis IO, Trihia H, Elston CW, Gelber RD, Goldhirsch A, Lindtner J, Cortes-Funes H, Simoncini E, Byrne MJ, Golouh R, et al. The importance of the histologic grade of invasive breast carcinoma and response to chemotherapy. Cancer 1998;83:1529-39.
47. Frkovic-Grazio S, Bracko M. Long term prognostic value of Nottingham histological grade and its components in early (pT1N0M0) breast carcinoma. J Clin Pathol 2002;55:88-92.
48. D'Eredita G, Giardina C, Martellotta M, Natale T, Ferrarese F. Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. Eur J Cancer 2001;37:591-6.

49. Kato T, Kameoka S, Kimura T, Tanaka S, Nishikawa T, Kobayashi M. p53, mitosis, apoptosis and necrosis as prognostic indicators of long-term survival in breast cancer. Anticancer Res 2002;22:1105-12.
50. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005;16:1569-83.
51. Lee AH, Pinder SE, Macmillan RD, Mitchell M, Ellis IO, Elston CW, Blamey RW. Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma. Eur J Cancer 2006;42:357-62.
52. Schoppmann SF, Bayer G, Aumayr K, Taucher S, Geleff S, Rudas M, Kubista E, Hausmaninger H, Samonigg H, Gnant M, Jakesz R, Horvat R. Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. Ann Surg 2004;240:306-12.
53. Kato T, Kameoka S, Kimura T, Nishikawa T, Kobayashi M. Blood vessel invasion as a predictor of long-term survival for Japanese patients with breast cancer. Breast Cancer Res Treat 2002;73:1-12.
54. Meunier-Carpentier S, Dales JP, Djemli A, Garcia S, Bonnier P, Andrac-Meyer L, Lavaut MN, Allasia C, Charpin C. Comparison of the prognosis indication of VEGFR-1 and VEGFR-2 and Tie2 receptor expression in breast carcinoma. Int J Oncol 2005;26:977-84.
55. Dales JP, Garcia S, Carpentier S, Andrac L, Ramuz O, Lavaut MN, Allasia C, Bonnier P, Charpin C. Long-term prognostic significance of neoangiogenesis in breast carcinomas: comparison of Tie-2/Tek, CD105, and CD31 immunocytochemical expression. Hum Pathol 2004;35:176-83.
56. Olivotto IA, Chua B, Allan SJ, Speers CH, Chia S, Ragaz J. Long-term survival of patients with supraclavicular metastases at diagnosis of breast cancer. J Clin Oncol 2003;21:851-4.
57. Nomura Y, Tsutsui S, Murakami S, Takenaka Y. Prognostic impact of second cancer on the survival of early breast cancer patients. Int J Oncol 1999;14:1103-9.
58. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. Br J Cancer 2006;94:1745-50.
59. Kollias J, Ellis IO, Elston CW, Blamey RW. Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg 2001;25:1117-24.
60. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jr., Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006;24:2028-37.
61. Voogd AC, van Oost FJ, Rutgers EJ, Elkhuizen PH, van Geel AN, Scheijmans LJ, van der Sangen MJ, Botke G, Hoekstra CJ, Jobsen JJ, van de Velde CJ, von Meyenfeldt MF, et al. Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. Eur J Cancer 2005;41:2637-44.
62. Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, Wong JS, Smith D, Bellon J, Connolly J, Schnitt S, Winer E, et al. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Radiat Oncol Biol Phys 2005;61:348-57.
63. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, Baker J, Walker M, Watson D, Hackett J, Blick NT, Greenberg D, et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res 2006;8:R25.
64. Obedian E, Fischer DB, Haffty BG. Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. J Clin Oncol 2000;18:2406-12.
65. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
66. Costa SD, Lange S, Klinga K, Merkle E, Kaufmann M. Factors influencing the prognostic role of oestrogen and progesterone receptor levels in breast cancer--results of the analysis of 670 patients with 11 years of follow-up. Eur J Cancer 2002;38:1329-34.

67. Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103-11.
68. Ferrero-Pous M, Hacene K, Bouchet C, Le Doussal V, Tubiana-Hulin M, Spyratos F. Relationship between c-erbB-2 and other tumor characteristics in breast cancer prognosis. Clin Cancer Res 2000;6:4745-54.
69. Haerslev T, Jacobsen GK, Zedeler K. Proliferating cell nuclear antigen (PCNA) and c-erbB-2 oncoprotein in breast carcinoma with correlations to histopathological parameters and prognosis. Oncology Reports 1995;2:99-105.
70. Louwman WJ, van Beek MW, Schapers RF, Nolthenius-Puylaert MB, van Diest PJ, Roumen RM, Coebergh JW. Long-term survival of T1 and T2 lymph node-negative breast cancer patients according to mitotic activity index: A population-based study. Int J Cancer 2005.
71. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530-6.
72. Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, Martiat P, Fox SB, Harris AL, Liu ET. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci U S A 2003;100:10393-8.
73. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009.
74. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66-71.
75. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Begin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 2004;6:R8-R17.
76. Eerola H, Vahteristo P, Sarantaus L, Kyyronen P, Pyrhonen S, Blomqvist C, Pukkala E, Nevanlinna H, Sankila R. Survival of breast cancer patients in BRCA1, BRCA2, and non-BRCA1/2 breast cancer families: a relative survival analysis from Finland. Int J Cancer 2001;93:368-72.
77. Ferrero JM, Ramaioli A, Formento JL, Francoual M, Etienne MC, Peyrottes I, Ettore F, Leblanc-Talent P, Namer M, Milano G. P53 determination alongside classical prognostic factors in node-negative breast cancer: an evaluation at more than 10-year follow-up. Ann Oncol 2000;11:393-7.
78. Haerslev T, Jacobsen GK. An immunohistochemical study of p53 with correlations to histopathological parameters, c-erbB-2, proliferating cell nuclear antigen, and prognosis. Hum Pathol 1995;26:295-301.
79. Mirza AN, Mirza NQ, Vlastos G, Singletary SE. Prognostic factors in node-negative breast cancer: a review of studies with sample size more than 200 and follow-up more than 5 years. Ann Surg 2002;235:10-26.
80. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, Ruby SG, O'Malley F, Simpson JF, Connolly JL, Hayes DF, Edge SB, et al. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:966-78.
81. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, Holmberg SB, Lindtner J, Erien D, Collins J, Snyder R, Thurlimann B, et al. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol 2004;15:875-84.
82. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 2003;95:1467-76.
83. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, Somkin C, Wickerham DL. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. Breast Cancer Res Treat 2005:1-10.
84. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. Cancer 1999;86:826-35.

85. Byers T, Sedjo RL. A weight loss trial for breast cancer recurrence: pre-menopausal, post-menopausal, both, or neither? Cancer Causes Control 2006;17:1-3.
86. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. Jama 2005;293:2479-86.
87. Brown JK, Byers T, Doyle C, Coumeya KS, Demark-Wahnefried W, Kushi LH, McTieman A, Rock CL, Aziz N, Bloch AS, Eldridge B, Hamilton K, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 2003;53:268-91.
88. Kroenke CH, Fung TT, Hu FB, Holmes MD. Dietary patterns and survival after breast cancer diagnosis. J Clin Oncol 2005;23:9295-303.
89. Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. Clin Cancer Res 2005;11:909s-17s.
90. Garcia-Closas M, Brinton LA, Lissowska J, Chatterjee N, Peplonska B, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Blair A, Kalaylioglu Z, Rymkiewicz G, et al. Established breast cancer risk factors by clinically important tumour characteristics. Br J Cancer 2006;95:123-9.
91. Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Wolk A. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. Int J Cancer 2006;119:1683-9.
92. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst 2005;97:1601-8.
93. Takeuchi H, Baba H, Kano T, Maehara Y. The time-related changes of the importance of prognostic factors in breast cancer. A sequential multivariate analysis of 1423 Japanese patients. Breast Cancer Res Treat 2005;94:273-8.
94. Zahl PH, Tretli S. Long-term survival of breast cancer in Norway by age and clinical stage. Stat Med 1997;16:1435-49.
95. Liu S, Edgerton SM, Moore DH, 2nd, Thor AD. Measures of cell turnover (proliferation and apoptosis) and their association with survival in breast cancer. Clin Cancer Res 2001;7:1716-23.
96. Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, Muir BB, Prescott RJ, Smith A. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. Lancet 1999;353:1903-8.
97. Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 2003;361:1405-10.
98. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 2005;97:1195-203.
99. Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, Anttila A, Lundin M, Isola J, Lundin J. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. Jama 2004;292:1064-73.
100. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet 2000;355:1822.
101. Johnstone PA, Norton MS, Riffenburgh RH. Survival of patients with untreated breast cancer. J Surg Oncol 2000;73:273-7.
102. Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER, Wolmark N. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet 2004;364:858-68.
103. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106.
104. Fisher B, Jeong JH, Anderson S, Wolmark N. Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. J Natl Cancer Inst 2004;96:1823-31.

105. Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, Pauletti G, Pegram MD, Slamon DJ. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 2006;24:1831-8.
106. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
107. Ernst MF, Voogd AC, Coebergh JW, Poortmans PM, Roukema JA. Using loco-regional recurrence as an indicator of the quality of breast cancer treatment. Eur J Cancer 2004;40:487-93.
108. Stefoski Mikeljevic J, Haward RA, Johnston C, Sainsbury R, Forman D. Surgeon workload and survival from breast cancer. Br J Cancer 2003;89:487-91.
109. Simunovic M, Rempel E, Theriault ME, Coates A, Whelan T, Holowaty E, Langer B, Levine M. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 2006;49:251-8.
110. Houterman S, Janssen-Heijnen ML, van de Poll-Franse LV, Brenner H, Coebergh JW. Higher long-term cancer survival rates in southeastern Netherlands using up-to-date period analysis. Ann Oncol 2006.

5.2

GENERAL DISCUSSION

5.2 General Discussion

Trends in incidence

Breast cancer incidence has been increasing in most industrialised countries for decades. The rise we observed in the southeast of the Netherlands before the introduction of mass screening was not only attributable to earlier detection of more tumours with lower malignant potential. The incidence of more aggressive tumours also increased (albeit to a lower extent), so there appeared to be a real increase in breast cancer incidence, either due to an increased exposure to risk factors or more exposed women.

In fact, the known hormonal risk factors for breast cancer such as early menarche, late age at birth of first child, low parity and postmenopausal hormone use have changed in a risk increasing way over the last decades, and this does not seem to have levelled off yet. Furthermore, obesity and alcohol consumption, particularly among women born since 1950, increased and physical activity decreased on the average, also without a turning point in sight.

The introduction of a mass screening programme also increased incidence rates through detection of small and slowly growing tumours. This increase is supposed to be temporary: when all slowly growing tumours have been discovered, only tumours arising since the last screening round will be detected. A decreasing incidence was observed for women aged 50-69 in the second half of the 1990s, and for women older than 70 since the year 2000, but in both age groups the incidence rates went up again in the more recent years.

The risk of breast cancer among women younger than 50 years appeared to have increased markedly in the more recent periods, which is probably also related to the more vigorous search for inheritable breast cancers since the end of the 1990s in the south of the Netherlands.

Future monitoring will have to exhibit whether incidence rates will increase any further, especially among women born since the 1960s. We did not yet see a decline of rates in postmenopausal women who stopped with postmenopausal estrogens in 2003 after the unfavourable publicity.[1] Additional research needs to investigate the specific etiology of breast cancer occurring at a very young age.

Trends in survival

Survival of breast cancer markedly increased over the past decades, which can be attributed to several factors. First, early detection played a major role. The improvement of diagnostic possibilities (mammography, cytology) allowed for diagnosis of smaller and non palpable tumours, already before the introduction of the mass screening programme 5-year survival improved from 48% in the 1960s to 75% in the 1980s. Also, as mentioned before, the mass screening programme positively affected survival rates. Part of these improvements are attributable to bias, e.g. lead time bias (an artifactual increase in time

from diagnosis to death because screened cancers are detected earlier in their natural history) and length bias (an artifactual decrease in hazard rates because some screen detected cancers progress too slowly to kill).

Improved treatment also lifted survival rates. Surgical treatment was always a major component of the treatment, and still is, but a large proportion of patients nowadays receives breast conserving surgery. Radiotherapy can be administered more precisely, with the dose exactly on the tumour, and less on the surrounding areas, megavoltage radiation being in use since 1974. Adjuvant chemotherapy changed towards more combination chemotherapeutics and also the introduction of tamoxifen for node-positive post-menopausal patients since the early 1980s and for node negative since the late 1980s.

The effect of the recent introduction of trastuzumab (Herceptin) for women with positive HER2 Neu receptor will be monitored in the coming years, not only to watch potential variation, but also to see whether survival improved in a population-based setting. Another reason is to carefully watch long-term effects.

Optimal treatment

Treatment plays a major role in duration and quality of life of women diagnosed with breast cancer. The line between under- and over treatment is however thin: sufficient treatment is needed to prolong life or to reduce recurrence and as little as possible should be given to prevent over-treatment with negative effects on quality of life due to serious side-effects.

Over-treatment can be limited by use of prognostic factors that distinguish women that will have a good prognosis without adjuvant systemic therapy. The mitotic activity index is such a measure, and can be assessed relatively straightforward. In a long-term analysis adjuvant therapy for node/negative women with tumours 2-5 cm (T2) with low MAI exhibited a prognosis comparable to T1 node negative tumours, so one might conclude that only those with a higher MAI (>10) should be eligible for adjuvant systemic therapy.

Histological type also appeared to be a good predictor of survival. Certain less frequent types (such as mucinous, medullary, and tubular carcinomas) have an excellent prognosis. For these patients treatment may consist of surgery with or without radiotherapy, but patients would not have to undergo adjuvant systemic therapy.

Under-treatment could occur among breast cancer patients who suffer from other serious diseases at the time of diagnosis of the breast cancer, especially if they are older. These patients have a worse prognosis, also after adjustment for age, due to a combination of increased death risk due to the concomitant disease and non-standard treatment.

Quite a few elderly patients have received treatment with tamoxifen only in the late 1980s/early 1990s, but since this was no longer recommended[2-4] most of them underwent surgery from the mid 1990s onwards. From the standard breast conserving

treatment (lumpectomy, axillary dissection and radiotherapy) axillary dissection and radiotherapy were often omitted in elderly patients, also related to the prevalence of comorbidity.[5]

The chance of receiving good quality of care as far as chemotherapy is concerned is reduced by old age, presence of co-morbidity and lower socio-economic status.[6] Dose reductions were more frequent among patients with obesity and lower education.[7]

Future studies should be conducted to clarify whether non-standard treatment is indeed more suited for elderly or chronically ill breast cancer patients when new therapies emerge. However, individualization and/or the identification of a large number of subgroups may be needed. The current treatment varies greatly, and watching the outcome of these various therapies in the sense of monitoring complications, recurrences and death may shed light on optimal treatment for this subgroup of patients.

This also applies to the uncommon breast tumours, which comprise almost 10% of the newly diagnosed tumours. This largely heterogeneous group amounts to a considerable number of new patients each year, which enhances the desirability of specific guidelines.

Patients from disadvantaged backgrounds also are less likely to receive adjuvant chemotherapy compared to those from higher socio-economic classes. Future studies will demonstrate whether this is only temporarily or a structural inequality in treatment differences. In this light monitoring of the new (and expensive) medication administration such as herceptin across socio-economic strata is worth while.

Long-term burden of disease

A considerable proportion of breast cancer patients will receive radiotherapy for recurrences or metastases after the first curative treatment, the cumulative proportion receiving radiotherapy within 8 years after diagnosis being about 70% and with longer follow-up probably up to about 80%, because of late presentation of metastases.

Another burden after initial diagnosis and treatment of breast cancer is the occurrence of second primary cancer. The risk of subsequent new primaries is dependent on treatment for the first cancer, common risk factors and genetic predisposition or chance. An absolute excess of 115 second primary cancers for every 10,000 breast cancer patients per year was observed, of which about 50% were breast cancers. The 15-year cumulative risk of developing a second primary breast cancer amounted to 10-13%.[8, 9]

Although survival of women with breast cancer appeared similar to that of women without the disease at about 20 years after diagnosis, the cause of death is still 5 times more often breast cancer than expected from the background population. This can partly be explained by a relatively healthy lifestyle of the breast cancer patients studied (most were born between 1910-1940) with regard to smoking and alcohol intake;[10, 11] a higher

prevalence of exposure to these factors will result in a higher mortality from cardiovascular disease in the background population compared to breast cancer patients.

Future perspectives

With an increasingly aging population and ongoing rising incidence the number of new breast cancer patients will increase from to about 11,500 in 2003 to 17,000 in 2015 in the Netherlands. Since survival has improved considerably, the number of women alive ever being diagnosed with breast cancer will almost double by that time to about 194,000. Of these (partly ex-) breast cancer patients, about 80% probably requires some form of health care either for initial treatment, the follow-up by the medical specialist, or for recurrences or metastases.[12]

For an average hospital in the Netherlands this means that in 2015 about 200 newly diagnosed breast cancer patients will require diagnosis and treatment, about 1200 are included in some form of routine follow-up schedule, 115 are treated for recurrences and about 80 for metastasis each year.

The question is how to address this rising care need. The number of attending and qualified physicians will be stable or even decrease in the next ten years, to rise again after that period. Training of (oncology) nurses and/or paramedics seems to be of help so these can address practical matters and take over some of the workload of physicians. Furthermore, the frequency of routine follow-up might be reduced or partly transferred to the general practitioners (although they will also experience an increasing non-oncology related workload due to the aging of the population).

Special attention should be given to patients from disadvantaged backgrounds. Not only to make sure that women from all socio-economic strata benefit equally from diagnostic and therapeutic progress, but also because co-morbidity (which is more prevalent in lower socio-economic classes) may complicate treatment of these patients.

With advanced age a considerable number of breast cancer patients will also suffer from co-morbidity at the time of cancer diagnosis. These serious other diseases in combination with the high attained age (and thus the frailty) of the patients will complicate standard treatment, so specific guidelines and/or individualisation of treatment is probably necessary. Furthermore, attention should be given to co-morbidity during the follow-up, not only to evaluate the effects on treatment response, but also to study the impact of co-morbidity arising after cancer diagnosis.

The use of population-based cancer registries allows for careful monitoring of trends in cancer incidence, treatment and survival. New diagnostic or therapeutic developments can be evaluated in unselected patients and variation in its use between hospitals or regions can be studied, provided that cancer registration occurs in a standardised way and the delay between diagnosis and registration is not too long, preferably between 6 and 12 months. Many of the parameters that treatment decisions are based on (age, tumour size, node status, tumour differentiation, and estrogen/progesterone receptor status) are already retrieved from the medical records.

Others, such as performance status or patient's preferences are not recorded and could also contribute to better evaluation of guideline adherence and outcome measures. Furthermore, a long-standing population-based cancer registry is an ideal tool for the monitoring of long-term effects, such as multiple primary cancers.

Another important issue, which currently gets more attention, is the quality of life of breast cancer patients. Most studies on long-term survivors reported good overall quality of life,[13] but specific problems like a thick and painful arm, problems with sexual functioning, and specifically among younger women also fatigue were reported among women who survived more than 5 years.[14] Treatment with chemotherapy increased the risk of feeling fatigued even 10 years after diagnosis. Multidisciplinary rehabilitation programs, such as 'Herstel en Balans' ('Recovery and Balance'), might be offered to survivors on a regular basis, especially to those feeling tired. A number of studies concluded that 'Herstel en Balans' could reduce fatigue.[15] The rehabilitation program, which started on a small scale in 1996 is nowadays geographically and financially adequately accessible for all patients with cancer. Referral to this program might need to be improved in order to ensure that every cancer patient in the Netherlands is able to follow a rehabilitation program after treatment.

References

1. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Jama 2002;288:321-33.
2. Gazet JC, Markopoulos C, Ford HT, Coombes RC, Bland JM, Dixon RC. Prospective randomised trial of tamoxifen versus surgery in elderly patients with breast cancer. Lancet 1988;1:679-81.
3. Robertson JF, Todd JH, Ellis IO, Elston CW, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. Bmj 1988;297:511-4.
4. Rubens RD. Age and the treatment of breast cancer. J Clin Oncol 1993;11:3-4.
5. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. Eur J Cancer 2005;41:779-85.
6. Ottevanger PB, De Mulder PH. The quality of chemotherapy and its quality assurance. Eur J Surg Oncol 2005;31:656-66.
7. Griggs JJ, Culakova E, Sorbero ME, van Ryn M, Poniewierski MS, Wolff DA, Crawford J, Dale DC, Lyman GH. Effect of Patient Socioeconomic Status and Body Mass Index on the Quality of Breast Cancer Adjuvant Chemotherapy. J Clin Oncol 2006.
8. Chaudary MA, Millis RR, Hoskins EO, Halder M, Bulbrook RD, Cuzick J, Hayward JL. Bilateral primary breast cancer: a prospective study of disease incidence. Br J Surg 1984;71:711-4.
9. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. Contralateral breast cancer and other second malignancies in patients treated by breast-conserving therapy with radiation. Int J Radiat Oncol Biol Phys 1988;15:277-84.
10. Louwman WJ, van Lenthe FJ, Coebergh JW, Mackenbach JP. Behaviour partly explains educational differences in cancer incidence in the south-eastern Netherlands: the longitudinal GLOBE study. Eur J Cancer Prev 2004;13:119-25.

11. Schrijvers CT, Coebergh JW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer 1997;80:1482-8.
12. SignaleringscommissieKanker, Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. KWF Kankerbestrijding, 2004.
13. Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV. Quality of life among long-term breast cancer survivors: a systematic review. Eur J Cancer 2005;41:2613-9.
14. van de Poll-Franse LV, Mols F, Vingerhoets AJ, Voogd AC, Roumen RM, Coebergh JW. Increased health care utilisation among 10-year breast cancer survivors. Support Care Cancer 2006;14:436-43.
15. Korstjens I, Mesters I, van der Peet E, Gijsen B, van den Borne B. Quality of life of cancer survivors after physical and psychosocial rehabilitation. Eur J Cancer Prev 2006;15:541-7.

Summary

Breast cancer is the most frequent cancer among women in the Netherlands, with over 11,000 new patients every year. Furthermore, it is the most important cause of cancer death among women and at middle age it is the most frequent cause of death, one in every five deaths is caused by breast cancer in this age group. This thesis presents registry-based studies on long-term trends in incidence, mortality and survival of breast cancer, as well as determinants of long-term survival and other aspects of the disease, e.g. second cancer and the use of radiotherapy.

In **chapter 2** we explored long-term trends in incidence, mortality and survival of breast cancer.

We studied the increase in breast cancer incidence according to tumour aggressiveness. The age-adjusted incidence of tumours with a low Mitotic Activity Index (MAI) increased 30% between 1975 and 1988-89, while the incidence of high MAI increased about 20%. For small tumours (T1) the odds for a high MAI decreased over time, whereas for T3 and T4 tumours the odds increased. These results indicated that the incidence of both less aggressive as well as more aggressive tumours increased preceding the mass screening programme, so there appeared to be a real increase in breast cancer incidence (**chapter 2.1**).

This was confirmed in our study of the long-term trends in incidence, mortality and survival. We found a sharp increase in breast cancer incidence since 1975 when mammography was introduced. For women younger than 50, the risk was especially increased in the more recent periods. Considering the recent trends in exposure to known risk factors, the peak in breast cancer incidence is not yet in sight. Mortality rates were stable for decades, but decreased since the early 1990s, especially for women younger than 70. Relative 5- and 10-year survival improved for each stage, and for each age-group. The impressive improvements in survival during the last three decades (taking stage migration into account) in combination with the increasing incidence, imply that the number of prevalent cases will continue to increase considerably in the next ten years (**chapter 2.2**).

Using the data from all Dutch cancer registries combined, the trends in occurrence and outcome of uncommon histological types of breast cancer were studied and also the impact of histological type on survival (**chapter 2.3**). The number of patients with uncommon tumours in the Netherlands has increased markedly since 1989, with about 700-800 new patients every year; for this largely heterogeneous group the incidence lies between those of cervical and ovarian cancer. The less frequent histological types of breast cancer were clearly other entities than invasive ductal carcinoma, as shown by differences in age at diagnosis, stage, and grade distribution. The trend in incidence rates over time was different from that of ductal carcinoma and relative survival rates also differed for the uncommon tumours, with very good survival rates for patients with cribriform or tubular cancer or phyllodes tumour, and poor survival for the lymphomas

and metaplastic tumours. Since all uncommon breast tumours combined comprise about 10% of all newly diagnosed cases, it becomes increasingly desirable to adapt guidelines for these types. Furthermore, communication to patients with these specific subtypes should reflect the very favourable prognosis of certain subtypes.

Chapter 3 of this thesis describes determinants of breast cancer survival.

The mitotic activity index was valuable in predicting long-term prognosis of node-negative breast cancer patients with tumours smaller than 5 cm (**chapter 3.1**). The relative survival among those with a T1 tumour and low MAI (<10) was similar to that of women without breast cancer. Only survival of women with T2 and high MAI (≥10) was significantly lower, so these patients might benefit from adjuvant systemic therapy.

The presence of serious co-morbidity at the time of diagnosis resulted in less extensive primary treatment and poorer survival (**chapter 3.2**). Radiotherapy was administered less often, being replaced by either another surgical procedure (mastectomy instead of breast conserving surgery) or adjuvant hormonal treatment. Survival was significantly worse, independent of age, stage and treatment for breast cancer patients who suffered from a previous cancer, cardiovascular disease, diabetes mellitus, cerebrovascular disease, or dementia, compared with those without these coexistent diseases. The discrepancy in survival between those patients with only breast cancer and those who also suffered from other chronic diseases increased with the rise of age.

Among breast cancer patients aged 50-69 years we investigated the variation in survival according to socio-economic status, before, during and after the implementation of the mass mammography screening programme (**chapter 3.3**). We found that the proportion of breast cancer patients with a low SES has decreased since the introduction of a mass biennial mammography screening programme (with a response rate >80%). Although stage distribution improved for all socio-economic groups, the proportion with advanced disease decreased the most in the highest socio-economic group. In the 1980s survival was similar for all socio-economic groups, but since the introduction of screening the survival of women with a high SES has improved more than that for low socio-economic classes, also after adjustment for age and stage. It seems that women from lower socio-economic strata benefited less from the introduction of the breast cancer screening programme than those with a higher SES, probably due to a higher prevalence of comorbidity and possibly suboptimal treatment (for both the cancer and the concomitant disease).

In **chapter 4** multiple primary cancers and events that arise during the course of the disease are discussed.

During the course of the disease, at least six months after initial treatment and diagnosis, many breast cancer patients are (again) treated with radiotherapy. The cumulative use of radiotherapy in a cohort diagnosed between 1996 and 2000 went from 54% during the first 6 months after diagnosis to 67% during the follow-up until 2005

(**chapter 4.1**). Wide variations existed in both primary and secondary radiotherapy referral, based on age, stage, type of surgical procedure and hospital.

The occurrence of new primary tumours during the long-term follow-up (up to 30 years) of women diagnosed with breast cancer is described in **chapter 4.2**. Women with a history of breast cancer have an elevated risk of second cancer of the breast, ovary, salivary gland, colon, connective tissue and skin, particularly at younger ages. However, an increased risk does not always correlate with a high absolute excess risk and burden for the population. Every year, 115 excess cancers were diagnosed among 10,000 surviving breast cancer patients, predominantly second breast, ovarian and colon cancer.

We also explored shifts in the pattern of causes of death of patients who survived at least 10 years after diagnosis when life expectancy almost normalizes. This is described in **chapter 4.3**. Breast cancer patients diagnosed and treated between 1960 and 1979 who have survived 20 years or more after diagnosis and are presumed to have a normal life expectancy were still at a 5-fold increased risk of dying from breast cancer. Mortality from other causes was lower, except for other cancers and respiratory disease. In this cohort mortality from cardiovascular disease was low.

In **chapter 5** (literature overview and discussion) we describe that the effects of traditional prognostic factors persist in the long term. More recent prognostic factors require a longer follow-up before evaluation. The prognosis of breast cancer patients who have survived at least 10 years is favourable, about 70% in most western populations, and increases over time up to 95%. Improved long-term survival may be achieved by earlier detection, more effective modern therapy and a healthier lifestyle.

With an increasingly aging population and ongoing rising incidence the number of new breast cancer patients will increase and since survival has improved considerably, the number of women alive ever being diagnosed with breast cancer will increase considerably to about 194,000 in 2015. About 80% of these women probably require some form of health care. For an average hospital in the Netherlands this means that in 2015 about 200 newly diagnosed breast cancer patients will require diagnosis and treatment, about 1200 are included in some form of routine follow-up schedule, 115 are treated for recurrences and about 80 for metastasis.

Patients from disadvantaged backgrounds generally do worse. It would be good medical practice that women from all socio-economic strata benefit equally from diagnostic and therapeutic progress, but also because co-morbidity (which is more prevalent in lower socio-economic classes) may complicate treatment of these patients.

At advanced age a considerable and increasing number of breast cancer patients will also suffer from co-morbidity at the time of cancer diagnosis. These serious other diseases in combination with the high attained age (and thus the frailty) of the patients will complicate standard treatment, so specific guidelines and/or individualisation of treatment is probably necessary. Furthermore, attention should be given to co-morbidity

during the follow-up, not only to evaluate the effects on treatment response, but also to study the impact of co-morbidity arising after cancer diagnosis.

The use of population-based cancer registries allows for the evaluation of new diagnostic or therapeutic developments in unselected patients, and variation in its use between hospitals or regions can be studied. Many of the parameters that underlie treatment decisions are already retrieved from the medical records. Others, such as performance status or patient's preferences are not recorded and should also contribute to better evaluation of guideline adherence and outcome measures.

Samenvatting

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen in Nederland met jaarlijks ruim 11.000 nieuwe gevallen. Bovendien is het de belangrijkste vorm van kankersterfte bij vrouwen, op middelbare leeftijd is het de belangrijkste doodsoorzaak, één op de vijf sterfgevallen wordt in deze leeftijdsgroep veroorzaakt door borstkanker. Dit proefschrift beschrijft onderzoek gebaseerd op de kankerregistratie naar de lange termijn trends in incidentie, sterfte en overleving van borstkanker, alsook determinanten van lange termijn overleving en andere aspecten die optreden gedurende het beloop van de ziekte, zoals meervoudige tumoren en het gebruik van radiotherapie.

In **hoofdstuk 2** worden de lange termijn trends in incidentie, sterfte en overleving van borstkanker besproken. De toename in de incidentie van borstkanker werd bestudeerd in relatie tot de agressiviteit van de tumor. De incidentie van tumoren met een lage Mitotische Activiteits Index (MAI) steeg 30% tussen 1975 en 1988-89, de incidentie van tumoren met een hoge MAI, de meer agressieve tumoren, nam met ongeveer 20% toe. Voor kleine tumoren (tot 2 cm) nam de kans dat het een agressieve tumor betrof af in de loop der tijd, voor grotere tumoren (>5 cm of met ingroei in de huid) werd de kans groter dat het een agressieve tumor betrof. De stijgende incidentie (die voorafging aan de introductie van de borstkankerscreening) betrof dus niet alleen de minder agressieve tumoren, maar ook de meer agressieve tumoren namen toe in de loop der tijd. Dit duidt op een reële toename van de incidentie (**hoofdstuk 2.1**).

Dit word bevestigd in de studie naar de lange termijn trend in incidentie, sterfte en overleving. We zagen een sterke toename van de borstkankerincidentie sinds 1975. Wanneer de (trends in de) bekende risicofactoren in ogenschouw worden genomen lijkt de piek in de incidentie nog niet in zicht. De sterftecijfers zijn decennia lang stabiel geweest, maar sinds begin jaren 90 neemt de sterfte af, met name bij vrouwen tot 70 jaar. De relatieve 5- en 10-jaarsoverleving werden gunstiger voor elk stadium, en voor elke leeftijdsgroep. De indrukwekkende verbetering van de overleving gedurende de laatste drie decennia in combinatie met de stijgende incidentie, zal resulteren in een aanzienlijke groei van het aantal prevalente patiënten in de komende tien jaar. (**chapter 2.2**).

Met de gegevens van de Nederlandse kankerregistratie werden de zeldzame histologische types van borstkanker bestudeerd. Gekeken werd naar de trends in incidentie en de relatie tussen de histologie en de overleving (**hoofdstuk 2.3**). Het aantal patiënten met zeldzame tumoren nam toe sinds 1989, tot zo´n 700-800 nieuwe patiënten per jaar. De incidentie van deze heterogene groep tumoren is vergelijkbaar met die van baarmoederhals- en eierstokkanker. De zeldzame tumoren onderscheiden zich van het meest voorkomende ductale carcinoom door een andere leeftijd bij diagnose, en een verschil in stadium en gradering bij diagnose. De relatieve overleving was ook anders, met een uitzonderlijk goede overleving van patiënten met een cribriforme, tubulaire of phyllodes tumour, en minder goede overleving voor patiënten met een lymfoom van de

borst of een metaplastische tumor. Omdat alle zeldzame tumoren tezamen ongeveer 10% van de borstkankers vormen is het belangrijk om de richtlijnen daarop aan te passen.

Hoofdstuk 3 van dit proefschrift beschrijft een aantal determinanten van overleving.

De mitotische activiteits index bleek een prognostische factor voor tumoren kleiner dan 5 cm (**hoofdstuk 3.1**). De relatieve overleving van vrouwen met een kleine tumor (<2 cm) en een lage MAI (<10) was vergelijkbaar met de overleving van vrouwen die nooit borstkanker hebben gehad. De overleving van vrouwen met een tumor van 2-5 cm en een hoge MAI (≥10) was significant lager, dus voor deze patiënten zou adjuvante therapie de overleving wellicht kunnen verbeteren.

De aanwezigheid van andere ernstige aandoeningen op het moment van diagnose van de borstkanker resulteerde in een minder agressieve behandeling en minder goede overleving (**hoofdstuk 3.2**). Radiotherapie werd minder vaak toegepast, vervangen door een andere chirurgische procedure (mastectomie in plaats van een borstsparende behandeling) of adjuvante hormonale therapie. De overleving was significant slechter, onafhankelijk van leeftijd, stadium en behandeling voor patiënten die een eerdere tumor gehad hebben, of die lijden aan hart- en vaatziekten, suikerziekte, of dementie in vergelijking tot borstkanker patiënten zonder bijkomende ziekten. De verschillen in overleving tussen patiënten met en zonder comorbiditeit namen toe met het stijgen van de leeftijd.

De variatie in overleving naar sociaal-economische status (SES) werd onderzocht bij vrouwen van 50-69 jaar oud, waarbij de periode vóór de invoering van de borstkankerscreening werd vergeleken met de periode waarin de screening werd geïmplementeerd en de periode erna (**hoofdstuk 3.3**). Het aandeel van de patiënten met een lage SES werd kleiner na de introductie van de screening. De stadiumverdeling werd gunstiger voor alle SES groepen, maar dit effect was het gunstigst in de hoogste SES klasse. Voorafgaand aan de screening was de overleving van de SES groepen vergelijkbaar, maar na de invoering van de screening verbeterde de overleving van de hoogste SES groep meer dan die van de laagste SES klasse. Het lijkt erop dat vrouwen uit de laagste SES groepen minder profiteren van de introductie van de screening dan zij met een hoge SES, waarschijnlijk door het vaker voorkomen van comorbiditeit en mogelijk door een minder optimale behandeling (van de borstkanker of de bijkomende ziekte)

In **hoofdstuk 4** wordt in gegaan een aantal factoren die te maken hebben met het beloop van de ziekte, zoals meervoudige tumoren en het gebruik van radiotherapie zowel als onderdeel van de primaire behandeling, als later tijdens de ziekte.

Veel borstkanker patiënten krijgen langer dan 6 maanden na diagnose en initiële behandeling opnieuw radiotherapie. Het cumulatieve radiotherapie gebruik in een cohort patenten met de diagnose tussen 1996 en 2000 liep op van 54% in de eerste 6 maanden

tot 67% tijdens de follow-up tot 2005 (**hoofdstuk 4.1**). Er was een grote variatie in de toepassing van zowel primaire als secundaire radiotherapie, afhankelijk van leeftijd, stadium, type chirurgie en ziekenhuis.

In **hoofdstuk 4.2** wordt het optreden van nieuwe primaire tumoren tijdens de borstkanker follow-up beschreven. Vrouwen met borstkanker hebben een verhoogd risico op een nieuw primair mammacarcinoom en kanker van de eierstokken, speekselklier, dikke darm, en huid, met name wanneer de eerste tumor op jonge leeftijd werd gevonden. Maar een verhoogd risico resulteert niet altijd in een groot aantal extra patiënten of een groot risico op populatie niveau. Elk jaar worden ongeveer 115 extra gevallen van kanker gevonden per 10.000 overlevende borstkanker patiënten, met name borst-, eierstok- en dikkedarmkanker.

Het patroon van doodsoorzaken bij borstkanker patiënten die minimaal 10 jaar na diagnose overleefd hadden werd bestudeerd in **hoofdstuk 4.3**. Vrouwen die tussen 1960 en 1979 werden gediagnosticeerd en behandeld hadden na 20 jaar een overleving die vergelijkbaar is met vrouwen zonder borstkanker. Toch was de doodsoorzaak nog vijf keer vaker borstkanker dan verwacht. De sterfte aan andere doodsoorzaken was lager, met name de sterfte aan hart- en vaatziekten.

In **hoofdstuk 5** wordt beschreven dat het effect van de meeste prognostische factoren ook aanhoudt op de lange termijn. De recentere prognostische factoren hebben op dit moment nog onvoldoende lange follow-up om een uitspraak over te kunnen doen. Vrouwen die minimaal 10 jaar na diagnose hebben overleefd hebben een gunstige levensverwachting, die oploopt tot 95%. De lange termijn overleving kan verbeteren door vroegere detectie, effectievere moderne therapie en een gezondere leefstijl.

Gezien de vergrijzende bevolking en de voortstijgende incidentie, zal het aantal nieuwe borstkanker patiënten nog toenemen. Doordat bovendien de overleving flink verbeterd is zal het aantal vrouwen dat ooit de diagnose borstkanker heeft gekregen en nog in leven is sterk toenemen, tot naar schatting 194.000 in 2015. Ongeveer 80% van deze vrouwen doet nog een beroep op een bepaalde vorm van de gezondheidszorg. Voor een gemiddeld ziekenhuis in Nederland betekent dit ongeveer 200 nieuwe patiënten per jaar voor diagnose en behandeling. Daarnaast zullen er ongeveer 1200 opgenomen zijn in een routine follow-up schema, 115 worden er behandeld voor recidieven en ongeveer 80 voor metastasen.

In het algemeen zijn patiënten uit lagere sociale klassen slechter af. Vrouwen uit alle sociale lagen zouden op een gelijk manier moeten profiteren van vooruitgang in diagnostiek en behandeling. Speciale aandacht is nodig voor bijkomende ziekten (die vaker voorkomen in lagere sociale klassen), omdat dat de behandeling van deze patiënten kan bemoeilijken.

Bij het stijgen van de leeftijd neemt het aandeel patiënten dat lijdt aan comorbiditeit toe. De kwetsbaarheid van deze patiënten bemoeilijkt een standaard behandeling, dus specifieke richtlijnen of meer individualisering van de behandeling is

noodzakelijk. Bovendien is het belangrijk aandacht te besteden aan het ontstaan van comorbiditeit na de diagnose, niet alleen om de behandeling van de tumor te kunnen evalueren, maar ook om de invloed ervan op de overleving te kunnen bepalen.

Het gebruik van population-based kankerregistraties maakt de evaluatie van nieuwe diagnostiek en therapieën mogelijk bij ongeselecteerde patiënten. Bovendien kan de variatie in de toepassing tussen ziekenhuizen of regio´s bestudeerd worden. Veel factoren die het behandelingsbeleid bepalen worden al geregistreerd vanuit het medisch dossier. Andere, zoals de functionele status of de voorkeur van de patiënt worden nog niet opgenomen en zouden kunnen bijdragen tot een betere evaluatie van uitkomstmaten en het afwijken of volgen van de richtlijnen.

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Curriculum Vitae

Marieke Louwman werd geboren in Den Haag op 30 december 1971. In 1990 behaalde zij het Atheneum diploma aan het Han Fortmann College te Heerhugowaard. In datzelfde jaar begon zij aan de studie 'Voeding van de Mens' aan de Landbouwuniversiteit Wageningen. Naast een afstudeervak op het gebied van voeding (foliumzuuropname) deed zij 2 afstudeervakken kankerepidemiologie: één met gegevens van de grote Nederlandse Cohortstudie naar voeding en kanker en één bij de afdeling Epidemiologie van het NKI/AvL (relatie radiotherapie en risico op contralateraal mammacarcinoom). In juni 1996 studeerde zij af; op dat moment werkte zij als onderzoeker bij de Vakgroep Humane Voeding, en zij bleef dat doen totdat zij in de zomer van 1997 als onderzoeker ging werken bij het Integraal Kankercentrum Zuid (IKZ) te Eindhoven. Daar verrichtte zij epidemiologisch onderzoek op het gebied van borstkanker, met speciale aandacht voor de lange termijn trends en tumor agressiviteit. Vanaf eind 1999 werkte zij bij het instituut Maatschappelijke Gezondheidszorg van het Erasmus MC, onder andere aan een studie naar het verband tussen sociaal-economische status en kankerincidentie. Vanaf april 2001 is zij opnieuw in dienst gekomen bij het IKZ, toen in de functie van senior-onderzoeker met als aandachtsgebied Public Health. Zij werkte mee aan de rapporten die verschenen ter gelegenheid van het 45- en 50-jarig bestaan van de Eindhovense Kankeregistratie en was betrokken bij een grote verscheidenheid aan landelijke en (multi-)regionale onderzoeksprojecten. Daarnaast verrichtte zij onderzoek op het gebied van borstkanker, determinanten van overleving en factoren die een rol spelen gedurende het beloop van de ziekte. De bundeling van de borstkankerstudies heeft uiteindelijk geresulteerd in dit proefschrift.

Sinds 1991 is zij samen met Ronald Vledder, hun dochter Eline is nu 4 jaar oud.

List of publications

In this thesis

Louwman WJ, van Diest PJ, van Beek MW, Schapers RF, Nolthenius-Puylaert MB, Baak JP, Coebergh JW. Trends in breast cancer aggressiveness before the introduction of mass screening in southeastern Netherlands 1975-1989. Breast Cancer Res Treat 2002;73:199-206. *(Chapter 2.1)*

Louwman WJ, Voogd AG, van Dijck JAAM, Nieuwenhuijzen GAP, Ribot J, Pruijt JFM, Coebergh JWW. On the Rising trends of incidence and prognosis of breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. Submitted *(Chapter 2.2)*

Louwman WJ, Vriezen M, van Beek MWPA, Tutein Nolthenius-Puylaert CJTMB, van der Sangen M, Roumen R, Kiemeney LA, Coebergh JWW. Uncommon breast cancer in persective: incidence, treatment and survival in the Netherlands. Int J Cancer; *In Press (Chapter 2.3)*

Louwman WJ, van Beek MW, Schapers RF, Nolthenius-Puylaert MB, van Diest PJ, Roumen RM, Coebergh JW. Long-term survival of T1 and T2 lymph node-negative breast cancer patients according to Mitotic Activity Index: a population-based study. Int J Cancer 2006;118:2310-4. *(Chapter 3.1)*

Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 2005;41:779-85. *(Chapter 3.2)*

Louwman WJ, van de Poll-Franse LV, Fracheboud J, Roukema JA, Coebergh JWW. Impact of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. Breast Cancer Res Treat; *In Press (Chapter 3.3)*

Vulto JCM, Louwman WJ, Poortmans PMP, Lybeert ML, Rutten HJT, Brenninkmeijer SJ, Coebergh JWW. Radiotherapy for breast cancer patients during the course of the disease: a population based study. Submitted *(Chapter 4.1)*

Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the South of the Netherlands, 1972-2001. Breast Cancer Res Treat 2005;93:91-5. *(Chapter 4.2)*

Louwman WJ, Klokman WJ, Coebergh JW. Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal. Br J Cancer 2001;84:700-3. *(Chapter 4.3)*

Soerjomataram I, Louwman WJ, Roukema JA, Ribot JG, Coebergh JWW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat; *In Press (Chapter 5.1)*

Other publications

Louwman MW, van Dusseldorp M, van de Vijver FJ, Thomas CM, Schneede J, Ueland PM, Refsum H, van Staveren WA. Signs of impaired cognitive function in adolescents with marginal cobalamin status. Am J Clin Nutr 2000;72:762-9.

Louwman WJ, van Dijck JAAM, Coebergh JW. H1 Epidemiologie. In: Handboek mammacarcinoom. Wobbes Th, Nortier JWR, Koning CCE (eds). Utrecht: De Tijdstroom. 2007. pp 13-27.

Louwman WJ, van Lenthe FJ, Coebergh JW, Mackenbach JP. Behaviour partly explains educational differences in cancer incidence in the south-eastern Netherlands: the longitudinal GLOBE study. Eur J Cancer Prev 2004;13:119-25.

Coebergh JWW, Janssen-Heijnen MLG, Louwman WJ, Voogd AC. Cancer incidence, care and survival in the south of the Netherlands, 1955-1999: a report from the Eindhoven Cancer Registry (IKZ) with cross-border implications. Eindhoven: Comprehensive Cancer Centre South (IKZ), 2001.

Crane LMA, Schaapveld M, Visser O, Louwman WJ, Plukker JTM, van Dam GM. Oesophageal Cancer in The Netherlands: increasing incidence and mortality but improving survival. Eur J Cancer, *In Press*

de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. J Invest Dermatol 2004;123:634-8.

de Vries E, Soerjomataram I, Houterman S, Louwman WJ, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of UV-radiation? Am J Epidemiol; *In Press*.

de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005;152:481-8.

Ernst MF, van de Poll-Franse LV, Roukema JA, Coebergh JW, van Gestel CM, Vreugdenhil G, Louwman MJ, Voogd AC. Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002. Breast; *In Press*

Houben MP, Louwman WJ, Tijssen CC, Teepen JL, Van Duijn CM, Coebergh JW. Hypertension as a risk factor for glioma? Evidence from a population-based study of comorbidity in glioma patients. Ann Oncol 2004;15:1256-60.

Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ, Coebergh JW. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer 2004;90:2332-7.

Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Coebergh JW. Age and co-morbidity in cancer patients: a population-based approach. Cancer Treat Res 2005;124:89-107.

Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005;55:231-40.

Janssen-Heijnen ML, Louwman WJ, van de Poll-Franse LV, Voogd AC, Houterman S, Coebergh JW. [Trends in the incidence and prevalence of cancer and in the survival of patients in southeastern Netherlands, 1970-1999]. Ned Tijdschr Geneeskd 2003;147:1118-26.

Janssen-Heijnen ML, Maas HA, Lemmens VE, Houterman S, Louwman WJ, Verheij CD, Coebergh JW. [The correlation of age and comorbidity with therapy and survival in cancer patients in North-Brabant and North-Limburg, 1995-2001]. Ned Tijdschr Geneeskd 2005;149:1686-90.

Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW, Van meten naar begrijpen. 50 jaar kankerregistratie. Integraal Kankercentrum Zuid (IKZ), 2005.

Koppert LB, Janssen-Heijnen ML, Louwman MW, Lemmens VE, Wijnhoven BP, Tilanus HW, Coebergh JW. Comparison of comorbidity prevalence in oesophageal and gastric carcinoma patients: a population-based study. Eur J Gastroenterol Hepatol 2004;16:681-8.

Kuijpens JL, Nyklicek I, Louwman MW, Weetman TA, Pop VJ, Coebergh JW. Hypothyroidism might be related to breast cancer in post-menopausal women. Thyroid 2005;15:1253-9.

Lybeert ML, Louwman M, Coebergh JW. Stable overall referral rates of primary radiotherapy for newly diagnosed cancer patients in the ageing population of South-Eastern Netherlands, 1975-1998. Radiother Oncol 2004;73:101-8.

Lybeert ML, Louwman WJ, Poortmans PMP, Vulto JC, Coebergh JWW. Trends in verwijzingen van patienten voor radiotherapie na de initiele diagnose van kanker in ZXuid-Nederland sinds 1988. Ned Tijdschr Oncol 2005;2:206-11.

Nyklicek I, Louwman WJ, Van Nierop PW, Wijnands CJ, Coebergh JW, Pop VJ. Depression and the lower risk for breast cancer development in middle-aged women: a prospective study. Psychol Med 2003;33:1111-7.

Reedijk AM, Janssen-Heijnen ML, Louwman MW, Snepvangers Y, Hofhuis WJ, Coebergh JW. Increasing incidence and improved survival of cancer in children and young adults in Southern Netherlands, 1973-1999. Eur J Cancer 2005;41:760-9.

Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001. Eur J Cancer 2005;41:2331-7.

Soerjomataram I, Louwman WJ, van der Sangen MJ, Roumen RM, Coebergh JW. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. Br J Cancer 2006;95:393-7.

van Lenthe FJ, Schrijvers CT, Droomers M, Joung IM, Louwman MJ, Mackenbach JP. Investigating explanations of socio-economic inequalities in health: the Dutch GLOBE study. Eur J Public Health 2004;14:63-70.

Voogd AC, Louwman WJ, Coebergh JW, Vreugdenhil G. [Impact of the new guidelines for adjuvant systemic treatment of breast cancer at hospital level]. Ned Tijdschr Geneeskd 2000;144:1572-4.

Vulto A, Louwman M, Rodrigus P, Coebergh JW. Referral rates and trends in radiotherapy as part of primary treatment of cancer in South Netherlands, 1988-2002. Radiother Oncol 2006;78:131-7.

Vulto AJ, Lemmens VE, Louwman MW, Janssen-Heijnen ML, Poortmans PH, Lybeert ML, Coebergh JW. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. Cancer 2006;106:2734-42.

Vulto JC, Louwman WJ, Poortmans PM, Coebergh JW. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999. Eur J Cancer 2005;41:2722-7.

Wieland AW, Louwman MW, Voogd AC, van Beek MW, Vreugdenhil G, Roumen RM. Determinants of prognosis in breast cancer patients with tumor involvement of the skin (pT4b). Breast J 2004;10:123-8.

Wijnhoven BP, Louwman MW, Tilanus HW, Coebergh JW. Increased incidence of adenocarcinomas at the gastro-oesophageal junction in Dutch males since the 1990s. Eur J Gastroenterol Hepatol 2002;14:115-22.