Discrepancies between guidelines and clinical practice regarding prostate-specific antigen testing

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Background. Most guidelines recommend a judicious use of prostate-specific antigen (PSA) testing, whereas in daily practice, an increase of the incidence of PSA testing has been shown. Accurate up-to-date PSA test incidence rates are, however, lacking.

Objective. To investigate the PSA test incidence rates in general practices over the past 10 years and to study which factors are associated with more frequent test use.

Methods. We performed a retrospective cohort study using the routine health care database of the Julius General Practitioners Network from 2002 to 2011, of which data were available from more than 65,000 male patients. We calculated the annual incidence of PSA testing rates per 1000 person-years. Co-morbidities were analysed by means of International Classification of Primary Care codes. Relative risks (RRs) of having a PSA test were estimated as the ratio of observed rates of co-morbidities in men who underwent the test compared with a control group, and 95% confidence intervals (CI) were calculated.

Results. From 2002 to 2011, the overall incidence rate of PSA testing in men ≥45 years increased almost 4-fold, from 15.5 to 54.3 per 1000 person-years. As from 2005, the incidence rates appear to increase more than those before 2005. Men with cardiovascular diseases, joint disorders, psychiatric diseases, respiratory diseases, overweight and diabetes mellitus were predisposed to undergo a PSA test, but men with urinary problems had the highest relative risk (RR 1.77, 95% CI 1.72–1.82).

Conclusions. From 2002 to 2011, PSA incidence testing rates increased, particularly in men with urinary symptoms and cardiovascular disease, despite several international guidelines that suggest a judicious use of PSA tests.

Keywords. Diagnostic test, epidemiology, incidence, mass screening, prostate-specific antigen, prostatic neoplasms.

Introduction

Prostate cancer is the most common non-cutaneous malignancy among men. Worldwide, it is estimated that in 2008, 903,500 new cases were presented, and 248,400 men died of the disease. In the USA, about one in six men will be diagnosed with prostate cancer during his lifetime and about 1 in 36 men will die of prostate cancer. The relatively low mortality rates are likely related to overdiagnosis and overtreatment of clinically insignificant tumours that grow slowly and are well differentiated, which is probably related to the increased use of prostate-specific antigen (PSA) tests. PSA was identified in seminal fluid in 1960 and introduced into clinical medicine in the mid 1980s. Since its introduction, the rate of PSA testing has increased tremendously. However, the test has several shortcomings. It is an unspecific serum marker with sensitivities ranging from 0.78 to 1.00 and specificities from 0.06 to 0.66. Nevertheless, it is the only widely used prostate cancer tumour marker nowadays. In contrast to previous thinking, it now seems that there is no single PSA cut-off value at which to recommend biopsy, and a continuum of prostate cancer exists across a spectrum of PSA values. No consensus exists yet regarding the translation of these results to clinical practice.
PSA screening has been extensively debated during the past few years. Two major randomized PSA screening studies [the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial], published simultaneously in 2009, showed conflicting results. While the PLCO trial showed a beneficial effect on mortality,8 the ERSPC did not. This discrepancy can be explained by differences in study design and a high contamination rate in the control group of the PLCO, which means that up to 52% of the control group also underwent PSA screening.8 However, the mortality benefit in the ERSPC was associated with a large amount of overdiagnosis and overtreatment, which can lead to an impaired quality of life due to treatment complications.

Because of the aforementioned disadvantages, the US Preventive Service Task Force recently recommended against PSA screening.10 Both European and Dutch guidelines also recommend a judicious use of PSA testing and advocate a shared decision making approach.11,12 Despite these conservative recommendations, it is known that PSA testing rates have increased in several countries.13–15 However, accurate data regarding the incidence rates of PSA tests in general practices in the Netherlands during a longer time period are lacking. Furthermore, based on our clinical experience, we hypothesized that PSA testing rates might be associated with various types of co-morbidity and maybe especially with those for which dedicated surveillance programs have been implemented during the past decade. For example, Crawford et al.16 showed that PSA testing occurred significantly more often in patients with at least one co-morbidity. As far as we are aware, nobody reported on the association between specific types of co-morbidity and screening.

Our aim therefore was to determine the PSA testing incidence rates in general practices over the last 10 years and to study which factors are associated with more frequent test ordering.

Methods

Design
We used the routine health care data as they are collected in the Julius General Practitioners Network (JGPN) database for years already to analyze the PSA incidence rates between 2002 and 2011. The part of the database we used comprises well-documented information from 25 general practice locations (80 GPs in total on average) thus including more than 65,000 adult male patients. We used readily available data of unselected patients, comprising approximately two-thirds of the total JGPN database. The patient population in JGPN is comparable to the Dutch population regarding urbanization, age and sex distribution, incidence and prevalence of different diagnoses and prescription of medication. Furthermore, the GPs in the network are representative for all Dutch GPs.11,18 Part of data (4 of the 25 locations) are collected from the academic primary care practices in the city area of Leidsche Rijn. These practice centres are members of the JGPN, but they also participate in the Utrecht Health Project. Since this project is located in a new part of the city, the population involved is relatively young and increasing; therefore, the proportion of data gathered from these practice centres grew from 10% to 25% during the 10 years we observed. Data collection for the JGPN database operates under a system of presumed consent. This means that consent will be assumed unless the inhabitant has made clear that he is unwilling to participate in providing anonymous data for research purposes. GPs recorded patient demographics, medical conditions and new disease episodes of illness in the patient’s electronic database during routine health care using the International Classification of Primary Care (ICPC).

Study population
Data from all men enlisted in the participating 25 practice centres between 2002 and 2011 were included in the study.

Outcome measures
The main outcome was the incidence rate of PSA tests performed between January 2002 and December 2011. ICPC codes of the disease episodes linked to the PSA test were analysed, and co-morbidities were included within an interval of 28 days before and after the PSA test. Based on our clinical experience, we investigated the following co-morbidities (ICPC codes): cardiovascular diseases (K71, K74, K75, K76, K77, K78, K80, K82, K83, K84, K86, K87, K89, K90, K91, K92), joint disorders (L84, L85, L86, L88, L89, L90), psychiatric diseases (P29, P76), respiratory diseases (R84, R85, R91, R95, R96), overweight (T82, T83) and diabetes mellitus (T90). Urinary problems were defined as (ICPC codes): U01, U02, U04, U05, U06, U07, U13, U29, U70, U71, Y06, Y73, Y85. From 2005 onwards, separately financed structured care for type 2 diabetes was developed and spread gradually over the network. The same happened with Chronic obstructive pulmonary disease (COPD) from 2008 onwards. Structured care for cardiovascular disease patients in general practice evolved slower and became reimbursed separately only in parts of the network after 2010.

Statistical analysis
Annual PSA incidence rates per 1000 person-years were calculated by dividing the number of PSA tests by the total number of person-years in a specific year. Relative risks (RRs) and corresponding 95% confidence
intervals (95% CIs) were calculated for different co-morbidities. Cases were considered positive for a specific co-morbidity if at least one of the corresponding ICPC codes was present. To calculate RRs, we created 2×2 contingency tables by using a control group from the same databases. Subjects were matched on contact date at the GP (2 weeks before and after the PSA test), age (2 years younger or older) and general practice. Men who underwent a PSA test in the year before and those diagnosed with prostate cancer in the past were excluded from the control group. Furthermore, subjects could be a control subject only once. SPSS software package version 18.0 was used for statistical analysis.

Results

Study population
The total size of the cohort varied from 48 856 person-years in 2002 to 67 912 person-years in 2011. The median age of the included men was 63 years (range 0–100), and this did not change substantially over time.

PSA tests
We considered a PSA of ≥4.0 ng/ml as elevated. In total, 7 258 PSA tests were carried out in 6650 men. With an increasing age, percentages of an elevated PSA raised from 0.6% in men younger than 45 to 42.2% in men older than 85. For further analysis, we only included PSA tests in men older than 45 years, leaving 6438 tests. Between 2002 and 2011, the incidence of PSA testing in men aged 45 years and older increased from 15.5 per 1000 person-years in 2002 to 54.3 per 1000 person-years in 2011 (Fig. 1), and the increase was higher as from 2005. In men aged ≥75 years, PSA testing rates increased from 29.2 per 1000 person-years in 2002 to 96.7 per 1000 person-years in 2011. Incidences of PSA screening in relation to different age categories are displayed in Fig. 2.

The top-five most common reasons for consultation related to PSA testing were (ICPC code): general disease not otherwise specified (A99), uncomplicated hypertension (K86), Diabetes Mellitus (T90), preventive respiratory immunization/vaccination (R44) and benign prostatic hypertrophy (Y85).

Co-morbidity
RRs for the various co-morbidities varied from 1.27 (95% CI 1.23–1.32) for cardiovascular diseases to 1.50 (95% CI 1.39–1.62) for overweight, i.e. overweight men had a 1.5 times higher risk to undergo a PSA test than non-overweight men. Men with urinary problems had a 1.77 times higher risk to undergo a PSA test (95% CI 1.72–1.82). In Table 1, RRs for all investigated

![Incidence of PSA tests among men ≥45 years per 1000 person-years, from 2002 to 2011](Figure 1)
Figure 3 shows the relation of different types of co-morbidities to screening incidences from 2002 to 2011.

Discussion

This database study among a large representative patient population in primary care shows an increase in the PSA test incidence rates, particularly after 2004, in the Netherlands. From 2002 to 2011, the overall incidence rate of PSA testing in men ≥45 years increased almost 4-fold, from 15.5 to 54.3 per 1000 person-years. After 2004, the incidence appears to increase more than that between 2002 and 2004, especially in men with cardiovascular diseases and urinary problems. Men with urinary problems had a 1.77 times higher risk of being tested than men without urinary problems (95% CI 1.72–1.82), but also men with other co-morbidities were more prone to get PSA testing.

This study has several strengths. We obtained information from a large database, representative for the Dutch population, over a period of 10 years. Moreover, to our knowledge, we are the first to study the relation between co-morbidities and PSA testing.

Some potential limitations should also be discussed.

First, the main limitation of using a routine health care medical database for research purposes is the

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>RR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Cardiovascular diseases</td>
<td>1.27</td>
<td>1.23, 1.31</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>1.28</td>
<td>1.23, 1.34</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.29</td>
<td>1.24, 1.35</td>
</tr>
<tr>
<td>Joint disorders</td>
<td>1.30</td>
<td>1.24, 1.36</td>
</tr>
<tr>
<td>Psychiatric diseases</td>
<td>1.31</td>
<td>1.23, 1.40</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.50</td>
<td>1.39, 1.62</td>
</tr>
<tr>
<td>Urinary problems</td>
<td>1.77</td>
<td>1.72, 1.82</td>
</tr>
</tbody>
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Cardiovascular diseases: K71 rheumatic fever/rheumatic heart disease, K74 angina, K75 acute myocardial infarction, K76 other/chronic ischaemic heart disease, K77 heart failure, K78 atrial fibrillation/flutter, K80 ectopic beats/extrasystole, K82 cor pulmonale, K83 non-rheumatic valve disease, K84 other heart disease(s), K86 essential hypertension without organ damage, K87 hypertension with organ damage/secondary hypertension, K89/TIA, K90 cerebral vascular disease, K91 atherosclerosis (ex. K76, K90), K92 peripheral artery disease. Joint disorders: L84 osteoarthritis/spondylodiscitis spine, L85 acquired deviation(s) spine, L86 low back pain with radiation, L88 rheumatoid arthritis/related condition(s), L89 coxarthrosis, L90 gonarthrosis. Psychiatric disorders: P29 other mental symptoms/complaints, P76 depression. Respiratory diseases: R84 malignancy bronchus/lung, R85 other respiratory malignancy, R91 chronic bronchitis/bronchiectasis, R95 emphysema/COPD, R96 asthma. Overweight: T82 adipositas, T83 overweight. Diabetes mellitus: T90 diabetes mellitus. Urinary problems: U01 painful urination, U02 urinary frequency/urgency, U04 incontinence, U05 other urination problems, U06 haematuria, U07 other urinary symptoms, U13 other bladder symptoms, U29 other urination problems, U70 pyelonephritis, U71 cystitis, Y06 prostate symptoms, Y73 prostatitis, Y85 benign prostatic hypertrophy.

co-morbidities are shown. Figure 3 shows the relation of different types of co-morbidities to screening incidences from 2002 to 2011.
fact that no additional information is available on the specific clinical features of patients that underwent a PSA test. The database provides only cases presented by patients to the primary care centres and what subsequently has been coded correctly into the Electronic Medical Record by GPs, nurses and assistants. We were therefore unable to correct our RRs for confounders, or to discover whether the patient, GP or practice nurse initiated PSA testing. However, our purpose was to perform a descriptive research regarding PSA testing rates in the Netherlands, regardless of detailed patient characteristics.

Second, misclassification due to missing data and differences in classification between the years and family physicians cannot be ruled out, and this may have resulted in either an overestimation or underestimation of the true incidence rates of co-morbidity. It is, however, unlikely that misclassification has affected the results substantially because over 90% of the patient contacts were coded and all participating family physicians received training regarding adequate coding.

Third, a large database with data from various parts of a primary care network was used. Participating practice centres may differ a in region and age distribution, as described in the materials and methods section. However, by comparing the PSA testing rates of both parts of the network, we found a similar trend. So we decided that pooling of the data was justified.

The overall increasing trend in PSA testing is consistent with the results of similar previous studies from both Europe and the USA. The prevalence estimates of the proportions of men who had a test in the last year vary widely across the world. It is estimated that in the USA, 51% of men aged 60–74 years had a PSA test in the last year, compared with PSA testing rates of approximately 6% in one year in the UK.
These differences might be explained by differences in the use of PSA tests in the work-up of lower urinary tract symptoms and in health check-ups. Moreover, insurance status has been shown to be associated with PSA testing.\textsuperscript{23,24} In the Netherlands, PSA tests ordered by GPs are fully covered, so the increasing trend of our study cannot be explained by the reimbursement system.

Recently, another Dutch study was published regarding the impact of the ERSPC results on PSA testing by Dutch general practitioners, which concluded that after the ERSPC publication PSA testing decreased significantly.\textsuperscript{25} However, that study only compared testing rates 12 months before and 12 months after the ERSPC publication. Moreover, a subanalysis performed in a hospital database showed no significant change in test ordering by GPs.

So far, nobody studied the association between co-morbidities and PSA testing rates. Our results show that men with different types of co-morbidities are more prone to get PSA testing, especially overweight men and men with urination problems. We assume that this finding can be explained by an increasing number of men who consult their GP concerning these problems, and then also undergo a PSA test. This might suggest inappropriate case finding. With an increase of co-morbidity and concomitant other reasons for laboratory testing, this phenomena is counterproductive. Another important observation was that PSA testing rates in men aged ≥75 years were even higher than in men aged ≥45 years. These results are in line with previous studies that also reported more frequent test ordering in older men.\textsuperscript{25,22} However, this might be the group of men less likely to benefit from prostate cancer screening. PSA screening is generally discouraged in men aged ≥75 years since early detection of prostate cancer will not have any clinical impact in these men.\textsuperscript{26}

After 2004, the incidence appears to increase more than that between 2002 and 2004, notably in men with cardiovascular diseases and urination problems. This suggests an increase in health check-up and symptom-related testing. One explanation might be that practice nurses and separately reimbursed structured care programs were implemented in primary care especially for patients with chronic diseases like type 2 diabetes, COPD and cardiovascular disease during our observation period from 2005 onwards. Patients with co-morbidity are invited and investigated more often and may, either by asking either by misapprehension of adequate case finding, have become prone to more frequent PSA testing. Another possibility is the influence of media campaigns. In 2003, preliminary results of the ERSPC were reported.\textsuperscript{27} As neither long-term follow-up data nor mortality results were presented at that time, it is unlikely that these publications have influenced PSA testing rates. In 2004, the Dutch Council of GPs published a new guideline regarding prostate cancer screening in the Netherlands.\textsuperscript{12,28} This guideline, however, recommend a judicious use of PSA tests. Other campaigns regarding prostate cancer, like Movember and Blue Ribbon, were introduced in the Netherlands in 2009 and 2007, respectively. Hence, we have to conclude that the reasons for the inflection point in PSA test ordering after 2004 are multiconditional.

Our results show that adherence among GPs to the guidelines, which recommend a judicious use of the test, could be ameliorated. Therefore, it is important to increase family physicians’ awareness on a more appropriate PSA testing. Moreover, this indicates the necessity to evaluate guidelines to improve the adherence. Furthermore, public beliefs and knowledge towards PSA testing may also be an important target in order to reduce unnecessary tests. Increasing patients’ knowledge on the advantages and disadvantages of PSA testing by patient educational materials might reduce consultation rates and, subsequently, PSA testing in daily clinical practice.

Conclusions

From 2002 to 2011, PSA incidence testing rates increased, particularly in men with urinary symptoms and cardiovascular disease, despite several international guidelines that suggest a judicious use of PSA tests.

Declaration

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Conflict of interest: none
Authors contributions:

EH participated in the database analysis, performed the statistical analysis and drafted the manuscript. DR participated in the database analysis and helped to draft the manuscript. MN participated in the design of the study, composed the database and helped drafting the manuscript. JB and JW participated in its design and coordination. MR participated in its design, coordination and statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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