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## Original Paper

# 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

P.N. Post,<sup>1,2</sup> P.J.M. Kil,<sup>3,4</sup> M.A. Crommelin,<sup>4,5</sup> R.F.M. Schapers<sup>4,6</sup>  
and J.-W.W. Coebergh<sup>1,2,4</sup>

<sup>1</sup>Comprehensive Cancer Centre South (IKZ), PO Box 231, 5600 AE Eindhoven; <sup>2</sup>Department of Epidemiology and Biostatistics, Erasmus University, Rotterdam; <sup>3</sup>Department of Urology, St Elisabeth Hospital, Tilburg; <sup>4</sup>Regional Study Group for Urological Oncology IKZ, Eindhoven; <sup>5</sup>Department of Radiotherapy, Catharina Hospital, Eindhoven; and <sup>6</sup>Department of Pathology, St Maartens Gasthuis, Venlo, The Netherlands

The incidence of prostate cancer has increased considerably over the past two decades, partly due to the increased detection of subclinical cases. In southeastern Netherlands, a region of almost 1 million inhabitants with good access to specialised 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 Standardised 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 per 100 000 in 1971 to 55 per 100 000 in 1989, included all grades as well as metastasised prostate cancer. The age-adjusted mortality mainly fluctuated in this period, but increased among men aged 55–64 years from 12 per 100 000 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 localised prostate cancer, presumably due to increasing opportunistic PSA testing, especially after 1993. A real increase in incidence may have occurred before 1993. However, pending results of randomised trials, judicious application of PSA testing seems justifiable to avoid unnecessary intervention without reducing mortality. © 1998 Elsevier Science Ltd. All rights reserved.

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## 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 is consistent with the worldwide observed high prevalence of prostate cancer at autopsy of 10–40% [3] and the increase in diagnostic procedures over time: in the U.S.A. between 1973 and 1986, a 30% increase in incidence appears to be partly attributable to

an increase in transurethral 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 U.S.A. increased by 82% between 1986 and 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 stabilisation or a

Correspondence to P.N. Post.

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subsequent decline. Indeed, in some areas of the U.S.A., a decline in incidence has now been observed [9, 10]. Similarly, increased diagnosis during TURP should have been followed by stabilisation of the incidence. However, the exponential rise in PSA testing from 1986 may have obscured the expected changes. Nevertheless, Potosky and associates made it plausible (by recognition of overestimation due to multiple hospitalisations and mortality patterns) that there was in part a true increase in risk between 1973 and 1986 [4]. In contrast to the U.S.A. [11], prostate cancer screening programmes have not yet been introduced in Europe, but a European randomised 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 south-eastern 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.

## MATERIALS AND METHODS

### Study population

Incidence rates were calculated using data from the Eindhoven Cancer Registry, which covers a region with almost 1 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 law, 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 Statistics Netherlands, indicate that prostate cancer data can be considered nearly complete from 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 km. The number of urologists increased from four in 1971 to 12 in 1978 and 15 in 1994. National hospital discharge data show that the number of TURPs increased from 1,900 in 1971 to 12 326 in 1985. PSA assessment was not introduced until 1990. In the 1970s, prostate cancer patients were usually treated symptomatically (TURP), often supplemented with anti-androgen or oestrogen treatment or castration. Since the early 1980s 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 1990s.

### 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 localised and incidental finding (T1), localised 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 metastasised. Because absence of metastases was not always recorded explicitly, we included both M0 and Mx in the non-metastasised categories. Since bone scan imaging only became widely available in the late 1970s, stage is presented from 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 from 1980.

### Urological care

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

### Data analysis

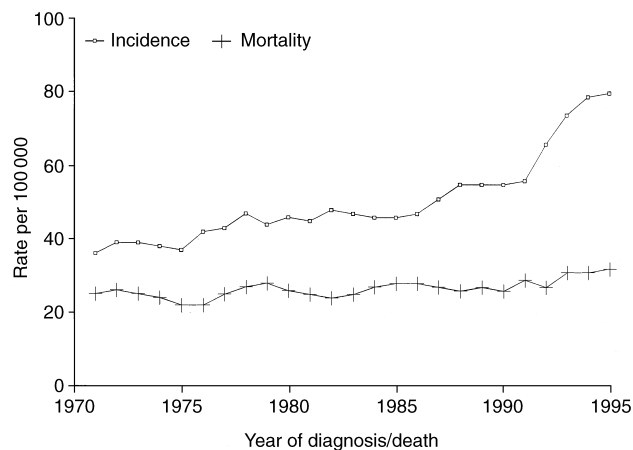
Age-specific rates (for 10-year age groups), as well as age-adjusted rates (European Standardised Rate), per 100 000 person-years were calculated. Furthermore, incidence rates according to stage and grade were calculated. Annual incidence and mortality rates are presented as 3-year moving averages: the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

## RESULTS

Between 1971 and 1995, 4,205 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 years. 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.

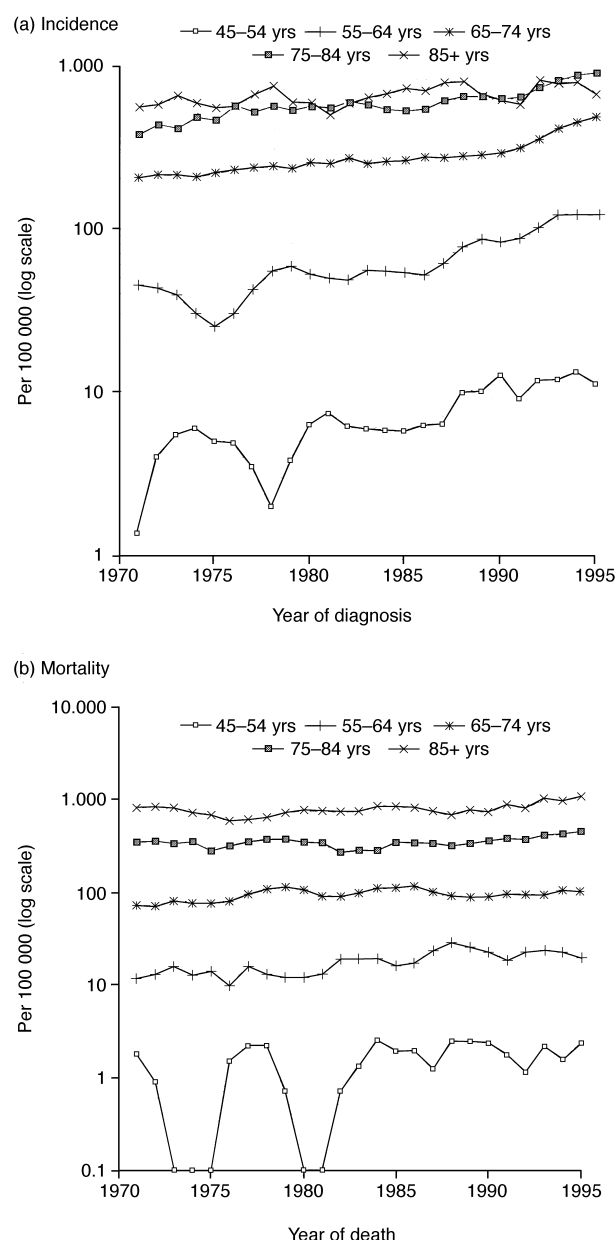
### Incidence

The age-adjusted incidence increased in the 1970s from 37 per 100 000 in 1975 to 46 per 100 000 in 1980 (Figure 1).



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

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 years). The incidence among men over 85 years of age showed marked fluctuations. Random variation due to the small number of men in this age group probably plays a role. In the early 1980s, the incidence of patients with unknown grade decreased markedly (Figure 3). The increase in incidence in this period included all grades, but after 1985 was mainly seen for moderately or well differentiated tumours. The exponential increase after 1991 was initially largely due to poorly and moderately differentiated cancer, but after 1993 it could be explained solely by well and moderately differentiated cancer.

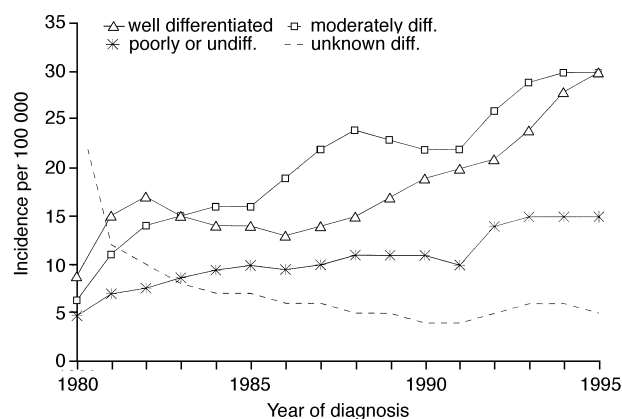


**Figure 2.** Trends in age-specific (a) incidence and (b) mortality rates for prostate cancer in southeastern Netherlands per 100 000 person-years, 1971–1995 (3-year moving averages).

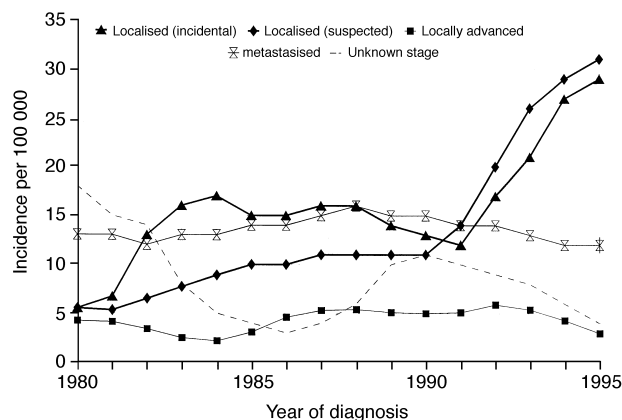
The increase in patients with incidental localised cancer paralleled a decrease in patients with unknown stage, but the incidence of metastasised cancer also increased in the late 1980s (Figure 4). Although patients with lymph node but no distant metastases were included in the category 'metastasised', only 7% of the metastasised patients between 1985 and 1989 were diagnosed without distant metastases. Subsequently, the incidence of metastasised cancer stabilised and decreased, although it continued to represent some 15% of the incidence in the 1990s. After a transient increase due to temporarily stricter registration practices around 1990, the incidence of patients with unknown tumour size declined again. The exponential increase in incidence after 1991 can be attributed to incidental cases, but also to suspected localised prostate cancer.

### Mortality

The age-adjusted mortality declined initially in the early 1970s but increased slightly from 22 per 100 000 in 1975 to 26 per 100 000 in 1980 (Figure 1). This increase was apparent for all age groups (Figure 2). In the 1980s, the age-adjusted mortality increased again slightly, mainly due to an increase among men aged 55–64 years, from 12 per 100 000 in 1980 to 25 per 100 000 in 1989. A small increase in the age-adjusted mortality from 26 per 100 000 in 1990 to 32 per 100 000 in 1995 was noted mainly for older age groups.



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



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

### 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 6-fold between 1970 and 1990, whereas the number of 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 localised cancer and 20% even exhibited metastasised 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 localised palpable and up to 30% were metastasised at diagnosis (17% were recorded as unknown).

## DISCUSSION

We report a 53% increase in the incidence of prostate cancer in southeastern Netherlands between 1971 and 1989 and a 43% increase in the 5 years after the introduction of PSA testing in 1990. Increases in incidence before the introduction of PSA testing have been reported in other European countries [17, 18] and the U.S.A. [4]. The increase in incidence in northern Sweden was due to low-grade cancer [17], but in Norway, the increase in the incidence of metastasised cancer was similar to that found for localised cancer. Moreover, a concomitant increase in mortality was observed [18]. In the U.S.A., the increase involved mainly localised prostate cancer [4]. An increase in incidence of 6.3% per year, mainly due to non-metastasised prostate cancer, was observed after PSA testing was introduced in Isère [13]. In the U.S.A., an even more pronounced increase was reported [6]. This dramatic rise has now been followed by a decline in different parts of the U.S.A., 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 1970s, 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-metastasised categories, a few Mx cases may have been misclassified. It is unlikely 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 two decades (in southeastern Netherlands from 258 per 100 000 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 per 100 000 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 [23] may have had a similar effect. Increased mortality due to prostate cancer should, therefore, be interpreted with caution, especially for males aged 75 years or more.

### Increased incidence or higher detection rate?

The increase in incidence in the 1980s was not only represented by low-grade prostate cancer but also by metastasised 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]. In spite of 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. The 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 non-lethal 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 testing is most likely to be an artifact caused by accelerated diagnosis. Although a further increase in incidence may have occurred, the diagnosis of prostate cancer has most likely recently been advanced 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 testing have not been proven. A European randomised 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 localised prostate cancer after 1990 seems to be attributable mainly to advanced diagnosis due to opportunistic PSA testing.

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