PROSTATE CANCER SCREENING

The role of biopsy, PSA,

PSA dynamics and isoforms

René Raaijmakers

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VROEGOPSPORING VAN PROSTAATKANKER
De rol van biopsie, PSA, PSA dynamiek en iso-vormen

Proefschrift

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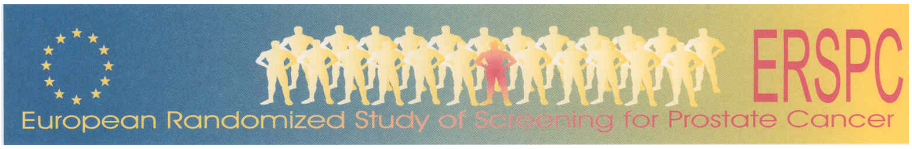

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LIST OF ABBREVIATIONS

AUC	Area Under the Curve
BLSA	Baltimore Longitudinal Study of Aging
BPH	Benign Prostate Hyperplasia
BPSA	Benign Prostate Specific Antigen
DRE	Digital Rectal Examination
ERSPC	European Randomized study of Screening for Prostate Cancer
hK2	human Kallikrein 2
iPSA	intact Prostate Specific Antigen
PLCO	Prostate, Lung, Colorectal and Ovary cancer
PCA3	Prostate Cancer Antigen 3
PCPT	Prostate Cancer Prevention Trail
PPV	Positive Predictive Value
pPSA	pro PSA
PSA	Prostate Specific Antigen
PSAV	Prostate Specific Antigen Velocity
PSADT	Prostate Specific Antigen Doubling Time
ROC	Receiver Operator Characteristics
TRUS	Transrectal Ultrasound

PART I

Chapter 1: Introduction, scope and outline of the thesis

Chapter 2: Diagnostic tests in screening for prostate cancer

INTRODUCTION, SCOPE AND OUTLINE OF THE THESIS

1

Introduction

"I believe it is no exaggeration to point out to all men around the age of 50 the advantage of an examination of the prostate even in the absence of symptoms as it is preferable to impugn the diagnosis than to ignore it"
Astraldi M.D. 1926

In the beginning of the past century, A. Astraldi urologist from Buenos Aires, Argentina, recognized the importance of early detection of prostate cancer and was unsatisfied with the available diagnostic tools he had to his disposal. The only diagnostic means for the urologist at that time were clinical symptoms, rectal palpation and radiographic imaging to assess bone metastases.
This motivated Astraldi to study the value of eosinophilia in prostate cancer. After concluding that this blood test was not reliable for the detection of prostate cancer because of the many diseases that could cause a variation, he was the first to perform prostate biopsy following the transrectal route [1] in order to be able to differentiate between prostate cancer, prostatitis and Benign Prostate Hyperplasia (BPH). He stated that biopsy of the prostate was at that moment the most effective way to detect prostate cancer and we still believe it is.
The research for a new marker of prostate cancer took a long way. Prostate Specific Antigen (PSA) was first demonstrated in prostatic tissue in 1970 [2]. It was purified from tissue in 1979 by Wang [3] and first measured in the serum a year later [4]. This was followed by the wide use of PSA as a clinical marker for prostate cancer in 1988 [5-8]. The availability of a simple blood test together with improved imaging of the prostate by transrectal ultrasound (TRUS) paved the way for opportunistic screening in the clinical practice and several screening programs [9]. Together with digital rectal examination (DRE), this trias prostatica (DRE, PSA and TRUS) could determine in a minimally invasive manner the need for TRUS-guided biopsy of the prostate.

Nowadays prostate cancer can be detected 11-12 years [10] before giving rise to clinical symptoms and the incidence of prostate cancer increased dramatically. As autopsy studies [11, 12] show that approximately 60% of men in their sixth and seventh decade of life have prostate cancer and generally do not die of it, the health care physicians and urologists were confronted with the problem of overdetection of prostate cancer. Over-diagnosed cancers are those screen-detected cancers which would not surface clinically during a life time. Optimal screening methods should diagnose those patients with prostate cancer who need to be treated while avoiding the diagnosis in patients who will not benefit from being diagnosed.
Important goals of the European Randomized Study of Screening for Prostate Cancer (ERSPC) are to evaluate the effect of screening on prostate cancer mortality and to determine the optimal screening methods. The impact of screening on quality of life is, especially in screening programs, an important issue. The studies in this thesis are performed in the setting of this large population-based screening study with the aim of analyzing available and new screening tools.

Scope

This thesis focuses on evaluating screening tools like DRE, TRUS, PSA, PSA dynamics, PSA isoforms and prostate biopsy for the detection of prostate cancer.
In order to optimize screening methods, some of these biomarkers and diagnostic procedures could be of value in reducing over-diagnosis and thereby have an impact on quality of life.
Whether prostate cancer screening reduces mortality is yet to be determined by producing level 1 evidence as it will be provided by the ERSPC and one other ongoing randomized trail in the near future [13].

Outline

In **chapter 2** we describe available diagnostic tests and their usefulness in early detection of prostate cancer in a screening setting. Complications of prostate biopsy and risk factors are addressed in **chapter 3**. The value of PSA dynamics, like PSA-Velocity (PSAV), PSA-slope and PSA-Doubling time (PSADT), is discussed in **chapter 4**. In **chapter 5** we evaluate the predictive value of baseline PSA progressing to PSA > 3.0 ng/ml or greater in a four year period in men who present with low PSA values at first screen. In connection with this study, **chapter 6** describes the risk of developing prostate cancer in this given 4 year period compared between the Dutch and the Japanese population. Furthermore we assess the value of percent free PSA (%fPSA) on tumour detection and tumour aggressiveness in a low PSA range in **chapter 7**. The role of biomarkers total PSA, free PSA, hK2, and their combinations in predicting minimal prostate cancer are described in **chapter 8**.

DIAGNOSTIC TESTS IN SCREENING FOR PROSTATE CANCER

2

Introduction

This chapter concerns the appropriateness of the screening tests for prostate cancer. We describe the sensitivity, specificity and positive predictive value (PPV) of commonly used diagnostic tests in prostate cancer screening. To calculate the "true sensitivity" the underlying prevalence of the disease has to be known. For most studies on prostate cancer detection, this is not the case. Therefore test characteristics are based on whether prostate cancer is detected by prostate biopsy. This is defined as "relative sensitivity".
Test characteristics of Digital Rectal Examination (DRE), Transrectal Ultrasound (TRUS) and Prostate Specific Antigen (PSA) will be discussed together with prostate biopsy and future prospectives.

Digital rectal examination
The DRE was the first method for evaluating the prostate. Early publications [14] before the PSA era, reported the PPV for DRE to be approximately 50%. A meta-analysis of more recent screening studies [15] reported a pooled PPV for DRE of only 17.3%. Pooled (relative) sensitivity and specificity were calculated to be 53.2% and 83.6% respectively over the whole PSA range.

A disadvantage of the DRE pointed out by several authors [16, 17] is inter-examiner variability irrespective of experience level. Concerning the ability of staging prostate cancer by DRE, Chodak and colleagues [18] reported a substantial clinical under staging comparing DRE outcome to radical prostatectomy specimens. Vis et al. [19] reported on "serendipity", the play of chance, when cancer is found on the opposite side of the suspected side of the prostate or when tumour volume is too small to be palpable. An other report from the same author [20] calculates that 289 DRE's and 41 biopsy procedures are needed to find one clinical significant prostate cancer in PSA range 0 to 2.9 ng/ml.

As the PPV depends on the prevalence of cancer in a certain population, it is also highly correlated to the PSA range [21]. Within the ERSPC the PSA ranges <1.0, 1.0 – 1.9, 2.0 – 2.9, 3.0 – 3.9, 4.0 – 10.0 and > 10.0 ng/ml showed an increasing PPV for DRE of 4%, 10%, 11%, 33%, 45% and 83%, respectively [22]. Others [23, 24] reported for PSA ranges <1.0, 1.0 - 2.5, 2.6 – 3.9, 4.0 – 10.0 and > 10.0 ng/ml, PPV's of 5%, 14%, 29%, 41% and 69% for white males attending a screening program in the United States of America. As these two sets of PSA dependent PPV's do not seem inconsistent, the conclusions regarding the low PPV at low PSA ranges were quite different. While the American authors concluded that the PPV of a suspicious DRE was "appreciable" in men with low serum PSA and recommended its continued use, the authors from the ERSPC concluded that DRE had "poor performance" at low PSA ranges. An intercontinental difference in mentality, medical and legal system may have led to this different interpretation.

The relatively low PPV's at low PSA ranges in combination with 50% minimal disease found when PSA <= 3.0 ng/ml [25], led to a change of protocol within the ERSPC as a whole. From February 1997 the biopsy indication was changed from PSA >= 4.0 ng/ml or positive DRE or TRUS to PSA >= 3.0 ng/ml regardless of DRE or TRUS outcome. A validation study [25] and several other studies [22, 26-31] seem to justify this omission of DRE and TRUS as a biopsy indication at low PSA ranges. However others [23, 24, 32] refer to the predictive value of DRE complementary to PSA testing and indicate that some potentially aggressive cancers may remain undetected if DRE would be omitted as a screening test at low PSA values.
The controversy about the value of DRE at low PSA values will be an ongoing issue until a conclusive evaluation of the screening tests for prostate cancer can be made after the conclusion of randomized screening studies. But recent data reporting the fate of cancers missed by this procedure over a 12 year period suggests that detection of these cancers may be safely delayed. [33]

Transrectal Ultrasound

Ultrasonography was developed as a military tool and expanded into medicine after World War II. The first applications of ultrasound in urology were established by Wild and Reid [34]. They introduced the first transducer probe in 1951 for rectal lesions, and later for ultrasonic study of the bladder. Watanabe improved the quality of the images by employing more modern techniques in 1968 [35]. In 1974 his group reported development of the "ultrasonic chair" (fig 1). The patient sat upright on a chair, while through the seat a probe equipped with an ultrasonic transducer, protruded. This probe entered the rectum for a scan of the prostate and bladder [36]. The instrument achieved commercial development and in 1977. Denis and Declerq [37] from Antwerp confirmed the former investigation results. Similar investigations were done by Squassabia in Rome and Schröder in Rotterdam [38].

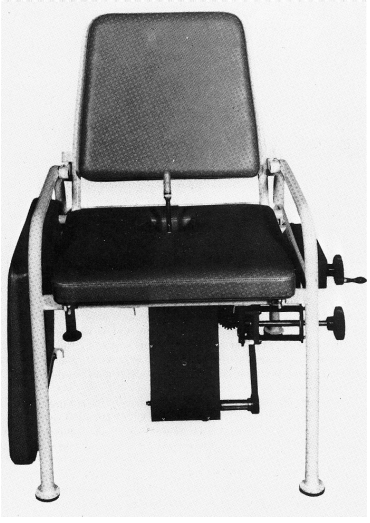

Figure 1: *The ultrasonic chair*

Since that time TRUS has undergone a continuous evolutionary process. Some of its abilities are undisputed, such as volume measurement, imaging of anatomy and for guidance of transrectal prostate biopsies. The use of ultrasonic imaging for early detection of prostate cancer or to demonstrate capsular penetration is more questionable.

The sensitivity of TRUS ranges from 17-57%. The specificity ranges from 40 to 63% [39]. The PPV of TRUS in screening programs ranges from 6.8% to 36.2% [24, 40-43] Moreover, in the PSA range below 4.0 ng/ml without a positive DRE, the PPV of the TRUS alone is 9% in the series of the ERSPC and 13% in series from Seattle [44]. In these low PSA ranges the value of TRUS is comparable to the value of DRE as a screening test for prostate cancer. However TRUS is not considered a valuable tool for screening purposes because of interobserver variations, costs and the non uniform presentation of prostate cancer. It is merely used as individual risk assessment and for guidance of prostate biopsies.

The sensitivity of TRUS detecting extraprostatic spread of cancer has been reported in several studies [45-49] and varies from 5% to 89%. The great variability in the performance is undoubtedly a reflection of different patient selection criteria, but it also denotes the operator dependent nature of the TRUS and the variability in equipment quality. The specificity distinguishing between T2 and T3 (extracapsular) prostate cancer in a later study was reported to be 42% [50]. Owing to limits of resolution and the fact that most pathologic upstaging is due to microscopic capsular extension, the value of TRUS in staging seems limited. More promising results have been reported from 3 Tesla MRI with endocoil and Dynamic Contrast Enhanced MRI with specificities of 88% and 97%, respectively [51, 52].

Personal test results on DRE and TRUS

The PSA dependent value of DRE and TRUS is also illustrated by personal test characteristics on DRE (Table 1) and TRUS (Table 2).

Table 1. Personal test values on DRE (n=1794)

PSA range (ng/ml)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*
< 2.0	-	-	-
2.0 - 3.0	14.5	90.7	21.1
3.0 - 3.9	14.8	89.3	23.5
4.0 - 9.9	26.8	82.5	38.7
>= 10.0	52.4	80.2	61.1
Total	25.5	86.3	33.5

Table 2. Personal test values on TRUS (n=1794)

PSA range (ng/ml)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*
< 2.0	-	-	-
2.0 - 3.0	7.2	88.9	10.0
3.0 -3.9	20.4	84.1	27.3
4.0 - 9.9	28.7	86.0	36.4
>= 10.0	40.5	70.4	44.7
Total	24.1	85.9	31.6

Table 3 compares individual test characteristics of several investigators within the second and third screening round of the Rotterdam section of the ERSPC. In order to make the tests more comparable the results of the initial screening round and men with PSA < 3.0 ng/ml, were not taken into account.

Table 3. Test characteristics of different investigators (A, B, C, D and E) on DRE and TRUS

	DRE			*TRUS*		
Investigator	*Sensitivity*	*Specificity*	*PPV*	*Sensitivity*	*Specificity*	*PPV*
	(%)	(%)	(%)	(%)	(%)	(%)
A	23.9	84.7	24.8	26.3	82.0	25.1
B	48.3	67.1	19.7	25.0	85.9	21.4
C	25.2	79.3	23.0	22.9	81.3	25.5
D	47.6	68.8	20.0	37.8	83.7	26.9
E	32.4	83.4	33.8	11.3	92.1	27.6

Prostate Specific Antigen

In the prostate, PSA is mainly secreted by the epithelial cells and is also present in prostate cancer cells. It is added to the semen and lyses the gel formed by seminogelins after ejaculation. The mechanism by which PSA leaks to the serum is unclear. Current opinion is that disturbance of the normal structure of the prostate with obstruction of prostatic acini and ducts induce leakage of PSA to the capillary blood. This hypothesis is supported by elevated PSA levels in the serum in conditions like BPH, prostatitis, prostate manipulation and prostate cancer.

The use of PSA in screening for prostate cancer was first described in 1991 by Catalona and colleagues [9]. They concluded that the combination of measurement of the PSA and performing rectal examination provided a better method of detecting prostate cancer than rectal examination alone. Since its introduction PSA has become a widely used test for the early detection of prostate cancer. Its use resulted in earlier prostate cancer detection and an increase in incidence. Whether PSA testing lowers prostate cancer mortality may be fully answered within several years.

In 2004 Stamey claimed that the PSA era is over [53]. As histological cancer parameters of radical prostatectomy specimens, specifically the volume of prostate cancers, loose their significant relationships with PSA over the years and prostatic size becomes the only predictor of PSA level in the last years. He suggests that PSA is only related to benign prostatic hyperplasia.
In the same year the data of the Prostate Cancer Prevention Trail (PCPT) [54, 55] gave way to discussion about the value of PSA and PSA cut-offs. In this study in which finasteride was compared to placebo, each participant in the placebo group underwent a biopsy procedure when PSA exceeded 4.0 ng/ml or when an abnormal DRE was palpated. End of study biopsies ensured a reliable biopsy-derived prevalence of prostate cancer in the placebo group. The prevalence of prostate cancer in men in the placebo group with PSA lower than 4.0 ng/ml was 18.7%. And 16.9% of these cancers contained high grade cancer (Gleason score >= 7). Even within this low PSA range, PSA level was a continuous directly related predictor of prostate cancer risk. No threshold could be identified below which no (high grade) cancer could be detected. Rather, there is a continuum of increasing risk with increasing PSA values. Patients and the health care community should no longer think of PSA values being dichotomous ("normal or abnormal") but see the PSA measurement in the light of other predictors of prostate cancer like family history, age, DRE, TRUS and (inversely related) prostate volume and IPSS. Instead of using PSA cut-offs and in order to help the patient and clinician to decide whether or not to undergo a prostate biopsy, a risk calculator based on the ERSPC data is available through the internet on www.uroweb.org and www.prostaatwijzer.nl.
Due to the lack of specificity of PSA and the inability to predict prostate cancer aggressiveness, other PSA related isoforms are under investigation.

PSA isoforms

Free PSA (fPSA)

Total PSA is composed of complexed PSA and free PSA. The largest portion of PSA in the serum is complexed to alpha-1-antichymotrypsine and a smaller part to alpha-2-macroglobulin. Uncomplexed PSA constitutes 5 to 50% of total PSA and is termed free PSA. In itself free PSA is composed of three subforms (fig 2). Pro-PSA (pPSA) is identified as the pro-enzyme or precursor form of PSA associated with cancer. Benign PSA (BPSA) is an internally cleaved or degraded form of PSA associated with benign transition zone prostate tissue and intact PSA (iPSA) is similar to native PSA but enzymatically inactive due to structural or conformational changes. As BPSA and iPSA are lower in cancer cases, free PSA is also expected to be lower in men with prostate cancer. Percentage free PSA is the ratio of free PSA and total (complexed and free) PSA, and is lower in men with prostate cancer [56].

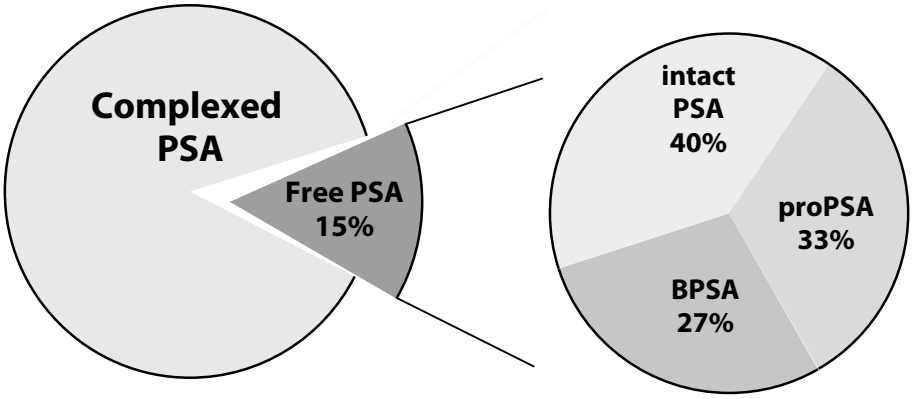

Figure 2: *Pie chart of total and free PSA (from S. Mikolajczyk)*

human Kallikrein 2 (hK2)

The PSA gene is a member of a human tissue kallikrein gene family that comprises 15 serine proteases encoded by a cluster of genes on chromosome 19q3 [57]. The genes are numbered hKLK1-15 and the corresponding proteins hK1-15. PSA is identical with hK3. hK2 is another prostate specific protease from the same family and shares 80% sequence homology. Serum concentrations of hK2 are 50 to 100 fold lower than those of PSA. While the expression of free PSA tends to decrease with increasing tumour grade, hK2 increases or remains constant. Results from tissue studies observed changes in the relative expression of hK2 versus PSA in process of carcinogenesis and prostate cancer progression. It was hypothesized that hK2 might be a useful biomarker especially for advanced and aggressive disease [58].

Prostate Biopsy

The diagnosis of prostate cancer can only be established following histologic evaluation of prostatic tissue. The earliest mention in literature of prostate biopsy was around 1900 when Mixter confirmed the diagnosis of prostate cancer by transperineal needle puncture and aspiration. In 1920 Goeller designed a transperineal prostate puncture device with a cutting point and a spiral. As mentioned in the introduction of this thesis, Astraldi was the first to use the transrectal approach. He used a trocar extractor device (fig 3) with a cutting edge and retrieved the biopsy material.

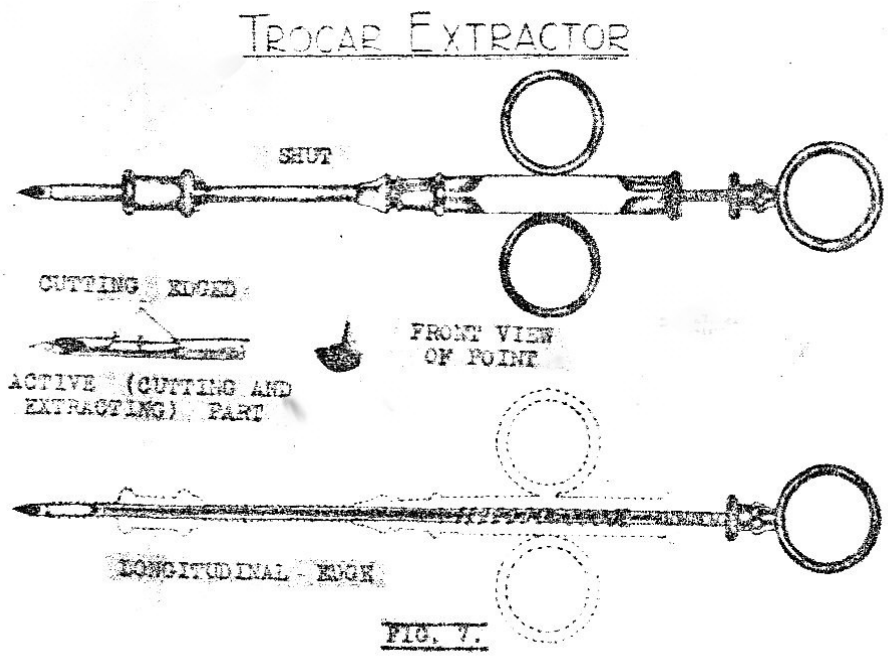

Figure 3. *The trocar extractor Astraldi used to perform the first prostate biopsies by rectal route*

The introduction of PSA generated a dramatic increase in the number of patients requiring prostate sampling. This stimulated the development of spring loaded biopsy guns which converted prostate biopsy into a quick outpatient clinic procedure without the need for systemic anaesthetics. The digitally directed biopsies of suspicious prostatic nodules were soon becoming obsolete after the development of high frequency transrectal ultrasound. In 1989 Hodge and colleagues [59] introduced the systematic sextant transrectal ultrasound guided biopsy (fig 4). This description took much of the subjectivity out of prostate biopsies and was called 'traditional' sextant biopsy later in time.
As 68 - 75% of the carcinomas are situated in the peripheral zone of the prostate [60] and because prostate cancer has a more transverse spread than posterior-anterior spread [61] the ERSPC applied laterally directed sextant biopsies (fig 5).

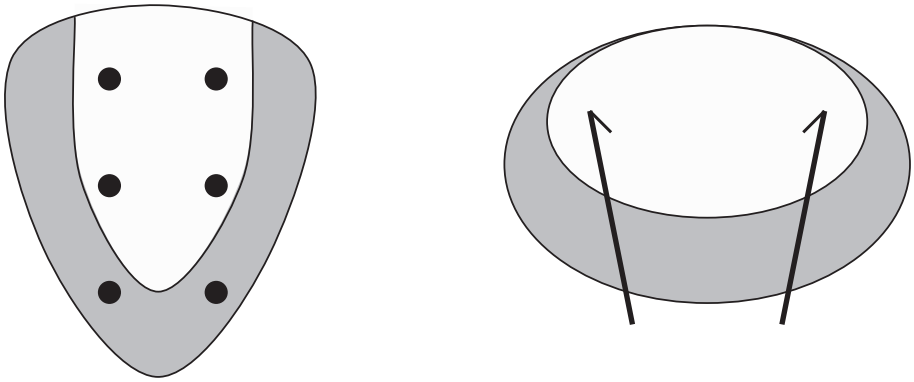

Figure 4: *Systematic sextant biopsy of the prostate*
Grey= peripheral zone, White : Central gland (consists of transition zone and central zone)

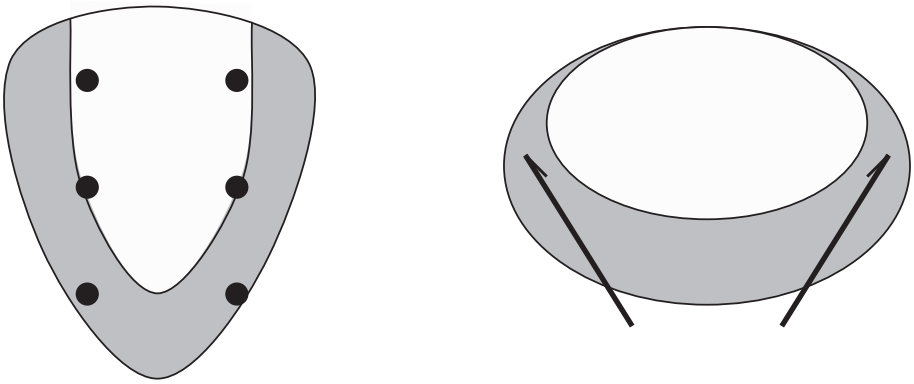

Figure 5: *Laterally directed sextant biopsy of the prostate*

Eskew et al. [62] proposed a 5 region scheme of prostate biopsies incorporating the traditional sextant biopsy with two more lateral directed biopsies on each site and three centrally placed biopsies (fig. 6). He also tested a 13-core regimen.

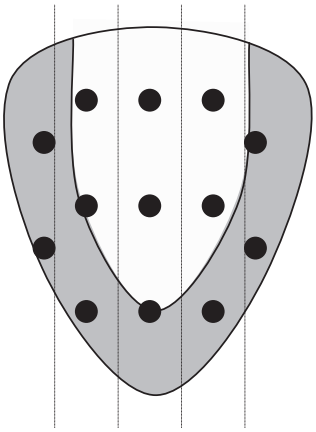

Figure 6: *Ten core biopsy scheme according to Eskew with 5 (longitudinal) regions*

The 12-core biopsy combines the traditional sextant biopsy with six laterally directed biopsies (fig 7). Presti et al. [63] analyzed the cancer yield of each of the 12 biopsy cores combining traditional with laterally directed sextant biopsy and proposed this 'optimal' 10-core biopsy scheme, omitting the two base cores of the traditional sextant biopsy (fig 8).

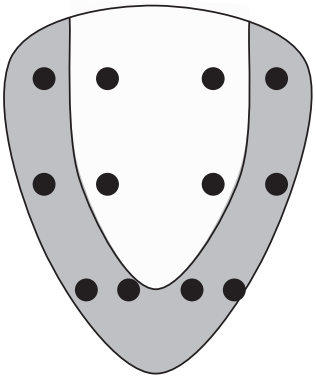

Figure 7: *Twelve core biopsy*

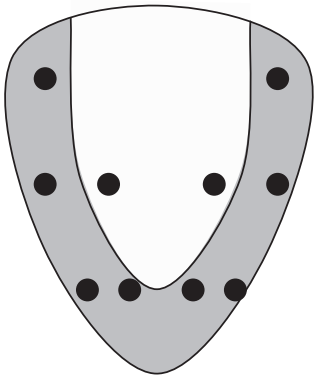

Figure 8: *Ten core biopsy by Presti*

The repeat biopsy rate has risen since the introduction of sextant biopsies. This is largely due to growing appreciation of the relatively high false-negative rates of biopsies. Repeat biopsies should be recommended for patients in whom an initial set of biopsies did not reveal cancer but in whom suspicion is high for the presence of malignancy. Such patients include, but are not limited to, those with a very high PSA level or a rapidly rising PSA level and those with a family history of prostate cancer. Many patients receiving repeat biopsies may require an additional session of repeat biopsies because the rate of cancer detection on the third set of biopsies is up to 30% [64].

Saturation biopsy has been proposed for men with persistent high suspicion for prostate cancer after previous negative sextant biopsies [65] and repeat biopsies. Depending on prostate volume the entire prostate is punctured up to 45 times in the operating room with anaesthesia support. Detection rate is approximately 34% and the complication rate is generally high.

The goal of prostate biopsy should be to maximize the certainty to diagnose life threatening tumour using the minimum number of cores possible in order to avoid the detection of clinically insignificant tumours. Vashi et al. [66] have created a mathematical model depending on age and prostate volume. Increasing age decreases the probability of finding a life threatening tumour and prostate size is inversely related to the probability of detecting a fixed tumour volume [67, 68]. Therefore the number of biopsies needed to detect a significant tumour is dependent upon these critical determinants. The recommended number of cores per prostate biopsy is summarized in table 4.

Table 4. Number of cores per biopsy needed based on age and prostate volume (Vashi JoU 1998)

	Patient age (yrs)					
Prostate volume (ml)	50	55	60	65	70	75
10	8	5	4	3	2	2
20	15	10	7	5	4	3
30	23	15	10	7	5	4
40		20	13	9	7	5
50			17	11	8	6
60			20	13	10	7
80				18	13	9

Another table is used for determining the number of cores per biopsy procedure with 90% certainty of cancer detection in function of prostate size and tumour size (table 5).

Table 5. Number of cores per biopsy to ensure 90% certainty of cancer detection depending on prostate volume and tumour volume (Vashi, JoU 1998)

	Tumour volume (ml)								
Prostate volume (ml)	0,1	0,5	0,75	1	1,5	2	3	5	8
10	10	5	4	3	3	2	2		
20	20	9	7	6	5	4	3	2	2
30		14	11	9	7	6	5	3	2
40		18	14	12	9	8	6	4	3
50			17	15	11	9	7	5	4
60				17	13	11	9	6	4
80					18	15	11	8	6

Future prospectives

The limitations of PSA as a biomarker for prostate cancer screening are the low specificity and the inability to distinguish between indolent and more aggressive prostate cancer. The need for biomarkers which are more specific and more selective for aggressive prostate cancer is evident. In response to this demand, several newer potential biomarkers have been identified and some are already being evaluated for detection and prognostic purposes.

Prostate Cancer Antigen 3 (PCA3), a non-coding mRNA is prostate specific and is highly expressed in prostate cancer specimens. PCA3 mRNA levels can be measured in the urinary sediment after a DRE. After normalisation to the urine PSA level a PCA3 score is obtained. First publications [69-72] report a large area under the ROC-curve of 72 - 87%. The value of PCA3 in predicting the outcome of repeat biopsies [73], was expressed with an AUC of 68%. A multicenter publication [74] reported an AUC of 66%. All the authors report far better test results compared to PSA.

Up to now all studies were performed using a PSA based population. Within the ERSPC Rotterdam a side study is launched in which the biopsy indication is depending on the PCA3 score only. Cut-off is PCA3 score > 10 (82% of the population), regardless of the PSA level. At this moment the PCA3 assay is commercially available and used as an aid in deciding whether repeat biopsies are indicated.

Another field of investigation are the gene fusion proteins. In approximately 60% of the prostate cancer patients there is a fusion between TMPRSS2 (androgen-regulated gene) and ERG (oncogene). In a pilot study [75] of 19 patient with prostate cancer, 42% of the patients had the TMPRSS2:ERG gene fusion detected. The assay was only directed towards one of the TMPRSS2:ERG isoforms, although this isoform is the most commonly detected in patients with TMPRSS2 fusions with members of the ETS family (for example ERG, ETV1). Another publication [76] demonstrated that 23 of the 29 prostate cancer samples had TMPRSS2: ETV1 fusions or ERG rearrangements.

Hessels and coworkers [77] tested both PCA3 and TMPRSS2:ERG on prostate cancer detection and conclude that the combination increases the test's sensitivity from 62% for PCA3 alone to 73% for the combination.
In a even more recent study [78] a multiplex biomarker analysis with several genes, PCA3 and TMPRSS2:ERG outperformed the PCA3 test alone (AUC 0.758 vs. 0.663 for PCA3).
Single marker tests ignore the heterogeneity of cancer development and may only detect a proportion of the prostate cancers, especially when not all prostate cancers express for example the TMPRSS2:ERG gene fusion. Best sensitivity and specificity can be obtained by the combination of several biomarkers and patient characteristics in multiplex panels and nomograms.
The P-Mark project aims to evaluate a large set of novel biomarkers and evaluate them for their clinical relevance. The markers that prove their clinical value will be validated together on a sample set from two European screening studies.

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PART II

Chapter 3: Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program.

Chapter 4: PSA change in the European study of screening for prostate cancer, section Rotterdam

Chapter 5: 4-year prostate specific antigen progression and diagnosis of prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam

Chapter 6: Prostate carcinoma detection and increased prostate-specific antigen levels after 4 years in Dutch and Japanese males who had no evidence of disease at initial screening.

Chapter 7: Prostate Cancer detection in PSA-range 2-3.9 mmol/l - Value of percent free PSA on tumour detection and tumour aggressiveness.

Chapter 8: hK2 and Free PSA, a Prognostic Combination in Predicting Minimal Prostate Cancer in Screen-Detected Men within the PSA Range 4-10 ng/ml.

COMPLICATION RATES AND RISK FACTORS OF 5802 TRANSRECTAL ULTRASOUND GUIDED SEXTANT BIOPSIES OF THE PROSTATE WITHIN A POPULATION BASED SCREENING PROGRAM.

3

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ABSTRACT

Objectives. Biopsy of the prostate has to be a relatively safe procedure and the participants have to be well informed about possible complications. Evaluation of complication rates and possible risk factors helps to improve the counselling of the patient and the safety of the procedure.

Methods. Within the biopsy protocol of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC), we evaluated 5802 transrectal ultrasound (TRUS) guided systematic sextant biopsies. All participants received prophylactic antibiotic therapy.

Results. We performed 5802 biopsy procedures. Haematuria lasting longer than 3 days and haematospermia were present at 22.6% and 50.4% of the procedures. More severe complications were far less frequent. Two-hundred participants (3.5%) developed fever after biopsy. Urinary retention was seen 20 times (0.4%) and hospitalization was needed in 27 cases (0.5%). Twenty-five of these men were admitted because of signs of prostatitis and/ or urosepsis.
Risk factor analyses revealed that an earlier episode of prostatitis was significantly associated with hospital admission and pain after biopsy. Characteristics of prostate hyperplasia like prostate volume, the transitionzone volume/ total prostate volume ratio and a higher International Prostate Symptom Score (IPSS) were all predictors of urinary retention.

Conclusions. Minor complications are seen frequently and major complications are rare. Assessments of risk factors before biopsy can help to improve the adequacy of counselling and precautionary measures can be taken to minimize the risk of complications after the procedure. TRUS guided sextant biopsy remains a safe procedure for the diagnosis of prostate cancer within the general population.

INTRODUCTION

Since the beginning of the past century biopsies of the prostate were used to diagnose prostate cancer. Encouraged by the excellent results of surgical opening of prostatic abscesses by the rectal route, Astraldi [1] was the first to apply the transrectal approach. In 1937 he stated that biopsy of the prostate is the most effective means to diagnose prostate cancer and we still think it is. TRUS guided systematic sextant needle biopsy of the prostate is considered a safe and common practice with few major but frequent minor complications [2, 3].

Although the outcome whether prostate cancer screening is effective in reducing mortality is to be determined, it is expected that the number of biopsy procedures performed in a generally healthy population will be growing. Within the ERSPC Europe-wide approximately 12,000 biopsies were performed so far. Because participation is on a voluntary basis in generally asymptomatic men, it is important that the screening and biopsy procedure is safe and well tolerated. Evaluation of complication rates and possible risk factors on large numbers is necessary to improve the safety and acceptance of the biopsy procedure. This also provides necessary information for adequate counselling, which is obligatory not only in a screening population but also in a clinical setting [2].

We have the opportunity to evaluate large numbers of prostate biopsies in a screening population. All biopsied participants received uniform treatment. Most studies on this subject give no or limited information on possible risk factors. We performed statistical analyses in order to determine risk factors on several complications.

MATERIAL AND METHODS

In the European Randomized study of Screening for Prostate Cancer, section Rotterdam, 41,925 men between 54 and 74 years old were randomized between the screening and control arm. They all signed an informed consent form. Of the 20,979 men randomized to the screening arm, 19,970 men (95.2%) filled out a prescreening questionnaire, an International Prostate Symptom Score (IPSS) form and had a serum prostate specific antigen (PSA) measurement done. These men were initially invited to the remaining two screeningtests: digital rectal examination (DRE) and transrectal ultrasonography (TRUS). Biopsy indication was originally set at a PSA cut-off value of 4.0 ng/ml or a suspicious DRE and/ or TRUS, independent of the PSA value. Halfway the first screening round a PSA cut-off value of 3.0 ng/ml was used as a biopsy indication, regardless of DRE and TRUS findings [4]. When no prostate cancer was found the participants were re-invited after four years for the second round. Currently, second and third round screening procedures are being performed.

We performed 6013 biopsies in 4943 men. This includes 211 additional repeat biopsies because of high-grade prostatic intra-epithelial neoplasia or suspicious for malignancy outcome of the first biopsy. The repeat biopsies were not taken into the evaluation because of a possible selectionbias. This leaves 5802 first sextant biopsies to evaluate.

All biopsies were performed by a resident urologist in an outpatient setting. No pre-biopsy cleansing enemas were used and the procedure was performed without anaesthesia. Acetylsalicylic-acid or oral anticoagulants were stopped 7 to 10 days before biopsy, after approval of the subscribing physician.
Participants were prescribed trimethoprim-sulfamethoxazole 960mg, before and after biopsy, as prophylactic antibiotic therapy. If the men were insulin dependent diabetics or recently used prednisone, they received ciprofloxacin prophylaxis. Five-hundred milligram before and after biopsy, and 500mg once a day for five consecutive days after biopsy.
TRUS was performed using a Bruel & Kjaer model 1846 mainframe and a 7 MHz biplanar endorectal transducer with the participant in the left lateral decubitus position. Prostate volume and transition zone volume were measured using a 5 mm step section planimetry. The systematic sextant biopsies were taken according to the technique which Torp-Pedersen et al. described previously [5]. An additional seventh biopsy was done in case of a hypoechoïc lesion.
Two to three weeks later when the participant was seen to discuss the biopsy outcome, a questionnaire regarding complications after biopsy was filled in by a staff-urologist. Fever above 38.5°C, haematuria longer then 3 days, haematospermia, pain after biopsy, medication use, hospital admission and other complications were recorded.
Correlations between complications and risk factors were analyzed by means of the Spearman correlation coefficient for ordinal variables and Pearson correlation coefficient for continuous distributed values. $P<0.05$ was considered statistically significant.

RESULTS

Cancer detection

Between June 1994 and August 2001, 27,556 screening procedures were performed in the first and second round. After 5802 biopsy procedures a total of 1321 (22.8%) prostate cancers were detected. No large differences in complication rates were seen between the rounds.

Complication rates

Of the 5802 biopsy procedures, 5676 (97.8%) post biopsy questionnaires were filled in by the staff-urologist. The complications were divided into two groups. Minor complications were defined as expected side effects of the biopsy procedure, causing minimal or no discomfort and requiring no additional treatment. Major complications were defined as adverse effects causing significant discomfort, disability or requiring additional treatment.
The most frequent minor complication was haematospermia (50.4%). Haematuria longer than three days was present in 22.6% of the participants.
Major complications were seen far less frequently. Two-hundred men (3.5%) developed fever after biopsy. Twenty men (0.4%) were diagnosed with urinary retention. Other complications are shown in table I.

Hospital admissions

Twenty-seven men (0.5%) were admitted at the hospital. Twenty-five of these admitted men (92.5%) were hospitalized because of signs of prostatitis and/ or urosepsis. One of them was admitted at the intensive care unit because of signs of a septic shock. All men received intravenous antibiotic therapy and recovered from the fever within days.

Table 1. Complication rates

	n	*%*
Number of biopsy procedures	*5676*	
Minor complications		
Haematuria > 3 days	1280	22.6%
Haematospermia	2858	50.4%
Rectal bleeding	75	1.3%
Voiding problems	48	0.8%
Major complications		
Pain after biopsy	286	7.5%
use of analgesics	18	0.3%
Fever	200	3.5%
use of antibiotics	187	3.3%
Hospitalization	27	0.5%
Urinary retention	20	0.4%
Nausea/ sickness	17	0.3%
Allergic reaction on antibiotic prophylaxis	6	0.1%
Epididymitis	4	0.07%
Perineal swelling/ haematoma	4	0.07%
DVT after stopping anticoagulant therapy	1	0.02%
Starting hernia inguinalis	1	0.02%
Temporary faecal incontinence	1	0.02%

Blood cultures were taken 23 times, 18 were positive for bacterial growth and 13 times the same bacteria were detected in the urine culture. Of these men with a proven urosepsis, Eschericha coli was the causing pathogen ten times. Nine were resistant against the antibiotic prophylaxis provided. Pseudomonas aeruginosa was detected twice and Klebsiella oxytoca once. The other two hospital admissions were because of cardiac arrhythmia and diverticulitis of the sigmoïd. Both patients recovered fully.

Risk factors

The complications and risk factors we evaluated are shown in table II. The possible risk factor of having prostate cancer has been left out of the analyses because of the supposed confounding influence of receiving the cancer diagnosis at the same time as the complications questionnaire is filled in. To determine whether a risk factor was associated with a complication we performed correlation analyses. When more than one risk factor was significantly correlated with a complication, a multiple regression analysis was performed to adjust for the effect of other independent variables.

Table 2. Correlations of risk factors and complications

Risk factor	*Correlation coefficient R (p-value)*							
	Haematuria > 3 days	*Haemato-spermia*	*Fever > 38.5°C*	*Pain after biopsy*	*Hospital admission*	*Urinary retention*	*Voiding problems*	*Rectal bleeding*
Diabetes	-0.004 (0.745)	-0.015 (0.259)	0.002 (0.906)	-0.018 (0.166)	-0.004 (0.773)	0.000 (0.984)	-0.003 (0.807)	-0.019 (0.149)
TUR-p earlier	-0.003 (0.842)	-0.109 (<0.001)•	0.011 (0.412)	0.003 (0.817)	0.031 (0.024)	0.026 (0.058)	0.013 (0.347)	0.000 (0.982)
Prostatitis earlier	0.023 (0.106)	-0.016 (0.270)	0.014 (0.342)	0.032 (0.024)•	0.035 (0.014)•	0.016 (0.275)	0.025 (0.081)	-0.004 (0.770)
Prostatitis in biopsy	0.009 (0.516)	-0.034 (0.010)	-0.004 (0.790)	0.029 (0.027)	-0.014 (0.301)	0.011 (0.401)	0.009 (0.478)	-0.011 (0.396)
Additional 7th biopsy	-0.016 (0.229)	0.007 (0.620)	-0.007 (0.573)	-0.004 (0.769)	0.017 (0.211)	-0.013 (0.340)	0.011 (0.391)	-0.011 (0.394)
Age	-0.005 (0.680)	-0.228 (<0.001)•	-0.010 (0.431)	-0.046 (<0.001)•	0.003 (0.832)	0.015 (0.265)	-0.016 (0.232)	-0.001 (0.916)
Prostate volume	0.096 (<0.001)•	-0.058 (<0.001)	0.003 (0.842)	0.011 (0.406)	0.013 ((0.344)	0.035 (0.009)•	0.009 (0.506)	-0.005 (0.727)
Transitionzone volume/ total vol.	0.049 (<0.001)	-0.078 (<0.001)•	0.020 (0.128)	-0.024 (0.074)	-0.090 (0.594)	0.027 (0.040)•	0.020 (0.138)	-0.024 (0.077)
IPSS	0.001 (0.962)	-0.020 (0.156)	0.005 (0.736)	-0.020 (0.408)	0.031 (0.025)	0.063 (<0.001)•	0.021 (0.139)	-0.004 (0.794)

• *still predictive after multivariate logistic regression.*

Haematuria was significantly correlated with larger prostate volume and an increasing ratio of transitionzone volume/ total prostate volume. After multivariate logistic regression only prostate volume remained significant correlated. The inversely correlation of advanced age, previous transurethral resection of the prostate (TUR-p) and larger transitionzone volume/ total prostate volume ratio, indicates that these risk factors are associated with less haematospermia. The first can possibly be explained by less sexual activity with increasing age and pre biopsy retrograde ejaculation must be the reason for less haematospermia after a previous TUR-p. No risk factor could be correlated to fever. A previous prostatitis is associated with pain after biopsy and hospital admission. Characteristics of prostate hyperplasia like prostate volume, the transitionzone volume/ total prostate volume ratio and a higher IPSS were all predictors of urinary retention. Aging seems to be correlated with less pain after biopsy and less haematospermia.

COMMENTS

TRUS-guided systematic sextant biopsy of the prostate is considered a standard procedure. To minimize morbidity and maximize safety and counselling information, continuous evaluation of complication rates and potential risk factors is necessary. This study is an update of earlier results published by Rietbergen et al. [6] in the same screening program.

The results of other recent publications on complication rates are shown in table III. Comparisons must be made with caution because of differences in sample size, population, biopsy protocol, definitions of complications and follow up. Percentages on fever, hospital admission and haematuria are comparable with those reported in literature. Urinary retention seems to appear less often in this population. Performing biopsy procedures in a generally healthy screening population may be the explanation. We found a large percentage of men with haematospermia (50.4%).

When reviewing these percentages in literature we see a large variation from 9.1% to 78.3% of the men reporting blood in the semen. Peyromaure et al. [7] were to our knowledge the only who also asked for having sexual intercourse in their post biopsy questionnaire. This was filled in at least one month after biopsy. Their large percentage (78.3%) relates to the number of men with haematospermia as a proportion of the men who had a sexual relationship at that time. When taken as a proportion of all of the men that could be evaluated on haematospermia, in 54.9% of men blood was seen in the semen. The large difference between these two percentages is due to men who did not have an ejaculation within the time of follow up. This may well explain the large differences of reporting haematospermia in literature. To report a reliable percentage on haematospermia, the question on having seen blood in the semen should be preceded by a question whether the man had an ejaculation during the follow up period.

Table 3. Review of recent literature.

Author (reference)	Year	No. Men	No. Biopsy cores	Enema	AB	Fever	Adm.	HU	HS	RB	RET
Rietbergen (6)	1997	1687	6-7	N	Y	4.2%	0.4%	23.6%	45.4%	1.7%	0.4%
Sieber (15)	1997	4439	6-8	N	Y	n.a.	<0.1%	n.a.	n.a.	n.a.	n.a.
Enlund (16)	1997	426	1-8	Y	N	2.9%	0.7%	21%	n.a.	21.7%	0.2%
Rodriguez (8)	1998	129	6-?	Y	Y	1.7%	0.8%	47.1%	9.1%	8.2%	1.6%
Deriveliotis (3)	1999	120	6	N[1]	Y	6.6%	1.6%	10.0%	29.1%	33.3%	4.6%
Manseck (20)	2000	162	10	n.a.	Y	0.6%	0%	17.9%	19.8%	4.9%	0
Djavan (18)	2001	1015	8	n.a.	Y	3.0%	n.a.	15.9%	9.8%	2.1%	2.6%
Peyromaure(7)	2002	289	10	Y	Y	3.7%	0%	74.4%	78.3%[2]	39.6%	n.a.
Present	2002	5802	6-7	N	Y	3.5%	0.5%	22.6%	50.4%	1.3%	0.4%

AB=antibiotics ; Adm.= admission at hospital; HU=haematuria; HS=haematospermia; RB=rectal bleeding; RET= urinary retention; N= no; Y= yes
n.a.=not available
[1] no enema but authors cleaned anterior rectal wall with antiseptic.
[2] percentage HS of the men who reported sexual intercourse.

Several studies on complications after prostate biopsy attempted to identify risk factors [6, 8-12]. Rodriguez et al.[8] conducted a prospective study in which several choices of antibiotic prophylaxis, number and sites of biopsies were used. The possible confounding effect of receiving the disturbing news of prostate cancer and reporting complications after biopsy at the same time was eliminated by conducting interviews before biopsy outcome was revealed. They found an association between the number of biopsies and the presence of fever. We did not find a correlation between the number of biopsies and any of the complications. No association of fever or chills with a history of urinary tract infections was found in their study. This is in accordance with our results. The authors also concluded that having prostate cancer was no risk factor for any of the complications, which supports our decision to leave out prostate cancer as a risk factor in the correlation analysis.

The use, type and duration of antibiotic prophylaxis are thoroughly discussed in literature. Placebo controlled studies [13, 14] report a benefit for antibiotic prophylaxis versus placebo in preventing signs of urinary tract infection. Sieber et al. [15] promoted the use of quinolones with a urinary tract infections rate of less than 0.1%. In his retrospective chart review study however no percentages of men with fever without the evidence of a positive urine culture are mentioned. Enlund and Varenhorst [16] did not prescribe any antibiotic prophylaxis and reported 2.9% of fever. We found a comparable 3.5% fever and a 0.5% admittance rate using a prophylaxis regimen of trimethoprim-sulfamethoxazole. Ciprofloxacin prophylaxis is only used in clinical patients and participants with a supposed higher risk of infectious complications (Insuline Depended Diabetes Mellitus and recent prednisone use) [12]. In our opinion prevention of development of resistant bacterial strains of this antibiotic is essential when performing a large screeningstudy in a relative small region. The finding that nine out of ten men with proven E. coli urosepsis caused by a trimethoprim-sulfamethoxazole resistant E. coli strain is put into perspective when considered the high number of biopsies without fever. Nonetheless, we now also prescribe ciprofloxacin prophylaxis when a history of infectious complications after prostate biopsy is recorded.

Although the biopsy procedure is generally associated with mild or no discomfort, several studies report a percentage of men with significant pain at biopsy ranging from 9.1% to 30% [2, 7, 17]. Some authors describe a clear relationship between the amount of discomfort and patient age with younger men experiencing more discomfort than older men [8, 18]. Our study confirms these findings. A recent survey of Davis et al. [19] among American urologists revealed that 33% of the responding urologist used no pre-biopsy anaesthesia. Analgesia or anaesthesia used by the remaining urologists were oral, parental, rectal suppository or gel or periprostatic nerve block. Whether there is a place for local anaesthesia in transrectal ultrasound biopsy remains to be determined. As the number of young men undergoing prostate biopsy and the number of biopsy cores increases, some type of analgesics or local anaesthetics may be useful to further reduce the amount of discomfort or pain at biopsy.

Pain after biopsy tends to be more severe in younger men and after an earlier prostatitis, according to our results. In pre biopsy counselling, men with these higher risks could be encouraged to take oral analgesics in case of pain after biopsy.

CONCLUSIONS

Minor complications like haematuria and haematospermia are frequently reported but are defined as expected side effects of the biopsy procedure. Major complications were in this large population represented in low percentages. Risk factors cannot be identified for the development of fever but anamnestic information like a previous history of prostatitis provides predictive information on pain after biopsy and hospital admission. Also prostate volume, the ratio transitionzone volume/total prostate volume and a high IPSS have a significant correlation with urinary retention. Assessments of risk factors before biopsy could help to determine whether a patient has an elevated risk to develop major complications. This knowledge can help to improve the adequacy of counselling and precautionary measures can be taken to minimize the risk of complications after the procedure. TRUS guided sextant biopsy remains a safe procedure for the diagnosis of prostate cancer within the general population.

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PROSTATE SPECIFIC ANTIGEN CHANGE IN THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER, ERSPC (SECTION ROTTERDAM)

4

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ABSTRACT

Objectives. To determine PSA Velocity (PSAV), PSA slope and PSA doubling time (PSADT) in men with positive biopsies, negative biopsies and no biopsy indications, 4 years after an initial screen. To use this information to improve test characteristics in the early detection of prostate cancer and to provide normal values of these parameters in screened men with and without evidence of prostate cancer.

Participants and methods. Within the European Randomized Study of Screening for Prostate Cancer (ERSPC, section Rotterdam), we identified 9575 men with a second determination of PSA, 4 years after the initial screening round. These were divided into three groups: men with a positive biopsy, a negative biopsy and those with no biopsy indication in the second round (PSA < 3.0 ng/ml). The predictive values of PSA dynamics for detection of prostate cancer were calculated.

Results. The mean PSAV of men with prostate cancer was 0.62 ng/ml/yr versus 0.46 ng/ml/yr for men with a negative biopsy (P=0.001). The mean PSA doubling time for men with prostate cancer is 5.1 years and men with a negative biopsy 6.1 years (P=0.002). PSADT for men with no indication for biopsy is 25.1 years. However ROC analyses show only moderate value of these test parameters in predicting biopsy outcome.

Conclusions. Mean values of PSAV, PSA slope and PSADT in a re-screened population differ significantly between men with and without prostate cancer. However in predicting biopsy outcome, PSA dynamics are of limited value.

INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is conducted in eight European countries. The primary endpoint is the evaluation of the effect of prostate cancer screening on disease specific mortality. Also evaluation and development of the most effective screening strategies is an important goal of this study.
The Dutch (Rotterdam) section of the ERSPC has recruited 42,376 participants randomized between a screening and control arm. The initial screening round is completed and screening results can be compared to the second round of screening which is still ongoing.
Prostate Specific Antigen (PSA) is an adequate test for prostatic disease (prostatitis, benign prostatic hyperplasia and prostate cancer), however it lacks specificity to serve as a reliable test for prostate cancer alone. We study PSA change over time, specifically PSA Velocity, PSA slope and PSA doubling time in men with a positive, a negative and no biopsy indication 4 years after the initial screening round.

PARTICIPANTS AND METHODS

After completion of four pilots studies [1] the ERSPC section Rotterdam started in June 1994. Men aged 55 to 74 years who were randomized to the screen group were invited to three screening tests: PSA measurement, digital rectal examination (DRE) and a transrectal ultrasonography (TRUS). The biopsy indication in this original protocol was set at PSA>= 4.0 ng/ml and/ or suspicious findings on DRE or TRUS. Lateral sextant biopsies were performed. In case of a hypoechoïc lesion a seventh lesion directed biopsy was performed. Initially men with a negative biopsy were invited for an additional screening procedure after one year, however this was omitted later as a result of policy change [2]. The second and third rounds were scheduled respectively four and eight years after the initial screening round. Halfway through the first round, men with suspicious findings on DRE or TRUS and a PSA value below 1.0 ng/ml were no longer biopsied because of a very low positive predictive value (PPV) in this low PSA range [3,4]. After April 1997 the biopsy indication was modified again to a cut-off value of PSA>= 3.0 ng/ml regardless of DRE or TRUS findings which were no longer used as screening tests. During the second round of screening two side studies were active. The first provided a biopsy indication for men with a PSA value in the second round between 1.0 and 2.9 ng/ml if their PSA value was doubled compared to the initial screening round [5]. In the second side study all men with a PSA >= 2.0 ng/ml were offered a biopsy and in addition free PSA and human Kallikrein 2 were determined [6]. Round 2 is completed for about 75% of men randomized to screening. The third round of screening has just started.
Up to January 2000, we used the Hybritech Tandem E assay, after that we used the automated version, the Beckman Access assay. An earlier study from this group [7] showed no significant differences between these two assays. Of the 21,210 men randomized to the screening arm, 19,970 (94.2%) men had a PSA value determined in round 1. Up to now 9,935 participants

had also a PSA measurement in the second round and could be used to determine the PSA change over a 4 years time period. We excluded 244 men with a PSA >= 3.0 ng/ml in round 2 who were not biopsied for medical or other reasons. Hundred and sixteen men with a PSA level lower than 3.0 ng/ml and in whom prostate cancer was detected according to one of the side study protocols were also excluded to because not all men were biopsied in this low PSA range. This leaves 9575 men who were divided into three groups. The first group consists of men with a positive biopsy in round 2. The second group were men with a negative biopsy result in the second round. The third group represents men who had no biopsy indication (PSA < 3.0 ng/ml) in round 2. The second and third group combined represent men with no prostate cancer detected after four years whether a biopsy procedure was performed or not. In the second round 337 men (3.5%) had prostate cancer detected by biopsy, 1352 participants (14.1%) had a negative biopsy in round 2, and 7305 men (82.3%) had no biopsy done in the second round because of a PSA value below 3.0 ng/ml. Table 1 shows the percentage of men in each PSA group at the beginning of the study.

Table 1. Percentage of men per initial PSA group

PSA group (ng/ml)	*Number*	*Percentage (%)*
0.1 - 0.9	4118	43.0
1.0 - 1.9	3277	34.2
2.0 - 2.9	1136	11.9
3.0 - 3.9	494	5.2
4.0 - 9.9	511	5.3
> 10.0	39	0.4
	9575	100.0

Positive predictive values (PPV) were defined as the number of men with prostate cancer diagnosed divided by the number of biopsies. The slope of PSA was calculated by taking the base 2 logarithms of the PSA values, the difference was divided by the time interval between PSA measurements. On the basis of this base 2 logarithmic equation, doubling time can be calculated as the reciprocal value of the slope. Mean values were compared with t-tests for normally distributed parameters and the Mann–Whitney U test for non-normal parameters. Two-sided P-values smaller than 0.05 were considered statistically significant. The predictive accuracy of the tests was assessed by receiver operator characteristics (ROC) analyses.
A permission to conduct this study was obtained from the Dutch Health Council Committee on the Population Screening Act.

RESULTS

Table 2 shows the participant characteristics per screening round and study group. The mean age is not significantly different between groups. Remarkably the mean initial PSA value of men with prostate cancer detected four years later is significantly lower than of men without prostate cancer while PSA value at diagnosis does not differ significantly. Prostate volumes and prostate volume change after four years also differ significantly between groups. Men with a negative biopsy have larger prostate volumes and a larger prostate volume increase in this four years interval.

Table 2. Participant characteristics per screening round and group

Mean	*Group 1 PCa (n=337)*	*Group 2 neg. biopsy (n=1352)*	*Group 3 no biopsy (n=7886)*	*P value 1 vs. 2*	*P value 1 vs. 3*	*P value 2 vs. 3*
Age round 1 (yrs) (number of men)	62.9 (n=337)	62.9 (n=1352)	61.5 (n=7886)	n.s.	<0.001	<0.001
Age round 2 (yrs) (number of men)	67.0 (n=337)	67.1 (n=1352)	65.6 (n=7886)	n.s.	<0.001	<0.001
PSA round 1 (ng/ml) (number of men)	3.1 (n=337)	3.7 (n=1352)	1.1 (n=7886)	<0.001	<0.001	<0.001
PSA round 2 (ng/ml) (number of men)	5.7 (n=337)	5.6 (n=1352)	1.2 (n=7886)	n.s.	<0.001	<0.001
prostate volume round 1 (ml) (number of men)	39.5 (n=240)	46.9 (n=1048)	31.3 (n=3354)	<0.001	<0.001	<0.001
prostate volume round 2 (ml) (number of men)	43.8 (n=334)	53.9 (n=1345)	38.5 (n=653)	<0.001	<0.001	<0.001
prostate volume change in 4 yrs (ml) (number of men)	5.9 (n=240)	9.3 (n=1044)	3.9 (n=175)	<0.001	0.053	<0.001

Figure 1 depicts the differences in positive predictive value of PSA between the initial and the second round of screening, stratified per PSA range. In round 1 the PPV increases when the PSA levels are higher. However in the second round of screening the relation of increasing PSA levels with higher PPV's, is lost. In search for other predictive PSA related parameters we compared PSA Velocity (PSAV), PSA slope and PSA doubling time (PSADT) between the different study groups.

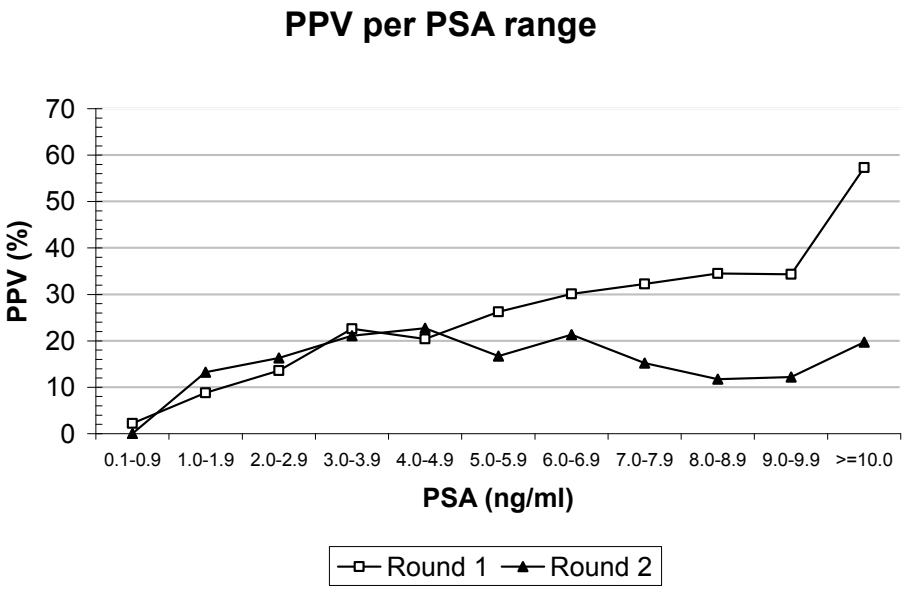

Figure 1.

Table 3 shows a mean PSAV of 0.62 ng/ml/yr for men with prostate cancer compared with 0.46 ng/ml/yr for men with a negative biopsy (P=0.001). Also the mean PSA slope and PSADT differed significantly in biopsied men with and without prostate cancer (P=0.002). The mean PSA doubling time in this screening population is 5.1 years (median 5.7 years) for men with prostate cancer and 6.1 years (median 7.1 years) for men with a negative biopsy. These means were significantly different with a P value of 0.002. PSADT for men without a biopsy indication in round 2 amounts to 25.1 years (median 20.7 years). For men without prostate cancer regardless whether a biopsy was performed or indicated (group 2+3) mean PSADT is 17.3 years (median 16.7 years). The change in biopsy indications in round 1 did not influence mean PSA dynamics.

Table 3. Mean PSA Velocity, PSA slope and PSADT for the different groups

Group	*Description*	*number*	*mean PSAV (ng/ml/yr)*	*range*	*mean PSA slope (1/yr)*	*range*	*mean PSADT* (yr)*
1	PCa	337	0.62	(-1.08 - 14.21)	0.195	(-0.24 - 1.51)	5.1
2	No PCa, biopsy done	1352	0.46	(-4.44 - 7.43)	0.163	(-0.56 - 1.12)	6.1
3	No PCa, no biopsy indication	7886	0.03	(-11.63 - 0.59)	0.040	(-1.52 - 0.98)	25.1
2+3	No PCa, regardless of biopsy done	9238	0.09	(-11.63 - 7.43)	0.058	(-1.52 - 1.12)	17.3
	P value 1 vs. 2		0.001		0.002		0.002
	P value 1 vs. 3		<0.001		<0.001		<0.001
	P value 1 vs. 2+3		<0.001		<0.001		<0.001

* range of PSADT is not available because in case of PSA decrease lower limit of PSADT is per definition not doubling time but 'halfing time' (T1/2). Upper limit PSADT is infinite in case of no PSA change

Using ROC analyses (Figure 2) we compared the relative sensitivity and specificity of the test parameters PSAV and PSADT in the biopsied men (group 1 and 2). PSADT showed a slightly larger area under the curve (AUC) than PSAV (0.573 vs. 0.549). However both AUC's were only moderately above 0.5 and therefore of limited use in predicting biopsy outcome.

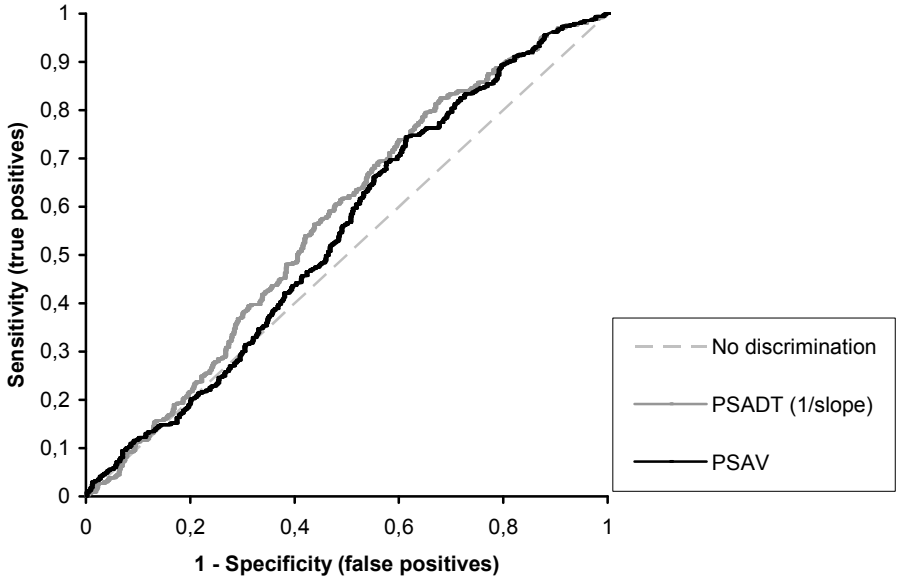

Fig. 2. *ROC curves PSAV and PSADT (=1/PSA slope)*

Concurring with this, PSA dynamics did not have an additional value on multivariate analyses. To answer the question whether PSAV or PSADT could improve specificity of testing (less unnecessary biopsies) we compared these two tests at a fixed sensitivity of 95% (95% of the tumours detected). As additional tests above the PSA cut off level of 3.0 ng/ml, PSAV has a specificity of 12.5% at a value of 0.02 ng/ml/yr. This means that 12.5% of the biopsies can be saved while still detecting 95% of the tumours. PSADT would save 13% of the biopsies.

DISCUSSION

The lack of specificity of the PSA measurements as only biopsy indicator is most easily pointed out by the observation that in only 20 to 30% of biopsied men with a PSA value above 4.0 ng/ml, prostate cancer is detected. This shows that approximately 70 to 80% of these men have a false positive test result. Similarly the loss of the relationship in the second round between ascending PPV's at increasing PSA levels also demonstrate the need for other tests to improve screening strategies. The use of PSAV, slope and doubling time has been described in screening and clinical applications [8-11] with various results. Because of

several differences in study design, number of participants, definition of groups, number of PSA measurements and calculation of PSADT, these studies cannot be properly compared. The first estimation of a normal PSA doubling time was made by Carter et al [12]. Their study group carefully selected 16 men without prostate cancer or benign prostatic hyperplasia and estimated PSADT, to range from 74 to 89 years in the corresponding age group (60 to 75 years). For men with local/ regional prostate cancer the PSADT was 2.4 years while we calculated the mean PSADT for men with prostate cancer to be 5.1 years. This result matches the PSADT for men with prostate cancer in several expectant management studies [13-15].
Our mean PSAV of men with prostate cancer in the second round of screening is 0.62 ng/ml/yr. This value is lower than the previously reported PSAV cut-off of 0.75 ng/ml/yr [8]. We think PSAV in a screening population will be generally lower than referred clinical patients.
Our study has some flaws. We were not able to calculate the PSA dynamics for more than two values because only few PSA measurements are available at this moment in the third round of screening. The intra individual variation of approximately 10-23.5% [8,16,17] can be reduced by using three or more consecutive PSA measurements. It is however to be expected that a relatively long interval between measurements (4 years) will compensate partly for the lack of additional measurements [18,19]. Using biopsy results for prostate cancer detection allows calculating 'relative' sensitivity, where biopsy is introduced as gold standard. The actual number of cancers which are not detected remains unknown.
This study also shows that screening results of several rounds cannot be considered together because of different predictive values with the same biopsy indication. It might be necessary to alter biopsy indications depending on participant's history of screening. PSA dynamics give moderate results in predicting prostate cancer in a screened population. Other parameters like prostate volume, volume increase, number of biopsies done earlier could be of significant value in detecting prostate cancer in a re-screened population. Also newer PSA derived serum markers like free PSA, pro PSA and hK2 are being investigated with respect to their predictive value on prostate cancer detection in re-screening rounds. We hope that improvement through the use of new molecular markers can be achieved.

CONCLUSIONS

Mean values of PSAV, slope and PSADT in a re-screened population differ significantly between men with and without prostate cancer. However in predicting prostate cancer on biopsy results PSA dynamics are of limited value.

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NOTES

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4-YEAR PROSTATE SPECIFIC ANTIGEN PROGRESSION AND DIAGNOSIS OF PROSTATE CANCER IN THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER, SECTION ROTTERDAM

5

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ABSTRACT

Purpose. The European Randomized Study of Screening for Prostate Cancer investigates the impact of screening on prostate cancer mortality and contributes to a better understanding of available screening tests. The present study evaluates the predictive value of a prostate specific antigen (PSA) increase to PSA 3.0 ng/ml or greater in a 4-year period in men who present with low PSA values (less than 3.0 ng/ml) at first screen.

Materials and Methods. A total of 42,376 men were randomized to screening vs control in Rotterdam. Of 6,467 men 5,771 had PSA values of less than 3.0 ng/ml, did not undergo biopsy at baseline and were re-screened after 4 years with PSA 3.0 ng/ml or greater as biopsy indication. PSA progression in a 4-year inter-screening interval is evaluated by determining the positive predictive values, detection rates and parameters of aggressiveness of round 2 cancers.

Results. PSA progression to more than 3.0 ng/ml occurred in 0.9%, 9.3% and 48.6% of men who presented with PSA values less than 1.0, 1 to 1.9 and 2 to 2.9 ng/ml, respectively, in round 1. Their respective positive predictive values amounted to 19.0%, 23.8% and 27.9%. Cancer detection rates increased with increasing PSA values in round 1. The distribution of low, moderate and high risk cancers depends on round 2 but not on round 1 PSA ranges.

Conclusions. PSA progression to the (arbitrary) cut-off value of 3.0 ng/ml and the diagnosis of prostate cancer in round 2 screening with a 4-year interval depends strongly on PSA values at the time of the 1st screen. These observations will be helpful to design future screening procedures. With levels less than 2.0 ng/ml PSA progression to levels of 3.0 ng/ml or greater is rare as it was seen only in 4.8% of all men.

Screening for prostate cancer remains a controversial issue in spite of recent evidence of a decreasing prostate cancer mortality in geographic areas were screening is prevalent [1,2]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1994 and is expected to produce data on prostate cancer mortality comparing the screening and control arms by 2008 or earlier [3]. Common evaluation is planned with the prostate cancer arm of the Prostate, Lung, Colon and Ovary (PLCO) screening trial of the National Cancer Institute [4].

Next to addressing the main end point (prostate cancer mortality), the ERSPC study group has the goal to improve the test procedures used for early detection of prostate cancer [5]. Screening by the use of prostate specific antigen (PSA) and rectal examination has been shown to be a sensitive procedure even with the use of a 4-year inter-screening interval [8]. On the other hand, PSA driven screening is associated with a dramatic amount of over-diagnosis varying from 50% to 700% depending on definitions [7-9]. If screening for prostate cancer is ever shown to be effective in terms of reducing prostate cancer mortality in a significant and relevant fashion screening procedures will have to be improved. Present uncertainties relate to the age when screening might be initiated, the use of PSA to determine biopsy indications, indications for further testing and the duration of the inter-screening interval [10-12].

The present analysis of data derived from the ERSPC section Rotterdam, The Netherlands, addresses the issue of PSA progression to 3.0 ng/ml or greater in a 4-year period in men with PSA values of less than 3.0 ng/ml at the initial screen who did not previously undergo biopsy. Such progression is then related to the diagnosis of prostate cancer with the use of a biopsy indication of 3.0 ng/ml PSA in the second round without the use of rectal examination. Since more than 70% of all men 55 to 74 years old present with PSA values less than 3.0 ng/ml, a better understanding of PSA progression and associated cancer diagnosis in this particular group may have a large impact in terms of avoiding unnecessary secondary screens, in terms of adapting screening intervals and, even, by backward extrapolation to determine the age at which the initiation of PSA testing may be useful to differentiate groups of men with and without a subsequent risk of prostate cancer. It has recently been shown that PSA levels greater than 3.0 ng/ml lose their predictive value for the presence of prostate cancer after its use in a first screening round [13].

MATERIALS AND METHODS

We studied a population of 6,467 men who were randomized to screening within the ERSPC, section Rotterdam and were eligible/ available for round 2 screening after 4 years.
The way the study population is derived is indicated in figure 1. About half way during the first round of screening the biopsy indications were changed. In 9,779 of 19,970 men during round 1 a biopsy was recommended if a PSA level of 4.0 ng/ml or greater, and/or an abnormal rectal examination and/or a suspicious transrectal ultrasound were found. As of

May 1997 the PSA cut-off for recommending a biopsy was decreased to 3.0 ng/ml, the use of rectal examination and transrectal ultrasound was discontinued. A total of 10,191 men were screened in this way and 9,650 were found not to have cancer. Of these, 3,183 have not completed their second screen, for reasons indicated in figure 1, leaving a study population of 6,467 men. Of these participants 696 presented with a PSA 3.0 ng/ml or greater during the first round and underwent biopsy. These men are included in figures 2 and 3 but not in tables 1 to 4, which are limited to the 5,771 men who presented with a PSA value less than 3.0 ng/ml during round 1 of screening.

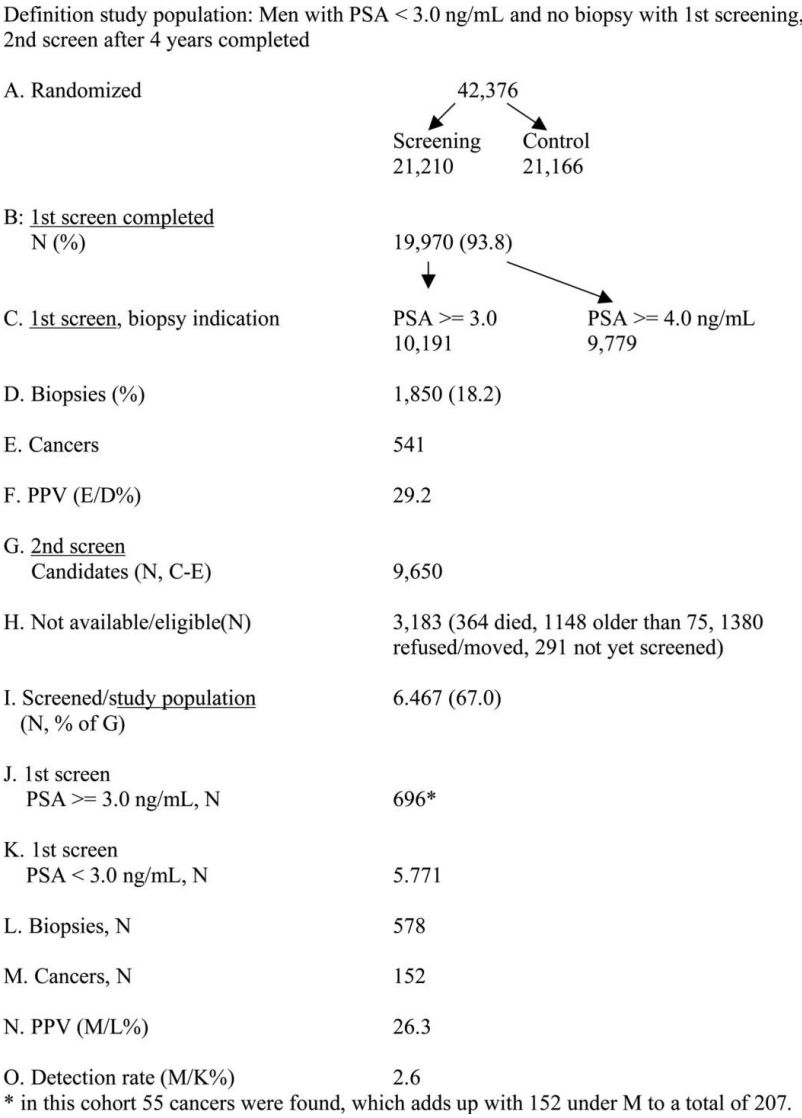

Fig. 1. *Consort diagram*

Biopsies were lateralized sextant biopsies according to the suggestions by Eskew et al. [14]. A seventh biopsy was taken from visible lesions.

The positive predictive value (PPV) was defined as the ratio of men with prostate cancer detected and the number of men who underwent biopsy. The cancer detection rate is defined as the number of men with prostate cancer detected divided by all men in this age range regardless of the presence of a biopsy indication.

Statistical analysis was done on commercially available software.

To estimate the aggressiveness of the cancers found in the second screening round the method designed by D'Amico et al. [15]. This method allows an estimation of the chance of 2-year PSA progression according to parameters which are available before treatment (PSA ranges, T classification and biopsy Gleason score). The classification was recently compared with the commonly used nomogram designed by Kattan et al. [16] and found to be equivalent in predicting progression [17]. The D'Amico algorithm was chosen for this reason and because it is applicable to cases treated by radical prostatectomy and radiotherapy, choices which are part of ERSPC. ERSPC Rotterdam was approved by the institutional review board of the Erasmus MC and by the Ministry of Health as required by the Dutch law. All participants signed a written informed consent.

RESULTS

Figure 2 shows the distribution of prostate cancer in PSA ranges relating to the first (fig. 2, A) and second (fig. 2, B) screens, 10,191 in men who initially presented with PSA 3.0 ng/ml or greater. While the proportion of men diagnosed in PSA range 4 to 9.9 ng/ml remains essentially unchanged in round 2, there is an obvious increase in the proportion of cancers detected in PSA range 3 to 3.9 ng/ml and a decrease of detection with PSA values 10.0 ng/ml or greater. Figure 3 shows the prevalence of screen detected cancers in round 2 according to the PSA ranges in which these men presented in round 1. Biopsies in both rounds were performed if PSA was 3.0 ng/ml or greater. Few cancers were diagnosed if round 1 PSA amounted to less than 1.0 ng/ml. Of all cancer cases 84% had presented with PSA values less than 4.0 ng/ml during round 1 of screening. This figure is an illustration of data presented in table 1.

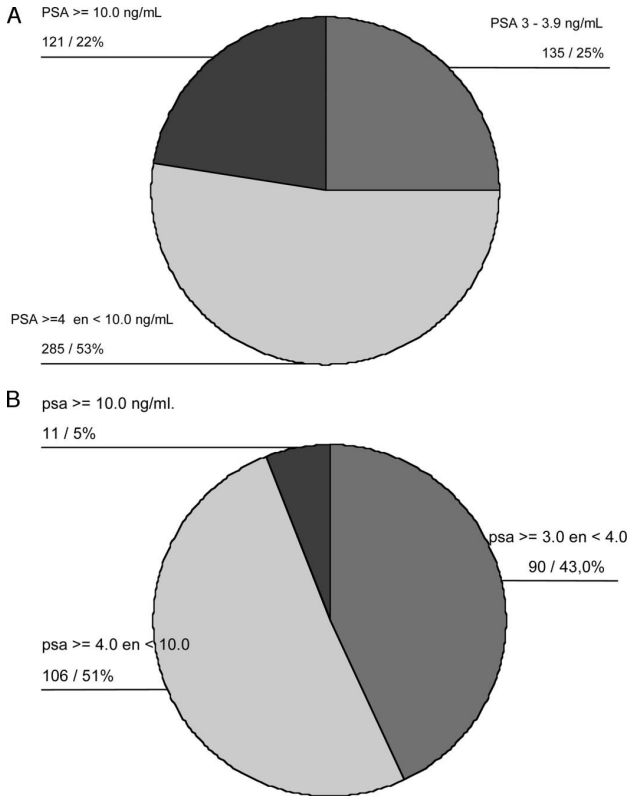

Fig. 2. *Distribution of prostate cancers in PSA ranges (biopsy indication PSA 3.0 ng/ml or greater). A, screen 1 (n=541). B, screen 2 (n=207).*

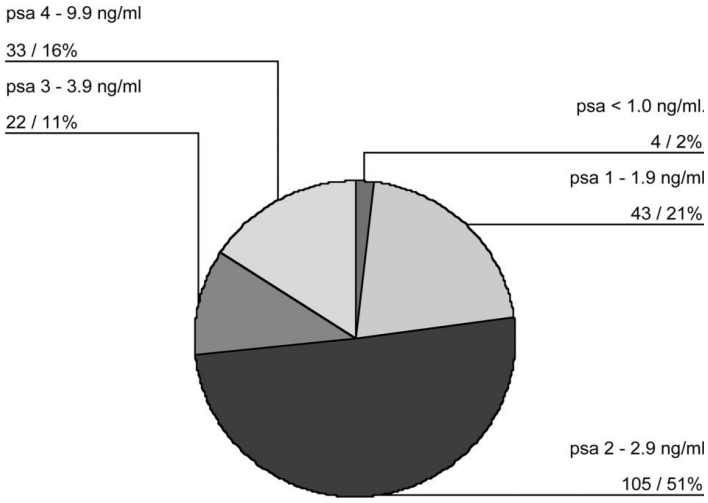

Fig. 3. *Distribution of 207 prostate cancers detected in screen 2, classified by PSA values at screen 1.*

Of the 6,467 men of this study population 5,771 (89.2%) had a PSA value in round 1 of less than 3.0 ng/ml and therefore did not have a biopsy indication during first round screening. On the other hand 10.8% had PSA 3.0 or greater in round 1 and underwent biopsy. These prostate cancers may have been missed in round 1. Table 1 shows detailed data on PSA progression in these men and the PPV for each PSA range 4 years before prostate cancer detection. The phenomenon that the PPV is smallest for those men who have the largest difference of PSA between round 1 and 2 (from less than 10 to 3.0 ng/ml or greater) will be discussed.

Table. 1. PSA progression and diagnosis of prostate cancers after 4 years

Round 1 PSA (ng/ml)	Less Than 1.0	1.0–1.9	2.0–2.9	Overall
No. pts	2,622	2,268	881	5,771
No. round 2 PSA 3.0 ng/ml or greater (%)	23 (0.9)	211 (9.3)	428 (48.6)	662 (11.5)
No. biopsy indication (%)	21 (91.3)	181 (85.8)	376 (87.9)	578 (87.3)
No. prostate Ca	4	43	105	152
PPV (%)	19.0	23.8	27.9	26.3
Ca detection rate	0.15	1.90	11.9	2.6

Differences in PPVs are not significant (Fisher's exact test, group 1.0 to 1.9 vs 2.0 to 2.9 ng/ml, p . 0.31).

PSA progression is rare and amounted to 0.9% and 9.3% (average 4.8%) in men who presented with PSA values of less than 1.0 and 1 to 1.9 ng/ml in round 1. Still, if PSA progression occurred in this group, the PPV was high and ranged between 19.0% and 23.8% indicating that 1 in 4 to 5 of these men was found to have cancer. Cancer detection rates increased dramatically

almost 80-fold with increasing PSA values in these low ranges observed in round 1. Table 2 shows the rates of PSA progression to PSA ranges 3 to 3.9, 4 to 9.9 and 10.0 ng/ml or greater in round 2 and the related numbers of cancers and PPV's which do not differ significantly.

Table. 2. PSA progression to 3.0 ng/ml or more and diagnosis of prostate cancer

Round 2 PSA (ng/ml)	No. Biopsied	No. Prostate Ca (%)	% PPV*
3–3.9	344	82 (54.0)	23.8
4–9.9	220	66 (43.4)	30.0
10 or Greater	14	4 (2.63)	28.6
Overall	578	152	26.3

* Differences are not significant, group 3 to 3.9 vs 4 to 4.9 ng/ml, p . 0.12, Fisher's exact test.

The results of the risk assessment using the algorithm suggested by D'Amico et al [15] according to baseline PSA ranges less than 2 and between 2 and 3 ng/ml is given in table 3. Arbitrary cut-offs of 2-year risk of recurrence after treatment of 0% to 10%, 11% to 20% and more than 20% were chosen. The figures suggest that a baseline range of less than 3.0 ng/ml PSA at baseline does not predict the absence of high risk cancers or a more favourable distribution of the risk of recurrence in round 2 if compared with higher baseline PSA ranges.

Table. 3. Risk assessment for 152 round 2 cancers according to baseline screen

Baseline Screen PSA (ng/ml)	0–1.9	2–3.0	Total
2-Yr risk of PSA recurrence after treatment:			
Low	18 (38.3)	32 (30.5)	50 (32.9)
Intermediate	23 (48.9)	60 (57.1)	83 (54.6)
High	6 (12.8)	13 (12.4)	19 (12.5)
Totals	47 (30.9)	105 (69.1)	152 (100)

In table 4 the result of the same risk assessment are given according to PSA levels at the time of the diagnosis of prostate cancers after round 2 screening. It is evident that the proportion of low risk cases decreases while the proportion of high risk cases increases with increasing PSA levels.

Table. 4. Risk assessment for 152 round 2 cancers according to PSA at diagnosis

PSAatDiagnosis(ng/ml)	0–3.0	3.0–10.0	GreaterThan10.0	Totals
2-Yr risk of recurrence after treatment:				
Low	47(57.3)	3(4.6)	–	50(32.9)
Intermediate	30(36.6)	50(75.8)	3(75.0)	83(54.6)
High	5(6.1)	13(19.7)	1(25.0)	19(12.5)
Totals	82(54.0)	66(43.4)	4(2.6)	152

DISCUSSION

Earlier recent reports from ERSPC section Rotterdam have addressed the issue of the value of PSA based detection in second round screening. One shows that the relationship between PSA levels and their positive predictive value seen in the first round is lost during the second round [13]. Harvesting of the larger tumours during the first round and insufficient time for re-growth of smaller tumours are likely explanations for this phenomenon. This is supported by the observation of lead times relating to the screening regimen used which are in the range of 10 to 13 years [7]. Search for alternative predictors included second round PSA, PSA velocity, PSA density, suspicion on rectal examination or ultrasound and prostatic volume [18]. Round 2 PSA, transrectal ultrasound suspicion and age but not PSA velocity, were significant positive predictors, prostatic volume and a previous negative biopsy [19] were negative predictors. Differences in results seen in these reports are most likely due to differences in the underlying populations.
The present report describes rates of PSA progression in men with negative first screens, establishes their predictive value in second round screening and relates baseline and second screen PSA ranges to risk factors at diagnosis.

The issue of PSA progression to PSA values greater than 4.0 ng/ml in a population based setting, the PSA cut-off commonly used as a biopsy indication in the past, has been addressed in 3 previous reports. Crawford et al. [20] evaluated PSA progression in a cohort of 27,863 participants in the PLCO screening trial of the National Cancer Institute. PSA changes after 4 years are reported according to initial PSA values. For PSA ranges 0 to 1, 1 to 2, 2 to 3 and 3 to 4 ng/ml 4-year average PSA progression rates to 4.0 ng/ml or greater of 1.4%, 6.6%, 13.4% and 77% are reported. Paez et al. [21] studied PSA change over time in 22,169 men with an initial PSA of less than 4.0 ng/ml derived from the central database of ERSPC (8 participating European countries). A total of 960 men (4.5%) converted to PSA 4.0 ng/ml or greater within a 42-month period. PSA conversions after 42 months for PSA less than 1, 1 to 2.5 and greater than 2.5 ng/ml amounted to 0.62%, 4.1% and 37.4%. Both authors concluded confirming a suggestion of Carter et al. [10] that longer screening intervals should be applied to men who present with PSA values less than 2.0 ng/ml at the initial screening. Ito et al. [22] reported on a Japanese demonstration project of screening and showed that of 7,757 men age 79 or younger 559 (7.2%) with baseline PSA levels of 4.0 ng/ml or less progressed to PSA 4.0 ng/ml or greater. The cumulative rates of freedom of such PSA progression of 5 years was 98.7%, 92.9%, 70.3% and 38.5% for men with PSA less than 1, 1 to 1.9, 2 to 2.9 or 3 to 3.9, respectively. None of these reports related PSA change to time to cancer detection in the same population. The data presented in this report show the change of the distribution of prostate cancers in PSA ranges from round 1 to round 2 in a homogeneous sample of men who were all screened by PSA only using a PSA value of 3.0 ng/ml or greater as a biopsy indications. Figures 2, A and B show an increase of the proportion of cases diagnosed in the PSA range 3 to 4 ng/ml and a decrease of those cases found with PSA values greater than 10 from round 1 to round 2. About half of the cancer cases are detected in both rounds in

the PSA range 4 to 10 ng/ml. These data are compatible with the notion that progression to biopsy detectable cancer occurs after the baseline screen within the lower PSA ranges. This interpretation is supported by the data shown in figure 3 and table 1. About half of all cases detected in round 2 had PSA values between 2 and 3 ng/ml 4 years earlier. A total of 27% of round 2 cases originally presented with PSA values greater than 3.0 ng/ml. In some of the men with PSA 3.0 ng/ml or greater in round 1, prostate cancers may have been missed by lateralized sextant biopsies in round 1 but a previous negative biopsy is not a significant predictor of a positive biopsy in round 2. A study of parameters of aggressiveness of round 2 cancers [23] and the extremely low rate of interval cancers which occurred during the complete 4-year interval between round 1 and 2 [6] suggest that those cancers that may have been missed were usually not aggressive and rarely led to non-curable lesions.

Table 1 contains the key message of our report. It confirms low 4-year PSA progression rates for PSA ranges 0 to 2.9 ng/ml. These progression rates especially for PSA values less than 2.0 ng/ml (4.8%) do not differ substantially from those observed by others [18-20] and confirm the first report suggesting a longer interval for men with PSA ranges less than 2.0 ng/ml.[10] Knowledge of the numbers of biopsies actually performed and the numbers of cancers detected allows the calculation of PPV's and cancer detection rates in a population that did not previously undergo biopsy. PPV values show a trend but do not differ significantly with increasing PSA ranges ($p = 0.31$). However, cancer detection rates increase substantially by a factor of 78 from the PSA range 0 to 1 vs. 2 to 3 ng/ml at the initial screen. The counterintuitive observation that the most pronounced PSA increase, eg from 0 to 0.9 to greater than 3.0 ng/ml, is not associated with a higher PPV is in line with the absence of an independent prediction by PSA velocity. Table 2 confirms that PSA ranges greater than the level of a biopsy indication do not predict higher rates of detectable cancer [13].

Considering the need to curb over-diagnosis and also the need to identify aggressive but locally confined cancers in future screening strategies it is necessary to learn to predict parameters of tumour aggressiveness by the use of pre-treatment diagnostic parameters. This is attempted by using the D'Amico nomogram which predicts the chance of 2-year PSA recurrence after radical prostatectomy or radiotherapy. The results are presented in tables 3 and 4. Summarized in a nutshell, low PSA levels at baseline screen do not allow excluding the occurrence of aggressive cancers 4 years later although their proportion is low with 12.5%. Neither do such low PSA values convincingly identify low risk cancers. However, if expectant treatment is applied, it should be used in those men who can be classified as having low or intermediate risks of PSA recurrence. The analysis includes PSA, the T-classification and the biopsy Gleason score. Specifically the T-category is considered to be the main parameter predicting potential curability of prostate cancer. A total of 96.6% of the 207 cancers found in round 2 were classified as T1 or T2 disease (61.4% T1c and 35.2% T2a-c). Only 3.4% of the cancers were locally advanced (T3a-c), none was metastatic. In the population of 152 cancers found in round 2 in men with initial PSA values less than 3.0 ng/ml, 96% had stage T1

or T2 cancers (64% T1c, 32% T2a-c). Clearly, in spite of the long screening interval of 4 years, second round screening in the setting of ERSPC section Rotterdam produces an additional stage shift in a more favourable direction. Finally, if second round cancers are classified according to PSA ranges at second round screening, it turns out that there is a positive relation between PSA levels and a higher risk of recurrence. Numbers are considered to be too small for a statistical analysis. The trend visible in table 4 as opposed to table 3 clearly indicates a direction for further study. Recent publications have shown that having every men who presents with low PSA values undergo biopsy is associated with PPV's ranging from 6.6% to 23.9% for PSA 0.5 or less to 3.0 ng/ml [24] and 15.7% for PSA 2 to 2.9 ng/ml. [25] However, this means in the setting of the present study that 5,771 instead of 578 men had to undergo biopsy. The value of biopsying all cases of low PSA is up for discussion.

CONCLUSIONS

Our data show that most cancers detected in second round screening after 4 years presented with low PSA values during round 1. It is likely that part of the cancers diagnosed in the second round with PSA values greater than 3.0 ng/ml were missed by sextant biopsies. It is unlikely however that a substantial number of these tumours progressed to non-curable stages at the time of diagnosis in round 2. The PPV in round 2 amounted to 19% to 27.9% for first screen PSA ranges of 0 to 3.0 ng/ml contrasting with the PPV of 7.9% for men with PSA 3.0 ng/ml or greater in round 1. This shows that the PSA cut-off of 3.0 ng/ml remains valid in second round screening allowing detection of cancer with about one of 4 to 5 indicated biopsies on average. PSA levels at the time of diagnosis of second round cancers but not the baseline PSA levels seem to be predictive of prostate cancer aggressiveness. The data presented in this report will be useful to reconsider recommendations for second round screening, for screening intervals and, by backward extrapolation, possibly also for determining the age at which screening should be initiated.

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EDITORIAL COMMENT

PSA testing is now widely used for the early detection of prostate cancer. In the United States the standard cut-off for determining whether a man needs further diagnostic follow up is 4 ng/ml. Others have proposed a cutoff of as low as 2.5 ng/ml. A large proportion of men who participate in screening programs have initial PSA levels well below 4 ng/ml. Thus, a substantial portion of PSA screening involves the sequential evaluation of PSA, often at yearly intervals, in men with initially low PSA levels. If low PSA levels are generally stable over time, then the probability of converting to a PSA greater than 4 ng/ml from a low PSA level within a few years may be quite small. Schroder et al report on results from the European screening trial, confirming our early work in this area derived from Prostate Cancer Awareness Week data. The PLCO screening trial has similarities to the European trial. We reported that among men with baseline PSA less than 1 ng/ml, 1.5% converted to a level greater than 4 ng/ml by year 5 (95% CI 1.2–1.7). Among men with baseline PSA of 1.0 to 1.99 ng/ml, 1.2% (95% CI 0.9–1.3) and 7.4% (95% CI 6.8–8.1) converted to PSA greater than 4 ng/ml by year 1 and 5, respectively. A total of 33.5% and 79% of men with an initial PSA of 2.0 to 2.99 and 3.0 to 4.0 ng/ml, respectively, developed levels greater than 4 by year 5 (reference

20 in article). Implementation of screening men less often with PSA levels of less than 1 ng/ml could save the health care system $500 million per year. We are pleased that the work of Schroder et al confirms our earlier findings in a European based screening program.

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REPLY BY AUTHORS

The authors are grateful for the comment and for the update on previously published data from the Prostate, Lung, Colon, and Ovary screening trial of the National Cancer Institute. It is rare for authors and reviewers to be in full agreement, as occurred with respect to our article.

However, I should like to add that the absolute cut-off of any PSA value is not the final answer with respect to the optimal way of screening men repeatedly. Strong negative predictors have been identified such as a previous negative biopsy and prostatic volume (references 18 and 19 in article). Their presence is likely to have a strong influence on the positive predictive value of any PSA cut-off. Positive and negative predictors will in the future have to be included as biopsy indications after previous screening.

PROSTATE CANCER DETECTION AND PSA INCREASE AFTER 4 YEARS IN DUTCH AND JAPANESE MALES WITHOUT EVIDENCE OF DISEASE AT INITIAL SCREENING

6

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ABSTRACT

BACKGROUND. In the current study, the authors set out to investigate the possibility that increased prostate-specific antigen (PSA) levels in Dutch and Japanese men without suspicious findings at initial prostate cancer screening were indicative of the risk of newly developing clinical malignancy in the Netherlands and Japan.

METHODS. Between 1992 and 2000, 2650 men ages 55–74 years who had PSA levels < 4.0 ng/ml. and no suspicious findings on digital rectal examination were entered into the current study from a population-based prostate cancer screening cohort in Gunma Prefecture, Japan. In addition, between 1994 and 1997, 3163 men with the same clinical background were entered into the current study from the Rotterdam (Netherlands) Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate carcinoma incidence and the cumulative probability of freedom from PSA increases to levels > 2.0, 3.0, and 4.0 ng/ml., respectively, after 4 years of observation were compared between the Japanese and Dutch populations. The predictive value of initial PSA level, age at study entry, and geographic location also were investigated using Cox proportional hazards models.

RESULTS. The overall risk of developing prostate carcinoma during the 4-year observation period was significantly higher for the ERSPC Rotterdam cohort (5.2%) compared with the Gunma cohort (1.6%). The cumulative probability of freedom from prostate carcinoma detection and freedom from an increase in PSA levels to >= 4.0 ng/ml. (PSA progression) decreased significantly with increasing initial PSA level and did not differ significantly between Japanese and Dutch patients whose initial PSA levels fell within the same range (0.0–0.9, 1.0 –1.9, 2.0 –2.9, or 3.0 –3.9 ng/ml.). Multivariate analysis also revealed that after controlling for age and initial PSA level, the probability of PSA progression was the same for Japanese and Dutch men. Initial PSA level was the only variable found to be significantly predictive of PSA progression on multivariate analysis ($P < 0.0001$).

CONCLUSIONS. The risk of developing prostate carcinoma within a given 4-year period is greater for Dutch males ages 55–69 years compared with their Japanese counterparts, because the former have higher PSA levels. Nonetheless, there appears to be no significant difference in prostate carcinoma risk between Dutch and Japanese males whose baseline PSA levels fall within the same range.

It is widely known that the probability of developing prostate carcinoma is strongly correlated with serum prostate-specific antigen (PSA) levels [1,2]. Thus, if the risk of a future increase in PSA levels is known, the future risk of developing prostate carcinoma can also be estimated. Two recent studies have investigated the cumulative risk of PSA increases to levels > 4.0 ng/ml. in males with initial PSA levels <= 4.0 ng/ml. [3,4]. In both American and Japanese males, the cumulative probability of such an increase over 5 years of follow-up was found to grow larger with increasing initial PSA level. These results suggest that baseline PSA level could serve as a useful predictor of future prostate carcinoma risk; however, the two studies that yielded these findings may have included numerous cases in which patients whose baseline PSA levels were within the reflex range of 0.0 –3.9 ng/ml. had abnormal findings on digital rectal examination (DRE) at initial screening.

Given the information that is currently available, we believe that an evaluation of the proportion of men with baseline PSA levels < 4.0 ng/ml. and normal findings on DRE at initial screening who develop detectable prostate carcinoma and experience PSA increases over the subsequent 4-year screening interval is warranted. The results of such an analysis may be strongly correlated with the risk of newly clinically manifested prostate carcinoma in the populations examined.

In the current study, the issue at hand was addressed by investigating patients from two large, population-based screening studies—one based in Europe and the other based in Japan.

MATERIALS AND METHODS

Between January 1992 and December 2000, 11,880 men ages 55–74 years had their serum PSA levels measured as part of a population-based prostate carcinoma screening study conducted in Gunma Prefecture, Japan. All participants received an invitation letter (including a fact sheet on prostate carcinoma screening) from the local government and chose to take part in the study on the basis of the information presented to them. Six thousand one hundred thirty-eight of the 11,880 participants also underwent DRE at initial screening. Of these 6138 men, the 2650 who had serum PSA levels < 4.0 ng/ml. and no suspicious findings on DRE and who underwent rescreening at least once within 4 years of baseline were enrolled in the current study. Although annual screening was recommended by the local government, screening practices were left to the patient's discretion. Of the 2650 men who were included in the current study, 1664 (62.8%) also underwent transrectal ultrasonography (TRUS) at initial screening and had no suspicious findings.

Between April 1994 and March 1997, after providing informed consent, 8922 male volunteers ages 55–74 years participated in the Rotterdam (Netherlands) Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Serum PSA levels were measured for all participants. Six thousand nine hundred eighty-three of the 8922 participants underwent both DRE and TRUS. Of these 6983 men, the 3163 who had PSA

levels < 4.0 ng/ml. and normal findings on DRE at initial screening and who underwent rescreening within 4 years of baseline were enrolled in the current study. All 3163 participants who were included in the current analysis also underwent TRUS at initial screening and had no suspicious findings.

The mean and median patient ages were 64.2 and 64 years, respectively, in the Gunma cohort and 61.8 and 61 years, respectively, in the ERSPC Rotterdam cohort. In the former cohort, the mean and median follow up durations were 2.95 and 3 years, respectively. Of the 2650 participants in the Gunma study, 465 (17.5%), 430 (16.2%), 524 (19.8%), and 1231 (46.5%), respectively, were followed for 1, 2, 3, and 4 years after initial screening. In contrast, all members of the ERSPC Rotterdam cohort were rescreened once, at 4 years after initial screening. At rescreening, DRE and/or TRUS were performed at least once for 2203 patients in the Gunma cohort (83.1%) and for all 747 patients in the Rotterdam cohort who had PSA levels >= 3.0 ng/ml. (23.6% of the Rotterdam cohort as a whole).

In the Gunma study, biopsy indications changed as follows over the course of the follow up period (which ran through December 2001): in 1992 and 1993, the cut-off value for PSA level as a biopsy indication was set at 6.0 ng/ml. for all age ranges; thereafter, the cut-off value was changed to 3.0 ng/ml. for men ages 55–59 years (1994–2001) and men ages 60–64 years (2000–2001), to 3.5 ng/ml. for men ages 65–69 years (2000–2001), and to 4.0 ng/ml. for men ages 70–74 years (1994–2001). In addition, over the period 1994–1999, the cut-off level was set at 4.0 ng/ml. for men ages 60–69 years. In the ERSPC Rotterdam cohort, biopsy was indicated for PSA levels >= 4.0 ng/mL and/or abnormal findings on DRE or TRUS through March 1997. Thereafter, the cut-off PSA level was changed to 3.0 ng/ml., regardless of findings on DRE or TRUS. One hundred thirty-five patients with initial PSA levels between 1.0 and 2.9 ng/ml. who experienced PSA doubling over the 4-year follow-up period also underwent prostate biopsy (regardless of DRE and TRUS findings) after providing informed consent.

DRE findings were considered abnormal if a nodular lesion, capsular irregularity, or firmness of the prostate was documented. TRUS findings were considered abnormal if a hypoechoïc lesion or capsular irregularity was evident.

In the Gunma study, men with abnormal findings on PSA testing, DRE, and/or TRUS were informed by mail about the necessity of additional urologic examinations. These additional examinations typically included TRUS-guided lateral sextant biopsy and two additional sets of transition zone biopsies (via the transperineal and transrectal routes). Site-directed prostate biopsy also was performed for patients with abnormal findings on DRE and/or TRUS. Alternatively, annual or quarterly PSA measurements were proposed for the follow-up of participants who chose not to undergo additional urologic examination and for whom immediate prostate biopsy was not recommended by a physician at an affiliated hospital. All biopsy specimens in the Gunma study were reviewed by two urologic pathologists from the Department of Pathology, Gunma University School of Medicine (Maebashi, Japan).

In the ERSPC Rotterdam cohort, TRUS-guided systematic sextant biopsy was performed via a transrectal approach. In addition, site-directed prostate biopsy was performed for patients

with abnormal findings on DRE or TRUS. Prostate biopsy was recommended for all patients who had abnormal findings on rescreening. All biopsy specimens in the Rotterdam cohort were reviewed by urologic pathologists from the Department of Pathology, Erasmus Medical Center (Rotterdam, The Netherlands).

In the Gunma study, serum PSA levels were measured at the Department of Urology, Gunma University School of Medicine, using the E-Test Tosoh II PA assay in conjunction with an AIA-600 analyzer (Tosoh, Tokyo, Japan). In the Rotterdam section of the ERSPC, PSA measurements were made at the Department of Clinical Chemistry, Erasmus Medical College, using the Tandem-E PSA assay (Beckman Coulter, Fullerton, CA). The two assays used have been shown to be equimolar in the recognition of free and total PSA in the serum and to yield nearly identical results[5]. The following formula could be used to convert total PSA levels as measured using the Tandem-E assay to total PSA levels as measured using the E-Test Tosoh II assay: $PSA_{Tosoh} = 0.9731 \times PSA_{Tandem} + 0.0361$ ng/ml. ($r = 0.9993$ [unpublished data]). Thus, we were able to compare serum PSA values measured by these two assays without making any corrections.

For cases in which follow-up occurred at 2–4 years from baseline, interval PSA levels were estimated using initial and final PSA values and the assumption that PSA levels changed over time in a simple exponential fashion. This procedure was used to estimate interval PSA levels at 1, 2, and 3 years after initial screening for all patients in the Rotterdam cohort. In the Gunma cohort, interval PSA levels were estimated for the 430, 524, and 1231 patients, respectively, who underwent follow-up at 2, 3, and 4 years after initial screening.

Data on patient ages and serum PSA levels at initial screening in both cohorts are presented in Table 1. Differences in these parameters were considered significant when P was less than 0.05 according to the Student t test, the Welch t test, or the X^2 test. Significant differences in mean patient age and PSA level at initial screening were found. In addition, the proportion of participants in younger age groups and the proportion of participants in higher PSA categories were significantly greater in the Rotterdam cohort than in the Gunma cohort.

Table 1. Baseline data for men undergoing screening for prostate cancer in ERSPC Rotterdam and Gunma study

Variables	Region						Statistical significance
	ERSPC Rotterdam			Gunma study			
n	3.163			2.650			
Age (years old)							
Mean ± S.D.	61,8	±	4,6	64,2	±	4,4	p<0.0001†
Median	61			64			
range	55	-	71	55	-	73	
Age distribution	n	(	%)	n	(	%)	
55-59	1.308	(	41%)	347	(	13%)	p<0.0001✻
60-64	970	(	31%)	1.062	(	40%)	
65-69	774	(	24%)	895	(	34%)	
70-74	111	(	4%)	346	(	13%)	
PSA (ng/ml)							
Mean ± S.D.	1,5	±	0,9	1,2	±	0,8	p<0.0001†
Median	1,3			1,0			
PSA distribution	n	(	%)	n	(	%)	
0.0-0.9 ng/ml	820	(	26%)	1.319	(	50%)	p<0.0001✻
1.0-1.9 ng/ml	1.542	(	49%)	907	(	34%)	
2.0-2.9 ng/ml	522	(	17%)	294	(	11%)	
3.0-3.9 ng/ml	279	(	9%)	130	(	5%)	

ERSPC Rotterdam=European Randomized Study of Screening for Prostate Cancer, section Rotterdam, Gunma study=population-based study of screening for prostate cancer in Gunma Prefecture, Japan
† Results of comparisons by Welch's t test
✻ Results of comparisons by χ2 test

In the Rotterdam cohort, probabilities of freedom from prostate carcinoma after a 4-year screening interval were calculated according to age group and PSA range. In contrast, in the Gunma cohort, the cumulative probability of freedom from prostate carcinoma over the course of the 4-year observation period was estimated using the Kaplan–Meier method. Differences between the two cohorts in terms of the likelihood of freedom from prostate carcinoma were assessed using the two-sided log-rank test, with the assumption that prostate carcinoma could not be detected during the first 3 years after initial screening in the Rotterdam cohort. Cumulative probabilities offreedom from PSA increases to levels >= 4.0 ng/ml. during the 4-year observation period also were estimated, with stratification

according to age and PSA level, using the Kaplan–Meier method, and cumulative probabilities of freedom from PSA increases to levels >= 2.0, 3.0, and 4.0 ng/ml. were compared between the Dutch and Japanese cohorts using the two-sided logrank test.
The prognostic utility of baseline PSA levels, age at initial screening, and geographic location was investigated using Cox proportional hazards modelling. For multivariate analysis, baseline PSA levels were divided into 4 categories (0.0–0.9, 1.0 –1.9, 2.0 –2.9, and 3.0 –3.9 ng/ml.), as was patient age at initial screening (55–59, 60–64, 65–69, and 70–74 years).

RESULTS

Of the 3163 men in the ERSPC Rotterdam cohort, 639 (20.2%) had PSA levels >= 3.0 ng/ml. after 4 years, and 569 of these 639 men underwent prostate biopsy. Another 135 participants (4.3%) who had PSA levels between 1.0 and 2.9 ng/ml. had biopsy indicated on the basis of PSA levels alone, in accordance with a side study protocol, and 128 of these participants subsequently underwent prostate biopsy. Thus, a total of 697 patients (22.0%) underwent prostate biopsy at 4 years after initial screening, and prostate carcinoma was detected in 164 (5.2%). Of the 164 patients diagnosed with prostate carcinoma, 79 (48%) and 85 (52%) had PSA levels < 4.0 ng/ml. and >= 4.0 ng/ml., respectively.
Of the 2650 men in the Gunma cohort, 215 (8.1%) had abnormal findings on DRE and/or TRUS and follow up PSA levels in the reflex range of 0.0 –3.9 ng/ml., and an additional 133 patients (5.0%) had PSA levels >= 4.0 ng/mL on follow up. A total of 133 patients (5.0%) underwent prostate biopsy, and prostate carcinoma was detected in 28 (1.1%; average time from initial screening, 2.6 years). Of the 28 patients diagnosed with prostate carcinoma, 9 (32%) and 19 (68%) had PSA levels < 4.0 ng/ml. and >= 4.0 ng/ml., respectively.
Table 2 presents cumulative probabilities of freedom from prostate carcinoma according to age at initial screening. The cumulative probability of freedom from prostate carcinoma at 4 years after initial screening was significantly lower in the Rotterdam cohort than in the Gunma cohort for patients ages 55–59, 60–64, and 65–69 years. The overall cumulative probability of freedom from prostate carcinoma at 4 years from baseline also was significantly lower in the Rotterdam cohort (94.8%) than in the Gunma cohort (98.4%).
Cumulative probabilities of freedom from prostate carcinoma according to initial PSA level are presented in Table 3. The likelihood of freedom from prostate carcinoma decreased significantly with increasing initial PSA level in both Dutch and Japanese men. Within each PSA group, the cumulative probability of freedom from prostate carcinoma was lower for Dutch patients compared with Japanese patients, but the difference was not statistically significant.

Table 2. Risk of developing screen detectable prostate cancer after 4 years of follow-up observations stratified by age range at initial screening in ERSPC Rotterdam and Gunma study.

Region	Age range at initial screening (years old)	No. of participants at risk				The risk of prostate cancer detection			Statistical significance
		Elapsed years after initial screening							
		1	2	3	4	No. of events observed	Rate of freedom from prostate cancer	95% Confidence Interval	
ERSPC Rotterdam	55-59	-	-	-	1.308	58	95,6%	(94,4% - 96,7%)	p<0.0001: ERSPC (all) < Gunma (all) p>0.05: All comparisons within ERSPC Rotterdam. p=0.0104: ERSPC (55-59) < Gunma (55-59) p=0.0003: ERSPC (60-64) < Gunma (60-64) p=0.0047: ERSPC (65-69) < Gunma (65-59) p>0.05: ERSPC (70-74) = Gunma (70-74) p=0.0387: Gunma (55-59) > Gunma (70-74) p>0.05: All the other comparisons within the Gunma study.
	60-64	-	-	-	970	53	94,5%	(93,1% - 96,0%)	
	65-69	-	-	-	774	47	93,9%	(92,2% - 95,7%)	
	70-74	-	-	-	111	6	94,6%	(90,3% - 98,9%)	
	All	-	-	-	3.163	164	94,8%	(94,0% - 95,6%)	
Gunma study	55-59	347	295	257	187	1	99,5%	(98,4% - 100%)	
	60-64	1.062	897	718	521	9	98,6%	(97,7% - 99,6%)	
	65-69	895	767	638	459	13	98,0%	(96,8% - 99,1%)	
	70-74	346	226	142	64	5	98,0%	(96,1% - 99,9%)	
	All	2.650	2.185	1.755	1.231	28	98,4%	(97,8% - 99,0%)	

ERSPC Rotterdam=European Randomized Study of Screening for Prostate Cancer, section Rotterdam, Gunma study=population-based study of screening for prostate cancer in Gunma Prefecture, Japan

Table 3. Risk of developing screen detectable prostate cancer after 4 years of follow-up observations according to initial PSA range in ERSPC Rotterdam and Gunma study.

Region	PSA range at initial screening (ng/ ml)	No. of participants at risk				The risk of prostate cancer detection			Statistical significance
		Elapsed years after initial screening							
		1	2	3	4	No. of events observed	Rate of freedom from prostate cancer	95% Confidence Interval	
ERSPC Rotterdam	0.0-0.9	-	-	-	820	6	99,3%	(98,7% - 99,9%)	p=0.0008: ERSPC (0.0-0.9) > ERSPC (1.0-1.9) p<0.0001: ERSPC (0.0-0.9) > ERSPC (2.0-2.9), ERSPC (3.0-3.9) p<0.0001: ERSPC (1.0-1.9) > ERSPC (2.0-2.9), ERSPC (3.0-3.9) p=0.0116: ERSPC (2.0-2.9) > ERSPC (3.0-3.9) p>0.05: ERSPC = Gunma (in the same initial PSA ranges) p=0.0036: Gunma (0.0-0.9) > Gunma (1.0-1.9)> Gunma (2.0-2.9) p<0.0001: Gunma (0.0-0.9) > Gunma (2.0-2.9), Gunma (3.0-3.9) p<0.0001: Gunma (1.0-1.9) > Gunma (3.0-3.9) p=0.0193: Gunma (2.0-2.9) > Gunma (3.0-3.9)
	1.0-1.9	-	-	-	1.542	43	97,2%	(96,4% - 98,1%)	
	2.0-2.9	-	-	-	522	63	87,9%	(85,1% - 90,8%)	
	3.0-3.9	-	-	-	279	52	81,4%	(76,7% - 86,0%)	
Gunma study	0.0-0.9	1.319	-1.095	884	616	1	99,9%	(99,8% - 100%)	
	1.0-1.9	907	762	615	439	8	98,7%	(97,7% - 99,6%)	
	2.0-2.9	294	235	182	129	9	94,5%	(90,8% - 98,2%)	
	3.0-3.9	130	93	74	47	10	88,5%	(81,3% - 95,7%)	

ERSPC Rotterdam=European Randomized Study of Screening for Prostate Cancer, section Rotterdam, Gunma study=population-based study of screening for prostate cancer in Gunma Prefecture, Japan

The overall cumulative probability of freedom from PSA increases to levels >= 4.0 ng/ml. at 4 years from baseline was significantly lower in the Rotterdam cohort than in the Gunma cohort (Table 4). In addition, after stratification according to patient age, the cumulative probability of freedom from such PSA increases was found to be significantly higher for patients ages 55–59 years compared with patients ages 60–64 years and patients ages 65–69 years in the Rotterdam cohort. Likewise, in the Gunma cohort, the cumulative probability of such PSA increases was significantly higher for patients ages 55–59 years compared with patients ages 60–64 years, patients ages 65–69 years, and patients ages 70–74 years. In addition, within each age group, except for patients ages 70–74 years, the cumulative probability of freedom from PSA increases to levels >= 4.0 ng/ml. was significantly lower in the Rotterdam cohort compared with the Gunma cohort.

PSA-stratified cumulative probabilities of freedom from PSA increases at 4 years after initial screening are presented in Table 5. In both Dutch and Japanese patients, the cumulative probability of freedom from PSA increases to levels >= 4.0 ng/ml. decreased in the following order with regard to initial PSA range: 3.0– 3.9 ng/ml., 2.0 –2.9 ng/ml., 1.0 –1.9 ng/ml., and 0.0 –1.9 ng/ml. The same trend was observed in our analyses of the cumulative probabilities of freedom from PSA increases to levels >= 2.0 and 3.0 ng/mL, respectively. Within each PSA group, there was no statistically significant difference between Dutch and Japanese patients in terms of the cumulative probability of freedom from PSA increases.

Table 4. Cumulative rate of freedom from PSA increase to 4.0 ng/ml or greater during 4 years of observations stratified by age range at initial screening in ERSPC Rotterdam and Gunma study (Exponential Model).

Region	Age range at initial screening (years old)	No. of participants at risk				The risk of PSA increase to 4.0 ng/ml or greater						Statistical significance
		Elapsed years after initial screening				No. of events expected				Cumulative rate of freedom from PSA increase	95% Confidence Interval	
						Elapsed years after initial screening						
		1	2	3	4	1	2	3	4			
ERSPC Rotterdam	55-59	1.308	1.294	1.273	1.240	14	21	33	46	91,3%	(89,7% - 92,8%)	p<0.0001: ERSPC (all) < Gunma (all) p=0.0292: ERSPC (55-59) > ERSPC (60-64) p=0.0002: ERSPC (55-59) > ERSPC (65-69) p>0.05: All the other comparisons within ERSPC Rotterdam. p=0.0038: ERSPC (55-59) < Gunma (55-59) p=0.0004: ERSPC (60-64) < Gunma (60-64) p=0.0008: ERSPC (65-69) < Gunma (65-59) p>0.05: ERSPC (70-74) = Gunma (70-74) p=0.0298: Gunma (55-59) > Gunma (60-64) p=0.0051: Gunma (55-59) > Gunma (65-69) p=0.0052: Gunma (55-59) > Gunma (70-74) p>0.05: All the other comparisons within the Gunma study.
	60-64	970	947	919	884	23	28	35	24	88,7%	(86,6% - 91,1%)	
	65-69	774	756	731	698	18	25	33	31	86,2%	(83,7% - 88,7%)	
	70-74	111	110	106	102	1	4	4	1	91,0%	(85,6% - 96,4%)	
	All	3.163	3.107	3.029	2.924	56	78	105	102	89,2%	(88,1% - 90,3%)	
Gunma study	55-59	347	294	254	183	1	3	2	2	96,9%	(94,6% - 99,1%)	
	60-64	1.062	889	702	502	15	18	14	5	93,7%	(92,0% - 95,5%)	
	65-69	895	755	620	441	16	16	16	7	92,2%	(90,1% - 94,2%)	
	70-74	346	222	139	62	11	3	3	1	91,9%	(87,5% - 96,4%)	
	All	2.650	2.160	1.715	1.188	43	40	35	15	93,4%	(92,3% - 94,5%)	

ERSPC Rotterdam=European Randomized Study of Screening for Prostate Cancer, section Rotterdam, Gunma study=population-based study of screening for prostate cancer in Gunma Prefecture, Japan

Table 5. Cumulative rate of freedom from prostate cancer and PSA increase during 4 years of observations according to initial PSA range in ERSPC Rotterdam and Gunma study (Exponential Model).

Region	PSA range at initial screening (ng/ ml)	PSA levels in consecutive screening (ng/ml)								
		≥2.0			≥3.0			≥4.0		
		No. of events expected	Cumulative rate of freedom from PSA increase	95% Confidence Interval	No. of events expected	Cumulative rate of freedom from PSA increase	95% Confidence Interval	No. of events expected	Cumulative rate of freedom from PSA increase	95% Confidence Interval
ERSPC Rotterdam	0.0-0.9	20	97,6%	(96,5% - 98,6%)	5	99,4%	(98,9% - 99,9%)	5	99,4%	(98,9% - 99,9%)
	1.0-1.9	506	67,2%	(64,8% - 69,6%)	146	90,5%	(89,0% - 92,0%)	53	96,6%	(95,6% - 97,5%)
	2.0-2.9	-	-		271	48,1%	(43,7% - 52,5%)	124	76,2%	(72,5% - 80,0%)
	3.0-3.9	-	-		-	-		159	43,0%	(37,1% - 48,9%)
Gunma study	0.0-0.9	22	97,3%	(96,2% - 98,5%)	7	99,3%	(98,7% - 99,9%)	5	99,6%	(99,2% - 99,95%)
	1.0-1.9	204	72,4%	(69,0% - 75,9%)	49	91,6%	(89,2% - 94,0%)	20	96,6%	(95,1% - 98,2%)
	2.0-2.9	-	-		105	54,3%	(47,1% - 61,5%)	50	74,6%	(68,1% - 81,1%)
	3.0-3.9	-	-		-	-		58	46,8%	(36,6% - 57,1%)
Statistical significance		p<0.0001: ERSPC (0.0-0.9) > ERSPC (1.0-1.9) p<0.0001: Gunma (0.0-0.9) > Gunma (1.0-1.9) p>0.05: ERSPC = Gunma (in the same initial PSA ranges)			p<0.0001: ERSPC (0.0-0.9) > ERSPC (1.0-1.9) > ERSPC (2.0-2.9) p<0.0001: Gunma (0.0-0.9) > Gunma (1.0-1.9) >Gunma (2.0-2.9) p>0.05: ERSPC = Gunma (in the same initial PSA ranges)			p<0.0001: ERSPC (0.0-0.9) > ERSPC (1.0-1.9) > ERSPC (2.0-2.9) >ERSPC (3.0-3.9) p=0.0001: Gunma (0.0-0.9) > Gunma (1.0-1.9) p<0.0001: Gunma (0.0-0.9) > Gunma (2.0-2.9) >Gunma (3.0-3.9) p<0.0001: Gunma (1.0-1.9) > Gunma (2.0-2.9) >Gunma (3.0-3.9) p>0.05: ERSPC = Gunma (in the same initial PSA ranges)		

ERSPC Rotterdam=European Randomized Study of Screening for Prostate Cancer, section Rotterdam, Gunma study=population-based study of screening for prostate cancer in Gunma Prefecture, Japan

Table 6 summarizes the results of Cox proportional hazards analysis. Neither age nor geographic location was independently predictive of PSA increases to levels >= 4.0 ng/ml. In contrast, initial PSA levels may be significantly predictive of such increases (P < 0.0001). Multivariate analysis also revealed that after controlling for age and initial PSA level, Japanese and Dutch patients did not have significantly different risks of experiencing PSA increases to levels >= 4.0 ng/ml.

Table 6. Significance of the parameteres for predicitng PSA progression using Cox's proportional Hazard model

Factor	Subdivided group being compared	Regression coefficient	p Value
Age (years old)	55-59 • 60-64 • 65-69 • 70-74	-0,001	0,986
Baseline PSA level (ng/ml)	0.0-0.9 • 1.0-1.9 • 2.0-2.9 • 3.0-3.9	1,595	<0.0001
Region	Gunma • Rotterdam	-0,08	0,451

DISCUSSION

To our knowledge, no study to date has investigated the risk of developing prostate carcinoma and having PSA levels >= 4.0 ng/ml. at 4 years after a negative prostate carcinoma screening examination. Our findings indicate that the risk of developing prostate carcinoma was greater for Dutch men compared with Japanese men within the same age group, and this difference was consistent with the observed differences in age-specific baseline PSA distributions between Dutch and Japanese patients.

The current study compared participants in two different screening trials–one based in Europe and the other based in Japan. Due to underlying differences in screening practices between these two regions, the comparability of cumulative prostate carcinoma incidence data may be limited. Specifically, prostate carcinoma detection rates at 4 years from baseline may have been biased by the following factors: 1) differences in screening modalities used; 2) differences in the PSA cut-off levels selected as indications for biopsy; 3) differences in biopsy methods used; 4) differences in compliance with biopsy recommendations among patients with abnormal findings; and 5) differences in histologic criteria between the ERSPC and Gunma studies.

With regard to initial screening methods, all participants in the Rotterdam cohort underwent screening via PSA testing, DRE, and TRUS; in contrast, 37.2% of all participants in the Gunma cohort (986 of 2650) did not undergo TRUS at study entry. Thus, patients who would have had abnormal findings on TRUS may have been enrolled in the current study. In the Rotterdam Section of the ERSPC, 8.6% of all men who had PSA levels < 4.0 ng/ml. and normal findings on DRE (447 of 4727) had abnormal findings on TRUS. Among these 447 patients, prostate carcinoma was detected in 38 (data not shown), corresponding to a 0.8% prevalence of prostate carcinoma among patients with normal DRE findings and PSA levels < 4.0 ng/ml.

This rate should not be used for the statistical adjustment of findings made in the Gunma cohort, however, because of the observed differences between Japanese and Dutch men in terms of baseline PSA distribution. Three additional participants in the Gunma study who had PSA levels in the reflex range of 3.1– 4.0 ng/ml. and no suspicious findings on DRE and/or TRUS and who were subsequently diagnosed with prostate carcinoma were excluded from the current study because of recent age-specific changes in PSA-related biopsy indications. Nonetheless, overall, it appears that the recruitment bias encountered in the current study was not substantial.

PSA cut-off levels did not differ dramatically between the Dutch and Japanese cohorts. Furthermore, although the biopsy procedures used in these two studies differed with regard to the route taken, the effects of this difference may have been minimized by the introduction of TRUS-guided sextant biopsy in both cohorts, provided that similar numbers of biopsy cores were obtained from Dutch and Japanese patients; consistent with this provision, the number of biopsy cores to be obtained from the peripheral zone was set at 6 in both the Rotterdam cohort and the Gunma cohort.

Although it appears that differences in screening modalities, PSA cut-off levels, and biopsy methods can be disregarded, variations in terms of compliance with biopsy recommendations may represent the most serious barrier to the accurate estimation of cumulative probabilities of freedom from prostate carcinoma. Among patients in the Rotterdam cohort who had PSA levels >= 3.0 ng/ml., the proportion who underwent prostate biopsy was relatively high (89% [569 of 639]). In contrast, of the men in the Gunma cohort who had PSA levels >= 4.0 ng/ml. or abnormal findings on DRE and/or TRUS, only a relatively small proportion (38% [133 of 348]) underwent biopsy. This discrepancy in terms of compliance rates may stem from differences in follow up strategies and study policies between Europe and Japan. Due to the low rate of compliance with biopsy recommendations, the rate of prostate carcinoma detection may have been underestimated in the Gunma study. In the Rotterdam cohort, prostate biopsy was recommended for all patients with abnormal findings on PSA testing, DRE, and/or TRUS, and biopsy was performed for all such patients except for those who had severe complications or were receiving anticoagulant therapy. Thus, using data from the Rotterdam cohort, it would be possible to estimate the number of prostate carcinoma cases that went undetected in men who did not undergo prostate biopsy despite having abnormal findings on PSA testing, DRE, and/ or TRUS. In the Gunma study, for men who had abnormal findings on DRE or TRUS, prostate biopsy tended to be performed immediately after it was recommended, especially for those whose PSA levels fell between the age-specific reference cut-off level and 10 ng/ml.; therefore, it would be difficult, using PSA distributions alone, to estimate the number of prostate carcinoma cases that went undetected among men with abnormal findings on PSA testing who did not undergo biopsy.

We were able to calculate the cumulative likelihood of freedom from PSA increases in both the Dutch and Japanese cohorts, with interval PSA levels being estimated using an exponential model. The probability of a PSA increase to levels >= 4.0 ng/ml. may be indicative of a patient's risk of developing prostate carcinoma, although the percentage

of patients who experience such PSA increases exceeds the actual prevalence of prostate carcinoma, because of the possibility of non-malignancy-related increases in PSA levels [6]. Nonetheless, comparison of the Dutch and Japanese cohorts with regard to the percentages of patients experiencing PSA increases to levels >= 4.0 ng/ml. (rather than with regard to the cumulative probability of prostate carcinoma detection) is likely to yield a more accurate estimate of the true relative cumulative likelihood of developing prostate carcinoma in each of these two cohorts. Comparisons of this type are objective and allow us to ignore differences in screening modalities, PSA testing cut-off levels, differences in prostate biopsy procedures, and, most importantly, significant differences in patient compliance with biopsy recommendations.

With regard to the concern that there may have been differences in histologic criteria between the Gunma study and the Rotterdam Section of the ERSPC, all histologic review of biopsy specimens in both cohorts was performed by urologic pathologists. Although interobserver variability in terms of Gleason grading may have been present, bias with regard to the diagnosis of cases as malignant or nonmalignant by urologic pathologists in Japan or the Netherlands would have been unlikely.

Only 28 cases of prostate carcinoma were found in the Gunma cohort, and when stratification according to baseline PSA or 5-year age range was performed, no stratum contained more than 13 cases. Thus, there may not have been adequate power to compare Dutch and Japanese patients within each stratum, although significant differences were found between the two cohorts in terms of the cumulative likelihood of freedom from prostate carcinoma at 4 years after initial screening for patients ages 55–59 years, patients ages 60–64 years, and patients ages 65–69 years. In contrast, comparisons of cumulative rates of freedom from PSA increases to levels >= 4.0 ng/ml. within each age group may have had adequate statistical power. Rates of freedom from such increases were significantly lower in the Rotterdam cohort than in the Gunma cohort for patients ages 55–59 years, patients ages 60–64 years, and patients ages 65–69 years. Among patients ages 70–74 years, however, there was no significant difference between the two cohorts in terms of the cumulative rate of freedom from such increases, just as there was no significant difference in the cumulative probability of freedom from prostate carcinoma within this age group. Taken together, these results confirm that the risk of developing prostate carcinoma is significantly higher for 55–69-year-old Dutch men with no suspicious findings on PSA testing or DRE than for their Japanese counterparts.

Epidemiologic surveys have revealed similar trends with regard to prostate carcinoma incidence in Japan and the Netherlands; the age-adjusted incidence of prostate carcinoma among Japanese males is 11.1 per 100,000, compared with 55.9 per 100,000 among Dutch males [7]. Based on rates of freedom from PSA increases, the cumulative probabilities of developing prostate carcinoma within a given 4-year period were 2.8 and 1.8 times greater for Dutch men compared with Japanese men within the 55–59-year-old and 60– 69-year-old age groups, respectively. In contrast, PSA increases were equally likely for Dutch males and Japanese males ages 70–74 years. Thus, differences in prostate carcinoma incidence between the Netherlands and Japan may be growing smaller with increasing age.

Cumulative rates of freedom from both prostate carcinoma detection and PSA increases did not differ significantly within initial PSA range groups between the Rotterdam and Gunma cohorts. These results confirm that the risk of developing screen-detectable prostate carcinoma may be the same for European and Japanese men with the same baseline PSA levels. Multivariate analysis also revealed that the cumulative probability of PSA increases to >= 4.0 ng/ml was not significantly different between the Dutch and Japanese cohorts after controlling for age and PSA levels at initial screening. Therefore, differences in the cumulative probability of developing prostate carcinoma within the 55–69-year-old age group may originate from higher baseline PSA levels in Dutch men compared with Japanese men.
The exponential phase of PSA elevation was shown to begin 7–9 years before clinical tumour detection [8]. Therefore, patients in the current study who were found to have prostate carcinoma may have already harboured minute, but potentially active, prostate carcinomas at initial screening. Yatani et al. [9] demonstrated that the prevalence of latent prostate carcinoma was 1.5 times higher in white U.S. men (34.6%) compared with Japanese men (20.5%). When those investigators subdivided latent prostate carcinoma cases into two groups according to pathologic features (latent infiltrative or latent noninfiltrative), the prevalence of the former type reflected the overall prevalence of clinical malignancy. The findings made in the current study demonstrate that the risk of developing screen-detectable prostate carcinoma is expected to be 1.8 times higher for Dutch men compared with Japanese men within the 60–69 year-old age range. Therefore, the difference in cumulative rates of PSA increases to levels >= 4.0 ng/ml may have originated from the difference in the prevalence of latent infiltrative prostate carcinoma. Although the probability of having potentially active prostate carcinoma may increase with increasing baseline PSA levels, this probability does not appear to differ between Dutch and Japanese men within the same baseline PSA category. Once an active tumour, even if minute, has developed, the risk of developing screen-detectable disease may be the same for Dutch and Japanese men. It is hypothesized that the difference in prostate carcinoma incidence between men in European countries and those in Asian countries may result from the difference in the promotion process up until the development of these minute tumours. Furthermore, it may be possible to predict relative differences in prostate carcinoma development between any pair of nations, provided that large screening databases of baseline PSA levels are available.

In conclusion, within the 55–69-year-old age range, the cumulative probability of developing prostate carcinoma over a 4-year observation period was 1.8 –2.8 times higher in Dutch males without any suspicious findings compared with their Japanese counterparts. The cumulative probability of developing prostate carcinoma significantly increased with increasing baseline PSA in both nations, and prostate carcinoma risk appeared to be equivalent for Dutch and Japanese males within each baseline PSA group.

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PROSTATE CANCER DETECTION IN PSA RANGE 2.0 - 3.9 NG/ML – VALUE OF PERCENT FREE PSA ON TUMOUR DETECTION AND TUMOUR AGGRESSIVENESS

7

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ABSTRACT

Purpose. To evaluate the positive predictive value (PPV) and cancer detection rate (CDR) in the PSA range 2.0 – 3.9 ng/ml and to assess the value of percent free PSA (%fPSA) on tumour detection and tumour aggressiveness in this low PSA range.

Participants and Methods. Out of 3,623 men who were attending the second round of screening within the European Randomized study of Screening for Prostate Cancer, section Rotterdam, 883 men had PSA values of 2.0 – 3.9 ng/ml. These men were offered a laterally directed sextant biopsy. Free PSA was prospectively determined from pretreatment sera. Cancers were classified as prognostically favourable and unfavourable by using biopsy results and other pretreatment diagnostic features.

Results. Using PSA range 2.0 – 3.9 ng/ml as a biopsy indication, 126 cancers were detected, resulting in a PPV of 17.1% and a CDR of 14.3%. By using %fPSA and setting relative sensitivity at 95%, 9% of biopsies could have been avoided.
Unfavourable tumour characteristics were found in 46.9% of the men with T1C tumours. Mean %fPSA was significantly lower for such men compared to men with favourable tumour characteristics. Ninety percent of the men with %fPSA lower than 10% had unfavourable tumour characteristics.

Conclusions. The PSA range 2.0 – 3.9 ng/ml is accessible for prostate cancer screening. Percent free PSA is of moderate value in avoiding unnecessary biopsies in the PSA range 2.0 – 3.9 ng/ml. However in assessing tumour aggressiveness on biopsy results, %fPSA is predictive and can be used to select treatment options, such as watchful waiting.

INTRODUCTION

Two important goals of the European Randomized study of Screening for Prostate Cancer (ERSPC) are to establish or disprove the effect of screening on prostate cancer mortality and to evaluate the screening tests.
In order to decrease cancer specific mortality it is important to detect those cancers, which are curable and pose a potential threat to the life of the participant.
By lowering the PSA threshold more curable cancers are detected and the lead time is assumed to be longer. On the other hand the risk of diagnosing and treating cancers, which may not pose a threat to the patient's life, will be higher. On this background an evaluation and optimization of screening tests is desirable.
Earlier studies [1] showed a low predictive value of digital rectal examination (DRE) and/ or transrectal ultrasonography (TRUS) for detecting prostate cancer in men with a PSA value less than 4.0 ng/ml. Also logistic regression analysis revealed that DRE and/ or TRUS miss 63.5% of prostate cancers in this PSA range. Eighty four percent of the cancers found in this PSA range on abnormal DRE and/ or TRUS alone, were histologically organ confined and approximately half of the tumours with a PSA lower than 4.0 ng/ml had aggressive characteristics on radical prostatectomy specimens.
In this paper we report the results of a side study in the second round of the Rotterdam section of the ERSPC in which every consecutive participant with a PSA value of 2.0 ng/ml or greater had a biopsy indication. We report the Cancer Detection Rate (CDR) and Positive Predictive Value (PPV) in this low PSA range. The value of percent free PSA (%fPSA) on tumour detection and tumour aggressiveness were tested within the PSA range 2.0 – 3.9 ng/ml.
This is to our knowledge the first study, which prospectively evaluates the detection rates and the value of %fPSA in these low PSA ranges on a large number of consecutive participants, in the setting of a randomized controlled trail.

PARTICIPANTS AND METHODS

The ERSPC, section Rotterdam

Within the Dutch (Rotterdam) section of the ERSPC, 42,376 men age 55 – 74 years, were randomized into a screening and control group. After a number of pilot studies [2] the study started in June 1994. Participants in the screening group were offered a PSA measurement, DRE and TRUS. Initially the biopsy indication was set on a PSA >= 4.0 ng/ml or a suspicious DRE or TRUS. Based on predictions by logistic regression [3], the European study group decided in February 1997 to screen by using PSA only and to biopsy all men with a PSA of 3.0 ng/ml or greater. After a screening interval of four years all participants within the above-mentioned age group were re-invited for the second round of screening. PSA measurement was done and when the PSA was equal or greater than 3.0 ng/ml, a DRE, TRUS and biopsy were performed.

The PSA 2.0 – 3.9 ng/ml study

The protocol of this side study was commenced in April 2001, within the second round of screening. During the first round 92.8% of these men were screened by biopsy indication PSA>= 3.0 ng/ml. The remaining 63 men (7.1%) had a biopsy indication when PSA was equal or above 4.0 ng/ml or a suspect DRE or TRUS. Prospectively all consecutive participants presenting with a PSA value equal or greater than 2.0 ng/ml were offered a DRE, TRUS and a laterally directed sextant biopsy. Within PSA range 2.0 to 3.9 ng/ml additional values of free PSA were determined. Percent free PSA was calculated by dividing free PSA by total PSA values. All participants of this side study signed an informed consent form and this study is approved according to the Dutch law on population screening.

Cancer Detection Rates (CDR) and Positive Predictive Values (PPV) were determined within this PSA range. The CDR is defined as the proportion of cancers of all those screened in the PSA range. The PPV is defined as the number of men who have a positive test and have cancer divided by those who have a positive test and were biopsied. A positive test in this study is a PSA equal or greater than 2.0 ng/ml. If in a given subgroup all men are biopsied, the PPV and the CDR are identical.

After the blood draw the serum samples were processed and refrigerated within 3 hours. Serum samples not analyzed the same day were stored at –70 C until analyzed. Total and free Hybritech® PSA were measured on Beckman Coulter's Access® immunoanalyzer.

Pathological classification

Features of aggressiveness for biopsy specimens were categorized according to Epstein et al [4,5]. Unfavourable tumour characteristics were defined as a PSA Density (PSAD) >0.1 ng/ml/g and/ or Gleason score >= 7 and/ or >= 3 tumour positive biopsy cores and/ or more than 50% tumour involvement in at least one of the cores.

Statistical analyses

Statistical analyses were done on commercially available software. Receiver Operator Characteristics (ROC) curves were constructed using Analyse-it Software. Mean values were compared with t-tests for normally distributed parameters and the Mann–Whitney U test for non-normal parameters. The predictive accuracy of the tests was assessed by ROC analyses. Multivariate logistic regression was performed using all available relevant parameters in a backward method.

RESULTS

From April 2001 up to December 2002, 3623 men were screened within the protocol of this side study. In 64% of these men the PSA value was lower than 2.0 ng/ml. Eight hundred eighty three men (24.4%) had a PSA value within the range 2.0 – 3.9 ng/ml and 419 men (11.6%) had a PSA value larger than 4.0 ng/ml. The percentage of men biopsied in PSA range 2.0 - 3.9 ng/ml was 83.4%. This did not differ significantly for the two PSA ranges. The number of detected prostate cancers, the PPV and CDR per PSA range are shown in table 1. The PPV in the PSA range 2.0 – 2.9 ng/ml and 3.0 – 3.9 ng/ml is 15.7% and 19.8% respectively. Similar results were obtained when the 63 men with a different biopsy indication in the first round where left out of the analyses.

Table 1. Positive predictive value (PPV) and cancer detection rate (CDR) per PSA range

PSA range (ng/ml)	*Number*	*Biopsied men (%)*	*PCa*	*PPV (%)*	*CDR (%)*
2.0 - 2.4	330	272 (82.4%)	41	15.1%	12.4%
2.5 - 2.9	246	206 (83.7%)	34	16.5%	13.8%
2.0 - 2.9	**576**	**478 (83%)**	**75**	**15.7%**	**13.0%**
3.0 - 3.4	173	143 (82.7%)	29	20.3%	16.8%
3.5 - 3.9	134	115 (85.8%)	22	19.1%	16.4%
3.0 - 3.9	**307**	**258 (84%)**	**51**	**19.8%**	**16.6%**
Total	883	736 (83.4%)	126	17.1%	14.3%

Tumour detection

Table 2 shows the patient characteristics of the biopsied men in the PSA range 2.0 –3.9 ng/ml. The mean value of %fPSA of men with prostate cancer detected is 17.0% versus 19.7% for men with a negative biopsy. This difference is significant (P<0.001). Mean age and PSA value did not differ significantly in this population. Prostate volume was significantly larger in men with no prostate cancer detected.

Table 2. Mean values age, prostatic volume, tPSA, fPSA and %fPSA biopsied men in PSA range 2.0 -3.9 ng/ml

Parameter	no PCa (n=610)	PCa (n=126)	P value
age (yrs)	66.3	67.0	ns
prostate volume (ml)	43.0	35.0	<0.001
tPSA (ng/ml)	2.7	2.8	ns
fPSA (ng/ml)	0.53	0.48	0.005
%fPSA (%)	19.7	17.0	<0.001

Table 3 shows the PPV's of tumour detection in the PSA range 2.0 – 3.9 ng/ml subdivided for the different %fPSA ranges. In two biopsied men the free PSA value was not determined, leaving 734 men. Lower %fPSA ranges are significantly associated with higher PPV's for tumour detection (Chi square, P<0.001).

Table 3. PPV per % free PSA range on tumour detection

% free PSA	*Biopsied men n (%)*	*PCa*	*PPV*
< 10%	38 (5.2%)	13	34.2%
10 - 15%	168 (22.9%)	39	23.2%
15 - 20%	227 (30.9%)	39	17.2%
20 - 25%	176 (24.0%)	20	11.4%
>= 25%	125 (17.0%)	15	12.0%
Total	734 (100%)	126	17.1%

P < 0.001 (Chi square)

Receiver operating characteristics curves show an area under the curve (AUC) for percent free PSA of 62% compared with 55% for total PSA (Figure 1). This indicates a slightly better discrimination between men with and without prostate cancer than total PSA alone in this PSA range. Only approximately 9% of the biopsies could be avoided detecting still 95% of the biopsy detectable tumours. On multivariate logistic regression %fPSA (P=0.001), free PSA (P=0.006), age (P=0.014) and prostate volume (P=0.020) were the most important predictors for detecting prostate cancer.

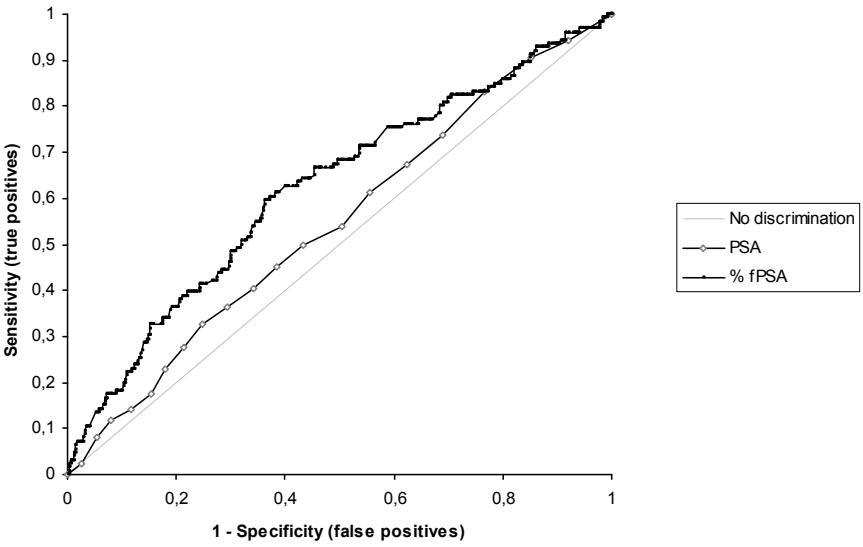

Figure 1. *ROC-curves for tumour detection. AUC(PSA)=55%. AUC(%fPSA)=62%. N=734.*

Tumour aggressiveness

Classification of aggressiveness of biopsy specimens according to Epstein as described in the participants and methods section, is validated in T1C tumours. Of the 126 prostate cancers found in this PSA range, 104 (82.5%) were found to have a non-palpable (T1C) tumour. Detailed biopsy results were available for 98 participants. Fifty-two men (53.1%) were classified as having favourable tumour characteristics and 46 (46.9%) had unfavourable tumour characteristics. Mean %fPSA was significantly lower for men with unfavourable tumour characteristics opposed to men with favourable tumour characteristics, respectively 15.4% versus 19.1% (P=0.006).

Table 4 shows that nine out of the ten men (90%) with a %fPSA value below 10% had indeed unfavourable tumour characteristics and the percentage of men with unfavourable tumour characteristics diminishes at higher %fPSA ranges (P=0.008).

Table 4. Distribution of men with unfavourable tumour characteristics per % free PSA range

% free PSA	PCa (n)	Unfavourable tumour characteristics (n)	Percent
< 10%	10	9	90%
10 - 15%	28	15	53.6%
15 - 20%	32	14	43.8%
20 - 25%	14	4	28.6%
>= 25%	14	4	28.6%
Total	98	46	46.9%

P = 0.008 (Chi square)

The AUC of receiver operating characteristics curves for %fPSA on discriminating between favourable and unfavourable tumour characteristics is 66% (Figure 2). On multivariate logistic regression %fPSA (P<0.001), free PSA (P=0.005), age (P=0.013) and prostate volume (P=0.020) were the most important predictors for unfavourable tumour characteristics prior to biopsy.

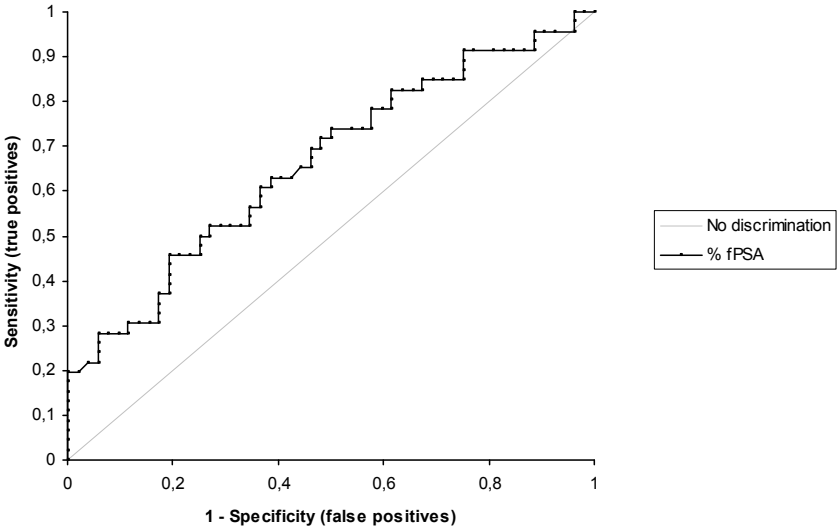

Figure 2. *ROC-curve %fPSA on tumour aggressiveness. AUC= 66%. N=98*

DISCUSSION

The use of a lower PSA cut-off as a biopsy indication will inevitably result in a decrease of the PPV and of relative sensitivity resulting in a larger proportion of men biopsied unnecessarily. Another concern and open question is the possible detection of more clinically insignificant tumours. This problem is addressed by classifying the detected cancers in two groups with a favourable and unfavourable prognosis. We also tested the value of percent free PSA in discriminating men with favourable and unfavourable tumour characteristics.

PPV and CDR in the PSA range 2.0 - 3.9 ng/ml

The definitions of PPV and CDR given in the method section allow differentiating between those men who had a biopsy indication and the 83.4% who were in fact biopsied. PPV and CDR would be identical if all men had been biopsied. An accurate determination of PPV and relative sensitivity of a test is only possible in a cohort of persons who all have undergone appropriate testing [6,7]. In this prospective biopsy study however, the proportion of those men who did not undergo testing is relatively small and the results can be considered as reasonably accurate with respect to the studied PSA ranges.

Our data show that the PSA range 2.0 - 3.9 ng/ml is accessible for cancer screening with a total PPV of 17.1% resulting from laterally directed sextant biopsies. This translates into 5.8 biopsies needed to detect one prostate cancer. Table 1 shows the PPV and CDR per PSA range in steps of 0.5 ng/ml. Based on these percentages one can choose cut-off values as they may appear useful.

Earlier studies related to ERSPC [8,9] showed that %fPSA can decrease the rate of unnecessary biopsies in the PSA range 4.0 – 10.0 ng/ml. Similar results in this PSA range were reported from other studies [10,11]. It was subject to this study whether similar improvement of relative specificity can be achieved in the lower PSA ranges. Unfortunately the improvement seen was only marginal. By setting relative sensitivity at 95% (allowing 5% of cancers to be missed) only 9% of biopsies could be saved as shown by ROC analysis in figure 1.

Catalona et al. [12-14] and Djavan [15] evaluated the value of %fPSA in the PSA range 2.6 - 4.0 ng/ml. These groups also reported a significantly different mean percent PSA value in men with and without prostate cancer. This translated into a moderate gain in omitting unnecessary biopsies in this PSA range and the AUC of the respective ROC curves ranged between 58.5 and 74.9%. However, in these studies not all men at risk were biopsied.

While in our study mean %fPSA differ significantly between cancer and non-cancer cases and although there is discrimination on multivariate analysis in relation to tumour detection, %fPSA adds only very little to total PSA in improving relative specificity (saving unnecessary biopsies).

In interpreting our results it must be taken into consideration that this study was carried out in a second round of screening. Test characteristics changed considerably for those tests that were used during the first round [16]. As mentioned above 92.9% of all men were biopsied during the first round if they presented with a PSA value of 3.0 ng/ml or higher. It is impossible to correct retrospectively for this problem and to relate our findings to a previously unscreened population. Still, the indication for a biopsy in men with a PSA value of 3.0 - 3.9 ng/ml in the first round probably decreased the PPV of this range and of higher PSA values in the second round. In men in this study with a PSA ranging from 2.0 to 2.9 ng/ml, no systemic biopsies were carried out in round 1. Hence, this PSA range is not influenced in this way and may in fact reflect the true PPV and CDR of a previously unscreened population.

Favourable and unfavourable tumour characteristics.

To determine tumour aggressiveness we used biopsy results and other pretreatment diagnostic findings. Although it might be more reliable to use data resulting from the pathological evaluation of radical prostatectomy specimens, the evaluation of pretreatment parameters is crucial for the development of future treatment strategies. We used the classification of biopsy results for T1C tumours according to Epstein [4] which was validated with the use of radical prostatectomy specimens. To be able to differentiate between favourable and unfavourable tumours we applied the results of the prospective evaluation of T1C cancers described by Carter et al [5]. We used the classification in which PSA-Density < 0.1 ng/ml /gram is considered to be predictive of favourable tumour characteristics (instead of

PSAD < 0.1 ng/ml/gram and PSAD between 0.1 and 0.15 ng/ml/gram with cancer less than 3 mm in one biopsy core). We find this classification easier to use and more reproducible in the clinical setting without compromising on the PPV and the negative predictive value (NPV) too much. The PPV and NPV in predicting pathological features of radical prostatectomy specimens through biopsy results are respectively 92% and 63%.
We then explored the relationship of %fPSA to those cancers classified as favourable and unfavourable. The data reproduced in table 4 showed us the distribution of unfavourable features within five groupings of %fPSA. It can be seen that nine out of ten men with a %fPSA below 10% have unfavourable tumour characteristics. Their proportion decreases steadily with an increasing %fPSA. This parameter may be useful to select and exclude patients for watchful waiting and other treatment regimens. The possible role of %fPSA in selecting treatment options should be further investigated preferably with respect to simpler and more reliable prognostic factors, which may become available in the future. Further improvement may also be possible by replacing %fPSA by either one of the different molecular forms of PSA, which are presently under study. Recent data [17,18] suggest the possibility that either -2 or -7 proPSA could be an active component within fPSA. Further studies are needed to investigate the usefulness of these molecular forms of PSA for improvement of test characteristics of PSA 2.0 - 3.9 ng/ml and of parameters of tumour aggressiveness.

CONCLUSIONS

The positive predictive value and cancer detection rate in the PSA range 3.0 – 3.9 ng/ml as a biopsy indication are comparable to higher PSA ranges in the second round of screening. Still 15.7% of the biopsied men in the PSA range 2.0 – 2.9 ng/ml have biopsy detectable prostate cancer. Percent free PSA is of moderate value in improving test characteristics in the PSA range 2.0 – 3.9 ng/ml. However in assessing tumour aggressiveness on biopsy results, %fPSA is predictive and can be used to select treatment options.

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hK2 AND FREE PSA, A PROGNOSTIC COMBINATION IN PREDICTING MINIMAL PROSTATE CANCER IN SCREEN-DETECTED MEN WITHIN THE PSA RANGE 4 - 10 NG/ ML.

8

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ABSTRACT

Objectives. The purpose of screening for prostate cancer is to decrease the disease-specific mortality. However not every screen-detected prostate cancer is a threat to the patient's life. The risk of overdetection and subsequent overtreatment in prostate cancer has been recognised. The purpose of this investigation was to evaluate the role of tumour markers total PSA, free PSA, and hK2, and their combinations in predicting minimal prostate cancer.

Methods. Within the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, The Netherlands, prebiopsy serum samples were analyzed for 100 selected men who underwent a radical prostatectomy for their screen-detected prostate cancer. All had a PSA value between 4 and 10 ng/ml prior to diagnosis. Minimal prostate cancer is defined as organ confined, no Gleason grade 4 or 5, and tumour volume <0.5 ml.

Results. Sera and tumour volumes from 91 men were available for analysis. Minimal prostate cancer was diagnosed in 16.5% of the selected cases. Mean tumour volume was 1.2 ml (range: 0.04–13.5); hK2, the algorithms hK2/fPSA, and hK2/%fPSA have significant correlations with tumour volume. Both algorithms also yielded the best test results in predicting minimal disease with an area under the receiver operator characteristics curve of 82%.

Conclusions. hK2 and percent free PSA have added prognostic value for the detection of minimal prostate cancer in screen-detected cases within PSA range 4–10 ng/ml. These biomarkers can possibly be used to select less invasive treatment options like active surveillance and to prevent overtreatment.

INTRODUCTION

The clinical introduction of prostate-specific antigen (PSA) as a serum marker for prostate cancer made it possible to set up large screening and early detection programs and studies in many parts of the world including the United States, Europe, and Japan. Screening allows the time of diagnosis to be advanced by at least 10 years [1]. However not every cancer detected will pose a threat to the patient's life. The risk of overdetection and subsequent overtreatment is high, especially in prostate cancer screening. Because of intensive screening and early detection protocols, many detected cancers are smaller and less life threatening [2]. Active surveillance has become a realistic option for patients with insignificant or minimal tumour characteristics [3].

PSA, digital rectal examination (DRE), and biopsy Gleason score are of limited use in predicting the stage, grade, and tumour volume after radical prostatectomy, especially in the PSA range of 4–10 ng/ml [4]. It is desirable to develop pretreatment biochemical tests that predict insignificant cancer to select the best treatment for the specific tumour characteristics found.

Human glandular kallikrein 2 (hK2) is like PSA (also called hK3), a serine protease, and the aminoacid sequence for hK2 is 80% homologous to that for PSA. Evidence suggests that hK2 is expressed at higher levels in prostate cancer than in normal prostate epithelium [5,6].

Free PSA (fPSA) is the proportion of total PSA (tPSA) that is not complexed to alpha1-antichymotrypsin and other serum antiproteases. Free PSA and percent free PSA (%fPSA) is believed to be lower in men with prostate cancer.

This paper describes the value of hK2 and fPSA and their combinations in predicting minimal prostate cancer characteristics in radical prostatectomy specimens of screen-detected men in the PSA range 4–10 ng/ml.

METHODS

Patient selection

All patients were participants of the first screening round of the European Randomized Study of Screening for Prostate Cancer, section Rotterdam, The Netherlands. PSA measurement, DRE, and a transrectal ultrasound (TRUS) with volume measurements of the prostate and the transition zone were performed in all men. We selected one hundred men with screen-detected prostate cancer in the PSA range 4–10 ng/ml who underwent a radical prostatectomy. To ensure an equal distribution of PSA values within this PSA range, we included a random selection of men with a PSA value of 4–7 ng/ml and all men with a PSA value between 7 and 10 ng/ml. All patients were operated on in hospitals in the vicinity of Rotterdam.

hK2 and fPSA were analyzed at a later time in archived, frozen, prebiopsy serum samples. hK2 was analysed with a research use–only assay. Free PSA was measured with the Beckman Coulter's Access immunoanalyzer.

Pathologic classification

All radical prostatectomy specimens were whole mounted and reviewed by one pathologist. Features of aggressiveness were categorised according to Epstein et al. [7]. Minimal prostate cancer was defined as organ-confined disease (OCD), Gleason score <= 6 (with no Gleason grade 4 or 5), and tumour volume <0.5 ml. Advanced prostate cancer was defined as Gleason score 7 or greater, established extraprostatic extension with positive margins, or positive seminal vesicles or lymph nodes. All tumours in between were defined as moderate prostate cancer. Tumour volume was measured morphometrically [8]. All cancer areas were circled on the slides. Gray-scale digital images of each histologic section were made with a digital camera. Digital morphometric analysis was subsequently performed with computer software for planimetry. Tumour volume was determined by totalling all measured tumour areas and total slide areas, and multiplying them by 4, which represents the thickness, in millimetres, of the slides.

Statistical analyses

Statistical analyses were done with commercially available software. Receiver operator characteristic (ROC) curves to predict insignificant cancers were constructed with Analyse-it Software. Mean values were compared with t-tests for normally distributed parameters and the Mann-Whitney U test for non-normal parameters. Pearson correlation coefficient was used for normally distributed variables and Spearman correlation coefficient for non-normal distributions. Univariate logistic regression analyses were performed on all available parameters individually. Backward and forward multivariate logistic regression analyses were performed with the use of parameters that were found to be predictive in the univariate analyses. In case of non-normality, we transformed the variable by its logarithm.

RESULTS

Of the 100 men selected for this study, only 91 had both sera and tumour volumes available for analysis. Clinical and pathologic distribution of stages and Gleason sums are depicted in Table 1. Mean tumour volume was 1.2 ml (range: 0.04–13.5). Only 15 patients in this cohort (16.5%) were classified as having minimal disease. Moderate disease was present in 67 men (73.6%), and 9 men (9.9%) were diagnosed with advanced prostate cancer. The groups with moderate and advanced prostate cancer were combined and compared with the minimal prostate cancer group to determine whether additional biochemical tests could correctly identify men with minimal disease.

Table 1. Clinical and pathological stage and Gleason score distribution

		Clinical			Pathological	
		n	%		n	%
Stage	T1c	59	64.8	T2	66	72.5
	T2	27	29.7	T3	21	23.1
	T3	5	5.5	T4	4	4.4
		Biopsy			Pathological	
		n	%		n	%
Gleason sum	<=6	66	72.5	<=6	53	58.2
	7	21	23.1	7	36	39.6
	>=8	4	4.4	>=8	2	2.2

Table 2 describes the means and ranges of patient characteristics, and of results of biochemical tests of men with minimal or moderate/ advanced prostate cancer. Mean values of fPSA, hK2, and their combinations differed significantly between minimal and moderate/ advanced prostate cancer.

Table 2. Mean values and ranges of characteristics at entry for cases (t-test and Mann-Whitney U tests)

	Minimal		Moderate/ advanced		P value
	(n=15)	(ranges)	(n=76)	(ranges)	
age (yrs)	63.3	(56.2-69.6)	64.4	(55.7-75.3)	0.382
IPSS	7.8	(0-24)	5.8	(0-23)	0.285
prostate volume** (cc)	45.5	(23-94)	40.4	(21-122)	0.31
tPSA (ng/mL)	6.9	(4.2-9.6)	6.8	(4.1-9.9)	0.824
fPSA**(ng/mL)	1.11	(0.6-2.6)	0.8	(0.3-2.5)	0.05*
% fPSA (%)	16	(8-28)	12	(4-28)	0.006*
hK2** (ng/mL)	0.086	(0.029-0.25)	0.133	(0.029-0.51)	0.02*
hK2/ fPSA	0.08	(0.02-0.27)	0.18	(0.02-0.49)	<0.001*
hK2/ %fPSA (ng/mL)	0.56	(0.18-2.56)	1.21	(0.15-4.16)	0.003*

* significant
** Mann-Whitney U

Table 3 shows the correlations of hK2 and combinations of hK2 with fPSA with tumour volume in the radical prostatectomy specimens. The ratio hK2/%fPSA resulted in the best correlation with tumour volumes, with a correlation coefficient of 0.42 and a $p < 0.001$. Also hK2/fPSA, hK2 alone, and age showed a significant correlation with tumour volume.

Tabel 3. Correlation coefficients with tumour volume

	Correlation Coefficients	P value
age (yrs)	0.27	0.01*
DRE	0.20	0.05
IPSS	0.17	0.119
prostate volume** (cc)	-0.09	0.38
Gleason sum**	0.20	0.053
tPSA (ng/mL)	0.15	0.172
fPSA** (ng/mL)	-0.14	0.199
% fPSA	-0.01	0.947
hK2** (ng/mL)	0.31	0.003*
hK2/ fPSA	0.34	0.001*
hK2/ %fPSA (ng/mL)	0.42	<0.001*

** significant correlation*

*** Spearman correlation coefficient*

Fig. 1 shows the ROC curves of %fPSA, hK2, and hK2/%fPSA predicting the presence of minimal cancer. Plotting in this manner shows the good performance of hK2 alone at high sensitivity levels. Percent fPSA also performs well at high specificity levels. The superimposed hK2/%fPSA plot seems to combine both effects, resulting in an area under the curve (AUC) of 82%. The ratio hK2/fPSA produced a similar curve, which is depicted in Fig. 2 and also shows an AUC of 0.82. Other AUCs and confidence intervals are shown in Table 4.

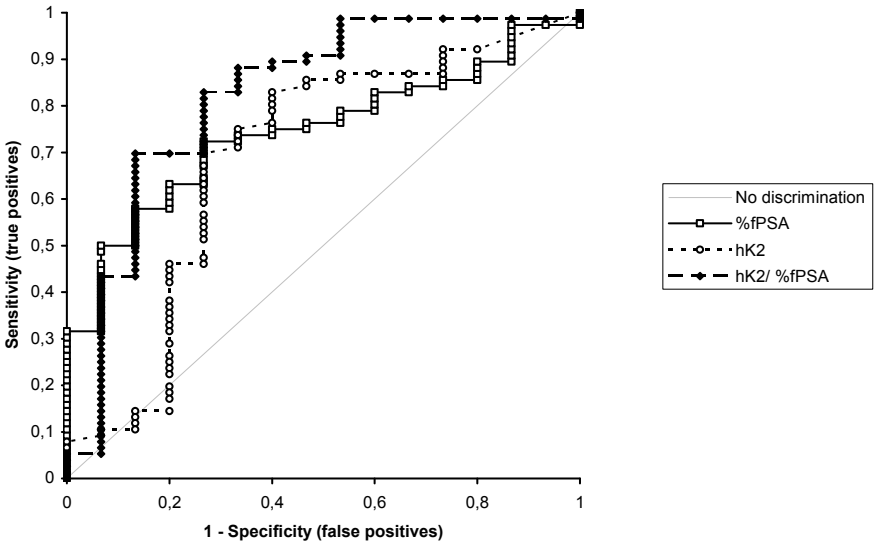

Fig. 1. ROC analyses for hK2, %fPSA and the algorithm hK2/ %fPSA

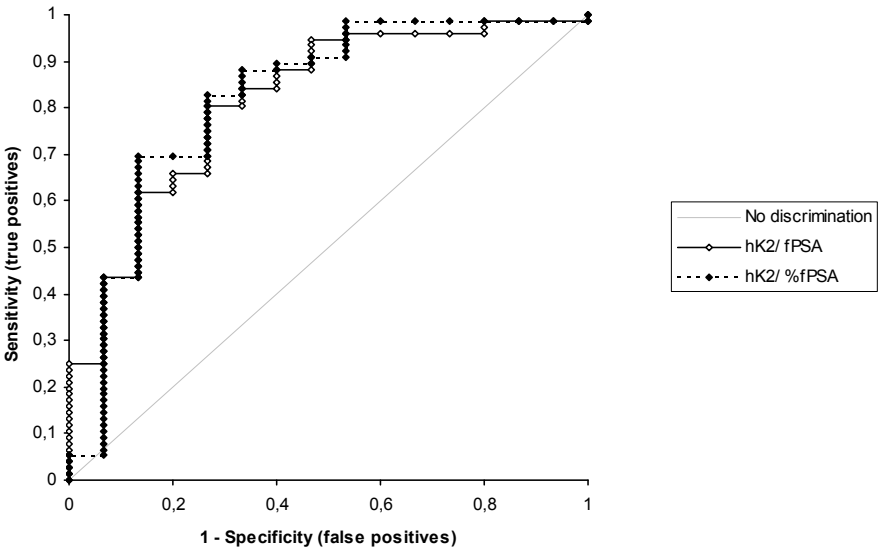

Fig. 2. ROC analyses for the algorithms hK2/%fPSA and hK2/fPSA in predicting minimal prostate cancer

Tabel 4. The area under the curve from the ROC analyses with 95% confidence intervals

	AUC	95% Confidence interval
age (yrs)	0.58	0.432 to 0.724
DRE	0.63	0.490 to 0.772
IPSS	0.57	0.394 to 0.754
prostate volume (cc)	0.58	0.411 to 0.747
biopsy Gleason sum	0.61	0.461 to 0.755
tPSA (ng/mL)	0.52	0,353 to 0,695
fPSA (ng/mL)	0.73	0,614 to 0,841
% fPSA	0.74	0,631 to 0,857
hK2 (ng/mL)	0.69	0,522 to 0,858
hK2/ fPSA	0.82	0,695 to 0,937
hK2/ %fPSA (ng/mL)	0.82	0,684 to 0,956

Table 5 shows cut-off values and specificity at a fixed sensitivity of 95% for the different biochemical tests. Depending on the personally preferred sensitivity or specificity level, a clinician could choose a cut-off level for the different diagnostic combinations.

Table 5. Cut-off levels and specificity or sensitivity for predicting minimal prostate cancer at fixed 95% sensitivity and specificity

	95% sensitivity		95% specificity	
	cut-off	specificity (%)	cut-off	sensitivity (%)
tPSA (ng/mL)	9.5	6.7	4.3	4.9
fPSA (ng/mL)	1.8	13.3	0.63	43.1
% fPSA	0.24	13.3	0.085	31.6
hK2 (ng/mL)	0.029	13.7	0.245	9.0
hK2/ fPSA	0.04	53.3	0.27	25.0
hK2/ %fPSA (ng/mL)	0.32	53.3	2.48	5.3

Logistic regression analyses were performed. First, all known preoperative parameters were tested in a univariate analysis. The results are depicted in Table 6.

Table 6. Univariate and multivariate analyses predicting minimal prostate cancer

	Univariate		Multivariate		
			backward		forward
	odds ratio	P - value	odds ratio	P - value	P - value
age (yr)	0.05	0.379			
tPSA (ng/mL)	-0.04	0.821			
DRE	1.44	0.069			
IPSS	-0.05	0.279			
prostate volume (cc)	-0.02	0.313			
transition zone volume (cc)	-0.02	0.173			
biopsy Gleason sum	0.64	0.102			
fPSA (ng/mL)	-1.16	0.029*	4.38	0.06**	0.289
% fPSA	-11.7	0.011*	-42.55	0.026**	0.073
hK2 (ng/mL)	2.36	0.017*		0.22	0.384
hK2/ fPSA	15.9	0.002*	66.12	0.031**	0.002***
hK2/ %fPSA (ng/mL)	2.11	0.005*	-6.47	0.074**	0.761

** significant with P<0.05 in the univariate logistic regression and used in the multivariate logistic regression*

*** significant and used in the equation after backward multivariate logistic regression*

**** significant and used in the equation after forward multivariate logistic regression*

The parameters that were individually able to make a significant prediction about the presence of minimal disease were tested in a multivariate logistic regression model in a forward and backward method. These parameters are fPSA, %fPSA, hK2, hK2/fPSA, and hK2/%fPSA.

Multivariate logistic regression analysis in a backward stepwise method, using these individually predictive variables, shows that fPSA, %fPSA, hK2/fPSA, and hK2/%fPSA were valuable contributors in predicting minimal prostate cancer. In the forward method only, hK2/fPSA, as the most valuable and significant parameter ($p = 0.002$), is to be used in the equation.

We also tested hK2, fPSA, and related algorithms in a model with "known" predictors like age, DRE, PSA, and biopsy Gleason sum. In the forward method again, only hK2/fPSA remained the only significant variable ($p = 0.002$) predicting minimal disease. In the backward method DRE ($p = 0.1$), tPSA ($p = 0.07$), %fPSA ($p = 0.03$), hK2/fPSA ($p = 0.03$), and hK2/%fPSA ($p = 0.06$) were valuable contributors.

DISCUSSION

The results of this study indicate that hK2, fPSA, and their combinations are valuable in predicting prostate cancer with characteristics of minimal disease in radical prostatectomy specimens of screen-detected cancers in the PSA range 4–10 ng/ml.

As shown in Table 2, mean age, prostate volume, and PSA did not differ significantly between the two groups. However fPSA, %fPSA, hK2, and the ratio hK2/fPSA did distinguish significantly between minimal and moderate/advanced prostate cancer.

An important feature of each tumour marker is its correlation with tumour volume. Significant correlations were found for hK2 and the algorithms hK2/fPSA and hK2/%fPSA, but not for fPSA or %fPSA alone, suggesting a relationship between hK2 and tumour volume.

The ROC curves show a good diagnostic performance by high AUCs for each hK2 and %fPSA alone, and a stronger effect for the ratio hK2/%fPSA. An explanation of this effect may be found in the position of fPSA as denominator and hK2 as numerator. Because the proportion of fPSA is lower in men with prostate cancer and the amount of detectable hK2 is higher in men with prostate cancer, the ratio could result in a test with more discriminating power. Higher ratios of hK2/fPSA and hK2/%fPSA are suggestive for moderate or advanced prostate cancer.

More important than a high AUC are the specific requirements of the test in the clinical situation. In this case, the test has to indicate the level of probability that a man with prostate cancer and a PSA value between 4 and 10 ng/ml has minimal disease, and thus whether expectant management for this man is an option. The sensitivity of this prediction obviously depends on the level of specificity, the probability of missing moderate or advanced prostate cancer. A high level of fixed specificity results in a more precise identification of men with minimal disease at the expense of not offering adequate treatment to those men with moderate or advanced prostate cancer. As shown in Table 5, the ratio hK2/fPSA at a fixed specificity of 95% actually means that 95% of men with minimal disease are correctly identified when active treatment is offered to men above a cut-off of 0.27 for hK2/fPSA; however, a sensitivity of 25% means only 25% of men with moderate/ advanced tumour will be offered active treatment.

In contrast, a high sensitivity for the identification of the men with moderate or advanced disease will be at the cost of offering overtreatment to some men with minimal disease. For example, at a 95% fixed sensitivity, 95% of men with moderate or advanced tumour is offered active treatment when hK2/fPSA >0.04 ng/ml is taken as the cut-off. Specificity at this point is 53.3%, which means 53.3% of the men below the cut-off are correctly labelled as having minimal tumour. Table 5 also outlines that, at a fixed sensitivity for identifying minimal prostate cancer of 95%, the ratios hK2/fPSA and hK2/%fPSA outperformed tPSA, fPSA, %fPSA, and hK2 alone, with a specificity of 53.3%.

Regarding the logistic regression, it attracts attention that PSA, DRE, and biopsy Gleason sum could not predict the presence of minimal disease in this cohort. Again the best predictors were fPSA, %fPSA, hK2/fPSA, and hK2/%fPSA.

Several publications [9–13] describe the value of hK2 combined with fPSA in discriminating between prostate cancer and no prostate cancer. General conclusions are that the ratio hK2/fPSA improves specificity and hence reduces the number of negative biopsies.

Haese *et al* [14–17] describes in several publications the value of hK2 and fPSA and their combinations in discriminating between OCD and non–organ-confined (NOCD) prostate cancer. Like this study they used pretreatment serum samples of men scheduled for radical prostatectomy, and concluded that inclusion of hK2 or the algorithm hK2 x (tPSA/ fPSA) improves the preoperative evaluation of patients who undergo radical prostatectomy by better discrimination between OCD and NOCD. Because %fPSA is calculated by the ratio fPSA/tPSA, hK2/%fPSA is the same expression as hK2 x tPSA/ fPSA. We use the algorithm hK2/%fPSA because we believe that it is easier to reproduce. Haese and colleagues focused on prediction of organ-confined tumours; we focused on the preoperative detection of minimal disease, which includes features of organ-confined prostate cancer, Gleason sum, and tumour volume, HK2, fPSA, and combined algorithms showed favourable test results in both studies.

In another publication Haese et al. [18] described a correlation between tumour volume, Gleason grade 4–5 volume scores, and hK2, suggesting the ability of this biomarker to reflect tumour aggressiveness. We also found a correlation of hK2, hK2/%fPSA, and hK2/fPSA with tumour volume.

Some weaknesses concerning our study deserve mention. The patient selection is not done in a prospective and sequentially enrolled manner. The serum samples were archived and analyzed later in time. However the sample stability of fPSA was taken into account. The unequal distribution of the groups and relatively small number of subjects used for the generation of the ROC curves could lead to an overestimation of the discriminating power. Another serious limitation of this evaluation, as in most of the above-mentioned studies, lays in the fact that hK2, fPSA, and the derived ratios were not used as biopsy indications. This means that PSA is the gold standard that determines the relative sensitivity of the test results. Sensitivity improvements, which may result from using the markers studied, cannot be shown in this setting. All expressions of sensitivity and specificity are "relative" because of the selection procedures used in this study.

Clinical application of these data would result in adding hK2 and fPSA determinations into the (prebiopsy or) pretreatment workup of a patient. The hK2/%fPSA and hK2/fPSA ratios could help the physician to identify men with characteristics of minimal prostate cancer. Consequently, the physician is aided in selecting the right treatment and preventing overtreatment. Further prospective studies with adequate sample size and power should evaluate the clinical usefulness of these biomarkers in predicting minimal prostate cancer.

CONCLUSIONS

The biomarkers hK2 and %fPSA are a powerful prognostic combination for the detection of minimal prostate cancer in screen-detected men within the PSA range 4–10 ng/ml. These biomarkers are likely to be useful in selecting less invasive treatment options like active surveillance and to prevent overtreatment. Their possible added value to other existing algorithms and nomograms [19,20] is to be evaluated in future research.

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GENERAL DISCUSSION

9

Chapter 2

This chapter entails an introduction of the most used diagnostic screening tests in prostate cancer screening. The history, use and value of digital rectal examination, transrectal ultrasound, PSA, prostate biopsy, other PSA isoforms and future prospectives are described.

Chapter 3

TRUS-guided prostate biopsy is the gold standard for the diagnosis of prostate cancer. However it is also the most invasive diagnostic tool in the screening procedure. With trends toward using a lower PSA cut-off and extended biopsy schemes, complications and risk factors of prostate biopsy need to be known to the urologist as well as the patient.

We reported the complications and risk factors of the biopsy procedure as practiced within the Rotterdam section of the ERSPC. Patients were offered laterally directed sextant biopsy (see Chapter 2, fig 5) with an additional seventh biopsy in case of a suspicious lesion. Minor complications were reported frequently. Hematuria lasting longer than 3 days was present in 22.6% of the cases and 50.4% of the men reported hematospermia.

Major complications were seen far less frequently. Fever after biopsy occurred in 3.5% of the participants and 0.5% of the men needed hospital admission.

These complication rates are in concordance with earlier and more recent comparable literature [1]. However, the range of reported complications is wide, reflecting different definitions and methodologies.

Also risk factors for complications of prostate biopsy were studied. We found more hematuria in men with larger prostate volumes. More pain after biopsy and more frequent hospital admission were reported after a previous episode of prostatitis and a correlation between having characteristics of Benign Prostate Hyperplasia (BPH) and developing urinary retention after biopsy. Young men experienced more pain after biopsy. This somewhat surprising outcome was confirmed by several studies. [2, 3]. These risk factor associations can be used for adequate counselling.

No risk factors for developing fever could be identified in our study. Rodriguez and Terris [3] found an association between the number of biopsy cores obtained and the presence of fever. Their number of biopsy cores ranged from 6 to 13.

Whether raising the number of biopsy cores is beneficial for the patient or participant depends on the potentially raised complication rate and the raised sensitivity of detecting significant prostate cancers. However, a further increase of the detection of non-aggressive cancers should be limited.

Complications rates of four randomised studies were systematically reviewed by Eichler [1] comparing the minor complications of the sextant protocol with 10 or 12-core protocols. No significant differences between the sextant and 10 to 12-core biopsy schemes were found for haematuria, haematospermia and infection. The 10 and 12-core tended to cause more rectal bleeding. Naughton [4] assessed pain scores to be higher in the 12-core scheme but the

difference was not significant. None of these studies mentioned major adverse events. In general, the reporting of adverse events was poor in studies using a biopsy scheme of more than 12 cores. Often extended antibiotic regimens or urinary catheterisation were used to prevent adverse effects. Eskew [5] reported with his 5-region scheme and 13 biopsy cores (see Chapter 2, fig 6) gross haematuria in 80% of the patients. Stewart [6] using saturation biopsies with a median of 23 cores, found haematuria necessitating hospital admission in 5% of the men and 4.5% urinary retention. Others [7] also report more urinary retention.

Cancer yield was increased using laterally directed sextant biopsies when compared with the traditional systematic sextant biopsy. Presti and co-workers [8] found and increase in CDR from 78% for the traditional sextant, to 83% for laterally directed sextant biopsies. This was compared to the 12-core scheme as gold standard. Analysis of thirteen 12-core scheme-studies[1] which added laterally directed sextant to the traditional sextant biopsy, revealed a mean cancer yield of 31% more than traditional sextant biopsies would detect. Schemes with 18 to 22 cores of the 5-region pattern did not show a significantly higher cancer detection rate than 12-core schemes or 10-core schemes of the 5-region pattern. Adding midline and transition zone biopsies lead to no significant increase in cancer yield. When applying additional laterally directed biopsies to the traditional sextant scheme, cancer was found most frequently at the lateral apex and lateral mid part of the peripheral zone of the prostate [9]. Presti proposed a 10-core scheme existing of six laterally directed biopsies added to the traditional sextant scheme with the omission of the two biopsies at the base of the prostate (see Chapter 2, fig 8).

As stated earlier, a gain in cancer yield is only beneficial to the patient or participant when more clinical significant cancers are diagnosed without further increasing the detection of clinical insignificant prostate cancer. Overdiagnosis is to be taken into account especially as in the second round of the ERSPC, section Rotterdam 42.6% of the men who underwent a radical prostatectomy turned out to have insignificant prostate cancer [10]. Up to now, few biopsy-studies also report the number of insignificant and significant cancers found by extending the number of biopsy cores. A longitudinal study from Chan [11] found only a trend towards more insignificant cancers when 9 or more biopsy cores were performed versus 8 or less (25.4% vs 22.6%). However this study has a potential bias against showing a significant difference because of increased core sampling in clinically suspicious cases.

Singh and co-workers [12] evaluated a 12-core biopsy scheme in a clinical practice. Cancer detection was increased by 31.3% compared to the traditional sextant protocol. However 45.2% of these cancers found uniquely at the extended laterally directed sites were found to be insignificant cancers (organ confined, tumour volume < 0.5ml and Gleason score < 7). Applying the traditional sextant protocol, 29.8% of the cancers were found to be insignificant. They state that 12-core biopsies however may offer potential for more reliable identification of insignificant cancers.

Haas et al. [13] performed 18-core biopsies on autopsy prostates of men with no evidence of prostate cancer and died from other causes. Unlike clinical studies they were able to identify cancers missed by the biopsies after analyzing the whole-mount prostate. The prevalence in

this group was 29%. (47 prostate cancers in 164 men) Their biopsy scheme consisted of the traditional sextant biopsy extended by 6 more lateral cores and 6 cores of the central zone. They found that the 18-core biopsy scheme detected 25 cancers of the 47 cancers detected by 4 mm step pathologic examination of the prostate. The 6 central zone cores did not yield more cancers than the 12-core scheme applied to the lateral and the mid peripheral zone. Significant tumour characteristics were found in 20 of the 47 cancers (43%). The sensitivity of detecting significant tumours by sextant biopsy was 55%, after 12-core biopsy the sensitivity increased to 80%. Of the 27 insignificant tumours (57%), only 3 were found by sextant biopsy (sensitivity 11%) and 9 were detected after 12-core biopsy, which increased the sensitivity of finding these cancers to 33%. From this publication can be concluded that central zone biopsies can be omitted. Eighteen (or 12) -core biopsy will miss 47% of the existent cancers and detects 33% of the insignificant cancers. Traditional sextant biopsy alone misses 31% of the significant cancers and detects only 11% of the insignificant tumours.

Whether by extending the biopsy scheme, the gain in cancer detection counterbalances the amount of possible overdiagnosis remains an important issue of debate. Complication wise, it is not advisable to puncture the prostate more than 12 times at first biopsy. Cancer yield is also not improved by taking more than 12 cores. Midline, transition zone and central zone biopsies seem of minor value. Cancer significance seems to be of critical importance in deciding whether sextant, 8, 10 or 12-core schemes are to be used. As prostate volume is inversely related to cancer detection [14, 15] and the probability to detect a life threatening tumour is dependent on age and tumour volume, it would be useful and safe to apply prostate volume and age as indicators for the number of cores per biopsy as proposed by Vashi [16] and other investigators [17]. They constructed a mathematical model to calculate the number of cores needed to diagnose a clinical significant tumour depending upon the volume of the prostate and patient's age (see Chapter 2, table 4). Another table (see chapter 2, table 5) is used for determining the number of cores per biopsy procedure depending on prostate size and tumour size. According to this table sextant biopsy would be sufficient detect a tumour with a volume of 2 cc in a 30 cc prostate. However to detect the same tumour in a 60 cc prostate, 11 cores would be needed to ensure 90% certainty of detection.

Several prospective randomized studies [18-27] have proven that reducing pain and discomfort can effectively be achieved by a periprostatic nerve block. Other methods are less effective. We feel this is only necessary when extended biopsies are taken.
The ideal antibiotic prophylaxis should be safe, have broad coverage and be economic. Trimethoprim-sulfamethoxazole has al these features and has proven to be effective. Quinolones may also be an excellent choice however this is a second line antibiotic and prevention of the development of resistant bacterial strain is essential when performing a large screening study in a relative small region. We use quinolones for higher risk patients and the treatment of post-biopsy infections. As sepsis after prostate biopsy is potentially life threatening, the use of antibiotic prophylaxis seems to be of crucial importance. Especially in a healthy volunteer population.

The use of an enema to prevent infection is according to several studies [18-20] obsolete. There is no proven increase in hemorrhagic complications with low dose aspirin [3, 21]

Figure 1 in **Chapter 4** illustrates the decreased Positive Predictive Value (PPV) of PSA in a population earlier screened with the use of PSA. In the initial screening round the PPV increases with ascending PSA ranges. However in round 2 this relationship is lost for PSA ranges which previously served as biopsy indication.
Stamey [22] suggests that due to extensive PSA screening, the PSA era is over in the USA. His group found that PSA levels correlated more with benign prostatic enlargement than with parameters related to prostate cancer. This is in line with our finding that prostate volume becomes an important predictor in the second round of the ERSPC [23]. Earlier Carter [24] showed that PSA did not discriminate between BPH and prostate cancer five years before the diagnosis and PSA Velocity (PSAV) did differentiate between those different diseases of the prostate. A PSAV cut-off of 0.75 ng/ml/yr yielded a sensitivity of 72% and a specificity of 90%.
We studied PSA dynamics like the PSAV, PSA slope and the PSA Doubling Time (PSADT) in a rescreened population. Mean values for each parameter were significantly different between men with biopsy detected prostate cancer, with negative biopsy results and men with no biopsy indication (PSA<3.0 ng/ml).
However in determining the ability to discriminate between cancer or no cancer in ROC analyses, PSA dynamics were of limited value.
Schröder et al [25] studied the predictive value of different PSAV cut-offs in a pre-screened cohort of men in the ERSPC Rotterdam, with an initial PSA below 4.0 ng/ml in round 1 and a PSA >= 4.0 ng/ml in the second round, four years later. The PPV's for the different PSAV cut-off values (0.25, 0.50, 0.75 and 1.0) were similar and did not improve the PSA cut-off of 4.0 ng/ml. PSAV > 0.75 showed a sensitivity of 29% and a specificity of 63%. The use of PSAV at all cut-off levels higher than 0.25 ng/ml/yr, would miss substantial numbers of cancers. However, the rate of aggressive cancers seems to increase with increasing PSAV, suggesting a role for PSAV in selecting more or less aggressive treatment modalities [26]. The authors conclude that further studies are needed to confirm this role. The study is like most others, subject to assignment bias resulting from the fact that it relates to a selected population.

The studies from the ERSPC could not confirm the results from Carter in the Baltimore Longitudinal Study of Aging (BLSA). The difference in study population is the most likely reason for this. Their study was performed using 18 men with prostate cancer who were clinically detected in the eighties and were therefore not likely to have been screen-detected. Our population is situated in a post-PSA era and all men were prescreened 4 years earlier. Furthermore the longer follow up of the Baltimore longitudinal study (7-25 years) and the availability of only two PSA values 4 years apart in our study, could contribute to the differences.

Newer studies report a moderate ability of PSA kinetics of predicting prostate cancer in screening or early detection programs [27-32] or are to be interpreted with care because of unconsidered selection and assignment biases [33, 34]. Regarding the value of PSAV in detecting more aggressive prostate cancer, Pinsky [35] found an association between PSAV and biopsy Gleason score, but among those men who underwent radical prostatectomy PSAV was not predictive of advanced pathological stage. However other studies [33, 36, 37] did find a correlation between PSAV and advanced prostate cancer and even prostate cancer death.

Results from the BLSA also show that men later on diagnosed with prostate cancer first show at a moderate linear increase in PSA over time. This slow increase of PSA is similar to those men diagnosed with BPH. However when the first clinical symptoms appear, the rise of PSA becomes exponential in men with prostate cancer. The time between the first detectable pathophysiological symptoms (i.e an elevation in PSA level) and the clinical symptoms (e.g. a suspect DRE) is called the pre-clinical diagnostic phase. Screening aims to detect cancer in this pre-clinical phase, however in prostate cancer this phase is relatively long and PSA levels of men with prostate cancer may be elevated but not significantly different from men with BPH. The difference between men with BPH and men with prostate cancer becomes clear when the exponential rise of PSA occurs. PSA dynamics are of use in distinguishing men with prostate cancer from men with no prostate cancer in this phase. However this is also the time when clinical symptoms occur, marking the end of the pre-clinical phase. As the leadtime (time between detection of a cancer by screening and clinical diagnosis if there had been no screening) in prostate cancer is calculated to be 11 years [38], it is likely that the cancer is detected before the exponential phase of the rise of PSA. Therefore, PSA-kinetics are of limited use in screening programs. This also subscribes the possibility that PSA dynamics can be of use in detecting those cancers that are closer to the clinical detection phase, i.e. larger or faster growing cancers. These are more likely to be found in non pre-screened men in a referral population.

In **Chapter 5** the value of initial PSA is described by evaluating the predictive value of a PSA increase to PSA 3.0 ng/ml or greater in a 4 year interval. Participants with a PSA < 2.0 ng/ml in round 1 shown a low progression rate to a PSA >= 3.0 ng/ml in the second round, 4 years later. The cancer detection rate in the second round of men with an initial PSA < 2.0 ng/ml was only 1% in contrast to 11.9% in men with PSA 2 – 2.9 ng/ml at baseline screen.
In the United States of America, annual screening of men for prostate cancer starting at age 50 [39, 40] is common practice. Several recently published studies concerning screening populations [41-45], find similar low progression rates from a baseline PSA < 2.0 ng/ml to biopsy indication level (PSA >=3 or 4 ng/ml). They propose longer screening intervals at least at these low baseline PSA levels. Screening costs could be reduced by 38 to 50% while delaying detection in only 2.4% of the cancers [41, 42].
A screening interval of 4 years for every participant, as practised within the ERSPC, would delay detection for about 16 months according to Crawford and co-workers[42]. Candas and

collaeges [41] calculate that this constant 4 year interval would cause delayed detection of 78% of the cancers and reduce costs by 75%.
However a recent study [46] comparing a 2- and a 4 -year screening intervals between the Swedish and the Dutch center of the ERSPC revealed no significant difference between the cumulative incidence of interval cancer. Also the cumulative incidence of aggressive interval cancer was low in general and not different between the two centers. Roobol et al. [47] investigated the cancer detection rate of men who initially presented with a PSA level below 1.0 ng/ml in the first round, over a total of three screening rounds. The low overall cancer detection rate of 0.47% over 8 years of follow up suggests that the screening interval of men aged 55 – 65 years with a plasma PSA concentration of <= 1.0 ng/ml, could be as long as 8 years with a minimal risk of missing aggressive prostate cancer at a curable stage. We believe that the screening interval should be risk adjusted, depending upon the initial PSA measurement. Men with a low baseline or initial PSA can be screened at longer intervals.
Lilja and coworkers [48] analyzed archived blood samples from men age 44 to 50 years, participating in a cardiovascular study. The men diagnosed with prostate cancer up to 25 years after blood draw, showed already higher amounts of all PSA forms and hK2, compared to controls. Furthermore the odds of developing prostate cancer in the following years increased dramatically at baseline PSA > 2.0 ng/ml, when compared to PSA levels <= 0.5 ng/ml. Additional data are needed before implementation in screening or early detections programs but it appears beneficial for both men and urologists to suggest a more frequent and elaborate risk evaluation for the small percentage of men (8%) with PSA > 2.0 ng/ml at age 44-50 years. And subsequently less frequent follow up for men with PSA values below median PSA values. A possible explanation of this early discrimitive power of PSA is that it may be less influenced by the BPH component in these relatively young men. Another interesting possibility described by the authors is that extracellular PSA or hK2 may have a causal effect on prostate cancer, rather than a consequential effect of prostate cancer. This means the rise of extracellular PSA or hK2 may trigger processes which promote the progression of prostate cancer.
Establishing an internationally standarized screening system based on baseline PSA and age might be difficult because of racial and ethnic differences around the world. Also the different incidence of prostate cancer between men from western counties and for example those from Asian countries could be problematic.

Chapter 6 reports the results from a similar study as described in the previous chapter. The PSA progression rates of prescreened men with low PSA ranges to PSA >= 4.0 ng/ml 4 years later were compared between Dutch and Japanese men participating in two different screening studies. We conclude that the risk and incidence of developing prostate cancer is larger in The Netherlands in the same age group of 55 to 69 yrs. This risk increases with higher initial PSA ranges. However there is no significant difference in prostate cancer risk between Dutch and Japanese men whose baseline PSA levels fall within the same range.
Others [45] have studied the same issues comparing American white males and black males.

They also concluded that a baseline PSA less than 2.0 ng/ml rarely progresses to PSA >4.0 ng/ml and that annual screening is not necessary for this group. They also found no differences of progression from baseline PSA between black and white people.
This means that baseline PSA may be an important tool in establishing an international standarized and optimal screening system regardless of race and ethnicity.

Chapter 7 concerns a side study performed within the second round of the ERSPC.
All men with a PSA level of 2.0 - 3.9 ng/ml were offered prostate biopsy regardless of DRE and TRUS findings. This was one of the first studies to asses the prevalence of prostate cancer in PSA range 2.0 - 2.9 ng/ml. The value of percent free PSA (%fPSA) on prostate cancer detection and aggressiveness was included in order to evaluate whether screening in these low PSA ranges could be improved.
The PPV of PSA range 2.0 - 2.9 ng/ml was 15.7% and the PPV of PSA 3.0 – 3.9 ng/ml was 19.8%. These PPV's were higher than expected in these low PSA ranges. Unfavourable tumour characteristics from biopsy specimens were found in 46.9% of the men. Percent free PSA was of moderate value in avoiding unnecessary biopsies but predictive in assessing tumour aggressiveness. This feature can be of use in selecting more or less radical treatment options.
Thompson et al [49] in the control group of the Prostate Cancer Prevention Trail (PCPT) evaluated the prevalence of prostate cancer at PSA ranges <= 4.0 ng/ml. In this study almost all participants underwent a prostate biopsy regardless of PSA level, as an end-of-study criterion. The PPV's of PSA level 0–1, 1–2, 2-3 and 3–4 ng/ml were respectively 8.8%, 17%, 23.9% and 26.9%. These PPV's are higher than our results in PSA range 2.0 to 3.9 ng/ml which may be due to allowing men with an age over 75 years in to the PCPT. Furthermore 16.9% of the cancer found with a PSA below 4.0 ng/ml in the control group, showed evidence of high grade prostate cancer (Gleason >=7). This stirred up the discussion whether PSA cut-offs should be lowered. While some urologists would advocate more aggressive biopsy strategies or further lowering of the PSA threshold in order to detect al cancers in these low PSA ranges, the ERSPC study group is of opinion that it is not necessary to identify all prostate cancers at first screen in the PSA range below 3.0 or 4.0 ng/ml [50]. This opinion is based upon data within the ERSPC which indicate already a 63% insignificant cancers after radical prostatectomy in the PSA < 3.0 ng/ml range [10], a mean over-detection rate of 54% and an estimated lead time of 11 years [38] which would allow detection and curative treatment when PSA has reached the 3.0 ng/ml level.
Making screening more sensitive by lowering the PSA cut-off will increase over-detection with minimal contribution in reducing prostate cancer mortality. Regarding the discrepancy between the incidence rate and the mortality rate we feel that for the time being a PSA threshold of 3.0 ng/ml provides a reasonable balance between an acceptable PPV and detecting clinically significant tumours [51]. Rather than lowering PSA thresholds, using PSA as a continuous variable for risk assessment together with other risk factors, seems more sensible regarding the increasing risk of over-diagnosis measurement. Once the outcome of

the ERSPC is known it will be possible to provide harder evidence on the usefulness of low PSA cut-offs.
Free PSA might be of more use in detecting clinically significant tumours. As 9 out of 10 men with a % fPSA < 10% showed unfavourable tumour characteristics, this could be of value in selecting treatment modalities.

In **Chapter 8** multiple PSA-forms, hK2 and combinations of these biomarkers were tested on predicting minimal or insignificant prostate cancer (organ confined, Gleason score <=7 and tumour volume < 0.5 ml) in men with PSA 4 -10 ng/ml, treated with radical prostatectomy. The mean values of fPSA, hK2 and their algorithms differed significantly, and especially hK2/ fPSA and hK2/ %fPSA showed large Area Under the Curves (AUC) in predicting minimal prostate cancer. Also in multivariate logistic regression analyses these ratios of biomarkers produced good discriminative values.
Free PSA representing the non-complexed portion of PSA in the serum, is believed to be associated with benign prostatic hyperplasia [52, 53]. The mechanism why low free PSA predicts tumour aggressiveness remains unclear. Several authors have reported a significant benefit of using % fPSA for staging [54, 55]. Others could not confirm these findings [56]. However the populations which showed benefit consistently fell within the PSA range <= 10 ng/ml.
The precise role of hK2 linked to more advanced prostate cancer is unknown yet. Tissue samples studies [57-60] from lymphatic metastases and high grade prostate cancer show an increased level of hK2 compared to benign or low grade tumour tissue. It has been suggested that changes in expression levels of hK2 are associated with carcinogenesis.
Steuber et al.[61] suggest a role for hK2 and free PSA in predicting biochemical recurrence after radical prostatectomy. In men with PSA levels <= 10 ng/ml these two markers significantly improved the predictive accuracy when added to a nomogram based on PSA, clinical stage and biopsy Gleason score [62]. Others [63] found that the ratios hK2/ fPSA and hK2/ %fPSA were predictive in differentiating between pT2 and pT3 tumours after radical prostatectomy.
Confronted with the diagnosis of prostate cancer, patient and urologist have to decide what treatment suites best. Besides clinical features, the ratio of hK2 and (%) fPSA can be decisive whether active surveillance or active treatment is indicated.

CONCLUSIONS:

Based on the data presented in this thesis the following conclusions can be made:
Prostate biopsy can be considered as a safe and effective procedure (if done with care). The number of biopsy cores taken should not be more than 12, regarding complications. Regarding the cancer detection rate and amount of insignificant cancers, a prostate volume dependent biopsy regimen could be of value.
PSA kinetics are of limited use in screening programs possibly due to the fact that most cancers are found during the pre-clinical detectable phase. However PSA dynamics can be

of use in detecting those cancers that are closer to the clinical phase, i.e. larger or faster growing cancers. These are more likely to be found in men in a referral population who were never screened before. Promising reports correlating PSA-Velocity to cancer aggressiveness may confirm this.

Men with a low baseline or initial PSA can be screened at longer intervals. Racial and ethnic differences seem to have no effect on the rate of progression to a higher PSA level. For this reason, baseline PSA may be an important tool in establishing an international standarized and optimal screening system.

Regarding prostate cancer at low PSA range a PSA treshold of >= 3.0 ng/ml. provides a reasonable balance between an acceptable PPV and finding significant cancers. Harder evidence on the usefulness of low PSA cut-offs can only be provided when the outcome of the ERSPC is known.

Free PSA in PSA range 2.0 – 3.9 ng/ml. is not usefull for cancer detection but has potential to point out cancers with unfavourable tumour characteristics. This can be used to select treatment options, especially in this low PSA range.

In PSA range 4–10 ng/ml the ratios hK2/ fPSA and hK2/ %fPSA predicts minimal prostate cancer. These PSA isoforms can be used to select less invasive treatment options like active surveillance and to prevent overtreatment.

As stated in the introduction of this thesis in the beginning of the 20th century prostate cancer was often diagnosed when clinical symptoms were already present. Curative treatment was rare at these stages. Now, at the beginning of the 21st century, due to screening tools and better treatment modalities, prostate cancer is usually detected and treated at a curable stage. However a new problem has arisen. Due to the variation in natural history of the detectable disease the "nowadays urologist" needs diagnostic tools that specify which cancers to treat and which cancers not to treat. Or better, which cancers to detect and which not to detect.

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SUMMARY

10

Chapter 1 describes the history of prostate cancer diagnosis. Initially prostate cancer was often detected due to clinical symptoms. Regarding the nature of prostate cancer with late onset of symptoms, this phase is associated a low probability of cure, especially in the early days when treatment modalities were limited. Since the introduction of PSA and other diagnostic modalities we are now able to diagnose prostate cancer in a pre-clinical and often curable phase. The incidence of prostate cancer has almost doubled in the Netherlands after the introduction of PSA. However, this presented a new problem. Overdetection and subsequent overtreatment demands critical evaluation of existing diagnostic tools and development of new prognostic methods to not only detect prostate cancer but also detect those cancers of the prostate that would influence the disease-specific mortality rate. These are two important goals of the ERSPC. First, to evaluate the effect of screening on prostate cancer mortality and second to determine the optimal screening methods.

Chapter 2 provides an introduction to the most commonly used screening modalities. The DRE as a screening test has a poor performance, especially at low PSA ranges. There is an ongoing discussion about the use of DRE at these low PSA ranges in screening programs.
Inspite of a rapidly improving technology, the TRUS as a tool for early detection of prostate cancer and staging is questionable. Other facilities like volume measurement, imaging of anatomy and guidance for biopsies are undisputed.
As the PPV of PSA increases at higher PSA levels, PSA seems a good marker for prostate cancer. However the marker lacks specificity because of other prostatic diseases that may cause the PSA level to rise. The use of a PSA cut-off level has become a point of discussion after the publication of results that showed that biopsy-detected prostate cancer, including high grade cancers, is not rare among men with PSA level of 4.0 ng/ml or less. More recent findings advocate interpreting the PSA value as a continuum of risk of cancer and aggressive prostate cancer in relation to other risk factors. These factors are included in risk calculators and nomograms.
A brief introduction of other PSA related isoforms as well as an overview of different biopsy schemes and future prospectives concludes this chapter.

Chapter 3 describes complication rates and risk factors of prostate biopsy. Inspite of being the most invasive diagnostic tool available for prostate cancer screening, this procedure can be considered as a safe and effective procedure, if done with care. An extensive review of recent literature revealed that the number of biopsy cores taken should not be more than 12, considering the complications of prostate biopsy. Whether by extending the biopsy scheme, the gain in cancer detection counterbalances the amount of possible overdiagnosis remains an important issue of debate. As the probability of detecting a life-threatening tumour is dependent on prostate volume, age and tumour volume, the number of biopsy cores to be taken could be individualized according to these parameters.

Chapter 4 investigates the value of PSA dynamics like PSA-Velocity, PSA Doubling Time and PSA slope. Although mean values of PSA dynamics are higher in men with prostate cancer, the test characteristics (sensitivity, specificity, PPV) of these different ways to calculate PSA change over time, perform poorly as diagnostic tools as shown in the ROC-curves. As in screening, the cancer is usually detected in the pre-clinical diagnostic phase, the rise of PSA at this phase is not clearly different from men with BPH. This makes PSA change in the setting of screening less useful. However when prostate cancer is detected when first clinical symptoms appear, the rise of PSA in men with prostate cancer is exponential while the PSA in men with BPH (or no cancer) is steadily rising. PSA dynamics can be of use in detecting those cancers that are closer to the clinical detection phase, i.e. larger or faster growing cancers. These are more likely to be found in non pre-screened men in a referral population.

Chapter 5 reports on the value of initial or baseline PSA in designing the optimal screening program. It evaluates the predictive value of a PSA progression to PSA 3.0 ng/ml or greater in a 4 year interval from baseline PSA of < 3.0 ng/ml. The low progression rate and the low cancer detection rate, in particular in the group with initial PSA below 2.0 ng/ml, may have a large impact in terms of avoiding unnecessary secondary screens. Baseline PSA may be useful to differentiate groups of men with or without a subsequent risk for prostate cancer. Screening intervals could be risk adjusted, depending upon PSA and age at initial screen.

Chapter 6 compares PSA progression rates in Dutch men to those in Japanese men participating in two different prostate cancer screening studies across the world. In order to establish an internationally standarized screening system based on baseline PSA and age, many difficulties can be expected concerning racial and ethnic differences and the different incidence of prostate cancer. It is concluded that the risk and incidence of developing prostate cancer is larger in The Netherlands. This risk increases with higher initial PSA ranges. However there is no significant difference in prostate cancer risk between Dutch and Japanese men whose baseline PSA levels fall within the same range. From this finding it can be concluded that baseline PSA may be an important tool in establishing an international standarized and optimal screening program regardless of race and ethnicity.

Chapter 7 concerns a study in which the PSA cut-off is lowered to 2.0 ng/ml and the value of a PSA isoform (% free PSA) is tested on tumour detection and aggressiveness in PSA range 2.0 – 3.9 ng/ml. The PPV of this PSA range was 17.1% which was higher than expected, however the PSA cut-off of the ERSPC was not further lowered because it will increase overdetection with minimal contribution in reducing prostate cancer mortality. The value of % fPSA in improving relative specificity, or saving unnecessary biopsies, was moderate. However in predicting tumour aggressiveness in biopsy cores, %fPSA was predictive and can be used to select treatment options.

Chapter 8 represents a study in which an effort is made to identify minimal prostate cancer from moderate or advanced prostate cancer with the use of free PSA and hK2. The development of pre-treatment biochemical tests that predict insignificant cancer are desirable to select the best treatment option for the specific tumour characteristics found. The ratios hK2/ %fPSA and hK2/ fPSA are a powerful combination in PSA range 4-10 ng/ ml, which is shown to be useful in differentiating between the cancers that need active treatment and the cancers that could be eligible for active surveillance. Their possible added value to other existing biomarkers and nomograms is to be evaluated in future research.

SAMENVATTING

11

Hoofdstuk 1 beschrijft de geschiedenis van het diagnosticeren van prostaatkanker. Vroeger werd prostaatkanker vaak gedetecteerd als gevolg van klinische symptomen. Rekening houdend met het natuurlijke verloop van prostaatkanker met een laat begin van symptomen is deze fase geassocieerd met een lage kans op genezing, zeker vroeger toen de behandelingsmogelijkheden nog beperkt waren. Sinds de introductie van PSA en andere diagnostische modaliteiten, zijn we in staat om prostaatkanker te diagnosticeren in een preklinische fase die ook vaak te genezen is. Na de introductie van PSA is de incidentie van prostaatkanker is bijna verdubbeld in Nederland. Hierdoor diende zich echter een nieuw probleem aan. Overdetectie en de daaruit volgende overbehandeling, vragen om kritische evaluatie van de bestaande diagnostische hulpmiddelen en de ontwikkeling van nieuwe prognostische methoden om niet alleen prostaatkanker maar juist die kankers van de prostaat die een invloed hebben op de ziekte specifieke mortaliteit. Dit zijn twee belangrijke doelstellingen van de ERSPC. Ten eerste, het effect van vroegopsporing van prostaatkanker op de prostaatkanker mortaliteit. Ten tweede, het bepalen van de optimale methoden ter vroegopsporing van prostaatkanker.

Hoofdstuk 2 geeft een introductie van de meest gebruikte screeningsmodaliteiten. Het rectaal onderzoek van de prostaat presteert slecht als screeningstest, zeker bij lage PSA waarden. Er is veel discussie over de waarde van het rectale onderzoek bij de vroegopsporing van prostaatkanker bij deze lage PSA waarden.
Ondanks snel verbeterende technologie is de transrectale echografie van de prostaat als hulpmiddel voor de vroege opsporing en stadiëring van prostaatkanker twijfelachtig. Andere modaliteiten zoals volume meting, in beeld brengen van de anatomie en het geleiden van de biopten, zijn onbetwist.
Wanneer men ziet dat de positief voorspellende waarde van PSA groter wordt bij stijgende PSA waarden, zou men kunnen concluderen dat PSA een goede marker voor prostaatkanker is. Echter, aangezien andere prostaataandoeningen ook een verhoogd PSA kunnen veroorzaken, heeft de PSA test een lage specificiteit. Het gebruik van PSA afkapwaardes is een discussiepunt geworden na publicatie van resultaten waaruit duidelijk werd dat het voorkomen van prostaatkanker, en tevens hooggradige prostaatkanker, niet zeldzaam is bij mannen met een PSA waarde lager dan 4.0 ng/ml. Meer recente artikelen pleiten voor het interpreteren van PSA als een continue risicofactor voor (agressieve) prostaatkanker, samen met andere risicofactoren. Deze factoren zijn in risico calculators en nomogrammen opgenomen.
Ter afsluiting van dit hoofdstuk een korte introductie van andere PSA gerelateerde isovormen, een overzicht van verschillende prostaatbiopsie schema's en een blik op de toekomst.

Hoofdstuk 3 beschrijft de complicaties en risicofactoren van prostaatbiopsie. Ondanks het feit dat biopsie het meest invasieve diagnostische middel bij de vroegopsporing van prostaatkanker is, kan deze procedure gezien worden als een veilige en effectieve methode.
Een uitgebreide analyse van recente literatuur laat zien dat het aantal prostaatbiopten dat per biopsie-procedure genomen wordt, niet meer dan 12 dient te zijn, wat betreft het aantal complicaties. Of het uitbreiden van het aantal te nemen biopten en de hogere kanker detectie kans opweegt tegen de hoeveelheid overdiagnose is nog steeds een belangrijk discussiepunt. Wanneer de kans op het detecteren van een levensbedreigende tumor afhankelijk is van prostaatvolume, leeftijd en tumorvolume, dan zou het aantal te nemen biopten op het individu afgestemd moeten worden afhankelijk van deze parameters.

Hoofdstuk 4 onderzoekt de waarde van verschillende berekeningen om de dynamiek van PSA te beschrijven. De gemiddelde waarden van PSA stijgingen zijn hoger in mannen met prostaatkanker. Echter de test karakteristieken (sensitiviteit, specificiteit en positief voorspellende waarde) van deze verschillende manieren om PSA verandering over tijd te berekenen, laten matige resultaten zien wanneer ze gebruikt worden als diagnostisch middel. Dit is het best geïllustreerd door de ROC-grafieken. Bij vroegopsporing van prostaatkanker is de tumor meestal ontdekt in een preklinische diagnostische fase, de PSA stijging in deze fase is niet duidelijk te onderscheiden van de mannen met BPH. Dit maakt dat PSA veranderingen bij screening van prostaatkanker minder van waarde is. Echter wanneer de prostaatkanker gediagnosticeerd wordt ten tijde van de eerste klinische symptomen, dan is de stijging van PSA exponentieel en duidelijk verschillend van het PSA verloop bij mannen met BPH (of zonder prostaatkanker). PSA dynamiek kan van waarde zijn bij die kankers die dichter bij de klinische detectie fase zitten, oftewel grotere of sneller groeiende tumouren. Deze zullen eerder gevonden worden in een naar het ziekenhuis verwezen populatie.

Hoofdstuk 5 rapporteert over de waarde van de eerste of uitgangswaarde van PSA bij het ontwerpen van een optimaal screeningsprogramma. Het onderzoekt de waarde van PSA progressie tot een waarde van 3.0 ng/ml of groter in een 4 jarig interval bij mannen met een uitgangswaarde van PSA onder de 3.0 ng/ml. Het lage aantal mannen dat een PSA progressie laat zien en het lage aantal kankers dat gevonden wordt, vooral in de groep met een eerste PSA onder de 2.0 ng/ml, kan een grote invloed hebben wat betreft voorkomen van onnodige vervolg PSA bepalingen en rectale onderzoeken. De eerste waarde van PSA kan van waarde zijn om groepen van mannen te onderscheiden met of zonder een aanzienlijk risico op prostaatkanker. Intervallen tussen screeningsonderzoeken zouden aangepast kunnen worden op het risico van prostaatkanker afhankelijk van PSA en leeftijd ten tijde van het eerste screeningsbezoek.

Hoofdstuk 6 vergelijkt PSA progressie tot verschillende drempelwaarden, in Nederlandse en Japanse mannen die meedoen in twee verschillende prostaatkanker screeningsstudies. Wanneer men een internationaal gestandaardiseerd screeningssysteem wil ontwikkelen gebaseerd op initiële PSA en leeftijd, kan men veel problemen verwachten wat betreft raciale en etnische verschillen en verschillende incidentie van prostaatkanker. De conclusies van dit onderzoek zijn dat het risico op prostaatkanker en de incidentie groter zijn in Nederland. Het risico wordt groter bij hogere initiële PSA waarden. Echter, er is geen significant verschil in het risico om prostaatkanker te krijgen tussen Nederlandse en Japanse mannen die dezelfde initiële PSA waarde hebben. Hieruit kan men concluderen dat de initiële PSA waarde een belangrijk middel kan zijn bij het ontwikkelen van een internationaal gestandaardiseerd screeningsprogramma ongeacht ras en etniciteit.

Hoofdstuk 7 betreft een studie waar de PSA afkapwaarde is verlaagd naar 2.0 ng/ml en de waarde van een PSA isovorm (% vrij PSA) getest wordt op tumor detectie en agressiviteit in het PSA bereik van 2.0 tot 3.9 ng/ml. De positief voorspellende waarde van deze lage PSA waarden was toch nog 17.1%. Niettemin werd de PSA afkapwaarde van de ERSPC niet verder verlaagd omdat dit in meer overdetectie zal resulteren, met minimale bijdrage aan het terugdringen van prostaatkanker mortaliteit. De waarde van % vrij PSA wat betreft het verbeteren van de relatieve specificiteit, ofwel het voorkomen van onnodige prostaatbiopsie procedures, is matig. Echter % vrij PSA is een goede voorspeller van tumor agressiviteit en kan gebruikt worden om behandelopties te selecteren.

Hoofdstuk 8 beschrijft een studie waarin met behulp van vrij PSA en hK2 minimale prostaatkanker wordt getracht te identificeren. De ontwikkeling van biochemische markers die minimale prostaatkanker kunnen identificeren is belangrijk wanneer men de juiste behandeling voor de specifieke tumorkarakteristieken wil selecteren. De algoritmen hK2/ %vrijPSA en hK2/ vrijPSA zijn in het PSA bereik van 4-10 ng/ml, krachtige combinaties die van nut kunnen zijn bij het differentiëren tussen kankers die om actieve behandeling vragen en kankers die in aanmerking komen voor een afwachtend beleid. De mogelijke additionele waarde van deze algoritmen ten opzichte van andere markers en nomogrammen zal geëvalueerd moeten worden in toekomstige onderzoeken.

PART IV

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Eur Urol. 2007 Nov;52(5):1358-64. Epub 2007 Apr 20.
First place Residents Corner Award. Best paper published in Eur. Urol. 2007

René Raaijmakers werd op 29 januari 1971 geboren in Eindhoven. Na eerst de HAVO doorlopen te hebben werd in juni 1990 de middelbare schooltijd afgesloten met het Atheneum B diploma. In verband met twee jaar uitloting in Nederland, uitgeweken naar Gent voor de studie Geneeskunde. In 1992 uiteindelijk ingeloot in Nederland en in 1999 het artsexamen gehaald aan de Erasmus Universiteit te Rotterdam. Eerste baan als agnio Heelkunde in Amsterdam. Toen weer terug naar Rotterdam als arts-onderzoeker op het screeningsbureau van de ERSPC van 2001 tot en met 2003 onder de bezielende leiding van Prof. Dr. F.H. Schröder. In 2004 werd gestart met de vooropleiding Heelkunde in het Ziekenhuis Bronovo te Den Haag bij Dr. van Rijn. In 2006 is de auteur van dit proefschrift begonnen met het perifere deel van de opleiding Urologie in Eindhoven met als opleider Dr. Hendrikx. Vanaf januari 2008 wordt het academische deel afgerond in het Academisch Ziekenhuis Maastricht of zoals het binnenkort zal gaan heten, het Maastricht Universitair Medisch Centrum.

René is in 2005 getrouwd met Marieke Kostwinder. In 2006 werd hun eerste dochter Julie geboren. Zoon Ties werd in 2007 geboren.

Wanneer je aan je dankwoord mag beginnen is het proefschrift eigenlijk af en heb je de mogelijkheid terug te kijken naar hoe het nu zover is gekomen. Het decor is een regenachtige zondagmiddag met een mix van Olympische Spelen, kinderliedjes en zingende, kirrende kinderen op de achtergrond. Papa zit weer achter de computer en mama houdt de kinderen bezig. De buienradar voorspelt dat ik nog tijd genoeg heb om dit laatste stukje te schrijven. Het begon in 2001 met een uitnodiging van professor Schröder om eens te komen praten naar aanleiding van mijn open sollicitatie naar een klinische plek als arts- assistent Urologie in Rotterdam. Aangezien klinische plekken schaars waren en de Urologie in Rotterdam een goede naam had, was dit te mooi om waar te zijn. Dat klopte ook. Met een bedenkelijk gezicht liep ik naar buiten als arts–onderzoeker op de prostaatkanker screening. Had ik hier wel goed aan gedaan? Wel goed dat die vraag over welk instrument ik speelde bij het Rotterdamsch Studenten Corps, pas na mijn toezegging kwam. Ik dacht toch duidelijk wat teleurstelling van zijn gezicht af te lezen.

Allereerst wil ik Professor Schröder bedanken. U hebt er voor gezorgd dat de wetenschappelijke vonk in mijn is aangewakkerd resulterend tot dit proefschrift en misschien nog wel veel meer. Tijdens mijn onderzoeksperiode heb ik veel op internationale podia mogen staan en geleerd dat de wetenschap niet alleen de mensheid dient maar ook een podium kan zijn voor mensen die op zoek zijn naar succes, macht en geld. Eerlijkheid is hierbij dan het eerste slachtoffer. De manier waarop u als een "gentleman" de wetenschap bedrijft is een voorbeeld voor velen. Integriteit, openheid en eerlijkheid staan hoog in uw vaandel. Ik hoop deze kwaliteiten ook in mijn verdere loopbaan namens u in ere te houden. Het feit dat u ook na uw 70^{e} levensjaar nauw betrokken blijft bij de urologie is het ultieme bewijs van onvermoeibare bevlogenheid. Het is een voorrecht om bij u te mogen promoveren.

Chris, bedankt dat je ook als mijn promotor wilt fungeren. Het feit dat ik je bij de voornaam mag noemen zegt veel over je toegankelijkheid. In ons gesprek over de voortgang van mijn promotie liet je het licht aan het eind van de promotie-tunnel zien.

Veel dank aan de dames van het screeningsbureau voor de gezellige tijd. Monique Roobol voor de hulp en wegwijzing in de verschillende programma's en databases, maar vooral je wijze raad als collega-promovendus. Wilma, je bracht serene wijze rust in ons kippenhok. Ada, je was een heerlijke bron van roddels en oppervlakkige ongerechtigheidjes. Conja, voor de wat diepere gesprekken. Ellen de Bilde en Lakshmi, jullie waren een verademing.

Ellen van den Berg en Monique van der Linde voor de afspraakjes met de professor.

Mark Wildhagen, "de advocaat van de duivel" bedankt voor je statische begeleiding.

Wim, Gerrit, Harry, Bert en Ries voor jullie vakspecifieke expertise.

Mijn directe collega assistenten, Ingrid en Jennie. Een apart zinnetje voor Stijn de Vries. Stijn, een meer collegiale en vriendelijke collega kan men zich niet wensen. Top, dat je mijn paranimf bent.

Oscar, helemaal uit Dubai voor mijn promotie, echt een speciale vriend en daarom mijn paranimf.

Ad voor de foto's en het ouderwetse typemachine kopij uit de oude doos en alle chirurgen en urologen die me gekneed hebben tot de dokter die ik nu ben.

Mijn ouders voor de basis. Pa, wordt het niet eens tijd voor een hK2/ vrij PSA bepaling?
En natuurlijk de deelnemers, meer dan 40.000 in en rond Rotterdam.

Degene die ik de meeste dank en tijd verschuldigd ben, is mijn Marieke die vele avonden en weekenden heeft opgeofferd omdat ik weer achter de computer moest zitten. Dat gaan we anders doen schat, ik hou van je. Julie en Ties, het was een heerlijke afleiding wanneer jullie weer kwamen tekenen bij papa op schoot achter het bureau.

PHD PORTFOLIO

Name PhD student: René Raaijmakers
Erasmus MC Department: Urology
Research School: -

PhD period: 2001-2003
Promotor(s): Prof. Dr. F.H. Schröder
Prof. Dr. C.H. Bangma
Supervisor: -

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication		
- Research Integrity		
- Laboratory animal science		
Research skills		
- Statistics		
- Methodology		
In-depth courses (e.g. Research school, Medical Training)		
- Medical Training/ residency, Erasmus University Rotterdam		
- Surgical/ Urological Training		
Presentations		
- Tumour characteristics of prostate cancer detected 4 years after an elevated PSA-value and an earlier tumour-negative biopsy. *Presentation DUA VI, Noordwijkerhout*	2001	5
- Complication rates and risk factors of 5802 transrectal ultrasound (TRUS) guided sextant biopsies of the prostate. *Moderated postersession AUA annual meeting, Orlando.*	2002	5
- Prostate cancer detection rates in PSA range 2.0 - 3.9 ng/ml. Predictive values of PSA, free PSA, hK2 and related algorithms. *Podium presentation AUA annual meeting, Orlando.*	2002	5
- Prostate cancer detection rates in PSA range 2.0 - 3.9 ng/ml. Predictive values of PSA, free PSA, hK2 and related algorithms *Poster presentation PACIOU/ DUA VII, Rotterdam.*	2002	5

-	Prostaatkanker detectie in PSA groep 2.0 - 3.9 ng/ml – Waarde van biomarkers vrij PSA en hK2 op tumourdetectie en agressiviteit. *Presentation NVU voorjaarsvergadering*	2004	5
-	PSA verandering in een screeningspopulatie. *Presentation NVU voorjaarsvergadering*	2004	5
-	ProPSA improves prostate cancer detection and tumour aggressiveness in the PSA range 2.0 - 3.9 ng/mL *Podium presentation AUA, San Francisco*	2005	5
-	Four year PSA progression and PCa detection in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam *Poster Presentation AUA, San Francisco*	2001-2003	25
-	Prostate cancer detection in Prostate Specific Antigen (PSA) range 2.0 – 3.9 ng/mL – A study without verification bias? *Poster Presentation AUA, San Francisco*		
-	HK2 en % vrij PSA, een krachtige combinatie in het voorspellen van minimale prostaatkanker in screen-gedetecteerde mannen met PSA 4 -10 ng/mL *Presentation NVU voorjaarsvergadering*		
-	Several presentations at international ERSPC meetings		

International conferences

-	AUA, Orlando	2002
-	AUA, Chicago	2003
-	AUA, San Francisco	2004
-	Several ERSPC meetings	2001-2004

Seminars and workshops

-	Presentation and writing skills	2002