Incidence and survival of prostate cancer since 1970

Piet Post

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CONTENTS

Publications and manuscripts based on the studies described in this thesis.

Post PN, Kil PJM, Crommelin MA, Schapers RFM, Coebergh JWW. Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry-based study in southeastern Netherlands, 1971-1995. *Eur J Cancer* 1998;34:705-709 (chapter 3.1).

Post PN, Stockton D, Davies TW, Coebergh JWW. Striking increase in incidence of prostate cancer in men aged < 60 years without improvement in prognosis. *Br J Cancer* 1999;79:13-17 (chapter 3.2).

Post PN, Straatman H, Kiemeney LALM, Coebergh JWW. Increased risk of fatal prostate cancer may explain the rise in mortality in The Netherlands. *Int J Epidemiol* (In press) (chapter 3.3).

Post PN, Kil PJM, Coebergh JWW. Trends in survival of prostate cancer in Southeastern Netherlands, 1971-1989. *Int J Cancer* (In press) (chapter 4.1).

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Post PN, Kil PJM, Hendrikx AJM, Poortmans PMP, Crommelin MA, Coebergh JWW. Trend and variation in treatment of localized prostate cancer in the southern part of the Netherlands, 1988-1996. *Eur Urol* (In press) (chapter 5.1).

Post PN, Kil PJM, Hendrikx AJM, Janssen-Heijnen MLG, Crommelin MA, Coebergh JWW. Co-morbidity in patients with prostate cancer and its relevance to treatment choice. (submitted) (chapter 5.2).

Post PN, Hendrikx AJM, Hansen BE, van der Heijden LH, Coebergh JWW. Long-term survival of prostate cancer in southeastern Netherlands. (submitted) (chapter 6.1).

Post PN, Hansen BE, Kil PJM, Coebergh JWW. Independent prognostic value of co-morbidity among men aged < 75 years with localized prostate cancer: a population-based study. (submitted) (chapter 6.2).

List of frequently used abbreviations

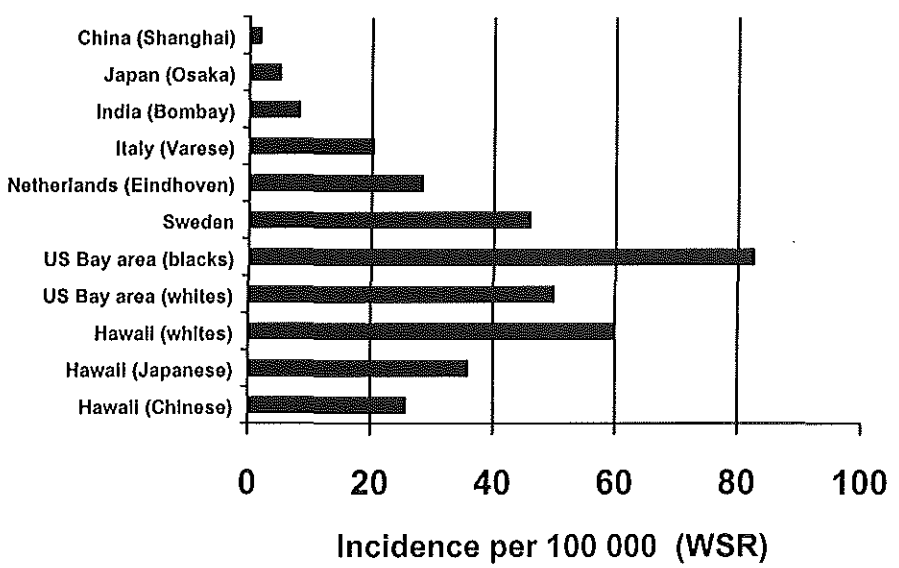
TURP	transurethral resection of prostate
BPH	benign prostatic hyperplasia
PSA	prostate-specific antigen
TNM	Tumour-Node-Metastasis classification
RR	relative risk
HR	hazard ratio
CI	confidence interval
SE	standard error
ESR	European Standardized Rate
WSR	World Standardized Rate
Eurocare	Collaborative study of European cancer registries concerning survival
IKZ	Integraal Kankercentrum Zuid

Chapter 1 Introduction

Increased incidence or just a higher detection rate?

In North America and many European countries, prostate cancer has become the second most common and in some countries even the most common cancer among men during the past two decades.[1] Since the age-specific incidence increases steeply after the age of 50 years, a considerable proportion of the increase in the crude incidence rate for prostate cancer is due to the ageing of the population. Moreover, decreases in mortality due to benign prostatic hyperplasia,[2] cardiovascular diseases[3] and lung cancer[4] may have increased the probability of a diagnosis of prostate cancer. However, the age-standardized incidence has increased considerably as well.[1] Therefore, one might assume that the risk of prostate cancer has increased over the past two decades. The aetiology, however, has not as yet been clarified.

Figure 1 *Age-adjusted incidence of prostate cancer in 1978-1983*



The very low incidence of prostate cancer among Asians as compared to populations in the USA and Northwestern Europe (Figure 1) has resulted in an extensive search for environmental risk factors such as diet, but unfortunately so far little progress has been made. A role for environmental factors is supported by studies of Japanese migrants. Since both early and late migrants show prostate cancer rates that are fairly similar to those for US born japanese, late-life events seem important in the aetiology.[5] Although the prevalence of latent prostate cancer is fairly similar for native Japanese and Japanese in Hawaii, the prevalence of the proliferative type of latent cancer was substantially higher among Japanese from Hawaii (19%) than those living in Japan (9%).[6]

Therefore, frequently used definitions of the various types of prostate cancer need to be distinguished. *Latent* prostate cancer is defined as prostate cancer found in a man in whom there was no clinical diagnosis or suspicion of prostate cancer before death.[7] It can subsequently be subdivided into a proliferative (more anaplastic and invasive) and a nonproliferative type.[6] Several investigators have tried to define a tumour as *insignificant* on the basis of its morphological characteristics. Tumours with a volume < 0.2 ml would be unlikely to reach a clinically significant size.[8,9] However, tumours found at autopsy are not necessarily insignificant. *Focal* cancer is a tumour present only in onesingle spot. *Incidental* prostate cancer is found unexpectedly in approximately 10% of patients who undergo transurethral resection of the prostate (TURP) for the treatment of symptoms of benign prostatic hyperplasia.[10] Increased use of TURP may have induced increased detection of latent tumours, thus causing an increase in the incidence.[11] The marked improvement in survival of Swedish patients with prostate cancer between 1960 and 1980 has been interpreted as evidence that increased diagnosis of latent ('non-lethal') prostate cancer cases has occurred (length time bias).[12] Since the late 1980s, increased detection of 'latent' tumours may have been accelerated by the introduction of improved diagnostic tools such as transrectal ultrasound, ultrasound-guided (random) biopsies and prostate-specific antigen (PSA) testing.[13] Detection of prostate cancer following a positive PSA test appears to move the diagnosis forward by up to 5-10 years,[14,15] also resulting in an increase in the incidence and improvement of survival (lead time bias). This does not, however, exclude a true increase in the incidence.

A true increase in incidence is likely if the increase in incidence is not limited to early low-grade prostate cancer only and if population-based mortality rates for prostate cancer have also increased. In most European countries, mortality due to prostate cancer has increased over the past two decades, although to a lesser extent than the incidence.[16] Mortality is less likely to be influenced by changes in detection methods. Nevertheless, since all cause mortality among men has been declining over the past two decades, the probability that prostate cancer has been recorded as the underlying cause of death may have increased. Analyses of mortality which aim to distinguish birth cohort effects (usually related to exposure to specific risk factors) from calendar period effects (usually related to changes in diagnosis or treatment) may distinguish an increased risk of fatal prostate cancer from increases that are due solely to increased detection.

Management of localized prostate cancer

While prostate cancer is detected with increasing frequency at an early stage,[13,17] the often protracted natural history has led to doubts on the need for curative treatment in

these cases. Several Sandinavian studies reported high 10-year survival rates of up to 87% for patients with localized and low-grade prostate cancer without curative treatment.[18,19] However, in an American study in which all original pathological specimens were reviewed, patients with moderately differentiated tumours exhibited a significantly shorter survival than those with well differentiated tumours.[20] No conclusive evidence is available that treatment with curative intent (radical prostatectomy or curative radiotherapy) will improve these results.[21] However, patients with poorly differentiated tumours have a worse a poorer prognosis, which can be approached by radical prostatectomy when confined to the prostate.[22] Radiotherapy with adjuvant hormonal treatment yields promising results for patients with locally advanced tumours.[23] Nevertheless, the in 1988 by Whitmore formulated intriguing questions remain puzzling: 'Is cure necessary for whom it is possible?' and 'Is cure possible in those for whom it is necessary?'.[24] Adverse effects of curative treatment are not negligible. Although sexual potency may be preserved after radical prostatectomy in 70% of patients in selected series,[25] population-based estimates of partial or full impotence amount to 50-60%.[26] Furthermore, symptoms of urinary incontinence occur in 10-30% of patients.[27] Impotence is less common after radiotherapy (20-30%), but symptoms of urinary incontinence in 10-20% and faecal incontinence in 20% of patients have been reported.[27,28] Therefore, the benefits and risks of the different treatment options are also dependent on the patient's age and concomitant diseases and leave room for patients' and physicians' preferences. Many urologists who master the technique of radical prostatectomy advocate it only if the estimated remaining life expectancy of the patient is more than 10 years.[29] However, the implicit assumption that mortality due to prostate cancer is to be expected more than 10 years after diagnosis is not undisputed.[19,30] Early mortality in elderly patients with localized prostate cancer might be due to concomitant diseases rather than their prostate cancer, which should have consequences for its management.

Aim of the thesis

The main objective of this thesis is to distinguish a spurious increase in the incidence of prostate cancer (due solely to a higher detection rate) from a true increase in the incidence, which can be rephrased in the first central question:

1 *Was the increase in incidence of prostate cancer real or just due to improved detection?*

Using regional, national and European cancer and cause of death registries, this question is addressed in studies of the incidence and prognosis of and mortality due to prostate cancer.

In chapter 3.1, trends in incidence and mortality rates are described for southeastern Netherlands. Chapter 3.2, a collaborative study of the Eindhoven and the East Anglian Cancer Registry, focuses on the age group below 60 years. In chapter 3.3, national mortality rates for prostate cancer are explored in an age-period-cohort analysis. Trends in survival of prostate cancer are investigated in chapter 4.1 for southeastern Netherlands and in chapter 4.2 for Europe. The variation in survival in Europe was also investigated.

The second part of the thesis focuses on issues related to management of localized prostate cancer, phrased as the second central question:

2 *What are the main determinants of treatment and survival of localized prostate cancer?*

The changes and variation in the management of localized tumours in the southern part of The Netherlands is described in chapter 5.1. Factors influencing the choice of treatment for these patients were investigated in chapter 5.2. Special attention was paid to co-morbidity in an investigation of its prevalence and relevance to choice of treatment. The long-term outcome of conservatively treated prostate cancer is described in chapter 6.1. In the last chapter before the general discussion (6.2), the independent prognostic value of co-morbidity was investigated in a cohort of patients recently diagnosed with localized prostate cancer in the southern part of The Netherlands.

Firstly, the study populations and general methods used for this thesis are discussed in chapter 2.

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Chapter 2 Study population and methods

The questions raised in the introduction were addressed in population-based registries. A cancer registry collects data on all newly diagnosed cases of cancer in a defined population. Obviously, use of these registries is essential for calculation of incidence, because it is the only way to obtain all newly diagnosed patients with cancer in a defined area. Furthermore, inclusion of all patients registered in a cancer registry in a specified period reduces selection bias in survival analyses to a minimum, provided that the registry can be considered complete. Since most studies were based on the Eindhoven Cancer Registry, which is the only long-standing cancer registry in The Netherlands, its development and methods will first be described. Specific methods of the East Anglian Cancer Registry and other European cancer registries which contributed data for two other studies in this thesis, are discussed briefly.

The Eindhoven Cancer Registry

Development

This regional cancer registry started in 1955 as part of a programme for nation-wide cancer registration. The Eindhoven Cancer Registry has been the sole cancer registry in The Netherlands functioning without interruption from that year, whereas most other regional registries discontinued their activities, until a successful nation-wide programme was established in 1984. Registration in southeastern Netherlands started in three hospitals in Eindhoven, when data were collected on new cancer patients during the consultant's weekly meeting and, subsequently, directly from pathology reports and patient records. Registration activities expanded together with the decentralized consulting services of radiotherapists from Eindhoven, where megavoltage facilities were introduced in 1972. More systematic registration procedures were developed according to international guidelines, especially since 1967, when a medical officer was appointed. In the early 1970s, the registry served 13 hospitals in a defined area in North-Brabant and middle and northern Limburg. After completeness and accuracy were evaluated in 1980-1983 and the data-base was computerized, the registry was included in the publications of the International Agency for Research on Cancer (IARC) concerning Cancer Incidence in Five Continents as of the period 1978-1982.[1]

Completeness

Although the registry started in 1955, based on analyses of referral patterns, it is likely that a significant proportion of several types of patients was missed by the registry for some types of cancer before 1971, including prostate cancer. Comparison of incidence with mortality rates illustrates this: only for men aged 85 or over, mortality rates exceeded the incidence rates in the early 1970s. Apart from some incompleteness of

cases diagnosed on clinical grounds only, this may also be due to misclassification of the underlying cause of death in this old age group with very high general mortality. Therefore, the registry is considered nearly complete for prostate cancer as of 1971. However, some increasing completeness can be assumed during the 1970s related to the settlement of urologists in the region. The number of urologists increased from 3 in 1971 to 12 in 1978 and 15 in 1994 (per 500,000 men). When a nation-wide programme for cancer registration was started, the area of the Eindhoven Cancer Registry enlarged and included also the central and northwestern part of the province of North-Brabant since 1986. Registration of cancer is not obligatory by national laws, but contracts with the pathological laboratories, hospitals and the regional radiotherapy institute ensure that virtually all newly diagnosed cases are reported to the registry. Cases identified on the basis of a death certificate only (DCO), of whom no clinical diagnosis was available, cannot be registered in The Netherlands. Moreover, autopsy rates are low in The Netherlands as compared to e.g. Sweden. Medical records from hospitals and the radiotherapy institutes have always been the basis for registration. Similar methods have been in use for the other cancer registries participating in the nation-wide Netherlands Cancer Registry, which published its first report for the year 1989.[2] Completeness of one of the participating regional cancer registries was estimated to be 96%-98%.[3,4] Furthermore, registration of the data by trained registrars was shown to be of high accuracy.[5]

Characteristics of the population

The population of southeastern Netherlands rose to almost one million inhabitants since the late 1970s with a pronounced ageing of the population. Probably promoted by the concentration of tobacco industries around Eindhoven, a high proportion of men in the region (>80%) used to smoke, which resulted in high mortality rates due to cardiovascular diseases and lung cancer.[6] Since 1960, smoking prevalences have decreased for men but increased for women up to the late 1960s.

The region is characterized by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres. Consequently, an analysis of socioeconomic variations in survival of prostate cancer in southeastern Netherlands barely revealed any differences between the highest and the lowest socioeconomic levels, when the same expected survival probabilities were used (5-year relative survival 61% vs. 59%).[7] The region covered by the whole Eindhoven Cancer Registry since 1986 is quite similar to the southeastern part and has a population of 2 million inhabitants, served by 16 large community hospitals and two radiotherapy institutes. The area does not contain university or specialized cancer hospitals.

Assessment of stage

Stage has always been recorded by the registry according to the Tumour-Node-Metastases (TNM) classification in use.[8] In order to obtain a classification system that could be used through the years, this classification was simplified as localized and incidental finding (T1), localized and palpable or visible on transrectal ultrasound imaging (T2) or locally advanced (T3 or T4). If lymph node involvement or distant metastases were recorded, stage was classified as metastasized. Because absence of metastases was not always recorded explicitly, patients recorded as Mx were also included in the non-metastasized categories (M0). This seems generally justified, because physicians do not always make a note of every negative finding. Since the introduction of PSA testing (between 1990 and 1993 in southeastern Netherlands) this may have increasingly taken place, since patients with PSA < 10 ng/ml are unlikely to show positive signs on bone scan present with a positive bone-scan imaging.[9] On the other hand, part of the patients did probably not undergo bone scanning, because their high PSA level indicated a very high probability of metastases.[10] Because bone scan imaging did not become widely available until the late 1970s, almost 70% of the patients diagnosed between 1971 and 1979 were classified with an unkown stage. Therefore, stage information is used only for patients diagnosed since 1980.

Since about 98% of cases comprise adenocarcinoma, no subdivison according to histological type is made generally. Histological grade of adenocarcinoma has also been registered routinely in the Eindhoven Registry since 1980. Grade information of patients diagnosed in the 1970s is not used, because it was registered infrequently in this period. Grade was scored according to the TNM classification of malignant tumors[8] by various pathologists from three Departments of Pathology in the eastern part and another three in the western part of the Eindhoven Cancer Registry. The Gleason score is not recorded routinely.

Assessment of co-morbidity

Since 1993, the Eindhoven Cancer Registry has documented serious co-morbidity in patients with newly diagnosed cancer. The main objectives were to describe the prevalence and prognostic value of this major prognostic indicator and to illustrate the complexity of care among patients with cancer and serious co-morbidity. Charlson and colleagues proposed a new method of classifying prognostic co-morbidity and developed a list of serious concomitant diseases. [11] This list has been the model for registration of serious co-morbidity in the Eindhoven Cancer Registry since 1993 (Table 1), but it was not possible to subdivide these diseases according to severity, as suggested by Charlson . Co-morbidity is scored at the same time when the cancer is registered, usually within 4-6 months of diagnosis. For co-morbidity, the trained registrars use medical records, including correspondence from specialists and general practitioners. As such, the reliability of co-morbidity registration is dependent on the

accuracy with which these diseases were documented. Furthermore, the accuracy may vary between physicians. Because a valid registration is also dependent on the quality of the registrars, a validation study was started in six hospitals to assess if they subtracted concomitant diseases correctly from the medical records. This was done in a random sample of 150 patients from six urologist firms diagnosed with prostate cancer in 1995. Urologists from the involved firms where the patients were diagnosed were asked to score co-morbidity according to the list used by the registry.

Table 1 *Classification of co-morbidity, according to an adapted list of Charlson et al.*[11]

Cardiovascular diseases
(myocardial infarction, heart failure, angina pectoris, intermittent claudication, abdominal aneurysm, previous CABG or PTCA)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Diabetes Mellitus (medically treated)
Other malignancies (except basal skin carcinoma)
Chronic obstructive pulmonary diseases (COPD)
Dementia
Tuberculosis and other chronic infections
Connective tissue diseases
(Besnier Boeck's disease [sarcoidosis], systemic lupus erythematosus [SLE], Wegener's granulomatosis)
Rheumatoid arthritis (only severe)
Kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
Bowel diseases (Chrohn's disease, colitis ulcerosa)
Liver diseases (cirrhosis, hepatitis)
Stomach disease (patients who received major surgery for ulcerative disease: Billroth II)

In case of disagreement, the author checked the medical records personally. Registration of co-morbidity was correct for 87% of patients. When the type of disease was examined, only 20% of diseases was registered incorrectly (Table 2). In most of these cases, serious co-morbidity was usually present, but the wrong type of disease was chosen from the list. Another part of this misclassification was due to unfamiliarity of the registrars with isolated terms such as CABG (Coronary Artery Bypass Grafting), PTCA (Percutaneous Transluminal Coronary Angioplasty), etc. This resulted in an underestimation of cardiovascular disease of 28%. This underestimation was also observed in similar validation studies for patients with lung cancer and for women with endometrial cancer. The category "co-morbidity not assessable" appeared to represent largely patients without any co-morbidity.

It is important to realize that these figures are dependent on the accuracy with which these diseases were documented in the medical records. Therefore, some additional underestimation of the prevalences is possible, although severe concomitant diseases are likely to be documented by most physicians, because they affect treatment choice and supportive care.

Table 2 *Percentages correctly registered by the Eindhoven Cancer Registry.*

	Correct		Overestimation		Underestimation		Total
	N	%	N	%	N	%	(100%)
COPD	15	(83)	2	(11)	1	(6)	18
Cardiovascular diseases	35	(70)	2	(2)	14	(28)	51
Other malignancy	12	(100)	0	(0)	0	(0)	12
Diabetes mellitus	9	(80)	0	(0)	2	(20)	11
Other diseases	4	(44)	3	(22)	3	(33)	10
Total	75		7		20		102

When 34 patients correctly registered as having no co-morbidity were included, the % correctly registered was (75+34)/(102+34)=80%.

East Anglian Cancer Registry and other European cancer registries

The East Anglian Cancer Registry covers a defined region in and around the cities of Cambridge, Ipswhich and Norwhich in the UK and uses similar methods of data collection as the Eindhoven Cancer Registry. In addition to active follow up, the East Anglian Registry receives notification of deaths from the Office of National Statistics. All 45 registries from 17 countries participating in the EUROCARE study (chapter 4.2) are comparable to the aforementioned and comply with the standards required by the IARC. [12] Because differences exist between countries in the proportion of patients registered by a death certificate only (DCO), these are excluded from the analyses in the specific studies.

Data-analysis

Calculation of incidence and mortality

Most of these calculations were based only on the southeastern part of the registry. Population data for each 5-year age group were obtained from Statistics Netherlands. The midyear population estimates were used for each individual year included in the study, to obtain the population at risk. Data on mortality due to prostate cancer were

also obtained from Statistics Netherlands. Because the age distribution of the region varies over time and between countries, incidence and mortality rates were age standardized by direct standardization to the European (ESR) or World (WSR) Standard population.

Calculation of survival

Most survival analyses were based on incident cases diagnosed in the long-standing southeastern part of the Eindhoven Cancer Registry. Apart from passive follow up, the vital status of all patients registered between 1955 and 1992 was actively followed up through municipal civil registries up to 1 April 1994. The cause of death could not be obtained in this way. Of all patients with prostate cancer diagnosed between 1955 and 1992, 51 (1.5%) were untraceable (mostly due to repeated moving) and 38 (1.1%) were lost to follow-up before the closing date, 1 April 1994. Because there is no unique personal number for every Dutch citizen, the registry cannot be linked with the national cause of death register. Therefore, relative survival was calculated generally. Relative survival is the ratio of the crude to the expected survival and its complement can be regarded as an estimate of mortality attributable to the disease studied, unless the study cohort differs substantially from the general population apart from the disease studied. [13] Expected survival probabilities were derived from life tables for the regional male population supplied by Statistics Netherlands.

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Chapter 3 Trends in incidence and mortality

3.1 Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction.

3.2 Striking increase in incidence of prostate cancer in men aged < 60 years without improvement in prognosis.

3.3 Increased risk of fatal prostate cancer may explain the rise in mortality in The Netherlands.

3.1 Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry based study in southeastern Netherlands, 1971-1995.*

Abstract

The incidence of prostate cancer has increased considerably over the past decades partly due to increased detection of subclinical cases. In Southeastern Netherlands, a region of almost 1 million inhabitants with good access to specialized medical care, prostate specific antigen (PSA) assays were not introduced until 1990, allowing us to investigate the nature of the increases in incidence. Age-adjusted (European Standardized Rate) and age-specific rates were calculated using incidence data from the population-based Eindhoven Cancer Registry and mortality data from Statistics Netherlands. The age-adjusted incidence, which increased from 36 in 1971 to 55 per 100,000 in 1989, included all grades as well as metastasized prostate cancer. The age-adjusted mortality mainly fluctuated in this period but increased among men aged 55-64 years from 12 in 1980 to 25 per 100,000 in 1989. After 1990, the age-adjusted incidence further increased to 80 per 100,000 in 1995, the increase representing mainly low-grade localized prostate cancer presumably due to increasing opportunistic PSA testing, especially after 1993.

A real increase in incidence may have occurred before 1993; on the other hand, pending results of randomized trials, judicious application of PSA testing seems justifiable to avoid unnecessary intervention without reducing mortality.

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* Post PN, Kil PJM, Crommelin MA, Schapers RFM, Coebergh JWW. *Eur J Cancer* 1998;34:705-709. Reproduced with permission from Elsevier Science.

Introduction

The incidence of carcinoma of the prostate has increased over the past two decades,[1] although a large proportion of the increase seems to represent subclinical cases which formerly remained undetected.[2] This fits in with the worldwide observed high prevalence of prostate cancer at autopsy of 10-40% and the increase in diagnostic procedures over time:[3] in the USA between 1973 and 1986, a 30% increase in incidence appears to be partly attributable to an increase in trans-urethral resection of the prostate (TURP).[4] This is a surgical procedure for the treatment of symptoms of urinary obstruction due to prostate cancer as well as benign prostatic hyperplasia (BPH). TURP in BPH patients is known to result in the incidental detection of prostate cancer in approximately 10% of cases.[5] Subsequently, the incidence in the USA increased by 82% from 1986 to 1991, due to an exponential increase in Prostate Specific Antigen (PSA) testing.[6] Several authors reported that an elevated serum PSA may precede prostate cancer by up to 5-10 years.[7,8] Increased detection of prevalent subclinical prostate cancer should be followed by stabilization or a subsequent decline. Indeed, in some areas of the USA a decline in incidence has now been observed. [9,10] Similarly, increased diagnosis during TURP should have been followed by stabilization of the incidence. However, the exponential rise in PSA testing as of 1986 may have obscured the expected changes. Nevertheless, Potosky et al. made it plausible (by recognition of overestimation due to multiple hospitalizations and by mortality patterns) that there was in part a true increase in risk between 1973 and 1986.[4]

In contrast to the USA,[11] prostate cancer screening programmes have not been introduced in Europe yet, but a European randomized study of screening for prostate cancer has been started.[12] Opportunistic PSA testing has been introduced in some parts of Europe, e.g. in Isère, France.[13] In Southeastern Netherlands, PSA testing was not introduced until 1990, giving us the opportunity to investigate the possible nature of changes in incidence. We studied trends in incidence and mortality rates and provided insight into the nature of these trends by describing changes in the distribution of stage and grade. Also, we estimated the contribution of the increase in TURP procedures by relating its application to the mode of diagnosis.

Methods

Study population

We calculated incidence rates using data from the Eindhoven Cancer Registry, which covers a region with almost one million inhabitants in Southeastern Netherlands. The development of this registry, which started in 1955, is described in detail elsewhere. [14]

Registration is not obligatory by national laws, but contracts with the pathological laboratories, hospitals and regional radiotherapy institute ensure that virtually all newly diagnosed cases are reported. Analysis of referral patterns and comparison with regional mortality statistics, derived from the Netherlands Statistics, indicate that prostate cancer data can be considered nearly complete as of 1971. Although representing less than 5%, non-pathologically confirmed cases are also registered. Cases identified by 'death certificate only' are not registered in the Netherlands due to privacy regulations. After notification, data are collected by trained registrars from patient records in community hospitals. The region offers good access to medical care with seven large community hospitals (originally 13), to which the distance has always been less than 25 kilometres. The number of urologists increased from 4 in 1971 to 12 in 1978 and 15 in 1994. National hospital discharge data show that the number of TURP increased from 1900 in 1971 to 12326 in 1985. PSA assessment was not introduced until 1990. In the seventies, prostate cancer patients were usually treated symptomatically (TURP), often supplemented with anti-androgen or oestrogen treatment or castration. Since the early eighties an increasing proportion has undergone radiotherapy, but radical prostatectomy was only rarely applied before 1990 and by specialists outside the region. Regional urologists increasingly performed this procedure in the nineties.

Stage and grade

Stage is recorded in the registry according to the TNM classification in use.[15,16] On the basis of the registered information, we classified stage as localized and incidental finding (T1), localized and palpable or visible on transrectal ultrasound imaging (T2) or locally advanced (T3-4). If lymph node involvement or distant metastases were recorded, stage was defined as metastasized. Because absence of metastases was not always recorded explicitly, we included both M0 and Mx in the non-metastasized categories. Since bonescan imaging became widely available in the late 1970s, stage is presented as of 1980.

Histological grading recorded according to the TNM classification of malignant tumours[16] was scored by up to 10 pathologists of three Departments of Pathology serving seven hospitals. Poorly and undifferentiated tumours were considered as one category. Because grade was unknown for a large proportion of cases in the 1970s, grade too is presented as of 1980.

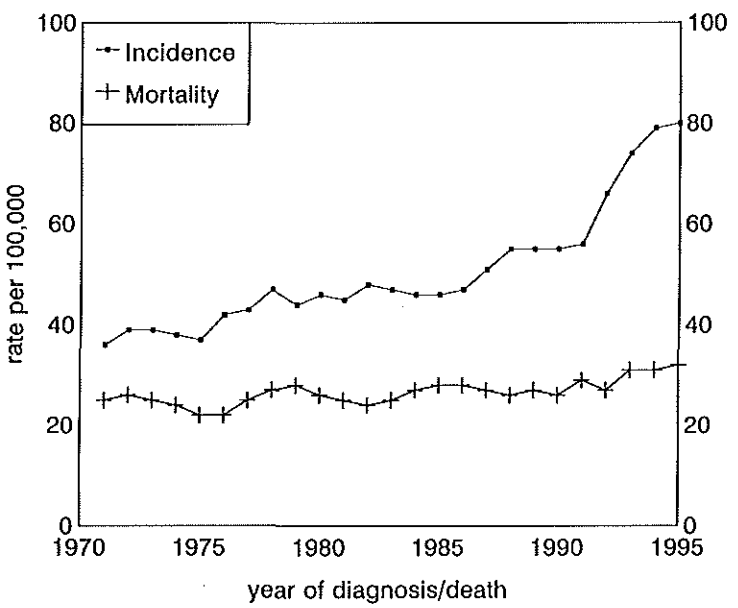
Urological care

Data on regional use of PSA assays were supplied by clinical chemists of the various community hospitals. We related TURP procedures to stage at diagnosis as of 1988 (when registration of treatment became more detailed).

Data analysis

We calculated age-specific rates (for 10-year age groups) as well as age-adjusted rates (European Standardized Rate) per 100,000 person-years. Furthermore, we calculated incidence rates according to stage and grade. Annual incidence and mortality rates are presented as 3-year moving averages: the incidence for a specific year is calculated as the mean for that year and the preceding and succeeding years.

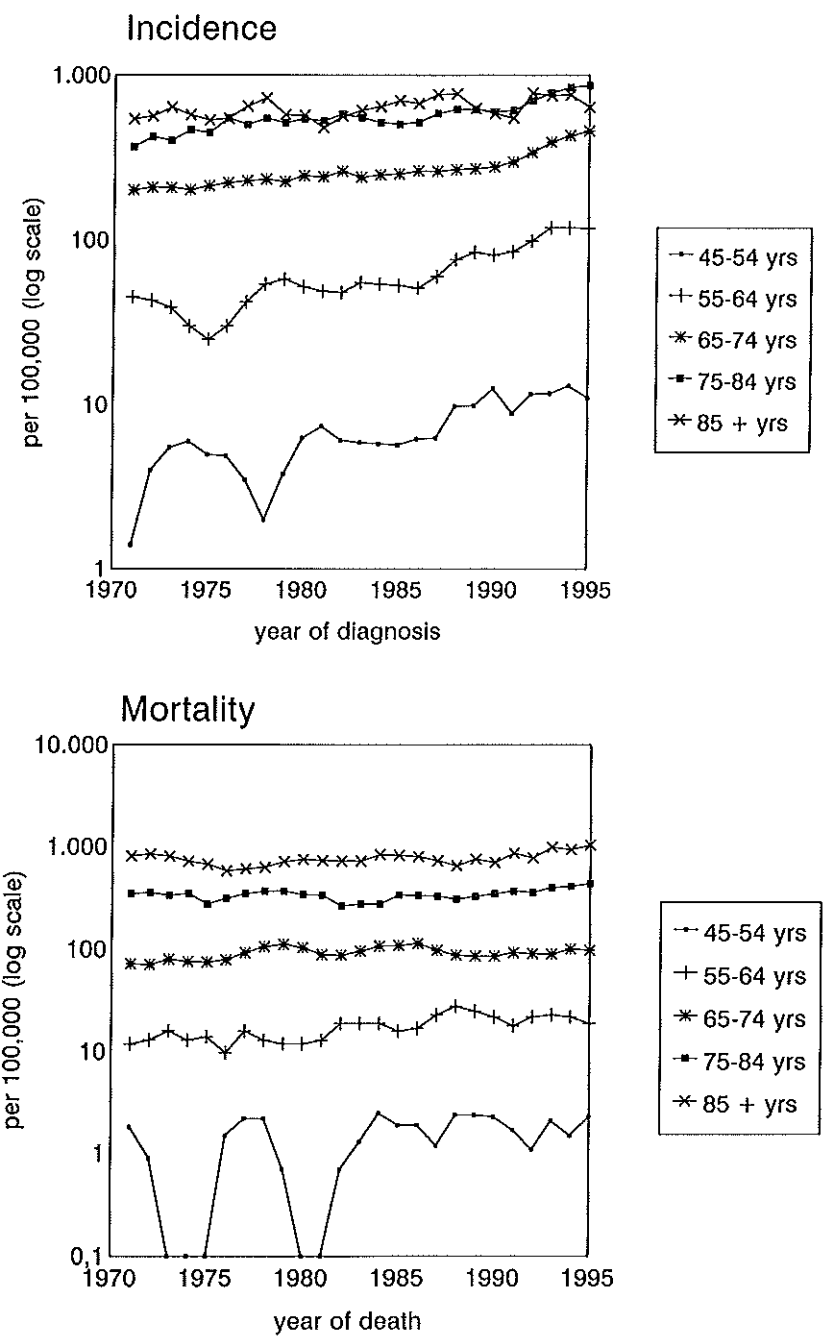
Figure 1 Trends in age-adjusted incidence and mortality rates for prostate cancer (European Standardized Rates) in Southeastern Netherlands per 100,000 person-years, 1971-1995 (3-year moving averages).



Results

Between 1971 and 1995, 4205 patients with newly diagnosed prostate cancer were registered. The mean age, 73 years, barely changed during the study period: 18% of patients were below 65 years and 40% were aged over 75. In total, 95% of all patients were diagnosed by histological examination of biopsies or TURP specimens, less than 1% on the grounds of cytological examination, 1% as a result of post mortem examination and 3%, mainly older men, only on clinical evidence.

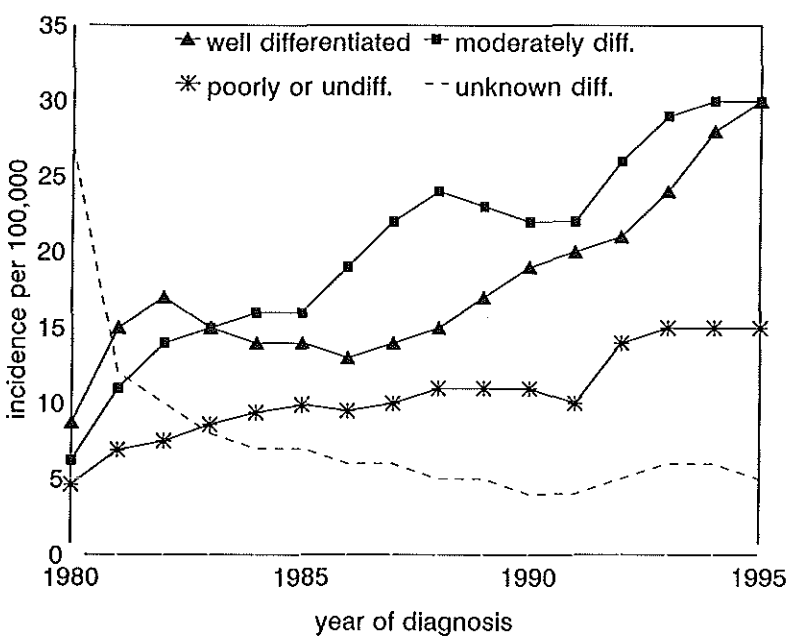
Figure 2 *Trends in age-specific incidence and mortality rates for prostate cancer in Southeastern Netherlands per 100,000 person-years, 1971-1995 (3-year moving averages).*



Incidence

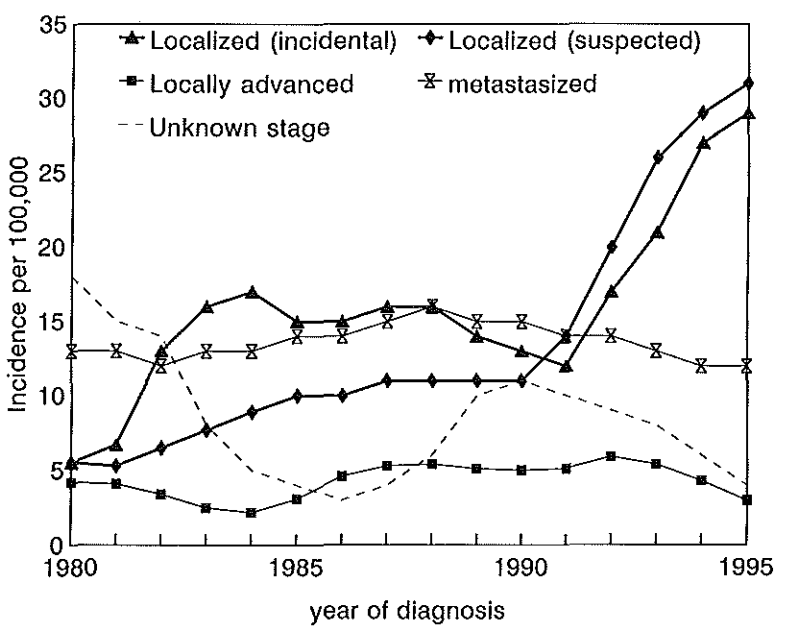
The age-adjusted incidence increased in the seventies from 37 in 1975 to 46 per 100,000 in 1980 (Figure 1). After 1985, the incidence further increased to 55 per 100,000 in 1988. An exponential increase in incidence was observed after 1991, resulting in an incidence rate of 80 per 100,000 in 1995. The increase in incidence was observed at all ages (Figure 2), but before 1990 it was more pronounced in the youngest age groups (below 65). The incidence among men over 85 showed marked fluctuations. Random variation due to the small number of men in this age group plays probably a role. In the early eighties, the incidence of patients with unknown grade decreased markedly (Figure 3). The increase in incidence in this period included all grades but after 1985 mainly moderately differentiated tumours. The exponential increase after 1991 was initially largely due to poorly and moderately differentiated, but after 1993 it could be explained solely by well and moderately differentiated cancer.

Figure 3 *Trends in prostate cancer incidence (European Standardized Rate) according to grade in Southeastern Netherlands, 1980-1995 (3-year moving averages).*



The increase in patients with incidental localized cancer parallelled a decrease in patients with unknown stage, but the incidence of metastasized cancer also increased in the late eighties (Figure 4). Although patients with lymph node but no distant metastases were included in the category 'metastasized', only 7% of the metastasized patients between 1985 and 1989 were diagnosed without distant metastases. Subsequently, the incidence of metastasized cancer stabilized and decreased, although it continued to represent some 15% of the incidence in the nineties. After a transient increase due to temporarily stricter registration practices around 1990, the incidence of patient with unknown tumour size has declined again. The exponential increase in incidence after 1991 can be attributed to incidental cases but also to suspected localized prostate cancer.

Figure 4 Trends in prostate cancer incidence (European Standardized Rate) according to stage in Southeastern Netherlands, 1980-1995 (3-year moving averages).



Mortality

The age-adjusted mortality declined initially in the early seventies but increased slightly from 22 in 1975 to 26 per 100,000 in 1980 (Figure 1). This increase was apparent for all age groups (Figure 2).

In the eighties, the age-adjusted mortality increased again slightly, mainly due to an increase among men aged 55-64 years from 12 in 1980 to 25 per 100,000 in 1989. Finally, a small increase in the age-adjusted mortality from 26 in 1990 to 32 per 100,000 in 1995 was noted mainly for older age groups.

PSA

PSA assays were introduced in two community hospitals in 1990 but did not become routine in all hospitals until 1993. The number of assays increased from 1,449 in 1990 to 13,506 in 1993, for which the proportion requested by general practitioners increased from 7 to 22%.

Role of TURP

In the Netherlands, the national number of TURP procedures increased sixfold between 1970 and 1990, whereas the number men aged 65 years or more (who underwent the majority of transurethral resections) only increased by 30% in the same period. Of the 408 prostate cancer patients undergoing TURP in Southeastern Netherlands between 1988 and 1991, only 38% were detected by this procedure, 29% had palpable localized cancer and 20% even exhibited metastasized prostate cancer (13% were registered as having an unknown stage). Moreover, the distribution of stage between 1980 and 1987 points in the same direction: 28% were staged as incidentally detected, 26% were localized palpable and up to 30% were metastasized at diagnosis (17% were recorded as unknown).

Discussion

We report a 56% increase in the incidence of prostate cancer in Southeastern Netherlands between 1971 and 1989 and a 43% increase in 5 years after PSA introduction as of 1990. Increases in incidence before introduction of PSA testing have been reported in other European countries [17,18] and the USA.[4] The increase in incidence in Northern Sweden was due to low grade cancer[17] but in Norway, the increase in the incidence of metastasized cancer was similar to that found for localized cancer. Moreover, a concomitant increase in mortality was observed.[18] In the USA, the increase involved mainly localized prostate cancer.[4] An increase in incidence of 6.3% per year, mainly due to non-metastasized prostate cancer, was observed after PSA was introduced in Isère.[13] In the USA, an even more pronounced increase in was reported.[6] This dramatic rise has now been followed by a decline in different parts of the USA, especially among older men.[9,10]

Validity and completeness

Every pathologically confirmed prostate cancer is reported to the registry. Furthermore, clinical cases are notified through medical records offices and the regional radiotherapy institute. Nevertheless, there may have been increasing ascertainment in the seventies, related to the marked increase in the number of urologists.

It is not likely that changes in the morphological interpretation of histological specimens influenced the incidence. Moreover, no changes occurred in the classification of grade.

Because patients recorded as Mx were included in the non-metastasized categories, a few Mx cases may have been misclassified. It is not likely that stage migration due to improved diagnostic techniques played an important role, because an increase in the category 'locally advanced' would then have been expected.[19] Furthermore the clinical stage was used.

Cardiovascular disorders generally tend to be recorded as the underlying cause of death more often than other chronic diseases such as cancer.[20] Since mortality from cardiovascular causes has decreased over the past decades (in Southeastern Netherlands from 258 in 1973-1982 to 192 per 100,000 in 1983-1992),[21] the probability that prostate cancer was recorded as the cause of death may have increased. Moreover, the decline in mortality due to BPH (in The Netherlands from 6.3 in 1970-1974 to 1.5 per 100,000 in 1985-1989) [22] may have resulted in an increase in mortality due to prostate cancer. Finally, the decline in incidence of male lung cancer since 1978 in Southeastern Netherlands may have had a similar effect. [23] Increased mortality due to prostate cancer should, therefore, be interpreted with caution, especially that found for males aged 75 years or more.

Increased incidence or higher detection rate?

The increase in incidence in the eighties was not only represented by low grade but also by metastasized prostate cancer, suggesting a genuine increase. Furthermore, less than 30% of all cases were detected incidentally during a TURP procedure. Regional mortality also increased in Southeastern Netherlands, albeit to a lesser extent. Moreover, analysis of national mortality data revealed a 20% increase in the age-adjusted mortality between 1970 and 1989, presumably due to an increased risk in consecutive birth cohorts up to men born in 1925. [24]

Despite the increased TURP rates, only 38% of the prostate cancer patients undergoing TURP, were diagnosed as a result of this procedure. The majority of patients underwent the TURP procedure for symptomatic relief of symptoms of urinary obstruction after cancer was suspected or already confirmed. Increased number of TURP procedures may, therefore, partly be a consequence of the increased incidence of prostate cancer rather than a cause.

A true increase in incidence would be in agreement with an increase in mortality due to prostate cancer in many countries [1], which is unlikely to be entirely an artifact.[25] Nevertheless, the marked improvements in survival of prostate cancer in Sweden between 1960 and 1980 suggest increased diagnosis of nonlethal prostate cancer. [2] Therefore, it is likely that the increase in incidence between 1971 and 1990 reflects both a higher detection rate and a true increase in incidence.

In contrast, the rapid increase in the incidence of prostate cancer after the introduction of PSA is most likely an artifact caused by accelerated diagnosis. Although a further increase in incidence may have occurred, the diagnosis of prostate cancer has most likely been advanced recently by several years, in agreement with studies linking serum banks with subsequent cancer diagnosis.[7,8] This would mean that more elderly men will live for several years with the knowledge of a diagnosis of prostate cancer before it eventually may lead to symptoms.
As yet, the benefits of early detection by PSA have not been proven. A European randomized screening trial is on its way, [12] but conclusive results will not be available for several years. Judicious application of PSA testing seems justifiable, in order to control the cycle of increasing intervention without evidence of reducing mortality.[26] For the time being, it may be useful to follow the recommendations of Kramer and associates: "inform each man about the current state of uncertainty, detail the risks and theoretical benefits ... Outside of the study setting, screening blood tests should only be done once the man is engaged in the decision process".[27] The Dutch Society of General Practitioners advises PSA determination only if the rectal examination is difficult to interpret and only if the man still has a considerable life expectancy. Case finding is discouraged.[28]

In conclusion, our results suggest that the increase in incidence of prostate cancer in Southeastern Netherlands before 1990 partly represents increased detection and partly reveals a true increase in incidence. The exponential increase in the incidence of low-grade localized prostate cancer after 1990 seems to be attributable mainly to advanced diagnosis due to opportunistic PSA testing.

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3.2 Striking increase in incidence of prostate cancer in men aged < 60 years without improvement in prognosis.*

Abstract

Increased awareness and improved diagnostic techniques have led to earlier diagnosis of prostate cancer and increased detection of subclinical cases, resulting in improved prognosis. We postulated that the considerable increase in incidence under age 60 is not only attributable to increased detection. To test this hypothesis, we studied incidence, mortality and relative survival for middle aged patients diagnosed in Southeastern Netherlands and East Anglia (UK) between 1971 and 1994. Prostate-specific antigen (PSA) testing did not occur before 1990. Between 1971 and 1989, the age-standardised incidence at ages 40-59 increased from 8.8 to 12.5 per 10^5 in the Netherlands and from 7.0 to 11.6 per 10^5 in East Anglia. Five-year relative survival did not improve in East Anglia and even declined in Southeastern Netherlands from 65% (95% Confidence Interval [CI] 47-83) in 1975-1979 to 48% (CI 34-62) in 1985-1989. Mortality due to prostate cancer among men aged 45-64 years increased by 50% in Southeastern Netherlands and by 61% in East Anglia between 1971 and 1989, but decreased slightly in the 1990s. Because other factors adversely influencing the prognosis are unlikely, our results indicate an increase in the incidence of fatal prostate cancer among younger men in the era preceding PSA testing.

* Post PN, Stockton D, Davies TW, Coebergh JWW. *Br J Cancer* 1999;79:13-17. Reproduced with permission from Churchill Livingstone.

Introduction

Worldwide, prostate cancer has been diagnosed with increasing frequency over the past decades.[1] This increase is partly due to increased application of transurethral resections of the prostate (TURP), [2] a procedure to treat symptoms of benign prostatic hyperplasia (BPH) and resulting in incidental detection of subclinical prostate cancer in approximately 10% of cases.[3] More recently, case finding by prostate-specific antigen (PSA) testing resulted in a further increase in the incidence. [4]
As a consequence, the prognosis of prostate cancer patients has improved in many countries, [5,6,7,8] because an increasing proportion was detected at a preclinical stage. In Southeastern Netherlands, overall 5-year relative survival improved modestly from 57% in 1970-1979 to 61% in 1987-1992, but the improvement occurred largely in elderly patients.[9] In the youngest age groups, the highest increase in incidence was observed in the 1980s in Southeastern Netherlands.[10] As TURP is about seven times less frequently applied in men under age 60 than in men over age 75[11] because of the lower prevalence of BPH[12] and the much lower incidence of cancer, it seemed that the increase in incidence at younger ages might not be caused by a higher detection rate. We studied trends in incidence and prognosis of patients with prostate cancer aged 40-59 years in Southeastern Netherlands and for comparison also in East Anglia, UK, which has a similar system of data collection and a more or less comparable system for health care provision. We also studied trends in mortality due to prostate cancer and analysed the changes in the distribution of grade, stage and the initial treatment applied. The main study period (1971-1989) is the time before the introduction of PSA testing, data for 1990-1994 are also included to provide some insight into more recent trends.

Patients and methods

Study population
We used data from two cancer registries, the Eindhoven Cancer Registry in Southeastern Netherlands and the East Anglian Cancer Registry in the United Kingdom. In both registries, most cases were identified by pathology reports, which are always sent to the registries, the remainder by medical record departments in the regional hospitals and the regional radiotherapy institute (Eindhoven) or the district general hospitals (East Anglia). Southeastern Netherlands has a population of almost 1 million inhabitants and is characterized by good access to specialized medical care provided in eight large community hospitals. National data show that TURP was increasingly applied between 1970 and 1990 and it was the main treatment modality for both cancer of the prostate and BPH in the 1970s. Radiotherapy was applied

increasingly after 1980, but radical prostatectomy rarely. PSA assessment was not introduced until 1990. In the Eindhoven Registry, vital status of all cases was followed up through municipal civil registries until 1 April 1994. Five patients (2.8%) were lost to follow-up before this date (mostly due to repeated moving home), and so were censored in the analysis. East Anglia has a population of around 2.2 million inhabitants and has three specialist hospitals with Oncology centres and a further six district general hospitals. The majority of the population lives in and around the three major cities of Cambridge, Ipswich and Norwich, guaranteeing them good access to specialised medical care. PSA assays were introduced in 1991. The East Anglian Registry receives notification of deaths of all individuals flagged as having cancer or where cancer is mentioned on the death certificate, from the Office of National Statistics. In addition, it actively follows up its patients 3 years after diagnosis and then every 5 years until death, guaranteeing nearly complete follow-up. Mortality data were obtained from Statistics Netherlands and the British Office of National Statistics.
The midyear population estimates were used for each individual year included in the study.

Analysis
The incidence rates per 100,000 person-years for the age band 40-59 were standardized to the European Standard Population. Since the median survival time is approximately 5 years, we calculated the age-standardised mortality rates for the age band 45-64 years. Poisson regression analysis was applied to model incidence and mortality, [13] using the GENMOD procedure of the statistical package SAS. The data were grouped in 5-year age groups and calendar periods for each registry, before they were pooled. Significance of terms in the models was tested with the likelihood-ratio test.
We calculated crude and relative survival rates using the actuarial (life-table) method. Relative survival, the ratio of the crude to the expected survival.[14] The expected survival was calculated from life tables derived from the regional mortality statistics and data were compiled into five year age groups and calendar year. A software package from the Finnish Cancer Registry was used to calculate the survival rates.[15] The rates were adapted during the course of the follow-up according to the changing age distribution of the patient groups (Ederer II option). Cases identified at death were excluded from the analyses. We used grade information as it was registered, scored according to the classification of malignant tumours.[16] Information about stage was only available in the Eindhoven Cancer Registry. Based on clinical TNM assessment,[17] we classified stage in 3 categories: small tumours confined to the prostate (T1-T2) without evidence of metastases were classified as localized; tumours

which invaded surrounding structures (T3-T4) but without evidence of metastases were classified as locally advanced; patients with distant or lymph node metastases were classified as metastasized. Grade and stage, both available as of 1980, are presented both with and without inclusion of the unknown cases. Differences in proportions were tested with the chi-square test (excluding unknown cases).
We classified initial treatment as TURP (including patients detected incidentally due to TURP); hormonal treatment; hormonal treatment after TURP; radiotherapy. (patients receiving radiotherapy after TURP or radiotherapy *and* hormonal therapy were included in the radiotherapy group) Treatment information was available for the main study period (1971-1989) in The Eindhoven Registry and from 1980 to 1989 in East Anglia.

Results

The number of patients aged 40-59 diagnosed with prostate cancer between 1971 and 1989 was 181 in Southeastern Netherlands and 384 in East Anglia, being 7% and 4% respectively of all patients with prostate cancer diagnosed between 1971 and 1989. The proportion of patients with a histologically confirmed diagnosis at ages 40-59 was more than 95% during the whole study period in both populations.

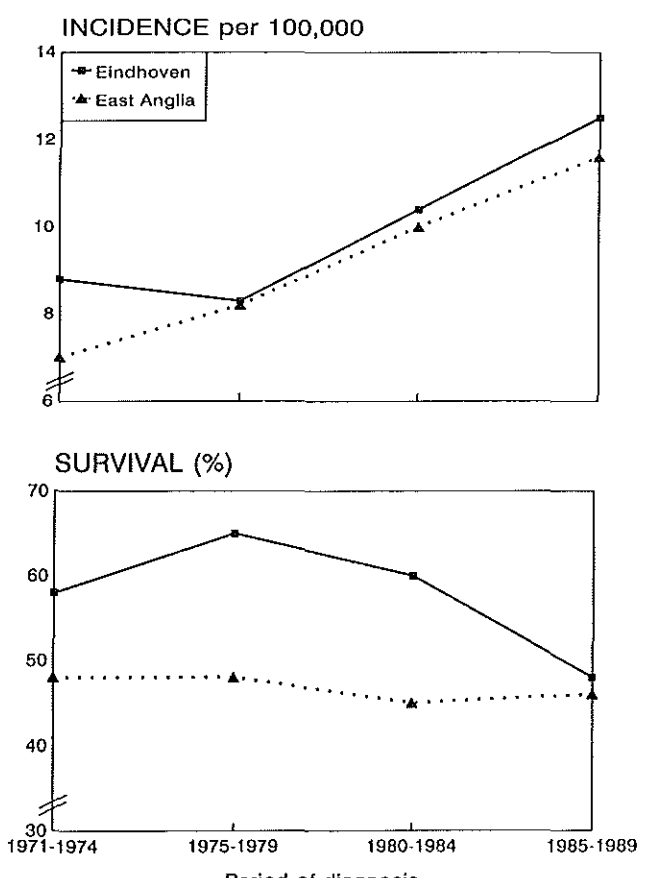
Table 1 *Risk ratios and 95% confidence intervals for incidence (40-59 years) of and mortality (45-64 years) due to prostate cancer in Southeastern Netherlands and East Anglia.*

	Incidence (40-59 yrs)		Mortality (45-64 yrs)	
	Risk ratio (95% CI)	No. of cases	Risk ratio (95% CI)	No. of cases
1971-1974 (ref)	1	82	1	82
1975-1979	1.11 (0.84, 1.47)	127	1.02 (0.77, 1.36)	108
1980-1984	1.33 (1.02, 1.73)	162	1.24 (0.95, 1.63)	140
1985-1989	1.53 (1.19, 1.99)	194	1.63 (1.26, 2.12)	195
1990-1994	1.91 (1.49, 2.46)	255	1.53 (1.18, 1.98)	191
p-value trend	0.0001		0.0001	

Between 1971 and 1989, the age-adjusted incidence rate for men aged 40-59 increased from 8.8 per 10^5 to 12.5 per 10^5 in Southeastern Netherlands and from 7.0 per 10^5 to 11.6 per 10^5 in East Anglia (Figure 1). The mean age at diagnosis of the patients in this age group barely changed over the study period, being 55.4 years in the Netherlands and 55.6 in East Anglia.

A multivariate model for the incidence up to 1994 was built containing age group, registry and calendar period (deviance 35.0; 34 degrees of freedom [df]). The risk ratio of the incidence increased for each subsequent period up to 1990-1994 (Table 1). The test for trend was significant (p = 0.0001) and the trend was similar in both registries. A similar result was obtained when the period 1990-1994 was excluded. The age-standardized mortality rate for prostate cancer among men aged 45-64 years increased between 1971 and 1989 from 7.4 to 11.1 per 10^5 in Southeastern Netherlands and from 7.5 to 12.1 per 10^5 in East Anglia. A model was built containing age group, calendar period and registry (deviance 47.1; 34 df). The risk ratio increased with each subsequent period up to 1985-1989, followed by a slight decline in 1990-1994 (Table 1). Nevertheless, the test for trend was significant (p=0.0001) and the trend was similar in both registries.

Figure 1 *Incidence rates per 100 000 person years (European Standardized Rate) (top) and 5-year relative survival rates (bottom) for prostate cancer patients aged 40-59 in Southeastern Netherlands and East Anglia.*



In Southeastern Netherlands, 5-year relative survival improved slightly in the early seventies, but declined from 65% (95% CI 47-83) in 1975-1979 to 48% (CI 34-62) in 1985-1989 (Figure 1). In East Anglia, 5-year relative survival was initially considerably lower, being 48% (CI 34-62) in 1971-1974 and slightly decreased to 46% (CI 36-56) in 1985-1989. The crude survival followed a similar trend.

Table 2 Trend in stage distribution (with and without unknown cases) of prostate cancer patients aged 40-59 in Southeastern Netherlands, 1980-1989.

	1980-1984	1985-1989	1990-1994
Number of cases	51	65	108
	% within period	%	%
Localized	40	53	57
Locally advanced	8	12	12
Metastasized	39	29	18
Unknown	13	6	13
Localized	47	56	66
Locally advanced	9	13	13
Metastasized	44	31	21
p-value χ^2	0.07		

In spite of an increase in the estimated proportion of patients with localized cancer from 47% in 1980-1984 to 56% in 1985-1989 in Southeastern Netherlands (Table 2), the estimated proportion of patients with poorly differentiated tumours increased from 15% to 25% (Table 3). The proportion of patients aged 40-59 years receiving radiotherapy increased from 21% in 1975-79 to 55% in 1985-89 in Southeastern Netherlands and radiotherapy has also been the main treatment modality in East Anglia between 1980 and 1989 (Table 4). The remainder of patients received endocrine therapy or TURP. Radical prostatectomy was only rarely applied before 1990 in both populations.

Table 3 *Trend in grade distribution (with and without unknown cases) of prostate cancer patients aged 40-59 in Southeastern Netherlands and East Anglia, 1980-1994 .*

	Southeastern Netherlands			East Anglia		
	1980-84	1985-89	1990-94	1980-84	1985-89	1990-94
n	51	65	108	111	129	147
	%	%	%	%	%	%
Well	36	34	41	24	22	25
Moderately	31	37	31	18	24	29
Poorly	12	23	22	18	21	22
Unknown	20	6	6	40	33	24
Well	46	36	44	40	33	33
Moderately	39	39	33	30	36	38
Poorly	15	25	23	30	31	29
p-value χ^2		0.6			p>0.1	

Discussion

We report a similar rise in the incidence of prostate cancer among men aged 40-59 years in Southeastern Netherlands and East Anglia and no improvement in prognosis in the era preceding the introduction of PSA testing. Improved diagnosis might explain the rise in incidence, but this does not seem to play an important role, because it should have resulted in the inclusion of more non-aggressive cases resulting in improved survival. Moreover, in spite of a more favourable stage distribution, we did not observe an increase in well differentiated tumours in this period.

Our findings are conditional on the accuracy of the cancer registries. Based on a comparison with mortality data and analysis of referral patterns, both registries can be considered virtually complete for prostate cancer as of 1971 and comply with the standards of the International Agency for Research on Cancer.[17] Few patients were lost to follow up, so that selective loss to follow-up is not likely to be an issue. Nevertheless, the study population was relatively small, especially in southeastern Netherlands. However, our findings are not compatible with a significant

improvement. Moreover, registry-based studies in other countries provided similar results.

In Sweden, 5-year relative survival for prostate cancer patients aged 45-54 improved from 42% in the early 1960s to 62% in the late 1970s, but it declined to 50% in the early 1980s. [5] In Scotland, it declined from 47% in 1978-1982 to 32% in 1983-1987 [6] In Switzerland (Vaud), the relative survival for patients aged below 60 slightly improved from 39% in 1974-1978 to 41% in 1979-1983,[8] whereas it also slightly improved for Finnish patients.[18] We do not know why the prognosis barely changed in East Anglia but deteriorated in Southeastern Netherlands. Lesser access to specialised care may have played a role in the initially lower survival in East Anglia, because the EUROCARE study showed that similar differences in survival existed between Southeastern Netherlands and Great Britain for patients with lung-, breast- and colorectal cancer, which may be related to differences in stage at diagnosis. [19] Increasing awareness of prostate cancer and early diagnosis did probably not become apparent before 1980 in East Anglia.

Table 4 *Trend in initial treatment of prostate cancer patients aged 40-59 in Southeastern Netherlands and East Anglia.*

	1971-1974	1975-1979	1980-1984	1985-1989
Eindhoven				
	%	%	%	%
Radiotherapy	0	21	38	55
Endocrine therapy	32	24	4	22
Endocrine + TURP	36	7	13	9
TURP	28	48	40	14
None	4		5	
East Anglia				
			%	%
Radiotherapy			42	46
Endocrine therapy			12	6
Endocrine + TURP			15	15
TURP			26	26
None /Unknown			5	7

Our hypothesis, that a genuine increase in incidence has occurred, is also supported by the increase in mortality due to prostate cancer below 65 years, which was similar in both populations, although it was followed by a small decline in 1990-1994. An

analysis of national mortality data of 1950-1989 showed an increase of mortality due to prostate cancer in consecutive birth cohorts up to men born around 1925 in The Netherlands. [20] In Norway, the increase in both incidence and mortality due to prostate cancer between 1957 and 1991 was highest in men below 60 years.[21] In the USA, mortality due to prostate cancer has started to decline since 1991-1995, in particular for men under age 75, [22] whereas it had increased slightly under age 65 in the years beforehand. [7] The decline, however, may be related to widespread introduction of early detection and intervention. Although we observed a considerable increase in cause-specific mortality, changes in mortality should be interpreted with caution. All cause mortality has been declining in both populations, also in this age group and in particular mortality due to cardiovascular causes declined in the Netherlands from 499 per 10^5 in 1970 to 301 per 10^5 in 1990 for men aged 45-64 years.[23] Due to the decrease in concurrent causes of death, the probability that prostate cancer was recorded as the cause of death may have increased. However, this explanation would be more plausible for mortality in older age groups.

Therefore, an increased risk of prostate cancer is not unlikely. As far as we know, only one etiologic study has focused on the age group below 60 years. This reported a relative risk (RR) of 1.9 for cigarette smoking, a RR of 1.4 for vasectomy, and a RR of 2.3 for early age at first sexual intercourse.[24] Recently, Rodriguez et al. reported a significant association of current smoking with fatal prostate cancer (RR 1.34) which was highest among men below 60 years (RR 1.83) but there was no association with the number of cigarettes smoked or with the duration of smoking at baseline for the cohort in 1982. Nor was there any increased risk for former smokers.[25] This, as well as results from other large studies, suggests that smoking adversely affects survival. Increased occurrence of a factor associated with a worse survival could be an alternative explanation of our findings. Smoking, however, is not a likely candidate, because the proportion male smokers decreased markedly from 95% in 1960 to 40% in 1981 in The Netherlands[26] and also in England.[1] Unfavourable changes in the health care system do not seem to play a role, because a larger proportion of the recent cases was detected at an earlier stage, at least in Southeastern Netherlands. Furthermore, radiotherapy was applied increasingly during the study period. Although a beneficial effect of radiotherapy on survival has not been proven defintively,[27] it seems unlikely that radiotherapy has been detrimental for prostate cancer patients. We, therefore, assume that increased incidence of fatal prostate cancer, of which the cause still needs to be unravelled, should explain our findings.

Although the incidence continued to increase, mortality due to prostate cancer decreased slightly in the 1990s. This could mean that the suggested genuine increase in incidence has come to a halt in the 1990s. Continuing studies of incidence and survival may provide more insight into the nature of the most recent increase in incidence.
From the current study, we conclude that increased detection of prostate cancer by TURP cannot explain the considerable increase in incidence between 1971 and 1989 in the age group below 60 years.

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3.3 Increased risk of fatal prostate cancer may explain the rise in mortality in The Netherlands.*

Abstract

Background. Several lines of evidence suggest that, as a result of improved diagnostic techniques, the increase in incidence of prostate cancer is due largely to increased detection of subclinical cases. Between 1971 and 1989, a considerable increase in incidence was found in Southeastern Netherlands among men aged below 60 years without an improvement in prognosis. We hypothesised that in addition to the increase due to increased detection, a genuine increase in incidence has occurred in the last two decades and that this should be reflected in national mortality rates.
Methods. Age-specific and age-adjusted mortality rates were calculated to determine whether mortality due to prostate cancer continued to increase after 1990. Using log-linear Poisson modelling according to Clayton & Schifflers, we estimated the contribution of period and cohort effects to prostate cancer mortality between 1955 and 1994.
Results. The age-adjusted mortality increased from 22 in 1955-1959 to 33 per 10^5 in 1990-1994 (European Standardised Rate). For men under the age of 65, the rates stabilised after 1989. The age-cohort model fitted the data better than the age-period model. Therefore, the increase in mortality can be explained largely by the increasing risk for successive birth cohorts for men born until 1930. However, more frequent reporting of prostate cancer as the underlying cause of death (partly attributable to a decline in competing causes of death) may have occurred as well.
Conclusions. Our findings suggest an increased risk of fatal prostate cancer in The Netherlands between 1955 and 1994.

* Post PN, Straatman H, Kiemeney LALM, Coebergh JWW. *Int J Epidemiol* (In press). Reproduced with permission from Oxford University Press.

Introduction

The incidence of prostate cancer has increased considerably over the past decades in most industrialised countries,[1] including The Netherlands.[2,3] Mortality rates for prostate cancer have increased to a lesser extent.[1,2] More than 6300 cases of prostate cancer are now detected yearly in The Netherlands, whereas the number of deaths due to prostate cancer amounted to 2374 in 1994.[3] An increase in mortality due to prostate cancer was found in consecutive birth cohorts, on the basis of mortality data up to 1989.[4] The prognosis for prostate cancer patients has improved in several countries , e.g. the USA[5] and Sweden,[6] presumably due to earlier diagnosis and increased detection of pre-clinical cases. In Southeastern Netherlands, the overall 5-year relative survival improved slightly, but it declined for patients aged 40-59 from 65% (95% confidence interval [CI] 47-83) in 1975-1979 to 48% (CI 34-62) in 1985-1989.[7] A decline in survival of prostate cancer patients below 60 years of age was also observed in other countries in this period, e.g. in Sweden. [6] We hypothesised that a real increase in risk may have occurred in the 1980s in the most recent birth cohorts, i.e. men born between 1920 and 1935. We chose to analyse mortality data, because trends in mortality due to prostate cancer are less likely to be influenced by changes in diagnostic procedures than trends in the incidence. In addition to calculation of age-specific and age-adjusted mortality trends, we performed an age-period-cohort analysis using national data up to 1994 to determine whether mortality due to prostate cancer continued to increase after 1989 in The Netherlands and whether this can be explained by either period or birth cohort effects.

Methods

The underlying cause of every death has been reported to Statistics Netherlands since 1900. The number of men recorded as having died of prostate cancer and the age-specific number of males in the Dutch population were abstracted from the annual publications of Statistics Netherlands for the years 1955-1994.[8,9] Four revisions of the International Classifications of Disease (ICD) were used in this period. In the sixth and seventh revisions, ICD code 177 was used as the definition for prostate cancer, in the eighth and ninth revisions ICD code 185. The definitions for the two codes were essentially the same. For statistical analysis, the number of deaths and the number of males in The Netherlands were compiled into five-year age groups and five-year calendar periods of death (Table 1).

Table 1 *Number of deaths due to prostate cancer and person years of observation in the Netherlands, 1955-1994*

a) Number of deaths

	55-59	60-64	65-69	70-74	75-79	80-84
1955-59	95	229	514	837	1036	867
1960-64	116	245	591	898	1299	1133
1965-96	132	325	654	1078	1512	1425
1970-74	138	314	689	1089	1553	1514
1975-79	140	339	799	1338	1693	1674
1980-84	163	410	879	1433	1889	1832
1985-89	210	529	919	1581	2116	2112
1990-94	195	519	1062	1766	2319	2496

b) Person years of observation

	55-59	60-64	65-69	70-74	75-79	80-84
1955-59	1244347	1055747	845088	640646	423388	218827
1960-64	1382245	1156572	940699	707939	475594	257087
1965-69	1462469	1274451	1015380	771006	521280	290946
1970-74	1506338	1343825	1110544	819823	554929	316949
1975-79	1580498	1388582	1171273	895203	588620	336228
1980-84	1710417	1462326	1218130	948617	644259	360135
1985-89	1757563	1588469	1284758	997095	688909	386452
1990-94	1821150	1369635	1417716	1073638	736525	424506

Mortality rates were calculated for these groups per 100,000 person years. We adjusted the rates for age according to the European Standard Population. Ages below 55 were ignored in the analysis, because less than 1% of prostate cancer deaths occur in this group.[3] The relation between the indexed age groups (a=1-6), periods (p=1-8) and cohorts (c=1-13) is shown in table 2. To estimate the separate effects of age, calendar period and birth cohort on the trend in mortality, a series of models containing the terms listed in table 3 was fitted sequentially, using the methods described by Clayton & Schifflers.[10,11] The GENMOD procedure of the statistical package SAS was used. To test the goodness-of-fit of the models with the observed mortality rates and to test the models against one another, deviances and differences of deviances with appropriate degrees of freedom were used.[10,11] We allowed for extra Poisson variation in the final age-cohort model.[12]

Results

The number of cases and person years of all observations used in the analyses are displayed in table 2. The age-adjusted mortality due to prostate cancer increased gradually from 22 in 1955-1959 to 26 in 1965-1969, stabilised in the early seventies and then further increased to 33 in 1990-1994 (Figure 1). The increase occurred initially in all age groups, but after 1989 only in the oldest age groups (Figure 2). The age-specific mortality rate declined slightly in 1990-1994 for men under the age of 65.
The results of statistical modelling of the observed rates are summarised in table 4 and 5. If a model is valid, the deviance is chi-square distributed with DF degrees of freedom. Large values of the deviance compared with DF indicate a lack of fit. The age-period model gave a poor fit, resulting in a p-value for the goodness of fit of 0.014. The AC-model fitted somewhat better (p=0.038) than the AP-model.
The fully parameterised age-period-cohort model did not fit the data better than the age-cohort model: the difference in deviances was not significant (p=0.088) (Table 4). The age-period-cohort model fitted the data better than the AP-model (p=0.026), but not better than the AC model, also when allowing for extra-Poisson variation (F-test: p=0.30) (Table 6). We, therefore, conclude that the AC-model with extra-Poisson variation provided a good description of the data (Figure 3). The plot of the standardised deviance residuals of the AC-model with extra-Poisson variation and the AC-model without extra-Poisson variation showed only small differences in the two types of residuals and no (extreme) outliers (Figure 4).

Table 2 *Relationship between age, period and cohort. (For illustration, birth cohort 1900-1909 is shown in* ***Italic****).*

Period	1955-1959 (1)	1960-1964 (2)	1965-1969 (3)	1970-1974 (4)	1975-1979 (5)	1980-1984 (6)	1985-1989 (7)	1990-1994 (8)
Age								
55-59 (1)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)	1910-1919 (9)	1915-1924 (10)	1920-1929 (11)	1925-1934 (12)	1930-1939 (13)
60-64 (2)	1890-1899 (5)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)	1910-1919 (9)	1915-1924 (10)	1920-1929 (11)	1925-1934 (12)
65-69 (3)	1885-1894 (4)	1890-1899 (5)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)	1910-1919 (9)	1915-1924 (10)	1920-1929 (11)
70-74 (4)	1880-1898 (3)	1885-1894 (4)	1890-1899 (5)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)	1910-1919 (9)	1915-1924 (10)
75-79 (5)	1875-1884 (2)	1880-1889 (3)	1885-1894 (4)	1890-1899 (5)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)	1910-1919 (9)
80-84 (6)	1870-1879 (1)	1875-1884 (2)	1880-1889 (3)	1885-1894 (4)	1890-1899 (5)	1895-1904 (6)	***1900-1909 (7)***	1905-1914 (8)

Table 3 List of models fitted consecutively using methods described by Clayton & Schifflers.[10,11]

The mortality rate Y_{ap} is fully specified as being the rate for age group a and cohort c, since c=A-a+p, where A is the number of age groups.
The left hand side of the equation is the expected value of the natural log of the mortality rate.
The right hand side of the equation is a linear combination of the effects of some or all of the factors: age, period and cohort.

Models considered	Equations of the model	Values of indices
AGE (A)	$E[\ln Y_a] = a_a$	a = 1,2,...,5,6
AGE+DRIFT (AD)	$E[\ln Y_{ap}] = a_a + \delta p$ or	p = 1,2,...,7,8
	$E[\ln Y_{ac}] = a_a + \delta c$	c = A–a+p, c=1,...,13
AGE+PERIOD (AP)	$E[\ln Y_{ap}] = a_a + \pi_p$	as before
AGE+COHORT (AC)	$E[\ln Y_{ac}] = a_a + \tau_c$	as before
AGE+PERIOD+COHORT APC)	$E[\ln Y_{apc}] = a_a + \pi_p + \tau_c$	as before

Figure 1 Age-adjusted mortality due to prostate cancer in The Netherlands, 1955-1994. (European Standardized Rate)

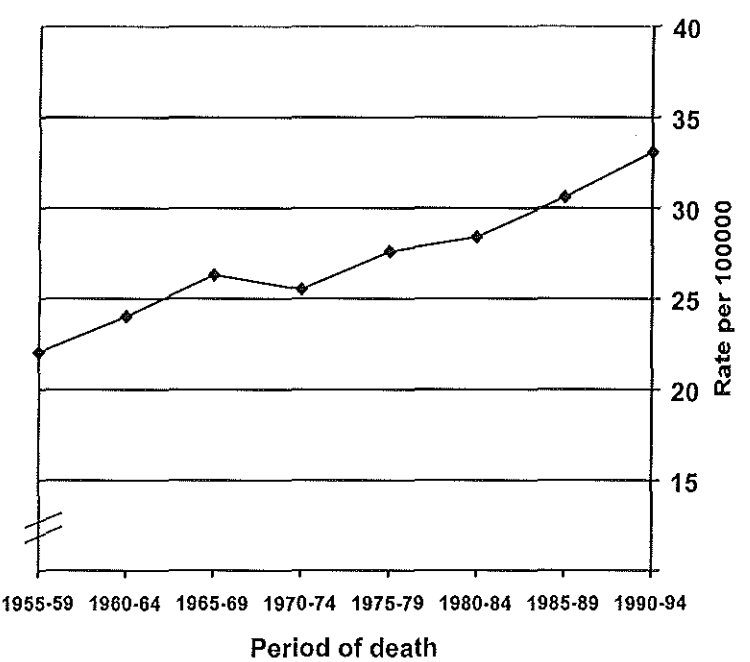


Figure 2 *Age-specific mortality rates for prostate cancer in The Netherlands, 1955-1994.*

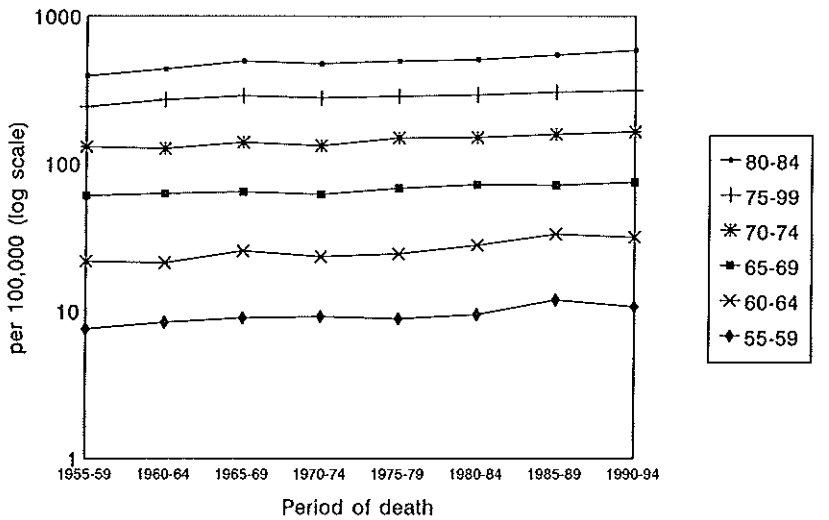


Table 4 *Goodness of fit tests of the models*

Model	Deviance	Degrees freedom	p-value
Age	418.5	42	< 0.001
Age+Drift	75.2	41	< 0.001
Age+Period	55.9	35	0.014
Age+Cohort	45.1	30	0.038
A+P+C	34.1	24	0.083

*Table 5 Successive testing of models**

Testing models	Difference in deviance	Degrees of freedom	p-value
Age+drift vs. Age	343.3	1	< 0.001
AP vs. Age+Drift	19.3	6	0.004
AC vs. Age+Drift	30.1	11	0.002
APC vs. AP	21.8	11	0.026
APC vs. AC	11.0	6	0.088

**The F-value for a test of the APC-model versus the AC-model in the presence of extra Poisson variation[12] was [(45.1–34.1)/6]/[34.1/24] = 1.29 with 6 degrees of freedom for the numerator and 24 degrees of freedom for the denominator (p-value is 0.30).*

The F-value for a test of the APC-model versus the AP-model in the presence of extra Poisson variation[12] was [(55.9–34.1)/11]/[34.1/24] = 1.39 with 11 degrees of freedom for the numerator and 24 degrees of freedom for the denominator (p-value is 0.24).

Figure 3 *Relative risk of mortality due to prostate cancer per birth cohort in The Netherlands + 95% confidence intervals, based on the Age-Cohort model (birth cohort 1935 is reference cohort).*

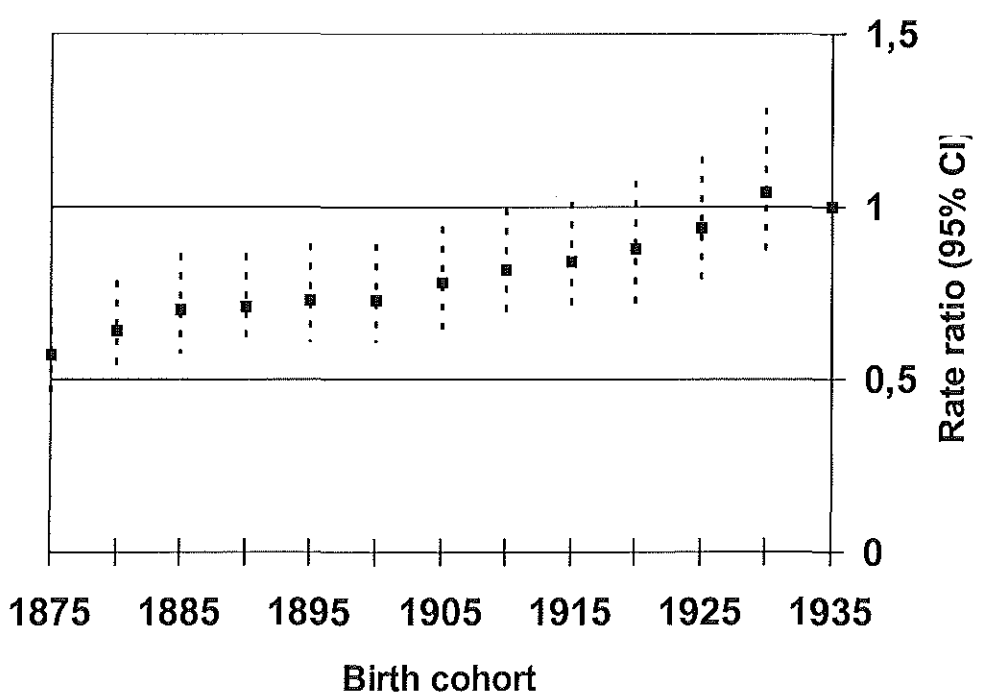
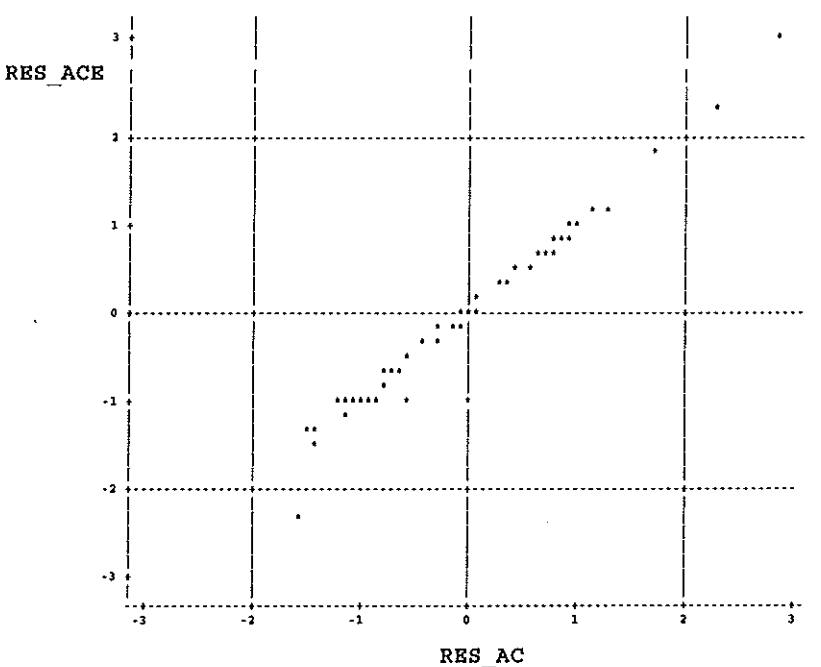


Table 6 *Parameters of the Age-Cohort model on the log scale (see Table 2) with and without extra Poisson variation.*

Age	para-meters	standard error (Se)	Se (extra Poisson variation)	Cohort	para-meters	Se	Se (extra Poisson variation)
55-59	-9.14	0.072	0.088	1875	-0.56	0.087	0.106
60-64	-8.08	0.081	0.099	1880	-0.45	0.082	0.101
65-69	-7.09	0.080	0.098	1885	-0.35	0.081	0.099
70-74	-6.28	0.080	0.098	1890	-0.34	0.081	0.099
75-79	-5.56	0.080	0.098	1895	-0.31	0.080	0.098
80-84	-4.97	0.080	0.098	1900	-0.31	0.080	0.098
				1905	-0.25	0.080	0.098
				1910	-0.20	0.080	0.098
				1915	-0.18	0.080	0.098
				1920	-0.13	0.080	0.099
				1925	-0.06	0.081	0.099
				1930	0.04	0.085	0.104
				1935	0.00	-	-

Figure 4 *Plot of standardized deviance residuals of the Age-Cohort-model without extra-Poisson variation (Res-ac) (x-axis) and the Age-Cohort-model with extra- Poisson variation (Res_ace) (y-axis).*



Discussion

Two main findings can be derived from our analyses. Firstly, mortality due to prostate cancer in The Netherlands continued to increase up to the period 1990-1994 and this increase can be described largely by an increased risk for consecutive birth cohorts since 1875. Secondly, prostate cancer mortality ceased to increase for men under the age of 65 after 1989.

The poor fit of the Age-Drift model indicated non-regular period and cohort effects. Although the fully parameterised Age-Period-Cohort model gave the best description of the data, this model is difficult to interpret. Because there are too many parameters in this model, age, period and cohort effects cannot be distinguished.[11] Since the Age-Cohort model was not significantly worse, an age-cohort model with extra Poisson variation describes the data reasonably well, suggesting birth cohort effects.

Mortality due to prostate cancer increased between 1975 and 1988 in most European countries (by 5-10% per 5-year period), except for Portugal, Spain and Yugoslavia.[1] This increase did not occur in a specific age group. Furthermore, an increasing cumulative mortality risk (30-74 years) was found for consecutive birth cohorts after 1910 (up to the 1940 birth cohort) in Denmark and Norway and to a lesser extent in Germany, Belgium, United Kingdom and The Netherlands.[1] In Norway, mortality due to prostate cancer increased to a similar extent as the incidence between 1957 and 1991, which was more pronounced in men under 60 years of age, but without a birth cohort effect. [13] On the other hand, no notable increases in mortality were reported for Northern Sweden between 1974 and 1989[14] or Isère (France) between 1979 and 1990.[15]

Analyses with mortality data available up to 1983 in Spain showed an increase in the risk for men born before 1891-1896, followed by a stabilization.[16] On the basis of mortality data up to 1991 from the database of the World Health Organisation, a pattern of an increasing risk was shown for men born around 1910 and earlier, followed by a slow increase (France, Canada, Australia) or stabilisation (USA, UK).[17] In a recent report concerning mortality in Europe, a cohort effect was found in most countries, which was most pronounced in Poland, Hungary, Greece and Spain. In some countries (e.g. Belgium, Denmark) there was a hint of reversal of trends in the cohorts of men born around 1940. Calendar period effects were negligible in most countries.[18]

Our results suggest that the risk of clinical prostate cancer has increased in The Netherlands. There could, however, be other reasons for our findings. Because the unequivocal determination of the cause of death is particularly difficult for the oldest subjects, changes in coding practices may have influenced the frequency of reporting prostate cancer as the underlying cause of death, against the background of the rising incidence of prostate cancer and the decline in mortality due to cardiovascular disease,[19] male lung cancer[20] and benign prostatic hyperplasia.[21]

This would, however, have resulted in stronger period than cohort effects. Nevertheless, the finding of an age-cohort model that fits might be explained in a different manner. If increased detection and consequently increased reporting of prostate cancer as the cause of death affect successive birth cohorts to different extents, changes in diagnostic procedures could mimic a cohort effect under some circumstances. For prostate cancer, incidence rates would have been more prone to spurious cohort effects, because increasing detection of subclinical prostate cancer is more likely to affect the incidence of prostate cancer than mortality. Since the prevalence of 'latent' prostate cancer at autopsy increases rapidly with age,[22] a higher detection rate is, indeed, likely to be more pronounced for older than younger ages. A spurious cohort effect on mortality rates could only be found if the vast majority of 'latent' cases of prostate cancer resulted in the reporting of prostate cancer as the underlying cause of death, but this does not seem to be a plausible assumption.

Delayed diagnosis resulting in a worse prognosis is not a likely explanation for increased mortality because, in fact, an increasing proportion of cases was detected at an organ-confined stage.[2] Furthermore, curative radiotherapy was applied increasingly.

If the mortality rate for prostate cancer has increased over the past decades, it seems that the contribution of increased detection to the increase in incidence is generally overestimated. However, the incidence of prostate cancer has been higher than the mortality attributable to this disease since the seventies and the trend has been a steady increase. [2] As a consequence, the mortality/incidence ratio in The Netherlands was 0.52 in 1990 and 0.38 in 1994.[3] Therefore, it seems likely that an increase in the risk of clinical prostate cancer has occurred in addition to a considerable artificial increase in the incidence.

However, a cause for this increased risk has not been established yet. Major genetic factors are responsible for approximately 9% of cases.[23] High dietary fat intake is one of the few rather consistently reported risk factors, but the evidence on alcohol intake, physical activity, vitamin D and risk factors in utero is still inconclusive.[24, 25]

In conclusion, mortality due to prostate cancer has continued to increase, which can be explained to a large extent by an increasing risk for successive birth cohorts up to those born around 1930. Analyses of mortality in other European countries point into the same direction.

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Chapter 4 Trends in prognosis

4.1 Trends in survival of prostate cancer in southeastern Netherlands, 1971-1989.*

Abstract

The increase in the incidence of prostate cancer over the past two decades is suggested to be due largely to increased detection of subclinical tumours.
To explore this assumption, we investigated trends in survival of prostate cancer in southeastern Netherlands, an area with almost 1 million inhabitants, where the age-adjusted incidence of prostate cancer increased by 53% between 1971 and 1989, i.e. before the introduction of prostate-specific antigen testing. Survival was calculated for all patients registered in the Eindhoven Cancer Registry between 1971 and 1989 (n=2562). In spite of earlier diagnosis, survival barely changed during this time period. Five-year relative survival improved slightly from 53% (95% confidence interval [CI] 47, 59) in 1975-1979 to 56% (CI 51-61) in 1985-1989. Stratified analyses suggested an improvement since 1980 for patients below 75 years with localized tumours but, despite possible stage migration, decreased survival for those with metastasized and/or poorly differentiated tumours. Patients below 75 years whose tumours were diagnosed unexpectedly during transurethral resection exhibited a relative survival of 85% 5 years and 68% 10 years after diagnosis.
Less extensive application of transurethral resection in The Netherlands might explain why our findings do not agree with those found in Sweden and the USA. Inference from country-specific trends in survival appears not necessarily generalizable to other countries with a similar increase in the incidence of prostate cancer.
We conclude from our study that earlier diagnosis of prostate cancer between 1971 and 1989 may be accompanied by an increased incidence of the aggressive variant.

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* Post PN, Kil PJM, Coebergh JWW. *Int J Cancer* (in press). Reproduced with permission from John Wiley & Sons, Inc.

Introduction

Investigation of trends in survival of prostate cancer may provide insight into the nature of recent increases in incidence. The considerable increase in incidence over the past two decades[1] is probably attributable to increased detection of subclinical cases that formerly remained undetected. This seems plausible, because a high prevalence of 'latent' prostate cancer (of up to 40% at age 70) was found in various autopsy studies of men who were not diagnosed nor even suspected of having prostate cancer before they died.[2] Due to improved diagnostic methods and increased application of transurethral resection of the prostate (TURP), an increasing proportion of these 'latent' carcinomas may be detected, thereby spuriously increasing the incidence and improving survival. The marked improvement in survival in Sweden between 1960 and 1980 is attributed to this phenomenon.[3] Since diagnostic intensity and survival differ between countries, e.g. in the Nordic countries,[4] it is not clear whether the findings for Sweden are applicable to other industrialized countries where a large increase in incidence has been reported. In Southeastern Netherlands, the incidence increased by 53% between 1971 and 1989, the increase representing low grade and localized but partly also poorly differentiated and metastasized cancer.[5] Data on changes in survival according to stage and grade are sparse in the literature, but may provide more insight into the cause of changes in survival. We studied stage-specific as well as grade-specific survival as of 1980 and investigated overall trends in survival since 1971.

Patients and methods

Study base

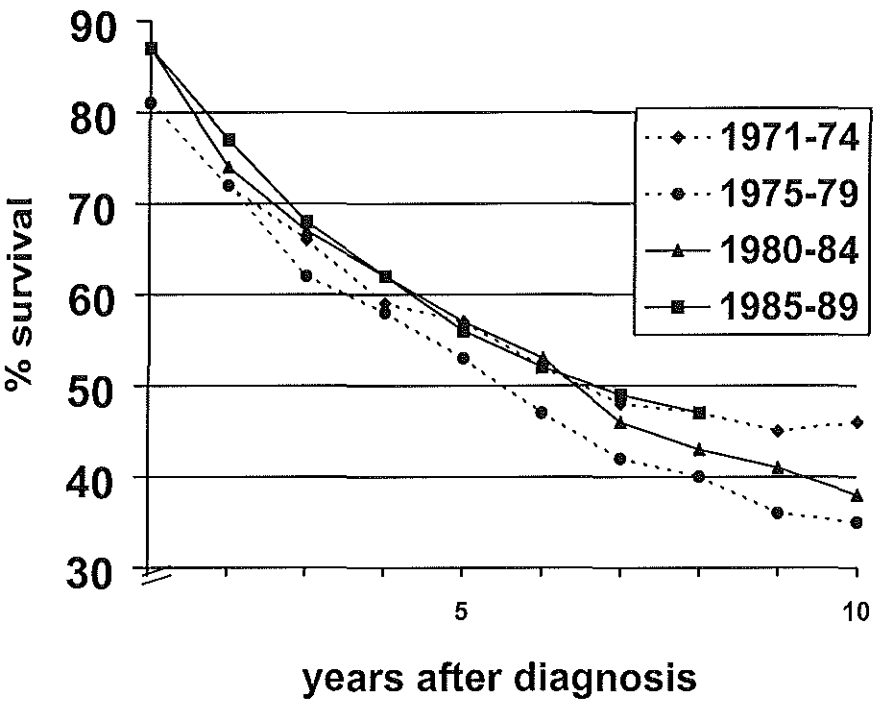
In this study, survival of patients with prostate cancer registered in the Eindhoven Cancer Registry was investigated. The registry covers a region with almost 1 million inhabitants in southeastern Netherlands with good access to specialized medical care. The methods of the registry are described in detail elsewhere.[6] Based on analysis of referral patterns and comparison with mortality data, the registry can be considered nearly complete for prostate cancer as of 1971.[5] Prostate cancer was usually diagnosed by means of histological examination of biopsies or tissue specimens obtained during TURP. TURP was the main treatment modality in the 1970s, often supplemented by hormonal or surgical castration. Radiotherapy has been prescribed increasingly since 1980, but radical prostatectomy rarely before 1988.

Analysis

The Vital status of all cases was checked with municipal civil registries until 1 April 1994. Of the 2583 patients registered between 1971 and 1989, 21 (0.8%) were untraceable (mainly due to repeated moving) and were, therefore, excluded from the survival analyses, resulting in a study cohort of 2562 patients. Another 28 (1.1%) were lost to follow up before the closing date and were censored in the analyses. The survival rates were calculated according to the actuarial (life table) method. Differences in survival were tested with the log-rank test. A Cox proportional hazards model was used to test a possible interaction between age group and period of diagnosis. Relative survival was calculated as the ratio of the crude to the expected survival. [7] The expected survival rates were calculated from life tables derived from the regional mortality statistics and compiled for five-year age groups and per calendar year for the regional male population. A software package from the Finnish Cancer Registry was used to calculate relative survival.[8]

The study period was divided into four intervals: 1971-1974, 1975-1979, 1980-1984 and 1985-1989. Survival was analyzed for the following 10-year age groups: 45-54, 55-64, 65-74, 75-84 and 85-94 years of age. Stage was recorded in the registry according to the TNM classification in use at the time.[9] On the basis of the registered information, we classified stage as localized and incidental finding (T1), localized and palpable (T2), locally advanced (T3-4), or as 'unknown' if not sufficient information was available for accurate staging. If lymph node involvement or distant metastases were recorded, stage was defined as metastasized. Because absence of metastases was not always recorded explicitly, we included both M0 and Mx in the non-metastasized categories. Since bone scans became widely available in the late 1970s, stage was reliably recorded as of 1980. Information on histological grade was used when registered; it was scored by up to 10 pathologists of three departments of pathology according to the classification of the World Health Organization in use at that time and also usable as of 1980.[9] Stratified survival analyses were performed on the basis of these categories since 1980 and for two age categories only: < 75 and ≥ 75 years of age. The chi-square test was used to test differences in proportions.

Figure 1 *Trends in relative survival of patients with prostate cancer in southeastern Netherlands, 1971-1989.*



Results

The mean as well as the median age at diagnosis of the 2562 patients was 73 years, 25% were aged 80 or over and 25% were aged 67 years or less.
Both crude and relative survival barely changed between 1971 and 1989 (Figure 1). Five-year relative survival decreased slightly in the 1970s from 57% (95% confidence interval [CI] 50%, 64%) in 1971-1974 to 53% (CI 47%, 59%) in 1975-1979). Subsequently, it returned to the initial level, being 56% (CI 51, 61) in 1985-1989. Relative survival decreased for patients aged 55-64 years from 76% in 1971-74 to 57% in 1985-1989 as well as for patients aged 45-54 years since 1980 (Table 1). A small improvement was observed for patients aged 75-84 years from 42% in 1971-74 to 48% in 1985-89. Cox regression analyses of crude survival indicated that the interaction between age group and period was not significant (p=0.12).

Table 1 *Trends in 5-year survival (crude and relative) of patients with prostate cancer diagnosed in southeastern Netherlands according to age group (standard error).*

	45-54 years		55-64 years		65-74 years		75-84 years		85-94 years	
	crude	relative	crude	relative	crude	relative	crude	relative	crude	relative
1971-74	43 (18)	45 (19)	67 (7)	76 (8)	48 (4)	64 (5)	23 (4)	42 (7)	13 (6)	48 (22)
1975-79	45 (18)	47 (19)	64 (5)	72 (6)	43 (3)	57 (4)	25 (3)	47 (5)	8 (4)	28 (13)
1980-84	53 (12)	55 (12)	53 (5)	59 (5)	44 (3)	58 (4)	31 (2)	58 (5)	7 (3)	41 (18)
1985-89	42 (10)	44 (11)	52 (4)	57 (5)	50 (2)	65 (3)	26 (2)	48 (4)	10 (4)	44 (19)

Table 2 *Change in stage distribution for patients with prostate cancer in southeastern Netherlands between 1980 and 1989.*

	< 75 years				≥ 75 years			
	1980-1984		1985-1989		1980-1984		1985-1989	
	n	%	n	%	n	%	n	%
Localized incidental	100	25	147	29	85	26	123	31
Localized palpable	59	14	126	24	53	16	66	17
Locally advanced	26	6	54	10	22	6	36	9
Metastasized	145	36	151	30	75	23	119	30
Unknown	76	19	38	7	95	29	53	13
Chi-square test								
including unknown cases:	p=0.001				p=0.001			
excluding unknown cases:	p=0.002				p=0.8			

Table 3 *Change in grade distribution for patients with prostate cancer in southeastern Netherlands between 1980 and 1989.*

	< 75 years				≥ 75 years			
	1980-1984		1985-1989		1980-1984		1985-1989	
	n	%	n	%	n	%	n	%
Well differentiated	131	32	164	32	103	31	94	24
Moderately differentiated	124	31	204	40	81	25	167	42
Poorly differentiated	72	18	101	20	60	18	85	21
Unknown differentiation	68	19	31	9	71	26	31	13
Chi-square test								
including unknown cases:	p=0.001				p=0.001			
excluding unknown cases:	p=0.2				p=0.001			

Survival by stage and grade

An increasing proportion of patients below 75 years were detected at an early stage during the 1980s (p=0.002) (Table 2), whereas the stage distribution for patients aged 75 years or over improved only slightly (p=0.8). An increasing proportion of patients in this older age group were diagnosed with moderately differentiated tumours (p=0.001) with a concurrent decrease in the proportion well differentiated (Table 3). The changes in grade distribution of patients below 75 years were less noteworthy.

Table 4 *Change in 5-year relative survival of patients with prostate cancer diagnosed in southeastern Netherlands according to stage (se = standard error).*

	< 75 years		>= 75 years	
	1980-1984	1985-1989	1980-1984	1985-1989
	% (se)	% (se)	% (se)	% (se)
localized incidental	80 (6)	88 (4)	81 (10)	74 (9)
Localized palpable	73 (8)	79 (5)	51 (11)	62 (12)
Locally advanced	60 (12)	51 (8)	59 (20)	30 (11)
Metastasized	31 (4)	24 (4)	16 (6)	20 (5)
Unknown	66 (7)	61 (11)	67 (10)	45 (13)

A total of 451 patients whose tumours were detected incidentally during TURP could be identified between 1980 and 1989, 245 of whom were below 75 years of age. Survival of these patients was shorter than that of the general male population, relative survival being 85% after 5 and 68% after 10 years.

When we excluded patients recorded as Mx (metastasis status not known), relative survival was nearly the same after 5 years (86%) and only slightly better after 10 years (70%). The majority (63%) of incidentally detected tumours was well differentiated, but 28% were moderately and 9% was poorly differentiated.

Since 1980, the prognosis for patients below 75 years with localized tumours has improved modestly, but it has deteriorated for locally advanced and metastasized cases (Table 4). A small decrease in survival was observed for patients aged 75 or over with incidentally detected tumours.

The prognosis improved for patients with well differentiated tumours but decreased for those with poorly differentiated tumours, especially for patients aged 75 years or over (Table 5). A small improvement was observed for patients with moderately differentiated tumours who were below 75 years but not for those who were 75 years of age or over.

Table 5 *Change in 5-year relative survival of patients with prostate cancer diagnosed in southeastern Netherlands according to histological grade (se = standard error).*

	< 75 years		>= 75 years	
	1980-84	1985-89	1980-84	1985-89
	% (se)	% (se)	% (se)	% (se)
well differentiated	78 (5)	86 (3)	69 (9)	81 (10)
moderately differentiated	47 (5)	64 (4)	61 (11)	45 (7)
poorly differentiated	27 (6)	24 (5)	35 (9)	25 (7)
unknown differentiation	69 (7)	42 (8)	48 (9)	37 (11)

Discussion

We observed no notable improvement in prognosis for patients with prostate cancer in Southeastern Netherlands between 1971 and 1989. An improvement in prognosis might be expected because 28% of incident cases between 1980 and 1987 were detected incidentally during TURP and stage distribution improved in this time period.[5]

Our findings do not agree with data from Sweden, where the prognosis improved markedly between 1960 and 1985.[3] A large improvement in survival was also reported in the USA between 1973 and 1989.[10] Several other reports concerning trends in survival since 1960 are available but unfortunately they cover several different time periods. Five-year relative survival improved modestly in Scotland from 44% in 1968-1972 to 47% in 1983-1987.[11] In Norway,[12] it improved from 42% in 1957-1961 to 59% in 1982-1986 and in Vaud (Switzerland) from 44% in 1974-1978 to 52% in 1979-1983. [13] In the Eurocare Study, a collaborative study of 45 cancer registries in 17 European countries since 1978, a modest improvement in prognosis from 55% to 59% was found only between 1986 and 1989.[14]

In the present study, survival was initially higher than in subsequent periods. This may be explained by increasing completeness of the registry in the 1970s.[5] Some of the more severe cases probably never underwent work-up in a hospital, because the number of urologists was still small in those days. (It increased from 3 per 400,000 men in 1971 to 12 in 1978). This decreases the chances of registration by the cancer registry, since this depends largely on notification by Pathology Departments and medical record departments in the hospitals. Selective loss to follow-up is not likely to be an issue, since migration rates are low in the region and all patients were actively followed up via municipal civil registries, resulting in only 1.9% lost to follow-up. Moreover, over 95% of cases were confirmed pathologically by histological examination of biopsies or tissue specimens obtained by TURP. A beneficial effect of treatment could probably not yet been expected, because most patients in the 1970s and a large proportion in the 1980s were treated conservatively. The unexpected decline in survival in the youngest age groups is discussed in detail elsewhere.[15]

A small improvement in survival was observed for localized prostate cancer versus decreased survival for locally advanced and metastasized cases, although the rather large confidence intervals do not allow firm conclusions. Changes in the assessment of stage due to new diagnostic techniques (stage migration) cannot explain these divergent trends, because an improvement in all stages would then be expected.[16] Furthermore, we used the clinical stage in our analyses, thereby minimizing the impact of staging procedures related to radical surgery. The cases detected incidentally during TURP exhibited a 10-year relative survival of 68%, which means that they also comprised lethal tumours. This was not due to the inclusion of patients with an unknown metastasis status (Mx), because survival was nearly the same after exclusion of these cases. Most of the incidentally detected cases were just classified as T1, not T1A or T1B. It is, however, not likely that many T1 cases were misclassified as such, because whenever the registrars had a reasonable doubt, the tumour classification was coded as unknown. However, it is possible that the majority of these cases should be classified as T1B, which would mean a significantly worse survival than T1A.[17] Indeed, almost 40% of these cases were moderately or poorly differentiated. The unexpected finding of prostate cancer probably occurred largely in patients whose tumours would soon have become clinically apparent without this procedure.

The lack of improvement in survival in our study may be explained by an increased occurrence of aggressive prostate cancer, which might have cancelled out the expected improvement due to earlier detection. Indeed, we did not observe an improvement in the grade distribution but, in contrast, more moderately and to a lesser extent more poorly differentiated tumours were detected during the late 1980s.

In the USA, the proportion of patients with poorly differentiated tumours neither declined substantially after the introduction of early detection measures in the 1990s, although an increased proportion of these tumours was detected at an organ confined state.[18] An increased risk of aggressive prostate cancer is also suggested by the increasing risk of mortality due to prostate cancer for consecutive birth cohorts up to men born around 1930 in most European countries,[19] although a cause for this development has not been found yet. Increased diagnosis of insignificant tumours, resulting in improved survival, such as reported for Sweden[3] did probably not occur in all countries to a similar extent. The effect of early detection by PSA testing and intervention by radical prostatectomy on survival could not yet be evaluated in our study, but early detection by PSA testing will produce improved survival even in the absence of treatment due to lead time bias.[20]

In conclusion, the lack of a notable improvement in survival of patients with prostate cancer between 1971 and 1989 in southeastern Netherlands may indicate that earlier diagnosis concurred with an increased incidence of aggressive prostate cancer.

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4.2 Variation in survival of patients with prostate cancer in Europe since 1978.*

Abstract

Since the incidence of prostate cancer has increased considerably over the past two decades in most European countries, knowledge of the variation in survival is pertinent. The collaboration across Europe in the Eurocare study has now been extended to 45 registries in 17 countries. We report on variation in relative survival according to age of 65728 patients diagnosed with prostate cancer between 1985 and 1989 and also explore time trends since 1978 for most countries.

Considerable variation in survival was found within and between countries with the highest survival in Switzerland (5-year relative survival 72%), followed by Germany (67%) and the Nordic countries (except Denmark). The lowest survival was found in Estonia (39%), preceded by Slovenia (40%), Denmark (41%) and England (45%). Between 1978 and 1986, relative survival barely changed over time, but it improved from 55% (95% confidence interval [CI] 53-57) in 1984-1986 to 59% (CI 56-61) in 1987-1989. A small but unexpected deterioration of survival for patients aged 45-54 from 61% to 56% was observed in the early 1980s.

It is likely that variation in both detection methods and treatment plays a role in the observed variation in survival, but more information is needed to assess each contribution.

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* Post PN, Damhuis RAM, van der Meyden APM and the Eurocare Working Group. *Eur J Cancer* 1998;34:2226-2231. Reproduced with permission from Elsevier Science.

Introduction

In most European countries, the incidence of prostate cancer has increased more than any other cancer over the past two decades.[1] Prostate cancer is mainly a cancer of old age. Being very uncommon at younger ages, the annual incidence increases steeply after age 50 to 1 per 100 men aged 80 and over. A very high prevalence of so-called 'latent' prostate cancer (of up to 40% at age 70) was found in various autopsy studies of men who had no clinical diagnosis or suspicion of prostate cancer before death.[2] An increasing proportion of these latent cancers has been detected due to the increased use of transurethral resection of the prostate (TURP). Application of this surgical procedure for the treatment of symptoms of benign prostatic hyperplasia results in the unexpected diagnosis of prostate cancer in approximately 10% of cases.[3] Since increased detection of subclinical cases not only results in an increase in the incidence,[4] but also in improved survival,[5] access to this surgical procedure in a region is an important determinant of the prognosis. Increased detection of insignificant tumours may be accelerated by the introduction of improved diagnostic techniques like transrectal ultrasound, ultrasound guided biopsy and prostate-specific antigen (PSA) testing (length time bias). Moreover, the diagnosis of prostate cancer following a positive PSA test appears to move the diagnosis forward by up to 5-10 years,[6] resulting in improved survival as well (lead-time bias).

Stage at diagnosis is an important determinant of prognosis. Once the disease has metastasised, cure is not possible anymore and treatment is directed primarily on relief of symptoms. If prostate cancer is detected at an early stage, curative treatment by radical prostatectomy[7]or radiotherapy[8] is possible. However, watchful waiting appears to provide similar results for patients with low-grade tumours.[9,10] There is no consensus about the usefulness of screening for prostate cancer. Large trials that address this issue are currently carried out in the USA and Europe.[11] Meanwhile, the incidence, mainly of low-grade cancer, has increased in several European countries following the introduction of opportunistic PSA testing.[12,13] Since there was no report on prostate cancer in the first part of the Eurocare study,[14] this is the first report on survival of prostate cancer across Europe. The collaboration across Europe in the Eurocare study has now been extended to 45 registries in 17 countries that have accumulated data on 3.5 million new patients most of them diagnosed between 1978 and 1992. We now report on variation in relative survival of patients with prostate cancer according to age from 1985-1989 and we also explore time trends since 1978 for most countries.

Patients and methods

Survival analysis was carried out on prostate cancer cases diagnosed between 1985-1989 in 17 countries recorded in 40 population-based registries. Some of these (in Finland, Denmark, Estonia, Slovenia, Iceland, Scotland, Slovakia) cover the whole country, some a large proportion (England) and the rest up to 20% (Sweden, The Netherlands, Germany, Austria, Switzerland, France, Italy, Spain, Poland). Cases discovered at autopsy (1.5%), patients known on the basis of a death certificate only (DCO) (4.6%) or patients first diagnosed with another tumour were not included (Table 1 shows percentages for each country).

Table 1 *Data quality by country for patients with prostate cancer (Eurocare II).*

	% DCO[#]	% histologically verified	% lost to follow up
Iceland	0.2	93	0
Finland	0.5	97	0.02
Sweden[*]	0	99	0
Denmark	0	92	0
Scotland	2.3	84	0
England	7.1	73	0.1
Netherlands[*]	0	98	1.8
Germany[*]	2.4	91	0
Austria[*]	1.5	83	0
Switzerland[*]	0.3	99	11
France[*]	0	97	0.4
Spain[*]	15	89	0
Italy[*]	3.6	79	0.6
Slovenia	6.7	84	0.1
Slovakia	8.1	81	0
Poland[*]	0.9	60	7.1
Estonia	0.1	66	0.7
Europe	4.6	83	0.1

[*] < 20% of the national population covered [#] % death certificate only

The protocol specified a minimum follow-up of five years. With respect to time trends, the following 3-year periods were used: 1978-1980, 1981-1983, 1984-1986, and 1987-1989. Age-specific survival was calculated for the following age groups: 55-64, 65-74 and 75-84 years of age.

Relative survival was computed as the ratio between the observed (crude) survival and the expected survival, derived from general mortality data.[15] Age-standardised survival could not be calculated for Iceland, The Netherlands and Poland because, in the data of these registries, one of the age strata contained no cases. General European estimates of survival were weighted according to the national incidence (reflecting the size of the population). Survival trends have also been computed as weighted rates. Changes in relative survival over time were calculated for the following age groups: 15-44, 45-54, 65-74 and 75-99 years of age. Only data from registries that could provide data for the entire period 1978-1989 were used for these calculations. Standard errors of survival, used for calculation of 95% confidence intervals, were calculated according to Greenwood's method.[16]

Table 2 Number of patients with prostate cancer diagnosed between 1985 and 1989 in Europe by age group and country (Eurocare II).

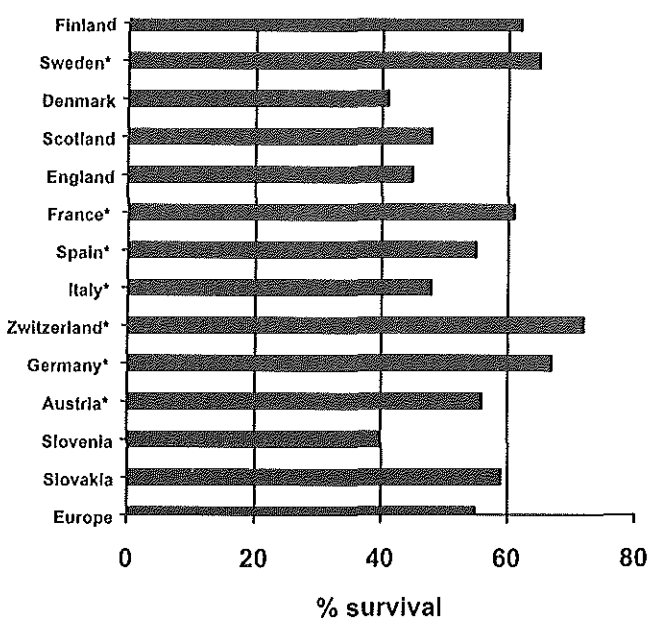
	Age (years)						Incidence per 10^5
	15-54	55-64	65-74	75-84	85-99	Total	in 1983-87[1]
Iceland	6	73	147	165	47	438	52
Finland	94	853	2101	2138	380	5566	36
Sweden*	41	436	1338	1473	292	3580	50
Denmark	102	817	2597	2773	650	6939	30
Scotland	85	638	2137	2159	457	5476	28
England	375	3213	10202	11423	2398	27611	23
Netherlands*	22	130	312	285	70	819	29
Germany*	32	190	373	386	54	1035	29
Austria*	3	49	130	163	19	364	52[2]
Switzerland*	16	129	391	433	103	1072	51
France*	34	332	755	869	163	2153	32
Spain*	31	234	670	738	133	1806	27
Italy*	72	531	1496	1619	274	3992	26
Slovenia	23	142	359	446	42	1012	19
Slovakia	70	508	1004	1031	112	2725	20
Poland*	13	105	167	127	25	437	12
Estonia	23	121	295	243	21	703	19
Europe	1042	8501	24474	26471	5240	65728	-

* < 20% of the national population covered
[1] World Standardised Rate, adapted from Parkin et al.[25]
[2] Incidence in 1988-1992

Results

Survival rates (age-standardised) within each country (including overall EU data)
The number of patients with prostate cancer in the Eurocare database was 65512, of which 15% was below 65 years of age and 48% was aged 75 years or older (Table 2). Considerable variation in survival was observed between countries, which was apparent by 1 year (Figure 1). Patients diagnosed in Switzerland had the highest survival (5-year relative survival 72%) followed by Germany and the Nordic countries, except Denmark. The lowest survival was observed in Estonia (39%), preceded by Slovenia and Denmark. Within Spain, Italy and France a geographical variation between different registries of up to 20% emerged, while hardly any variation in survival was found within England (data not shown; see Eurocare II monograph.[17]

Figure 1 *Five –year relative survival of patients with prostate cancer diagnosed between 1985 and 1989 in Europe.*[1]



* < 20% of the national population covered
[1] Age-standardised survival could not be calculated for Iceland, The Netherlands and Poland, because one of the age strata contained no cases.

Table 3 *Age-specific 1- and 5-year relative survival of patients with prostate cancer in Europe, 1985-1989 (Eurocare II)*

	55-64 yrs		65-74 yrs		75-84 yrs	
	%	%	%	%	%	%
	1	5	1	5	1	5
Iceland	98	77	93	70	90	60
Finland	92	58	93	64	89	63
Sweden*	95	66	94	68	91	64
Denmark	87	40	87	45	80	39
Scotland	88	54	83	50	77	45
England	86	48	83	46	76	44
Netherlands*	86	58	93	66	86	46
Germany*	94	71	91	73	87	58
Austria*	89	72	95	64	78	48
Switzerland*	95	64	94	73	92	77
France*	90	58	92	68	85	56
Spain*	86	54	87	50	81	45
Italy*	88	55	87	53	78	43
Slovenia	81	43	75	41	74	41
Slovakia	84	52	80	55	75	64
Poland*	74	43	71	42	60	25
Estonia	75	33	74	40	68	41
Europe	89	58	88	60	82	51

* < 20% of the national population covered

Survival rates depending on age distribution for each country

Taking all participating countries together, 5-year relative survival of patients aged between 55 and 64 years was slightly lower than those aged between 65 and 74 years (58% vs. 60%), whereas survival of patients aged between 75 and 84 years was substantially lower (51%) (Table 3). The lower survival for the ages 55-64, which was generally already apparent within 1 year, was observed in most countries, except Iceland, United Kingdom, Italy and Slovenia. Five-year relative survival for patients aged between 75 and 84 years was by far the lowest in Poland (25%), and the highest in Switzerland (77%), followed by Sweden and Slovakia (both 64%).

Change in survival over time 1978-1989 for each country

Overall, survival barely changed before 1986. Only between 1984-1986 and 1987-1989 a modest but significant improvement was observed from 55% (95% confidence interval [CI] 53-57) to 59% (CI 56-61) and was mainly due to an improvement in survival for patients aged 65 or over (Table 4).

Table 4 *Change in 5-year relative survival of patients with prostate cancer in Europe over time by age group, 1978-1989 (Eurocare II)*

	15-44	45-54	55-64	65-74	75-99	all ages*
	%	%	%	%	%	% (95% CI)
1978-80	56	61	57	52	61	56 (53-59)
1981-83	47	56	61	53	43	55 (53-58)
1984-86	49	58	60	50	48	55 (53-57)
1987-89	57	60	61	55	59	59 (56-61)

* age-standardized

Table 5 *Change in age-standardised 5-year relative survival for each country,# 1978-1989 (Eurocare II)*

	1978-80	1981-83	1984-86	1987-89
	%	%	%	%
Iceland	55	61	65	66
Finland	55	56	60	63
Sweden*	60	60	62	67
Denmark	40	38	41	40
Scotland	44	43	44	49
England	44	44	46	43
Netherlands*	52	60	55	56
Germany*	72	70	64	68
Switzerland*	55	49	60	60
France*	56	50	54	69
Italy*	39	46	46	53
Poland*	29	-	44	33
Estonia	35	31	32	43
Europe	56	55	55	59

* < 20% of the national population covered

excludes Austria, Spain, Slovenia and Slovakia, where registries did not contribute data for the whole period 1978-1989.

This improvement occurred predominantly in France, Italy and Estonia and to a lesser extent in Sweden, Scotland and Germany (Table 5). Between 1978 and 1983, survival had already improved in Iceland, Finland and Italy. Relative survival of patients under the age of 55 years deteriorated unexpectedly in the early 1980s (Table 4), followed by a return to the initial value in 1987-1989.

Discussion

Variation in survival

Considerable variation was observed in survival of patients with prostate cancer in Europe. The lowest rates were found in East European countries (except Slovakia) and the United Kingdom, the highest in Switzerland and the Nordic countries (except Denmark). The very high survival in Switzerland may be biased due to the high proportion that was lost to follow-up (11%) due to emigration [17]. Barriers to specialised care, resulting in delayed diagnosis, played probably a role in the lower survival in the Eastern countries. Delayed diagnosis may also be caused by hesitance to consult a physician due to limited awareness of prostate cancer among the general public. However, international differences in how and when to treat prostate cancer may result in variation in survival as well. Increased inclusion of insignificant cases (e.g. detected unexpectedly by TURP) results in spuriously improved survival rates.[5] Similar mortality rates for prostate cancer in the Nordic countries, but strikingly lower survival in Denmark could be explained by the rather reserved attitude of Danish physicians which appears to result in limited diagnosis of asymptomatic prostate cancer cases .[18] In Table 6, variation in survival is shown in relation to age-standardised incidence for most participating countries. Countries at high incidence also exhibit relatively high survival, suggesting more intensive diagnostic activity leading to earlier stages.The low incidence and survival rates in the Eastern countries may also indicate that the incidence only represented symptomatic cases. Although variation in the occurrence of co-morbidity influences survival, [19] using relative survival (so correcting for expected survival) should have removed most of this variation.[15] Differences in treatment applied may explain part of the variation in survival. Along with the reserved attitude of Danish physicians with respect to diagnosis, only a minority of patients used to receive curative treatment in Denmark.[20] In Great Britain, radical prostatectomy has been advocated only for a small minority of patients.[21] Although early diagnosis makes curative treatment (radical prostatectomy or radiotherapy) accessible, the benefit of treatment of especially low-grade tumours is not undisputed.[10] Interpretation of the international variation in survival is difficult without proper information on the differences in the proportion of insignificant tumours, stage at diagnosis and treatment.

Standardised monitoring of staging procedures, tumour characteristics and treatment by registries participating in the Eurocare study should provide a better understanding of the observed differences in survival.

Table 6 *Incidence (World Standardised Rate), adapted from 3 volumes of Cancer Incidence in Five* Continents[25-27] *in relation to relative survival.*

	Incidence (WSR)			Relative survival*	
	1978-82	1983-87	1988-92	1981-83	1987-89
Iceland	36.2	52.4	61.0	H	H
Finland	34.2	36.1	41.3	H	H
Sweden	45.9	50.2	55.3	H	H
Denmark	27.7	29.9	31.0	L	L
Scotland	23.3	27.8	31.2	L	L
England	20.9	23.1	28.0	L	L
Netherlands (Eindhoven)	28.3	28.9	35.6	H	H
Germany (Saarland)	28.7	28.9	35.9	H	H
Austria	-	-	51.6	-	H
Switzerland	50	51	50	M	H
France (Calvados)	26.8	31.8	50.5	M	H
Spain (Navarra)	20.5	26.8	27.2	-	H
Italy (Varese)	20.3	25.5	28.2	L	H
Slovenia	18.7	18.6	20.7	-	L
Slovakia	15.8	19.9	22.0	-	L
Poland (Warsaw)	11.5	11.9	15.7	L	L
Estonia	-	18.8	21.6	L	L

* H: High survival (> 50%); L: Low survival (< 50%); M (=50%).

Trend in survival

Overall, survival of prostate cancer patients barely changed in Europe. In Sweden, a marked improvement in survival was observed between 1960 and 1980, which was attributed largely to increased diagnosis of insignificant ('nonlethal') cases.[5] A similar improvement might have occurred in other European countries between 1960 and 1980, but this time period was not included in the Eurocare study. We observed only a modest improvement between 1978 and 1989, in contrast to the USA, where 5-year relative survival improved from 71% in 1978 to 83% in 1987.[22] Therefore, increased diagnosis of insignificant tumours seems to play a limited role only in Europe in the time period studied.

Relative survival did not improve in the age band 45-54 years, as might have been expected, but even deteriorated (transiently) in the early 1980s. A large increase in incidence under age 60 was reported for Southeastern Netherlands and East Anglia (UK) without an improvement of prognosis.[23] Multivariate analyses of mortality between 1955 and 1992 revealed an increasing risk for consecutive birth cohorts up to men born around 1930 in most European countries (except France and Italy).[24] However, the assumption of an increased risk of fatal prostate cancer has not yet been supported by evidence of a specific risk factor.

In conclusion, a large variation in survival was observed within Europe, for which the role of early diagnosis, diagnosis of insignificant tumours and the variation in treatment is difficult to disentangle. In spite of increased awareness of prostate cancer, survival improved only modestly since 1978.

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Chapter 5 Determinants of treatment of localized prostate cancer

5.1 Trend and variation in treatment of localized prostate cancer in the southern part of The Netherlands, 1988-1996.

5.2 Co-morbidity in patients with prostate cancer and its relevance to treatment choice.

5.1 Trend and variation in treatment of localized prostate cancer in the southern part of The Netherlands, 1988-1996.*

Abstract

Objective. To investigate whether the large increase in incidence of early prostate cancer has led to subsequent increased application of curative treatment and whether similar patterns of treatment were observed in the various hospitals in the area of this investigation.
Methods. Using the Eindhoven Cancer Registry, all patients newly diagnosed with prostate cancer between 1988 and 1996 in the southern part of The Netherlands were included in the study. Initial treatment was analysed for 4073 patients, of whom the proportion with clinically localised prostate cancer (T1-T3, M0-Mx) increased from 52% in 1988-1990 to 74% in 1994-1996.
Results. The proportion of patients with localized prostate cancer treated with radical prostatectomy increased from 11% to 34% among patients under age 70. Especially in 1994-1996, a group of smaller hospitals with a rather low proportion treated with radical prostatectomy (5%-52%: n=11) could be distinguished from a group of larger hospitals with a large proportion treated with radical prostatectomy (35%-67%: n=5). Radiotherapy was a more frequent option in hospitals with low radical prostatectomy rates. The proportion of patients aged 70-74 years undergoing radiotherapy increased from 31% to 41%. Over 80% of the patients of 75 years or over were treated conservatively during the whole study period.
Conclusion. Increased detection of localized prostate cancer resulted in increased application of curative treatment for patients under 70 years of age, but a substantial variation was observed between hospitals in the application of radical prostatectomy and radiotherapy.

* Post PN, Kil PJM, Hendrikx AJM, Poortmans PMP, Crommelin MA, Coebergh JWW. *Eur Urol* (In press). Reproduced with permission from Karger AG Basel.

Introduction

Different treatment options are available for patients presenting with localized prostate cancer. Long-term survival rates for untreated patients with small low-grade tumours of up to 87% at 10 years have been reported by several studies, as summarized by Chodak et al.[1] Nevertheless, the large increase in the incidence of early prostate cancer in the 1980s resulted in an even more pronounced increase in the use of radical prostatectomy in the USA.[2] In The Netherlands, the incidence, mainly of low grade prostate cancer, increased by almost 50% following the introduction of prostate specific antigen (PSA) testing in the 1990s. [3,4] Curative treatment is not necessarily the optimal treatment option for all of these patients, due to the protracted natural history and the frequently occurring concomitant diseases with negative impact on the life expectancy of these patients.[5] Perioperative mortality or other cardiopulmonary complications of surgery occur in about 10% of patients aged 75 years or over and in up to 5% of patients aged 65-69.[6] Application of curative treatment results in sexual dysfunction in the vast majority of patients, symptoms of urinary incontinence in 10-30% of patients treated with radical prostatectomy and symptoms of bowel or bladder irritation in up to 30% of patients undergoing radiotherapy.[7] No conclusive guidelines for the treatment of localised prostate cancer could be established by a 'guidelines panel' convened by the American Urological Association (AUA).[8] We were interested in the management of the increasingly at an early stage detected prostate cancer in our area. Since the Eindhoven Registry started to cover the whole southern part of The Netherlands in this year, we were able to describe the changes in treatment for the southern part of The Netherlands since 1988.
We investigated whether the observed exponential increase in incidence of early prostate cancer has led to subsequent increased application of curative treatment. We also assessed the variation in treatment between hospitals in the region.

Patients and methods

Data were obtained from the population-based Eindhoven Cancer Registry in the southern part of The Netherlands. Initially, the registry started in the southeastern part, as described in detail elsewhere[9] and can be considered virtually complete for prostate cancer since 1971.[4] Registration in the southwestern part, using similar methods as in the southeastern part, reached completeness in 1988. Nowadays, the registry covers almost the whole southern part of The Netherlands (excluding the province of Zeeland and the southern part of the province of Limburg) The region has a population of more than 2 million inhabitants and offers good access to specialised medical care supplied in 16 community hospitals and two large radiotherapy centres. The region does not include university or specialised cancer hospitals.

The distance to a hospital has always been less than 30 kilometres. In the 1970s, prostate cancer patients were usually treated symptomatically with transurethral resection of the prostate (TURP), frequently followed by hormonal or surgical castration. Radiotherapy has been applied increasingly since the early 1980s, but radical prostatectomy was only rarely performed before 1988.

Since 1988, initial treatment has been registered in more detail. We distinguished the following categories: radical prostatectomy (usually retropubic); prostatectomy followed by radiotherapy; radiotherapy; hormonal treatment only (including orchidectomy, anti-androgens and LH-RH-analogues); TURP only (mainly performed before the diagnosis of prostate cancer); expectant management; and a last category containing patients with unknown treatment or patients with treatments other than those listed above. For some of the analyses, a more crude classification was used: radical prostatectomy (1), radiotherapy (2) or other treatment (3). In this classification, the few patients receiving radical prostatectomy followed by radiotherapy were included in the 'radical prostatectomy 'group.

Because preliminary analyses revealed large differences in the application of radical prostatectomy, the hospitals were grouped in type A hospitals (with $\leq$ 10 prostatectomies per year: n=11) and type B hospitals (with more than 10 prostatectomies per year: n=5). This division corresponds roughly to hospitals with less than 500 beds (type A) and hospitals with at least 500 beds (type B).

Clinical and pathological stage is recorded in the registry according to the TNM classification in use.[10] On the basis of the registered information, we simplified the T classification as T1, T2 (includes since 1992 tumours that are not palpable, but visible on transrectal ultrasound, usually performed after a positive PSA test),[10] T3 or T4. If lymph node involvement or distant metastases were recorded, stage was defined as metastasized. Because absence of metastases was not always recorded explicitly, we included both M0 and Mx in the non-metastasized categories in case of a T1-T3. Treatment patterns were described after exclusion of M1, N1+ and T4 patients. The chi-square test was used to test differences in proportions.

Results

Between 1988 and 1996, 5411 patients with prostate cancer were diagnosed in the southern part of The Netherlands, of whom 4073 had localized disease. The proportion of patients with advanced prostate cancer (M1/N1+/T4) decreased from 33% in 1988-1990 to 19% in 1994-1996 (p=0.001), which was mainly attributable to the doubling of cases with T2 tumours (Figure 1).

Figure 1 Trend in stage distribution of patients with prostate cancer diagnosed in the southern part of The Netherlands between 1988 and 1996.

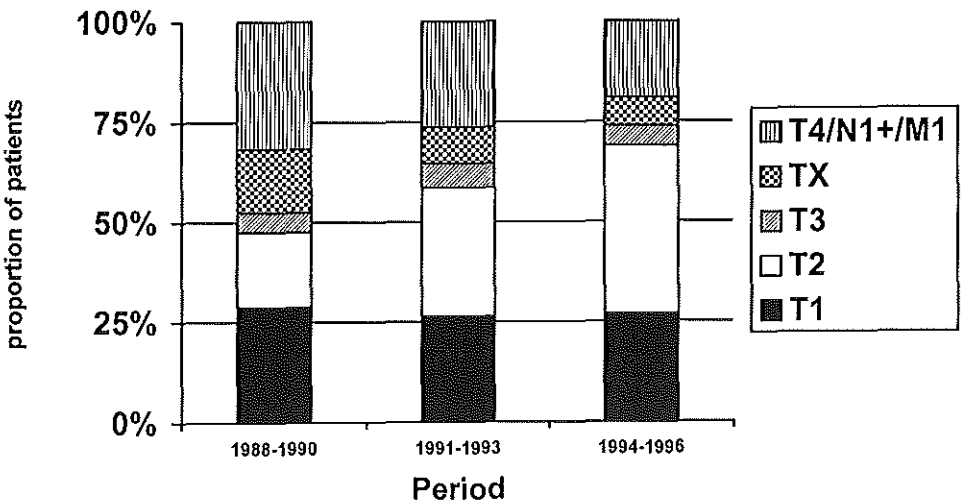
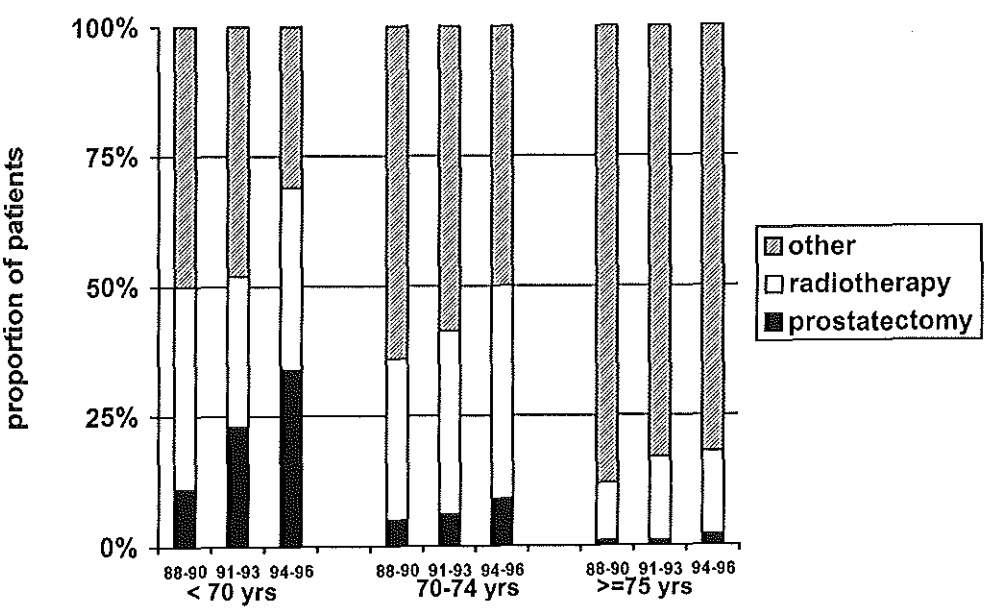


Figure 2 Proportion of patients treated for localized prostate cancer in the southern part of The Netherlands by age group, 1988-1996.



Trend in treatment

The increase in patients with potentially curable prostate cancer resulted in increased application of both radical prostatectomy (mainly under age 70) and radiotherapy (only for patients aged 70 or over) (Figure 2). The number of patients receiving radiotherapy remained almost twice as high as the number of prostatectomies (Figure 3). The changes in treatment are displayed in more detail in table 1. For patients under age 70, the proportion treated with radical prostatectomy increased threefold from 11% to 33%. The proportion of patients treated and usually detected by 'TURP only' decreased considerably from 30% in 1988-1990 to 10% in 1994-1996. Radiotherapy remained the main curative treatment option in patients aged 70-74 years, in whom we also observed an increase in radical prostatectomies from 5% to 9%. Hormonal treatments were applied rather consistently through the years and especially among patients over 75 years of age, in whom the proportion detected by TURP also decreased. An increasing proportion received no initial treatment at all.

Treatment according to T classification

Radical prostatectomy was most frequently applied in patients under age 70 with T2 tumours and infrequently for T3 tumours (Table 2). In contrast, radiotherapy was the most frequently applied treatment for patients under age 75 with T3 tumours and the second option in T3 patients over 75 years of age. 35% of clinical T2 and 15% of T1 tumours of the patients undergoing radical prostatectomy, were upstaged to T3, whereas a smaller proportion of clinical T3 was downstaged (Table 3). Less than 5% of the patients regarded suitable for radical prostatectomy appeared to have positive lymph nodes. Hormonal treatment was the main option in patients over 75 years, except for T1 patients of whom the majority was detected and treated by TURP only. A considerable proportion of Tx patients under 75 received curative treatment.

Variation in treatment

Substantial variation in treatment appeared to exist between large and smaller hospitals, especially in the most recent period, 1994-1996. Patients diagnosed in larger hospitals (type B) underwent radical prostatectomy more than twice as much than those diagnosed in smaller (type A) hospitals (Table 4). The proportion of patients under the age of 70 undergoing prostatectomy in 1994-1996 ranged from 5% to 52% in smaller hospitals (type A) from 37% to 67% in the larger hospitals (type B). Radiotherapy was more often applied in patients diagnosed in the smaller hospitals. No notable differences in age, stage or grade distribution were observed between the two hospital categories.

Table 1 *Trend in treatment for patients with localized prostate cancer (M0-MX, T1-T3) in the southern part of The Netherlands, 1988-1996.*

	< 70 years			70-74 years			≥ 75 years		
	88-90	91-93	94-96	88-90	91-93	94-96	88-90	91-93	94-96
Number of patients	348	471	707	191	272	458	406	537	683
	%	%	%	%	%	%	%	%	%
Radical prostatectomy	11	23	33	5	6	9	1	1	2
Radiotherapy	39	29	35	31	37	41	11	16	16
Hormonal treatment	15	20	14	20	22	25	35	45	42
TURP only*	30	22	10	40	29	11	45	28	17
Expectant management	1	2	4	3	3	9	5	6	17
Unknown/other	3	5	3	1	4	5	2	4	5

* Usually the mode of incidental diagnosis

Table 2 *Treatment of patients with localized prostate cancer (M0-MX, T1-T3) in relation to Tumour classification in the southern part of The Netherlands, 1988-1996.*

	< 70 years				70-74 years				≥ 75 years			
Clinical stage	T1	T2	T3	TX	T1	T2	T3	TX	T1	T2	T3	TX
Number of patients	561	688	121	156	327	417	67	110	579	664	99	284
	%	%	%	%	%	%	%	%	%	%	%	%
Radical prostatectomy	21	31	8	17	9	7	0	7	1	1	0	1
Radiotherapy	29	39	58	15	30	41	58	13	10	22	24	5
Prostatectomy and radiotherapy	0	2	2	3	0	2	2	3	0	0	0	1
Hormonal treatment	10	17	24	26	16	26	39	24	30	50	61	36
TURP only*	36	6	5	18	43	9	6	24	48	14	7	25
Expectant management	4	1	2	8	6	4	1	15	8	9	5	19
Unknown/other	2	3	2	14	1	1	1	22	2	3	3	13

* Usually the mode of incidental diagnosis

Figure 3 *Number of patients with prostate cancer treated curatively in the southern part of The Netherlands, 1988-1996.*

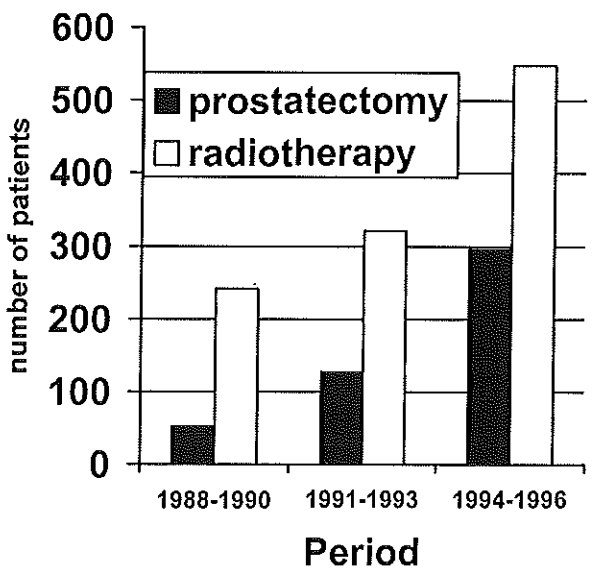


Table 3 *Comparison of clinical and pathological T- and N-classification in patients treated with radical prostatectomy in the southern part of The Netherlands, 1988-1996.*

T classification

	pT1	pT2	pT3	pT4	pTx
	%	%	%	%	%
cT1	28	50	15	1	6
cT2	1	51	35	1	12
cT3	0	8	84	0	8
cTx	13	54	27	2	4

N classification

	pN0	pN1	pN2	pNx
	%	%	%	%
cN0	83	4	1	12
cNx	65	2	1	32

Table 4 *Variation in treatment of patients under age 70 with localized prostate cancer (M0-MX, T1-T3) in the southern part of The Netherlands, 1994-1996.*

	Type A hospital #		Type B hospital #	
	n	%	n	%
Radical prostatectomy	77	19	149	47
Prostatectomy and radiotherapy	4	1	10	3
Radiotherapy	176	44	73	24
Hormonal treatment	64	16	36	12
TURP only*	27	11	43	9
Expectant management	16	4	11	3
Unknown/other	18	5	5	2

* Usually the mode of incidental diagnosis

#Type A: < 10 radical prostatectomies per year; Type B: ≥ 10 per year

Discussion

The large increase in the proportion of patients with localised prostate cancer since 1990 in the southern part of The Netherlands was followed by an increased application of radical prostatectomy and curative radiotherapy. The increased application of radical prostatectomy was restricted largely to men under 70 years of age. In contrast, the almost six-fold increase in radical prostatectomy rates in the USA extended to men over 75 years of age.[6] As far as we know, no reports from other European countries are available for comparison. In the Amsterdam region in The Netherlands, the proportion of patients under age 60 treated with radical prostatectomy increased from 11% in 1991-1992 to 42% in 1993-1994. The proportion of patients aged 60-74 who underwent radical prostatectomy increased from 4% to 11%, for whom the proportion undergoing radiotherapy increased from 14% to 22%.[11] Although increased detection of prostate cancer at an earlier stage is a likely cause of increased application of curative treatment in our region, it may also (partly) be due to the fact that an increasing number of urologists were trained to perform this procedure.

Indeed, a questionaire among all 28 urologists in the southern part of The Netherlands in 1995 (response 68%) showed that 70% of the respondents performed radical prostatectomy and that the majority started doing this between 1988 and 1992.

The proportional increase in localized tumours is most likely due to increasing opportunistic PSA testing, which resulted in an increase in the age-adjusted incidence in southeastern Netherlands from 55 per10^5 in 1990 to 80 per 10^5 in 1995, the increase representing mainly localized cases.[4] This would explain why T2 tumours increased in particular: besides small palpable tumours, this category represents tumours that were not palpable, but visible on transrectal ultrasound, e.g. performed after a positive PSA test.[10] A similar exponential increase in the incidence of localized prostate cancer was observed in other countries like the USA[2] and the Isère region in France.[12]

The majority of prostatectomies in our region was applied in five large community hospitals (to which almost half of the patients with prostate cancer were admitted). Since radiotherapy was a more common treatment option in the other hospitals, the proportion of patients treated with curative intent in 1994-1996 did not vary substantially between hospitals (74% of patients under age 70 in the five large hospitals and 64% in the smaller hospitals). Such variation in the application of radical prostatectomy was also observed between but not within states in the USA (twice as low in New England and Mid-Atlantic regions compared to Pacific and Mountain regions).[6] No conclusive evidence of superiority of one of the options is currently available,[8] although most patient series suggest a better outcome for surgically treated patients[13,14] than for irradiated patients.[16] However, these comparisons are hampered, because candidates for radiotherapy generally appear to have more concomitant diseases[15] and the lymph node status is usually not known in these patients. In contrast, radical prostatectomy is generally cancelled if lymph node metastases are discovered before or during operation. Indeed, radiation series provide fairly similar survival rates as the radical prostatectomy series at 10 years, if all patients are staged with pelvic lymphadenectomy and those with positive lymph nodes are excluded from the analyses.[17] Unfortunately, evidence from randomized trials is very sparse. When population-based outcomes for patients with well and moderately differentiated tumours were analysed retrospectively by an intention to treat principle, the differences in outcomes for prostatectomy, radiotherapy or conservative treatment appears to be very small after 10 years. Patients with poorly differentiated tumours are more likely to benefit by curative treatment.[18] The A.U.A. guidelines panel recommended to offer radical prostatectomy or radiotherapy to patients with a life expectancy of at least 10 years. Surveillance is recommended for those with a limited life expectancy and/or a low-grade tumour.[8] A wait and see policy may not be accepted easily by the last category of patients, especially if prostate cancer is detected through PSA testing. In our region, most of these patients were offered some kind of non-aggressive treatment, which raises the question whether these patients should have undergone a PSA test in the first place.[19]

The regional variation in the application of radical prostatectomy and radiotherapy seemed largely dependent on the preference of the consulted urologist. However, since treatment-related morbidity varies between the different modalities,[7] the patient's appreciation of the risks and expected benefits will become more important.

Monitoring of treatment and follow-up of patients with localized prostate cancer seems important, in order to be able to inform future patients well-considered of the actual risks and benefits of the different treatment options. However, randomized trials remain the preferred source of evidence.

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5.2 Co-morbidity in patients with prostate cancer and its relevance to treatment choice.

Abstract

Objective. Since prostate cancer has become a frequently occurring disease in elderly men and an increasing proportion is offered curative treatment, the benefits and risks of the different treatment options have to be balanced taking the patient 's age and concomitant diseases into account. We assessed the prevalence of co-morbidity among patients with prostate cancer in relation to tumour and patient characteristics. We also analyzed if co-morbidity was a determining factor in the treatment choice for patients with localized prostate cancer.

Patients and methods. Serious co-morbidity was recorded in the Eindhoven Cancer Registry (according to Charlson's list of serious diseases) for all patients with prostate cancer newly diagnosed between 1993 and 1996 in the southern part of The Netherlands (n=2941). We also assessed with logistic regression which factors determined the choice of treatment.

Results. The prevalence of at least one serious concomitant disease was 38% for patients aged 60-69 years, 48% for 70-74 years and 53% for those aged 75 years or over, cardiovascular and chronic obstructive lung diseases being most frequent. Patients aged 60-69 years were more likely to be treated with radical prostatectomy in case of a moderately differentiated tumor confined to the prostate, when younger of age and when diagnosed in a hospital with a high case load. Presence of co-morbidity was of little influence.

Conclusion. Co-morbidity was frequently present in patients with prostate cancer, but the decision of urologists in southern Netherlands to apply radical prostatectomy was determined largely by the patient's age and the urologist's experience.

Introduction

Increased detection of localized prostate cancer after the introduction of prostate-specific antigen (PSA) testing[1,2] has led to increased application of radical prostatectomy in the U.S.A.,[3] and also in the southern part of The Netherlands.[4] However, controversy exists about the need to treat these patients aggressively, since several studies reported high 10-year survival rates of up to 87% for low grade prostate cancer managed expectantly.[5] Therefore, radical prostatectomy is advocated by many urologists only if the estimated remaining life expectancy of the patient is more than 10 years.[6] The presence of concomitant diseases is important in the appraisal of the life expectancy of a patient with prostate cancer.[7,8]

Although co-morbidity has received increasing attention, the exact prevalence of serious concomitant diseases in patients with prostate cancer is not known generally. The Eindhoven Cancer Registry in the southern part of The Netherlands has been collecting information about serious co-morbidity in all patients with newly diagnosed prostate cancer since 1993. We report here the age-specific prevalence of serious co-morbidity in patients with prostate cancer. Furthermore, we investigated which factors determined the decision of urologists in the southern part of The Netherlands to apply radical prostatectomy for patients with localized prostate cancer between 1993 and 1996, with special reference to co-morbidity.

Patients and methods

Data were extracted from the Eindhoven Cancer Registry. This registry started originally in the southeastern part of The Netherlands. Since 1988, it covers almost the whole southern part of The Netherlands (only excluding the province of Zeeland and the southern part of the province of Limburg) with a population of more than two million inhabitants. The area offers good access to specialized medical care supplied in 16 community hospitals and two large radiotherapy institutes. The registry may be considered nearly complete for prostate cancer since 1971.[2] Presence of co-morbidity is recorded for every patient with a newly diagnosed cancer since 1993. Registration clerks extract information on co-morbidity from the medical records along with the registration of details of diagnosis and treatment of cancer (usually within 3-6 months after diagnosis). Co-morbidity was recorded using a slightly adapted list of serious diseases developed by Charlson and associates (Table 1).[9] Only diseases with possible impact on the prognosis are recorded.

Table 1 *Classification of co-morbidity, according to an adapted list of Charlson et al.*[9]

Cardiovascular diseases
(myocardial infarction, heart failure, angina pectoris, intermittent claudication, abdominal aneurysm)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Diabetes Mellitus (medically treated)
Other malignancies (except basal skin carcinoma)
Chronic obstructive pulmonary diseases (COPD)
Dementia
Tuberculosis and other chronic infections
Connective tissue diseases
(Besnier Boeck's disease [sarcoidosis], systemic lupus erythematosus [SLE], Wegener's granulomatosis)
Rheumatoid arthritis (only severe)
Kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
Bowel diseases (Chrohn's disease, colitis ulcerosa)
Liver diseases (cirrhosis, hepatitis)
Gastric disease
(patients who received major surgery for ulcerative disease (BII)

A validation study was undertaken among 150 patients diagnosed in 1995 to determine if the registration clerks extracted co-morbidity correctly from the medical records (Internal report Eindhoven Cancer Registry, 1997). Registration of the number of serious concomitant diseases was correct for 87% of the patients. When the type of co-morbidity was examined in more detail, 20% of diseases was registered incorrectly. In most of these cases, serious co-morbidity was usually present, but an error was made in classifying the disease (e.g. cardiovascular instead of cerebrovascular disease). Another part of this misclassification was due to unfamiliarity of the registrars with terms such as CABG (Coronary Artery Bypass Grafting), PTCA (Percutaneous Transluminal Coronary Angioplasty), when used without a mentioning of the underlying disease. This resulted in an underestimation of the prevalence of cardiovascular disease by 28%. We could not correct this type of (supposedly random) misclassification in the current study.

Clinical stage is recorded in the registry according to the TNM classification in use.[10] On the basis of the registered information, we simplified the T classification as T1, T2, T3 or T4. If lymph node involvement or distant metastases were recorded, stage was defined as metastasized. Because absence of metastases was not always recorded explicitly, we included both M0 and Mx in the non-metastasized categories T1-T3. However, this category may be mixed with patients who did not undergo staging procedures, because their high PSA level indicated a very high probability of

metastases.[11] Histological grading recorded according to the TNM classification of malignant tumors[9] was scored by up to 20 pathologists of six Departments of Pathology. Poorly and undifferentiated tumors were considered as one category in our analyses. Treatment was classified in three categories: radical prostatectomy (usually retropubic) (1), radiotherapy (2), or other (non-curative) treatment like hormonal treatment and expectant management (3). Patients undergoing both radical prostatectomy and radiotherapy (n=21) were included in the radical prostatectomy group.

Trends and variation in treatment are reported in more detail elsewhere.[4] Because the substantial variation in application of radical prostatectomy between hospitals (only general hospitals in this region), the hospitals were grouped in type A hospitals (n=9) (with < 200 newly diagnosed patients with prostate cancer during the study period and type B hospitals (n=7) (with ≥ 200 newly diagnosed patients per year).

The role of various patient and tumor characteristics was investigated in relation to the application of curative treatment for patients aged 60-69 years with localized (T1-T3 M0-Mx) prostate cancer. This age group was chosen, because most urologists do not apply radical prostatectomy for patients aged over 70 years of age. Logistic regression was applied to determine the independent impact of age, co-morbidity, tumour characteristics and hospital size, taking radical prostatectomy as the dependent variable. [12] The likelihood-ratio test was used to test models against each other.

Results

The study consisted of 2941 patients diagnosed with prostate cancer between 1993 and 1996 in the southern part of The Netherlands. The prevalence of the various concomitant diseases by age group is presented in table 2. The most frequently occurring concomitant diseases were cardiovascular diseases, chronic obstructive pulmonary diseases (COPD), and other cancer. Most frequent combinations were cardiovascular disease and COPD (2.7%) and cardiovascular disease and diabetes (2.1%). As expected, the prevalence of co-morbidity increased strongly with age, but it did not vary appreciably with respect to grade or stage (data not shown). The prevalence of at least one concomitant disease was 38% for patients below aged 60-69 years, 48% for those aged 70-74 and 53% for patients aged 75 or over.

Table 2 *Prevalence of co-morbidity in patients with prostate cancer by age group in the southern part of The Netherlands, 1993-1996.*

	< 60 years n=227	60-69 years n=904	70-74 years n=699	≥ 75 years n=1111
	%	%	%	%
No co-morbidity	78	62	52	47
One co-morbidity	17	30	32	37
≥ 2 co-morbidities	5	8	16	16
Cardiovascular	8	16	19	18
CVA	2	3	3	7
Diabetes	2	5	8	8
Other cancer	8	7	9	12
COPD	5	8	17	14
TBC	1	1	3	1
Dementia	0	0	1	2
Billroth II	1	1	2	3
Other	0	2	1	2

Application of curative treatment

These analyses were restricted to patients aged 60-69 years with clinically localized prostate cancer (n=736). Radical prostatectomy was less commonly applied for patients aged 65-69 years (Table 3). Older patients more frequently underwent radiotherapy, but also other treatment without curative intent. Most patients recorded as Mx underwent other than curative treatment (such as hormonal treatment and expectant management). Treatment practices did not vary substantially over co-morbidity.

The logistic regression analyses (Table 4) indicate that for every year of age increase, a patient was 0.9 times less likely to undergo prostatectomy as a younger one (OR per year increase = 0.9; CI = 0.8, 0.9). For example, according to the multiplicative logistic model, a 65 year old is $(0.9)^5 = 0.6$ times less likely to undergo prostatectomy than a 60 year old man. Furthermore, radical prostatectomy was carried out more often when patients had a small tumour (T2) that was moderately differentiated and when diagnosed in a hospital with a high case load.

Year of incidence did not have additional influence. Patients with at least one co-morbidity were 0.8 times less likely to undergo radical prostatectomy, but this was not significant (p=0.2).
Neither did presence of 2 or more concomitant diseases contribute significantly to the choice of treatment.

Table 3 *Application of treatment of localized prostate cancer (T1-T3, M0-Mx) for patients aged 60-69 years (n=736) in relation to tumor- and patient characteristics.*

	prostatectomy	radiotherapy	other treatment[1]
	%	%	%
age (years)			
60-64	32	31	37
65-69	22	37	41
metastasis			
unknown	13	11	76
no	29	41	30
grade			
well diff.	21	38	41
moderately	35	33	32
poorly	23	31	46
unknown	4	46	50
tumor size			
T1	13	26	51
T2	30	37	33
T3	6	62	32
Tx	28	22	50
co-morbidity			
0	28	33	39
1	23	38	41
≥ 2	25	37	38
hospital[2]			
A	14	45	41
B	37	25	37

[1] Other treatment includes hormonal treatment, TURP only and expectant management
[2] hospital A: < 200 newly diagnosed patients. Type B : ≥ 200 patients.

Table 4 Unadjusted and adjusted odds-ratios for receiving radical prostatectomy for patients aged 60-69 years with localized prostate cancer (T1-T3, M0-Mx).

	Univariate			Multivariate		
	OR	CI	p-value	OR	CI	p-value
Age	0.9	0.8- 0.9	0.0001	0.9	0.8 – 0.9	0.0001
Metastasis			0.0001			0.0005
Unknown (ref.)	1			1		
No	2.8	1.7 – 4.7		2.6	1.5 – 4.6	
Grade			0.0002			0.0002
Well diff (ref.)	1			1		
Moderately	2.0	1.4 - 2.9		2.3	1.5 – 3.5	
Poorly	1.1	0.7 – 1.7		1.2	0.7 – 2.0	
Unknown	0.1	0.02 – 1.03		0.2	0.02 – 1.2	
Tumor size			0.002			0.0007
T1 (ref.)	1			1		
T2	1.5	1.0-2.1		1.2	0.8-1.9	
T3	0.2	0.1 – 0.7		0.1	0.04-0.4	
TX	1.3	0.7 – 2.6		1.9	0.9-4.0	
Co-morbidity			0.2			0.3
No (ref.)	1			1		
1	0.7	0.5 – 1.0		0.7	0.5 – 1.1	
≥2	0.9	0.5-1.6		1.0	0.5-1.9	
Hospital type[1]			0.0001			0.0001
A (ref.)	1			1		
B	3.7	2.6-5.3		4.1	2.8-5.9	

OR = odds ratio; CI = 95% confidence interval

[1] hospital A: < 200 newly diagnosed patients; B: ≥ 200 patients

Discussion

In this population-based study of almost 3000 patients with newly diagnosed prostate cancer in the southern part of The Netherlands, up to 38% of patients under age 60-69 and 53% of those aged 75 years or older had at least one serious concomitant disease Because all serious concomitant diseases were recorded, our results are likely to provide a realistic picture of the burden of co-morbidity relevant to the treatment choice. Our prevalence estimates of co-morbidity may be underestimated slightly, since the prevalence of cardiovascular disease was underestimated in a sample of 150 patients diagnosed in 1995. This may indicate that the overall prevalence of co-morbidity was 1-3% higher than we report here. Random misclassification caused by incorrect registration of co-morbidity (in about 10% of patients) may have confounded our estimates as well. Although comparisons with other studies may be hampered because of differences in definitions, age range and selection, some data are presented for comparison. The prevalence of chronic diseases in Dutch general practices was lower: the overall prevalence of one or more chronic diseases in men aged 65 or over was 23%. The prevalence of diabetes mellitus was 3%, of chronic ischemic heart disease 8% and COPD 4%.[13] The prevalence of COPD among elderly Finnish men was estimated to be 12.5%,[14] which is fairly similar to our estimates.

Choice of treatment

Patients most likely to undergo radical prostatectomy were of younger age, had moderately differentiated and clinically localized tumors and were usually admitted to a hospital with urologists performing radical prostatectomy frequently. Patients with a T2 tumour probably underwent radical prostatectomy more fequently because T1 tumours partly represented patients whose tumours were detected incidentally during TURP who did not receive further treatment and because patients with T3 tumours underwent radiotherapy more frequently.[4] Age was an important decisive factor, even in the age range 60-69 years. This seems justifiable, because radical prostatectomy provides better results for a younger man.[6] In spite of its impact on life expectancy,[8] co-morbidity was not a significant factor in the decision to apply radical prostatectomy in our region between 1993 and 1996. In a cohort of 261 consecutive prostate cancer patients treated with radical prostatectomy between 1989 and 1995 in Nashville Tn, 20% had an estimated life expectancy of less than 10 years due to co-morbidity.[15] In a cohort of 276 patients treated consecutively with curative intent between 1980 and 1991 in a Veteran Affairs Medical Center in the USA, patients undergoing radical prostatectomy had significantly less co-morbidity than those undergoing radiotherapy.[16] Urologists may recently have become increasingly aware of the role of co-morbidity after two studies emphasizing its impact on survival were published.[7,8] However, we did not observe a different result for the more recent years. More evidence on the impact of co-morbidity on survival might change the attitude of physicians. The importance of hospital size in the treatment choice suggest a crucial role for the urologist's experience.

Since other population-based estimates of factors influencing treatment choice are to our knowledge not available for comparison, we do not know to what extent our results are applicable to other regions.

In conclusion, serious co-morbidity appeared to be present in about half of the patients with prostate cancer in our population-based series. It barely influenced the choice of treatment of patients aged 60-69 years and diagnosed between 1993 and 1996 in the southern part of The Netherlands, which was determined largely by the patient's age, tumour characteristics and the urologist's experience.

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Chapter 6 Determinants of survival

6.1 Long-term survival of prostate cancer in southeastern Netherlands.
6.2 Independent prognostic value of co-morbidity among men aged < 75 years with localized prostate cancer: a population-based study.

6.1 Long-term survival of prostate cancer in southeastern Netherlands.

Abstract

Being detected increasingly at an early stage, few and conflicting results have been reported for the long-term outcome for prostate cancer beyond 10 years. The vast majority of the prostate cancer patients diagnosed between 1955 and 1984 in Southeastern Netherlands, with a population of almost 1 million inhabitants, did not receive curative treatment. We calculated the prognosis for 10-year survivors of prostate cancer diagnosed in the era preceding prostate-specific antigen (PSA) testing to determine how long these patients exhibited excess mortality.

All patients under age 70 diagnosed with prostate cancer and registered in the population-based Eindhoven Cancer Registry between 1955 and 1984 were included in the study. Relative survival was calculated for those who survived for at least 10 years (n=174). Initially, these patients still exhibited an almost 25% mortality risk in excess, but this decreased and no excess mortality was found after 15 years.

Introduction

Whilst the incidence of localized prostate cancer has been increasing rapidly,[1,2] much controversy exists about the optimal management of patients with early detected prostate cancer. Survival rates of up to 87% at 10 years for conservatively managed patients led to doubts on the need for radical surgery in these cases,[3,4] because it results in treatment related morbidity in a considerable proportion of patients.[5] Therefore, radical prostatectomy is advocated by many urologists only if the estimated remaining life expectancy of the patient is more than 10 years. Extended follow-up of conservatively managed patients revealed only slightly lower survival rates at 15 years (81%) in one,[3] but a continuing risk of death due to prostate cancer beyond 10 years in two other recent studies.[6,7] In view of these conflicting results, it remains uncertain whether patients who survived for 10 years or more remain at risk of death due to prostate cancer and would benefit from curative treatment. If prostate cancer carries a notable mortality risk after 10 years, radical treatment might be justifiable for those patients with an estimated remaining life expectancy of at least 10 years. In Southeastern Netherlands, the region of the Eindhoven Cancer Registry, most prostate cancer patients were treated conservatively in the seventies. An increasing proportion underwent radiotherapy since 1985,[8] but radical prostatectomy was not performed more than incidentally before 1988. This makes this cancer registry also suitable to study the prognosis for long-term survivors of prostate cancer who still had a considerable life expectancy at diagnosis, because their outcome closely resembled that of untreated disease. Because information about stage and grade was lacking for a large number of cases diagnosed before 1980, we could not define subcohorts on the grounds of stage or grade. We calculated relative survival rates for patients under age 70 at diagnosis who had survived for at least 10 years and were diagnosed between 1955 and 1984.

Patients and methods

Study Population

Patients were identified through the Eindhoven Cancer Registry. This registry covers Southeastern Netherlands, a region with a population of approximately two million inhabitants. The development and methods of this registry, which started in 1955 in an area with 300,000 inhabitants, are described in detail elsewhere.[9] Analyses of referral patterns and comparison with regional mortality data indicated that the registry can be considered nearly complete for prostate cancer as of 1971.[10] We also included cases diagnosed between 1955 and 1970 in the study.

However, the incompleteness of the registry before 1971 may have been selective, because the more severe cases, which probably never received work up in a hospital, were more likely to be missed by the cancer registry in those days.
Nevertheless, since we selected only those patients who survived 10 years or more, it is unlikely that this would have resulted in significant bias. Nevertheless, we did a separate analysis after exclusion of patients diagnosed before 1971.

Over 95% of cases were identified through pathology reports, which were always sent to the registry. Less than 5% were identified by medical record administrations in the regional hospitals or the regional radiotherapy institute, because they were diagnosed on clinical evidence only. The pathological diagnosis was established by histological examination of biopsies or tissue specimens obtained by TURP. Cases identified by 'death certificate only' cannot be registered in The Netherlands. Early diagnosis by PSA testing was not introduced until 1990.

Analysis

All patients with prostate cancer diagnosed between 1955 and 1984 in Southeastern Netherlands and under age 70 at diagnosis were included in the study. The initial cohort consisted of 643 patients. The vital status of all patients was checked with municipal civil registries until April 1 1994. 9 patients (1.4%) were untraceable (mostly due to repeated moving home) and were, therefore, excluded from the analyses, resulting in a study cohort of 634 patients. Another 10 patients (1.5%) were lost to follow up before the closing date and were censored in the analyses. Survival rates were calculated according to the actuarial (life-table) method. Relative survival was calculated as the ratio of the observed to the expected survival,[11] using a software package from the Finnish Cancer Registry.[12] Expected survival rates were calculated from life tables derived from the regional mortality statistics and compiled for five-year age groups and per calendar year for the regional male population. The expected survival rates were adapted during the course of the follow-up according to the changing age distribution of the patients (Ederer II option). Patients who died or were censored before 10 years were not included and so did not affect the cumulative relative survival beyond 10 years.

Results

The mean age of the cohort was 64 years (median age 65). Table 1 shows the age distribution and period of diagnosis of the cohort. A total of 437 patients died within the first 10 years of diagnosis so that the cohort of 10-year survivors represented 30% of the original cohort (Table 2).

Table 1 *Characteristics of the cohort of patients with prostate cancer under age 70 at diagnosis.*

Patient characteristics	Number	%
Age at diagnosis (yrs)		
< 55	39	6.2
55-59	92	14.5
60-64	174	27.4
65-69	329	51.9
Year of diagnosis		
1955-1959	9	1.4
1960-1964	25	3.9
1965-1969	55	8.7
1970-1974	113	17.8
1975-1979	188	29.7
1980-1984	244	38.5

Table 2 *Experience of the cohort of patients under age 70 at diagnosis in the first 10 years after diagnosis.*

Interval (year)	no. at start interval	no. of deaths during interval	no. withdrawn alive	Cumulative observed survival
1-5	634	287	5	55%
6-10	342	150	18	30%

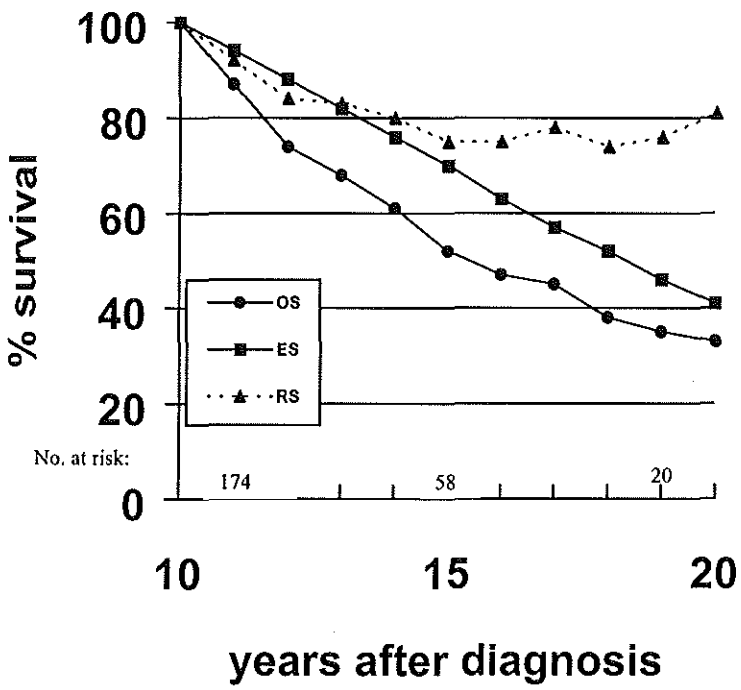
The mean age of the 174 patients who survived at least 10 years was 63 years (median age 64). Characteristics of these patients at diagnosis are displayed in table 3.
Most patients were between 60 and 69 years of age. Most 10-year survivors received only symptomatic treatment by TURP or hormonal treatment (including castration). A minority underwent radiotherapy.

Table 3 *Characteristics of of patients with prostate cancer under age 70 at diagnosis who survived for 10 years or more in southeastern Netherlands, 1955-1984.*

Patient characteristics	Number	%
Age at diagnosis (yrs)		
50-54	11	6.3
55-59	38	21.8
60-64	48	27.6
65-69	77	44.3
Year of diagnosis		
1955-1959	2	1.1
1960-1964	8	4.6
1965-1969	19	10.9
1970-1974	37	21.3
1975-1979	59	33.9
1980-1984	49	28.2
Initial treatment		
TURP only	75	43.1
hormonal	16	9.2
TURP + hormonal	42	24.2
radiotherapy (RT)	11	6.3
TURP + RT	23	13.2
hormonal + RT	2	1.2
TURP + RT + hormonal	3	1.7
unknown	2	1.1

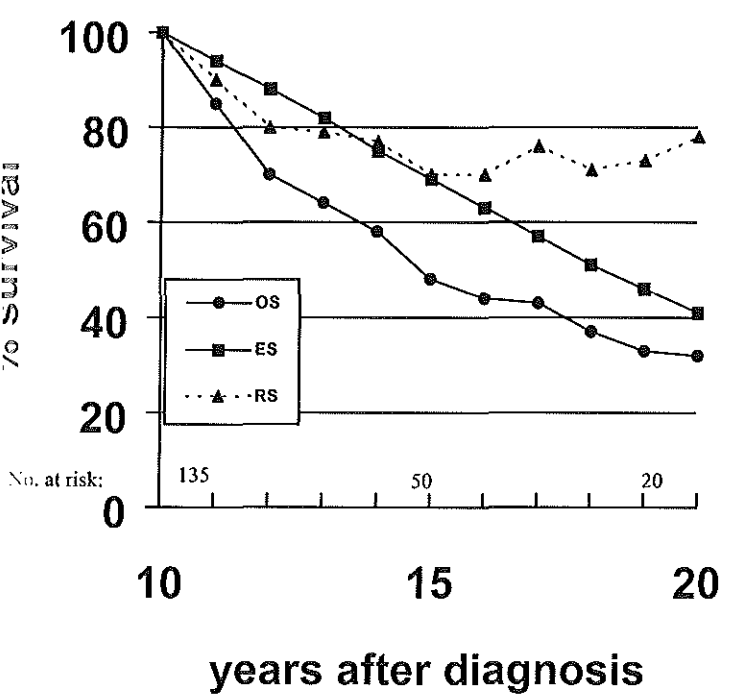
Relative survival of the 10-year survivors decreased by about 20% (Figure 1). Subsequently, the death rate of the cohort was similar to that of the general male population of the same age, relative survival leveling off at approximately 75%-80%.

Figure 1 *Observed (OS), expected (ES) and relative survival (RS) of patients with prostate cancer aged below 70 years at diagnosis (1955-1984) who survived 10 years or more.*



When we excluded patients diagnosed before 1971, the results barely changed: relative survival leveled off at 80% after 15 years (data not shown).
Because it is not unlikely that radiotherapy would have altered the prognosis, we performed separate analyses after exclusion of the 39 patients who received radiotherapy. The death rate of this cohort was initially higher than was found for the whole cohort, relative survival being 70% at 15 years (Figure 2). Subsequently, relative survival leveled off, indicating no deaths in excess from this point. When patients aged 70 years or over were included in the analyses, relative survival exceeded 100% 18 years after diagnosis (data not shown), suggesting a lower risk of mortality in the cohort of prostate cancer survivors than the general male population of the same (old) age.

Figure 2 Observed (OS), expected (ES) and relative survival (RS) of patients with prostate cancer aged below 70 years at diagnosis (1955-1984) who survived 10 years or more after exclusion of patients who underwent radiotherapy.



Discussion

Patients diagnosed with prostate cancer in southeastern Netherlands between 1955 and 1984 exhibited only a small increased risk of mortality if they had survived 10 years or more. About 15 years after diagnosis, the death rate among 10-year survivors barely differed from that found for the general age-matched male population.
Adolfsson et al. found an excess mortality up to approximately 18 years after diagnosis in their study of 10-year survivors.[6] Although application of radiotherapy might explain the better survival in our study, it is unlikely that this would have had a substantial effect on survival, because it was only applied for a minority of patients. In fact, exclusion of the 22% of patients who received this treatment resulted in a slightly lower relative survival at 15 years but no increased mortality hereafter. We do not know on what grounds patients were selected to undergo radiotherapy. Most patients underwent TURP or hormonal treatment, which is not considered to be curative. We have no evidence that awareness of prostate cancer resulting in earlier detection occurred earlier in the Netherlands than in Sweden. Although southeastern Netherlands has been an area with a large proportion of smokers since the 1960s,[13] differences in co-morbidity cannot be an explanation of the difference between our study and the Swedish study, since the survival rates were corrected for background mortality. We did not try to correct the expected survival rates for socioeconomic status, but a previous analysis of socioeconomic variations in survival of prostate cancer in Southeastern Netherlands revealed hardly any differences between the highest and the lowest socioeconomic levels, when the same expected survival probabilities were used (5-year relative survival 61% vs. 59%).[14] Patients with low grade, localized prostate cancer diagnosed in Orebro county in Sweden had a corrected survival of 85% at 10 years and 81% at 15 years, indicating few deaths due to prostate cancer beyond 10 years.[3] Hugosson et al found a continued risk of mortality due to prostate cancer beyond 10 years, which decreased with extended follow-up.[7] Relative survival of American patients diagnosed with prostate cancer between 1974 and 1991 continued to decline up to 15 years after diagnosis.[15] We found only a small excess mortality beyond 10 years. However, patients in our study cohort are likely to be different from patients nowadays detected with prostate cancer. Whilst patients diagnosed in the 1970s usually consulted their physician because of symptoms of cancer, most patients are nowadays detected on the basis of a positive PSA test before symptoms arise.

Since PSA testing appears to advance the diagnosis of prostate cancer by up to 5-10 years,[16] these patients might carry an increased mortality risk up to 15 years after diagnosis. So, our results do not justify a modification of the rule to offer radical prostatectomy only if a patient has a life expectancy of at least 10 years. Further study

is needed to identify those patients who are at risk of progression and may benefit from curative treatment.

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6.2 Independent prognostic value of co-morbidity among men aged < 75 years with localized prostate cancer: a population-based study.

Abstract

Context. Co-morbidity has been shown to have significant prognostic value for patients who were diagnosed with localized prostate cancer in the 1970s. However, the impact of co-morbidity might be different for those diagnosed by means of a positive prostate-specific antigen (PSA) test.
Objective. To investigate which prognostic factors apply for patients with localized prostate cancer diagnosed in the era of PSA testing.
Design. Population-based cohort study with 2.9 years (1.5-4.5) of follow-up
Setting. Eindhoven Cancer Registry
Patients. All 894 patients < 75 years with localized (T1-T3 M0) prostate cancer diagnosed between 1993 and 1995 in southern Netherlands.
Main outcome measures: Three-year overall and relative survival; Cox regression analyses of overall survival.
Results. co-morbidity was the most important prognostic factor, especially for those below 70 years (n=579): patients with one concomitant disease were 1.9 times more likely to die than those without co-morbidity (95% Confidence interval [CI] 1.4-3.6), whereas the hazard ratio (HR) was 3.7 (CI 2.0-6.9) for two or more diseases. This was not due to age or reduced application of curative treatment for these patients. Poor differentiation of the tumor was also an important prognostic factor; this became increasingly apparent 2 years after diagnosis (HR 3.4, CI 1.5-7.7).
Conclusions. Co-morbidity had decisive influence on the prognosis for patients with localized prostate cancer. However, a poorly differentiated tumor was also a highly significant factor, even within 3 years of diagnosis.
Implications. It seems more appropriate to look at the patient's co-morbidity rather than age when evaluating the risk of early death.

Introduction

Whilst prostate cancer is being detected with increasing frequency at an early stage in the ageing population,[1,2] uncertainty about optimum primary management still exists.[3] Although prostate cancer can be a potentially fatal disease, the high prevalence of co-morbidity in the elderly population[4] raises the question of which disease puts the patient at the highest risk, his malignant process or his co-morbidity. Moreover, when patients with low grade prostate tumors are managed conservatively, they exhibit only a low probability of dying due to prostate cancer within 10 years of diagnosis.[5] Co-morbidity had a major impact on the prognosis of such patients when diagnosed in the 1970s.[6] However, it is unclear whether these findings apply to today's practice. Some have argued that tumors diagnosed following a positive PSA test or rectal examination are more aggressive than those detected incidentally during transurethral resection of the prostate,[7,8] which comprised a considerable proportion of cases in the study by Albertsen. On the other hand, survival may be underestimated, because diagnosis of prostate cancer on the basis of a positive PSA test appears to advance the diagnosis by an average of 5-10 years.[9,10,11] Serious co-morbidity has been recorded routinely for all patients registered in the Eindhoven Cancer Registry since 1993, giving us the rather unique opportunity to study its impact on survival independent of other patient and tumor characteristics. PSA testing was introduced in this area between 1990 and 1993.[2] We studied survival in a population-based cohort of 1337 patients below 75 years of age with prostate cancer diagnosed between 1993 and 1995, 894 of whom had localized disease.

Patients and methods

Study population

Data were extracted from the Eindhoven Cancer Registry. This registry was started originally in the southeastern part of The Netherlands. Since 1986, it covers almost the entire southern part of The Netherlands (excluding only the province of Zeeland and the southern part of the province of Limburg) with a population of more than two million inhabitants. The area offers good access to specialized medical care supplied in 16 community hospitals and two large radiotherapy institutes. PSA assays were introduced between 1990 and 1993 in the regional hospitals and PSA testing has been applied increasingly by general practitioners since 1992.[2]

However, no formal screening program exists in The Netherlands, as its potential benefit is currently assessed in a large randomized screening trial.[12]

The increase in the proportion of patients with a clinically localized tumor (from 52% in 1988-1990 to 74% in 1994-1996) in southern Netherlands resulted in a threefold increase in the proportion treated by radical prostatectomy.[13] Curative radiotherapy has been another frequent treatment option in the 1990s. The large variation in the proportion of patients undergoing radical prostatectomy or radiotherapy between the various regional hospitals could be related to the experience of the urologists involved. The registry may be considered nearly complete for prostate cancer since 1971.[2] Presence of serious co-morbidity has been recorded for every patient with a newly diagnosed cancer since 1993.[4] Registration clerks extract information on co-morbidity from the medical records along with the registration of details of diagnosis and treatment of cancer, usually within 3–6 months of diagnosis. Co-morbidity was recorded, using a slightly adapted list of serious diseases developed by Charlson and associates (Table 1).[14] Only diseases with a possible impact on the prognosis are recorded.

Table 1 *Classification of co-morbidity, according to an adapted list of Charlson et al*[14]

Cardiovascular diseases
(myocardial infarction, heart failure, angina pectoris, intermittent claudication, abdominal aneurysm)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Diabetes Mellitus (medically treated)
Other malignancies (except basal skin carcinoma)
Chronic obstructive pulmonary diseases (COPD)
Dementia
Tuberculosis and other chronic infections
Connective tissue diseases
(Besnier Boeck's disease [sarcoidosis], systemic lupus erythematosus [SLE], Wegener's granulomatosis)
Rheumatoid arthritis (only severe)
Kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
Bowel diseases (Chrohn's disease, colitis ulcerosa)
Liver diseases (cirrhosis, hepatitis)
Gastric diseases (patients who underwent major surgery for ulcerative disease: Billroth II)

A validation study was undertaken among 150 patients diagnosed in 1995 to determine whether the registration clerks extracted co-morbidity correctly from the medical records (Post et al, internal report, 1997). Registration of the number of serious concomitant diseases was correct for 87% of the patients.
When the type of co-morbidity was examined in detail, 20% of the diseases were registered incorrectly.

In most of these cases, serious co-morbidity was usually present, but an error was made in classification of the disease (e.g. cardiovascular instead of cerebrovascular disease). Another reason for misclassification was unfamiliarity of the registrars with terms such as CABG (Coronary Artery Bypass Grafting), PTCA (Percutaneous Transluminal Coronary Angioplasty), if used without mentioning the underlying disease. This resulted in an underestimation of cardiovascular disease by 28%. We could not correct this type of (presumably random) misclassification in the current study. The number of co-morbidities was used as main covariate, distinguishing the following categories: No co-morbidity; 1 co-morbidity or ≥2 co-morbidities. Additional analyses were done for the most frequent specific types of co-morbidity.
Clinical stage is recorded in the registry according to the TNM classification in use.[15] On the basis of the registered information, we simplified the clinical tumor classification as T1, T2, T3 or T4. If lymph node involvement or distant metastases were recorded, stage was defined as metastasized. If information on staging was lacking, stage was coded as unknown. Histological grading recorded according to the TNM classification of malignant tumors[15] was scored by several pathologists of six Departments of Pathology. Patients with undifferentiated tumors (<1%) were included in the category poorly differentiated tumors in our analyses. Treatment was separated in three categories: radical prostatectomy (usually retropubic) (1), radiotherapy (2), and other (non-curative) approaches such as hormonal therapy and expectant management (3). Patients undergoing both radical prostatectomy and radiotherapy (n=13) were included in the radical prostatectomy group.

Analysis

Vital status of all patients was checked at least up to 1 July 1997. In addition to passive follow-up, this information was also supplied by regional urologists and the two Departments of Radiotherapy. Vital status of the remaining patients was checked with their general practitioners and the Central Bureau of Genealogy, an institution that registers every death of a Dutch citizen via the municipal civil registries. We could not trace 26 patients (1.9%) in this way. Because the Central Bureau of Genealogy is unlikely to miss deaths occurring in The Netherlands, these patients were censored alive at the closing date, 1 July 1997. Overall survival was assessed with the Kaplan Meier method. Deaths occurring after the closing date were disregarded. In addition to overall survival, relative survival was calculated for the various strata. Relative survival is the ratio of the observed to the expected survival.[16] The expected survival probabilities were calculated from life tables derived from the regional mortality statistics. Relative survival is an estimate of the mortality attributable to the diseases studied, unless the study cohort differs from the general population in some aspect distinct from the index disease.

Hence, relative survival for patients with different co-morbidity levels should not be interpreted as estimates of mortality due to prostate cancer, because relative survival for patients with co-morbidity is also determined by the difference in co-morbidity between these patients and the general age-matched population. Differences in survival were tested with the log rank test. Cox proportional hazard regression analysis was used to estimate simultaneously the contributions of various explanatory variables to overall survival.[17] Significance of terms in the models was tested with the likelihood-ratio test. Cox proportional hazards regression analysis is a valid approach only if the hazard rate (risk of death) can be assumed to be constant over time. The validity of this assumption was checked for all covariates in the model and a time dependent variable was introduced in the model for the variable with varying hazard over time.

To estimate the result of excluding cases recorded with an unknown metastasis status (Mx), we performed separate analyses including these cases. Because knowledge of prognostic factors is particularly important for patients who are generally considered to be fit to undergo radical prostatectomy, we performed separate analyses for patients below 70 years of age.

Results

Almost 70% of patients had a tumor confined to the prostate (Table 2). The survival analyses involved 894 patients registered as M0 and clinical stages T1-T3. The mean age of these patients was 67 years (median age 68; range 45-74.9). Characteristics of this subcohort are presented in table 3. Most patients had T1 or T2 tumors of low grade malignancy. Serious co-morbidity was present in 40% of the patients, whereas 10% had two or more serious diseases. Most of the patients underwent curative treatment. The remainder received hormonal treatment, TURP only, unknown or no treatment. The mean age did not differ notably over the various strata, except for treatment and co-morbidity. Patients treated with radical prostatectomy were younger than those treated otherwise (63 vs. 68 years of age). Patients with ≥ 2 concomitant diseases were older than those with one and those without co-morbidity (69 vs. 67 vs. 65 years of age). Prevalence of co-morbidity did not vary significantly over either stage or grade.

Table 2 Distribution of clinical stage within the cohort. Number of cases (%) per T and M combination.

	T1	T2	T3	T4	Tx	all T
M0	**281 (31)**	**492 (54)**	**77 (8)**	14 (2)	**44 (5)**	908 (68)
Mx	98 (42)	73 (31)	13 (6)	5 (2)	46 (19)	235 (18)
M1	24 (12)	100 (52)	28 (14)	18 (9)	24 (12)	194 (15)
All M	403 (30)	665 (50)	118 (9)	37 (3)	114 (8)	1337 (100)

Survival analyses

During a median follow-up of 2.9 years (range 1.5-4.5) , 137 patients died. Overall survival was 85% at 3 and 78% at 4 years, relative survival 94% and 89% respectively. A total of 21 patients died within 1 month of diagnosis. All of them had received noncurative treatment and most of them (67%) were aged 70-74 years.

Patients without co-morbidity (3-year survival 89%) had a better prognosis than those with one (80%) or those with two or more concomitant diseases (73%) (Table 3). Patients with poorly differentiated tumors exhibited a significantly lower survival rate (3-year survival 74%) than those with moderately (86%) and well differentiated tumours (88%). Relative survival was also significantly shorter for patients with poorly differentiated tumors (p=0.001). Patients with a tumor coded as T3 seemed to have a worse prognosis than other patients, but the difference was not significant (p=0.4).

Multivariate analyses

In the Cox regression analysis, survival decreased with increasing age, when co-morbidity was present or when the tumor was poorly differentiated. Because the strong effect of a poorly differentiated grade was unexpected, we examined this effect by interval. Since the hazard was not constant over time, a time-dependent variable for poorly differentiated grade was introduced. Poorly differentiated cancer appeared to be significant only after 1 year and the hazard ratio increasing to 3.6 after 2 years of observation (Table 4). The risk of death for a patient with moderately differentiated cancer (not significant) was constant over time as was the hazard for the other co-variates. Co-morbidity was the most important prognostic factor (p=0.0001): hazard ratio for one concomitant disease was 1.4 (CI 1.0-2.0) and for two or more 2.3 (CI 1.4-3.6). The hazard ratio for patients with 3 or 4 concomitant diseases (n=23) was not significantly different when considered as a separate category. The hazard ratio (HR) for co-morbidity decreased slightly when all significant factors were modelled together.

Table 3 *Characteristics of and univariate survival rates for the cohort of patients with localized prostate cancer.*

Variable	n	%	No. of deaths	3-year survival (95% CI)	p-value log rank test	3-year relative survival (CI)	p-value
All	894	100	137	85 (83-87)	-	94(91-97)	
Age					0.003		0.9
< 60 years	128	14	15	88 (82-94)		90 (83-97)	
60-64	171	19	18	92 (88-96)		95 (90-100)	
65-69	280	31	42	85 (79-91)		95 (90-100)	
70-74	315	35	62	80 (76-84)		94 (77-111)	
Tumor size					0.4		0.3
T1	281	31	40	86 (82-90)		96 (91-101)	
T2	492	55	73	85 (81-89)		94 (90-98)	
T3	77	9	17	77 (65-89)		88 (76-100)	
Tx	44	5	7	82 (68-96)		92 (78-106)	
Grade					0.002		0.001
G1	331	37	37	88 (84-92)		99 (97-101)	
G2	346	39	50	86 (82-90)		95 (91-99)	
G3	182	20	44	74 (66-82)		83 (75-91)	
Gx	35	4	6	85 (71-99)		94 (78-110)	
No. of concomitant diseases					0.0001		0.03
0	538	60	64	89 (85-93)		97 (94-100)	
1	261	29	46	80 (74-86)		90 (84-96)	
≥ 2	95	11	27	73 (63-83)		84 (73-95)	
Treatment					0.0003		0.06
radical prostatectomy	221	24	18	90 (84-96)		99 (95-103)	
curative radiotherapy	365	41	52	85 (81-89)		96 (91-101)	
hormonal treatment	170	19					
TURP only	88	10	67*	79 (73-85)*		87 (79-95)*	
no initial treatment	33	4					
unknown/other	18	2					

*All noncurative treatments together

The negative impact of co-morbidity was independent of treatment: when treatment was included in this model, the hazard ratio for co-morbidity did not change further. Neither did the hazard ratio change for patients with poorly differentiated tumors, although they underwent curative treatment to a lesser extent than those with moderately differentiated tumors. Inclusion of cases recorded as Mx did not change the results (data not shown). The most important concomitant diseases with an independent impact on survival were a second cancer, COPD, renal disease and to a lesser extent cardiovascular disease (Table 5).
Because the effect of co-morbidity varied over different age strata (the only significant interaction), a separate Cox analysis was performed for patients below 70 years, the age group that is of particular interest with respect to treatment choice. Stage and grade distribution were similar in this age group. Within this subcohort, age did not contribute significantly to the model, the presence of co-morbidity being more important (Table 6). Inclusion of cases coded as Mx did not change the results for this age category notably (data not shown).

Discussion

In this large population-based study of patients diagnosed with localized prostate cancer between 1993 and 1995, co-morbidity was the most significant prognostic factor in the first three years after diagnosis, followed by histological grade. Unlike other studies, our study has the advantage that it included patients diagnosed in the era of PSA testing, so that the results should be applicable to patients diagnosed today. Compared to the study of patients diagnosed in the 1970s,[6] we conclude that the impact of co-morbidity has become even more important. This finding agrees with studies linking serum banks to subsequent diagnosis of prostate cancer: diagnosis of prostate cancer on the basis of a positive PSA test may advance the diagnosis by up to 5-10 years.[9,10,11] The negative impact of co-morbidity on survival might be caused by holding these patients back from curative treatment.[4] However, we found that the co-morbidity itself produced an adverse effect on survival regardless treatment. The rather frequently occurring cardiovascular diseases, another cancer and COPD contributed the most to this effect on survival. Two concomitant diseases had the largest impact on survival, whereas the infrequent occurrence of 3 or more diseases did not contribute further. In a cohort study of patients treated with either surgery or radiotherapy, highly significant hazard ratios (adjusted only for age) were found for patients with two or more concomitant diseases; these ratios increased significantly as the number of concomitant diseases increased.[18]

Table 4 *Results of cox regression analyses of non-metastasized cases (n=894).*

	univariate		multivariate		multivariate + treatment	
variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
age (per year)	1.06 (1.02-1.1)	0.0008	1.05 (1.01-1.08)	0.01	1.04 (1.002-1.07)	0.04
cT classification		0.27				
T1 (reference)	1	-				
T2	1.1 (0.7-1.6)					
T3	1.6 (0.9-2.9)					
Tx	1.0 (0.5-2.2)					
Grade		0.002		0.0009		0.001
G1 (reference)	1		1		1	
G2	1.3 (0.9-2.0)		1.4(0.9-2.1)		1.5 (1.0-2.3)	
G3 (0-1 year)	1.0 (0.4-2.3)		1.0 (0.4-2.3		1.0 (0.4-2.3)	
G3 (1-2 years)	2.4 (1.3-4.6)		2.3 (1.2-4.4)		2.3 (1.2-4.3)	
G3 (≥ 2 years)	5.1 (2.3-11.2)		3.6 (1.9-6.7)		3.5 (1.9-6.6)	
Gx	1.6 (0.7-3.7)		1.5 (0.6-3.5)		1.5 (0.6-3.5)	
No. of concomitant diseases		0.0003		0.002		0.002
0 (ref)	1		1		1	
1	1.5 (1.04-2.2)		1.4 (1.0-2.0)		1.3 (0.9-2.0)	
≥ 2	2.7(1.7-4.2)		2.3 (1.4-3.6)		2.3 (1.4-3.7)	
Treatment						0.002
noncurative (ref)					1	
prostatectomy					0.4 (0.3-0.7)	
radiotherapy					0.6 (0.4-0.9)	

HR = hazard ratio; CI = confidence interval

Table 6 *Results of cox regression analyses of non-metastasized cases (only < 70 years at diagnosis: n=579)*

	univariate		multivariate		multivariate + treatment	
variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
age (per year)	1.1 (1.0-1.1)	0.05	1.03 (1.0.-1.1)	0.2	1.03 (1.0-1.1)	0.4
cT classification						
T1 (reference)	1	0.2				
T2	1.2 (0.7-2.1)					
T3	2.1 (1.0-4.6)					
Tx	0.8 (0.2-2.6)					
Grade		0.004		0.008		0.01
G1 (reference)	1		1		1	
G2	1.3 (0.7-2.3)		1.3 (0.7-2.4)		1.4 (0.8-2.6)	
G3 (0-1 year)	0.6 (0.1-2.6)		0.6 (0.1-2.5)		0.6 (0.1-2.5)	
G3 (1-2 years)	3.0 (1.3-7.0)		2.8 (1.2-6.6)		2.8 (1.2-6.7)	
G3 (≥ 2 years)	5.0 (1.8-14.0)		3.4 (1.5-7.7)		3.3 (1.5-7.6)	
Gx	2.6 (1.1-6.6)		2.6 (1.1-6.6)		2.5 (1.0-6.2)	
No. of concomitant diseases		0.0001		0.0002		0.0004
0 (ref)	1		1		1	
1	1.9 (1.2-3.2)		1.8 (1.1-2.9)		1.7 (1.02-2.8)	
≥ 2	4.2 (2.3-7.9)		3.7 (2.0-6.9)		3.6 (1.9-6.8)	
Treatment						0.1
noncurative (ref)					1	
prostatectomy					0.5 (0.3-0.97)	
radiotherapy					0.9 (0.6-1.5)	

HR = hazard ratio; CI = confidence interval

Table 5 *Type of co-morbidity and its impact on survival (n=894)*

type of co-morbidity	n	%	no. of deaths	univariate HR (CI)	multivariate HR (CI)[1]
none	538	60	64	1	1
cardiovascular disease	146	16	65	1.7 (1.2-2.6)**	1.5 (1.0-2.2)#
CVA	21	2	13	1.7 (0.7-4.1)	1.8 (0.7-4.5)
Diabetes mellitus	54	6	22	1.4 (0.8-2.6)	1.3 (0.7-2.4)
Other cancer	71	8	41	2.0 (1.3-3.3)**	1.9 (1.2-3.1)**
COPD	104	12	54	2.1 (1.4-3.1)**	1.7 (1.1-2.7)*
Dementia	2	0.2	2	-	-
Kidney diseases	3	0.3	3	11 (3.4-33.8)**	11 (3.4-35.5)**
Bowel diseases	2	0.2	0	-	-
Liver diseases	6	0.7	2	1.3 (0.2-9.2)	1.2 (0.2-8.8)
Billroth II	15	1.7	6	1.4 (0.4-4.4)	1.7 (0.5-5.2)

[1] adjusted for age and grade
*p<0.05 **p<0.01 #p=0.06

Co-morbidity had a greater impact in our study among patients aged < 70 years. Since age did not contribute significantly, it may be beter to look at co-morbidity instead of age in this age group when evaluating the patient's risk of early death.

Established prognostic factors

Clinical T-classification did not have a significant prognostic value. Pathological T classification has a strong prognostic value,[19] but the overall agreement between clinical and pathological stage has been shown to be weak.[8] In our study population, about 25% of the patients with T1-T2 tumors were upstaged to T3 after pathological examination of the radical prostatectomy specimens.[13] We only examined the role of *clinical* T classification in the current study, because its influence would be relevant to treatment choice. Moreover, pathological T classification is generally only known for patients undergoing radical prostatectomy. In a cohort of 938 irradiated patients with clinically localized prostate cancer diagnosed in the PSA era, both grade and clinical T classification (T1-T2 vs. T3-T4) were independent prognostic factors, whereas pretreatment PSA level had an additional strong prognostic value after a follow-up of 3.5 years.[20] Patients with clinical T4 tumors were not included in our analyses, which might also explain why we could not demonstrate a significant prognostic value for T classification. Pretreatment PSA levels were not readily available for our cohort and thus were not included in our analyses.

Patients with poorly differentiated cancer exhibited a substantial risk of dying, even within 3 years of diagnosis. Poor differentiation had an increasing adverse effect on survival, when patients survived more than one year. This would mean that the estimated lead time of 5-10 years does not apply for patients with this type of cancer.

Hence, our findings do not agree with the only study differentiating between aggressive (metastasized or poorly differentiated) and non-aggressive tumors, in which no difference in lead time distributions between the two types was found.[9] Nevertheless, a more rapid growth of poorly differentiated tumors is likely to be responsible for our observations.

Although definite conclusions cannot be drawn after a follow-up period of only 3 years, our results show that early mortality was not negligible in this interval, making knowledge of prognostic factors for this interval relevant to treatment choice. Whereas any effect of curative treatment on well differentiated tumors is questionable,[21] patients with moderately differentiated tumors may benefit from radical treatment.[22] However, if these patients have at least two other diseases, the uncertain beneficial effect should be balanced against its perioperative risks as well as other treatment-related morbidity such as urinary incontinence, impotence and disturbances in rectal function.[23]

In southeastern Netherlands, survival decreased for patients with poorly differentiated tumors (their proportion having increased) between 1980 and 1989, i.e. the period preceding the introduction of PSA testing.[24] In the USA, survival improved for patients with poorly differentiated tumors after the introduction of early detection measures in the 1990s.[25] This discrepancy might be explained by less extensive PSA testing in The Netherlands, where no formal screening program takes place. Moreover, the adverse effect of poor differentiation in the current study may be amplified by inadequate treatment. Radical prostatectomy can cure these patients, if the tumor is confined to the prostate.[26] In case of a locally advanced tumor, radiotherapy with adjuvant hormonal treatment seems preferable.[27,28] About one-quarter of the patients with poorly differentiated cancer was treated with radical prostatectomy, but radiotherapy was not combined with hormonal treatment in the period studied.

Patients treated with curative intent exhibited a better survival than those treated otherwise. However, the effect of radiotherapy seemed stronger for patients over 70 years of age than those of younger age (patients over 70 were barely treated with radical prostatectomy). Since it is unlikely that radiotherapy has a better effect for older patients, this is likely to be the effect of confounding by indication rather than a real treatment effect. This may be caused by selecting patients for curative treatment on the basis of other (unknown) factors than we corrected for, e.g. the clinical presentation of the patient at diagnosis. Moreover, it is unlikely that a treatment effect would be apparent within 3 years of diagnosis.

Issues of validity

Charlson's method of classifying prognostic co-morbidity was used to score co-morbidity in our study,[14] but diseases were not subdivided according to severity.

However, only serious co-morbidity is considered by the Eindhoven Cancer Registry. For example, diabetes mellitus is recorded only if under active management. Misclassification of co-morbidity will be limited, since the concomitant diseases are taken directly from the medical records of the patients. Moreover, a validation study among patients with prostate cancer diagnosed in 1995 showed that 87% of the patients were registered with a correct number of diseases. Since the number of diseases was our main co-variate, random misclassification (likely only for 13% of patients) has at most diluted the prognostic impact of co-morbidity.
The histological grade of biopsies was scored by several pathologists from six Departments of Pathology. Although inter-observer variation is likely to have occurred in this way, we feel that this would not have weakened our study. On the contrary, it makes the results applicable in daily practice.
Since our study was population-based, selection bias will be limited to a minimum. The only exclusion criteria were age (75 years or over) and positive (M1) or unknown (Mx) evidence of metastases. Some of the patients recorded as Mx may have been excluded unjustly, because staging procedures were omitted due to the poor general condition of the patient. However, exclusion of these cases did not change the results.

Conclusions

Although a longer study period is needed to draw definite conclusions, our results underscore the important role of co-morbidity in early mortality among men with localized prostate cancer. It seems more appropriate to look at the patient's co-morbidity rather than age when evaluating the risk of early death. Patients with serious co-morbidity and well or moderately differentiated tumors may be unlikely to benefit from curative treatment. However, poor differentiation was a strong determinant of early mortality, even within 2 years of diagnosis. Since this observation is not compatible with a lead time of 5-10 years, poorly differentiated tumors seem to represent fast-growing tumors. Patients with these tumors may benefit from curative treatment, regardless of concomitant diseases.

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Chapter 7 General discussion

Main findings of the thesis

The main finding of this thesis is the observation that the incidence of prostate cancer increased considerably between 1971 and 1989 (before the introduction of PSA testing) in southeastern Netherlands, the sole region with a long-standing cancer registry in The Netherlands. Initially, the increase in incidence (in the 1970s) was probably related to the increase in the number of urologists who performed transurethral resection of the prostate with increasing frequency. However, between 1980 and 1989, the increase not only represented low-grade tumours but also high grade and even metastasized cancer. After the introduction of PSA testing, the incidence further increased, but mainly for low-grade localized prostate cancer. Survival did not improve between 1971 and 1989, confirming that the increase was unlikely to represent mainly 'insignificant' tumours. To increase the sample size, incidence and survival for men aged < 60 years were investigated in a collaborative study with the East Anglian Cancer Registry, which uses similar methods of data collection. Both incidence and mortality increased in this age group between 1971 and 1989, whereas survival of these patients decreased or remained unaltered, indicating an increased incidence of fatal prostate cancer among men below 60 years. A decline in survival at this age was also observed in analyses with the Eurocare Study, a collaborative effort of 45 cancer registries in 17 countries. Mortality due to prostate cancer increased to a lesser extent and may partly be caused by decreases in mortality due to other major causes of death[1,2] and benign prostatic hyperplasia.[3] However, analyses of national mortality data revealed an increased risk for consecutive birth cohorts for men born in 1875 up to those born around 1930. This observation as well as the increased incidence of both low and high grade prostate cancer and the lack of improvement in survival point to an increased incidence of fatal prostate cancer, in particular for those born between 1925 and 1934. Introduction of PSA testing and other diagnostic tools resulted in a further increase in incidence that appeared to be due largely to advanced diagnosis and probably also a higher detection rate for formerly undiagnosed cases.

International comparisons

Studies of trends in the incidence of prostate cancer before the introduction of PSA testing indicate an increase in low grade and/or localized tumours in the USA[4] and Sweden,[5] which resulted in a marked improvement in survival between 1960 and 1980.[6,7] In Norway, the incidence of more aggressive prostate cancer increased as well, although survival improved between 1957 and 1986.[8] In the USA, 5-year relative survival improved from 70% in 1973-77 to 95% in 1988-1993, but the improvement among men aged < 60 years was very limited before 1988.[9] In view of the rather small improvement that was observed in the EUROCARE study (chapter 4.2), it seems reasonable to conclude that increased detection of insignificant tumours was fairly limited, but may vary between countries.

Introduction of (opportunistic) PSA testing in southeastern Netherlands resulted in a pronounced increase in the incidence between 1991 and 1995, the increased incidence representing solely low-grade and localized tumours during this period. A similar and even exponential increase was observed in the USA[4] between 1986 and 1992 and in the Isère region in France,[11] also after the introduction of PSA testing. This increase is most likely an artifact caused by advanced diagnosis, based on the fact that a high PSA level may precede clinical prostate cancer by up to 5-10 years.[12-14] This assumption was supported by fluctuating trends in several areas in the USA: after a peak in incidence was reached, the incidence dropped to the level recorded a few years before the peak.[15-17] Part of the recent increase in incidence may be due to increased diagnosis of insignificant tumours that formerly remained undetected. However, there is no convincing evidence that this has occurred to a large extent, since most tumors detected by screening are moderately differentiated tumours (Gleason 5-7).[15-18] On the other hand, increased use of multiple core biopsies and detailed examination of radical prostatectomy specimens might have resulted in 'up-grading' of tumours formerly classified as well differentiated.[19] Nevertheless, pathological findings on impalpable tumours of patients who underwent radical prostatectomy point into the same direction: only 17% of these tumours may be considered insignificant (on the basis of small tumour volume and low grade), whereas 37% was classified as advanced (capsular penetration, seminal vesicle invasion, etc.).[20] However, 22% of tumours detected in cystoprostatectomy specimens of men not suspected of having prostate cancer (which would closely resemble latent prostate cancer) were also advanced.[21-22] Therefore, conclusions about the significance of diagnosed tumours on the basis of pathological findings are tentative.
Furthermore, clinical significance is determined not only by pathological but also by patient characteristics, such as age and co-morbidity.[23]

An increased risk of (fatal) prostate cancer between 1970 and 1990 can be assumed to have occurred in The Netherlands, but also in other European countries.[24]
However, too little is known about the aetiology of prostate cancer to be able to attribute the increase to a specific risk factor. Only old age, black race and a positive family history are established risk indicators.[25] However, the putative risk factor(s) responsible for the assumed increased risk of fatal prostate cancer should have occurred with increasing prevalence over the past decades and should affect men born between 1925 and 1934 in particular. This putative risk factor may initiate prostate cancer at young age, but may also (as suggested by Carter and coworkers)[26] promote the transition from latent to invasive cancer at an older age. Studies adressing putative risk factors might be more successful if the focus is on poorly differentiated cancer, since it represents potentially fatal disease.

Management of localized prostate cancer

From the increase in incidence of mainly localized prostate cancer, we now turn to the optimal and actual management of this type of cancer, which includes curative radiotherapy and radical prostatectomy .
A few years ago, a guidelines panel of the American Urologic Association (AUA) concluded that no conclusive evidence of the superiority of one of the treatment options for clinically localized prostate cancer existed.[27] Since radical treatment is associated with undesirable side effects such as impotence and urinary incontinence in up to 30-50% of patients, [28-29] overtreatment should be avoided.
The recent increase in the incidence of prostate cancer in the southern part of The Netherlands resulted in increased curative treatment, but mainly for patients under age 70. The proportion of patients in this age group who underwent radical prostatectomy ranged from 5% to 67% in the various general hospitals. Radical prostatectomy was performed more often in larger hospitals. Presence of co-morbidity had little influence on the physician's decision to perform radical prostatectomy, which was determined largely by age, tumour characteristics and the urologist's experience. Co-morbidity should influence the treatment choice, because most urologists consider radical prostatectomy only if a patient has a life expectancy of at least 10 years. [30] This is not easy to assess at the individual level, but co-morbidity remains an important determinant of the life expectancy of these patients. [31] For curative radiotherapy, such a rule does not exist probably because there is not a notable risk of mortality. The 10-year rule was based on the observation that cause-specific survival is very high for patients with localized and low grade prostate cancer.[32] Patients with prostate cancer diagnosed in southeastern Netherlands between 1955 and 1984 exhibited a small excess risk of death compared to the general age-matched population, if they had

survived for 10 years, but no excess after 15 years. This observation, as well as the results from other recent studies,[33-34] suggests that the risk of death from prostate cancer is still present 10 years after diagnosis, but it fades away with increasing follow up. Moreover, a recent study of American patients managed conservatively in the 1970s and 1980s (in which all pathology specimens were reviewed) showed that patients with well differentiated tumours (Gleason 2-4) are virtually not at risk of dying from prostate cancer, even 15 years after diagnosis.[35] Co-morbidity had a substantial impact on the risk of death from all causes,[31] but not on prostate cancer-specific survival for these patients.[35] It is, however not clear whether these findings apply to patients diagnosed on the basis of a positive PSA test. The routine registration of co-morbidity in the Eindhoven Cancer Registry gave us the rather unique opportunity to address this issue in a population-based setting. In agreement with the estimated lead time of 5-10 years for PSA detected tumours, [12-14] co-morbidity had decisive impact (which was stronger than age) on 3-year survival of patients with prostate cancer diagnosed between 1993 and 1995, especially below 70 years of age. Intermediate grade tumours did not incur a significantly worse survival than a well differentiated tumour in the first 3 years following diagnosis. However, poor differentiation was a highly significant prognostic factor, becoming increasingly important 2 years after diagnosis.

Although the benefit of curative treatment for patients with well differentiated tumours is doubtful,[35] its role for patients with moderately differentiated tumours has yet to be defined. Since co-morbidity appeared to be an important determinant of early mortality, it should be taken into account in the choice of treatment of these patients. Hoewever, it is probably of less importance for patients with well differentiated tumors (who do not seem to need curative treatment) and patients with poorly differentiated tumors (who need proper treatment).

Methodological considerations

Most of the studies in this thesis are based on data from the Eindhoven Cancer Registry in the southern part of The Netherlands. The methods of the East Anglian Cancer Registry and the other registries participating in the Eurocare study (chapter 4.2) are comparable to those used in the Eindhoven Cancer Registry and comply with the standards required by the IARC.[36] Since this registry used to cover a relatively small region, one may wonder whether inference from this region is generalizable to other regions. As described in chapter 2, the region is characterized with good access to medical care. Since access to specialized medical care is supposed to be an important determinant of both incidence and survival, the inferences have to be considered in relation to the specific customs and traditions of a country. A striking

feature of the region of southeastern Netherlands is the high proportion of smokers, especially among males.[2] This has resulted in a high incidence of lung cancer and cardiovascular diseases. Although smoking is not associated with an increased risk of prostate cancer,[37] the adverse effect of smoking on survival may lead not only to lower survival, but also to higher mortality rates for prostate cancer.[38] Therefore, an increase in the proportion smokers over time might lead to increased mortality due to prostate cancer. However, this is not a likely explanation because, on the contrary, the proportion of smokers has decreased since 1960.[2]

An important feature of the Eindhoven Cancer Registry is the high quality of data on stage and grade. Due to rather strict coding rules, misclassification of stage is unlikely, because stage was coded as unknown whenever the registrars had a reasonable doubt. Stage data were not used for the period when the proportion unknown was > 25% (i.e. before 1980). Grade data are of similar high quality and are based on judgements of several pathologists from three Departments of Pathology in the eastern part and for one study (chapter 6.2) three other Departments of Pathology in the western part as well. Since histology was not reviewed, interobserver variation is likely to have occurred in this way.[39] However, systematic misclassification is unlikely. Moreover, no changes in the morphological interpretation of histological specimens have occurred during the study period and there is no reason to assume that Dutch pathologists score histological grade differently from those from other countries.

The assessment of co-morbidity, described in detail in chapter 2, can be assumed to be of fairly high quality. However, although co-morbidity is responsible for the main selection bias, any real effects of treatment can only be estimated when patients are randomized over different treatment options. Residual confounding is likely in nonrandomized studies. This may be caused by selecting patients for curative treatment on the basis of other factors than co-morbidity, e.g. the clinical presentation of the patient at diagnosis.

The prognostic studies in this thesis did not have prostate cancer specific survival as main outcome but overall or relative survival. When a specific disease is studied, one is usually interested only in mortality attributable to the disease studied. Hence, overall survival would not be an approporiate outcome. Relative survival (the ratio of the crude [observed] to the expected survival) is an estimate of mortality attributable to the disease studied, unless the study cohort differs from the general population apart from the index disease.[40] Relative survival is an appropriate outcome when studying survival for population-based cohorts, as in this thesis. Moreover, when relative survival is used, noncancer deaths among cancer patients (e.g. related to treatment) are also counted.[41]

However, the life tables used for expected survival probabilities are stratified for age and gender, but not for other factors associated with longevity such as socio-economic

status and co-morbidity. Therefore, relative survival was not the main outcome in the chapter on co-morbidity. It is, however, not likely that correction for socio-economic status would have modified our findings, since specialized medical care is equally accessible for all socio-economic classes in The Netherlands. Moreover, a previous analysis of socio-economic variations in the survival of prostate cancer in Southeastern Netherlands barely revealed any differences between the highest and the lowest socioeconomic levels, when the same expected survival probabilities were used (5-year relative survival 61% vs. 59%).[42]

Conclusions and implications

The increase in the incidence of prostate cancer between 1971 and 1989 can be attributed to a higher detection rate related to the increased supply of urologists, but also to an increased risk of fatal prostate cancer. Early detection of prostate cancer by PSA testing since 1990 has resulted in an additional increase in the incidence of mainly low-grade tumours due largely to advanced diagnosis. A causal factor for the assumed increased risk of fatal prostate cancer has yet to be demonstrated.
The management of localized prostate cancer is still surrounded with many uncertainties. A result of this thesis is the importance of co-morbidity among patients with localized prostate cancer, especially for those aged below 70 years. The excess risk of death appears to decrease over time for patients with prostate cancer.
The role of curative treatment was not addressed in this thesis. Randomized trials of radical prostatectomy versus observation are under way in Sweden[43] and the USA,[44] but results will not be available for many years. Simultaneously, randomized trials adressing the benefit of early detection and treatment are currently being carried out.[45,46]

Pending these trials, follow-up studies of patients with localized prostate cancer are necessary. Cancer registries can supply a feasible framework for such studies, provided that representatives of all involved medical disciplines play an active role. These studies may provide insight in quality of care for all patients, including those excluded from trials. Furthermore, such a study setting facilitates studies of determinants of recurrence and survival. Stage and grade should then uniformly be assessed and side effects of treatment recorded as well.
Furthermore, the vital status of all patients should be followed up and preferrably the cause of death recorded using unambiguous criteria.

PSA testing outside the research setting should only be done once the man is engaged in the decision process and after he is informed about the current state of uncertainty and the risks and theoretical benefits.

When prostate cancer is diagnosed, patients with well differentiated tumours should be informed of the unlikely benefit of radical treatment. The possible benefit of radical treatment of moderately differentiated tumours and its side effects should be discussed with the patient. It seems more appropriate to look at the patient's co-morbidity rather than age when evaluating the risk of early death. Since poorly differentiated cancer entails a high risk of early death, when possible, radical treatment is preferred for patients presenting with these tumours. A search for a noninvasive screening test specific for high grade cancer deserves priority in research. Intensive investigation of risk factors for this fatal form of prostate cancer is another way of dealing with this disease.

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A large number of papers describing an increase in the incidence of prostate cancer have been published over the past two decades. However, a high prevalence of so-called 'latent' prostate cancer of up to 30% was found in several autopsy studies of men aged 70 or older without a clinical diagnosis or suspicion of prostate cancer before death. Therefore, it is generally assumed that the increase is partly due to increased detection of these latent tumours by improved urological techniques such as TURP, PSA testing and fine needle biopsies. However, it is unclear whether this would explain the whole increase in incidence or that an increased risk of prostate cancer has occurred as well. This question was addressed in this thesis.
Most of the studies are based on data from the Eindhoven Cancer Registry, which collects information on every newly diagnosed cancer in a defined area in the southern part of The Netherlands with since 1987 approximately two million inhabitants. For a few studies, collaboration with other European cancer registries took place.

In southeastern Netherlands, the age-adjusted incidence increased from 36 per 10^5 in 1971 to 55 per 10^5 in 1989 (i.e. before introduction of PSA testing). This increase represented after 1980 not only low grade but also poorly differentiated and metastasized prostate cancer (chapter 3.1)
The conclusion that an increase in the incidence of significant prostate cancer occurred in this period was confirmed by studies of trends in survival: survival barely changed between 1971 and 1989 in southeastern Netherlands.
Five-year relative survival (an estimate of cause-specific survival) improved in Europe only from 55% in 1984-1986 to 59% in 1987-1989, according to a collaborative study of 45 European cancer registries (the Eurocare study), although relative survival varied substantially between countries (chapter 4.2). A marked improvement in survival would be expected if increased diagnosis of latent cancer (which should not result in death of the patient) had occurred to a large extent.

Special attention was directed to men aged below 60 years in a collaborative study with the East Anglian Cancer Registry. In this age group (in which fewer diagnostic procedures take place), both incidence and mortality due to prostate cancer increased by about 50% between 1971 and 1989, whereas relative survival barely changed or even decreased during the study period (chapter 3.3). In addition, no improvement in relative survival was found for this age group in the Eurocare study.

An increased risk of fatal prostate cancer could explain this observation, which was further investigated in an age-period-cohort analysis of national mortality data (chapter 3.2). Mortality due to prostate cancer increased for all age groups from 55 years up to 1989 and for men aged 65 or over up into the 1990s. Furthermore, the age-cohort model but not the age-period model described the data satisfactorily, which showed an

increased risk for each subsequent birth cohort from men born between 1870 and 1879 up to men born between 1925 and 1934. This suggests increased exposure to an hitherto unknown risk factor.
Introduction of opportunistic PSA testing in southeastern Netherlands resulted in a further increase (up to 80 per 10^5) in mainly low grade localized prostate cancer presumably due to advanced diagnosis and probably also increased detection of insignificant tumours. However, compared to e.g. the USA, where PSA testing has been widely propagated and used, the increase was rather modest (chapter 3.1).

The second part of the thesis concerns the mangement of localized prostate cancer. An increasing proportion of patients (mainly < 70 years) with localized tumours were treated with radical prostatectomy, although radiotherapy remained an important alternative (chapter 5.1) A striking variation in the proportion treated with radical prostatectomy (ranging from 5% to 67% in the various general hospitals) was present.

Whereas no conclusive evidence of superiority of one of these treatment options is currently available, the choice of treatment was determined largely by the patient's age, tumour characteristics and the urologist's experience. Co-morbidity was barely taken into account, although this was present in about 50% of patients aged 70 or over (chapter 5.2).

Patients with prostate cancer diagnosed between 1955 and 1984 in southeastern Netherlands (largely treated without curative intent) only exhibited a small excess mortality if they had survived 10 years after diagnosis, whereas no excess was observed at 15 years (chapter 6.1).
Co-morbidity had a large impact on survival for patients diagnosed between 1993 and 1995 (in the era of PSA testing), especially for patients below 70 years of age (chapter 6.2). This was of more importance than age. A poorly differentiated tumour was the second most important prognostic factor, even after the rather short mean follow-up period of 3 years.

Sinds 1970 hebben onderzoekers uit talloze landen een toename in de incidentie van prostaatkanker gerapporteerd. Wanneer echter op systematische wijze lijkschouwingen worden verricht bij oudere mannen bij wie gedurende hun leven geen aanwijzingen waren voor prostaatkanker, wordt bij ongeveer 30% van de mannen van 70 jaar en ouder een latente vorm van prostaatkanker aangetroffen. Aangezien de afgelopen decennia diverse verbeterde urologische technieken (zoals transurethrale resectie van de prostaat, PSA bepalingen en dunne naald biopsieën) zijn geïntroduceerd, wordt algemeen aangenomen dat de toename in incidentie voor een deel is veroorzaakt door een toename in de diagnose van deze latente gevallen van prostaatkanker. Het is echter onduidelijk of dit de hele toename in de incidentie kan verklaren of dat er daarnaast een werkelijk verhoogd risico op prostaatkanker is opgetreden. Dit was de belangrijkste onderzoeksvraag in dit proefschrift.
Hierbij werd in hoofdzaak gebruik gemaakt van gegevens die verzameld zijn door de kankerregistratie van het Integraal Kankercentrum Zuid, waarin alle nieuw ontdekte gevallen van kanker zijn geregistreerd voor een nauw omschreven gebied in het zuiden van Nederland met sinds 1987 ongeveer 2 miljoen inwoners. Voor enkele studies werd samengewerkt met andere Europese kankerregistraties.

In Zuidoost Nederland nam de voor de leeftijd gestandaardiseerde incidentie toe van 36 per 10^5 in 1971 tot 55 per 10^5 in 1989 (dus voor de introductie van PSA bepalingen). Deze toename betrof na 1980 ook slecht gedifferentieerde en bij diagnose gemetastaseerde tumoren (hoofdstuk 3.1).
De conclusie hieruit dat er een toename in de incidentie van klinisch belangrijk prostaatkanker is opgetreden, werd bevestigd door studies betreffende trends in de prognose: de prognose veranderde nauwelijks tussen 1971 en 1989 in zuidoost Nederland (hoofdstuk 4.1).
De 5-jaars relatieve overleving (een benadering van de prostaatkanker specifieke overlevingskans) verbeterde in Europa slechts van 55% in 1984-1986 naar 59% in 1987-1989 in een samenwerkingsproject van 45 Europese kankerregistraties (de Eurocare studie), hoewel de relatieve overleving sterk varieerde tussen de verschillende landen (hoofdstuk 4.2).
Speciale aandacht werd geschonken aan mannen onder de 60 jaar. In deze leeftijdsgroep (die minder prostaat gerelateerde diagnostiek ondergaat) namen zowel de incidentie als de sterfte aan prostaatkanker met 50% toe tussen 1971 en 1989, terwijl de relatieve overleving niet veranderde of zelfs verslechterde gedurende deze periode (hoofdstuk 3.3). Er werd ook een kleine verslechtering in de relatieve overleving waargenomen in de Eurocare studie.
Een toegenomen risico op een fatale vorm van prostaatkanker zou deze bevindingen kunnen verklaren, hetgeen nader werd bestudeerd door middel van een leeftijd-periode-geboortecohort analyse (hoofdstuk 3.2). De sterfte ten gevolge van

prostaatkanker nam in heel Nederland sinds 1955 toe voor alle leeftijdsgroepen vanaf 55 jaar tot aan 1989 en voor mannen van 65 jaar en ouder tot aan 1994. Voorts bleken de sterftegegevens adequaat beschreven te kunnen worden met een leeftijd-cohort model, hetgeen een toegenomen risico liet zien voor elk opeenvolgend geboortecohort van mannen geboren tussen 1870 en 1879 tot aan mannen geboren tussen 1925 en 1934. Dit suggereert een toegenomen blootstelling aan een totnogtoe onbekende risicofactor.
De introductie van PSA bepalingen in zuidoost Nederland leidde tot een verdere toename in de incidentie (tot 80 per 10^5) van hoofdzakelijk laaggradige en tot de prostaat beperkte tumoren als gevolg van vervroegde diagnose en mogelijk ook toegenomen detectie van latente tumoren. Vergeleken met bijvoorbeeld de Verenigde Staten, waar screening met behulp van PSA wijdverspreid wordt gepropageerd en uitgevoerd, was de toename echter bescheiden. (hoofdstuk 3.1)

Het tweede deel van dit proefschrift gaat over determinanten van behandeling en prognose van lokale prostaatkanker.
Een toegenomen deel van de patiënten (vooral onder de 70 jaar) met deze tumoren onderging een radicale prostatectomie, hoewel curatieve radiotherapie een belangrijk alternatief bleef (hoofdstuk 5.1). Er werd een opmerkelijke variatie tussen de verschillende regionale ziekenhuizen waargenomen in het percentage patiënten dat een radicale prostatectomie onderging (dit varieerde van 5% tot 67%).
De keuze van behandeling werd in belangrijke mate bepaald door de leeftijd van de patiënt, tumor kenmerken en de ervaring van de uroloog. Ernstige bijkomende ziekten (co-morbiditeit) kwamen bij ongeveer de helft van de patiënten van 70 jaar en ouder voor, maar speelden bij de behandelingskeuze een ondergeschikte rol. (hoofdstuk 5.2).
Oversterfte bleef bij patiënten die tussen 1955 en 1984 met prostaatkanker waren gediagnostiseerd in zuidoost Nederland na 10 jaar nog te bestaan, maar werd niet waargenomen na 15 jaar (hoofdstuk 6.1).
Co-morbiditeit had grote invloed op de overleving van patiënten met lokale prostaatkanker gediagnostiseerd tussen 1993 en 1995 (de periode na introductie van PSA testen), vooral bij patiënten onder de 70 jaar (hoofdstuk 6.2). Dit was van meer belang dan de kalenderleeftijd van de patiënt. Een slecht gedifferentieerde tumor was ook een zeer belangrijke prognostische factor, zelfs al na de vrij korte studieperiode van gemiddeld 3 jaar.

Sûnt 1970 hawwe ûndersikers út withoe folle lannen beskreaun, dat it tal nij ûntdutsen gefallen (ynsidinsje) fan prostaatkanker tanommen is. As op systematyske wize lykskôgingen dien wurde by âldere manlju, by wa't doe't se noch libben, gjin prostaatkanker konstatearre waard, wurdt by likernôch 30% fan de manlju fan 70 jier of âlder prostaatkanker oantroffen. Der wurdt oer it generaal ûndersteld, dat dizze latinte tumoaren faker opspoard wurden troch de ferbettere urologyske techniken lykas TURP, PSA-hifking en biopsysk ûndersyk mei fine nullen. It is lykwols net dúdlik, of dit de hiele taname yn ynsidinsje ferklearje kin, of dat der sprake wêze kin fan in grutter risiko op prostaatkanker. Op dit probleem giet dit proefskrift neier yn.
Hjirby waard yn haadsaak gebrûk makke fan gegevens dy't sammele binne troch de kankerregistraasje van het IKZ, wêryn alle ny ûntdutsen gefallen fan kanker registrearre binne foar in nau omskreaun gebiet yn Zúd Nederlân mei sûnt 1987 sa likernôch twa miljoen ynwenners. Foar in stikmannich stúdzjes waard gearwurke mei oare Europeeske kankerregistraasjes.
De ynsidinsje naam yn Súdeast Nederlân ta fan 36 de 10^5 yn 1971 en ta oan 55 de 10^5 yn 1989 (foar de yntroduksje fan PSA-hifking). Dit tanimmen nei 1980 wiist net allinnich op in lege graad fan, mar ek op in net botte differinsearre en útsaaide prostaatkanker (haadstik 3.1).
De konklúzje dat der yn dizze perioade in wichtige taname pleats fûn fan de ynsidinsje fan prostaatkanker, waard befêstige troch stúdzjes oangeande trends yn de prognoaze: yn Súdeast Nederlân feroare tusken 1971 en 1989 de prognoaze amper.
Relatyf oerlibjen (in skatting fan de oarsaak foar spesifyk oerlibje fan prostaatkanker) ferbettere neffens in mienskiplike stúdzje fan 45 Europeeske kankerregistraasjes (de Eurocare stúdzje) inkeld fan 55% yn 1984 oan 59% ta yn 1987-1989, alhoewol't dat relatyf oerlibjen wol gâns fariearret tusken de lannen (haadstik 4.2). In gruttere ferbettering yn oerlibjen kin ferwachte wurde, as tanimmende diagnoaze fan latinte kanker (dy't net liedt ta de dea fan de pasjint) yn in gruttere omfang pleats fine soe.
Spesjale oandacht waard skonken oan manlju ûnder de 60 jier. Yn dit âlderdomsskift (dêr't minder diagnostysk ûndersiik yn dien wurdt) namen sawol de ynsidinsje as it oantal deaden as gefolch fan prostaatkanker tusken 1971 en 1989 ta, wylst it relatyf oerlibjen amper feroare, earder minder waard yn dizze perioade (haadstik 3.3). Yn de Eurocare stúdzje waard yn dit âlderdomsskift ek gjin ferbettering waarnommen yn it relatyf oerlibjen. Dizze waarnimming soe te ferklearjen wêze troch in tanommen risiko fan fatale prostaatkanker, dy't yn de âlderdoms-perioade-skift analyze neier ûndersocht waard mei gegevens fan alle deaden yn Nederlân as gefolch fan prostaatkanker (haadstik 3.2).
As gefolch fan prostaatkanker naam de stjerte foar alle âlderdomsskiften fanôf 55 jier oan 1989 ta en foar manlju fan 65 jier of âlder oant yn de njoggentiger jierren. Boppedat bliek net it âlderdoms-perioade-model, mar it âlderdomsskift-model dizze gegevens befredigjend te beskriuwen, dat in tanimmend risiko sjen liet foar elk

opinoar folgjend berte-skift fan manlju berne tusken 1870 en 1879 en manlju berne tusken 1925 en 1934. Dit suggerearret in tanommen bleatstelling oan in risiko-faktor, dy't oant no ta ûnbekend is. De yntroduksje fan de opportunistyske PSA-hifking resultearre yn in fierder tanimmen (boppe 80 de 10^5) fan yn haadsaak lokalisearre prostaatkanker fan lege graad as gefolch fan, nei alle gedachten, betidere diagnoaze en it tanommen opspoaren fan ûnbetsjuttende tumoaren.
Yn ferliking mei bygelyks de USA, dêr't PSA-hifking wiidferspraat propagearre en brûkt waard, wie it tanimmen lykwols beskieden.It twadde diel fan dit proefskrift giet oer de behanneling fan beheind lokalisearre prostaatkanker. In grutter tal pasjinten (benammen dy fan ûnder de 70 jier) mei lokalisearre tumoaren waard behannele mei radikale prostatektomy (it radikaal fuortheljen fan de prostaat), alhoewol't radioterapy (bestrieling) oerbleau as in wichtich alternatyf (haadstik 5.1). Der bestie in opmerklike fariaasje yn it persintaazje behannelingen fan pasjinten (benammen dy ûnder de 70 jier) mei lokalisearre tumoaren dy't behannele waarden mei prostatektomy (yn de ferskate sikehûzen in skaal fan 5% oant 67%). Wylst op't heden net foldwaande dúdlik is, hokker behanneling de bêste is, waard de kar fan de behanneling meast bepaald troch de âlderdom fan de pasjint, de tumor-karakteristiken en de ûnderfiningen fan de urolooch. Earnstige ko-morbiditeit (bykommende sykten) waard by likernôch 50% fan de pasjinten yn de âlderdom boppe 70 jier oantroffen, mar der waard kwealik rekken mei hâlden by de kar fan behanneling (haadstik 5.2).
By pasjinten dy't tusken 1955 en 1984 mei prostaatkanker, diagnostisearre wienen (meast behannele sûnder útsicht op betterskip), koe in lytse ferheging fan it stjertesifer konstatearre wurde, as hja langer as 10 jier nei de behanneling libben, wylst dat fan nei 15 jier net sein wurde kin (haadstik 6.1). Ko-morbiditeit hie in grutte ynfloed op it oerlibjen fan pasjinten dy't diagnostisearre wienen tusken 1993 en 1995 (yn it tiidrek fan PSA-hifking), benammen foar pasjinten ûnder de 70 jier (haadstik 6.2). Dat wie wichtiger as de âlderdom. In botte differensearre tumor wie ek in tige wichtige prognoastyske faktor, sels al yn dizze stúdzje fan 3 jier.

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Piet Post werd op 13 april 1965 geboren te Oudenbosch. Na diverse malen met zijn Friese ouders binnen Nederland te zijn verhuisd, behaalde hij in 1983 het diploma gymnasium ß aan de Rijksscholengemeenschap te Heerenveen. Datzelfde jaar begon hij met de studie Geneeskunde en behaalde in 1990 het artsexamen aan de Rijksuniversiteit Groningen. De militaire dienstplicht vervulde hij als onderdeel-arts bij de Geneeskundige Compagnie te Assen. Nadat hij door een ongeval bijna een jaar niet inzetbaar was, volgde een aanstelling als Beroepsofficier-arts voor 1 jaar (1993-1994). Gedurende dit jaar volgde hij tevens met succes de postdoctorale opleiding Epidemiologie aan de Vrije Universiteit te Amsterdam. In 1994 werd hij aangesteld als wetenschappelijk medewerker bij het Instituut Epidemiologie & Biostatistiek van de Erasmus Universiteit te Rotterdam. In deze hoedanigheid verrichtte hij het onderzoek, dat beschreven wordt in dit proefschrift, bij het Integraal Kankercentrum Zuid (IKZ). Tevens voltooide hij in deze periode de 'MSc in Clinical Epidemiology' opleiding van het Netherlands Institute for Health Sciences (NIHES).

IKZ
INTEGRAAL KANKERCENTRUM ZUID

Voor dit onderzoek werd gebruik gemaakt van gegevens van de kankerregistratie 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 ziekenhuizen en in de thuiszorg in het gebied Noord-Brabant en Noord-Limburg.

Eén van de activiteiten van het IKZ is de kankerregistratie, waarbij het gaat om het verzamelen en bewerken van gegevens over alle vormen van kanker. Deze registratie is in 1955 gestart in het oostelijk deel van de regio. Zij heeft inmiddels veel informatie over kanker in Nederland voortgebracht.

De gegevens die door de registratie-medewerkers worden verzameld betreffen onder andere demografische kenmerken van patiënten, gebruikte diagnostiek, toegepaste behandeling en follow-up. Sinds 1993 worden bovendien eventuele bijkomende ziekten (co-morbiditeit) geregistreerd.
Clinici en wetenschappelijk onderzoekers gebruiken de gegevens van de kankerregistratie voor velerlei onderzoek. Hierdoor wordt bijvoorbeeld inzicht verkregen in het voorkomen van kanker, de effecten van preventieve maatregelen en de benodigde toekomstige voorzieningen. Een overzichtspublicatie met informatie over het voorkomen en de prognose van de verschillende vormen van kanker over de periode 1955-94 is bij het IKZ te verkrijgen.

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