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Prostate cancer: Trends in incidence, survival and mortality in the Netherlands, 1989–2006

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ABSTRACT

Background: Prostate cancer occurrence and stage distribution changed dramatically during the end of the 20th century. This study aimed to quantify and explain trends in incidence, stage distribution, survival and mortality in the Netherlands between 1989 and 2006.
Methods: Population-based data from the nationwide Netherlands Cancer Registry and Causes of Death Registry were used. Annual incidence and mortality rates were calculated and age-adjusted to the European Standard Population. Trends in rates were evaluated by age, clinical stage and differentiation grade.
Results: 120,965 men were newly diagnosed with prostate cancer between 1989 and 2006. Age-adjusted incidence rates increased from 63 to 104 per 100,000 person-years in this period. Two periods of increasing incidence rates could be distinguished with increases predominantly in cT2-tumours between 1989 and 1995 and predominantly in cT1c-tumours since 2001. cT4/N+/M+-tumour incidence rates decreased from 23 in 1993 to 18 in 2006. The trend towards earlier detection was accompanied by a lower mean age at diagnosis (from 74 in 1989 to 70 in 2006), increased frequency of treatment with curative intent and improved 5-year relative survival. Mortality rates decreased from 34 in 1996 to 26 in 2007.
Conclusions: The increase of prostate cancer incidence in the early 1990s was probably caused by increased prostate cancer awareness combined with diagnostic improvements (transrectal ultrasound, (thin) needle biopsies), but not PSA testing. The subsequent peak since 2001 is probably attributable to PSA testing. The decline in prostate cancer mortality from 1996 onwards may be the consequence of increased detection of cT2-tumours between 1989 and 1995. Unfortunately, data on the use of PSA tests and other prostate cancer diagnostics to support these conclusions are lacking.

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1. Introduction

In the last decades of the 20th century, prostate cancer incidence increased in most high-income countries. It is generally accepted that a large part of this increase can be accounted for by earlier (and increased) detection due to more frequent digital rectal examination as a consequence of greater prostate cancer awareness, incidental diagnosis due to the increasing use of transurethral resection of the prostate (TURP) and developments in diagnostic techniques such as transrectal ultrasound (TRUS) imaging and thin needle biopsies.[1–4]

In the late 1980s, PSA testing became available.[5] Particularly in the United States of America (USA), but also in other high-income countries, a further steep increase in prostate cancer incidence was observed after the introduction of PSA testing.[6] Welch et al. calculated that from 1986 to 2005 an excess of at least one million men were diagnosed with and treated for prostate cancer in the USA due to PSA testing.[7] Recently, the European Randomised Study of Screening for Prostate Cancer (ERSPC) showed a 20% decrease in prostate cancer related mortality in study participants as an effect of programmed population-based PSA testing.[8] However, PSA testing is not routine practice yet in the Netherlands.[9] Consequently, whether PSA testing is responsible for the observed decrease in the incidence of metastasised tumours and mortality in the Netherlands over the past 15 years is questionable.

New therapies or improvements in existing therapies can also cause trends or trend changes in prognosis. Radical surgery and radiotherapy (external-beam radiotherapy and brachytherapy) are available for the treatment of localised prostate cancer and, for advanced disease, these treatments are sometimes combined with hormonal therapy.[10] It is not known whether changes in the application of these therapies have had an effect on trends in the prognosis of patients with prostate cancer in the Netherlands.

Insight in incidence, disease stage and mortality patterns may reveal a need for policy changes. Prostate cancer represents a large burden for society and with the ageing population the number of newly diagnosed patients in the Netherlands is expected to rise from 9500 patients in 2006 to an estimated 15,000 in 2015.[11] The number of prevalent patients for whom periodical check-ups will be necessary is expected to increase even more dramatically. The aim of this population-based study was to identify and explain temporal trends in prostate cancer incidence, disease stage, survival and mortality in the Netherlands from 1989 to 2006.

2. Methods

The Association of Comprehensive Cancer Centres (CCCs) has registered data of all newly diagnosed neoplasms in the Netherlands since 1989. The resulting nationwide Netherlands Cancer Registry (NCR; www.ikcnet.nl) is considered to be of very high quality due to the standardised identification of new cases of cancer through the national automated pathology archive (PALGA), the national registry of hospital discharges (LMR), haematology departments and radiotherapy institutions, and because of the thorough training and testing of the registrars. After identification of new cases, these registrars abstract data from the medical files in all Dutch hospitals. Computerised consistency checks and re-abstraction and re-entry of data further improve the quality of the data. Completeness is estimated to be at least 95%.[12] Population-based data concerning prostate cancer diagnoses between 1989 and 2006 were analysed for the purpose of this study.[11] One of the eight CCCs (CCC South) began with cancer registration in the 1950s. Therefore, we were also able to make use of data from CCC South for the period 1970–1988 in order to investigate longer term trends in overall incidence.[13] The data from the CCC South were used only for the long-term evaluation of overall incidence and mortality. For the calculation of survival, the NCR links its database with the population-based demography registry that keeps data on vital status of all Dutch citizens. This nationwide demography database was started in 1995. Four of the eight CCCs contributing data to the NCR have retrospectively collected vital status data for all patients diagnosed before 1995. Mortality data, obtained from Statistics Netherlands, were available from 1970 to 2007.[14]

Histology was coded according to the International Classification of Diseases for Oncology (ICD-O).[15] Differentiation was graded using the World Health Organisation (WHO) grading system until 2003, after which it was replaced by the Gleason score.[16] Histological grading was categorised as well differentiated (WHO grade 1 or Gleason score 2–6), moderately differentiated (WHO grade 2 or Gleason score 7) or poorly differentiated (WHO grade 3 or Gleason score 8–10). Patients with undifferentiated (grade 4) tumours (<1%) were included in the category 'poorly differentiated tumours'.

Clinical stage was recorded strictly according to the formal TNM classification in use at the time of diagnosis and grouped into cT1a/b, cT1c (existing since 1993), cT2, cT3, cT4/N+/M+ or 'unknown' (cTx) if insufficient information was available for accurate staging.[17] For patients who had undergone a radical prostatectomy, the clinical and post-surgical T-stage were crosstabulated to evaluate trends in clinical overstaging and understaging by period of diagnosis.

The first-line treatment (or treatment combination) was recorded. Patients who were incidentally diagnosed with prostate cancer in TURP specimens and who received no further treatment, were categorised into the 'no therapy'-group.

The study period was divided into three 5-year periods and one 3-year period: 1989–1993, 1994–1998, 1999–2003 and 2004–2006. Patients were grouped into three age categories in order to identify age-specific trends in stage distribution and treatment (<65, 65–74 and $\geqslant$75 years) and into five age categories for incidence and mortality rates (45–54, 55–64, 65–74, 75–84 and $\geqslant$85 years).

2.1. *Statistical analysis*

Annual incidence and mortality rates for the period 1989–2006 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European Standard Population (European Standardised Rates (ESRs)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). To calculate this, a regression line was fitted to

the natural logarithm of the rates, using the calendar year as a regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and x = calendar year; then EAPC = $100 * (e^a - 1)$).[18] Incidence rates were also calculated per age group, differentiation grade and clinical stage. Treatment administration was described as percentage per age group and calendar period.

Follow-up of all patients was calculated as the time from diagnosis to death or to 1st January 2008. Five-year relative survival was used to estimate disease-specific survival. Relative survival was calculated as the absolute survival among cancer patients divided by the expected survival for the general male population with the same age.[19] For the stage-stratified survival analysis, the pTNM classification was used. If pTNM was not available, cTNM was used. Traditional cohort-based relative survival analysis was used for the period 1989–2003 which represents the survival of patients diagnosed during 1989–2003. Period-based relative survival analysis was used for the most recent period 2004–2006, in order to obtain a more up-to-date estimate for this period.[20] Survival trends were quantified as the mean annual percentage change (MAPC) from 1989 to 2006 as estimated by a linear regression model. This calculation assumes that the rates increased or decreased at a constant rate over the entire period. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

3. Results

3.1. Age-specific incidence

A total of 120,965 patients were diagnosed with prostate cancer between 1989 and 2006. The annual number of diagnoses more than doubled from 4201 in 1989 to 9516 in 2006. The mean age at diagnosis decreased from 74 years in 1989 to 70 in 2006.

Prostate cancer incidence rates gradually increased in the CCC South catchment area between 1970 and 1989, with an EAPC of 1.9% (95% CI: 1.1–2.7%). Thereafter, the incidence in the whole country increased steeply from 63 per 100,000 person-years in 1989 to 90 in 1995, with an EAPC of 7.1% (95% CI: 4.5–9.8%) (Fig. 1). Incidence rates remained stable between 1995 and 2000 (EAPC –0.9%; 95% CI: –5.9% to 3.8%), but rose from 88 in 2000 to 104 in 2006 (EAPC 3.6%; 95% CI: 1.1–6.1%). The CCC South data in the period 1989–2006 showed the same pattern as the nationwide data.

Age-stratified incidence rates increased over time for men under the age of 75 years (Fig. 2). Incidence rates for men aged 65–74 years rose from 1989 until 1995 (EAPC 8.9%; 95% CI: 5.9–12.7%), were stable until 2000 (EAPC 0.7%; 95% CI –2.9% to 4.4%) and then rose again until 2006 (EAPC 4.5%; 95% CI: 0.8–8.4%). For men aged 55–64 incidence rates increased throughout the study period: EAPC 17.7% (95% CI: 0.8–37.3%) from 1991 to 1994 and 5.8% (95% CI: 4.9–6.8%) from 1994 to 2006.

For men over 75, incidence rates increased until 1994, but then decreased until 2006 with EAPCs of –1.8% (95% CI: –2.7% to –0.9%) for men aged 75–84 and –7.4% (95% CI: –12.1% to –2.7%) for men over 85.

3.2. Stage-specific incidence

Since the introduction of the cT1c-category in the TNM classification for PSA-detected prostate cancer in 1993, cT1c-tumour incidence rose to 35 per 100,000 person-years in 2006

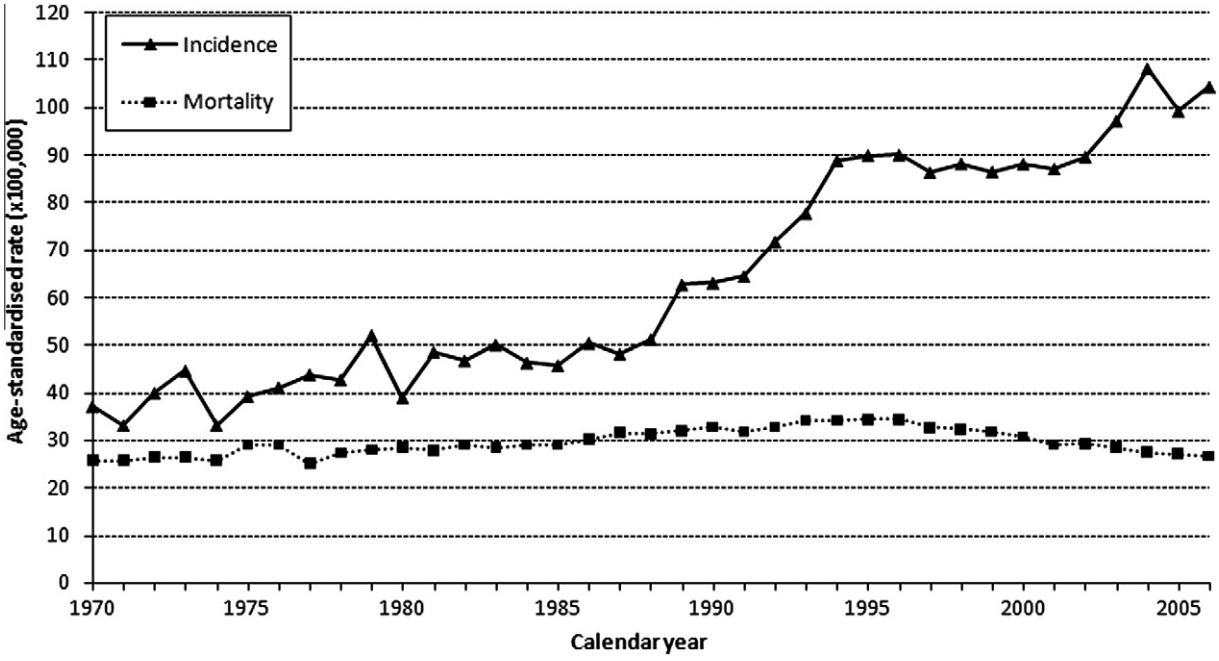

Fig. 1 – Age-standardised rates (European Standard Population) for incidence and mortality of prostate cancer in the Netherlands 1970–2006 (incidence rates 1970–1988: data Comprehensive Cancer Centre South; incidence rates 1989–2006: data Netherlands Cancer Registry – no differences between CCCS and NCR data in period 1989–2006; mortality rates 1970–2006: Statistics Netherlands).

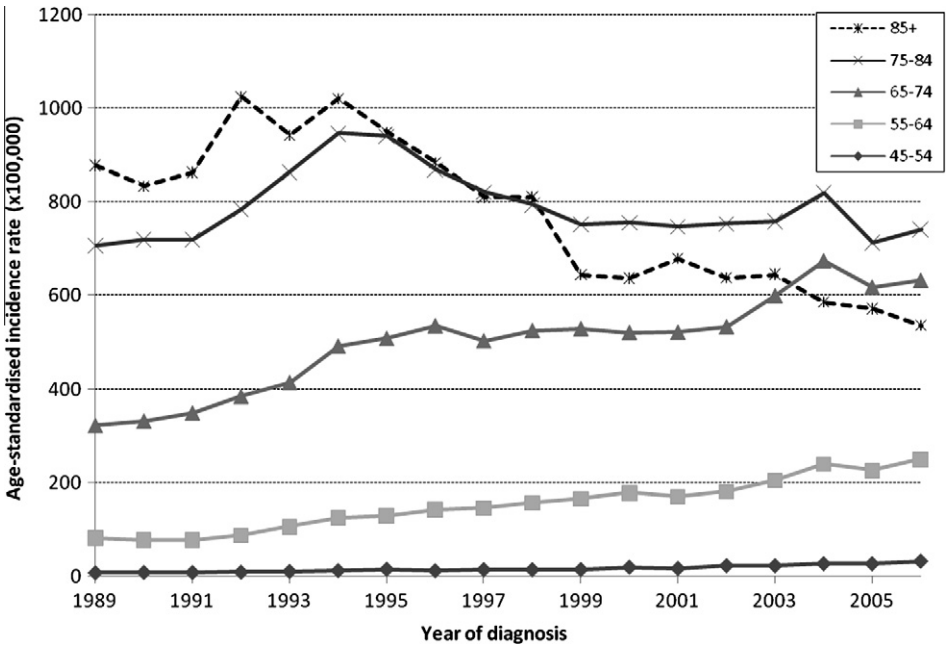

Fig. 2 – Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989–2006, stratified by age category.

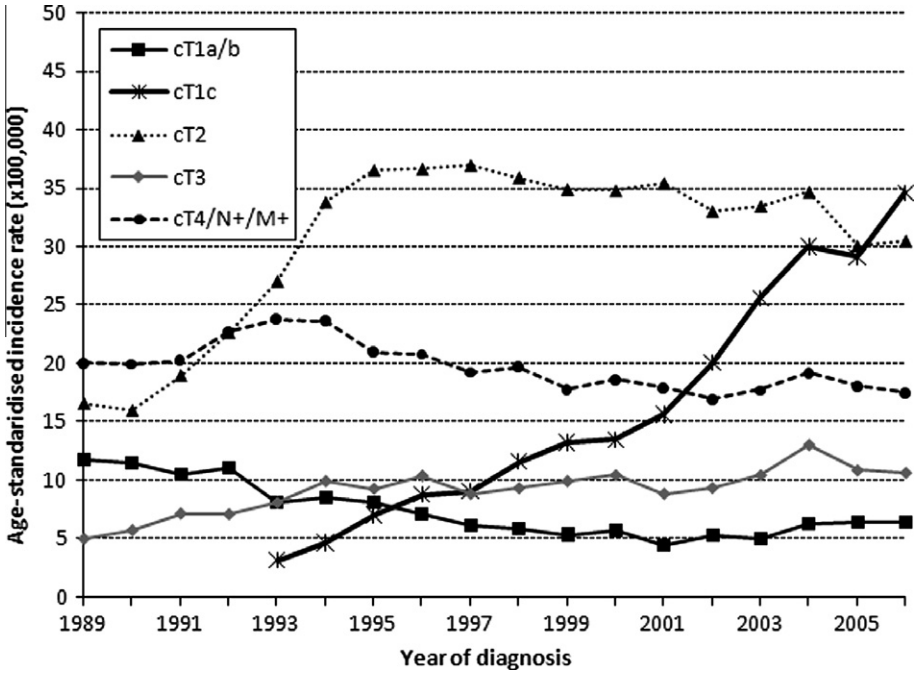

Fig. 3 – Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989–2006, stratified by clinical stage.

(EAPC: 18.2%; 95% CI: 16.0–20.5%) (Fig. 3). The largest increase was observed from 2001 onwards. The incidence rate for cT1a/b-tumours dropped from 1992 to 1993 and decreased further until 2001. The incidence rate of cT2-tumours increased from 19 in 1989 to 37 in 1995 (EAPC 16.7%; 95% CI: 13.5–20.0%) and then decreased to 30 in 2006 (EAPC –1.6%; 95% CI: –2.7% to –0.5%). After increasing from 1989 to 1994 (EAPC 12.4%; 95% CI: 6.0–19.3%), the incidence rate of cT3-tumours remained stable until the end of the study period (EAPC 1.4%; 95% CI: –0.2 to 3.0). The incidence rate of cT4/N+/M+-tumours decreased from 1993 to 1999 (EAPC = –4.5%; 95% CI: –6.6% to –2.2%), after which it remained stable. In absolute numbers, the annual number of diagnosed cT4/N+/M+-tumours increased gradually from 1345 cases nationwide in 1989 to 1614 in 2006.

Age-stratified analysis of these data shows that the increase in cT1c-tumours was most markedly present in men under 75 years of age and that increase seemed to accelerate

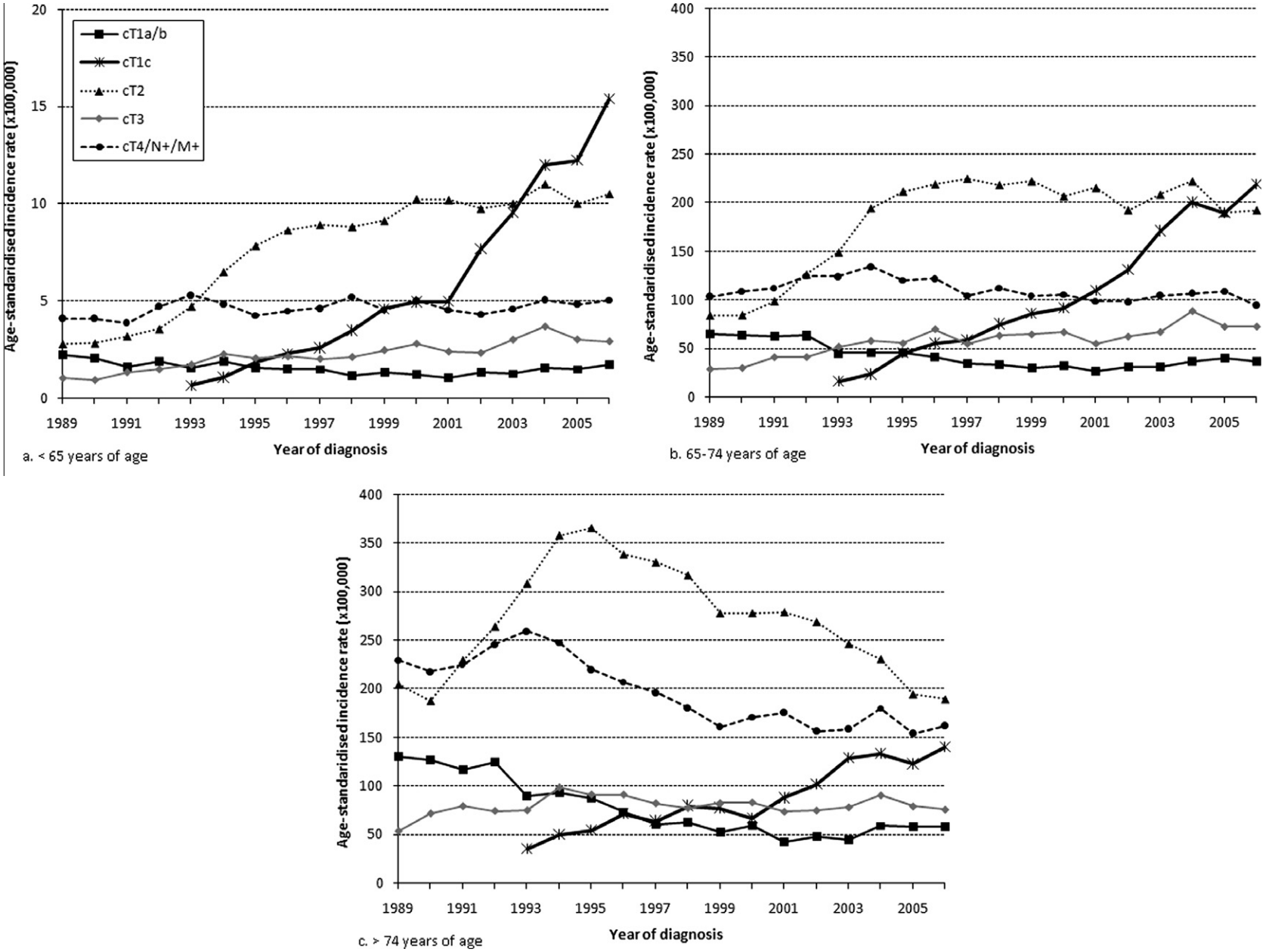

Fig. 4 – Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989–2006, stratified by clinical stage in three age categories: (a) <65 years of age, (b) 65–74 years of age and (c) >74 years of age.

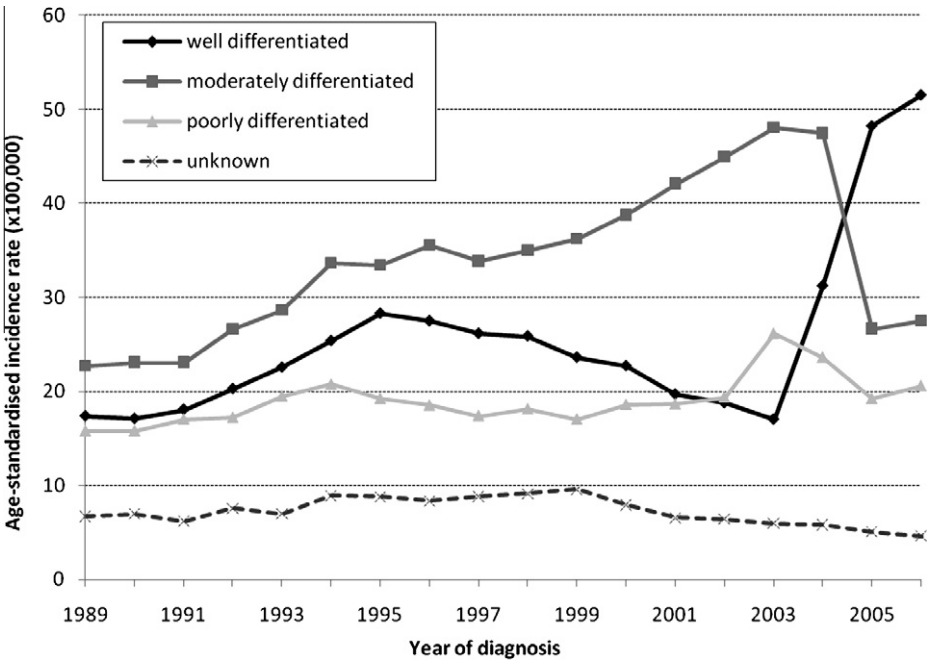

Fig. 5 – Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands, stratified by grade of differentiation (until 2003 the WHO grading system was used to determine differentiation; from 2004 onwards the Gleason scoring system was used: Gleason score 2–6 = well differentiated, Gleason score 7 = moderately differentiated, Gleason score 8–10 = poorly differentiated).

from 2001 onwards (Fig. 4a–c). The incidence rate of cT2-tumours rose quickly until the mid-1990s for all age categories, after which it remained stable for men under 75 and decreased for men over 75. The incidence rate of cT3-tumours gradually increased for men under 75 and remained nearly constant for men over 75. The decrease in cT4/N+/M+-tumour incidence from 1993 to 1999 was most clearly present for men over 75.

The incidence rate of well-differentiated tumours increased from 1991 to 1995 (EAPC 8.3%; 95% CI: 5.5–11.2%) and then decreased until 2003 (EAPC –6.1%; 95% CI: –9.2% to –2.9%) (Fig. 5). For moderately differentiated tumours, the EAPC was 5.5% (95% CI: 4.2–6.9%) from 1989 to 2003. Since 2003, the incidence of well-differentiated tumours increased, while moderately differentiated tumours decreased.

3.3. *Clinical understaging*

17,117 patients underwent a radical prostatectomy. For these patients, both cTNM and pTNM were known. Approximately one third of these patients who were considered cT2 ($n = 8868$) were clinically understaged and had pT3 ($n = 2675$) or pT4 ($n = 246$). Patients classified as cT3 were overstaged in 27% of the cases with a known pT-classification ($n = 136/499$). The amount of understaging of cT2- and cT3-tumours remained relatively constant during the last three periods of diagnosis. Clinical overstaging of cT3-tumours occurred more frequently over time, rising from 18% in 1989–1993 to 37% in 2004–2006.

3.4. *Treatment*

For 1333 patients (1.1%) the primary treatment was not registered. These patients were excluded from this analysis. Over time, patients under 75 with cT1- and cT2-tumours more frequently underwent radical prostatectomy. Patients aged 65–74 with localised tumours underwent surgery less frequently than their younger counterparts. Still, the percentage of men undergoing radical prostatectomy almost doubled to 20% between 2004 and 2006. Radiotherapy as sole therapy increased mainly through increased application of brachytherapy. Active surveillance was chosen less often (from 38% of all cT1-tumours in 1989 to 9% in 2006). The latter group included patients with incidental prostate cancer found during TURP. Patients under 75 with cT3-tumours received concurrent radiotherapy and hormonal therapy in more than 70% of cases since the late 1990s. Patients over 75 with localised disease most often received either no therapy (60%, 30% and 20% of the patients with cT1-, cT2- and cT3-tumour, respectively) or hormonal therapy.

For cT4/N+/M+ prostate cancer the only available therapy is hormonal therapy. This was given to 80–90% of the patients in all age categories. The combination of radiotherapy and hormonal therapy was chosen for approximately 10% of patients under 75 years of age (data not shown).

3.5. *Survival*

Five-year relative survival significantly increased in all age categories under 85 and all stages (Fig. 7). The age-stratified analysis showed that men aged 45–54 had the highest MAPC with 1.8% annual increase (95% CI: 1.2–2.3%). This increase declined gradually with every higher age category to 1.3% (95% CI: 1.0–1.6%) for men aged 75–84 and no change for men over 85 years of age. The stage-specific increase in survival was strongest for men with pT3/pT4-tumours with a

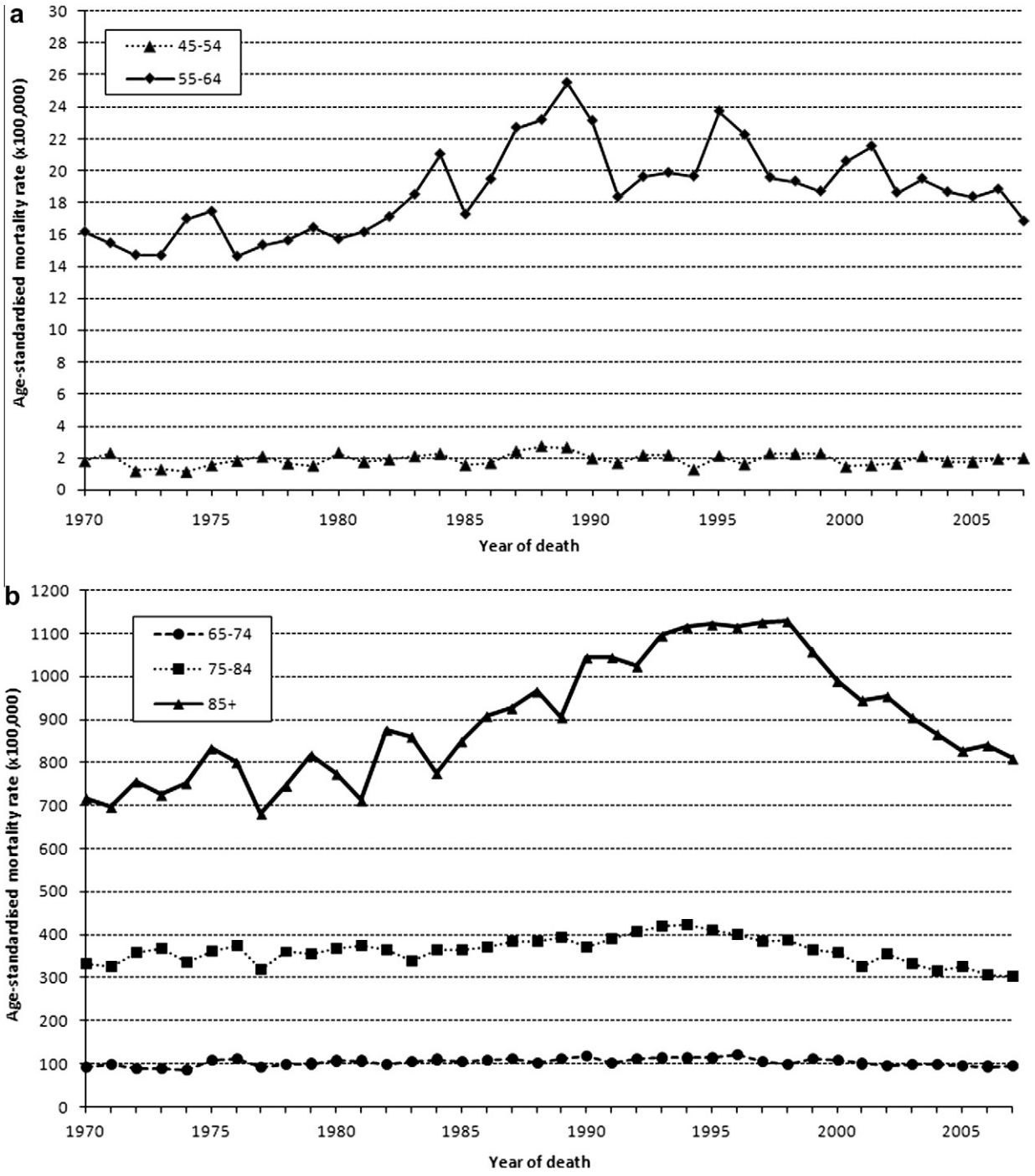

Fig. 6 – Age-standardised mortality rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1970–2006, stratified by age category: (a) 45–54 years, 55–64 years; (b) 65–74 years, 75–84 years, 85+ years.

MAPC of 1.6% (95% CI: 1.2–2.0%). Locally extended or metastatic cancer had the lowest MAPC with 0.4% annual increase in survival (95% CI: 0.2–0.7%).

3.6. *Mortality*

Disease-specific mortality rates increased from 1970 until 1995 (from 26 to 34 per 100,000 person-years) (EAPC = 1.2; 95% CI: 1.0–1.3%) and then decreased to 26 in 2007 (EAPC = –2.5%; 95% CI –3.0% to –2.0%) (Fig. 1). This pattern was observed for all men over 65 years of age (Fig. 6) and was most evident in men over 85 years of age, with an EAPC from 1996 to 2007 of –3.4% (95% CI: –4.0% to –2.8%).

4. Discussion

4.1. *Age-specific incidence*

Between 1989 and 2006, two periods with significant increases in prostate cancer incidence were observed. The increase in

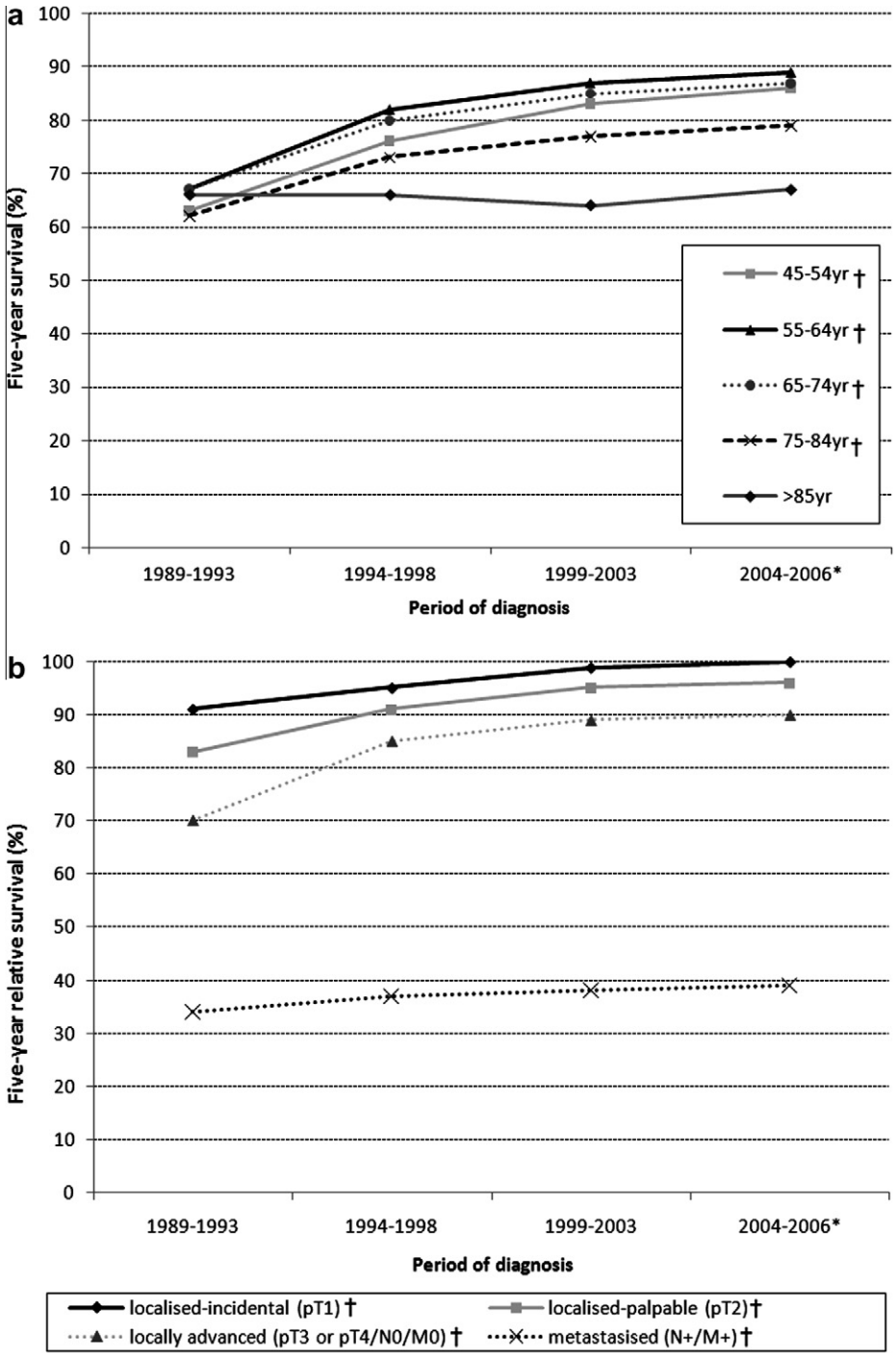

Fig. 7 – (a) Five-year relative survival from prostate cancer by period of diagnosis, stratified by age category (*calculation by period analysis for period of diagnosis 2004–2006); (b) 5-year relative survival from prostate cancer by period of diagnosis, stratified by pathological stage (*calculation by period analysis for period of diagnosis 2004–2006); †significant change ($p < 0.05$) in 5-year relative survival.

the first period, from 1989 to 1995, is often explained as an effect of PSA testing.[13,21,22] However, arguments exist against this explanation. In the Netherlands, PSA testing was introduced relatively slowly, although valid population-based data about the use of PSA tests throughout the study period are not available. An interim analysis of the Rotterdam section of the ERSPC found 8% effective contamination in the control arm between 1997 and 2000.[23] Also, according to a Statistics Netherlands survey, in 2001 only 14% of men over 45 years of age had a PSA measurement in the previous 5 years.[9] Moreover, the increase in incidence from 1989 to 1995 was present in all age categories, while PSA testing in asymptomatic men would be expected to be used less frequently among the elderly (over 75 years of age) because of reservations towards

treatment for men with a relatively short life expectancy (less than 10 years). Although the percentage of men over 75 years of age who had a PSA test in the previous 5 years (40%) is approximately equal to the percentage of men between 55 and 75 years of age, 43% of all the men over the age of 70 who reported having had a PSA test, was between 70 and 74 years of age (Dr. Bruggink, Statistics Netherlands, personal communication). A difficulty with the interpretation of these percentages, though, is that with these numbers one cannot distinguish whether these PSA tests were the first to be undergone by the interviewed men. This is unfortunate as the first PSA test is the most important one when testing for prostate cancer. Very likely, men who have had PSA tests before, will remain to be tested at a later age by their GP or urologist.

4.2. *Stage-specific incidence*

Unfortunately, there is no detailed information available about PSA-detected tumours before 1993, as the cT1c-category was only introduced in the cTNM classification (and the NCR registry protocol) in 1993. Therefore, the cT1a/b-category is heterogeneous until 1992, comprising both TURP-detected and PSA-detected prostate cancer. The stage-specific analyses from 1993 onwards reveal that cT1c-tumour incidence continuously increased and was accompanied by a decrease in the incidence of cT1a/b-tumours until 2001. This increase, together with the increase in cT2-tumour incidence until 1995 and the decrease in cT4/N+/M+-tumour incidence from 1993 to 1999, results in the biphasic increase observed in the overall incidence.

From these data, it can be deduced that the rise of prostate cancer incidence in the early 1990s was mainly caused by an increase in cT2-tumours, probably due to more frequent digital rectal examinations (DREs) and technical improvements in diagnostics, such as TRUS imaging and the use of (thin) needle biopsies. Because cT1c-tumour incidence continued to rise while the incidence of all other stages stabilised since 2000, PSA testing must have caused the subsequent peak from 2000 to 2006. This is further supported by the fact that incidence rates increased only for patients under 75 years of age and by the results of the Statistics Netherlands survey, which showed that the percentage of men over 45 years of age who had their serum PSA measured in the previous 5 years rose from 14% in 2001 to 26% in 2008.[9] Direct population-based data to support this are not available, however.

Incidence rates of locally extended and metastatic (cT4/N+/M+) disease evidently decreased from 1993 to 1999, particularly in men over 65. As interventions directed at detection of cancer in an earlier stage need time to show their beneficial effect on metastasised disease or mortality, a delay between the rise in localised tumours and decrease in metastasised tumours is to be expected. Also, one might expect to see a rise of localised prostate cancer in a younger age category, followed by a decrease in more advanced disease in an older age category. This study found a difference in onset of the increase in localised prostate cancer (1989/1990) and decrease of metastasised prostate cancer (1993) of approximately 4 years. This corresponds reasonably well to the effect of early detection of prostate cancer on mortality as observed in the ERSPC, which only became apparent after 7–8 years.[8] Thus, some change must have occurred around 1990, most probably an increased use of DRE, TRUS imaging and (thin) needle biopsies, but not yet PSA testing. However, this conclusion is somewhat speculative. Other factors might also have contributed to a rise in localised prostate cancer and the subsequent decrease in metastasised disease.

From 1995 to 2003, more moderately differentiated tumours were detected, whereas the incidence of well-differentiated tumours decreased. Knowing that the incidence of cT1c-tumours increased in the same period, this could indicate that PSA testing was effective in detecting moderately differentiated tumours. The trend continued until the registration protocol was changed from the WHO grading system to the Gleason scoring system in 2004. Unfortunately, these systems are not easily interchangeable, as the WHO grading system is based on cellular and nuclear characteristics and the Gleason scoring system on growth patterns. The sudden changes in well-differentiated and moderately differentiated tumours around 2004 were most probably caused by this change in protocol.

Other western countries have shown similar increases in prostate cancer incidence in the study period. The situation in the United Kingdom (UK) might resemble the Dutch situation. In the UK, similar trends were seen with regard to prostate cancer incidence and mortality.[24] In the UK, as in the Netherlands, PSA uptake was considerably lower than in the USA, as illustrated by an overall annual rate of 6.0% for PSA testing in men aged 45–84 with no previous diagnosis of prostate cancer between 1999 and 2002.[25] Consequently, it is possible that the rise in prostate cancer incidence in the UK in the early 1990s and the decrease in mortality since the mid-1990s was also caused by an increased prostate cancer awareness. Without an analysis of stage-specific data from the UK, however, this will remain unclear.

The overall prostate cancer incidence in the Netherlands is still considerably lower than in, e.g. Sweden and North America.[26,27] Interestingly, however, prostate cancer incidence has been decreasing in the USA since 2001.[28] This might indicate that the 'prevalent pool' of prostate cancer cases in the USA is being exhausted. The following years will show whether a similar trend will occur in the Netherlands and other western countries.

4.3. *Treatment*

Over time, patients under 65 with localised (cT1- and cT2-) tumours more often underwent surgery (radical prostatectomy). At the same time, the proportion of patients who received no therapy/TUR-only decreased. This might again be explained by PSA testing. Since PSA became available, patients who were otherwise eligible for TURP may now have had a PSA test with, if indicated, subsequent random prostate biopsies prior to the resection. This would result in an increasingly smaller proportion of prostate cancers detected at TURP.[29]

Patients under 75 with cT3-tumours received radiotherapy in 50% of the cases in the early 1990s. Since 1999, the combination of radiotherapy and hormonal therapy was chosen for over 70% of cT3-patients. This reflects that this combination is considered the gold standard for cT3 prostate cancer, as

proposed by Bolla and colleagues in 1997.[30] In addition to this indication, our data showed that, with time, this combination was also given more often to patients under 75 with cT1- and cT2-tumours.

Men over 75 years have a life expectancy shorter than 10 years.[31] As a result, according to the guidelines, the majority of patients over 75 with a cT1-tumour did not receive therapy. Those who received treatment were most often treated with hormonal therapy. As for the younger patients, combined radiotherapy and hormonal therapy for cT3-tumours were applied more frequently with time.

Treatment options for cT4/N+/M+ prostate cancer are still very limited. Hormonal treatment remained the cornerstone of treating extensive disease, reflected by the fact that over 90% of these patients in all age categories received hormonal treatment. A small minority received radiotherapy in addition to the hormonal treatment.

4.4. *Survival*

Survival from prostate cancer improved for all stages and age categories, except for patients over 85. Tumour stage and grade changes may have played a role in this. With the development of new imaging techniques, tumour staging became more precise. This could result in upstaging, for example, of what previously would have been recorded a large cT2-tumour to a minimal cT3-tumour, consequently increasing survival in both strata. Also, a grade shift could have been caused by the insight that Gleason scores lower than 6 should not be based on needle biopsy material, an advice stated by Epstein in 2000 and adopted by the ISUP in 2005.[32–34] However, as a decrease in prostate cancer mortality was also observed, this suggests that a genuine improvement of prostate cancer specific survival is also present.

4.5. *Mortality*

Prostate cancer mortality rates in the Netherlands have decreased since the mid-1990s. In most western European countries, a leveling-off of prostate cancer mortality rate has also been observed since the mid-1990s.[35] Another study comparing 1985–1989 with 1995–1998 found that prostate cancer mortality for males between 65 and 84 years declined by 4% in the EU and 6% in the USA.[36]

The decrease in prostate cancer mortality in the Netherlands might again be attributed to PSA testing. However, we have argued that PSA testing probably did not cause the decrease in incidence of metastasised cancer from 1993 to 1999. A similar argument can be put forward for the mortality rates although, again, we cannot support this with hard data. As the decrease in mortality started in 1996, the change most probably took place around 1990 (assuming approximately 7 years lag-time before an intervention shows an effect on mortality rates[8]) and was therefore most probably due to an increased use of DRE, TRUS and needle biopsy rather than to PSA testing. In addition to this, more precise staging and, subsequently, better treatment might also have contributed to the decrease in prostate cancer mortality. Unfortunately, it is not possible to disentangle the extent to which these factors have played a role in the observed trends.

5. Conclusion

The NCR data presented here have shown that prostate cancer incidence increased between 1989 and 2006. This increase was most likely caused by an increased application of DRE in combination with technical improvements in diagnostics (TRUS, (thin) needle biopsies), whereas the subsequent peak in prostate cancer incidence from 2000 to 2006 can be attributed to PSA testing. The decline in prostate cancer mortality from 1996 onwards may be the consequence of the increased detection of cT2 prostate cancer from 1989 to 1995. Other unobserved factors may also have played a role in causing these trends.

Prostate cancer was more often detected in an early stage and treated with a curative intent, leading to a decreased incidence of metastatic prostate cancer, a lower mortality rate and increased survival. Thus, it can be said that significant progress has been made against prostate cancer in the Netherlands. However, this progress has come at the expense of considerable overdiagnosis. With the rising burden of prostate cancer due to the ageing population, major improvements are still needed in the areas of biomarkers and detection, imaging and staging in order to avoid overdiagnosis.

Conflict of interest statement

None declared.

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