Trends in incidence and prognosis in female breast cancer since 1955

Registry-based studies in south-east Netherlands

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Druk : Elinkwijk b.v. Utrecht

Trends in incidence and prognosis in female breast cancer since 1955
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Trends in incidentie en prognose van borstkanker bij vrouwen sinds 1955
Studies gebaseerd op een kankerregistratie in Zuidoost-Nederland

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 15 maart 1995 om 13.45 uur

door

Hendrik Willem Nab

geboren te Zetten

Promotiecommissie

Promotor	Prof. dr. A. Hofman
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Overige leden	Prof. dr. H-O. Adami
	Prof. dr. F.T. Bosman
	Prof. dr. A.L.M. Verbeek

Acknowledgements

This thesis is a product of a joint research investigation of the Comprehensive Cancer Centre South, Eindhoven (Director Mr. E.L.F. Graafland), and the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam (Head Prof. A. Hofman).

The author acknowledges the collaboration in various phases of this thesis with the Comprehensive Cancer Centre South (J.W.W. Coebergh, MD, PhD, L.H. van der Heijden, BSc, M.A. Crommelin, MD, H.M. Kluck, MD, PhD and M.Th. Verhagen-Teulings, MD); the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam (Prof. A. Hofman, MD, PhD, W.C.J. Hop, MSc and P.G.H. Mulder, PhD); the Department of Radiology, University Hospital Nijmegen (L.J.Th.O. van Erning, PhD, N. Karssemeijer, PhD and J.H.C.L. Hendriks, MD, PhD); the Department of Epidemiology, Catholic University Nijmegen (Prof. A.L.M. Verbeek, MD, PhD).

The studies in this thesis were financially supported by the Dutch Cancer Society (Nederlandse Kankerbestrijding - Koningin Wilhelmina Fonds) (grant IKZ-90-01), the Comprehensive Cancer Centre South (IKZ), and the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam.

Financial support for the publication of this thesis from the Dutch Cancer Society (Nederlandse Kankerbestrijding - Koningin Wilhelmina Fonds), The Comprehensive Cancer Centre South, Eindhoven (IKZ), Rotterdam Medical Research Foundation (ROMERES) and from the Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen) is gratefully acknowledged.

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Contents

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- Nab HW, Crommelin MA, Heijden LH van der, Kluck HM, Coebergh JWW. Breast cancer in south-east Netherlands, 1960 - 1989: trends in incidence and mortality. Eur J Cancer 1993; 29A: 1557-60 (chapter 3.1).

- Nab HW, Beek M van, Crommelin MA, Heijden LH van der, Kluck HM, Coebergh JWW. Toegenomen incidentie van borstkanker in Zuidoost-Nederland tussen 1960 en 1989. Ned Tijdschr Geneeskd 1992; 136: 1765-70 (chapter 3.1).

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Chapter 1. Introduction

1.1 Natural history

1.2 Epidemiology

1.3 The scope of this thesis

1.1 Natural history

Indirect evidence forms the basis of our knowledge of the natural history of human breast cancer. It is assumed that breast cancer starts by subtle molecular changes within a cell, called the induction phase, leading to the creation of a malignant cell. This phase is followed by multiplication and progressive growth of the cancer cell, most often leading to disseminated disease and to the death of the patient.[1]

From clinical observation it can be concluded that the range in growth rates of breast cancer is wide, and probably also the moment and pattern of metastatic dissemination. Some cancers disseminate early, but others may disseminate late or not at all.[2] From serial mammographies it appeared that growth rates, expressed as tumour volume doubling times, ranged from about two months to several years.[3,4] The site of metastasis is also highly variable, as well as the response to therapy.[5] Together, this illustrates the heterogeneity of breast cancer.

1.2 Epidemiology

Assessment of incidence and mortality is an important epidemiologic tool in quantifying the problem that a specific cancer poses to society in general, and to various subgroups of the population, in particular. In addition to knowledge of the absolute occurrence of cancer, differences between populations, and data about time trends, are even more important because they can give rise to hypotheses concerning the etiology and biology of cancer. These data can also be applied to test hypotheses generated by clinical and experimental oncology.[6] Incidence trends with time are of particular interest since they imply changes in exposure to environmental factors. These trends can be used to predict the future magnitude of the cancer problem and to estimate future demands for the prevention, diagnosis, and treatment of cancer in the community.

The natural source of data on the occurrence of cancer has for long been the hospital where most cancer patients were treated. Hospital-based rates, however, always reflect the selection for admission to the hospital. This admission depends on several factors including socio-economic status, distance to the hospital, and level of specialisation of the physicians. Therefore, these rates may not be highly representative for the general population. Trends in incidence are even more difficult to

estimate reliably from these data, because the various factors on which admission to a specific hospital depend can vary over time, thus artificially leading to changes in estimated incidence rates.

A cancer registry aims to cover a population living in a defined area, providing data on morbidity from all types of cancer, during a longer period of time. Such rates can be used for comparison with rates provided by other population-based cancer registries, and also trends can be calculated. Many of these trends in cancer become even more evident when examined in a population-based cancer registry that has been existing for a long time. Currently the oldest cancer registry still in function is the Connecticut Cancer registry, USA, which started in 1935.[7,8] The Eindhoven Cancer Registry is the oldest population-based cancer registry in the Netherlands and collects data on cancer patients since 1955.

Incidence rates

Incidence rates are based on the newly diagnosed cases of cancer and are an important indicator of the amount of cancer experienced by the population. Thus, data from the cancer registries in most countries in Europe and North America show that breast cancer is the most frequent cancer among females in the Western World. The reported incidence of female breast cancer from these cancer registries varies widely throughout the world. For many years, incidence rates have been highest in North America and northern Europe, intermediate in southern Europe and Latin America, and lowest in Asia and Africa.[7,9-11] The highest incidence rates in Cancer Incidence in Five Continents volume VI, for the period between 1983 and 1987, were observed in San Francisco, USA, after age-adjustment according to the World Standard Population being 104 per 100,000 person-years. Other cancer registries in the USA reported rates of mainly between 70 and 100, while rates in Canada were between 60 and 70. Rates in countries in Oceania were about 60, in Central and South America between 25 and 40, and in Asiatic countries mostly between 20 and 30, whereas the only three (north) African cancer registries reported rates between 3 and 10 per 100,000 person-years.

Within Europe in the period 1983-1987 there were striking differences between the northern and western countries with rates between 50 and 80, and the eastern and southern countries, with rates between 30 and 50. In this period, in the Eindhoven

area the incidence rate was 73 and in the Maastricht area it was 68. These rates belong to the highest in Europe. In a report of the Netherlands Cancer Registry breast cancer also appeared to be the most frequent malignancy in Dutch women in the period 1989-1991, involving 32% of all new primary cancers.[12]

Since decades the (age-adjusted) incidence rates of breast cancer have been increasing steadily in most parts of the developed world.[13-17] For example, in Connecticut, the rise was about 1% a year since 1940. The increase in incidence was greatest in countries with the initially lowest rates. In more recent years, steep increases in breast cancer incidence rates have been reported in several Asian and central European countries.[18] Thus, differences in incidence rates between countries have decreased over time.

It should be noted that all the above-mentioned incidence rates included both first and second primary breast cancers. For second primary breast cancer, the population at risk consists of the women surviving a first primary breast cancer, a group whose number is determined by the incidence and prognosis of first breast cancer. Changes in time in incidence, or prognosis of first primary breast cancer, may lead to changes in incidence of second breast cancer and may thus inflate overall incidence rates.

Worldwide, incidence rates rise steeply with age until about 45 - 55 years, the age of the menopause, after which the risk increases much more slowly with increasing age. This decline in the slope of the age-incidence curve is more marked in areas with a low risk of breast cancer than in areas with a high risk; in some countries, such as Japan, breast cancer risk actually decreases after menopause.[7] This phenomenon means that differences in incidence rates are less marked among premenopausal women than they are among postmenopausal women. The marked increase in the youngest birth cohorts in countries with relatively low rates, in particular, might be the cause of the levelling off of the age-specific rates after menopause.[19] In some studies, it was shown that irregularities in cross-sectional age-specific incidence curves resulted from the birth cohort-wise change in risk.[19,20] This indicates that birth cohort-specific rates can be valuable to detect changes in risk.

Detection and treatment

Throughout most of the 20th century, breast tumours were only discovered by physicians on physical examination of patients who had complaints and symptoms. Most of these women had advanced disease at diagnosis, with ulcerated lesions in the breast or with painful axillary lymph nodes.[21,22] The traditional concept was that breast cancer was a local-regional disease to be managed by radical mastectomy. In the 1970s in the Netherlands this therapy yielded to modified radical mastectomy, and since the 1980s, breast-conserving approaches. These techniques, combining surgery and radiotherapy,[23] have provided an alternative to mastectomy in early disease.[24-26] Postmastectomy radiotherapy for node-negative patients was used with decreasing frequency, and systemic adjuvant therapy (cytotoxic and hormonal) was increasingly administered for node-positive patients.[27] Better public education enabled women to practice breast self-examination and faster consult their physician in case a suspicious lump was discovered, leading to earlier detection of the disease.[28] During the past 20 to 30 years physicians have been gaining experience how to diagnose this cancer at an early stage, even before physical signs and symptoms become evident. This also changed patients' expectations with regard to the operation and the prognosis.

Early detection has become an important aspect of current breast cancer management, which has been greatly facilitated by the introduction of many new diagnostic techniques, such as mammography, echography and fine needle aspiration biopsy.[29-31] In south-east Netherlands, mammography was gradually introduced between 1972 and 1979, and cytology between 1979 and 1986.[32] Mammography today is capable of detecting breast tumours which are not apparent by physical examination. There was a steady reduction in the amount of radiation given, without decreasing imaging capacities. Screening mammography for breast cancer was started in a part of the region covered by the Eindhoven Cancer Registry in 1991. The value of mammography for early detection in recent years has been enhanced by technical advances in the mammographic systems. They consist of better imaging of breast tissue, improvements in film quality and processing, and refined techniques of imaging.

The development of sophisticated digital radiographic systems has created interest in the possibilities with computer-aided diagnosis in radiology.[33] Digital mammograms can be sent anywhere electronically, allowing speedy communication between departments.[34] Furthermore digital mammograms are ready for computerized enhancement

procedures for improving the visibility of abnormalities,[35,36] or by automatic detection procedures,[37] which may be particularly helpful in large scale use.[38] Some studies have indicated the potential of digital radiography as a procedure to improve the detection performance of radiologists for microcalcifications in mammograms.[39,40] An important issue for future prospects of digital mammography is the question whether high resolution digital mammography degrades the detectability of tumours and microcalcifications as compared to conventional mammography.[41-43]

For most of this century women with breast cancer have been treated with radical mastectomy or modifications of that procedure. Notable changes have occurred, and now breast conserving therapy can be applied in early disease. Orthovoltage radiotherapy was replaced by megavoltage radiotherapy, because of the latter's ability to achieve comparable results with shorter treatment and fewer complications. Hormonal and cytotoxic therapy were introduced, first for treatment of advanced disease. Before the mid-1970s, postoperative adjuvant systemic therapy was not used in the Netherlands; now it is a major component of treatment strategies, and the adjuvant supportive care improved e.g. by better management of (postoperative) thrombosis and infections.[44] Although some of these changes probably had a positive impact on the outcome of the disease, there are only few reports on improved survival rates for breast cancer in the general population. This is especially true for long-term survival. Because of earlier detection over time, with an inherent improvement of the prognosis, it is important to control for the influence of tumour stage on outcome when assessing improvements in prognosis in time. In most population-based studies, regarding long-term survival, this was not possible because the stage of the disease was not known to a satisfactory extent to the registry.

Prognosis

Since 1973, the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, collects data on cancer patients of nearly 10% of the population of the United States. In this patient group, five-year relative survival rates varied from 93% for patients with localized disease, 71% for regional disease and 18% for patients with distant metastases at diagnosis.[45]

In many studies it appeared that as the primary tumour size increases, survival decreases, regardless of lymph node status; and as lymph node involvement

increases, survival status also decreases regardless of tumour size. The TNM stage probably combines the most powerful and widely used prognosticators.[46-51] There is an abundance of other known or suspected prognostic indicators of patients or tumour characteristics for disease recurrence.[52,53] Their prognostic power has often been well assessed in groups of patients, but remains limited.[46,52-55] Methods to derive prognostic information by measuring several factors together, in most cases offer limited additional information.[56-58] In contrast to factors to predict short-term survival, little attention has been given to evaluation of factors that predict survival among patients who have survived a longer time following the primary diagnosis.[59-61] The identification of the time interval during which prognostic factors have their greatest influence has importance since this determines their practical value during the follow-up, and may also add to knowledge on the related biological mechanisms.

Although it is customary to report recurrence and survival data in breast cancer at 5- and 10-year follow-up intervals, long-term follow-up studies show that breast cancer may recur more than a decade after it has been initially diagnosed. Despite relatively favourable 5- and 10-year survival rates, in many studies 75 to 90% of all deaths that occurred in women with a diagnosis of breast cancer were actually caused by this disease.[62,63] The long-term risk for a recurrence makes the question of curability important. Some researchers consider breast cancer as a disease that can not be cured,[64-66] while others think that a cure is possible after a long enough period.[67,68] This issue is also important because of the advisability of a life-long follow-up.

Mortality

In the 1980s the highest breast cancer mortality rates (age-adjusted according to the World Standard Population) were observed in North Western Europe, with rates between 20 and 30 per 100,000 person-years, being lowest in Scandinavia and a few southern and eastern European countries.[69,70] Both in the USA and Canada, with the highest incidence rates, mortality rates are somewhat lower. In contrast, in almost all African and Asian countries mortality rates have been very low (i.e. between 3 and 13 per 100,000 person-years).[70-72] Considerable upward trends in mortality rates were observed in many of the countries where they were initially relatively low, whereas they remained almost unchanged, or only slightly increased in countries with relatively high rates.[13,16]

1.3 The scope of this thesis

In this thesis it is tried to describe and interpret the changes in incidence and prognosis of breast cancer in south-east Netherlands in the last three decades. These trends give insight in the occurrence of and death due to breast cancer, and may point to etiologic factors. Birth cohort analyses were included to identify putative risk factors affecting women of a certain age group in a certain time period. The rates in the youngest birth cohorts may also give a sensitive indication for future trends. The validity of the estimated incidence and mortality rates will be discussed.

Digital mammography is a potentially promising new technique for visualisation. In a separate study, detectability of breast cancer by digital mammography was compared with conventional mammography to explore the possibilities with this new diagnostic tool.

The short-term and long-term prognosis of breast cancer was investigated, and the influence of age and stage at diagnosis, and period of diagnosis on survival was assessed. This was done within different intervals of follow-up, to identify the time interval during which prognostic factors have their greatest influence. It was attempted to determine whether and when patients with breast cancer could be considered cured. Additionally, long-term survival and prognostic factors were studied in a group of carefully staged and documented patients in a large local general hospital.

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Chapter 2. Patients and methods

2.1 The Eindhoven Cancer Registry

2.2 Assessment of incidence, mortality and survival

2.3 Comparison of conventional and digital mammography

2.1 The Eindhoven Cancer Registry

History

In the early 1950s in the Netherlands, recognition emerged of the need for national cancer morbidity statistics in addition to mortality data. An ambitious approach was developed to create a national cancer registry with the voluntarily cooperation of all specialists in the hospitals. In 1955 the Eindhoven Cancer Registry (ECR) started as the cancer registry of the Radiotherapy Institute in the city of Eindhoven, and in many other places cancer registries began functioning. In the first years of the ECR the clinical data of new cancer patients were recorded in three hospitals in the city of Eindhoven. In 1960 close cooperation developed with the local pathologists, who reported all newly diagnosed cancer patients to the registry. There was a gradual increase in the number of participating hospitals.

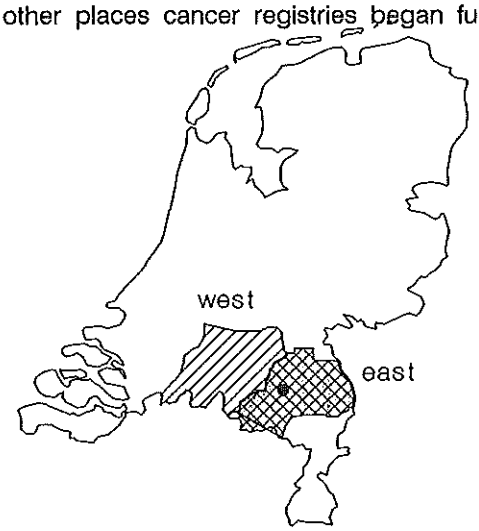

Figure 1. *The area covered by the IKZ in 1989. The dot represents the city of Eindhoven. Only data of the eastern part (ECR) was included in the studies.*

In the first years, the aim of the registry was mainly to collect data on patients with cancer that would serve as a basis for study of the prognosis in unselected patients. Tumour characteristics of every new patient were collected, and a follow-up system was introduced. The aim was to provide reliable morbidity statistics for the presentation of therapeutic results. It was also aimed to assess accurate incidence rates, which was stimulated by the International Association of Cancer Registries and the International Agency for Research on Cancer in Lyon, France. Thus, the achievement of completeness became increasingly important.

After some years this concept appeared to be too ambitious. Only in a few places was registration almost complete, and few studies were done using the available data. It became apparent that it was impossible to register all variables that were needed for the many research questions. In 1969, this resulted in a reorganisation of the cancer

registries. From then completeness was aimed for only the registries of Den Haag, Rotterdam, Friesland, and the region covered by the Eindhoven Cancer Registry.[1] The follow-up of the patients by the registry was cancelled. In 1974 the three other existing regional population-based cancer registries were terminated, leaving the ECR as the only population-based cancer registry in the Netherlands.

In the early 1970s 13 hospitals participated in the Eindhoven Cancer Registry. The department of radiotherapy in Eindhoven was responsible for its functioning until 1979. In 1979 the Association of Cooperating Hospitals in Oncology (SOOZ) was established, as the beginning of a comprehensive cancer centre, which now guaranteed and supervised the activities of the Eindhoven Cancer Registry. In 1982 it became a part of the newly founded Comprehensive Cancer Centre South (IKZ, Figure 1). The aim of the IKZ is to improve care for cancer patients in the province of North Brabant and northern Limburg. Besides cancer registration, it hosts tumour study groups, and coordinates regional activities on cancer prevention, screening, postgraduate education and psychosocial care. The Comprehensive Cancer Centre South is one of the nine regional comprehensive cancer centres in the Netherlands. Since 1989 the nine regional comprehensive cancer centres in the Netherlands have established a national cancer registry.

Population at risk

Between 1955 and 1969 the registry covered about 15 municipalities in the neighbourhood of the city of Eindhoven, with approximately 300,000 inhabitants. Since the 1970s the covered area consisted of south-east North Brabant and the middle and northern part of the province Limburg. This area remained largely unchanged thereafter, with the exception of the middle of the province Limburg, which has been covered by the cancer registry of Limburg (IKL) since 1988. In 1989 the covered area by the ECR had increased to 51 municipalities with about 1 million inhabitants. Since 1988 the IKZ also covers the western part of the province Brabant; resulting in a total covered population of about 2.2. million people. There was a gradual increase in the number of older women, and after about 1965 a marked decrease in the number of children, resulting in a noteworthy aging of the population (Figure 2).

Registry procedures

The cancer registry receives notifications of newly diagnosed cases from the pathology departments in the region. In addition, secretariats of departments of surgery and other hospital departments and the regional radiotherapy institute voluntarily notify the registry when a cancer is diagnosed. Data are derived from the medical records of the newly diagnosed patients during regular visits to the hospitals and from the regional radiotherapy institute. Then the relevant information for the cancer registry is copied on registration forms from the patients' files by trained registration personnel of the registry. The sources of information on cancer patients have been the same since 1955.

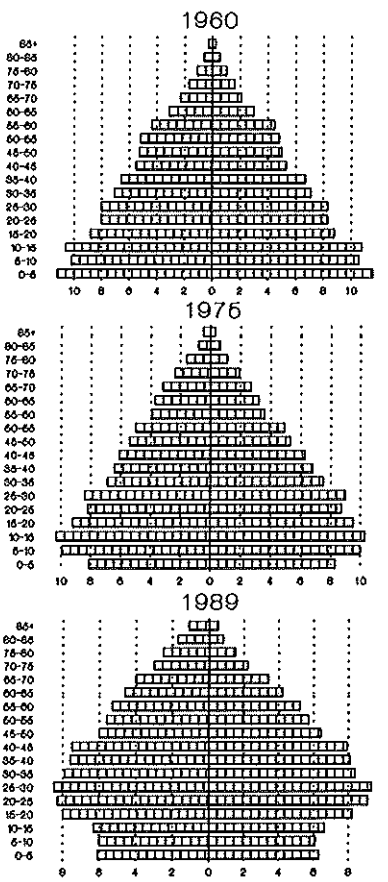

Figure 2. *Percentages of females (l) and males (r) in se Netherlands by 5-year age group in three different years.*

Individuals are uniquely identified in the registry. The registry can be considered as a regional pooled archive of all cancer patients. Coding of the reported diseases was done by the registry's staff according to the international Classification of Diseases (ICD). Since 1955 the 7th Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO, 1952) was used. The 8th (WHO, 1965) and 9th (WHO, 1977) revision came into effect in later years, and since 1988, the International Classification of Diseases for Oncology (WHO, 1976) has also been used. The registry maintains a centralized continuously updated record for every cancer case, where the data of the multiple sources are brought together. Completeness of records, data consistency and the possibility of duplicate records are often checked; since 1987 also with computer programs. Inclusion was attained in Cancer

Incidence in Five Continents, Volume V and VI.[2,3] In order to assess the clinical management of patients with breast cancer as related to treatment guidelines, in 1984 a "Documentation Project" regarding breast cancer was initiated by the "Regional Breast Cancer Study Group".

2.2 Assessment of incidence, mortality and survival

Incidence and mortality

For data about patients, used for the investigations in this thesis, registration methods were analyzed. All diagnoses of cancer, whether microscopically confirmed or not, were included as incident cases. Incidence rates of first primary breast cancers were calculated by municipality, and compared with rates in the city of Eindhoven. A core area was defined, which was gradually extended in later periods. Information on the size and composition of the population, subdivided into age, sex and municipality was derived yearly from the department of Population Statistics of the Dutch Central Bureau of Statistics (CBS). The CBS has a system of continuous population enumeration, based on population registers in the different municipalities. Regional mortality rates were obtained from the cause of death register at the CBS. Overall (crude), and age-specific incidence and mortality rates were calculated.

As age is the single most important determinant of risk for cancer, valid comparison of rates between areas or between different periods of diagnosis can be hampered if the age structure of the populations in areas differ. To overcome this problem, age-standardization was undertaken, according to the direct method, with the "World Standard Population", as reference population.[4]

Incidence rates by year of diagnosis imply that the population at a given time consist of several birth-year cohorts. The trend in observed rates could well reflect some characteristic which is not related to the time-period but, instead, to different exposures of the cohorts living during that period. Furthermore, incidence rates by year of diagnosis may be more influenced by changes in detection and in registry procedures than are birth cohort-related patterns. The latter may be more likely to reflect true changes in disease risk,[5-7] and it is thought that when strong environmental factors are responsible for changing risk they generally affect successive birth cohorts.[8]

One would therefore like to assess the degree of risk due to age, year of birth and year of diagnosis or death. Year of birth, age at diagnosis and year of diagnosis, however, are closely related in that when any two of them are known, the third can be determined. This correlation among the factors is a major source of difficulty in trying to interpret the effect of each of these factors on cancer incidence. This limitation is often called the identification problem. Discussion has centred on methods to estimate the linear effects of the variables age, period and cohort simultaneously by using some arbitrary constraints, without reaching consensus.[9-14]

In this thesis an alternative analysis was used to study birth cohort-related trends of breast cancer incidence. A time-trend in incidence rate was assessed based on age at diagnosis and year of diagnosis, and birth cohort deviations from this trend were determined.

Survival

The observed survival rate in a patient group accounts for all deaths, regardless of cause. While this is the true reflection of total mortality in the patient group, the main interest usually focuses on a specific disease of the patients, and some of the patients die from other diseases; particularly in older age groups. Thus, for reasons not necessarily related to the disease of the patients, the observed survival rates of old and young patients are not comparable. Whenever reliable information is available on cause of death, a correction can be made for deaths due to causes other than the disease under study. Patients who died from other causes are thus considered as withdrawn from the risk of dying from the disease. The resultant is now called the disease-specific survival, or net survival. The gap between the observed and disease-specific survival represents mortality due to other causes. In this thesis one study is included based on data of patients diagnosed in a general hospital, the Sint Joseph Hospital in Eindhoven (now Veldhoven), in which causes of death were carefully traced, making it possible to calculate disease-specific survival. Also the date of diagnosis of a recurrence was registered, and considering recurrence as an event, recurrence-free survival could be estimated.

As in many other cancer registries, causes of death are unknown in the Eindhoven Cancer Registry and, therefore, it is impossible to calculate disease-specific survival rates. In order to eliminate the effect of mortality from other diseases on survival rates,

relative survival rates were calculated. A relative survival rate has been defined as the ratio of the observed survival rate in the patient group to the expected survival rate. The expected survival rate is calculated in a group similar to the group of patients at the beginning of the interval with respect to all possible factors affecting the survival, except the disease under study. The relative survival rate may be interpreted as the survival rate of the patients when mortality due to other causes has been eliminated as a cause of death.

Observed survival rates were calculated with the actuarial method.[15] Expected survival rates were calculated from life tables supplied by the Netherlands Central Bureau of Statistics, compiled according to 5-year age groups and year of diagnosis for the regional female population. The expected survival rates were estimated using the method of Hakulinen,[16] with Chiang's approximation.[17]

Multivariate regression analyses, according to Cox and Hakulinen were used to estimate the relative risks for events and deaths in the various groups,[18,19] and to detect whether the effects were the same in the various intervals of follow-up. The multivariate model from Hakulinen will be further explained in the analyses.

2.3 Comparison of conventional and digital mammography

In comparing two sets of mammograms it may be found that the radiologists's responses in one series yield both true-positive and false-positive frequencies which are greater than those elicited by the other. It is possible that these differences are due to differing detectability of malignancies on the mammograms. However, it is also possible that the higher true-positive and false-positive fractions are the result of a tendency to 'over-read' by the observer, which can be explained by a lower confidence threshold for one series of mammograms than for the other.

The Receiver Operating Characteristic (ROC) curve is a method of analysis which separates these two factors, by plotting the true-positive fraction against the false-positive fraction as the confidence threshold is varied.[20,21] This analysis describes the disease detectability that is independent from both disease prevalence and decision threshold effects.

A ROC study was performed to objectively compare the detectability of tumours and microcalcifications on conventional mammograms with digital mammograms. For this purpose two sets of images were collected: one of tumours and the other set of

microcalcifications. All mammograms were selected from the archive of the Dutch National Expert and Training Centre for Breast Cancer Screening. Mammograms were digitized and displayed on a high resolution monitor with the possibility to enhance contrast.

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Chapter 3. Incidence and early detection

3.1 Breast cancer in south-east Netherlands, 1960-1989: trends in incidence and mortality*

Abstract

Temporal trends in incidence and mortality in breast cancer were examined in south-east Netherlands using data from the population-based Eindhoven Cancer Registry. In the period 1960-1989 the incidence rate of first primary breast cancer approximately doubled in all age groups. The increase mainly occurred before 1975 and after 1985, when no screening activities were performed. This trend appeared to be a result of an average yearly increase in incidence of localised and distant tumours with both 4.6%, whereas the incidence of regional tumours did not change. Simultaneously, breast cancer mortality remained unchanged in women aged under 60, and only increased by a yearly average of 0.7% in women aged 60-74 and of 0.9% in women aged 75 and over. These differing trends in incidence and mortality, which can only partially be explained by earlier detection, suggest an improved survival of breast cancer.

* Nab HW, Voogd AC, Crommelin MA, Kluck HM, Heijden LH van der, Coebergh JWW. Breast cancer in south-east Netherlands, 1960 - 1989: trends in incidence and mortality. Eur J Cancer 1993; 29A: 1557-60

Introduction

The incidence of breast cancer in females shows a large variation between countries, with the highest rates in North America, Australia and northwest Europe, and the lowest rates in Africa, Asia and the Middle East.[1] In northern European countries age-adjusted incidence rates are almost twice those of southern and eastern Europe.[1] It is well documented that the incidence of female breast cancer has increased in many countries over the past decades.[2,3] In Europe the geographical variation in breast cancer mortality has become smaller since the 1950s, because rates have increased, especially in countries with initial low rates.[4]

We investigated temporal trends in incidence and mortality in breast cancer in an unscreened population in south-east Netherlands between 1960 and 1989 using the population-based Eindhoven Cancer Registry. We differentiated between first and second primary breast cancers, and between invasive tumours and ductal carcinomas in situ (DCIS), as a precursor of invasive breast cancer.[5]

Subjects and methods

Data used for this study came from the Eindhoven Cancer Registry, which was founded in 1955 and became part of the Comprehensive Cancer Centre South in 1983. The registry covered a growing area; between 1960 and 1969 it consisted of 15 municipalities with approximately 300,000 inhabitants. In 1989 it had increased to 51 municipalities with about 1 million inhabitants in an area of 2500 km^2. The data were derived from copies of the pathologist's reports, from the patient records in the community hospitals and from the regional radiotherapy institute. Since 1975, data on patients with in situ tumours were also registered. Registration methods remained unchanged during the study period, although coding became more refined. Both in old and new municipalities covered by the registry completeness could be assumed from analyses of referral patterns and registration procedures as well as various comparisons of incidence, for instance with cancer mortality. The composition of the population, subdivided into age, sex and municipality was derived yearly from the department of Population Statistics of the Dutch Central Bureau of Statistics (CBS). Regional mortality rates were obtained from the cause of death register at the CBS.

Data on all new patients with primary breast cancer were analyzed since 1960, when all patients with cancer were reported by local pathologists to the registry.

Stage at diagnosis was recorded on basis of clinical examination, supplemented by the pathologist report. Stage was classified into three categories: localised, if the cancer was confined to the breast regardless of size; regional, if it passed the bounds of the breast, remaining in its immediate neighbourhood, or to the regional lymph nodes; distant, if it involved tissues beyond those immediately draining or neighbouring the breast.

Contralateral breast cancer and ipsilateral breast cancer differing in histology from the previous breast cancer and diagnosed more than two months after the first, were considered as a second primary.

Annual crude rates were computed per 100,000 person-years with the regional female population as denominator, and age-specific rates for the age groups 30-44, 45-59, 60-74 and 75 years and over. Stage-specific trends in incidence were calculated, assuming that patients with unknown stage had a similar stage distribution as patients with a known stage in the same year. Age-adjustment was performed by direct standardisation according to the World Standard Population (WSR: World Standardized Rate).[1] For the display of time-trends 3-year running averages were used. For comparison reasons, incidence rates of second primaries were also calculated per 100,000 person-years. To reduce the chance that previous (first) breast tumours would be unknown at the registry these rates are given only since 1965. The trend in incidence of second primary DCIS was displayed as a five-year running average because of small numbers. To summarise a trend in incidence- or mortality rates, a linear regression line was fitted to the data, and the slope of the line expressed in terms of the average yearly percentage change. A p-value for the significance of the slope of the line was calculated.

Results

Incidence and stage distribution of first primary breast cancer

Between 1960 and 1989, 7169 patients developed a first primary invasive breast cancer. The mean age at diagnosis increased from 57 years in the 1960s to 60 years between 1985 and 1989. The crude incidence rate of first primary breast cancer increased from 35 per 100,000 in 1960-1961 to 93 in 1988-1989, age-adjusted from 37

in 1960-1961 to 70 in 1988-1989. Three periods can be recognized: a fairly constant increase between 1960 and 1973, a plateau between 1974 and 1983 and a sharp increase after 1983. The average yearly increase in incidence was 2.0% for both age groups 30-44 and 45-59, 1.7% for age group 60-74 and 2.4% for age group 75 years and over (p-values < 0.001) (Figure 1).

Stage at diagnosis was unknown for 4% of the patients in 1960-69, for 11% in 1970-79 and for 4% in 1980-89. The incidence rates of both localised and distant tumours increased with an yearly average of 3.6% ($p < 0.001$), whereas the incidence rate of regional tumours did not significantly change ($p = 0.5$). This resulted in a marked increase in the percentage of localised tumours from 37% in the 1960s to 54% in the 1980s and of distant tumours from 4% to 7%, whereas the percentage of regional tumours decreased from 59% to 39%. There was a significant trend towards a more favourable stage with time (chi-square for trend: $p < 0.001$), which continued in the 1980s.

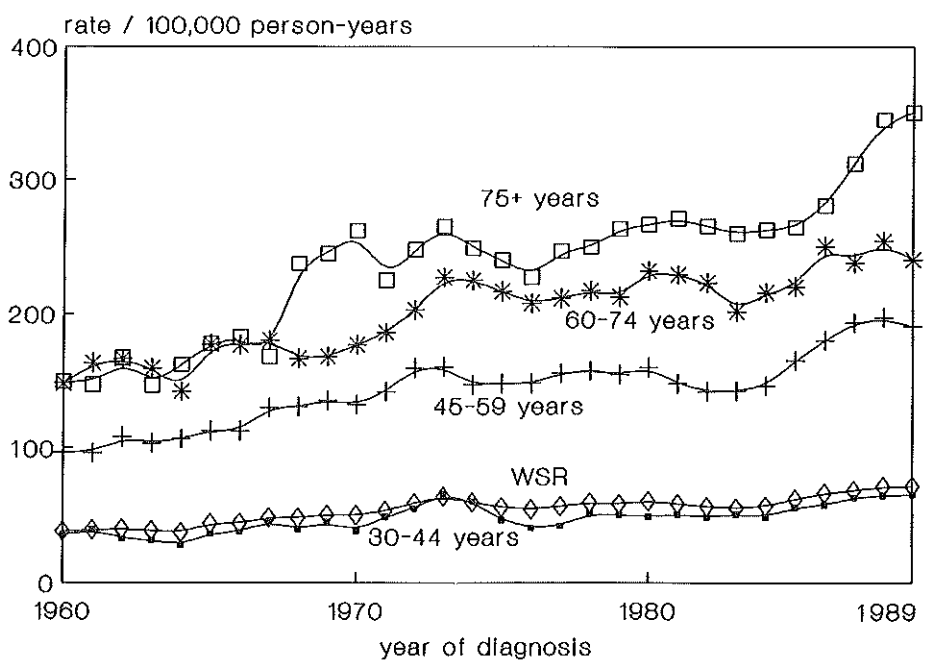

Figure 1. *Age-specific incidence rates per 100,000 person-years in south-east Netherlands*

Incidence of second primary breast cancer and DCIS

Between 1965 and 1989, 414 second primary invasive breast cancers were detected. The age-adjusted incidence rate increased gradually from 1.7 per 100,000 in 1965-1966 to 5.8 in 1988-1989. Between 1975 and 1989, 91 DCIS were detected as a first primary, and 11 as a second primary. The age-adjusted incidence of first primary DCIS increased from 0.2 per 100,000 in 1975-76 to 2.1 in 1988-89 ($p < 0.001$), and of second primary DCIS from 0.05 in 1975-79 to 0.3 in 1985-89.

Mortality

Since 1960 there was no significant trend in breast cancer mortality in women aged under 60 years, whereas for age group 60-74 an average yearly increase of 0.7% occurred ($p = 0.047$), and of 0.9% for age group 75 years and over ($p = 0.03$) (Figure 2). Breast cancer mortality showed a peak in all age groups in the mid-1970's,

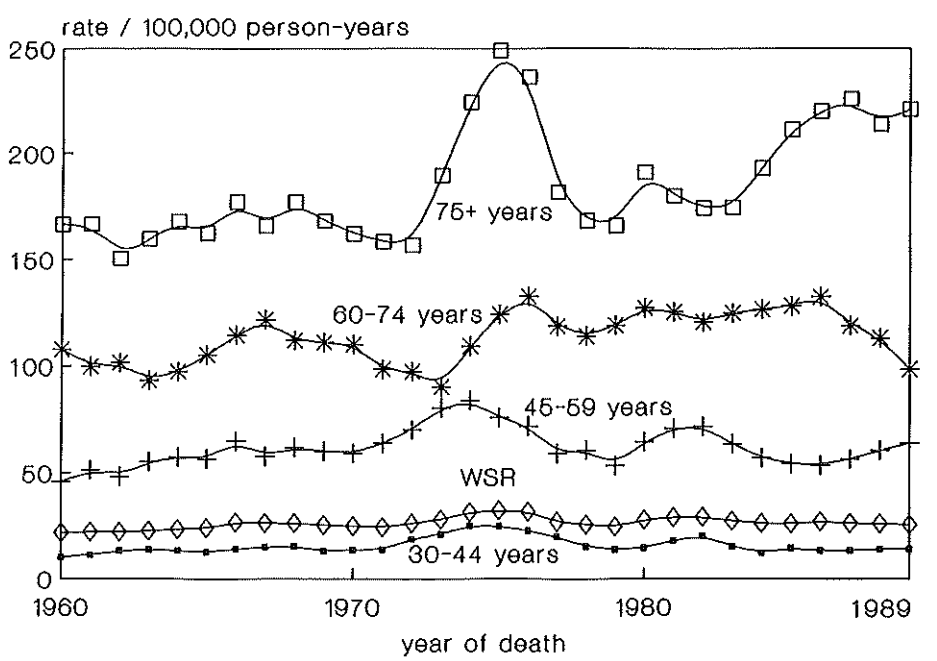

Figure 2. *Breast cancer mortality in south-east Netherlands per 100,000 person-years in four age groups*

and a sharp increase in the oldest age group in the last 5 years of the study period (1985-89). Age-adjusted breast cancer mortality increased from 21.8 per 100,000 in 1960-61 to 25.4 in 1988-89 ($p = 0.046$). Simultaneously, total female mortality decreased considerably with 20 to 40% in the various age groups ($p < 0.001$); age-adjusted from 588 to 367 per 100,000. Breast cancer as a cause of death increased in all age groups, mainly in women aged 75 years and over, although in this group only 2-3% of total mortality was due to breast cancer.

Discussion

As in many other countries in Europe, the incidence rate of breast cancer in south-east Netherlands has increased, at least since 1960, and approximately doubled in every age group. It can be accounted for by an increase in localized and distant tumours, whereas incidence rates of regional tumours levelled. Simultaneously, breast cancer mortality remained almost unchanged (except for women of 75 years and over). The marked decrease in deaths due to other causes, however, made breast cancer proportionally a more important cause of death.

Some under-registration may partly explain the increase in incidence in the oldest age group in the 1960s, although the markedly increased breast cancer mortality rate affirms this trend. A more accurate registry can probably not be the reason for the overall increase in incidence, because cooperation with surgeons, pathologists and radiotherapists has always been very good. Furthermore, the period 1955-59, in which under-reporting was probably highest, was excluded from the study.

Among the risk factors the higher age of women at first birth, a lower fertility rate, earlier menarche, delayed menopause and use of exogenous oestrogens and contraceptives may be involved.[6-9] However, the changes of these risk factors would rather explain the increase in women under 60 years and not the increase in the elderly. The increase in incidence of second primary breast cancer can largely be explained by the increasing number of women alive with a first primary.

In the study region mammography was gradually introduced between 1974 and 1978 and cytology between 1979 and 1987, making earlier detection possible. Although stage at diagnosis gradually became more favourable it is unlikely that earlier detection can explain the fairly continuous increase in incidence, because a large part of the increase would then be temporary.[10] Furthermore, the increase in

incidence of localized tumours did not lead to a decrease of tumours in higher stages, and mortality did not decrease.

Due to better detection modalities and the increasing number of patients with axillary lymph node dissection, gradually more lymph nodes were detected, leading to higher registered stages in actually unchanged tumours.[11,12] This affirms the trend towards earlier diagnosis, which may be attributed to better diagnostic techniques and to the growing awareness in women of the significance of breast lumps.

The differing trends in incidence and mortality, can partly be explained by earlier detection and suggest an improved survival, which is possibly due to better treatment results.[13] Furthermore, current diagnostic aids may also enable detection of slower growing tumours which previously would remain undetected.[14,15]

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3.2 Is the peak in breast cancer incidence in sight? A study conducted in south-east Netherlands*

Abstract

Breast cancer is the most frequent malignancy in the Western World, and increases in the incidence have been observed worldwide. We investigated temporal trends in breast cancer incidence in south-east Netherlands between 1960 and 1989 by birth cohort analysis, using data of the Eindhoven Cancer Registry. An overall time-trend in incidence rate was estimated, based on age and year of diagnosis. Rate ratios were calculated, as the ratio of the observed versus the expected incidence rates, which was based on the estimated time trend. In this unscreened population the age-specific incidence increased for every successive birth cohort in the period 1880-1949. Women born between 1940 and 1949 had the highest age-specific incidence rates with an excess of 10% (RR 1.10, 95% CI 1.01-1.22). The incidence rates in women born after 1949 declined and were 21% lower than expected by the estimated secular trend (RR 0.79, 95% CI 0.64-0.96). This decrease in women aged under 40, suggests that the peak in incidence of female breast cancer may be in sight. It remains unclear which risk factors are responsible for this changing trend.

* Nab HW, Mulder PGH, Crommelin MA, Heijden LH van der, Coebergh JWW. Is the peak in breast cancer incidence in sight? A study conducted in south-east Netherlands. Eur J Cancer 1994; 30A: 50-2

Introduction

Breast cancer is the most common form of cancer in women in industrialised countries,[1] and an increasing incidence has been reported in both industrialised and developing countries.[2-5] In the Netherlands the incidence rate is among the highest in Western Europe.[1] Temporal changes in the incidence of breast cancer, and especially birth cohort-related changes in incidence may point to etiologic factors that affected a specific age-group at a certain period and indicate future trends. Using data of the Eindhoven Cancer Registry, we investigated trends in breast cancer incidence rates by a birth cohort analysis in south-east Netherlands, over the period 1960 -1989.

Materials and methods

The population-based Eindhoven Cancer Registry has collected data of all cancer patients in south-east Netherlands since 1955. We analyzed trends in the incidence rates of first primary invasive female breast cancer diagnosed between 1960 and 1989 by a birth cohort analysis. Age-specific incidence rates were calculated by year of diagnosis and by 10- and 20-year birth cohort since 1880. There is no consensus, in analyzing temporal trends, whether the linear effects of the variables age, period and cohort are identifiable,[6-11] and, therefore, we estimated an overall time-trend in the incidence. Observed incidence rates by birth cohort were compared with predicted rates, based on the estimated time-trend in the whole study period.

Registry

Data on first primary breast cancers were obtained from the Eindhoven Cancer Registry,[1] which was founded as a hospital-based registry in 1955, and became population-based in 1960. From 1960 to 1969 the area of registration was the south-eastern part of the Dutch province of North Brabant, and it has been extended to the northern part of the adjacent province of Limburg since 1970, now covering about 1 million residents. The registry is routinely informed of newly diagnosed cases of cancer by pathology laboratories, the regional radiotherapy department and hospital medical archives in the community hospitals. Data are collected from medical records by the registry staff during regular visits to the hospitals. Referrals to specialised clinics outside the region are traced.

The present material comprises 7,106 cases of first primary breast cancer diagnosed in women aged 20-89 years during the period 1960-89. All histologic types are included, with the exception of precancerous or in situ lesions. The composition of the population, subdivided into calendar year, 5-year age groups and municipality, was derived from the department of Population Statistics of the Netherlands Central Bureau of Statistics.

Data analysis

Poisson regression analysis was used to study trends in incidence, with the observed number of patients taken as a Poisson variate. The expected number of patients was considered as a log-linear function of a number of potential predictors, calculated from year and age at diagnosis. In this function the logarithm of the number of women at risk served as offset. The relevant predictors were forwardly selected by means of likelihood ratio tests in a maximum likelihood estimation procedure. For each year of diagnosis and age, residuals were calculated as the difference between the observed and predicted number of cases. These values were checked for overdispersion with respect to the Poisson variation around the predicted number of cases. We examined whether the residuals showed a systematic pattern with the predictors, indicating that some alternative model could provide a better data description. Model parameters were selected on the basis of the significance of their contribution to the model and on the basis of residual analyses. Dummy variables were defined to indicate birth cohorts (of 10 and 20 years) between 1880 and 1969, and tested for their contribution to the selected model by means of likelihood ratio tests. In this way a time-trend in incidence rate was assessed and rate ratios between the observed and expected rates for every birth cohort were calculated. A separate analysis was performed on data of women under 50 years.

Results

There was a fairly consistent secular trend towards a higher incidence of breast cancer in every successive birth cohort between 1880-89 and 1940-49 (Figure 1). Age-specific incidence increased more markedly in birth cohort 1940-49 as compared to all previous cohorts, with a rate ratio of 1.10 (95% CI 1.01 - 1.22), suggesting a higher risk of developing breast cancer than predicted.

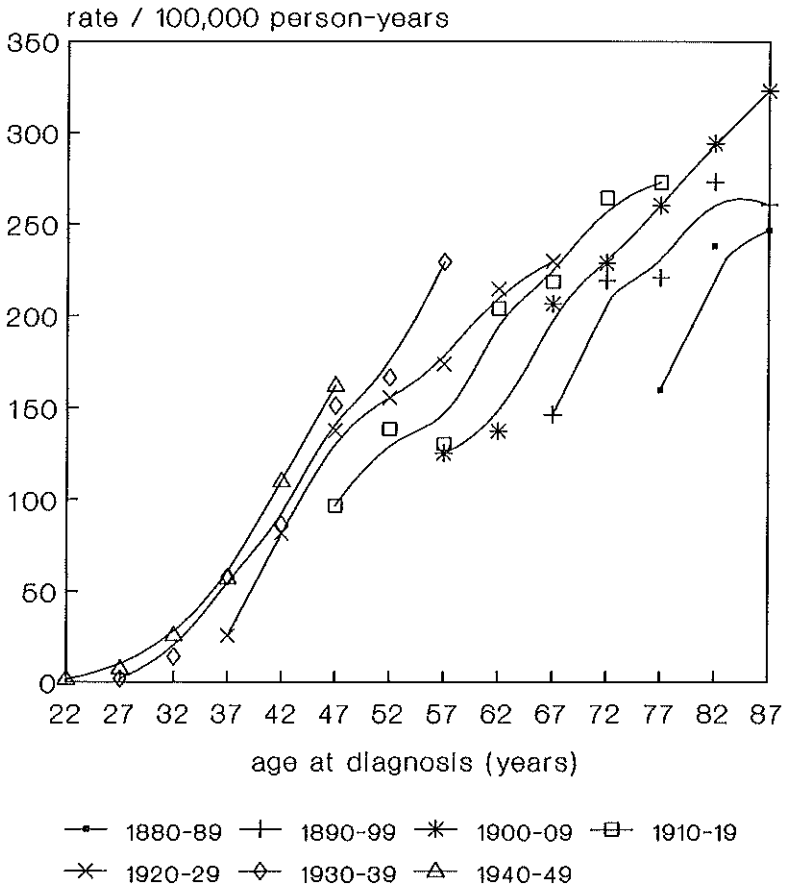

Figure 1. *Age-specific incidence rates of breast cancer, according to 10-year birth cohort, diagnosed between 1960 and 1989.*

A decrease in incidence was observed in birth cohort 1950-59, continuing in birth cohort 1960-69, with a rate ratio significantly lower than one (RR 0.43, 95% CI 0.20-0.96). Birth cohorts 1950-59 and 1960-69 combined also had a rate ratio significantly lower than one (RR 0.79, 95% CI 0.64 - 0.96) (Figure 2). Rate ratios based on an analysis comprising women under 50 years were very similar to those based on the total group, albeit with larger confidence intervals.

Discussion

The steady increase in incidence is in line with the rise in incidence in many industrialised countries.[2-5] These results also confirm the reports from Washington

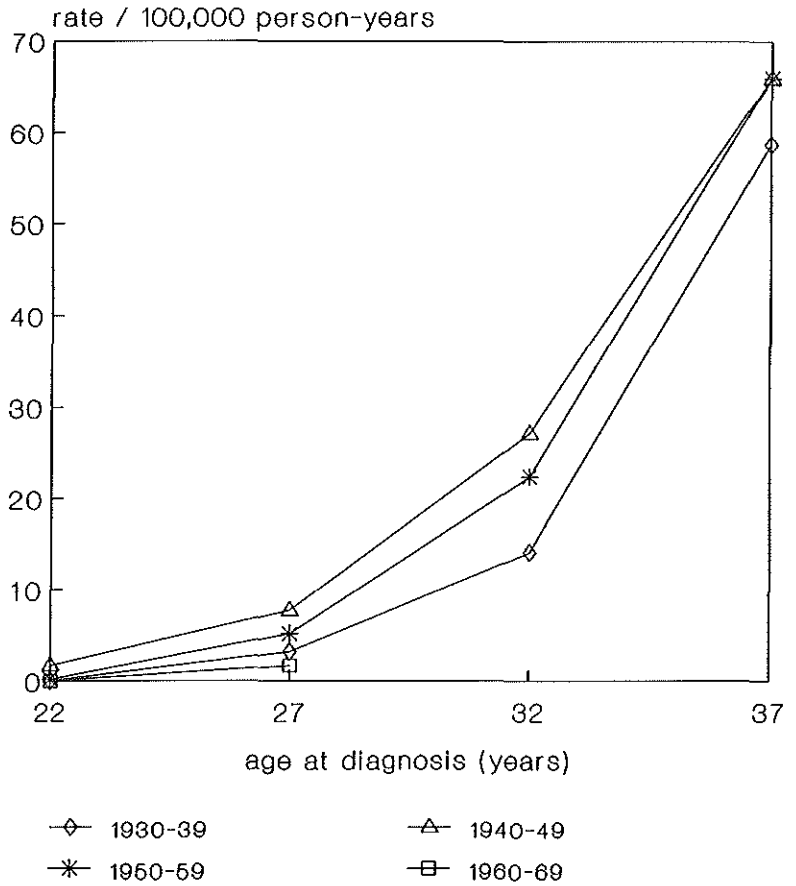

Figure 2. *Incidence rates in the youngest birth cohorts. The rates are the means of 5-year age groups, being indicated by their mid-ages.*

State[12] and Sweden[13] on an increased risk for women born between 1940 and 1949. However, in our population this increase does not continue in women born after 1949 and actually turns into a decrease.

A decrease in the incidence rates has been reported only in the United States, in women of 50 years and older. This was explained as the end stage of a transitory rise in incidence caused by temporary increased detection of tumours by screening mammography.[14] In south-east Netherlands the decrease in incidence appeared in women under 40 years, who underwent no screening. Although alterations in detection modalities, such as increased use of mammography, can produce short-term changes in incidence, it is unlikely that this afflicted especially the youngest women in

our study region. On the contrary, we may be observing the first signs that the increase in incidence during the last decades is coming to an end.

The observed overall increase in incidence can probably not be explained by a more accurate registry over time, because close cooperation with pathologists, surgeons and radiotherapists has always existed and no major changes in the methods of registration occurred during the study period. In the 1970s the introduction of new diagnostic techniques such as mammography, cytology and echography resulted in earlier detection. While incidence rates can rise temporarily due to earlier detection, this cannot be the sole cause of the fairly continuous increase,[15] even if some otherwise dormant disease may be detected.

This leads to the probability of changes in etiologic factors over time, such as earlier menarche,[16] later menopause,[17] and increases in the energy intake in early life,[18] all of them relevant in this population. As incidence rates are generally higher in women having fewer children at a later age,[19-21] the increase may in part be attributed to a marked decrease in family size since 1965. However, this would primarily affect women born after 1930, but would not be in concordance with the decrease in women born after 1949.

Although the exact reasons for the changes are unknown two risk factors may be related to the increased incidence in birth cohort 1940-49. Especially, women aged 20-30 years received high doses of oral oestrogens and progestagens in the early 1970's;[22-26] additionally, this group had a high exposure to X-rays,[27,28] because women aged 10-20 years were regularly screened by X-ray for tuberculosis in the 1950s and 1960s. Which risk factors might explain the decrease in the youngest birth cohorts remains unclear.

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3.3 Comparison of digital and conventional mammography: a ROC study of 270 mammograms

Abstract

Observer performance tests were conducted to study the visibility of malignancies in digital mammography. The detectability of tumours and microcalcifications was studied separately. For this purpose two sets of images were used, one for tumours consisting of 150 mammograms and one for microcalcifications containing 120 mammograms. Images were digitized at a resolution of 2048 x 2048 pixels using a 12-bit CCD camera. Conventional film mammograms were read on a lightbox, whereas digital mammograms were viewed on a high-resolution monitor. Two experienced radiologists read both sets independently, and ranked their judgements about the presence or absence of tumours or microcalcifications on a confidence-rating scale. Results were evaluated using receiver operating characteristic (ROC) analysis. No statistical differences were found between judgements based on conventional and digitized mammography.

* Nab HW, Karssemeijer N, Erning LJTO van, Hendriks JHCL. Comparison of conventional and digital mammography: a ROC study of 270 mammograms. Medical Informatics 1992; 17: 125-31

Introduction

Mammography is a sensitive method for detection of breast cancer. It is the only diagnostic procedure with a proven capability for detecting early stage, clinically occult breast cancer.[1,2] Mammographic findings are also important in deciding on the kind of treatment which should be recommended.[3,4] In order to improve the sensitivity and specificity of screening mammography the introduction of digital techniques is considered.

Digital mammography offers many potential advantages over conventional screen-film techniques, particularly in image display, transmission and processing.[5-10] Image manipulation, like filtering or interactive windowing, can be used to enhance particular features of the image for improvement of the visibility of abnormalities. A digital mammogram can be obtained in several ways. For instance, in a storage phosphor digital radiography system, film is replaced by a photostimulable imaging plate which temporarily stores the X-ray energy pattern.[11] Afterwards the latent image on the imaging plate is read out by a scanning laser beam and stored as a digital image. As an alternative digital mammograms may be obtained by digitization of conventionally recorded film images.[12] For the purpose of studying diagnostic performance using digital mammography this has the advantage that conventional film archives can be used.

The question wether or not a spatial resolution of 0.1 mm per pixel is enough to perform digital mammography, without significant losses compared with film, will be addressed in this study. Spatial resolution is a crucial issue for future prospects of digital mammography. Previous researchers[13-16] generally report rather poor results on the detectability of microcalcifications in digital mammography. It is not clear, however, to what extent these results can be explained by reduction of spatial resolution only. Also image noise may decrease diagnostic accuracy. For instance, in comparison with conventional screen/film systems photostimulable phosphor plates used in references 14 and 15 have a considerably lower signal to noise ratio in the high frequency range (> 2 lp/mm).[17] Another point is that some of the previous studies evaluate the quality of digital mammograms after making hardcopies on film.[14,16] Apart from the fact that this introduces some extra loss of image quality it does not take advantage of digital display facilities, such as interactive optimization of contrast by changing window-

width and window-level. It appears that application of these techniques may compensate to some extent for the effects of limited spatial resolution.[18,19]

An experiment was designed to compare digital and conventional mammography avoiding some the shortcomings of earlier studies. Mammograms were digitized with a high-quality CCD camera at a pixel size of 0.1 mm and a 12 bit contrast resolution. Digitization noise was verified to be small compared to film/screen noise already present in the conventional mammograms. Digitized mammograms were read on a digital display system.

Methods

ROC study design

The performance of radiologists reading digital mammograms was investigated by means of a ROC study. For this purpose two sets of images were collected: one to study the detectability of tumours and the other to study the detectability of microcalcifications. The former consisted of 150 mammograms, including 75 cases with malignancies but without microcalcifications and 75 mammograms without malignancies. To increase the sensitivity of the study the contralateral mammograms were used as normals in this set. This made the pathologic and non-pathologic images look very alike, except for the abnormality. All malignant cases were pathologically confirmed. The second set, consisting of 120 mammograms, included 60 mammograms with pathologically proven microcalcifications and 60 without.

All mammograms were selected from the archive of the Dutch National Expert and Training Centre for Breast Cancer Screening. To have up-to-date quality the cases were selected from the past 5 years. Mammography was performed with a "Senograph 500T" (General Electric / Compagnie Général de Radiologie) with "Min R" screens and "OM-1" film (Kodak). Only mediolateral oblique views were used. Mammograms which showed very clear abnormalities were excluded from the study.

In a randomized sequence two experienced radiologists read both the conventional films and digitized images. The digitized set was read first. To avoid a reading order effect, which could favour the conventional readings, there always was at least an interval of two months between a digital and conventional session showing the same image.

To enable ROC-analysis the observers ranked their judgements independently on a 10-point confidence rating scale regarding the presence or absence of a tumour, and on a 5-point confidence rating scale regarding the presence of microcalcifications. Different scales were used because judging malignant aspects of tumours involves more image features than detection of calcifications. To familiarize radiologists with digital mammography a teaching file was read first, consisting of mammograms that were not included in the test. The conventional films were viewed on a light box, allowing the possibility of magnification with a looking glass. The digital images were viewed on two 1024 x 1024 monitors. One monitor was used to display the full mammogram at reduced resolution, while the other was used to pan through the image at full resolution and for zooming. To enhance contrast the readers could alter window-width and window-level.

Image digitization and conversion

Each image was digitized within a 20 x 20 cm^2 field of view. To obtain a pixel size of 0.1 mm the size of the image matrix was chosen as 2048 X 2048. A 12-bit CCD camera with a maximum resolution of 4096 x 4096 was used for digitization (Eikonix 1412). Because the resolution of this camera is two times higher than the resolution needed for this study, for each pixel four independent sensor elements are available. In consequence, digitization can be performed in different ways. We compared the following two methods: 1) averaging the output of the four neighbouring sensor elements per pixel and 2) using the output of one sensor element only. In the latter case the sampling aperture is four times smaller than the pixel area. Changing the sampling aperture without changing the sampling distance enables a trade-off between image blur and noise. A smaller sampling aperture also reduces the blurring caused by the optical system of the CCD camera, which appeared to be considerable. Results of both methods were compared on a number of mammograms containing clusters of microcalcifications. Using the latter method the images were noisier, but most calcifications did have a higher contrast. Regarding the problem of calcification detection using a small sampling aperture seemed somewhat better. Therefore this method was chosen to digitize the image set. It was verified that the variance of the pixel values due to digitization noise was small compared to the variance due to film/screen noise for optical densities below 2.0.[20]

The CCD camera quantizes the sensor output to 12-bit pixel values. These pixel values are proportional to the amount of transmitted light energy during exposure of the sensor. This 12-bit scale, however, is very inefficient from the viewpoint of information storage, as the absolute noise level of the pixel values due to film- and digitization noise strongly increases with the pixel value itself. By converting the pixel value scale using an iso-precision criterion, the number of bit per pixel can be reduced without significant loss of information.[20] In this conversion the quantization increments are chosen proportional to the standard deviation of the pixel values. As a result the variance of the pixel values in the converted image is independent of the pixel value. The 12-bit camera output was converted to an 8-bit iso-precision scale. The additional quantization error introduced by this conversion is very small. By applying this 12- to 8- bit conversion the size of image storage needed for each mammogram was reduced from 8 to 4 Mb.

For clinical evaluation the digital mammograms were transmitted via a local area network[21-23] to a Diagnostic Reporting Console (Siemens DRC-20). Before display the pixel values were converted back again to the original scale.

Results

ROC analysis was used to analyze the results of our experiments. This method was chosen because in ROC analysis differences in diagnostic capacity can be distinguished from effects of the decision criterion.[24] The ROC curves of the individual radiologists are presented in figures 1 and 2.

The area under a ROC curve is a good measure for the performance of an observer in detecting abnormalities, regardless of his decision threshold. For each curve this area was calculated using the software package Feasible.[25] Table 1 shows the total scores of both radiologists for both experiments; the pooled results are also shown.

The statistical significance of the differences between pairs of curves was tested by using the program CORROC2 (available from Dr. Charles E. Metz, University of Chicago), which was designed especially for analyzing correlated data. ROC curves are likely to be correlated because they result from readings of the same data. The hypothesis that the areas under the curve for the conventional and digital readings are equal was tested. For both tumour and microcalcification detection this hypothesis could not be rejected ($p > 0.1$), neither for the individual readers nor for the com-

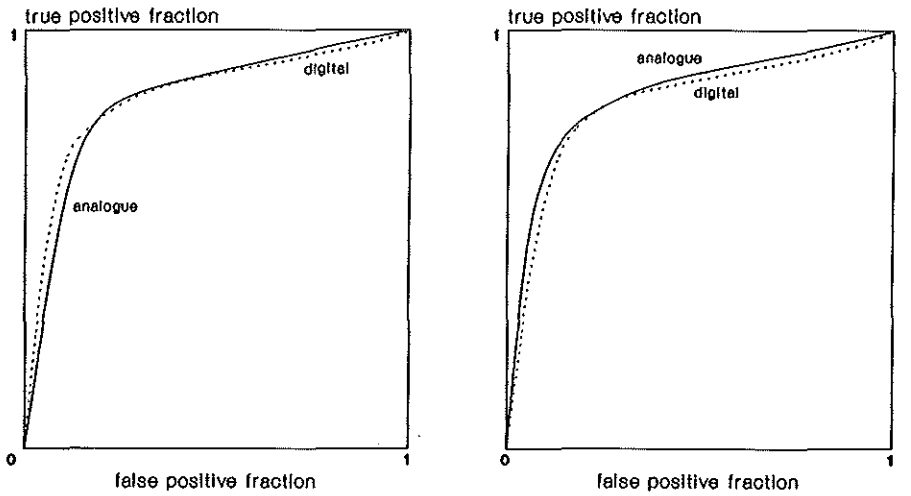

Figure 1. *ROC curves for tumour detection by both observers*

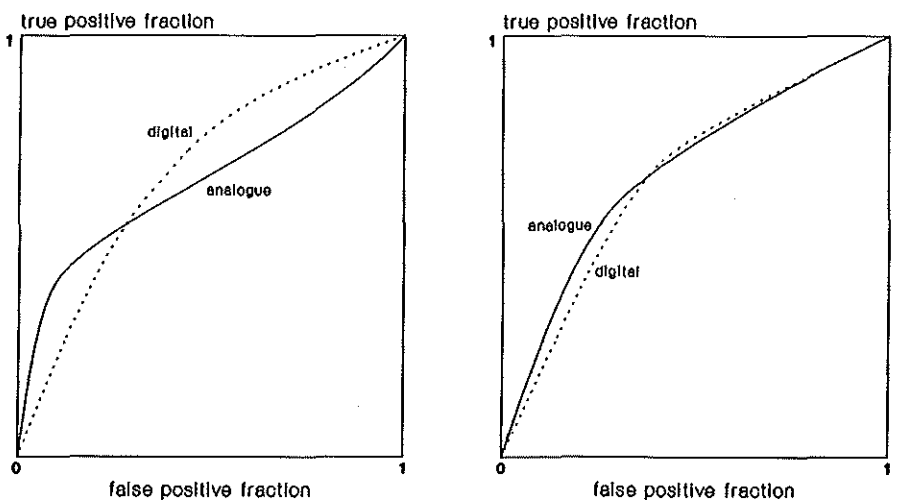

Figure 2. *ROC curves for microcalcification detection by both observers.*

bined results using pooled data.

The statistical power of the study can be calculated using the method described by Hanly,[26] which takes into account the correlation of the data. For the pooled data it was calculated that in our experimental set-up the probability of detecting a 5% difference between the areas under the ROC curves for calcification detection was 80% (Table 1).

Table 1

Areas under ROC curves for individual observers and for pooled data of both observers.

	Area under ROC curve			
	Analogue	**SD**	**Digital**	**SD**
Tumours				
Observer 1	0.856	0.031	0.853	0.031
Observer 2	0.849	0.032	0.812	0.035
Pooled	0.845	0.023	0.832	0.023
Microcalcifications				
Observer 1	0.689	0.052	0.713	0.049
Observer 2	0.701	0.050	0.677	0.051
Pooled	0.695	0.036	0.694	0.036

Discussion

In this study the detectability of microcalcifications and tumours on mammograms, digitized with a 0.1 mm pixel size, did not differ significantly from the detectability of these abnormalities on conventional film mammograms. No improvement of the visibility of tumour masses was found, although image contrast could be markedly improved using digital display. It is noted, however, that the radiologists participating in this study were not familiar with using interactive manipulation of contrast

In a previous investigation Chan et al.[16] reported a lower detectability of microcalcifications in digitized mammograms, using the same 0.1 mm pixel size. Probably, this may be explained by a higher quality of the digitization and display procedure we used. Chan et al. performed their study on hardcopies of the digitized images on film, thus introducing some extra loss of image quality and making interactive contrast manipulation by the observers impossible. It is unlikely that the disagreement with the results reported by Chan et al. is due to the statistical power of our study. Although we used only two observers the number of images was much larger. Chan et al. used only 12 images with calcifications and 20 normals, where nine readers judged the set. It follows that the total number of observations is about equal as in our study. Besides, in their study not all of the nine observers were radiologists, and expert mammographers were used to establish the ground truth. In our study the observers were experts and all cases, both normals and abnormals, were verified by pathological examination.

In setting up this study we tried to keep close to the usual clinical setting. However, there were some differences. No clinical information was provided and for each case only one mammogram was presented, i.e. without contralateral or older mammograms. Furthermore, a percentage of 50% abnormal mammograms is not usual in the screening or clinic. Therefore, the individual ROC curves obtained are not applicable to the clinical situation. The relative difference, however, between digital and conventional mammography remains valid, because it is very unlikely that the unusually large number of abnormal mammograms has influenced the reading on both modalities differently.

It is noted that the fact that the areas under the ROC curves in figures 1 and 2 are not close to unity indicates that the images were not too easy to read. To maximize the statistical power of a comparative ROC study the cases included should be of intermediate difficulty. A reasonable rule of thumb seems to be to choose the cases as such that the mean area under the ROC curves of the two modalities being compared roughly lies near 0.75 or 0.8.[24] Table 1 shows that the mean areas under the curve in this study are in the range 0.69 - 0.86. This indicates that the composition of the set was fairly good, although we feel that the microcalcification set might have been slightly too difficult. The present study provides information about detectability of tumours and microcalcifications. Features of individual calcifications and clusters are important to differentiate various types. These features may be somewhat distorted by digitization using 0.1 mm pixels, due to blur and aliasing. To find out if this distortion is acceptable, further experiments are to be performed.

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Chapter 4. Prognosis

4.1 Changes in long term prognosis for breast cancer in a Dutch cancer registry*

Abstract

Objectives: To assess whether the long-term survival in patients with breast cancer has changed with time.

Design: Population-based descriptive study.

Setting: The Eindhoven Cancer Registry in south-east Netherlands.

Subjects: 2052 patients with first primary breast cancer diagnosed between 1955 and 1974.

Main outcome measures: Overall survival and relative survival.

Results: Overall survival was 35% (727 patients) after 10 years, 21% (267) after 20 years and 15% (25) after 30 years. The corresponding relative survival rates were 43%, 34%, and 34%, respectively. Survival improved from 1955 onwards for all ages and all tumour stages. Improvement was observed in both overall and relative survival. Prognosis was strongly related to the stage at diagnosis in the first 10 years of follow up but independent of stage after 10 years. Survival of patients still alive after 19 years became similar to that of the general female population.

Conclusions: Short term and long term survival improved considerably in all age groups. This improvement was most marked for patients who were diagnosed with a localised tumour. Patients who survive for 19 years may be considered cured.

* Nab HW, Hop WCJ, Crommelin MA, Kluck HM, Heijden LH van der, Coebergh JWW. Improved long-term prognosis in breast cancer: survival rates since 1955 in a Dutch cancer registry. Br Med J 1994; 309: 83-6

Introduction

Breast cancer is the most common malignancy in Dutch women. It makes up about 30% of all new primary cancers,[1] and 22% of cancer deaths in women.[2] Over the past 30 years the incidence of breast cancer in south-east Netherlands has roughly doubled in all age groups, with a clear trend towards an earlier stage at diagnosis.[3] Simultaneously, breast cancer mortality has remained unchanged in women aged under 60 and increased slightly in older women. These differing trends between incidence and mortality, which have been observed in many countries,[4-7] suggest increasing survival rates with time. However, most reports on improved survival for breast cancer patients have only a short follow-up[5,7-9] or do not control for the influence of tumour stage on survival outcome.[7,10]

We investigated trends in long-term overall and relative survival of 2052 women in whom breast cancer had been diagnosed between 1955 and 1974.

Patients and methods

The study included all women with a first primary breast cancer diagnosed between 1955 and 1974 in south-east Netherlands, who were followed up until 1991. Data came from the Eindhoven Cancer Registry, which was founded in 1955 and has been part of the Comprehensive Cancer Centre South Netherlands since 1983.[1] The data were derived from copies of the pathologists' records, patients' files in the community hospitals, and the regional radiotherapy institute. The registry covered an area in south-east Netherlands with about 300,000 inhabitants in 1955 and over 900,000 since 1970; this increase was largely due to expansion of the area covered by the registry in 1970. Patients from the newly included area had a similar age distribution to patients in the original region at the time of the expansion. The incidence of breast cancer in this population could be estimated from 1960 onwards.[3,11]

From 1955 to 1974 the registry collected data on 2098 new breast cancer patients, and for 2052 of these patients information about vital status was obtained from population administrations for up to 1 July 1991. A total of 100 women (5%) were lost to follow-up after varying intervals, and in the analyses these patients were considered to have withdrawn alive. Tumour stage at diagnosis was recorded on the basis of clinical examination, supplemented by the pathologist reports and was classified into

three categories: localised (cancer confined to the breast regardless of size), regional (cancer spread beyond breast but still in its immediate neighbourhood or extended to the regional lymph nodes, and distant (cancer having involved tissues beyond those immediately draining or neighbouring the breast). In 137 patients tumour stage could not be classified into one of these categories.

Survival was calculated as overall and relative survival, relative survival being the ratio of the observed rates to the expected rates. Expected survival rates were calculated from life tables (supplied by the Netherlands Central Bureau of Statistics), compiled according to five year age groups and year of diagnosis for the regional female population.[12] Actuarial survival curves were computed,[13] according to age category ($\leq$ 50, 51-65, and $>$ 65), year of diagnosis (1955-9, 1960-4, 1965-9, 1970-4), and tumour stage. The log-rank test was used to assess the significance of differences in survival. The prognostic value for the overall survival of several factors simultaneously was assessed using the Cox proportional hazards model.[14]

Mortality due to breast cancer

The excess risk of death due to breast cancer was modelled with a program of the Finnish Cancer Registry.[15] In this model the annual excess mortality was allowed to depend simultaneously on age, tumour stage, and year of diagnosis. Excess mortality was the difference between observed mortality and expected mortality. Expected mortality was determined by the age of the patients and the time of diagnosis. The excess mortality presumably reflected deaths due to breast cancer. In both analysis methods we assumed that the various factors had a proportional effect on the outcome. As this assumption appeared to be violated when the total follow up after diagnosis was considered, separate analyses were performed for the first and second five year interval of follow-up and for the next 10 year of follow up. This was achieved by considering only patients who were alive at the beginning of each interval, while patients who survived to the end of the interval were considered as withdrawn from the study (censored).

In all analyses all variables were initially taken to be categorical, but we found that the factor of primary interest, year of diagnosis, had estimated effects that were roughly linear with more recent diagnosis. Therefore this factor was introduced in the models with the numerical codes 0, 1, 2 and 3 for the times of diagnosis (1955-9, 1960-4, 1965-9, 1970-4), thereby allowing tests for linear trend to be performed. Within

each of the three intervals of follow up considered we investigated whether the effect of time of diagnosis, depended on tumour stage or age of patients at diagnosis by incorporating appropriate interaction terms in the models. In the final model, after adjustments for age and tumour stage, the death rate among patients whose cancer was diagnosed in one five year period was compared with the death rate in the next five year period of diagnosis as an indicator of the change in prognosis over time. Other statistical methods were used as indicated in the text, and significance was set at the 5% level.

Table I

Number (%) of patients with breast cancer according to age, tumour stage and primary treatment.

	Period of diagnosis				
	1955-59 (n=240)	**1960-64** (n=273)	**1965-69** (n=393)	**1970-74** (n=1146)	**Total** (n=2052)
Age (years)					
22-50	101 (42)	102 (37)	138 (35)	451 (39)	792
51-65	77 (32)	103 (38)	154 (39)	382 (34)	716
> 65	62 (26)	68 (25)	101 (26)	313 (27)	544
Tumour stage					
Localised	67 (28)	84 (31)	154 (39)	392 (34)	697
Regional	143 (60)	174 (64)	206 (52)	586 (51)	1109
Distant	17 (7)	10 (3)	17 (4)	65 (6)	109
Unknown	13 (5)	5 (2)	16 (4)	103 (9)	137
Primary treatment					
Surgery	49 (20)	45 (17)	96 (24)	412 (36)	602
Radiotherapy	18 (8)	24 (9)	23 (6)	73 (6)	138
Surg + radiother	169 (70)	200 (73)	270 (69)	638 (56)	1277
Other or none	4 (2)	4 (2)	4 (1)	23 (2)	35

Results

The age distributions of the patients (mean age 56.5 years, range 22-95) did not differ significantly between the four sets of patients diagnosed grouped according to time of diagnosis (Kruskal-Wallis test, $p = 0.7$) (Table I). Tumour stage tended to be more favourable with more recent diagnosis (Chi-square test for trend, $p = 0.04$). Patients' age did not correlate with tumour stage at diagnosis. Primary treatment for localised tumours showed a slight shift from combined surgery and radiotherapy, to surgery only. The proportions of patients treated by adjuvant chemotherapy and hormonal therapy (including ovariectomy) increased slightly from none and 1% (2) respectively of those whose cancers were diagnosed in 1955-9 to 2% (24) and 2% (27) of those

with cancers diagnosed in 1970-4. In addition, the proportions of patients treated by secondary chemotherapy and secondary hormonal treatment rose from 2% (4) and 2% (5) respectively among those with cancer diagnosed in 1955-9 to 13% (152) and 19% (223) respectively among those with cancer diagnosed in 1970-4. In total 1172 (52%) patients survived five year after diagnosis, 727 (35%) survived 10 years, 267 (21%) survived 20 years, and 25 (15%) survived 30 years. The corresponding relative survival percentages were 57%, 43%, 34% and 34% respectively. Prognosis was considerably worse for patients with distant metastases at diagnosis, and so survival of such patients was analyzed separately.

Overall survival

For patients without distant metastases at diagnosis 10-year survival rates were 26%, 31%, 34%, and 39%, for the patients with cancers diagnosed in 1955-9, 1960-4, 1965-9 and 1970-4 respectively. Cox regression showed that, during the first five years of follow up, tumour stage was an important prognostic factor that significantly depended on age ($p < 0.001$), with the prognostic value of stage being highest in the youngest patients (Table II).

Table II

Age adjusted death rate ratios (SE) for patients with breast cancer during different intervals of follow up according to tumour stage and time of diagnosis. Values calculated by Cox regression, and only patients with localised and regional disease included.

	Interval of follow-up		
	Year 1-5 (n = 1806)	**Year 6-10** (n = 923)	**Years 11-20** (n = 602)
	Regional stage of tumour[a]		
Patients age (years)			
22-50	2.6 (0.6)		
51-65	2.3 (0.5)	1.8 (0.2)	1.1 (0.2)
> 65	1.1 (0.2)		
	Period of diagnosis[b]		
Tumour stage			
Localised	0.77 (0.05)	0.95 (0.05)	0.8 (0.06)
Regional	0.93 (0.03)		

[a]*Localised disease used as reference category and given value of 1 for each follow up interval. Rate ratios significantly dependent on age for the first follow up interval and represent effect of tumour stage for first period of diagnosis (1955-9): for each subsequent diagnostic period rate ratios increased by 21% because of greater improvement in survival for localised disease compared with regional disease.*
[b]*1960-4 vs 1955-9, 1965-9 vs 1960-4, 1970-4 vs 1965-9. Rate ratios significantly dependent on tumour stage for the first follow up interval.*

Survival improved with more recent diagnosis for both localised and regional tumours ($p < 0.05$) although improvement was greater for localised disease (Table II).

In the second five years of follow up, tumour stage at diagnosis was again an important independent prognostic factor (Table II). The improvement in overall survival in this follow-up interval was small and not significant ($p = 0.3$). In the second 10 years of follow up survival did not differ between patients with different tumour stage at diagnosis. In this interval survival improved substantially with more recent diagnosis ($p < 0.05$), but this improvement was not significantly different from that seen in the second five year of follow up. Unsurprisingly, overall mortality was strongly related to age in all intervals of follow up.

Median survival of the group of 109 patients with distant disease at diagnosis was 0.9 years. Of these patients, 29 survived for 2 years, and only nine survived for more than five years. Age adjusted death rates declined by 20% compared with diagnoses made five years earlier ($p < 0.01$), and this improvement in survival was apparent in all age groups.

Relative survival

Relative survival improved with more recent diagnosis, particularly for patients with localised tumours at diagnosis (Figure 1). Table III shows that, in contrast to overall survival (Table II), the excess risks of dying in the first five years of follow up in relation to stage at diagnosis did not differ significantly between the various age groups. In this interval of follow up the reduction in the excess death rates for patients with localised disease was 28% ($p < 0.01$) compared with patients diagnosed five years earlier: for patients with regional disease this figure was significantly less at 7% ($p = 0.08$).

In the second five years of follow up excess risk of dying also depended significantly on tumour stage at diagnosis and not significantly on the period of diagnosis. In the second 10 years of follow up the excess risk of dying did not depend on tumour stage at diagnosis, and in this follow up interval the reduction in excess death rates was 23% ($p < 0.01$) compared with patients diagnosed five years earlier. Excess mortality was not significantly related to the age of patients in any of the follow-up intervals.

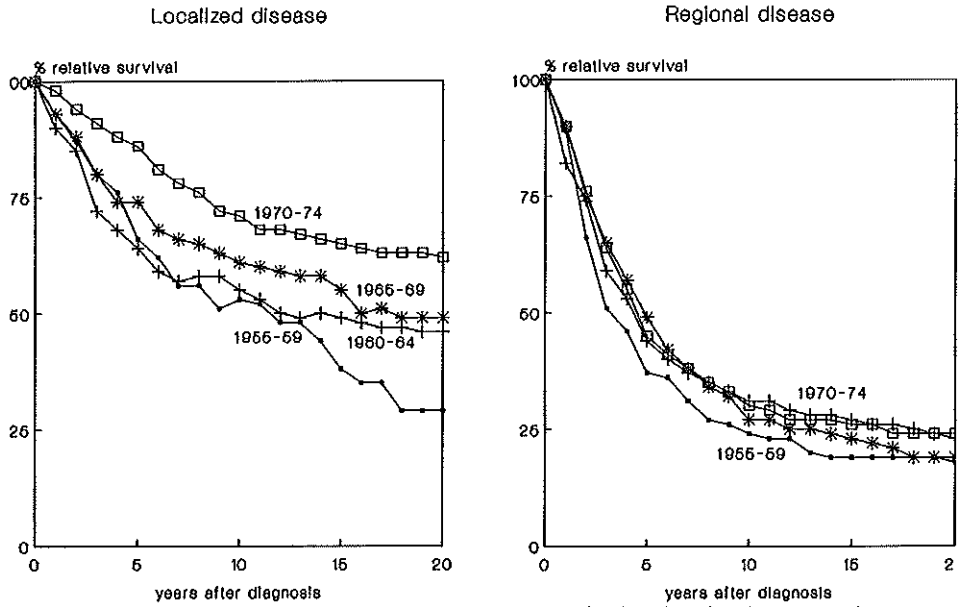

Figure 1a. *Percentage relative survival of patients with localized and regional stage. Patients are grouped according to period of diagnosis.*

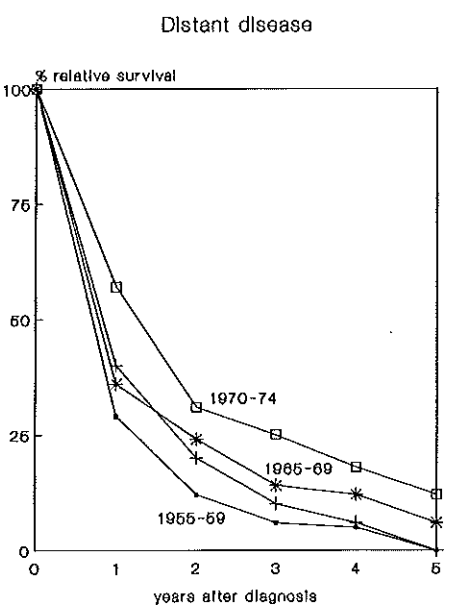

Figure 1b. *Percentage relative survival of patients with distant stage at diagnosis. Patients are grouped according to period of diagnosis.*

For patients with distant disease at diagnosis, the excess death rates decreased significantly by 22% ($p < 0.01$) compared with patients diagnosed five years earlier.

Annual relative survival rates for the patients gradually increased and reached 100% at 19 years, implying that the subsequent survival rate of patients who survive that long does not differ from that of women of a similar age in the general population of the region.

Table III

Age adjusted ratios (SE) of excess risks of death for patients with breast cancer during different intervals of follow up according to tumour stage and time of diagnosis. Only patients with localised and regional disease included.

	Interval of follow up		
	Years 1-5 (n=1806)	**Years 6-10** (n=923)	**Years 11-20** (n=602)
		Regional stage of tumour[a]	
	2.1 (0.5)	2.3 (0.3)	1.2 (0.3)
		Period of diagnosis[b]	
Tumour stage			
Localised	0.72 (0.07)	0.98 (0.07)	0.77 (0.09)
Regional	0.93 (0.04)		

[a]*Localised disease used as reference category and given value of 1 for each follow up interval. Excess risk for first follow up interval represents effect of tumour stage for first period of diagnosis (1955-9): for each subsequent diagnostic period excess risk increases by 29% because of greater improvement of survival for localised disease compared with regional disease.* [b]*1960-4 vs 1955-9, 1965-9 vs 1960-4, 1970-4 vs 1965-9. Excess risk significantly dependent on tumour stage for first follow up interval.*

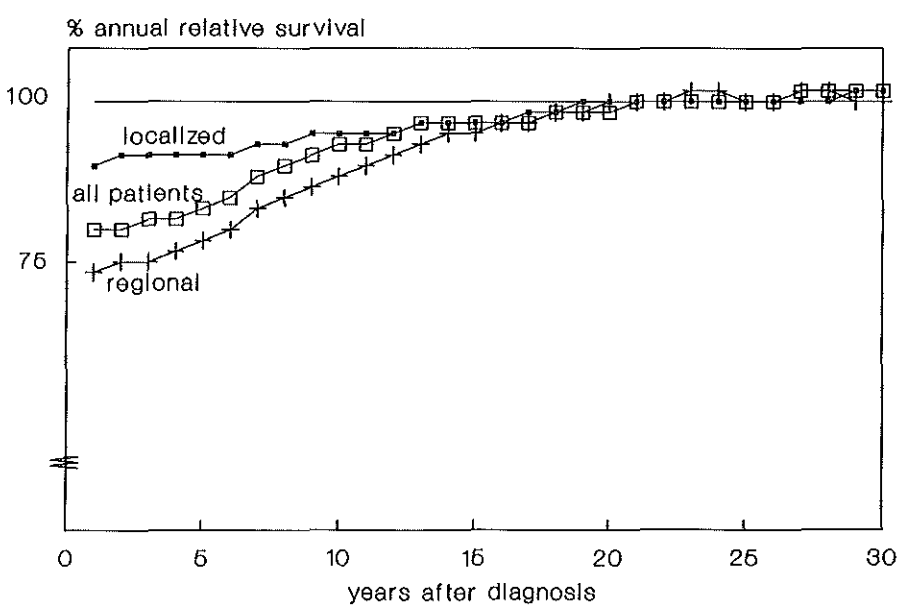

Figure 2. *Annual relative survival rates of patients with breast cancer diagnosed between 1955 and 1974.*

Discussion

The prognosis for patients in south-east Netherlands with a diagnosis of breast cancer improved substantially between 1955 and 1974. This improvement occurred in both short and long term survival and was present at all ages. The improvement in relative survival (Table III) was similar to that for overall survival (Table II) and showed that improvement was greatest for patients with localised tumours at diagnosis. The improved survival we found is consistent with the report of increased incidence of localised and distant tumours but stable mortality in south-east Netherlands in the same period.[3] Possible reasons for the improved survival include better treatment, earlier detection, and diagnosis of less aggressive tumours.

Since the 1960s various claims have been made about more effective treatments consisting of hormonal and cytotoxic treatment. Cytotoxic treatment, which was introduced in the study region in the 1970s and mostly given for a recurrence, possibly contributed slightly to the improvement of survival. Supportive care such as prevention of complications and treatment of comorbidity may also have improved, thereby helping to improve the prognosis of breast cancer. Although we adjusted for tumour stage, the trend towards earlier detection may nevertheless have had an impact on the results, since within the three robust stage groups a trend is also likely. For example, localised tumours detected in the 1970s were probably generally smaller than localised tumours detected in the 1950s (residual confounding). However, the substantial improvement in relative survival was also observed when we used the more refined staging of the tumour, node, metastases (TNM) classification to analyze the results for the 1396 patients for whom suitable information was available (data not shown). Alternatively, increasing numbers of patients may have been allocated to higher tumour stages because of more extensive staging procedures,[16] resulting in a more favourable outcome in all stages.[17] An increase in the proportion of less aggressive tumours is also possible.[18]

While some reports have shown that patients with breast cancer have increased mortality compared with the normal population for as long as they are followed up,[19-21] other studies have found that such patients' mortality approaches or equals that of the normal population after varying intervals.[22,23] In our study breast cancer patients had the same mortality rate as the general female population after 19 years and might therefore be considered cured after that time.

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4.2 Improved prognosis of breast cancer since 1970 in south-east Netherlands*

Abstract

Despite many new advances in breast cancer therapy since the 1970s, there are only few reports on improved prognosis in a general population. A follow-up of more than 10 years is rarely reported, and a differentiation according to stage of the disease or between follow-up intervals is seldom made. Our purpose was to assess whether prognosis of primary breast cancer improved in patients diagnosed between 1970 and 1984 in south-east Netherlands, and to distinguish between different stages and follow-up intervals. Data from 4,467 breast cancer patients diagnosed between 1970 and 1984 were derived from the population-based Eindhoven Cancer Registry. Follow-up was attained up to 1 July 1991. Relative survival rates, as the ratio of the observed to the expected rates, were calculated. In a multivariate analysis a change in prognosis over time was computed with adjustment for age and stage; this was done separately for 5-year follow-up intervals. The relative survival rates were 69% after 5 years, 55% after 10 years and 50% after 20 years. Relative survival, after adjustment for age, was strongly related to the stage of the disease in the first 5 years of follow-up, less markedly between 5 and 10 years, and to a small, borderline significant, extent after 10 years of follow-up. Relative survival rates increased markedly over time, during the whole interval of follow-up. This increase was apparent in all age groups and in all stages, except for those with distant disease at diagnosis. The observed improvement in survival is unlikely to be explained by the increased use of adjuvant chemo- and hormonal therapy. Other factors, such as a change in the natural history of the disease in this period, cannot be ruled out.

* Nab HW, Hop WCJ, Crommelin MA, Kluck HM, Coebergh JWW. Improved prognosis in breast cancer since 1970 in south-east Netherlands. Br J Cancer 1994; 70: 285-8

Introduction

In the past twenty years the application of mammography, cytological examinations and echography has facilitated earlier diagnosis of breast cancer. Simultaneously, less mutilating surgery and hormonal and cytotoxic therapy were introduced. These treatments have proved their efficacy in academic settings.[1] Nevertheless, there are only few reports on improved survival rates in a general population.[2-6] Moreover, follow-up of more than 10 years is rare,[3] and differentiation according to stage [2,4,6]or between follow-up intervals is seldom made. We investigated trends in relative survival rates of breast cancer in women diagnosed between 1970 and 1984 in south-east Netherlands according to stage and interval of follow-up.

Subjects and methods

The study comprised female patients with a first primary invasive breast cancer diagnosed between 1970 and 1984 in south-east Netherlands, with follow-up until 1991. Data came from the Eindhoven Cancer Registry, which was founded in 1955 and has been part of the Comprehensive Cancer Centre South since 1983.[7] The data were derived from the patients' files in the community hospitals, from copies of the pathologists' records, and from the regional Radiotherapy Institute. The registry covered a densely populated area in south-east Netherlands with about 900,000 inhabitants since 1970. Incidence rates could be estimated from 1960 onward in this population.[8]

In the period 1970-1984, 4,549 new breast cancer patients were registered. Information about the vital status up to 1 July 1991 was obtained from the population administrations. Of the patient group, 82 women (1.8%) could not be traced, leaving 4,467 patients for survival analysis. Of this remaining group, 48 women (1.1%) were lost to follow-up after varying intervals of time.

Tumour stage at diagnosis was recorded based on the pathologist's report at surgery and, otherwise, on the basis of clinical examination. Stage was classified according to the tumour-node-metastasis (TNM) system of the Union Internationale Contre le Cancer, version 4, 1987.[9]

Relative survival was calculated as the ratio of the observed actuarial rates to the expected actuarial rates. Expected survival rates were calculated from life tables for

the regional female population (supplied by the Netherlands Central Bureau of Statistics), compiled according to 5 year age groups and year of diagnosis.[10]

Actuarial survival curves were computed according to age group,[11] tumour stage and period of diagnosis (1970-74, 1975-79, 1980-84). The excess risk of death due to breast cancer was modelled using a program of the Finnish Cancer Registry.[12] In this model the annual excess mortality is allowed to depend simultaneously on age, stage and period of diagnosis. The excess mortality is obtained by taking the difference between the observed mortality and the expected mortality. The latter is determined by the age of the patients and the calendar period. The excess mortality presumably reflects deaths in which breast cancer is the cause. In this analysis method it is assumed that the various factors have a proportional effect on the excess death rate. As this assumption appeared to be violated when the total follow-up interval after diagnosis was considered, separate analyses were performed for each 5 year interval. In the analyses all variables were taken to be categorical in the first instance. Because the factor of primary interest, i.e. diagnostic period, had estimated effects which were roughly linear with increasing period, it was introduced in the models using the numerical codes 0, 1, 2 for the subsequent periods of diagnosis, thereby allowing tests for linear trend to be performed. We investigated whether the diagnostic period effect depended on stage or age of patients at diagnosis by incorporating interaction terms in the models. In the final model death rate ratios were expressed as the ratio of two death rates in two groups of patients diagnosed in two consecutive 5 year periods, with adjustment for age and stage, as an indicator of the change in prognosis over time. Other statistical methods are indicated in the text. P-values given are two-sided; 5% was considered the limit of significance.

Results

The mean age of the patients in the three periods increased from 56.7 years in 1970-74 to 59.2 years in 1980-84 (Kruskal-Wallis test, $p < 0.001$) (Table I). Of the total patient group 16% could not be staged because of unknown tumour size (T) in 31%, unknown nodal status (N) in 16%, unknown metastatic spread (M) in 13% and a combination of these in 40%. The known TNM stage factors in the patients with incomplete stage did not suggest a disproportionate presence of early or advanced disease in this group. Among the TNM-staged patients there was a trend towards a

more favourable stage distribution over time (chi-square test for trend, p = 0.003). Tumour stage correlated with the age at diagnosis: older patients generally had a more advanced stage at diagnosis (chi-square test for trend, p < 0.001). Among patients with stages I-III a shift in type of treatment over time was observed from only surgery towards surgery combined with adjuvant therapy. Chemotherapy was increasingly administered (Table I).

Table I

Number (%) of patients with breast cancer according to age, stage and primary treatment.

	Period of diagnosis			
	1970-74 No. (%)	**1975-79** No. (%)	**1980-84** No. (%)	**Total** No. (%)
Age (yrs)				
20-39	129 (12)	153 (10)	162 (9)	444 (10)
40-49	276 (25)	319 (20)	380 (21)	975 (22)
50-59	240 (22)	383 (25)	397 (22)	1020 (23)
60-69	271 (24)	366 (24)	385 (22)	1022 (23)
70+	202 (18)	339 (22)	465 (26)	1006 (22)
Stage				
I	161 (14)	275 (18)	374 (21)	810 (18)
II	431 (39)	478 (31)	757 (42)	1666 (37)
III	250 (23)	347 (22)	360 (20)	957 (22)
IV	63 (6)	132 (8)	116 (6)	311 (7)
Unknown	213 (19)	328 (21)	182 (10)	723 (16)
Primary treatment				
Surgery	382 (34)	517 (33)	399 (22)	1298 (29)
+ radiotherapy	591 (53)	842 (54)	959 (54)	2392 (54)
± radiotherapy + hormonal therapy	23 (2)	14 (1)	48 (3)	85 (2)
± radiotherapy + chemotherapy	21 (2)	71 (5)	267 (15)	359 (8)
No surgery	101 (9)	116 (7)	116 (6)	333 (7)
Total	1,118 (100)	1,560 (100)	1,789 (100)	4,467 (100)

Observed survival rates at 5, 10 and 20 years were 63%, 44%, and 30%, respectively, and the corresponding relative survival percentages were 69%, 55%, and 50%. The 5 year relative survival rates improved steadily from 61% for patients diagnosed in 1970-74 to 74% for patients diagnosed in 1980-84 (p < 0.001). The 10 year relative survival rates increased from 47% to 61% over the same period (p < 0.001). In univariate analysis this increase was apparent in stages I-III (Figure 1). The 10-year relative survival rate for stage I was 82%, for stage II 60%, for stage III 33%, and for stage IV 7%. These four survival rates were significantly different from each other (p < 0.001).

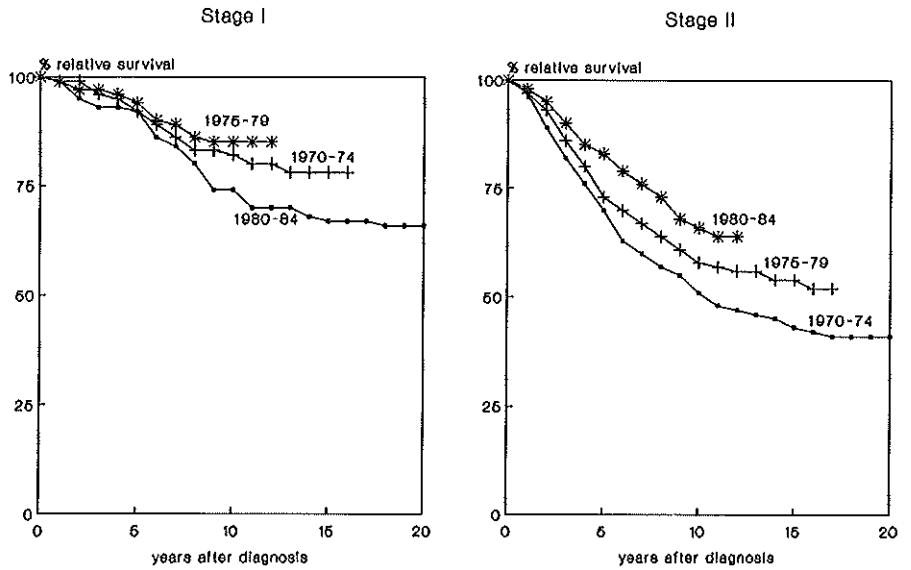

Figure 1a. *The relative survival of breast cancer patients (stage I and II) diagnosed between 1970 and 1984. Patients are grouped according to period of diagnosis.*

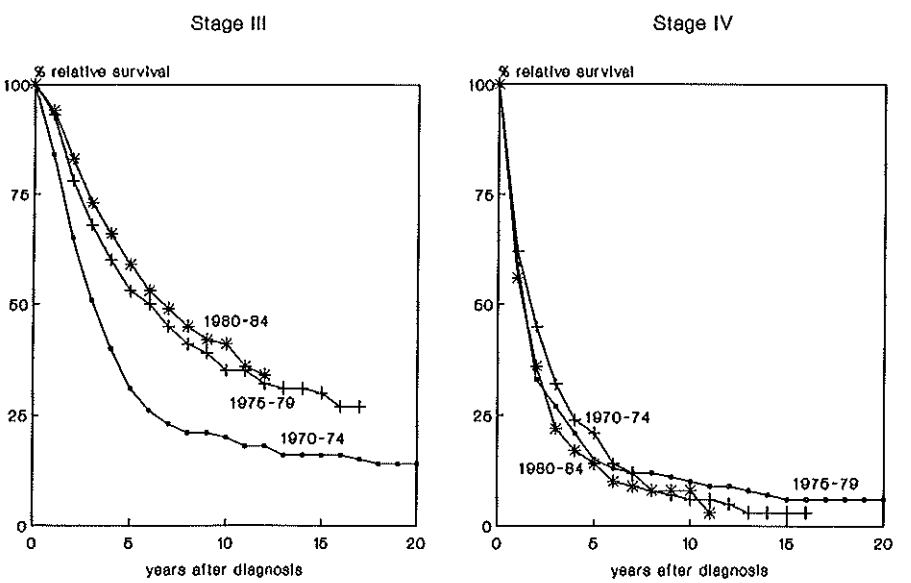

Figure 1b. *The relative survival of breast cancer patients (stage III and IV) diagnosed between 1970 and 1984. Patients are grouped according to period of diagnosis.*

The group of patients with distant metastases at diagnosis (stage IV), was analyzed separately in multivariate analysis.

The median survival of patients without distant disease at diagnosis was 7.5 years. The 5 year relative survival of this patient group improved steadily, from 63% in 1970-74 to 78% in 1980-84 ($p < 0.001$). Using multivariate analysis the independent influence of age at diagnosis on relative survival was small: only for the patient group aged under 40 years in the first 5 years of follow-up there was a borderline significantly worse prognosis. Stage at diagnosis was an important independent prognostic factor, but its effect diminished during the follow-up (Table II).

Table II

Excess death rate ratios (and 95% confidence intervals) for each 5 year follow-up interval of patients with breast cancer, according to age group, stage, and period of diagnosis.

	Follow-up interval		
	0-5 years (n = 3433)	**5-10 years** (n = 2273)	**10-15 years** (n = 1063)
Age group (yrs)			
20-39	1.3 (1.0-1.7)	1.3 (0.9-1.8)	0.6 (0.2-1.5)
40-49	0.9 (0.7-1.1)	1.1 (0.8-1.5)	0.9 (0.5-1.7)
50-59*	1	1	1
60-69	0.9 (0.7-1.1)	0.9 (0.7-1.3)	1.5 (0.7-3.0)
70+	1.1 (0.9-1.4)	1.1 (0.7-1.8)	0.2 (0.01-60)
Stage			
I*	1	1	1
II	3.4 (2.4-4.9)	1.7 (1.3-2.4)	1.5 (0.7-3.0)
III	9.1 (6.3-13)	3.3 (2.4-4.7)	2.3 (1.0-5.2)
Period of diagnosis			
versus 5 years earlier diagnosed	0.7 (0.6-0.8)	0.8 (0.7-0.97)	0.6 (0.4-1.1)

**Reference category. This table gives the results from the final model in which only patients with stages I-III were included. For patients with unknown stage the age-adjusted excess death rate ratios (95% CI) according to period of diagnosis were 0.9 (0.8-1.2), 0.9 (0.7-1.5) and 0.9 (0.3-3.4) for the three follow-up intervals, respectively. For patients with distant disease at diagnosis the age-adjusted excess death rate ratio (95% CI) was 1.0 (0.9-1.1) for the first 5 years of follow-up.*

Period of diagnosis was also a significant and independent prognostic factor in the first and the second 5 years of follow-up, but not statistically significant thereafter. The estimated improvement in relative survival compared to patients diagnosed 5 years earlier, was 30% for the first 5 years of follow-up ($p < 0.001$), 20% in the second 5 years of follow-up ($p = 0.02$) and 40% for the third 5 years ($p = 0.07$). This improvement according to diagnostic period did not significantly differ between the three separate stage groups, and was apparent in all age categories. Among the patients with unknown stage, age-adjusted relative survival improved by 10% ($p > 0.1$).

Between 1970 and 1984 the 311 patients (7%) with distant disease at diagnosis had

a median observed survival of 1.2 years. Of these patients, 37% survived 2 years, and only 14% for more than 5 years. Relative survival rates, after adjustment for age, in this group of patients did not change significantly (Table II).

Discussion

The prognosis of breast cancer patients with non-metastatic disease, diagnosed between 1970 and 1984 in south-east Netherlands improved markedly in all age groups and during the whole follow-up interval of 15 years. The increased survival rates, together with earlier diagnosis, concur with the earlier reported marked increase in breast cancer incidence and stable mortality in this region.[8]

Explanations for this improvement may include better therapy, earlier diagnosis and inclusion of less aggressive cancer types, while the general improvement of life expectancy has been corrected by using relative survival. More effective treatments include hormonal and cytotoxic therapy, of which the latter in particular was increasingly administered as adjuvant, and also as secondary treatment. Clinical trials have indicated an improved prognosis in patients who received adjuvant chemo- or hormonal therapy.[1] In our series (besides occasional use in stage I patients) the percentage of patients with stage II or III disease receiving adjuvant chemo- or hormonal therapy increased from 2% and 10%, respectively, in 1970-74 to 22% and 27%, respectively, in 1980-84. However, when multivariate analysis was repeated while excluding all patients who received adjuvant chemo- or hormonal therapy, the estimated reductions in excess death rates thus found were very similar to those shown in Table II. Therefore, it can be concluded that the increasing use of these treatment modalities is unlikely to be the cause of the observed improvement of prognosis.

Although some reports suggest that chemotherapy does improve survival in advanced breast cancer,[13] and indeed the percentage of patients with distant metastases at diagnosis who received chemotherapy increased from 19% in 1970-74 to 56% in 1980-84, a change in prognosis in this group could not be determined.

Prevention of complications and better treatment of comorbidity may have had a favourable impact on survival rates. The effect of better radiotherapy (megavoltage therapy was introduced in 1973) on survival was probably limited.[14,15]

The reported overall relative survival rates are similar to survival rates in some other European cancer registries,[6,16] but population-based data on trends in relative survival rates according to stage are rare. Although such data can demonstrate to which degree survival rates in cancer patients improved in the general population, improvements cannot be attributed to specific causes.

Moreover, some questions remain about the validity of this considerable improvement in survival rates. Although an adjustment was made for the increase in early stage over time, using multivariate analysis, earlier detection may still have had a small impact on stage-specific outcome, since within the stage groups a trend towards earlier detection is also likely.[17] Furthermore, in later years, an increasing number of patients may have been allocated to higher stages owing to introduction of more extensive staging procedures, particularly axillary nodal clearance.[18] This may also have contributed to a slightly more favourable outcome in all stages.[19] As relative survival also improved in the patients with unknown stage at diagnosis, bias caused by this group of patients is probably small.

It seems justified to conclude that the improvement in prognosis in short-term as well as in long-term survival is real, and is in accordance with the diverging trends in incidence and mortality in this region. This improvement in prognosis cannot be attributed to a decrease in other causes of death. However, detection of less malignant cancer, or a change in the natural history of the disease in this period, cannot be ruled out.[20]

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4.3 Long-term prognosis of breast cancer: an analysis of 462 patients in a general hospital in south-east Netherlands*

Abstract

In this study the long-term prognosis was analysed of all 462 consecutive female breast cancer patients who were diagnosed and carefully staged between 1970 and 1980 in a 600 bed community hospital in Eindhoven, south-east Netherlands. Follow-up of recurrence and causes of death was obtained until 1 January 1993. Observed survival rates at 5, 10, and 20 years were 66%, 45%, and 32%, respectively, and the corresponding breast cancer-specific survival rates were 71%, 54% and 44%. The yearly risk for a recurrence of breast cancer after treatment steadily decreased from 10% the first year to 1% after 10 years.

In a multivariate survival analysis both tumour size and nodal status appeared to be equally important prognostic factors in the first 5 years after diagnosis. After 5 years only tumour size had independent prognostic value, which was not significant any more after 10 years. In patients with a tumour size $\leq$ 2 cm and without lymph node involvement at diagnosis, the risk for a recurrence was found to be negligible after 10 years. Those patients may be considered cured, although a search for early diagnosis of a second primary breast cancer in this group is still advisable.

* Nab HW, Kluck HM, Rutgers EJT, Coebergh JWW, Hop WCJ. Long-term prognosis of breast cancer: an analysis of 462 patients in a general hospital in south-east Netherlands. Eur J Surg Oncol (in press)

Introduction

Although the percentage of long-term survivors after breast cancer is relatively high, a cure is not likely to be attained up to at least 15 years.[1-6] Because decisions on continuation of routine control visits should be well founded, more detailed knowledge regarding the time periods during which prognostic factors have their greatest influence may be of practical value.[7] This may also add to the knowledge on the related biological mechanisms.

However, in breast cancer contrary to factors to predict short-term survival, little is known about the factors that predict survival among patients who have survived a longer time following the primary diagnosis.[6,8-10]

This report presents survival rates of carefully staged and documented breast cancer patients diagnosed between 1970 and 1980 in a general hospital in south-east Netherlands, with follow-up until 1993. The prognostic potential of tumour size, nodal status and age group is investigated within different follow-up intervals.

Material and methods

The study includes all patients with breast cancer diagnosed between 1970 and 1980 in the Sint Joseph Hospital in Eindhoven (now Veldhoven), a community hospital of about 600 beds. Clinical staging was done according to the UICC classification, 1968.[11] Tumour size was measured by the pathologist and divided into three categories: pT1 ($\leq$ 2 cm), pT2 (2-5 cm), or pT3 (> 5 cm). Axillary lymph node status was divided in three categories: pN0 (lymph node negative), pN1 (lymph node positive, without involvement of the apex and without extra nodal growth), or pN2 (lymph node positive with involvement of the apex of the axilla, or with extra nodal growth). Up to 1974 pre-operative biopsy of the apex was usual, thereafter complete axillary clearance was common. The presence of distant metastasis was screened by clinical and laboratory investigations, routine chest radiographs, and by more advanced techniques, if indicated. Overall, four surgeons were involved in the treatment of breast cancer patients, who mainly used radical (before mid-1976) and modified radical (after mid-1976) mastectomy. Patients with central or medial tumour localisation received adjuvant radiotherapy at the parasternal lymph nodes. Patients with pT3 tumours

and/or 3 or more axillary lymph nodes received radiotherapy at the supraclavicular, axillary and parasternal lymph nodes and the chest wall.

Table 1
Characteristics of the patient group.

	patients no.	%
Clinical stage		
I	103	22
II	204	44
III	115	25
IV	34	7
unknown	6	1
Tumour size		
pT1	134	29
pT2	246	53
pT3	60	13
unknown	22	5
Lymph nodes		
pN0	231	50
pN1	101	22
pN2	101	22
unknown	29	6
Total	462	100

Observed (actuarial) survival curves were computed,[13] according to age category (under 50, 50-65, 65+ years), tumour size, and nodal status. In 1979 adjuvant CMF treatment was introduced for premenopausal axillary lymph node positive patients, and only 18 patients received this therapy.

After primary treatment patients were seen in the out-patient clinic every 3 months in the first 2 years, every 6 months up to 5 years, and annually thereafter.[12] In this period of diagnosis in Eindhoven there were two other general hospitals. To our knowledge there was no particular case selection.

Active follow-up was carried out up to 1 January 1993. Causes of death could be traced. Death from breast cancer included only those patients with known metastases. Only 12 patients (3%) were lost to follow-up after variable intervals of observation.Breast cancer-specific survival was calculated by considering patients withdrawn from the study at the moment of non-breast cancer death. Disease-free survival was calculated for patients without distant disease at diagnosis up to a recurrence, the end of the study, or to death. Differences in survival were assessed with the log-rank test, also after adjustment by stratification for other variables. The Cox proportional hazards model was used to simultaneously evaluate the prognostic importance of age, tumour size and nodal status.[14] This was done separately for the first and second 5-year follow-up interval, and for the subsequent 10-year interval. Other statistical methods are indicated in the text. P-values given are two-sided; five percent was considered the limit of significance.

Results

The number of patients according to clinical stage, pathological tumour size and lymph node status is listed in Table 1. Overall, 462 patients were included with a mean age at diagnosis of 57 years (range, 23 to 90 years). Age category did not correlate with pathological tumour size or lymph node status (Kruskal-Wallis tests, p-values > 0.1). During the first 5 years of follow-up, 158 women were reported dead: 132 (84%) due to breast cancer. After 10 years another 99 women had died: 70 (71%) due to breast cancer, and after 20 years another 37 women had died: 24 (65%) due to breast cancer. Observed survival rates for the total group at 5, 10, and 20 years were 66%, 45%, and 32%, respectively; the corresponding breast cancer-specific survival rates were 71%, 54% and 44%. In patients without distant metastasis at diagnosis the risk for a recurrence steadily decreased from an annual 10% in the first two years after treatment to about 1% after 10 years; thereafter, this decrease continued. Clinical stage predicted breast cancer survival very well ($p < 0.001$, Figure 1).

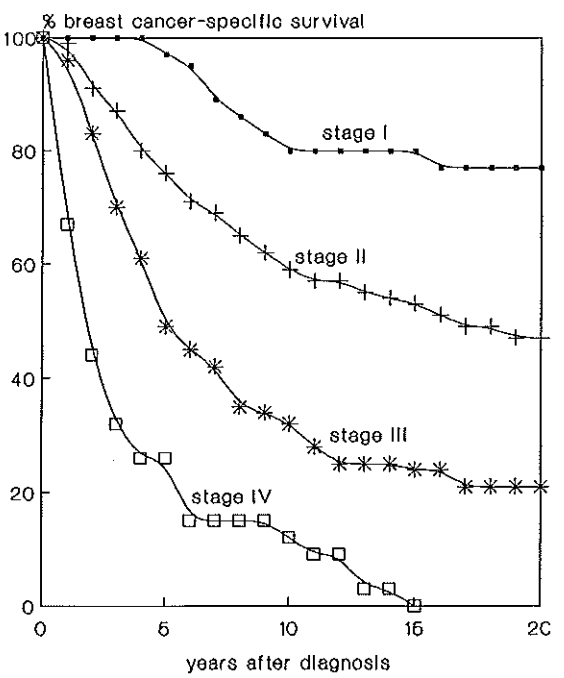

Figure 1. *Breast cancer-specific survival according to clinical stage at diagnosis.*

Within the node negative patient group (pN0), prognosis in pT1 patients was significantly better than in pT2 and pT3 patients ($p < 0.01$), but prognosis was not significantly different between pT2 and pT3 patients ($p > 0.2$; Figure 2). Among the node-positive patients, pT1 patients had a more favourable prognosis than pT2 and pT3 patients ($p < 0.01$), and pT2 than pT3 patients ($p < 0.01$, Figure 2). After 10 years of follow-up, 72% of the pT1N0 patients ($n = 79$), were free of recurrence; of these women, only 1 patient had a recurrence afterwards. In fact, of the 79 pT1N0 patients surviving for 10 years, there was only 1 recurrence in the remaining 488 cumulative follow-up years.

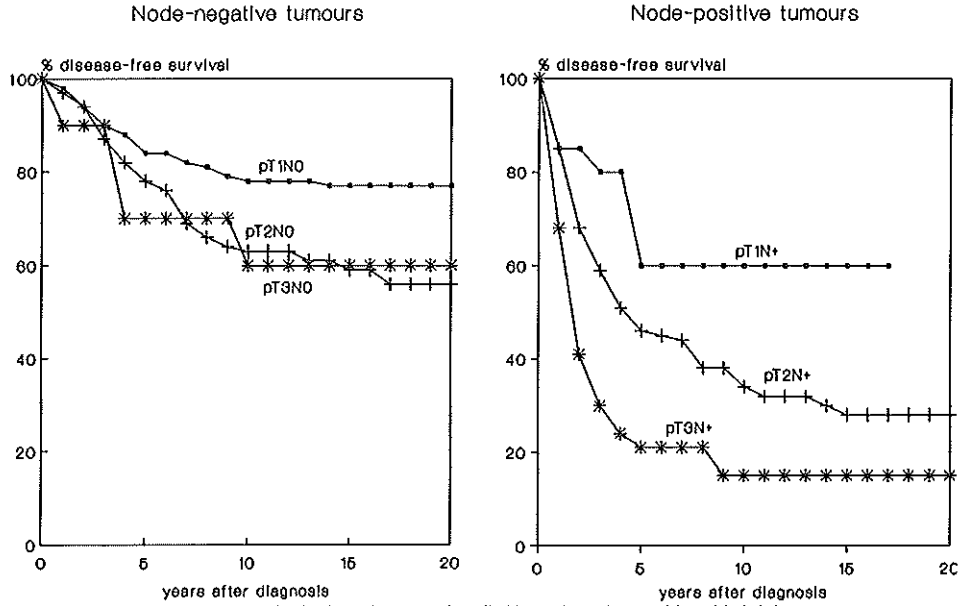

Figure 2. *Disease-free survival of node-negative (left) and node-positive (right) breast cancer according to tumour size.*

In the first 5 years of follow-up both tumour size and lymph node status were significant prognostic factors for disease-free survival, with approximately equal power in a Cox regression analysis (Table 2).

Table 2

Rate ratios (95% CI) for disease recurrence per follow-up interval, according to age, postoperative tumour size and nodal status.

	Follow-up interval		
	0-5 years	**5-10 years**	**10-20 years**
Age group (years)			
< 50[a]	1	1	1
50-65	0.8[b] (0.5-1.1)	0.8[b] (0.3-1.8)	1.0 (0.1-17)
65+	0.7[b] (0.5-1.0)	1.5[b] (0.7-3.5)	10 (1.0-104)
Tumour size			
pT1[a]	1	1	1
pT2	2.0 (1.3-3.1)	6.4[b] (2.2-19)	4.3[c] (0.4-41)
pT3	3.4 (1.9-5.8)	5.7[b] (1.2-26)	
Nodal status			
pN0[a]	1	1	1
pN1	1.9 (1.3-2.7)	0.9[b] (0.4-2.1)	0.5[d] (0.1-5)
pN2	3.5 (2.4-5.2)	1.2[b] (0.4-3.2)	

[a]*Reference category.* [b]*Estimates are not significantly different from each other.* [c]*Estimate for pT2 and pT3 combined versus pT1.* [d]*Estimate for pN+ versus pN0.*

The second 5 years of follow-up, tumour size was again an important prognostic factor, in contrast to nodal status. After 10 years of follow-up the prognostic effect of tumour size remained, although to a smaller extent. The independent effect of age on prognosis, adjusted for tumour size and nodal status, was very small: only the oldest age group had better prognosis the first 5 years of follow-up and a worse prognosis after 10 years of follow-up; however, both these estimates were only borderline significant.

Discussion

The present analysis shows that the prognostic influence of tumour size remains present for a longer time period as compared to nodal status. This finding is in line with the results reported by Toikkanen et al.[10] Their study among 10-year survivors of breast cancer, showed that tumour size remained a significant prognostic factor after 10 years of follow-up, whereas nodal status only predicted survival the first 10 years of follow-up. The finding that the prognostic effect of nodal status has disappeared after 5 years is in agreement with the results reported by Lipponen et al.[8] They found that the marked prognostic influence of both tumoursize and nodal status diminished steadily during the first 5 years of follow-up, becoming non-significant after 5 years of follow-up.

In this analysis of breast cancer survival the influence of prognostic factors considerably changed over time. Therefore, it is advised to distinguish between short follow-up intervals in survival analyses of breast cancer.

An earlier analysis of this patient group showed that the great majority of local recurrences were detected during routine control visits,[12] and that the intensive search for distant disease by routine follow-up means did not appear to be beneficial to the patients. From this study it was concluded that follow-up after treatment of primary breast cancer should be limited to taking the history, physical examination with emphasis on the loco-regional status, and an annual mammography for the detection of contralateral breast cancer. In the present analysis it appeared that the risk for a recurrence steadily decreased during follow-up, and that after 10 years of follow-up it became very small, particularly in patients with pT1N0 tumours. Weighing the advantage of a very small chance for detecting a recurrence against the disadvantage of many follow-up visits and examinations, we conclude that pT1N0 breast cancer

patients who survived for 10 years may be considered cured, with no need for further routine follow-up visits for the detection of metastasis. However, the increased risk for a contralateral breast cancer,[15,16] may well warrant a search for early diagnosis of a second primary breast cancer.[17]

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4.4 Comparison of the relative survival rates calculated with the methods of Hakulinen and Ederer

Introduction

In a cancer registry, the causes of death of patients most often are not known and, thus, disease-specific survival cannot be calculated. For this reason, the concept of relative survival was developed.[1] For estimation of the relative survival rate the observed survival of the patient group and the expected survival of the general regional population, matched for age, need to be known. Knowledge on cause of death is not necessary.

The relative survival rate has been interpreted as the proportion of patients alive at the end of the interval with respect to the patients alive at the beginning of the interval, and death of the patients is assumed only to be caused by the disease under study. Thus the disease-specific survival is estimated, assuming that the patients are subject to two independent forces of mortality: that under study, and all other causes.[2,3]

Currently available methods

Several methods exist for deriving the expected survival rate. In the first method proposed by Ederer (Ederer I), the probability of surviving e.g. 5 years after diagnosis is obtained from the relevant life tables for all individuals in the study cohort and summed to get the expected number of survivors after 5 years.[1] The expected survival rate is obtained by dividing by the initial size of the cohort, and relative survival is then estimated as the ratio of the observed survival (actuarial) and the expected survival rate.

In the second method of Ederer (Ederer II) the expected probability of dying is estimated at the beginning of every considered interval (e.g. year of follow-up) for each individual still at risk at that time.[4] The sum of these probabilities gives the expected number of deaths in the interval. The first and second method of Ederer clearly differ since in the first method the expected survival is based on the initial cohort, and according to the second method the expected survival is yearly adapted, based on the age-distribution of the patients still alive in the study group.

When patients are included in a study during a longer period of time, with a common closing date, different groups may have different potential follow-up times. For example when the incidence rate among the elderly in particular rises relatively fast, an increasing proportion of elderly patients is included in the analysis. In general, a relatively large proportion of elderly patients will then have a potentially short follow-up time, due to the common closing date. According to the first method of Ederer this will result in a biased estimation of the relative survival, while this is not the case according to the second method. Hakulinen developed a correction for this potential heterogeneity in patient withdrawal,[5] but he retained to the basic principle of calculating an expected survival which depends only on the initial composition of the cohort and on the potential time of follow-up. The Ederer I and Hakulinen estimates of expected survival rates use weights corresponding to the expected survival at diagnosis in the subgroups.[6]

Estève (statistician of the IARC) developed a method based on a maximum likelihood method.[6] His model was compared with the model of Hakulinen in a colorectal cancer data set, of the Registry of Digestive Cancers of the Côte d'Or.[7] The results from both programs were very similar.

Recently another method was proposed by Verheul et al, called the 'rate-adjusted background mortality'.[8] In this approach expected mortality is continuously adapted to the group under observation, in order to have a matched group regarding age, sex, and calendar year at any time. This method is very similar to the Ederer II method.

Essentially there are two different methods for the calculation of relative survival: the method of Hakulinen and the method of Ederer (II). In the present study the relative survival rates calculated by both methods were compared, using data on breast cancer patients diagnosed in south-east Netherlands since 1955 to assess the differences between both methods in estimated relative survival.

Patients

To investigate the differences in outcome between the Hakulinen method and the Ederer II method, relative survival rates calculated by both methods were compared for breast cancer patients diagnosed in south-east Netherlands since 1955. Data of the Eindhoven Cancer Registry were used, and information on the vital status of the patients up to July 1, 1991 was obtained.

For comparability with other published data,[9,10] two patient groups were separately analyzed: the first group consisted of breast cancer patients with a first primary breast cancer diagnosed between 1955 and 1974, and the second group consisted of patients diagnosed between 1970 and 1984. Relative survival rates were calculated with the method developed by Hakulinen, and with the second method of Ederer. Rates were calculated for the total patient group, and for the subgroups of age and stage at diagnosis. The differences between both relative survival percentages were calculated by subtraction.

Results

In patients diagnosed between 1955 and 1974, the relative survival estimates were generally very similar for both methods. Differences between both methods were less than 1% for all the subgroups up to 20 years of follow-up, with the only exception of patients aged over 65 years. In the latter group, only after 10 years of follow-up, relative survival calculated with the Ederer II method was 1.4% higher after 10 years and 9% higher after 20 years as compared to the Hakulinen method (Table I). According to both methods relative survival became 100% after 19 years.

Table I

Relative survival rate (%) for patients diagnosed between 1955 and 1974 calculated with the methods of Hakulinen and Ederer (II).

	10-year relative survival		20-year relative survival	
	Hakulinen	**Ederer**	**Hakulinen**	**Ederer**
Stage group				
localized	66.6	66.1	56.3	56.4
regional	29.0	28.8	21.5	21.5
Age group (yr)				
≤ 50	43.7	43.7	33.7	33.8
51-65	41.0	40.9	33.0	32.3
> 65	43.7	45.1	48.9	58.0
All patients	42.7	42.7	34.5	35.0

Among patients diagnosed between 1970 and 1984, all differences between both methods in the various subgroups (up to 15 years follow-up) were less than 1.5%. Even in the patient group aged over 70 years, the 15-year relative survival rates were similar for both methods (Table II).

Table II

Relative survival rate (%) for patients diagnosed between 1970 and 1984 calculated with the methods of Hakulinen and Ederer (II)

	10-year relative survival		15-year relative survival	
	Hakulinen	**Ederer**	**Hakulinen**	**Ederer**
Stage group				
I	81.7	82.2	76.0	77.3
II	60.0	60.1	52.5	52.5
III	32.7	32.3	28.1	27.9
Age group (yr)				
≤ 40	53.4	53.5	50.1	50.1
41-50	60.0	60.0	52.5	52.5
51-60	55.9	55.8	50.1	50.0
61-70	51.1	51.0	46.3	46.1
> 70	50.3	50.2	54.7	55.2
All patients	54.8	54.3	50.1	49.4

Discussion

From the results of this study it can be concluded that any differences in estimated relative survival rates in patients with breast cancer between the second method of Ederer and the method of Hakulinen were very small in most cases. Only in the group of patients aged 65 years and older, diagnosed between 1955 and 1974, differences became most apparent after 20 years of follow-up.

In the 1960s the incidence of breast cancer in the group aged 65 years and over, increased relatively fast,[11] resulting in a proportional increase in elderly patients. This increase has led to a marked heterogeneity in patient withdrawal. Hakulinen developed his method for this phenomenon in particular and showed, among hypothetical cohorts of patients, his method to be more reliable in estimating relative survival than the second method proposed by Ederer.[5] Therefore, at least in this particular subgroup, relative survival estimates from the method of Hakulinen should be preferred. It is also possible that the observed difference between both methods in this group of patients is solely due to small numbers, because after 20 years only 24 patients in this age group were still alive.

In both the methods of Verheul and Ederer (II) the observed mortality in the study group determines which patients will form the basis of the calculation of the expected mortality in the next interval. Thus, the expected survival rate of the patients is

dependent on the observed survival in the study group. Hakulinen let the expected survival depend only on the initial composition of the cohort, on the year of follow-up, and on the potential time of follow-up.

From a purely statistically point of view the method of Hakulinen does not seem to be incorrect, because in estimating disease-specific survival of the whole cohort, by using relative survival, it is necessary to assume that causes of death are independent. Based on this assumption, the expected survival should not be influenced by the way the cohort is modified by the cause of death under study.

The method of Hakulinen has been supported by the IARC,[6,12] and according to Estève, the Ederer I method (or the Hakulinen method) is currently the method of choice for survival data from cancer registries.[6]

Although the methods available for the calculation of the expected survival are essentially different, the estimated relative survival rates appeared to be very similar in most breast cancer patient groups. In one instance, however, differences became noteworthy. For purposes of comparison with other data, it is advised to explicitly report the method used for the calculation of the expected survival rates.

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Chapter 5. General discussion

5.1 Topics

5.2 Validity of the studies

5.3 Explanations for the changes in incidence

5.4 Explanations for the improved prognosis

5.5 Conclusions

5.1 Topics

The general aim of these studies was to describe and interpret the changes in incidence and prognosis in south-east Netherlands. The findings have been reported. Now, firstly, the validity of these results will be discussed. Secondly the possible explanations for the observed changes will be discussed. Finally, the inferences of this thesis will be addressed and some suggestions for further research will be provided.

5.2 Validity of the studies

In this chapter, firstly, the potential bias in the studies will be addressed. Secondly, the influence of early detection on the assessed rates will be considered. Finally, the diagnostic criteria and the possibility of regression will be discussed.

Incidence and mortality

A registry tries to include all new patients with cancer in a certain area, so that trends in incidence in time or comparison of rates between registries reflect true differences in risk of cancer, and not artefacts of the registration process. Unavoidable under-registration by a registry results from cancer cases that remain undiagnosed by the medical system. This is more likely to occur for patients of old age, in rural areas and for cancers arising deeply in the chest and abdomen.

A defect in the registries' case-finding procedures is another possible source of incompleteness. In the ECR incompleteness is minimized by using multiple source reporting, collecting information from many sectors of the health care system, although death certificates were not available as an additional source for registration. Nevertheless, non-hospitalized patients are easily missed, because their names will appear in only a few, if any, sources of information. In the 1960s in the two other Dutch cancer registries in Friesland and Den Haag,[1] it was found that almost all cancer patients were treated by specialists, and that only 5-8% of the cancer patients were not hospitalized during their disease. Therefore, it can be concluded that this source of incompleteness was probably small.

An additional comparison with the data of the Danish cancer registry revealed that in the early 1960s breast cancer incidence rates in this country were more or less

comparable with the incidence rates in Friesland and Den Haag. Rates in both these Dutch cities were also very similar to the rates in Eindhoven.

In this thesis the incidence rate of breast cancer was calculated since 1960, in a core region of municipalities closely surrounding the city of Eindhoven, as the centre of the registry. Rates in the separate municipalities were compared with rates in the city of Eindhoven, assuming that the calculated incidence rates in Eindhoven were most reliable.

The accuracy and completeness of the Registry was also evaluated during 1981-83. From analyses of referral patterns, registration procedures and various comparisons of incidence, a.o. with cancer mortality, completeness could be assumed for most tumours.[2] More recently a comparison was made between the 1992 data of the ECR with data of the National Medical Registry (LMR), which registers diagnoses of all hospital patients. In this comparison only $3^0/_{00}$ additional patients with breast cancer were found. The denominator, the population estimation, is probably very reliable, because it is continuously registered.

The number of missed cases was probably small because breast cancer is an early detectable tumour, and in the Netherlands breast cancer patients are seldomly treated by general practitioners only, thus easily leading to registration.[3] Moreover, incidence in this region is roughly similar nowadays to that in many other affluent societies,[4] and also long-term trends are comparable.[5] The observed increase in breast cancer incidence in the 1960s was affirmed by the increase in breast cancer incidence in the three other Dutch cancer registries in those years.[6] Nevertheless, in the 1960s there might have been some underregistration in the oldest age group.

Duplicate registrations were avoided by registration of name, date of birth and address, and by record linkage procedures.

In many countries data on mortality, contrary to incidence, often have been recorded nationally for many years, and are thus widely used as a proxy measure of cancer occurrence. For these reasons, mortality data have for long been preferred to incidence data. Mortality is the product of incidence and prognosis and therefore seems a rather redundant measure when incidence and prognosis are known. However, incidence rates can be strongly influenced by the detection methods used, and the introduction of a better detection modality can lead to a sudden increase in the number of detected cancers. This sudden increase inherently consists of a group of relatively early diagnosed patients, with favourable prognosis. It is unlikely that

these patients lead to the same increase in mortality. In fact, mortality may even decline due to the better prognosis for tumours with less advanced stage at diagnosis. Hence, mortality rates are often less influenced by short-term changes in detection modalities than are incidence rates, and they may even be influenced in the opposite direction.

Mortality rates are based on death certificate data, which are sampled by the death register of the CBS in the Netherlands. In south-east Netherlands, autopsy is not a routine practice and mortality statistics are probably more accurate in areas where autopsy is common. Moreover, these patients often are older persons with multiple medical problems, and death is frequently the culmination of these problems. To ascribe the cause of death to only one condition may represent a simplification. On the other hand, from a comparison of hospital diagnoses with underlying cause of death on death certificates, it appeared that of all cancers breast cancer is a tumour the least prone to problems of misclassification.[7,8]

A disadvantage of using only mortality data is that mortality depends on prognosis, and changes in prognosis influence mortality rates, without an obligatory change in the risk of getting the disease. In studying risk factors it is meaningful that the date of death is usually later in time than the date of diagnosis of the disease.[9] The relationship between the exposure and death of the patient may, therefore, be less clear than between the exposure and the diagnosis of the disease.

It can be concluded that there are limitations to both incidence and mortality data, and they should preferably be interpreted in combination with each other.

Survival

The observed survival, breast cancer-specific, and relative survival rates were used as an estimate of prognosis. Observed survival (crude survival) offers the true outcome of the disease: the percentage patients alive after a certain period of time. An advantage of disease-specific survival is that only death due to breast cancer is considered, which is most often the primary interest. A disadvantage is that it depends on knowledge of the cause of death, which is difficult to assess, and often not available. In the study of patients managed in the Sint Joseph Hospital, causes of death were carefully traced and could thus be considered relatively reliable. Disease-specific survival, however, in some instances can be an underestimation of the effect

of the disease on mortality, because therapy-related deaths (e.g. postoperative embolism, cardiovascular disease due to radiotherapy, and second cancers) are often not attributed.[10,11] On the other hand, it may be an overestimation to assume that all deaths in cancer patients are caused by the cancer.

An advantage of relative survival is that excess mortality is considered, regardless of cause. A problem is that the expected survival rates have to be estimated, which should be that of a group similar to the patient group regarding all factors associated with longevity, and free of the disease under study. The available regional life tables are stratified for gender, age and geographic area, but not for many other factors associated with longevity, e.g. socio-economic status, and occupation. Although in the Netherlands the influence of these socio-economic factors is probably limited,[12] mortality due to other causes in the reference group, is determined by many factors, of which only few can be matched for. Consequently, the expected survival rate is an approximation of what would have been expected, taking into account only a few prognostic parameters.

Two different ways to calculate expected survival were discussed in detail in chapter 4.4. Both methods are essentially different, but a comparison between the two methods indicated that differences in relative survival rates, as derived from both methods were generally very small. In the only exception with quite different estimates in the oldest patient group the method of Hakulinen was preferred, which was used in some studies in this thesis.

In another study, in which both disease-specific and relative survival rates were calculated, it appeared that both estimates of prognosis yielded to very similar results.[13] Thus, the methods used for calculating prognosis cannot be held responsible for the observed improved survival rates.

Stage at diagnosis

Assessment of stage at diagnosis is subject to inter-observer variability. In the past few decades, a diversity of improvements in clinical and surgical staging evaluation has occurred, and the intensity of these staging investigations influences the assessed stage. For example, pathological N-staging depends on the number of lymph nodes removed, to the level to which the axilla is dissected, and how accurately the removed lymph nodes are assessed by the pathologist.[14,15]

Nowadays advanced medical imaging (CT-scan, echography) may show early metastases that would not have become evident in the past. This can result in upward migration of the disease stages, of actually unchanged tumours. Stage for stage survival rates can seem to improve as a result of this phenomenon, which is caused by the increasing effort done to get staging information. The more intensive search for axillary nodes by axillary lymph node dissection became common in the region during the 1970s. Tumour size is less likely to be influenced by staging procedures, and in both ECR survival analyses the results were affirmed in the patient group with most reliable information regarding tumour stage at diagnosis.

Early detection and incidence rates

The introduction of a better detection modality, or an increase in detection efforts, such as screening, will give rise to an increase in incidence rates because of the detection of some tumours that were previously detected later in time, or not at all. After some time, a steady state will be reached and rates will decrease to about the previous level, causing a spike in incidence rates.[16] Assuming constant baseline incidence rates, rates will now be somewhat higher than before, because of the additional detection of cases that would not have been detected before, because of the patients' death due to other causes.[17] Because of higher overall death rates, this small overall increase applies to older patients, in particular.

In the early 1980s the USA breast cancer incidence started to rise more rapidly than before, followed by a decline in 1989 and 1990. This spike in incidence was considered the predictable result of the introduction of population screening, which comes to a new steady state after a period of advancing diagnosis.[18-20] In south-east Netherlands the decrease in the incidence rates in women aged under 40 is unlikely to be caused by the artefactual spike phenomena, because the decrease in incidence was not present in women over 40 years of age. In this region there has been earlier detection, mainly because of the gradual increase in mammography during the 1970s.[21] This probably caused a slight increase in incidence rates, spread over a longer period of time without apparent spike. This may have some relevance for the marked increase in the 1980s, in particular for the oldest patient groups, but cannot explain the long-term secular trend in incidence rates.

Early detection and survival rates

When cancers are detected earlier, a part of the increase in survival can be explained by the amount of time the date of diagnosis has been advanced by the application of a better detection modality (lead-time bias).[22] Relative survival rates will improve along with cancers that are smaller and some will be in a less advanced disease stage. For assessing improvements in survival, the best method would be to subtract the lead-time from the group diagnosed in later years. This adjustment could not be made because it is not known to which cases this applies, and the rate of disease progression varies widely. In the studies in this thesis survival rates were adjusted for the stage of disease, because an earlier diagnosis generally implies an earlier stage at diagnosis. Especially in the older data only broad stage groups could be made, such that there will remain an effect of lead-time bias on the assessed improvement in survival (residual confounding).[23] Therefore, the results were also analyzed in small patient groups with most reliable information regarding tumour stage at diagnosis, and in situ carcinomas were excluded. In general results were confirmed within these stage groups.

There was no screening program in the registration area in the study period and most mammograms were made because of clinical suspicion. When mammography and other diagnostic aids are used in case of minor complaints, or only on request of the patient, it can also be regarded as a sort of screening. In such a setting slow-growing tumours are most likely to be detected. Since patients with slow-growing tumours tend to have longer survival times, survival rates can be improved even if earlier detection of the tumour has no benefit (length bias). This was probably the case for a small proportion of (older) women.

Diagnostic criteria and regression

In general it is not difficult for a pathologist to differentiate between malignant and benign tumours, but there is no sharp boundary between non-malignant and malignant groups of cells. Thus it is quite possible to diagnose a lesion as an early breast cancer that is actually not a cancer, and never would become a cancer.[24,25] Some studies regarding overdiagnosis are relevant:

- In autopsy studies in situ cancer has been detected in a higher proportion of women than would have been expected,[26] but the proportion of invasive carcinoma was small. Also the prevalence of small in situ or invasive carcinomas in the contralateral breast of women with breast cancer has been reported to be as high as 45-50%. This figure is considerably higher than the expected 12.5% cumulative risk of contralateral breast cancer 20 years after diagnosis of the initial tumour.[27]
- In the population screening program in Nijmegen it was estimated that 10% (combination of invasive carcinomas and ductal carcinomas in situ) more tumours were detected than would have been found without population screening.[17]
- In women with breast cancer undergoing total mastectomy of the contralateral breast, unsuspected breast carcinoma was found in 17%,[28] and in women with breast cancer undergoing blind biopsy of the contralateral breast, breast cancer was found in 12%,[29] more than two-third of them being carcinoma in situ, so that the percentage of occult invasive carcinoma in these women (who are known to be at increased risk for breast cancer) was less than 7%.

Some of these additionally found tumours may be purely explained by early detection of cases that otherwise would have been found some years later. Some others may be cases diagnosed as cancer, that would regress, remain stable, or progress too slowly to become clinically apparent during the patient's lifetime.[30] This may apply particularly to some of the in situ cancers which, therefore, were analyzed separately.

Another problem is that in the more recent periods due to the increasingly vigorous search for lumps more breast lumps may have been considered histologically cancer though being biologically benign. This would produce an artificial increase in incidence and an improvement in survival. Although they did not review slides, participating pathologists and surgeons in the ECR region consider this phenomenon as unlikely to be important regarding invasive cancer in the study period.

5.3 Explanations for the changes in incidence

There has been a steady increase in incidence since 1960. This increase was present in all birth cohorts between 1880-1889 and 1940-49. Thereafter, this increase did not continue, but actually declined. Simultaneously prognosis improved substantially, also after adjustment for stage at diagnosis. Although one should be cautious about

providing explanations retrospectively, the possible causes for these striking findings will be discussed in this section.

Risk factors

The following factors have repeatedly been identified as potentially responsible for the increasing breast cancer risk, albeit without a clear mechanism of action. It is often suggested that reproductive history plays a role, in particular the exposure to oestrogens, which is supported by the protective effect of oophorectomy.[31] It has often been found that an early age at first birth,[32-36] and a high parity have a small protective effect on the risk of breast cancer.[32,34,36-38] In south-east Netherlands women had their first childbirth steadily later, and had less children, and the increase in incidence seems to be in line with the marked decrease in family sizes since about 1965.[39] On the other hand, from long-term studies in Connecticut and Iceland with a similar increasing incidence as in south-east Netherlands, it appeared that the increase in incidence could not be explained by reproductive changes.[40,41]

Early menarche and late age at menopause are also well-established but weak risk factors.[31,33,35,42] In the Netherlands there has been a shift towards earlier menarche and later menopause, which may have had its effect on incidence.

Oral contraceptive use has been suspected of increasing the risk of breast cancer in women up to about 45 years of age or before the first full term pregnancy,[43-55] although many studies have failed to find this association.[56-61] Possibly, the higher hormone doses, which were used shortly after the introduction of the contraceptive pill, led to a small increased risk of breast cancer in birth cohort 1940-49.[47,51,62-66]

A small risk from oestrogen replacement therapy is likely, particularly among current users, who were treated for a long time,[67-74] although some studies refute these findings.[75-78] The widespread use of oestrogen-replacement therapy in the Netherlands may have contributed to some extent to the higher incidence among postmenopausal women.

A role for diet, in the etiology of breast cancer has been suspected for some time, based on animal studies and on the correlation between national fat consumption and breast cancer rates.[79,80] Although this relationship was affirmed in some studies,[81-84] in most cohort and case-control studies an association between high fat intake or energy intake and breast cancer incidence was not found.[85-95] There remains the

possibility that diet during adolescence, when breast tissue is growing rapidly, is more important than the adult diet, or that some specific constituents of the diet are important.[96,97] However, there are few indications that this has played an important role in south-east Netherlands.

An increased risk of breast cancer has been reported consistently for radiation exposure from various sources, including the atomic bomb explosions in Japan,[98] and medical treatments involving repeated exposure to radiation, such as fluoroscopic chest radiography for tuberculosis,[99-101] and for medical diagnostic radiology workers.[102] The carcinogenic effect of radiation on the breast appears to be greatest when exposure occurred around menarche and decreases with increasing age at exposure.[98-101] This can have some relation with the peak in breast cancer incidence in the birth cohort 1940-49, because women aged 10-20 years were regularly screened by X-ray for tuberculosis in the 1950s and 1960s.

To conclude, much of the etiology of breast cancer is still unexplained, and most of the established risk factors for breast cancer are associated with only a modest increase in risk, with a relative risk most often not higher than two. Part of the increase in breast cancer risk may be associated with an earlier age at menarche, delayed parenthood and a decreased birth rate. Which other risk factors are important for the marked changes in incidence remains unclear.

Competing risks

When two diseases (disease A and B) share important common risk factors the changes in incidence or prognosis in disease A can influence the incidence of disease B. When mortality of disease A declines because of a decline in risk factors, the mortality of the disease A will also decline. When the reduction in mortality in disease A is caused by better treatment, more people survive, who are at high risk for the disease B, and thus the incidence of this disease may increase. In south-east Netherlands mortality from all other causes has declined sharply during the past three decades, in particular for cardiovascular disease. It can not be excluded that these reductions have had an impact on breast cancer incidence, but it is thought to be small for age-adjusted rates.[103]

Relative survival rates are less influenced, because by dividing observed rates by expected survival rates, an adjustment is performed for lower expected death rates in time.

5.4 Explanations for the improved prognosis

Better treatment

Surgical techniques differed in the 1980s from the 1960s mainly in that they were less radical, and improved surgical treatment alone is unlikely to explain the greatly improved survival rates. Megavoltage radiotherapy was introduced, and better radiotherapy might have had an effect on local failure rates, but a large effect on survival is also unlikely.[104] Adjuvant chemotherapy and tamoxifen have only a small effect on survival rates, and were given to only a few patients. Perhaps there was some slight additional effect from chemotherapy after recurrence.[105-109]

Improved supportive care, including prevention of complications such as thrombosis and infections and better treatment of comorbidity, may also have had an effect on better prognosis. Nowadays most patients with breast cancer may still die due to their disease, but death is delayed because of the combined medical treatments for complications and diseases.

Change in malignancy

In the city of Turku, Finland, breast cancers diagnosed in 1980-84 were compared with those diagnosed in 1945-65.[110] It appeared that the 1980-84 carcinomas were more often well differentiated, had lower mitotic counts, less nuclear pleomorphism, more often had a well-defined tumour margin, and had less tumour necrosis. It was concluded that this change could have partly contributed to the improvement in survival in stages II-IV.

In another study, using data of a large health maintenance organization in the USA,[111] it was found that most of the increase in incidence, from the mid-1970s to the mid-1980s, occurred for oestrogen receptor-positive tumours, which have a relatively favourable prognosis. This increase was seen in all stages, and was particularly marked in women aged over 60 years of age.

The nature of breast cancers found nowadays may be different from those found decades ago. Such a change can be due to an overall change in the natural history of breast cancer, to a relatively large increase in incidence of particularly less aggressive tumours, or to a combination of these.

5.5 Conclusions

In south-east Netherlands the incidence rate of female breast cancer has increased, at least since 1960. Age-adjusted incidence rates about doubled in the last three decades. This increase was especially marked in the 1980s, but did not continue in women born since 1950. The long-term increase in incidence was also observed in most other countries with available data,[5] and a decline in the youngest birth cohorts was also observed in Scotland.[112] The observed decrease in the youngest birth cohorts may suggest that the increase in age-adjusted rates is coming to an end. However, the numbers of women with breast cancer will expectedly continue to rise for many years, due to the large number of women born during the post World War II baby boom.[113]

The observed long-term secular increase in incidence is in line with rates in many other affluent societies, and reflects changes in known and unknown risk factors. Among the risk factors, the higher age of women at first birth, a lower fertility rate, earlier menarche and delayed menopause may be involved, and earlier detection of tumours also played a small role. The majority of risk factors responsible for the overall steady increase in incidence is, however, still unknown.

Earlier diagnosis caused a change for the majority of patients with advanced disease at diagnosis towards a small localized lump in the breast. Early detection, in particular by mammography, has become an important aspect of current breast cancer management. A problem in interpreting mammograms is that radiologists do not detect all carcinomas that are visible.[114] Some reasons for this can be distraction by other image features, or simple oversight.[115] The efficacy and efficiency of the readings might be improved if a computerized detection system could assist radiologists by indicating locations of suspicious abnormalities in mammograms.[115,116]

In one report conventional and digital mammography showed comparable diagnostic results. This study was later affirmed in a larger data set using the same resolution,[117] showing that digitization even improved the detectability of the larger, low

contrast objects, whereas for small objects the detectability did not change. With the future aid of automatic detection procedures, and advanced image manipulation techniques, it is expected that in the near future the detectability of breast cancer can be further improved with digital mammography.

Prognosis of breast cancer patients improved markedly. This improvement was present in all age and stage groups. The apparent earlier detection played a major role in this overall improvement. Improved cancer treatment probably had only a limited effect on this change. Although data regarding this aspect are very scarce, an increased detection of tumours with favourable histological characteristics may have played a role.

Several studies addressed the issue when breast cancer patients could be considered cured, some of them showing excess death rates due to breast cancer for 20,[116,119] up to 40 years.[120] In the long-term follow-up study included in this thesis it was affirmed that breast cancer affects the prognosis for more than a decade. Prognosis equalled that of the general population after 19 years. This was similar to the results found in a patient group diagnosed between 1945 and 1965 in the city of Turku, Finland, with a percentage of cured patients of about 34% after 20 years.[13] Additionally, a cure was reported among Italian breast cancer survivors after 18 years.[121] In the patient group diagnosed between 1970 and 1980 in the Sint Joseph Hospital in Eindhoven, with more detailed information on stage at diagnosis and recurrence in patients with the most early stage at diagnosis the risk for a recurrence was so marginal after 10 years, that it was concluded that they would not need further follow-up. Although results regarding cure are contradictory, it is clear that the prognosis of patients with breast cancer becomes better the longer they survive, and after a long enough period of follow-up the risk for a recurrence obviously becomes very small.

A remarkable feature of breast cancer was the stability in age-adjusted breast cancer mortality, as the ultimate measure of the impact of the disease. This stability in mortality rates, has occurred during a period of dramatic changes in other diseases. The overall age-adjusted mortality decreased markedly and breast cancer as a cause of death increased. Maybe the combined medical efforts for detection and treatment have compensated the increase in risk factors. Considering breast cancer as a 'mixture' of diseases, with different survival times, one aggressive subtype, apparently

not influenced by early detection and treatment, caused the stable breast cancer mortality, whereas the less malignant subtypes increased in incidence.

The features of breast cancer have changed considerably since 1955. Then breast cancer was relatively seldom, most often diagnosed in an advanced stage, and in spite of very mutilating surgery, it had a poor prognosis. This has changed toward a more common disease, with some therapeutic options including less mutilating surgery, and with a relatively good prognosis. Although breast cancer has been feared by many women, it should no longer be considered as invariably lethal.

Research topics

The papers in this thesis have identified various areas of priority for further research:

There are only few studies comparing the aggressiveness of tumours found years ago with more recent tumours. More detailed knowledge about these differences might give more insight as to why prognosis improved.

Long-term survival analysis with reliable data regarding cause of death can show which method of calculating relative survival estimates most precise disease-specific survival.

Although after 19 years survival became similar to the reference population we do not know whether causes of death were also similar. The possibility exists that although overall survival is equal, the pattern of death is different between the groups, and still shows a higher mortality for breast cancer. A study of patterns of death in long-term survivors might elucidate this issue.

Given the improving survival of first primary breast cancer, incidence of contralateral breast cancer is also increasing, now reaching about 10% of all breast cancers. Presentation of combined incidence rates of first and second primaries should therefore be avoided, and the real incidence of second primary breast cancer be calculated on the yearly prevalence of women with a first primary breast cancer.

Digital mammography, although a very promising technique for early detection of breast cancer, has not yet proven very useful clinically in the detection of breast cancer. Introduction of digital mammography in a screening program should be tested. New automatic detection procedures and computer image-manipulation techniques should now be developed to further enhance efficiency.

Breast cancer screening is being introduced in the Netherlands. Screening results in the detection of lesions that may be early stages of cancer but generally involve complicated diagnostic procedures, treatment and follow-up. Screening will also cause short-term changes in incidence and probably a decrease in mortality in the screened group. Therefore the cancer registry should monitor these trends together with the Central Bureau of Statistics. Continued monitoring of breast cancer incidence and mortality, combined with the completion of survival analyses, may give us further insight regarding the trend in the actual breast cancer onset rate.

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Summary

This thesis addresses the incidence and prognosis in south-east Netherlands since 1955. Population-based data were derived form the Eindhoven Cancer Registry. Between 1960 and 1989 the crude incidence rate of first primary breast cancer increased from about 35 per 100,000 person-years to 93, and adjusted for age from 37 to 70. This approximately doubling in rates was present in all age groups, and was mainly the result of an increase in localised and, to a lesser extent, distant tumours. Based on the estimated time-trend it appeared that age-specific incidence increased for every successive birth cohort in the period 1880-1949. The incidence rates in women born after 1949 declined and were 21% lower than expected by the estimated secular trend. This decrease in women aged under 40, suggests that the peak in incidence of female breast cancer may be in sight.

The observed long-term secular increase in incidence is in line with rates in many other affluent societies, and reflect changes in known and unknown risk factors. Among the risk factors, the higher age of women at first birth, a lower fertility rate, earlier menarche and delayed menopause may be involved, and earlier detection of tumours also played a small role. The majority of risk factors responsible for the overall steady increase in incidence, and for the decrease in the youngest birth cohorts, is still unknown.

There was a continuous trend towards earlier detection of the disease, being greatly facilitated by the introduction of many new diagnostic techniques, such as mammography. This resulted in a marked increase in the percentage of localised tumours from 37% in the 1960s to 54% in the 1980s and of distant tumours from 4% to 7%, whereas the percentage of regional tumours decreased from 59% to 39%. This trend towards a more favourable stage with time continued in the 1980s.

To further improve detectability, the introduction of digital mammography is considered. This technique offers the possibility of manipulating the mammograms to improve the visibility of cancers, and for using advanced automatic detection procedures. From a comparison of conventional mammograms with base-line digital mammograms at the Dutch National Expert and Training Centre for Breast Cancer Screening in Nijmegen, it appeared that diagnostic results for both methods were comparable, without using advanced techniques of image manipulation in digital mammograms. Therefore, it is expected that in the near future the detectability of

breast cancer can be further improved by digital mammography, when adequate computer programs for automatic detection and image-manipulation techniques become available.

Two studies on prognosis were population-based, and addressed in particular changes in prognosis in time. The first study was on 2,052 patients with a first primary breast cancer diagnosed between 1955 and 1974. For patients without distant metastases at diagnosis 10 year survival increased steadily from 26% for patients diagnosed in 1955, to 39% for the patients diagnosed in 1970-74. Relative survival rates were calculated as the ratio of the observed to the expected survival rates and are used as an estimate of breast cancer-specific survival. Relative survival rates improved for all stages and all age groups for the whole follow-up period of 20 years. This improvement was most marked for patients who were diagnosed with a localised tumour. Prognosis was strongly related to the stage at diagnosis in the first 10 years of follow up but independent of stage after 10 years. Survival of patients still alive after 19 years became similar to that of the general female population, suggesting a cure for these patients.

In the second population-based survival study, changes in prognosis were investigated among 4,467 breast cancer patients, diagnosed between 1970 and 1984. The 5 year relative survival of this patient group improved steadily, from 63% in 1970-74 to 78% in 1980-84. This increase was apparent in all age groups and in all stages, except for distant disease. After adjustment for age, relative survival was strongly related to the stage of the disease in the first 5 years of follow-up, less markedly between 5 and 10 years and to a small, borderline significant, extent after 10 years of follow-up. The observed improvement in survival could not be contributed to the increased use of adjuvant chemo- and hormonal therapy, which only became popular in the 1980s.

Prognosis was also analyzed in the patient group, diagnosed between 1970 and 1980 in the Sint Joseph Hospital in Eindhoven (now Veldhoven). These patients were carefully staged, and follow-up of recurrence and causes of death were attained until 1993. Observed survival rates at 5, 10, and 20 years were 66%, 45%, and 32%, respectively, and the corresponding breast cancer-specific survival rates were 71%, 54% and 44%. The yearly risk for a recurrence of breast cancer after treatment steadily decreased from 10% the first year to 1% after 10 years. In this study both tumour size and nodal status appeared to be equally important prognostic factors in

the first 5 years after diagnosis. After 5 years only tumour size had independent prognostic value, which was no longer significant after 10 years. In patients with a tumour size ≤ 2 cm and without lymph node involvement at diagnosis, the risk for a recurrence was found to be negligible after 10 years.

Notwithstanding the marked changes in incidence and prognosis, simultaneously breast cancer mortality remained almost unchanged. It is possible that the combined medical efforts have compensated the increase in prevalence of known and unknown risk factors. Other possibilities are a change in aggressiveness of the disease in time, an increase in incidence of a less malignant subtype in particular, or a combination of those.

The features of breast cancer have changed considerably in three decades. Breast cancer became a more common disease, feared by many women but no longer to be considered as necessarily lethal.

Samenvatting

Dit proefschrift behandelt de trends in incidentie en prognose van borstkanker bij vrouwen in Zuidoost-Nederland sinds 1955. De gegevens over de patiënten in deze regio waren afkomstig van de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ) in Eindhoven. Tussen 1960 en 1989 nam de incidentie van borstkanker toe van circa 35 per 100.000 persoonsjaren tot 93, en gecorrigeerd voor de veranderingen in leeftijdsopbouw van 37 tot 70. Deze toename was aanwezig bij alle leeftijdsgroepen. Met name de incidentie van tumoren met alleen lokale uitbreiding nam toe, en voor een kleiner deel van tumoren met metastasen op afstand. Uit een nadere analyse bleek dat de incidentie in deze periode bij vrouwen geboren tussen 1880 tot 1949 bij elk volgend geboortencohort toenam, maar dat de incidentie bij vrouwen geboren na 1949 weer daalde. Bij deze groep vrouwen onder de 40 jaar was de incidentie 21% lager dan verwacht op basis van de geschatte trend in de tijd. Deze afname kan een eerste aanwijzing zijn dat de piek van de incidentie van borstkanker bij vrouwen in zicht is.

De waargenomen lange termijn toename in de incidentie komt overeen met wat in veel andere Westerse landen wordt gezien, en geeft de veranderingen in bekende en - met name - onbekende risicofactoren weer. Onder de bekende risicofactoren die mogelijk een rol spelen zijn vooral van belang de toegenomen leeftijd van vrouwen bij de geboorte van hun eerste kind, de afname van het aantal kinderen per vrouw, de vroegere menarche, en een gemiddeld latere menopauze. Vroegere detectie van tumoren was tevens verantwoordelijk voor een klein deel van de stijging in de incidentie. Het grootste deel van de risicofactoren, verantwoordelijk voor de gestage toename in de afgelopen dertig jaar en ook voor de afname in de jongste geboortencohorten, is echter onbekend.

In de periode van onderzoek was er een continue trend naar vroegere diagnostiek van de ziekte, die met name mogelijk werd gemaakt door de introductie van nieuwe diagnostische technieken, zoals mammografie. Dit resulteerde in een sterke toename van het percentage tumoren met alleen lokale uitbreiding: van 37% in de jaren zestig tot 54% in de jaren tachtig, en van 4% tot 7% voor tumoren met metastasen op afstand; het percentage tumoren met regionale uitbreiding nam tegelijkertijd af van 59% tot 39%. Deze trend naar een steeds gunstiger stadium bij diagnose zette zich ook in de jaren tachtig voort.

Voor verder verbetering van de diagnostiek van borstkanker wordt veel verwacht van digitale mammografie vanwege de mogelijkheid om de afbeeldingen te verbeteren en tumoren automatisch te detecteren met computerprogramma's. Daarom werd bij het Landelijk Referentie Centrum voor bevolkingsonderzoek op Borstkanker in Nijmegen de detecteerbaarheid van borstkanker op conventionele mammogrammen vergeleken met onbewerkte digitale mammogrammen. Het bleek dat de detectie met beide methoden ongeveer even goed was. Er kon nog geen gebruik gemaakt worden van beeldbewerking en automatische detectie, maar de verwachting is dat met de introductie van deze technieken de diagnostiek en efficiëntie verder verbeterd kunnen worden.

Voor dit proefschrift werden twee studies verricht naar de veranderingen in de prognose van borstkankerpatiënten op populatienivo. De eerste studie betrof 2052 patiënten met een eerste primaire borstkanker gediagnostiseerd tussen 1955 en 1974. De 10-jaarsoverleving van patiënten zonder metastasen op afstand verbeterde geleidelijk aan, van 26% voor de patiënten gediagnostiseerd tussen 1955 en 1959 tot 39% voor de patiënten gediagnostiseerd tussen 1970 en 1974. Van deze patiënten werd ook de relatieve overleving berekend, die werd gebruikt als schatting van de borstkankerspecifieke overleving. De relatieve overleving verbeterde voor alle stadia en alle leeftijdsgroepen, voor de gehele follow-up periode van 20 jaar. Deze verbetering in de prognose was het meest uitgesproken bij patiënten met een tumor met alleen lokale uitbreiding. De eerste 10 jaar na de diagnose was de prognose sterk gerelateerd aan het stadium, maar daarna niet meer. De prognose van patiënten die na 19 jaar nog in leven waren, was gelijk aan die van de vrouwelijke bevolking in de regio. Daarom kunnen deze patiënten op dat moment als genezen worden beschouwd.

De tweede studie naar de veranderingen in de prognose van patiënten op populatienivo betrof de 4467 patiënten gediagnostiseerd tussen 1970 en 1984. De waargenomen relatieve 5-jaarsoverleving van deze groep verbeterde ook, van 63% voor de patiënten gediagnostiseerd in 1970-74 tot 78% in 1980-84. De 10-jaarsoverleving verbeterde van 39% naar 49%. Deze toename was in alle leeftijdsgroepen en in alle stadia aanwezig, met uitzondering van patiënten bij wie tijdens de diagnose metastasen op afstand werden vastgesteld. Na correctie voor leeftijd bleek dat de eerste 5 jaar na de diagnose de relatieve overleving sterk gerelateerd was aan het stadium van de ziekte bij de diagnose. Dit verband was veel minder sterk tussen 5

en 10 jaar follow-up en minimaal wanneer de patiënten 10 jaar hadden overleefd. De waargenomen verbetering in de prognose kan niet verklaard worden door het meer toepassen van adjuvante chemo- en hormonale therapie.

De prognose voor de groep patiënten die tussen 1970 en 1980 gediagnostiseerd werd in het Sint Joseph Ziekenhuis in Eindhoven (tegenwoordig Veldhoven) werd apart geanalyseerd omdat zij heel zorgvuldig was gestadiëerd en vervolgd. Van deze patiënten werden tevens het eventuele moment van recidief en de doodsoorzaken nagegaan. Bij hen was de waargenomen overleving na 5, 10, en 20 jaar respectievelijk 66%, 45%, en 32%, en de borstkankerspecifieke overleving 71%, 54% en 44%. Het jaarlijkse risico op een recidief na behandeling nam geleidelijk af, van 10% in het eerste jaar tot 1% na 10 jaar. In deze studie bleek gedurende de eerste 5 jaar na de diagnose zowel de tumorgrootte als de okselklierstatus een ongeveer even belangrijke prognostische waarde hebben. Na 5 jaar echter, bleek alleen tumorgrootte nog onafhankelijke prognostische waarde te hebben. Bij patiënten met een tumor niet groter dan 2 cm en die bij de diagnose geen aangedane lymfeklieren hadden, bleek het risico op een recidief na 10 jaar verwaarloosbaar klein te worden.

Ondanks de grote veranderingen in de incidentie en prognose, bleef de afgelopen dertig jaar de sterfte aan borstkanker vrijwel onveranderd. Het is mogelijk dat de medische vorderingen in de diagnostiek en de therapie de toename in de prevalentie van risicofactoren hebben gecompenseerd, waardoor verbeteringen in de diagnostiek en therapie opwogen tegen de stijging in de incidentie. Andere mogelijke verklaringen zijn dat de agressiviteit van de ziekte is veranderd, dat vooral de incidentie van een minder agressieve variant van borstkanker toenam, of een combinatie hiervan.

De kenmerken van borstkanker zijn de afgelopen dertig jaar aanzienlijk veranderd. Vroeger was deze ziekte vrij zeldzaam en werd meestal in een laat stadium ontdekt. De therapie was ingrijpend en de prognose vrij matig. Tegenwoordig komt borstkanker veel vaker voor, maar wordt meestal in een vrij vroeg stadium ontdekt. De therapeutische mogelijkheden zijn mettertijd sterk toegenomen en zijn minder ingrijpend geworden. De prognose is tegenwoordig relatief goed. Al met al is borstkanker veel meer een 'gewone' ziekte geworden. De ziekte wordt nog steeds gevreesd door veel vrouwen, maar wordt steeds minder vaak als vrijwel onherroepelijk dodelijk beschouwd.

Dankwoord

In dit proefschrift beschrijf ik enkele studies die werden uitgevoerd bij de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ). Mevrouw M.Th. Verhagen-Teulings verzamelde daarvoor met enkele medewerkers vele jaren op grondige wijze gegevens die essentieel waren voor het onderzoek. De financiering werd geregeld door Dr. J.W.W. Coebergh, die ook een creatieve bijdrage aan het onderzoek leverde. L.H. van der Heijden was behulpzaam met velerlei computerprogramma's, die veelal door hemzelf waren ontwikkeld. De continuïteit van computerzorg werd gewaarborgd door L. van de Wal, die altijd bereid was de moeilijkste computerknopen te ontwarren. De jarenlange ervaring bij de behandeling van borstkankerpatiënten van Dr. H.M. Kluck en M.A. Crommelin kwam goed van pas. Dr. P.P. Razenberg zorgde voor een structurele onderzoeksbasis bij het IKZ waarin het goed toeven was. Met mijn collega onderzoekers alhier heb ik altijd fijn samengewerkt.

Als thuisbasis diende de afdeling Epidemiologie & Biostatistiek van de Erasmus Universiteit Rotterdam. Prof. dr. A. Hofman zorgde er als promotor voor dat het overzicht behouden bleef, stimuleerde en gaf snel en deskundig advies. Met de statistici ir. W.C.J. Hop en dr. P.G.H. Mulder overlegde ik vaak en ik was steeds weer onder de indruk van hun snelle inzicht in de materie. Met de collega's hier was het contact altijd prettig.

Een deel van het onderzoek werd uitgevoerd bij de sectie Fysica en Informatica van het instituut Radiodiagnostiek. W. Guyt gaf veel hulp bij de computersoft- en hardware. Dr. N. Karssemeijer leerde me veel over digitalisering. Dankzij de dynamiek van dr. ir. L.J.T.O. van Erning kon er altijd veel op deze afdeling, ook op niet gangbare uren. De radiodiagnosten van het Landelijk Referentie Centrum voor bevolkingsonderzoek op Borstkanker, Dr. J.H.C.L. Hendriks en C. Boetes besteedden veel tijd aan het beoordelen van de mammogrammen, en gaven nuttige adviezen voor mogelijke verbetering van de digitale mammogrammen. Op de afdeling Epidemiologie van de Katholieke Universiteit Nijmegen leerde Prof. Dr. A.L.M. Verbeek me de eerste beginselen van de epidemiologie.

Van de paranimfen L.H. van der Heijden en drs. A.C. Voogd had ik veel steun. De leden van de beoordelingscommissie ben ik erkentelijk voor de voortvarende wijze waarop zij het manuscript hebben getoetst.

Curriculum vitae

Henk Nab werd geboren op 23 oktober 1961 in Zetten in de Betuwe. Hij studeerde geneeskunde aan de Katholieke Universiteit Nijmegen. Na zijn doctoraal-examen deed hij een jaar onderzoek naar de effectiviteit van geneesmiddelen op de afdeling Experimentele Neurologie, Academisch Ziekenhuis Nijmegen. Na zijn artsexamen werd hij aangesteld als wetenschappelijk medewerker bij de afdeling Epidemiologie, Katholieke Universiteit Nijmegen, en bij de sectie Fysica en Informatica van de afdeling Radiodiagnostiek, Academisch Ziekenhuis Nijmegen. Hier bestudeerde hij de mogelijkheden van digitale mammografie. Eind 1990 werd hij aangesteld als wetenschappelijk medewerker bij het Instituut Epidemiologie & Biostatistiek, Erasmus Universiteit in Rotterdam, waar hij verder werd opgeleid in de epidemiologie. In deze functie analyseerde hij de gegevens van de kankerregistratie van het Integraal Kankercentrum Zuid te Eindhoven (IKZ). Hij was tevens als docent epidemiologie verbonden aan enkele opleidingsinstituten. Sinds 1994 werkt hij als klinisch beoordelaar bij het Directoraat van het College ter Beoordeling van Geneesmiddelen. Hij is geregistreerd als epidemioloog A.

H.W. Nab

Trends in incidentie en prognose van borstkanker bij vrouwen sinds 1955

Dit proefschrift behandelt de trends in incidentie en prognose van borstkanker bij vrouwen in Zuidoost-Nederland sinds 1955. Voor dit onderzoek werd gebruik gemaakt van gegevens van het Integraal Kankercentrum Zuid (IKZ) in Eindhoven. Het IKZ werkt aan integrale zorg voor mensen met kanker en ondersteunt hulpverleners die daarbij betrokken zijn in het ziekenhuis en in de thuiszorg in het gebied Noord-Brabant en Noord-Limburg.

Een van de activiteiten van het IKZ is de kankerregistratie: het verzamelen en bewerken van gegevens over alle vormen van kanker. Deze registratie is in 1955 gestart in het oostelijk deel van de regio. De registratie heeft als enige in Nederland de tand des tijds doorstaan en stond qua werkwijze model voor de Nederlandse Kankerregistratie die in 1987 van start ging. Zij heeft inmiddels veel informatie over kanker in Nederland voortgebracht, veelal door onderzoek in samenwerking met de Erasmus Universiteit in Rotterdam.

De gegevens die door speciaal opgeleide medewerkers worden verzameld, betreffen onder andere de demografie, gebruikte diagnostiek, toegepaste behandeling en de follow-up. Clinici en wetenschappers gebruiken deze informatie voor velerlei onderzoek. Hierdoor wordt bijvoorbeeld inzicht verkregen in het vóórkomen van kanker, de effecten van preventieve maatregelen en de benodigde toekomstige voorzieningen.

Naast standaardgegevens worden aanvullende gegevens verzameld voor specifiek onderzoek. Dit onderzoek richt zich veelal op prognostische factoren en het beschrijven van zorgpatronen. Momenteel vinden deze zogeheten documentatieprojecten binnen het IKZ plaats op het gebied van mammacarcinoom, maligne gynaecologische tumoren en de ziekte van Hodgkin. Deze documentatieprojecten bieden een instrument om de kwaliteit van zorg te toetsen.

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