

# Impact of Individual Risk Assessment on Prostate Cancer Diagnosis

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# **Impact of Individual Risk Assessment on Prostate Cancer Diagnosis**

**De invloed van een individuele risicobepaling op een prostaatanker diagnose**

## **Proefschrift**

ter verkrijging van de graad van doctor aan de  
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Pa en Ido, voor jullie



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# Part 1

## General Introduction

Chapter 1

The prostate

Chapter 2

Should screening be offered to asymptomatic men?

*Expert Review Anticancer Therapy 2010*

Chapter 3

Scope and outline of the thesis

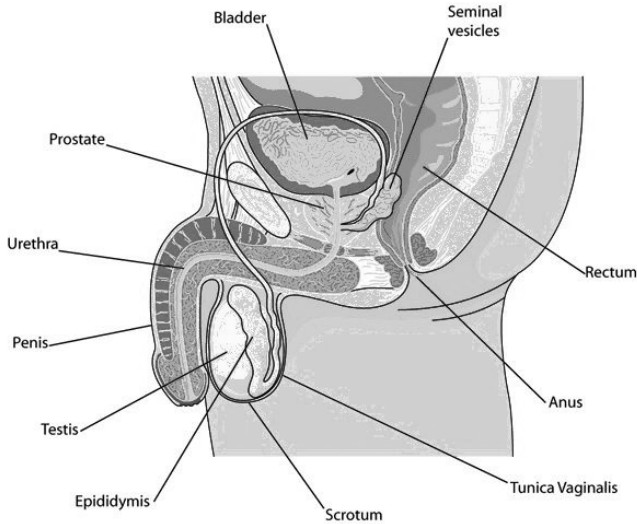


# Chapter 1

The prostate

## PROSTATE

The prostate is a male gland that is located beneath the urinary bladder and surrounds the proximal urethra (Figure 1) in the lower pelvis. The main known function of the prostate is to produce a liquid that usually constitutes 20–30% of the volume of the semen. This prostatic fluid helps prolonging the lifespan of sperm. The other contributors to the ejaculate are spermatozoa and seminal vesicle fluid.



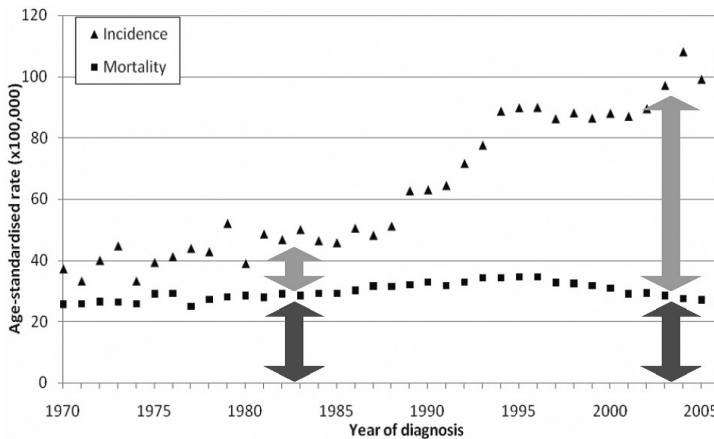
**Figure 1.** Location prostate obtained from <sup>1</sup>

## PROSTATE CANCER

Prostate cancer (PCa) is a major health problem. It is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in men in Europe<sup>2</sup>. In 2008, 14% (903 500) of total new cancer cases and 6% (258 400) of total cancer deaths were related to PCa<sup>2</sup>. Incidence rates have increased rapidly in the last two decades. This is possibly caused by the aging population, an increased awareness of PCa and the early detection of PCa by PSA testing. In the Netherlands, the incidence of PCa has increased from 40-50/100 000 person years in the early 1980's to about 90-110/100 000 in 2005; however mortality rates have remained stable and even decreased during the last years (Figure 2). This may be explained by incorrect estimation of the cause of death, improvement of treatment, and PSA screening<sup>3-5</sup>.

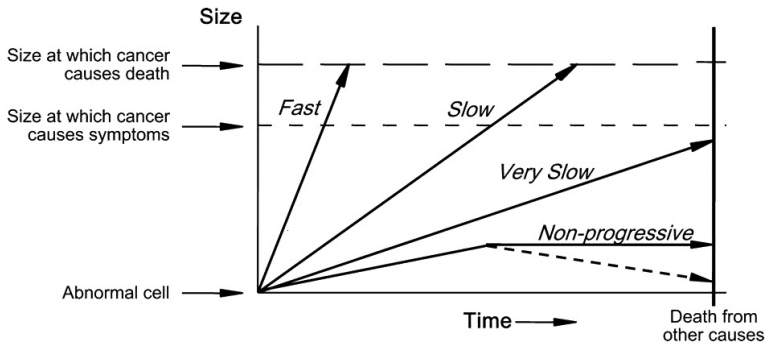
PCa is rare below the age of 50 years<sup>6</sup>. PCa is a disease of elderly men; incidence rates but also mortality rates increase with age<sup>7-8</sup>. In the Netherlands in 2009, of all men who

were diagnosed with PCa 12.2% was under the age of 60, 59.2% between 60 and 75 years, and 28.6% from the age of 75 years. In 2010, of all men who died of PCa 2.4% was under the age of 60, 29.7% between 60 and 75 years, and 67.9% from the age of 75 years<sup>6</sup>.



**Figure 2.** Age-standardized rates (European Standardized Rate) for incidence and mortality of prostate cancer in the Netherlands between 1970 and 2005 and the proportion of relative favourable prostate cancer diagnoses (dark grey arrows) and relatively unfavourable prostate cancer diagnoses (black arrows). (incidence rates 1970-1988: data Comprehensive Cancer Centre South; incidence rates 1989-2006: data Netherlands Cancer Registry – no difference between CCCS and NCR data in period 1989-2006-; mortality rates 1970-2006: Netherlands Cancer Registry)

PCa begins as a small focus or several foci within the prostate. The natural history of PCa is not well known and hence we can not accurately predict which tumours shall progress malignantly; leading to symptoms and death, and which tumours will remain relatively benign; tumours that do not lead to symptoms during men's lifetime or to death or tumours that do not progress. The heterogeneity of PCa progression is depicted in Figure 3.



**Figures 3.** Heterogeneity of cancer progression. The arrow labeled “fast” represents a fast-growing cancer, one that quickly leads to symptoms and to death. The arrow labeled “slow” represents a slow-growing cancer, one that leads to symptoms and death but only after many years. The arrow labeled “very slow” represents a cancer that never causes problems because the patient will die of some other cause before the cancer is large enough to produce symptoms. The arrow labeled “non-progressive” represents cellular abnormalities that meet the pathological definition of cancer but never grow to cause symptoms—Alternatively, they may grow and then regress (dotted line). Obtained from<sup>9</sup>

## SYMPTOMS OF PROSTATE CANCER

The majority of the PCa originates in the peripheral zone of the prostate, approximately 70%<sup>10</sup>. These cancers cause no symptoms, particular in their early stages, because they begin in the outer peripheral zone and grow outwards the prostate. These tumours may be palpated by digital rectal examination (DRE). Furthermore, PCa originates in about 25% of the cases in the transition zone and 5% in the central zone<sup>10</sup>. In more advanced cases, the cancer may press on the urethra leading to possible lower urinary tract symptoms, haematuria or complete obstruction of the urinary flow<sup>11</sup>. Locally advanced or metastatic PCa may lead to symptoms like pain, fatigue, malaise, and weight loss. PCa usually metastasizes first to the lower spinal or the pelvic bones causing back or pelvic pain. More seldom PCa can metastasize to the liver and lungs and can cause pain in abdomen and chest. In most cases PCa manifests clinically at the time of metastasis<sup>12</sup>. With an increase in PSA screening, more men are diagnosed with PCa without having symptoms of the disease and that would never become clinically apparent. PSA screening increasing the risk of overdiagnosis.

## OTHER DISORDERS OF THE PROSTATE

Other disorders of the prostate are prostatitis and benign prostatic hyperplasia (BPH). Prostatitis is an infection of the prostate gland and about 50% of men develop symptoms during lifetime<sup>13</sup>. Prostatitis often causes pain in perineum of pelvis. Other

frequent symptoms are: obstructive urinary symptoms due to swelling of the inflamed prostate, an unpleasant sensation of sudden urgency to urinate, discomfort during urinating, fever, and recurrent urinary tract infections. In case of bacterial infection antibiotics are indicated. BPH is a benign prostate enlargement which affects more than 50% of men in the age of >60 years<sup>14</sup>. BPH is associated with bladder outlet obstruction and lower urinary tract symptoms that include urinary urgency, a decreased urinary stream force, and stream interruption of the stream, an increased urinary frequency, the persistent sensation that the bladder has insufficiently emptied, and nocturia<sup>15</sup>. These symptoms occur due to the increased pressure of the prostate on the urethra. BPH is usually treated with medication such as 5-alpha-reductase inhibitors in order to shrink the prostate and slowing its growth or with transurethral resection that is performed with the aim to remove the obstructing portion of enlarged prostate tissue.

## **DIAGNOSIS OF PROSTATE CANCER**

The most common tests used in the diagnosis of PCa are the serum prostate-specific antigen (PSA) test, digital rectal examination (DRE), transrectal ultrasound (TRUS) and prostate biopsy.

### **PSA**

Serum PSA can be measured with a blood test, it is a protein produced by prostate epithelial cells which have leaked into the bloodstream. An increased PSA level indicates an increased risk of PCa. A low PSA level does not exclude PCa (PSA <3 ng/ml)<sup>16-17</sup>. However, PSA is not PCa specific. This means that an increased PSA level can also be caused by other reasons, such as an enlarged normal prostate gland i.e. BPH or a leakage of PSA into the bloodstream due to prostatitis or an obstruction.. PSA is not only used for the detection of PCa, but also for evaluation of PCa treatment and PCa follow-up in patients. More about PSA as a screening tool is discussed in Chapter 2.

### **DRE**

The prostate can be palpated by inserting a lubricated finger into the rectum to examine the adjoining prostate (DRE). The prostate is examined for the presence of nodules or indurations which are usually considered suspicious for PCa and to assess the prostate size. A suspicious DRE is associated with PCa<sup>18</sup>. The value of DRE in PCa screening is described in Chapter 2.

## TRUS and prostate biopsy

TRUS provides echographic images of the prostate. This allows the physician to examine the gland for abnormalities such as hypoechogenic lesions which have been associated with PCa and to measure prostate volume more accurately which may help interpretation of PSA results<sup>19-20</sup>. However, the performance of TRUS as a screening tool is relatively poor with only 3.5% of a biopsy of hypoechogenic lesions being positive for PCa<sup>19</sup>.

The 'gold standard' for the investigation of PCa is the prostate biopsy. The recommended method is the TRUS guided systematic prostate biopsy, an other method is the transperineal laterally directed biopsy<sup>21</sup>. For many years the lateralized sextant biopsy technique was in use. However, it has been reported that up to 23% of biopsy-detectable PCas are missed with this technique compared to extended biopsy schemes of 10 or 12 core biopsy<sup>22</sup>. Now, at a glandular volume of 30-40 ml, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive<sup>23</sup>. Additional cores should be obtained from suspicious areas assessed with DRE and/or TRUS<sup>21</sup>. Nevertheless, the optimal number and location of biopsies needed to identify patients with PCa at the earliest stage possible for optimal treatment, outcome and survival, is still not known<sup>24</sup>.

## Prediction models

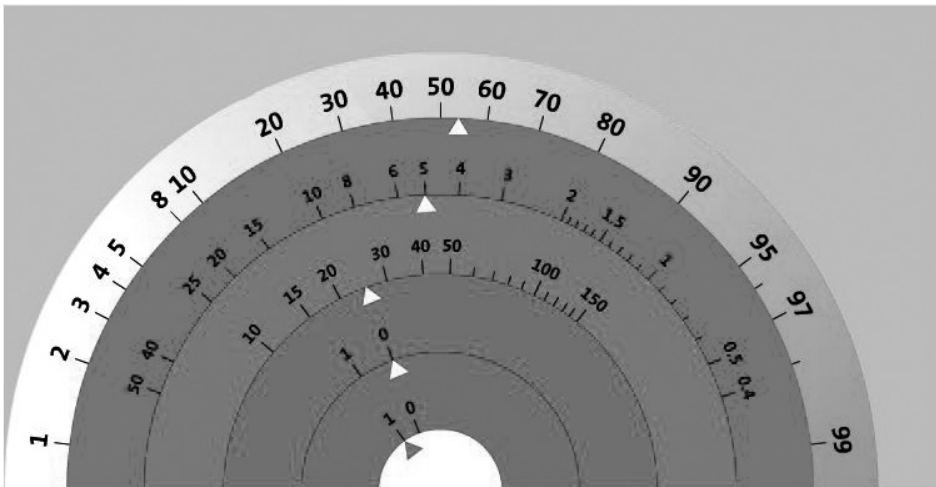
The three tests; serum PSA, DRE and TRUS have all their specific strength and weakness in predicting the presence of PCa. Combining these *three* tests might increase the predictive capability. This can be done by including them into a prediction model. Nowadays, increasingly prediction models are used to calculate the probability on a positive prostate biopsy using beside serum PSA several PCa risk factors, such as family history, outcomes of DRE and TRUS, age, a prior negative biopsy, and prostate volume. The outcome assists physicians and their patients in the decision-making whether or not to perform a biopsy<sup>25</sup>. These prediction models increase the specificity of serum PSA. The European Randomized study of Screening on Prostate Cancer (ERSPC) risk calculator (RC) is such a prediction model.

## The ERSPC risk calculator

The ERSPC risk calculator estimates the probability of having a biopsy detectable PCa (level 1-4) and the probability on indolent PCa (level 5) ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)), using multivariable logistic regression models. The ERSPC risk calculator is based on the ERSPC data of men aged 55-75 years screened in Rotterdam. Level 1 calculates the probability on PCa using outcome of questions about age, family history, and urinary symptoms. Level 2 uses only PSA to assess the individual PCa probability at biopsy. These two levels can be used by layman, but also by a physician. Level 3 estimates the probability on a positive sextant prostate biopsy in unscreened men, using next to serum PSA, the outcome of DRE and TRUS (hypoechogenic lesion yes/no),



and TRUS assessed prostate volume (Figure 4)<sup>26</sup>. A prostate biopsy was recommended if the probability on a positive biopsy was  $\geq 20\%$ . This 20% threshold is comparable to the positive predictive value of a PSA of  $\geq 4$  ng/ml in a general screening population. Level 4 calculates the probability on a positive prostate biopsy of men who have previously had PSA screening, but have either had no biopsy or one that was negative. This level uses the same predictors as level 3. However, the ERSPC risk calculator consists also of a level that can be used in cases of a PCa diagnosis.



start again

#### Result

The chance of having a positive biopsy is **54%**

The chance of having a high grade or advanced prostate cancer\* is **23%**

\*Defined as Gleason score  $\geq 7$  and/or T stage  $> T2B$

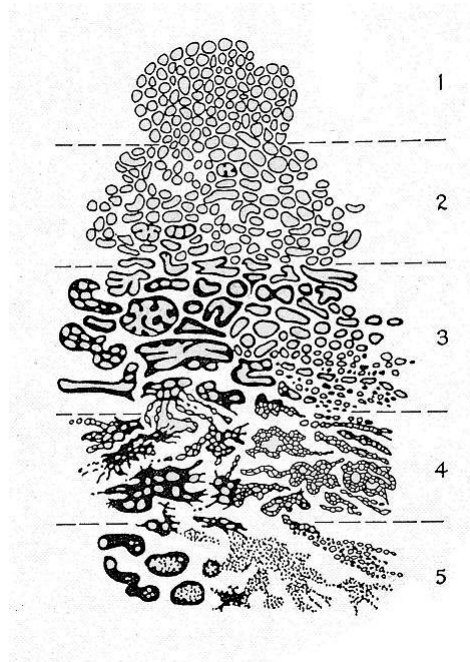
- Transrectal ultrasonography (TRUS) (0/1)
- Rectal examination (DRE) (0/1)
- Prostate volume (cc)
- PSA (ng/ml)

**Figure 4.** The European Randomized study of Screening on Prostate Cancer risk calculator level three; the probability on a positive sextant prostate biopsy. Obtained from <sup>29</sup>

In the recent updated version of the risk calculator (May 2012) this is level 5 (previously this was level 6 and is called level 6 in this thesis). This level calculates the probability on potentially indolent PCa using the outcome of serum PSA, pathological results at biopsy and TRUS assessed prostate volume<sup>27</sup>. The outcome can be used when considering treatment options; active treatment or active surveillance. As a decision rule, active surveillance is recommended if  $P(\text{indolent}) > 70\%$ , and active treatment in other cases. This 70% threshold was based on a study where an existing clinical RC was validated and adapted towards a screening setting, resulting in a 94% sensitivity (actively treating important PCa) and a 32% specificity (resulting in applying active surveillance to 68% of potentially indolent PCa)<sup>27</sup>.

Indolent or insignificant PCa are terms that are often used interchangeable. However, the term indolent refers to pathologic characteristics of the tumor and has been frequently preferred in prediction models, but does not take into account important patient-related factors such as age and comorbidity. Indolent disease refers to a cancer that would be never clinical manifest according to its pathological features and cause no mortality because of its favourable tumour characteristics<sup>28</sup>. Insignificant PCa refers to both pathologic characteristic and to patient-related factors. Insignificant cancer is used for all cancers that cause no morbidity, including indolent cancers and cancers that harbour more aggressive features, but cause no morbidity due to competing other causes of death, such as comorbidity. For example a PCa Gleason 3+4 is not indolent, but can be insignificant in a man with heart failure.

When there is a PCa suspicion (based on PSA, and/or outcomes of DRE and/or TRUS, and/or the outcome of a PCa risk calculator), the PCa diagnosis is made by histological examination of prostate tissue. This tissue is taken from the prostate by TRUS-guidance needle biopsy. The pathological biopsy outcome is used besides the PSA and tumor stage to assess the degree of aggressiveness of the PCa; the number of positive cores, the extent of PCa tissue involved in cores, and the Gleason score<sup>27</sup>.



**Figure 5.** Grades of differentiation of cancer cells, ranked according to the original grading system. Obtained from <sup>30</sup>

## TUMOUR GRADING AND STAGING

The Gleason score is the most commonly used system for grading adenocarcinoma of the prostate and expresses the aggressiveness of the tumour<sup>31</sup>. This system gives a grade for differentiation of the cancer from 1 to 5; 1 is well differentiated and 5 is poorly differentiated (Figure 5). The Gleason score is the sum of the two most common patterns and ranges from 2 to 10. In cases where 3 or more patterns of a tertiary Gleason grade 4 or 5 are present, then the Gleason score consists of the dominant and highest patterns. If one pattern is identified the primary is doubled. This grading system was updated in 2005<sup>30</sup>. A Gleason score 2-4 should not be given on prostate biopsies, the originally considered Gleason pattern 3 is now Gleason pattern 4, and all cribriform cancers should be graded pattern 4. "Cribriform" means perforated with very small holes or "sieve-like". Thus, Gleason score 6 now presents tumors lacking cribriform and poorly formed glands with a better prognosis<sup>30</sup>. After application of the modified Gleason score on needle prostate biopsy, a substantial shift in Gleason score distribution occurred: Gleason score 6 decreased with the new grading system from 48 to 22% and Gleason score 7 increased from 26 to 68%<sup>32</sup>.

The Gleason score and outcome of Tumour/Node/Metastasis (TNM, Table 1) classification are important parameters to assess the aggressiveness and extent of the disease, but are also applied for PCa prognosis. The most common way to assess the clinical T-

**Table 1.** Tumour, node, metastasis (TNM) classification of prostate cancer (2002 version)

T-primary tumour	Tx: Primary tumour cannot be assessed	T1a: Tumour was incidentally found in less than 5% of prostate tissue resected
	T0: No evidence of tumour	T1b: Tumour was incidentally found in greater than 5% of prostate tissue resected
	T1: Tumour present, but not detectable clinically or with imaging	T1c: Tumour identified by needle biopsy performed due to an elevated serum PSA
	T2: Tumour confined within the prostate	T2a: Tumour involves one-half one lobe or less T2b: Tumour involves more than one-half of one lobe, but not both T2c: the tumour is in both lobes
T3: Tumour extends through the prostatic capsule	T3a: Extracapsular extension in periprostatic tissue T3b: Invasion of seminal vesicle(s)	
T4: Tumour is fixed or invaded adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall		
N-regional lymph nodes	Nx: Regional lymph nodes cannot be assessed	
	N0: No regional lymph nodes metastasis	
	N1: Metastasis in regional lymph nodes	
M-distant metastasis	Mx: Distant metastasis cannot be assessed	M1a: Non-regional lymph nodes
	M0: No distant metastasis	M1b: Bones
	M1: Distant metastasis	M1c: Other sites

stage of the tumour is by DRE or TRUS. The distinction between intra capsular ( $T \leq T2$ ) and extracapsular ( $>T2$ ) disease is an important factor in treatment decisions. The definite T-stage or pathological tumour stage can be obtained after radical prostatectomy.

## TREATMENT

Treatment options for PCa are based on the Gleason score and TNM classification. Also taken into consideration are: serum PSA level, number of positive biopsy cores, life expectancy, comorbidity, age, quality of life, and the patient's personal preference. In addition, treatment choice can also be recommended according to whether the risk category is low, intermediate, or high and referring to the risk of recurrence after therapy. These risk categories are based on the outcome of clinical stage, Gleason score and PSA value according to d'Amico et al.<sup>33</sup>. Low risk was defined as clinical stage  $\leq T2a$ , Gleason score  $<7$ , PSA value  $\leq 10$  ng/ml. Intermediate risk was defined as clinical stage T2b, Gleason score 7 and PSA value 10-20 ng/ml. Men with high risk PCa have clinical stage  $\geq T2c$ , Gleason score  $>7$  and PSA value  $>20$  ng/ml. Treatment decision-making for PCa, even in clinically localised disease, has become increasingly complex due to the various treatment options available and the lack of high-quality evidence from randomized control studies regarding to that one therapy will be better over another<sup>34-35</sup>. However, some treatment recommendations based on the literature can be made. The standard management of localized PCa (stage  $\leq T2c$ ) includes radical prostatectomy (open, laparoscopic or robot-assisted), radiotherapy (external-beam or brachytherapy) and active surveillance. Active surveillance is recommended in men with low risk PCa and means that the disease is actively monitored according a protocol with PSA tests, DRE and prostate biopsies<sup>21</sup>. Active surveillance may avoid the risk on physical side-effects due to active treatment. Active treatment is indicated with curative intent when progression of the disease occurs. Prospective analyses of men undergoing such an active surveillance (AS) strategy show favourable 10-year PCa-specific survival rates approaching 98%<sup>36-37</sup>. There is no data of randomized controlled trials available.

Radical prostatectomy and Watchful Waiting have been compared in a randomized controlled study<sup>38</sup>. This study showed that cancer-specific survival rates are in favour of radical prostatectomy in men younger than 65 years who have a life expectancy of  $\geq 10$  years during a median follow-up of 12.8 years<sup>38</sup>. However, the data is mainly based on men who had no screen-detected PCa. There are no randomized controlled studies to compare the outcome of radical prostatectomy versus radiotherapy, although observational data suggest that radical prostatectomy and radiotherapy showed similar survival<sup>39-40</sup>. Though both treatment options are associated with physical side-effects,<sup>41-42</sup> main adverse outcomes after surgery are erectile dysfunction and urinary incontinence

and after radiotherapy erectile dysfunction, bowel problems, urinary irritations, urinary incontinence<sup>41-42</sup>. Erectile dysfunction and urinary incontinence occur more frequent after surgery than after radiotherapy<sup>41-42</sup>. Two studies illustrate that erectile dysfunction and urinary incontinence decline five years after surgery or radiotherapy<sup>43-44</sup>. Erectile dysfunction was observed in 79% and 88% five years after surgery and in 63% and 64% five years after radiotherapy<sup>43-44</sup>. Urinary incontinence was observed in 14% and 31% after surgery and in 4% and 13% after radiotherapy<sup>43-44</sup>.

Alternative treatment options in men with clinically localized PCa are focal therapies, such as cryotherapy and High Intensity Focused Ultrasound. Cryotherapy aims to destroy prostate cancer cells by freezing the cells. Whereas High Intensity Focused Ultrasound aims to destroy the cancer cells using high energy waves, thus damaging cancer tissue by mechanical and thermal effects as well as cavitation<sup>45-46</sup>. Currently, focal therapy of PCa can not be recommended as alternative therapy outside clinical trials<sup>21</sup>.

Watchful waiting is indicated if active treatment is not an option due to age or comorbid conditions and hormonal therapy is not yet indicated. With watchful waiting, treatment is only indicated when the patient suffers from symptoms due to progression of the disease (palliative treatment). Dependent on the stage of the disease, this treatment may consist of androgen deprivation, radiotherapy, local desobstruction or chemotherapy.

Metastasized PCa cannot be cured and will in time lead to death if comorbidity does not infer earlier. Temporary suppression of the PCa is possible using different options of endocrine therapy<sup>47</sup>. Research showed no differences in terms of survival between the various palliative therapies. If endocrine therapy is not effective any more chemotherapy may be an option to reduce symptoms and prolong life for a few months<sup>48-49</sup>.

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# Chapter 2

## Prostate cancer screening

### Should prostate-specific antigen screening be offered to asymptomatic men?

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**ABSTRACT**

The benefits of population-based prostate cancer screening are the detection of clinically important prostate cancers at an early, still curable, stage and the subsequent reduction of prostate cancer-specific mortality. However, a prostate-specific antigen (PSA)-based prostate cancer screening program is currently insufficient to warrant its introduction as a public health policy. The main reasons are insufficient knowledge regarding the optimal screening strategy and overdiagnosis and overtreatment of indolent prostate cancers that are unlikely to lead to complaints or death. In some countries, guidelines have been developed on screening for prostate cancer, but the diversity of recommendations illustrates the limited knowledge on the optimal strategy. Therefore, men should be well informed about the benefits and potential harms of PSA screening in order to enable them to make an informed decision. Although a mortality reduction can be achieved by early detection of prostate cancer, patients and physicians must be aware of the current side effects of screening. Algorithms that advise screening at a young age (<55 years), with screening intervals of less than 4 years and low PSA thresholds (<3 ng/ml) for prostate biopsy seem premature and are not supported by evidence.

## BACKGROUND

Prostate cancer (PCa) is the most frequently diagnosed cancer and was the third most common cause of death in Europe in 2006<sup>1</sup>. In the USA, PCa is the most common nonskin cancer and the second leading cause of cancer death in men<sup>2</sup>. Prostate-specific antigen (PSA) screening programs for PCa are not officially endorsed by governmental organizations. There is evidence that systematic population-based screening with an interval of 4 years can lower PCa mortality<sup>3</sup>. The debate on whether to screen asymptomatic men is ongoing, because of the side effects of screening, that is, overdiagnosis and overtreatment of potentially indolent PCas. Furthermore, the optimal screening algorithm has still to be determined. This has resulted in a large variation in guidelines worldwide, and this diversity of recommendations illustrates the limited knowledge on the optimal strategy.

Using the vast amount of scientific literature available, with the limited 'high-quality' literature from randomized controlled trials, we addressed the question, which men should be screened and according to which screening algorithm? First, we will discuss the incidence and mortality of PCa, the methods of screening for PCa and the use of nomograms. The benefits and potential harms of PCa screening will be weighed. Furthermore, the current guidelines regarding PCa screening will be described. The best current evidence is used to arrive at a recommendation to men who consider screening for PCa. Finally, we described how the field will evolve in the next 5 years.

## INCIDENCE AND MORTALITY OF PROSTATE CANCER

The incidence rates of PCa differ around the world. Asia has the lowest incidence and mortality rate (Table 1)<sup>4</sup>. The highest rates are found in the USA, probably owing to a high rate of PSA screening<sup>5</sup>. These incidence rates may be influenced by diverse genetic and environmental factors, such as lifestyle, air quality, diet, nutrition, chemicals and of course screening activity<sup>6</sup>. After the introduction of the PSA test in the USA in the mid-1980s the incidence of PCa increased and peaked in 1992 at 179 per 100,000 in white men and in 1993 at 250 per 100,000 in black men<sup>7</sup>. In the UK, the incidence rate of PCa peaked several years later in 2006 at 97 per 100,000 men<sup>101</sup>. By contrast, mortality declined each year after 1994 in the USA, almost four-times the rate of decline in the UK<sup>8</sup>. This difference may be caused by the early detection of advanced cancer with PSA screening in the USA and the absence of screening in the UK. PSA screening reduces the detection of advanced PCas with subsequent screening rounds<sup>9,10</sup>. In addition, national treatment policies might have affected the metastasis rate.

The lifetime risk of being diagnosed with PCa is 15.8% in the USA, that is, one out of every six men is confronted with the diagnosis of PCa<sup>102</sup>. In the European Union the lifetime

risk of being diagnosed with PCa is 5.9%<sup>11</sup>. The risk of being diagnosed with PCa under the age of 55 years is very low<sup>5,101,102</sup>. The lifetime risk of dying from PCa is 2.8% in the USA<sup>102</sup> and 4% in the UK<sup>101</sup>. The large discrepancies between the incidence and the mortality rates are largely due to the fact that a lot of men die with PCa rather than from PCa.

**Table 1.** Age-standardized incidence (world standard population) and mortality rates for prostate cancer in Asia, Europe and America, 2002 estimates

World region	Incidence per 100,000	Mortality per 100,000
Eastern Asia	3.8	1.9
South Central Asia	4.4	2.8
South-Eastern Asia	7	4.5
Western Asia	10.9	6
Eastern Europe	17.3	9.7
Southern Europe	35.5	13.2
Northern Europe	57.4	19.7
Western Europe	61.6	17.5
Central America	30.6	15.5
South America	47	18
Northern America	119.9	15.8

Data from Globocan: Cancer incidence, Mortality and Prevalence Worldwide. 2002<sup>4</sup>

## METHODS OF SCREENING FOR PROSTATE CANCER

The aim of screening for any type of cancer is to increase the chances of successful treatment through the early detection of the disease. There are three types of screening interventions: mass screening (population based), selective screening (screening only high-risk populations) and opportunistic screening (individual screening on request, often as part of a medical consultation). Mass or population-based screening is defined as the systematic examination of asymptomatic men. Usually, screening take place within a trial or study and is initiated by a screener. Selective screening is offered to known high-risk groups. However, individuals with increased risk who are not part of these known risk groups are not offered screening.

The aim of opportunistic screening is the detection of early cancer and represents individual cases and is initiated by the patient or physician<sup>12</sup>. A disadvantage of screening the whole population is the detection of a larger number of men with potentially indolent cancer compared with selective or opportunistic screening.

Within a population eligible for PCa screening, four groups can be identified: those diagnosed with PCa that would not have developed cancer symptoms during their lifetime (overdiagnosis); those diagnosed with cancer at an early stage that might oth-

erwise have led to symptoms and/or the need for more aggressive curative treatment if detected at a later stage; those diagnosed with cancer at a curable stage with aggressive disease that might otherwise have progressed to metastatic disease if detected at a later stage; and, those diagnosed with cancer at the same stage as it would have been diagnosed clinically and involves cancers that are too late for curative therapy.

Ideally, screening should detect only those PCa cases that are in groups two and three, because these groups can benefit from screening.

Various criteria have to be fulfilled before a population-based screening program for PCa is justified, such as a proven relevant mortality reduction, insight into the effect of screening on quality of life, cost-effectiveness and the ability to control the potential harms of screening on PCa, that is, overdiagnosis and overtreatment of PCa<sup>3,13</sup>.

## HOW TO SCREEN FOR PROSTATE CANCER?

The most commonly used screening tools for PCa are a serum PSA test<sup>14</sup> and digital rectal examination (DRE). If an elevated PSA level (in general  $\geq 3.0$ – $4.0$  ng/ml) and/or the DRE show abnormalities, a prostate biopsy is indicated.

### Prostate-specific antigen

An increased serum PSA level is not specific for the presence of PCa, since it can occur in prostatitis, benign prostate hyperplasia and urinary retention. Therefore, PSA has limited sensitivity and specificity in the detection of PCa. This leads to false-positive and false-negative results, even if a certain threshold value is applied<sup>15–17</sup>. False-positive results lead to 'unnecessary' additional testing, that is, a prostate biopsy. False-negative results lead to missed PCa diagnoses. In a study within a screening setting applying a biopsy cut-off of 3.0 ng/ml or higher, 75.9% of the men biopsied had a benign result, that is, the positive predictive value (PPV) of a PSA cut-off of 3.0 ng/ml was 24.1%<sup>3</sup>. Another study applied a biopsy if the PSA level was 4.0 ng/ml or higher and reported a PPV of 10.4–17.9% over a total of four screening rounds<sup>9</sup>. Since PCa is present across the entire PSA spectrum, it is difficult to identify a valid PSA cut-off level that balances sensitivity and specificity in indicating a biopsy<sup>16–19</sup>. Schroder et al. concluded in their study that PSA cut-off levels between 2.5 and 4.0 ng/ml provide a reasonable balance between excessive detection rates and the risk of missing relevant cancers<sup>18</sup>. It is suggested that in men with a PSA level below 3.0 ng/ml, biopsy can safely be delayed, on the basis of a 12-year follow-up period.

Prostate-specific antigen is the only serum marker routinely used. The PSA isoforms, such as complex and free PSA, help to differentiate between PCa and benign prostatic hyperplasia more accurately, especially for patients with a PSA level between 2 and 10 ng/ml<sup>20</sup>.

### Digital rectal examination

In a population-based screening setting DRE has a limited predictive value in the low PSA ranges<sup>21,22</sup>. However, a significant number of PCas is solely detected on the basis of an abnormal DRE. Okotie et al. evaluated 36,000 men, of which 3568 (10%) had PCa; 18% of the PCa cases were detected solely by DRE and 20% of these cancers had a Gleason score of 7 or higher<sup>23</sup>. The PPV of DRE is associated with an increased serum PSA level, even at PSA levels of 4 ng/ml or lower<sup>21,23</sup>. In addition, men with a suspicious DRE have more chance of detecting PCa than men with a normal DRE. The combination of a PSA level of at least 3 ng/ml with a suspicious DRE demonstrated significantly more PCas with a Gleason score above 7, which are defined as potentially aggressive cancers<sup>24</sup>.

So, despite the observer variability of DRE and low predictive value, DRE might be of value in detecting potentially aggressive PCas.

### Prostate biopsy

Prostate cancer is diagnosed by histology. For many years a lateralized sextant biopsy technique was in use. It has been reported that approximately 22% of biopsy-detectable PCas are missed with a lateralized sextant biopsy technique<sup>25</sup>. Several different biopsy schemes were developed in which the number of biopsy cores is related to total prostate volume and age<sup>26-28</sup>. Vashi et al. developed a model that calculates the number of cores needed for optimal detection, taking into account the age and prostate volume<sup>28</sup>. If the biopsy result shows atypical small acinar proliferation (ASAP) a repeat biopsy is warranted<sup>29</sup>.

### Nomograms

Recently, nomograms have been developed based on different PCa risk factors to predict the probability of the presence of a biopsy-detectable tumor (Table 2). There are many biological factors that influence the risk of PCa, such as a positive family history, race (African-Americans are at higher risk as compared with Caucasians) and age<sup>30,102</sup>. Clinical determinants are an abnormal DRE, an elevated PSA level or a relatively small prostate volume<sup>30-32</sup>. Higher PSA levels, abnormal DRE, older age and African-American race were reported to be predictive for high-grade disease (Gleason score  $\geq 7$ )<sup>33</sup>.

**Table 2.** Web-based nomograms for the prediction of the prediction of the presence of a biopsy detectable prostate cancer

Nomogram	Variables	Website
The cancer risk calculator for prostate cancer (USA)	Age, race, family history of PCa, PSA, DRE, previous prostate biopsy, taking finasteride yes/no	<a href="http://www.tinyurl.com/caprisk">www.tinyurl.com/caprisk</a> <sup>105</sup>
Prostate risk-indicator (Europe)	PSA, DRE, prostate volume and outcome TRUS	<a href="http://www.prostatecancer-riskcalculator.com">www.prostatecancer-riskcalculator.com</a> <sup>106</sup>
Prostate cancer nomogram (Canada)	Age, DRE, PSA, percent free PSA, sample density	<a href="http://www.nomogram.org">www.nomogram.org</a> <sup>107</sup>

DRE: Digital rectal examination; PCa: Prostate cancer; PSA: Prostate-specific antigen; TRUS: Transrectal ultrasound

These nomograms can improve the diagnostic value of PSA alone by adding other potential predictive risk factors, that is, outcome of DRE, total prostate volume and outcome of transrectal ultrasonography (TRUS) examination<sup>34</sup>. The use of these nomograms can result in a considerable reduction of unnecessary biopsies. A recent study demonstrated 33% fewer biopsies if both the PSA cut-off of 3 ng/ml or higher and a calculated probability cut-off of 12.5% were applied. The PPV of the lateralized sextant biopsy increased from 29% to approximately 40%. This improvement in PPV was achieved with a marginal loss of the detection of aggressive PCa<sup>35</sup>.

If PCa is diagnosed, it can be classified as clinically relevant (i.e., threatening the life or well-being of the patient) or clinically insignificant (i.e., latent cancer and asymptomatic). Clinically insignificant PCas are small, well differentiated PCas with a low risk of morbidity and or mortality during the patient's lifetime. Epstein et al. introduced the term insignificant PCa based on a clinical parameter and biopsy criteria: PSA density of below 0.15 ng/ml, stage T1c, Gleason score of 6 or lower, presence of tumor in two or fewer cores and no more than 50% involvement by the tumor in any single core<sup>36</sup>. This definition of insignificant PCa is frequently used, but has never been subjected to prospective analysis, that is, in an active surveillance setting. Variations of these criteria have been reported and criteria have been added over time<sup>37</sup>. Based on these criteria, various multivariate prediction tools have been developed to calculate the probability of the presence of clinically insignificant PCa<sup>38,103</sup>. These nomograms only predict small, low-grade, low-stage pathology on prostatectomy, but none had actually been validated in an active surveillance cohort. The calculated probability of a clinically insignificant PCa can be an aid for physicians in making treatment decisions<sup>39-41</sup>.

The use of nomograms has limitations<sup>42</sup>. The physician should ensure that it was developed in the same population as the population in which the nomogram is used, to provide equally accurate predictions in his/her patients. The large number of nomograms for the same purpose makes it difficult to choose the most adequate. An adequate nomogram is validated for the setting where the development data originated

from. Some nomograms are also externally validated in populations that have similar characteristics. Nomograms can assist physicians in the clinical decision making during the entire screening process from the risk of having a biopsy-detectable PCa to survival after the development of metastatic disease<sup>43,44</sup>.

## **BENEFITS OF PROSTATE CANCER SCREENING**

The results of two large randomized screening trials, initiated to assess the effect of early detection on PCa specific mortality, have recently been presented; the Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) in the USA and the European Randomized Study of Screening for Prostate Cancer (ERSPC) in eight European countries (Belgium, Finland, France, Italy, Spain, Sweden, Switzerland and the Netherlands). Both studies were initiated in 1993<sup>3,13</sup>.

The PLCO randomly assigned 76,693 men aged 55–74 years to receive screening or usual medical care. Men randomized to the screening arm were offered annual PSA testing for 6 consecutive years and a DRE for the first 4 years. A PSA level of 4 ng/ml or higher and/or a suspicious DRE were considered abnormal and needed further assessment. Cumulative incidence of PCa was 7.3 and 6.0% for the screening and control arm after a median follow-up of 7 years.

The PCa death rate was 2.0 (50 deaths) per 10,000 person-years in the screening arm and 1.7 (44 deaths) in the control arm (relative risk (RR): 1.13; 95% CI: 0.75–1.70). Screening did not lead to a significant reduction in PCa mortality during the first 7 years of the trial, with similar results up to 10 years, at which time 67% of the data were complete. The treatment distributions were similar in the two arms within each tumor stage.

In the screening arm the rate of compliance with PSA testing was 85% and with biopsy recommendations 40%. Contamination, that is PSA testing in the control arm, was 40–52% and 41–46% for DRE. No results are available for adjustment of non-attendance and contamination.

The ERSPC randomly assigned 182,000 men aged 55–74 years to the intervention or the control arm. Men in the screening arm were offered PSA testing and DRE at 4-year intervals (one center used a 2-year interval). A total of 162,243 men aged 55–69 years were included for mortality analysis. Cumulative incidence of PCa after a median follow-up of 9 years was 8.2% and 4.8% for the intervention and control arm, respectively.

The ERSPC demonstrated a relative PCa mortality reduction of 20% (RR:0.80; 95% CI: 0.65–0.98;  $p < 0.04$ ) after a median follow-up of 9 years. This mortality reduction coincided with an excess PCa incidence in the screening arm of 34 per 1000 men. This resulted in 1410 men that needed to be screened and 48 men that needed to be treated in excess of the clinical situation, to prevent one death from PCa. Among men between



the age of 50–54 years at baseline, the number of events was small, and showed no obvious screening effect.

The trial had a compliance rate of 82% of those who accepted the offer of screening. The average rate of compliance with biopsy recommendation was 85.5%. The results of this study are influenced by non-attendance in the intervention arm and contamination in the control arm. After adjustment for non-attendance and contamination based on the Dutch data of the ERSPC, the RR of dying of PCa in men actually screened versus not screened was 31%<sup>45</sup>.

In contrast to the ERSPC, the PLCO did not find a PCa mortality reduction in men randomized to the screening arm. The results of the PLCO were influenced by the large contamination rate of the control arm and the low compliance for biopsy in the screening arm. These have a negative effect on the power of the trial. In addition, men were allowed to have one screening within 3 years before enrollment and an unlimited number of earlier PSA screenings. Next to this, men may have been screened without their knowledge<sup>46</sup>. This pre-screening effect is reflected in the similar tumor stages in both the control and screening arm, 94.3 and 96% clinical stage 1 and 2, respectively<sup>9</sup>. The ERSPC data had sufficient statistical power, with sensitivity analysis taking into account non-attendance and contamination. The ERSPC found an effect of screening on PCa mortality by applying a predefined significant limit of  $p < 0.05$ <sup>47</sup>. The PCa mortality reduction as found in the ERSPC might also have been caused by differences in treatment distribution between the two arms. However, there are no facts supporting this explanation<sup>48</sup>.

### **Beneficiary effect on stage & grade distribution of prostate cancer**

Screening results in a significant decrease in stage and grade<sup>9,10,49-51</sup>. Aus et al. reported a reduction of 48.9% of metastatic PCa after a follow-up of 10 years for those randomized to the screening arm. The number of men with metastatic disease at the time of diagnosis was 24 in the screening arm compared with 47 in the control arm<sup>50</sup>. This was confirmed by data from the Dutch part of the ERSPC. This study reported a significant difference in the number of men diagnosed with metastatic disease between the screening and control arms of 0.6 and 8%, respectively. Also within the screening arm, the number of men with a Gleason score of 7 or higher at subsequent screening rounds decreased significantly from 36.2% at the first screening round to 22.3 and 12.5% in the subsequent screening rounds<sup>51</sup>. Within the PLCO similar trends were observed. At the first screening round more men were likely to have cancers with Gleason score 7–10 and clinically advanced tumors than at subsequent screening rounds<sup>9</sup>.

Consequently, the mortality reduction achieved through screening is attributable to earlier detection of high-grade disease, and PSA screening increases the overdiagnosis of low-grade disease.

If a PSA-based cut-off is used as indication for biopsy, PCas could be missed owing to sampling error of the gland. However, with repeat screening visits, earlier missed cancers can most likely be detected at a later stage in which the cancer is still curable. This is a result of the relatively long lead time of PCa, that is, the time of the diagnosis is brought forward in time as compared with the clinical setting. Draisma et al. reported that the original MISCAN model, fitted to the data of the Dutch part of the ERSPC, predicted a mean lead time of 7.9 years and to the USA data a mean lead time of 6.9 years. Among screen-detected PCas that would have been diagnosed during the patient's lifetime, the mean lead time ranged from 5.4 to 6.9 years using three different models<sup>52</sup>. Other studies estimated lead time in comparison with detection rates in a population-based trial setting with baseline incidence, and reported a mean lead time of between 5 and 12 years<sup>53,54</sup>.

## POTENTIAL HARMS OF PROSTATE CANCER SCREENING

The ERSPC and the PLCO warned of the coinciding amount of overdiagnosis and overtreatment<sup>3,13</sup>. In addition, data of the effect on screening on quality of life and cost-effectiveness are currently lacking<sup>3</sup>.

### Overdiagnosis and overtreatment of prostate cancer

Screening advances the early diagnosis of potentially clinically relevant PCas that require active treatment. Screening, however, also detects potentially clinically insignificant cancers. These PCas are those that would not have been diagnosed without screening and would not have led to symptoms or death during the patient's lifetime. Between 27 and 56% of all cancers detected in men aged 55–75 years in the screening arm of the Dutch part of the ERSPC can be classified as potentially clinically insignificant PCa, that is, a PCa not causing disease-specific mortality<sup>53</sup>. These clinically insignificant PCas are identified by tumor-related variables and are frequently associated with low PSA levels<sup>10,55</sup>. In practice, these cancers are usually actively treated, despite their indolent character, resulting in so-called overtreatment<sup>56</sup>. Active surveillance is a treatment strategy that aims to avoid overtreatment. It consists of closely monitoring the PCa for progression within the time frame when PCa is still curable. Curative treatment is indicated when progression occurs. The criteria for switching to delayed curative treatment are based on medical and non-medical reasons. These criteria need, however, to be validated and adapted. The benefit of active surveillance can be the delay of active treatment with possible complications for a few years or more<sup>57</sup>. Prospective trials such as the recently initiated web-based Prostate Cancer Research International: Active Surveillance (PRIAS) study have been initiated to further investigate the criteria for selection of clinically insignificant cancers, and those for monitoring progression<sup>55,58-60,104</sup>.

## Quality of life

The potential harms of screening, such as unnecessary biopsies through a false-positive PSA test, overdiagnosis and overtreatment, might have a negative effect on mental and physical health.

Men who underwent a PSA test can experience uncertainty related to the PSA test, even if the PSA test is normal or elevated, which will lead to further assessment<sup>61</sup>. Carlsson et al. demonstrated that 34% of the men who were waiting for the outcome of the PSA test and 55% of the screened men who need further investigation (DRE and prostate biopsy) reported anxiety. For both, the first screening round was compared with subsequent rounds and showed a significant difference in anxiety levels. Men who had a high level of anxiety at the first screening round had more than a 30-fold increased risk of reporting a high level of anxiety in further rounds compared with men who reported no anxiety<sup>62</sup>. Mental and self-rated overall health worsened significantly immediately after the diagnosis of PCa. This effect disappeared, however, after 6 months<sup>63</sup>.

Active treatments for localized PCa are radical prostatectomy, external-beam radiotherapy and brachytherapy. These treatments are associated with changes in quality of life domains, that is urinary, bowel, erectile, sexual dysfunctions, anxiety and depression<sup>64,65</sup>. A man's decision regarding treatment can be influenced by cancer-related anxiety<sup>66</sup>. An active surveillance strategy induces stress for cancer progression in some men. Steinbeck et al. reported that men, actively treated or not actively treated, are concerned about the progression of their disease and the possible rise of their PSA level<sup>67</sup>. However, van den Bergh et al. concluded that men included in a protocol-based program for active surveillance had favorable anxiety and distress scores compared with the reference values for anxiety and distress and the groups of patients who underwent other treatments<sup>68</sup>.

## CURRENT GUIDELINES ABOUT PROSTATE CANCER SCREENING

Since population-based screening is not accepted as a standard healthcare policy, various organizations developed guidelines that have resulted in a diversity of recommendations about individual PSA testing in asymptomatic men. These guidelines differ with respect to age at which PSA testing should begin, the PSA cut off for prostate biopsy and follow-up screening (Table 3). In general, guidelines for PSA screening recommend testing between the ages of 50 and 75 years, but there are other guidelines that recommend screening to start at the age of 40 years.

**Table 3.** Recent guidelines of different organizations regarding prostate-specific antigen screening in asymptomatic men

Organization	Guideline
American Urological Association (AUA)	Recommend PSA screening for men aged 40 years or older and for men have a life expectancy of at least 10 years in order the physician discusses the pros and cons of PSA screening. Subsequent testing at intervals determined by baseline <sup>72</sup>
American Cancer Society (ACS)	Recommend annual PSA screening beginning at the age of 50 and have a life expectancy of at least 10 years in order the physician discusses the pros and cons of PSA screening and the patient agrees to be screened. The discussion should include an offer for testing to men at average risk of PCa. Screening before the age of 50 in men with high risk i.e. race, family history of PCa <sup>108</sup> .
US Preventive Services Task Force (USPSTF)	Recommend no PSA screening because of a lack of evidence about the balance of the benefits and harms of PSA screening. However, screening is unlikely benefit men > 75 years <sup>73</sup> .
European Urological Association (EUA)	Recommend that PSA screening and DRE should be offered from the age of 45 years with a life expectancy of at least 10 years. However, PSA screening is unnecessary in men ≥ 75 years and a PSA level ≤ 3 ng/ml at their first screening visit, because they have a low risk of dying from PCa <sup>12</sup> .
National Health Services (NHS) of UK	Recommend that men concerned about prostate cancer should be offered a PSA test but only after fully informed consent following discussion of the limitations of the test with their physician <sup>92</sup> .

DRE: Digital rectal examination; PCa: Prostate cancer; PSA: Prostate-specific antigen

Starting PSA screening at younger ages is questionable, because of the low incidence of PCa. This is confirmed in a retrospective study of 12,078 men in the age range of 40–96 years, divided into two groups of under 50 and 50 years and over. The prevalence of PCa was 4.4% for men under 50 years and 14.4% for aged 50 years or over<sup>69</sup>. In the ERSPC study, the number of men with PCa, in the age range of 50–54 years at baseline, was low with no obvious effect of screening on PCa mortality<sup>3</sup>. However, other studies suggested that the outcome of a single PSA test before the age of 50 years or younger is a strong predictor of PCa and advanced PCa diagnosed up to 25 years later<sup>70,71</sup>. Schroder et al. suggested that a PSA of 1.5 ng/ml or higher in men older than 50 years represents an indicator for greater than average future risk of PCa<sup>32</sup>. This can be stratified by using additional prebiopsy information<sup>30</sup>. The American Urological Association recommends testing at the age of 40 years, because a baseline PSA level above the median value of 0.6–0.7 ng/ml for men in their 40s indicates higher risk for PCa in the future<sup>72</sup>. Rationales for screening at this age are: the PSA level is more specific and not influenced by a prostatic enlargement and the risk of dying from PCa among men older than 50 years may be decreased if detecting lethal cancer earlier.

Prostate-specific antigen testing is not recommended in men aged over 75 years for various reasons, those being that these men have a limited life expectancy, increased comorbidity and a low risk of dying from PCa because the percentage of cancers that are found by screening are, for a large part, indolent<sup>73,74</sup>. However, men aged 75 years or older may have high-grade disease and might therefore have a substantial risk of dying from PCa<sup>75</sup>. A drawback of age-based screening criteria is that these criteria ignore substantial variation in life expectancy and comorbidity in this age group<sup>76</sup>. The long natural history of PCa detected with screening was confirmed by Ulmert et al. In this study, a

total of 5722 men aged 50 years or younger were included and two blood samples, approximately 6 years apart, were analyzed. In this study, with very low screening intensity, the median time from blood draw to PCa diagnosis was 16 years<sup>77</sup>.

In conclusion, PSA-driven screening and screening intervals need further exploration.

Most guidelines stress the importance of individuals having to make an informed decision regarding PSA testing after being given balanced information regarding the pros and cons of PSA screening (Table 3). To support men in making an informed decision, different interventions have been developed, that is, leaflets, also called aids. These interventions include evidence-based information about the prostate, PCa, incidence, symptoms, the PSA test and further research tests and a list of the benefits and harms of PSA screening. The interventions enhance informed decision making about PSA screening for physicians and patients; they can use the interventions for shared decision making<sup>78-80</sup>. Examples of web-based aids are described in Table 4.

**Table 4.** Web-based aids for prostate cancer screening

Developer (location)	Name of aid	URL
Healthwise Decision Points (USA)	Should I have a PSA test?	<a href="http://www.med.nyu.edu/healthwise/article.html?hwid=aa38144">http://www.med.nyu.edu/healthwise/article.html?hwid=aa38144</a> <sup>109</sup>
Prostate Cancer Risk Management Program (UK)	A PSA decision Aid	<a href="http://www.prosdex.com/index_content.htm">http://www.prosdex.com/index_content.htm</a> <sup>110</sup>
European Randomized study of Screening for Prostate Cancer (The Netherlands)	Prostate-riskindicator	<a href="http://www.prostatecancer-riskcalculator.com/via.html">http://www.prostatecancer-riskcalculator.com/via.html</a> <sup>111</sup>
Centers for Disease Control and Prevention (USA)	Prostate cancer screening: A decision guide	<a href="http://www.cdc.gov/cancer/Prostate/pdf/prosguide.pdf">http://www.cdc.gov/cancer/Prostate/pdf/prosguide.pdf</a> <sup>112</sup>

PSA: Prostate-specific antigen

Recently, an aid combining information with a risk calculator has been developed. This device consists of evidence-based information from the Dutch part of the ERSPC and various levels of risk assessment, each representing a step in the decision making process of PCa screening. The first level of this web-based tool, developed for lay men, uses information based on family history, age and urinary function to estimate the risk of PCa<sup>103</sup>.

## EXPERT COMMENTARY

There is no unanimous opinion about if and how to perform PSA screening. There is very strong evidence that population-based screening can reduce PCa mortality. However, screening also induces overdiagnosis and overtreatment<sup>3,13</sup>. These adverse effects of PSA screening need to be lowered to acceptable levels, and the uncertainties of screening with respect to quality of life and cost-effectiveness need to be determined.

We conclude that the consequences of intensive screening algorithms starting at a young age, with relatively short screening intervals and low PSA thresholds for prostate biopsy (<3 ng/ml), definitely need further exploration before any evidence-based recommendations can be made. To answer the question 'Should PSA screening be offered to asymptomatic men?' is therefore premature. However, men who have made an informed decision about undergoing a PSA test by weighing its potential benefits and harms cannot be refused such a test.

Currently, many men are being screened without their knowledge<sup>81</sup>. These men were not offered the opportunity to make an informed decision about having a PSA test. Physicians play an important role in counselling men about the benefits and harms of screening by PSA test.

## **FIVE-YEAR VIEW**

In our opinion, the overdiagnosis and the potentially related overtreatment can be reduced during the coming years. A more targeted approach, by offering tailored information and individual risk assessment, will be a first step towards reaching this goal. Multivariate nomograms predict the individual risk at different stages during the screening process. In addition, the search for markers that identify men at risk and distinguish clinically relevant cancer from clinically insignificant cancer is essential. Development in imaging technologies has improved lesion detection and staging of PCa, especially MRI. PET tracers are under development, which may further improve the accuracy of imaging<sup>82</sup>. Meanwhile, further research needs to focus on active surveillance strategies and the identification of the PCas suitable for this approach.

We conclude that the development of an optimal PCa screening algorithm needs to maintain the potential to reduce mortality and at the same time reduce the currently existing overdiagnosis and overtreatment.

Apart from early detection, prevention is an option in the management of PCa. The use of  $\alpha$ -reductase inhibitors, that is, finasteride or dutasteride, reduces the incidence of PCa<sup>83</sup>. Finasteride is a selective type-2 5 $\alpha$ -reductase inhibitor while dutasteride is a type-1 and -2 5 $\alpha$ -reductase inhibitor. Both compounds reduce the level of dihydrotestosterone by 65–70% and 90%, respectively<sup>83</sup>.

The Prostate Cancer Prevention Trial (PCPT) demonstrated that with a daily dose of finasteride 5 mg over 7 years, the risk of developing PCa was reduced by approximately 25% in men aged over 55 years<sup>84</sup>. The Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE trial) showed that dutasteride reduces the risk of detectable PCa by 23% in men who received dutasteride over 4 years<sup>85</sup>. Furthermore, finasteride enhanced the detection of PCa by improving sensitivity of PSA<sup>86,87</sup> and DRE88. Men using 5 $\alpha$ -reductase

inhibitors who developed PCa had a lower tumor volume<sup>89,90</sup>. However, PCPT found an increase in high-grade cancer (Gleason score 7–10) in the finasteride group (37%) compared with the control group (22%)<sup>84</sup>. By contrast, the REDUCE trial observed no increase in high-grade cancer<sup>85</sup>. This potentially unfavorable outcome of the PCPT was based on biases including sampling density bias and additional analysis demonstrated finasteride to be safe and effective in the reduction of PCa<sup>90,91</sup>. Additional data from the REDUCE trial are required to elucidate this issue.

Prostate cancer research should focus not only on early detection of PCa, but also on controlling the overdiagnosis and overtreatment and risk-reduction strategies through chemoprevention. The focus might be on combining the two strategies, that is, PSA screening and chemoprevention and its implementation into daily practice.

## KEY ISSUES

- The European Randomized study of Screening for Prostate Cancer reported a relative prostate cancer (PCa) mortality reduction of 20% with prostate-specific antigen (PSA) screening in men aged 55–69 years. After adjustment for non-attendance and contamination, the relative risk reduction per man actually screened is approximately 30%.
- The Prostate, Lung, Colorectal and Ovarian Screening Trial did not detect a PCa mortality reduction. This might be the result of a considerable contamination rate in the control arm and non-attendance with the protocol in the screening arm.
- A screening program for PCa cannot currently be justified as a public health policy because of the coinciding overdiagnosis and overtreatment, and the unknown issues with respect to quality of life and cost-effectiveness.
- The outcome of a single PSA test before the age of 50 years or younger is a strong predictor of PCa and advanced PCa. However, it is unknown what the effect on the rate of unnecessary testing, overdiagnosis and overtreatment will be when starting early detection at a younger age.
- Various screening tests are used to screen men for PCa. A prostate biopsy is indicated if PSA is greater than or equal to 3–4 ng/ml or digital rectal examination is suspicious. The optimal number of cores taken with a prostate biopsy in a screening setting is debated.
- Various nomograms have been developed that might assist physicians in clinical decision making during the process of screening. The process of screening consists of different steps, from the risk of having a biopsy-detectable PCa to survival after the development of metastatic disease.
- Unnecessary prostate biopsies and overdiagnosis of insignificant cancers can be reduced by using individualized risk assessment.

- An individual risk estimation and well-balanced information regarding the benefits and harms of PSA testing support men in making an informed decision.
- Research for better markers that identify men at risk and distinguish clinically relevant cancer from clinically insignificant cancer is essential.
- During the next 5 years PCa research should focus not only on early detection of PCa, but also on controlling the overdiagnosis and overtreatment and risk-reduction strategies through chemoprevention. The focus might be on the combination of strategies and its implementation into daily practice.



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# Chapter 3

Scope and outline of the thesis

## SCOPE

Current prostate-specific antigen (PSA) screening practice leads to two important unwanted side effects; first of all screening induces many unnecessary prostate biopsies and secondly it leads to overdiagnosis and overtreatment of prostate cancer<sup>1-5</sup>. The large amount of unnecessary prostate biopsies, as well as the overdiagnosis and overtreatment might be reduced by using prediction models. These models, using individual risk estimations, support the identification of men at increased risk for prostate cancer and the identification of potentially indolent disease after a prostate cancer diagnosis. Traditionally, urologists have not used prediction models in their standard practice. The aim of this thesis was testing a decision aid for men considering PSA testing and applying risk-based strategies. The data of the studies described in this thesis are the result of an active implementation of these tools.

## OUTLINE

In **Chapter 4** (part two of this thesis), an intervention study describes the effect of a leaflet including individualized risk assessment of having a biopsy detectable prostate cancer on informed decision making of men, i.e. knowledge about prostate cancer and PSA screening, attitude towards undergoing a PSA test, and intention to have a PSA test. Informed decision making was defined as a choice that is based on relevant knowledge, consistent with the decision maker's value and behaviourally implemented.

Part three of this thesis focuses on using the recommendation of a prostate cancer risk calculator in decision making regarding a prostate biopsy. In **Chapter 5**, the compliance of urologists and patients with 'biopsy' or 'no biopsy' recommendations of the European Randomized study of Screening on Prostate Cancer (ERSPC) risk calculator level three and their reasons for non-compliance was analyzed, and the determinants of patients' compliance were assessed. In **Chapter 6**, the impact of a risk-based approach as compared to clinical judgement was studied with respect to the proportion of men biopsied and the positive predictive value, i.e. how many prostate cancers were found among those undergoing a prostate biopsy.

In part four of this thesis, the validity of prostate cancer risk calculators outside their development setting is assessed. In **Chapter 7**, the performance of the ERSPC risk calculator which calculates the probability of a positive prostate biopsy was therefore assessed in a contemporary Dutch clinical cohort and, in **Chapter 8**, in two ERSPC screening cohorts in Sweden and Finland. In **Chapter 9**, the development and validation of a new risk calculator including serum PSA, outcome of DRE and DRE assessed prostate volume as alternative to TRUS is presented.



In part five, **Chapter 10** contains an evaluation of the use of the ERSPC risk calculator level six for the selection of men diagnosed with prostate cancer suitable for active surveillance. Urologists' and patients' compliance with treatment recommendations based on the risk calculator as well as their reasons for non-compliance were evaluated. Furthermore, differences between patients who comply and do not comply with the recommendation of the risk calculator were studied. Finally, patients' perception of active surveillance and their knowledge of the disease are assessed (**Chapter 11**).

The studies described in previous chapters and future planning is discussed in **Chapter 12** (part six), and summarized in part seven of this thesis.

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# Part 2

## Informed decision making on PSA testing

Chapter 4

Informed decision making on PSA testing for the detection of prostate cancer:

An evaluation of a leaflet with risk indicator

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# Chapter 4

## Informed decision making on PSA testing for the detection of prostate cancer: An evaluation of a leaflet with risk indicator

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## ABSTRACT

**Background:** Population-based screening for prostate cancer (PCa) remains controversial. To help men making informed decisions about prostate specific antigen (PSA) screening a risk indicator ([www.uroweb.org](http://www.uroweb.org)) was developed. This risk indicator is embedded in a leaflet that informs men about the pros and cons of PCa screening and enables calculation of the individual risk of having a biopsy detectable PCa.

**Aim:** To assess the effect of providing a leaflet including individualized risk estimation on informed decision making of men, i.e. knowledge about PCa and PSA screening, attitude towards undergoing a PSA test and intention to have a PSA test.

**Methods:** An intervention study among 2000 men, aged 55–65 years, randomly selected from the population registry of the city of Dordrecht, the Netherlands, in 2008. Men were sent a questionnaire on knowledge of PCa, attitude and intention to have a PSA test. Men without a history of (screening for) PCa were sent the leaflet and Questionnaire 2 within 2 weeks after returning Questionnaire 1. Validated health and anxiety measures were used.

**Results:** One thousand and twenty seven of 2000 men completed Questionnaire 1 (51%), of whom 298 were excluded due to a history of (screening for) PCa. Of the 729 remaining men, 601 completed Questionnaire 2 as well. At the second assessment significantly more men met the requirements of informed decision making (15% versus 33%,  $p < 0.001$ ), more men had relevant knowledge (284/601, 50% versus 420/601, 77%,  $p < 0.001$ ) and the intention to have a PSA test had increased ( $p < 0.001$ ).

**Conclusions:** Providing information on PCa screening combined with individualized risk estimation enhanced informed decision making and may be used for shared decision making on PSA screening of physicians and patients.

## INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, with the third cause of death in Europe in 2006<sup>1</sup>. Population-based screening on PCa remains controversial although it has shown to reduce PCa mortality by 20% in a randomised screening trial (ERSPC)<sup>2</sup>. This mortality reduction was associated with a high risk of overdiagnosis, i.e. detection of cancers that in the absence of screening would not have been diagnosed within the person's lifetime. Between 27% and 56% of all cancers detected in the screening arm of ERSPC (section Rotterdam, the Netherlands) can be classified as potentially indolent, for which invasive treatment may not be necessary<sup>3,4</sup>.

While lacking more specific biomarkers, the most commonly used screening tool for PCa is the prostate-specific antigen (PSA) test, despite its known weaknesses resulting in false-positive and false-negative results<sup>5,6</sup>. The false-positive results create uncertainty and 'unnecessary' additional testing<sup>2,7</sup>. At the same time men are encouraged to consider PSA screening by media reports, social network, experiences with PCa of friends and family<sup>7,8</sup>. A possible way out of this dilemma is the use of multivariable prediction models or nomograms<sup>5</sup>. They can improve the diagnostic value of PSA screening by increasing its relative specificity by adding other potential predictive risk factors to the decisional process<sup>5,9</sup>. Based on the screening data from the ERSPC (section Rotterdam, the Netherlands) a multivariable model was developed and translated into a user friendly instrument<sup>10</sup>. This 'Prostate Risk Indicator' (PRI) provides balanced information on the pros and cons of having a PSA test for PCa and enables men and their physicians to calculate the risk of having biopsy detectable PCa. This may support men making informed choices about having a PSA test or not<sup>10-13</sup>.

The purpose of this intervention study was to assess the effect of providing a leaflet with individualized risk estimation on informed decision making of men. We used Marteau's definition of an informed choice, i.e. 'a choice, that is based on relevant knowledge, consistent with the decision maker's value and behaviourally implemented'<sup>14</sup>.

In this study the following hypotheses were tested:

- The number of men who are able to make an informed choice on PSA screening will increase after the provision of a leaflet including an individualized risk estimation.
- The leaflet with risk indicator will have no impact on the generic health related quality of life and the generic anxiety of men.

## **MATERIALS AND METHODS**

### **Study population and procedure**

For this study, a random sample of 2000 men, age 55–65 years from the population registry of the city of Dordrecht, the Netherlands, were sent a letter with information about the study and a questionnaire (Questionnaire 1) on PSA screening, in July 2008. Men who returned the completed Questionnaire 1 were sent a paper version of the PRI including information about PCa and the pros and cons of PCa screening and a risk indicator to calculate their own estimated risk of having PCa. This paper version will be referred to as 'leaflet'. The leaflet and Questionnaire 2 were sent within 2 weeks after men returned Questionnaire 1. Men with a history of PCa or PSA screening were excluded from the second assessment. Actual decisions on PSA screening and PSA test results were not studied.

### **Intervention**

The PRI is based on the screening results of 6288 men participating in the initial screening round of the ERSPC section Rotterdam, the Netherlands. The PRI as a whole exists of balanced evidence based information about the prostate, PCa, incidence, symptoms, the PSA test and further research tests which may be carried out, a list of pros and cons of PSA screening (Appendix A) plus 6 decision levels ([www.uroweb.org](http://www.uroweb.org))<sup>15</sup>. Level 1 uses information on family history, age and urinary function to calculate a rough estimation on the probability of having a biopsy detectable PCa. In the study described here the leaflet including the information and level 1 of the risk indicator were evaluated.<sup>16</sup> This leaflet is an extended version of earlier consumer information about prostate cancer screening published by the Dutch Cancer Society. An independent organisation tested the leaflet with a target population which was not involved in this study. Results showed that the provided information was balanced and accurate.

### **Questionnaires**

#### *Respondents' characteristics*

Questionnaire 1 contained items on age, education, marital status, employment status, and co-morbidity. Educational level was classified as low (no education, primary school or lower education), intermediate or high (higher education or university degree). Employment status was classified as paid job, unpaid job or retired. The unpaid group existed of men who did not work due to health problems, were jobless, looked after the children, did the housekeeping or had voluntary jobs. The prevalence of co-morbidity was assessed using a standard list of 11 chronic diseases, including asthma, hyperten-



sion, diabetes, and cancer. Men were asked which disease(s) they currently were experiencing or had experienced during the past year.

### *Informed choice*

We used Marteau's definition of an informed choice, i.e. 'a choice that is based on relevant knowledge, consistent with the decision maker's value and behaviourally implemented'<sup>14</sup>. This implies that an informed choice to undergo a screening test occurs when an individual has relevant knowledge about the test, has a positive attitude towards undergoing a test, and does undergo it. If an individual has relevant knowledge about the test, has a negative attitude, and does not undergo it, he also makes an informed choice. All other combinations reflect uninformed choices.

We measured informed choice, i.e. knowledge, attitude towards undergoing a PSA test and intention to have a PSA test, before and after men were provided with the leaflet including the risk indicator.

### *Knowledge*

To assess whether respondents had relevant knowledge on PCa we included 21 items covering disease and symptoms, diagnostic process, treatment and side-effects of treatment (Appendix B). Response options were true, not true, and don't know. Per correct answer, one point was added to the total 'Knowledge of PCa' score. We defined relevant knowledge as sufficient if 15 knowledge items (70%) were correctly answered.

Additionally, respondents were asked in both questionnaires to give a self-perceived risk estimation of having PCa. In Questionnaire 2 respondents were also asked to report the individualized risk as estimated by the risk indicator. Marteau considers risk perception of the condition being screened for as part of the knowledge element<sup>14</sup>. However, the reported self-perceived risk and the individualized risk estimation by the risk indicator cannot be scored as 'correct' or 'incorrect' and were thus not integrated in the 'knowledge' score.

### *Attitude*

The attitude towards undergoing a PSA test was measured by an attitude scale based on the Theory of planned behaviour and adapted from Marteau's multidimensional measure for informed choice<sup>14,17</sup>. It contained four items, e.g. I consider having a PSA test a good idea—not a good idea, harmful—not harmful, scored on a seven point scale. Scores were transformed to a scale ranging from 0 to 100. Scores equal to or lower than 50 indicate a negative attitude; scores above 50 indicate a positive attitude towards PSA screening.

### *Intention*

We did not study actual participation in PSA screening and thus do not know if choices were behaviourally implemented. Instead we used the reported intention to have a PSA test.

### *Psychological measures*

Both questionnaires consisted of the following validated self-reported psychological measures:

- (1) The Short form health survey (SF-12) was used to measure generic health related quality of life<sup>18</sup>. The 12 items are used to construct physical and mental component summary measures (PCS-12 and MCS-12) that are scored using norm-based methods, where the mean and standard deviation (SD) are 50 and 10 in the general US population. A one-point difference can be interpreted as one-tenth of a SD<sup>19</sup>.
- (2) The validated Dutch translation of the State Trait Anxiety Inventory (STAI-6) was used to measure generic anxiety<sup>20</sup>. This scale contains six items, e.g. feeling calm, relaxed or worried. Scale scores range from 20 to 80, scores above 44 indicate a high level of anxiety<sup>21</sup>.

Questionnaire 2 also included the following items:

- (1) The Prostate Cancer Anxiety subscale, one out of three subscales of the validated Dutch translation of the Memorial Anxiety scale for Prostate Cancer (MAXPC)<sup>22</sup>. Eight of the 11 items were used, for example, being scared of having PCa, not wanting to deal with feelings about PCa. Item scores were transformed to ranges of 0 to 33, with higher scores indicating more PCa-specific anxiety.
- (2) The validated Dutch translation of the Decisional Conflict Scale (DCS), was used to measure the level of decisional conflict about having a PSA test or not, containing three subscales<sup>23</sup>. The first subscale 'Uncertainty' (three items) refers to the level of uncertainty a patient experiences about making a health care decision. The second subscale 'Factors contributing' (nine items) relates to, e.g. feeling supported in decision making and values. The third subscale 'Effective decision making' (four items) measures the extent a man perceives the decision as effective, based on information and personal value. Scores range from 0 to 100, with scores above 37.5 indicating a decisional conflict<sup>24</sup>.

## Statistical analysis

The statistical analysis included descriptive statistics. Men who completed both questionnaires were compared with men who only completed Questionnaire 1 to assess potential selection bias. The Chi-square test was used for categorical variables and unpaired t-test for continuous variables.

To compare the outcomes of the sequential questionnaires of each participant, the Wilcoxon Signed Rank test was used for categorical variables and the paired t-test for continuous variables. Regulations for missing items in the STAI-6, MAX-PC, DCS and attitude towards PSA screening were conducted according to the guidelines of the SF-36 Health Survey Manual<sup>25</sup>.

Correlations between the risk estimations as calculated by the risk indicator versus scores of the attitude towards undergoing a PSA test, the intention to have a PSA test and PCa specific anxiety, respectively, were calculated. The Spearman's rho was used for the categorical variable and the Pearson correlation for continuous ones.

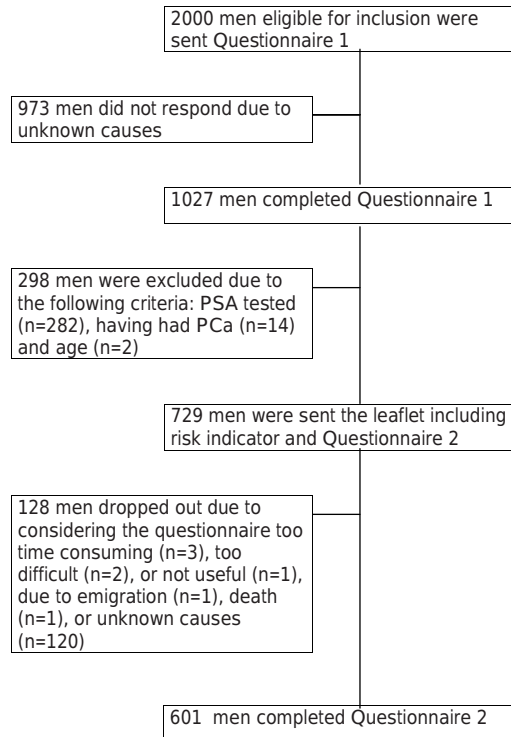
Analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, IL). P-values less than 0.05 were considered statistically significant.

## RESULTS

### Respondents' characteristics

In July 2008, 2000 questionnaires were sent to men aged 55–65, of which 1,027 (51%) were completed and returned. Two hundred and ninety eight men were classed as ineligible since they had previously been PSA tested ( $n = 282$ ), had been diagnosed with PCa ( $n = 14$ ) or were outside the required age range ( $n = 2$ ). Subsequently the leaflet and Questionnaire 2 were sent to the remaining 729 eligible men, of whom 601 men completed Questionnaire 2 (82%) (Figure 1).

Table 1 shows the characteristics of the participants who completed both questionnaires ( $n = 601$ ). Their mean age was 59.5 years (SD 2.9), 244/601 (41%) had an intermediate education and 187/601 (31%) were highly educated, 506/601 (85%) were married, 342/601 (58%) had a job and 169/601 (28%) were retired. The average number of comorbid conditions was less than one, but ranged between zero and six. This cohort did not differ significantly from the 128 men who only completed Questionnaire 1.



**Figure 1.** Profile of the study population

PSA: Prostate-specific antigen; PCa: Prostate cancer

**Table 1.** Characteristics of the participants

	Men who completed Questionnaire 1 and 2 n=601	Men who only completed questionnaire 1 n=128	p-value
Age (years)			0.187
Average (SD, range)	59.5 (2.9, 55-65)	59.2 (2.6,55-64)	
Educational level (%)			0.360
Low	169 (28)	44 (34)	
Intermediate	244 (41)	49 (38)	
High	187 (31)	35 (27)	
Marital status (%)			0.950
Married or cohabiting	506 (85)	107 (84)	
Single	93 (16)	20 (16)	
Employment status (%)			0.049
Paid job	342 (58)	86 (68)	
Unpaid job	84 (14)	18 (14)	
Retired	169 (28)	23 (18)	
Comorbidity			0.902
Average number of conditions (range)	0.8 (0-6)	0.8 (0-4)	

### Informed choice

Significantly more men met the requirements of informed choice, 81/535 men (15%) at the first versus 174/522 men (33%) at the second assessment ( $p < 0.001$ ). These men had adequate knowledge and their intention to have a PSA test or not reflected their attitudes towards the PSA test (Table 2).

**Table 2.** Aspects of an informed choice before and after receiving the leaflet, i.e. sufficient adequate knowledge, attitude towards having a prostate-specific antigen (PSA) test and intention to have a PSA test

*Before receiving the leaflet, n=601*

	Intention to have a PSA test		Total
	Yes	No	
Sufficient adequate knowledge#, positive attitude	28*	182	210
Insufficient adequate knowledge, positive attitude	37	176	213
Sufficient adequate knowledge#, negative attitude	6	53*	59
Insufficient adequate knowledge, negative attitude	3	50	53
Total	74	461	535

*After receiving the leaflet, n=601*

	Intention to have a PSA test		Total
	Yes	No	
Sufficient adequate knowledge#, positive attitude	76*	228	304
Insufficient adequate knowledge, positive attitude	18	58	76
Sufficient adequate knowledge#, negative attitude	9	98*	107
Insufficient adequate knowledge, negative attitude	8	27	35
Total	111	411	522

\* Men in these categories meet the predefined criteria of an informed choice

# Sufficient adequate knowledge: at least 15 out of 21 correctly answered knowledge questions

PSA: Prostate-specific antigen

### Knowledge

Men’s knowledge on PCa increased significantly for 16 of the 21 questions and for the total scores. Significantly more men were classified as having sufficient relevant knowledge (284, 50% versus 420, 77%,  $p < 0.001$ )(Table 3).

The self-perceived risk estimation of having PCa decreased significantly ( $p < 0.001$ ), with 383 (71%) estimating their risk to have PCa as  $\leq 15\%$  before versus 458 (90%) after receiving the leaflet. Men who intended to undergo PSA screening estimated their risks on having PCa as higher than men who did not (25% versus 13% with an estimated risk of  $\geq 15\%$ , respectively). Risk estimations as calculated with the risk indicator did not differ significantly from self-perceived risk estimations at the second assessment ( $p = 0.19$ ). The intention to have a PSA test and PCa-specific anxiety were associated with higher levels of estimated risk as calculated by the risk indicator ( $r(512) = 0.202, p < 0.001$ , and  $r(512) = 0.133, p = 0.003$ , respectively).

**Table 3.** Frequencies with percentage of sufficient adequate knowledge and the mean of total knowledge score and per knowledge category, i.e. the average number of items that was answered correctly before and after receiving the leaflet

	Before n=601	After n=601	p-value
Sufficient adequate knowledge	284 (50%)	420 (77%)	<0.001
Total knowledge score (range 0-21)	13.5	16.2	<0.001
Disease and symptoms (range 0-9)	5.9	7.3	<0.001
Diagnostic process (range 0-5)	3.6	4.3	<0.001
Treatment (range 0-4)	2.4	2.8	<0.001
Side effects of the treatment (range 0-3)	1.7	1.8	0.150

### Attitude

The number of men with a positive attitude towards undergoing a PSA test decreased significantly (437, 78% versus 415, 72%,  $p < 0.001$ , Table 4).

### Intention

At the second assessment more men reported the intention to have a PSA test (86, 14% versus, 126, 21%,  $p < 0.001$ , Table 4). The number of men with a positive attitude and the intention to have a PSA test increased as well (67, 16% versus 104, 27%).

**Table 4.** Considerations, intention and attitude towards the prostate-specific antigen (PSA) test and self-estimated risk of prostate cancer by respondents before and after receiving the leaflet, and risk estimation as calculated by the risk indicator

	Before n=601	After n=601	p-value
Considering to have a PSA test (%)	134 (22.3)	154 (25.6)	0.052
Attitude towards undergoing a PSA test			0.008
Negative attitude (%)	124 (22.1)	161 (28.0)	
Positive attitude (%)	437 (77.9)	415 (72.0)	
Intention to have a PSA test within 3 months (%)	86 (14.3)	126 (21.0)	<0.001
Self-estimated risk of having prostate cancer by respondents (mean, SD, range)	14.1 (16.0, 0-100)	9.8 (11.6, 0-50)	<0.001
Risk between 0 - 25%	450 (83.2)	448 (90.1)	
26 - 50%	84 (15.5)	49 ( 9.9)	
51 - 75%	3 ( 0.6)		
76 -100%	4 ( 0.7)		
Risk estimation of having prostate cancer as calculated by the risk indicator (mean, SD, range)		10.5 (10.6, 0-80)	
Risk between 0 - 25%		482 (94.1)	
26 - 50%		21 ( 4.1)	
51 - 75%		5 ( 1.0)	
76 -100%		4 ( 0.8)	

## Psychological measures

At the second assessment mental health had increased and generic anxiety had decreased significantly (Table 5). The number of men with 'high-anxiety' decreased from 74 (12%) to 40 (7%). The average score of the PCa specific anxiety (MAX-PC) was low; the majority of men had no PCa specific anxiety (512, 89%). Furthermore, the low average decision conflict score (DCS) indicated that the majority of men did not have a decisional conflict about having a PSA test or not (350, 65%). The scores of the subscale 'uncertainty' showed that 363 men (65%) were certain about their choice of having a PSA test or not.

Five hundred and eighty one men (97%) reported to have read the leaflet completely, of whom 553 men (92%) indicated to have understood the information.

**Table 5.** Average scores (SD) of Short form health survey (SF-12) and State Trait Anxiety Inventory (STAI- 6) before and after receiving the leaflet and Memorial Anxiety scale for Prostate Cancer (MAX-PC) and the Decisional Conflict Scale (DSC) after receiving the leaflet

	Before n = 601	After n = 601	p-value
SF-12 Generic Health Status (Range 0-100, higher scores indicate <i>better</i> health)			
Physical health (PCS-12)	50.4 ( 9.1)	51.5 ( 7.4)	0.572
Mental health (MCS-12)	52.1 ( 9.9)	53.0 ( 9.0)	0.005
STAI- 6 Generic Anxiety score (Range 20-80, higher scores indicate <i>more</i> anxiety)	33.3 ( 9.6)	30.9 ( 8.2)	<0.001
MAX-PC Subscale Prostate cancer anxiety (Range 0-33)		4.5 ( 5.3)	
DCS Decision conflict Scale total score (Range 0-100)		32.8 (12.6)	
3 subscales:			
Uncertainty		40.1 (21.7)	
'Factors contributed'		33.0 (12.7)	
Effective decision making		27.3 (14.0)	

## DISCUSSION

After providing information on PCa and individualized risk estimates with a prostate risk indicator, the number of men with sufficient relevant knowledge on PCa improved significantly and their intention to have a PSA test or not better reflected their attitude towards the PSA test. The number of men who met the requirements of informed decision making increased significantly as well.

The concept of informed choice as defined by Marteau and (adaptations of) her attitude scale have to our knowledge not yet been applied to assess the impact of an intervention on numbers of informed choices in PSA screening. Although we found that the rate of informed choices increased from 15% to 33%, the majority of men still made an uninformed choice. This was mainly due to value-inconsistency, for instance having

a positive attitude towards PSA screening but no intention to undergo it. No intention to have a PSA test was related to a low risk estimation of having PCa as calculated by the risk indicator. Since in this study men were both informed about PCa (screening) and provided with an individualized risk estimation of having PCa, we cannot formally separate the effect of providing information from that of providing individualized risk estimates rather than average risks. It seems plausible however, that providing decision-relevant knowledge such as individualized risk estimates will influence individuals' attitude towards having PSA screening.

The number of men who intended to have a PSA test increased while the number of men with a positive attitude decreased. A possible explanation is that men were better informed about the pros and cons of PSA screening after the intervention, resulting in some men in an attitude that turned negative (22/601, 6%) and in others in an intention to have a PSA test (40/601, 7%). However, a large number of men still had a positive attitude towards PSA screening without the intention to have PSA screening (252/601, 42%).

Volk and colleagues and Gattellari and colleagues assessed the impact of decision aids on knowledge, intention and uptake of PSA screening in randomized designs. Gattellari and colleagues found improved knowledge and a reduced interest in PSA screening<sup>26</sup>. Volk and colleagues concluded that intervention subjects were more knowledgeable of prostate cancer screening than were control subjects and that the decision aid appeared to promote informed decision making<sup>27</sup>.

Several limitations are worth mentioning. The non-response on Questionnaire 1 of 49%, although found more often in questionnaire studies in the general population, may have biased the study findings. Only the age of the non-respondents was known and that did not differ significantly from the respondents' age.

In the Netherlands it is forbidden by law to offer PSA tests within a screening context. This had two consequences for our study. Firstly, we could not follow-up on identifying who actually had the PSA test. If a man wanted to have a PSA test after he participated in our study, he needed to go to his general practitioner and ask for it. Since it is unknown to us who these general practitioners are, we could thus not assess whether choices were behaviourally implemented. Instead we used the reported intention to have a PSA test to assess informed choice. However, due to all kind of barriers people can be prevented to perform their intended behaviour, resulting in differences between intended choice and the final behaviour<sup>28</sup>. Secondly, we did not want to give the respondents in our study the impression that they should have an opinion about PSA testing and that they should consider having such a test themselves. Therefore the DCS and MAX-PC were included only in Questionnaire 2.

Furthermore, we used a non-validated questionnaire on PCa knowledge. Different measures have been developed, but have limited validity and reliability<sup>29</sup>. The advantage



of our knowledge measure, that overlaps with the validated 10-item PROCASE Knowledge Index,<sup>30</sup> is that it contains items about the process of screening, PCa and treatment for PCa. We defined sufficient relevant knowledge as 15 or more (70%) correct answers. This is an arbitrary choice. If a cut off point of 17 correct answers had been used, the results would still have shown an increase in the number of informed choices. Defining sufficient relevant knowledge is a general problem of informed decision making: 'what is it they need to know and whose business is it to decide that'<sup>31</sup>.

Pros of our study include the large number of respondents and the use of validated measures to assess generic health related quality of life, anxiety, PCa-specific anxiety, and attitude towards screening, as was recommended by Edwards and colleagues<sup>32</sup>.

Although the number of men making informed choices about PSA screening increased after the intervention, further improvement is still needed. Providing decision-relevant knowledge such as individualized risk estimates may be a useful addition to Marteau's concept of informed choice. We recommend further research, preferably in a randomized design, into providing individualized risk estimations rather than average risks on attitudes towards the PSA test and on the intention to undergo it by comparing groups receiving the leaflet with versus without the risk indicator. Furthermore, we recommend further research into the assessment of attitude towards individuals' own participation in screening rather than general attitudes towards a screening test.

## CONCLUSIONS

The leaflet including a risk indicator enhanced knowledge about pros and cons of PSA screening and PCa, made men less positive towards screening, enhanced informed decision making, and did not adversely affect men in terms of causing anxiety or negatively influencing mental health. After the intervention most men reported no decisional conflict about having a PSA test or not.

The leaflet including a risk indicator promises to be a useful tool for shared decision making on PSA screening of physicians and patients.

**Appendix A.** Summary of the pros and cons of prostate-specific antigen (PSA) screening ([www.uroweb.org](http://www.uroweb.org))

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*Arguments for PSA screening*

- If the result of the PSA test is favourable this will calm down my worries.
  - The PSA test can help to find prostate cancer (PCa) at an early stage and before it leads to complaints.
  - If as a result of a positive PSA test I undergo successful treatment I may have a better chance of cure and may live longer.
  - If the treatment is successful in an early stage, I may be spared the late symptoms of PCa such as spread of the tumour to other parts of my body (metastases).
- 

*Arguments against PSA screening*

- If my PSA value is elevated and further study does not show PCa I will have undergone medical testing for nothing and this will have caused unnecessary anxiety.
  - The PSA test can miss PCa. After a normal result I may feel relieved for no good reason or may still remain worried.
  - An elevated PSA test may detect a slow growing tumour which would otherwise never have given me any trouble.
  - I may be confronted with the possible complications of the treatment of PCa.
- 

**Appendix B.** 21 statements to assess respondents' knowledge of prostate cancer

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*Disease and symptoms (nine items)*

- The prostate is located in the belly\*
  - Prostate cancer (PCa) is the second leading cause of cancer death among men\*
  - The chance to be diagnosed with PCa declines with aging
  - A man with early-stage PCa has a slow urinary stream
  - PCa does not necessarily cause symptoms\*
  - Urinary problems of old men are caused by benign prostate hypertrophy\*
  - Through a prostate biopsy PCa's can be found that would never have caused complaints\*
  - The 'old man ailment' is an early stage of PCa
  - Someone who has the 'old man ailment' does not get PCa
- 

*Diagnostic process (five items)*

- If the prostate specific antigen (PSA) test is favourable, it is not necessary to assess the PSA test ever again
  - If the PSA test result is unfavourable, a prostate biopsy is necessary to know whether there is PCa or not\*
  - PCa can be diagnosed early by a PSA test and if indicated a prostate biopsy\*
  - Using a PSA test PCa will always be found
  - If the test results of the prostate biopsy are favourable, i.e. no cancer, it is not necessary to repeat the biopsy
- 

*Treatment (four items)*

- Early-stage PCa is responding well to treatment\*
  - In most cases, metastatic PCa cannot be curatively treated\*
  - After surgery or radiotherapy, PCa will always be gone
  - In case of a small prostate tumor, found by PSA testing and biopsy, the doctor may recommend not to treat the tumor but to repeat PSA tests regularly\*
- 

*Side-effects treatment (three items)*

- Urinary incontinence may occur after surgery or radiotherapy of (early detected) PCa\*
  - Prostatectomy may cause side-effects, for example erectile dysfunction\*
  - Radiotherapy to treat PCa, does not cause side-effects
- 

\*Indicates a correct statement

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# Part 3

## **Using the recommendation of a prostate cancer risk calculator in decision-making about the need of a prostate biopsy**

Chapter 5

Compliance with biopsy recommendations of a prostate cancer risk calculator

*BJUI 2012*

Chapter 6

The impact of a prostate cancer risk calculator on prostate biopsies taken and positive predictive value: an empirical evaluation

*Submitted*



# Chapter 5

## Compliance with biopsy recommendations of a prostate cancer risk calculator

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## ABSTRACT

**Objectives:** To assess both urologist and patient compliance with a 'no biopsy' or 'biopsy' recommendation of the European Randomized study of Screening for Prostate Cancer (ERSPC) Risk Calculator (RC), as well as their reasons for non-compliance.

To assess determinants of patient compliance.

**Patients and methods:** The ERSPC RC calculates the probability on a positive sextant prostate biopsy ( $P(\text{posb})$ ) using serum prostate-specific antigen (PSA) level, outcomes of digital rectal examination and transrectal ultrasonography, and ultrasonographically assessed prostate volume. A biopsy was recommended if  $P(\text{posb}) \geq 20\%$ .

Between 2008 and 2011, eight urologists from five Dutch hospitals included 443 patients (aged 55-75 years) after a PSA test with no previous biopsy. Urologists calculated the  $P(\text{posb})$  using the RC in the presence of patients and completed a questionnaire about compliance.

Patients completed a questionnaire about prostate cancer knowledge, attitude towards prostate biopsy, self-rated health (12-Item Short Form Health Survey), anxiety (State Trait Anxiety Inventory-6, Memorial Anxiety Scale for Prostate Cancer) and decision-making measures (Decisional Conflict Scale).

**Results:** Both urologists and patients complied with the RC recommendation in 368 of 443 (83%) cases.

If a biopsy was recommended, almost all patients (96%; 257/269) complied, although 63 of the 174 (36%) patients were biopsied against the recommendation of the RC. Compliers with a 'no biopsy' recommendation had a lower mean  $P(\text{posb})$  than non-compliers (9% vs. 14%;  $P < 0.001$ ).

Urologists opted for biopsies against the recommendations of the RC because of an elevated PSA level ( $\geq 3$  ng/mL) (78%; 49/63) and patients because they wanted certainty (60%; 38/63).

**Conclusions:** Recommendations of the ERSPC RC on prostate biopsy were followed in most patients. The RC hence may be a promising tool for supporting clinical decision-making.



## INTRODUCTION

The decision to perform a prostate biopsy is commonly based on the serum prostate specific antigen (PSA) level. However, serum PSA lacks specificity, and therefore can induce many unnecessary prostate biopsies and lead to overdiagnosis of prostate cancer (PCa). This disadvantage can be reduced by using individual risk estimation<sup>1,2</sup>. Prediction models for PCa screening have been developed to calculate the risk of a positive prostate biopsy combining multiple predictors, i.e. patient and disease characteristics and test results<sup>3</sup>. This scientific application intends to be supportive in decision-making of urologists and their patients with respect to the need of performing a prostate biopsy. Traditionally, physicians implicitly estimate a particular probability of a diagnostic or prognostic outcome. However, physicians' estimations are often influenced by both subjective and objective factors, e.g. faulty reasoning or conclusions and beliefs about evidence<sup>4-6</sup>. Prediction models usually perform better than clinical judgment alone when predicting a probability<sup>4</sup>. However, the use of prediction models is not standard practice.

A prediction model, the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator (RC), has been developed with data of the ERSPC, using multivariable logistic regression analysis. The RC consists of six levels ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)) and has been described previously<sup>1,7</sup>. We implemented two of its six levels in five Dutch hospitals in 2008; level 3, which calculates the probability of a positive sextant prostate biopsy (P(posb)), and level 6, which calculates the probability of a potentially indolent PCa. The present study addresses the third level, which is based on the data of unscreened men. This level calculates the P(posb) using next to serum PSA (<50 ng/ml), the outcomes of digital rectal examination (DRE) and transrectal ultrasound (TRUS), i.e. the presence of hypoechoic lesions and prostate volume. Adding these predictors improved the diagnostic value of the serum PSA by increasing its relative specificity<sup>8</sup>.

To date, few publications showed that a prediction model influenced the behaviour of both physicians and patients<sup>9,10</sup>. To our knowledge, it was unknown whether the use of a PCa RC influenced the behaviour of urologists and patients. The present study aimed to evaluate the impact of the recommendation of the ERSPC RC on the decision of urologists and patients with respect to taking prostate biopsies. A biopsy was recommended if the P(posb) was  $\geq 20\%$ . We assessed (1) the compliance of urologists and patients with 'no biopsy' or 'biopsy' recommendations, as well as reasons for non-compliance; (2) differences between patients who were compliant and patients who were non-compliant with 'no biopsy' recommendations; (3) determinants of compliance in patients with 'no biopsy' recommendations.

## PATIENT AND METHODS

### Study population

From October 2008 until April 2011, eight urologists of five participating Dutch hospitals included patients in the study. At the start of this implementation project, the urologists agreed upon the use of the ERSPC RC in decision-making about prostate biopsies to diagnose PCa, and to subsequently complete a questionnaire. At a research meeting, the urologists were informed about the study procedure, the development of the web-based RC, the aim of the RC (reducing unnecessary biopsies), and the use and interpretation of its outcome.

We included patients aged 55-75 years who recently had a PSA test or had an indication for a PSA test, had a PSA level of  $<50$  ng/ml and considered a prostate biopsy without having had a previous prostate biopsy. All patients provided informed consent to undergo a TRUS, to use the RC by the urologist, and completed a questionnaire.

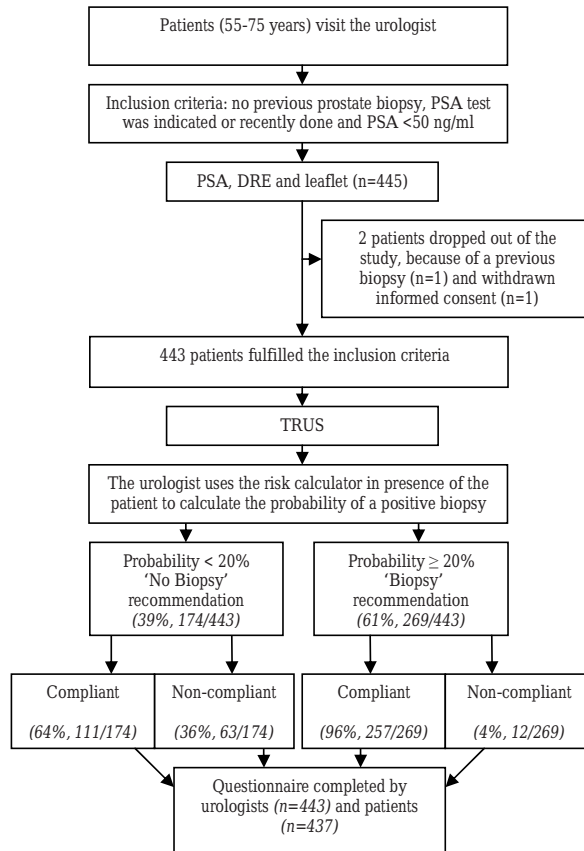
### Study procedure

Patients were included according to the study protocol (Figure 1). During a first visit, patients underwent a PSA test (unless this had already been performed within the previous three months), a DRE and received a leaflet about the study. This leaflet explained the RC, the different tests on PCa, and the study procedure. Patients underwent a TRUS during the same or next visit and, right after the TRUS, the urologist was to calculate the  $P(\text{posb})$  by using the RC in presence of the patient. At the same visit, the decision to perform the biopsy (or not) was made. If the  $P(\text{posb})$  was  $\geq 20\%$  a prostate biopsy was recommended. This 20% threshold is comparable to the positive predictive value of a PSA of  $\geq 4$  ng/ml. The recommendation of the RC may be opposite that of the clinical judgement of the urologist and/or the view of the patient. Urologists and patients received a questionnaire after they had made a decision about the need of a biopsy.

### Questionnaires

Urologists were asked to complete a questionnaire on the use of the RC, the compliance of urologist and patient with the recommendation of the RC, and on clinical characteristics (serum PSA, outcome DRE and TRUS) and the  $P(\text{posb})$ .

Patients were asked to complete a questionnaire containing their age, marital status, education level, employment status, and co-morbidity. Marital status was classified as married or cohabiting and single. Education level was defined as low (no education, primary school or lower education), intermediate, and high (higher education or university degree). Employment was classified as having a paid job, having an unpaid job and being retired. Comorbidity was defined with a list of 11 chronic diseases and men were asked which disease(s) they were currently experiencing or had experienced in the



**Figure 1.** Flow chart of the patients

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

past year. This list is a slightly adapted version of the Charlson Comorbidity Index<sup>11</sup>. The validated measures included in the questionnaire are outlined below.

The 12-item Short Form Health survey was used to measure general health related quality of life<sup>12</sup>. The 12-items are used to construct physical and mental component summary measures, using norm-based methods with a mean (SD) of 50 (10) in the general U.S. population. Total scores are in the range 0-100, with higher scores indicating better health. A one-point difference can be interpreted as one-tenth of the standard deviation.

The State-Trait Anxiety Inventory-6 was used to measure generic anxiety<sup>13</sup>. This scale consists of six items, e.g. feeling calm, relaxed or worried. Scale scores are in the range 20-80, with higher scores indicating more anxiety. Scores >44 indicate a high level of anxiety<sup>14</sup>.

The subscale PCa anxiety of the Memorial Anxiety Scale for Prostate Cancer was used and consists of 11 items, e.g. 'I had a lot of feelings about PCa, but I did not want to deal with them' and 'just hearing the words 'prostate cancer' scared me'<sup>15</sup>. The total score are in the range 0-33, with higher scores indicating more PCa-specific anxiety.

The Decisional Conflict Scale (DCS), which consists of 16 items, was used to assess the level of decisional conflict considering the choice of having a prostate biopsy<sup>16</sup>. Total scores range are in the range of 0-100, with higher scores indicating a higher level of decisional conflict. DCS scores <25 are associated with implementing the final decision about a biopsy without conflict, and scores of >37.5 are associated with decision delay or feeling unsure regarding the decision<sup>17</sup>.

The involvement of the urologist in the decision-making process was assessed by the following question 'Who had the most influence in the treatment choice, you or your urologist?', with five response options 'you' (1), 'you/both'(2), 'both (3)', 'both/urologist'(4), and the urologist (5). We recoded these options in three decision categories: patient-based (option 1 or 2), shared (option 3) and urologist-based decision (option 4 or 5). The involvement of the environment was assessed by use of a similar question.

Informed choice was assessed using the definition of Marteau et al., i.e. 'a choice that is based on relevant knowledge, consistent with the decision-maker's value and behaviourally implemented'<sup>18</sup>. An informed choice is made if a man has sufficient knowledge, a positive attitude towards having a biopsy and undergoes a biopsy or if he has sufficient knowledge, a negative attitude and does not undergo a biopsy. The other combinations reflect uninformed choices. PCa knowledge was assessed using 19 items of the previously published knowledge questionnaire, containing items about disease and symptoms, diagnostic process, treatment and side effects of treatment<sup>19</sup>. The total score is in the range 0-19. Sufficient knowledge was defined as  $\geq 13$  correctly answered knowledge items. Attitude was measured using an attitude scale based on the Theory of planned Behaviour<sup>18,20</sup>. The scale contains four items, e.g. 'I consider having a prostate biopsy for myself a good idea-not a good idea'. Scale scores are in the range 0-100, where scores >50 or  $\leq 50$  indicated a positive or negative attitude, respectively.

### Statistical analysis

The protocol of the present implementation study prescribed that urologists were to use the RC in every eligible patient. In this study, we analysed the cases in which the RC was used.

The numbers of urologists and patients compliant and non-compliant with the recommendation of the RC were assessed. Reasons for non-compliance were described.

We assessed the differences between patients who were compliant and non-compliant with a 'no biopsy' recommendation of the RC by Chi-square tests for categorical variables, and by Mann-Whitney U tests and t-tests for continuous variables. Logistic regression analysis was used to assess determinants of patients' compliance with a 'no biopsy' recommendation of the RC, using demographic characteristics (age, marital status, education level, employment status, comorbidity), medical measurements (outcomes of PSA test, DRE and TRUS), mental health (12-item Mental Component Summary), physical health (12-item Physical Component Summary), generic anxiety (State

Trait Anxiety Inventory-6), PCa specific anxiety (Memorial Anxiety Scale for Prostate Cancer), decision-related measurements (DCS), P(posb), PCa knowledge, attitude, the influence of the urologist and the environment, and informed choice. Analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of the study population

In the present study, 443 patients were included with a 'no biopsy' or a 'biopsy' recommendation of the RC (Figure 1). Their mean (SD) age was 64(5) years, 362 (85%) were married/cohabiting, 156 (37%) had an intermediate education level, 165 (39%) were highly educated, and 253 (59%) were retired (Table 1). The median (range) number of comorbid conditions was 1.0 (0-4, Table 1). Of these 443 patients, 368 (83%) were compliant with the recommendations (Figure 1). Of all patients, 72% (320/443) underwent a biopsy and 31% (138/443) was diagnosed with PCa; 8% (11/138) of diagnosed patients were non-compliant with a 'no biopsy' recommendation and 92% (127/138) were compliant with 'biopsy' recommendation of the RC. The median number of prostate biopsy cores taken was 8 (5th-95th percentile, 8-12 cores).

### A 'no biopsy' recommendation of the risk calculator

A 'no biopsy' recommendation was given to 174 patients (Figure 1). In 63 of these 174 cases (36%), the urologist and patients were non-compliant. If urologists were non-compliant, patients were neither. The most common reason reported by urologists for being non-compliant with a 'no biopsy' recommendation was a PSA of  $\geq 3$  ng/ml (78%, 49/63; range 3.1-10.6), 47 of these 49 patients had no suspicious DRE and TRUS. In these cases, the urologists reported 38 times that patients wanted to be certain about having PCa or not, and 11 times that patients followed the advice of the urologist to opt for a prostate biopsy (Table 2).

In one hospital, significantly more patients (53/53) were biopsied with a 'no biopsy' recommendation of the RC than in the other four other hospitals (3/23, 2/5, 2/24, 3/69,  $p < 0.001$ ).

Patients who were compliant with a 'no biopsy' recommendation, and thus did not opt for a biopsy, had lower PSA levels than men who were non-compliant (median 4.1 vs. 4.7 ng/ml,  $p = 0.001$ , Table 1). These patients also reported lower mean levels of generic anxiety (32 vs. 36,  $p = 0.011$ , Table 4), a lower mean P(posb) (9% vs. 14%,  $p < 0.001$ , Table 1) and less often a positive attitude towards a biopsy (60% vs. 84%,  $p = 0.001$ , Table 5). Compliers reported a greater influence of the urologist in decision-making about not having

**Table 1.** Characteristics and clinical characteristics of the whole group of patients and subdivided into patients who got a 'no biopsy' recommendation and who got a 'biopsy' recommendation

	Recommendation: NO BIOPSY*		P-value ***	Recommendation: BIOPSY**		Total n=443
	Compliant n=111	Non-compliant n=63		Compliant n=257	Non-compliant n=12	
Age (years) mean (SD, range)	63 (5, 55-75)	64 (5, 55-75)	0.74	65 (5, 55-75)	64 (6, 56-75)	64 (5, 55-75)
Marital status (%)			0.50			
Married or cohabiting	95 (87)	50 (83)		206 (83)	11	362 (85)
Single	14 (13)	10 (17)		42 (17)	0	66 (15)
Educational level (%)			0.95			
Low	23 (21)	14 (23)		65 (26)	2	104 (24)
Intermediate	37 (34)	20 (33)		96 (39)	3	156 (37)
High	48 (45)	26 (44)		85 (35)	6	165 (39)
Employment status (%)			0.64			
Paid job	44 (41)	23 (38)		69 (28)	4	140 (33)
Unpaid job	9 (8)	3 (5)		22 (9)	0	34 (8)
Retired	55 (51)	34 (57)		157 (63)	7	253 (59)
Comorbidity						
Median number of conditions (range)	1 (0-4)	1 (0-3)	0.40	1.0 (0-4)	1.0 (0-2)	1.0 (0-4)
Clinical characteristics						
PSA ng/ml median (sd, range)	4.1 (2.5, 0.1-11.2)	4.7 (2.2, 1.4-12.0)	0.001	7.4 (7.4, 2.2-50.0)	6.6 (2.7, 4.3-13.9)	6.1 (6.4, 0.1-50.0)
Suspicious DRE (%)	3 (3)	6 (10)	0.051	97 (38)	4	110 (25)
Suspicious TRUS (%)	4 (4)	2 (3)	0.88	85 (33)	2	93 (21)
P(posb) (%) **** mean (SD, range)	9 (5, 1-19)	14 (5, 3-19)	<0.001	47 (22, 20-98)	28 (12, 20-66)	32 (25, 1-98)

\* Calculated probability of having a positive prostate biopsy <20%

\*\* Calculated probability of having a positive prostate biopsy ≥20%

\*\*\* P-value for the difference between who were compliant and non-compliant with the recommendation: 'no biopsy'.

\*\*\*\*Range 0-100%, where higher scores indicate a *higher* probability of having prostate cancer

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

a prostate biopsy than non-compliers (46% vs. 40%,  $p=0.048$ , Table 5). Compliers made an informed choice less often than non-compliers (28% vs. 47%,  $p=0.015$ ). In a multivariable logistic regression analysis, the strongest determinants for non-compliance were informed decision-making (odds ratio, OR, 3.9; 95% CI 1.7-8.9,  $p=0.001$ ), P(posb) (OR 1.2 per 1% increase; 95% CI 1.1-1.3,  $p<0.001$ ), and generic anxiety (OR 1.0; 95% CI 1.0-1.1,  $p=0.049$ ).

**Table 2.** Reasons for non-compliance of urologists and patients with recommendations by the risk calculator, as reported by urologists

Reasons to opt for a prostate biopsy contrary to the recommendation by the risk calculator (Calculated probability <20%) (n=63)		Number of patients with a calculated probability of	
		<10%	10%-20%
Urologists	Patients		
- The patient had an elevated PSA level ( $\geq 3$ ng/ml) (n=49)	- I wanted certainty about having PCa or not (n=38) and I have a family history of PCa (n=1)	8	30
	- The urologist advised a biopsy (n=11)	3	8
- The patient had a suspicious digital rectal examination (n=4)	- The urologist advised a biopsy (n=4) and I also wanted certainty (n=2)	1	3
- Patient considered a calculated risk of $\geq 20\%$ too high (n=3)	- The urologist advised a biopsy and I wanted certainty (n=2)	1	1
	- Similar to urologist (n=1)		1
- Patient wanted a prostate biopsy (n=2), because his brother has PCa (n=1)	- I wanted certainty about having PCa (n=2), because my brother has PCa (n=1)		2
- Patient had a increasing PSA level (10.7 ng/ml) (n=1)	- The urologist advised a biopsy		1
- The patient found his calculated risk too high (n=1)	- The urologist advised a biopsy		1
- Unknown (n=3)	- Unknown		3

PSA: Prostate-specific antigen; PCa: Prostate cancer

**Table 3.** Reasons for non-compliance of urologists and patients with recommendations by the risk calculator, as reported by urologists

Reasons not to opt for a prostate biopsy contrary to the recommendation by the risk calculator (Calculated probability $\geq 20\%$ ) (n=12)		Calculated probability (%)
Urologists	Patients	
- The patient has comorbidities (n=1)	- The urologist did not recommend a biopsy, because I have other diseases	30
- The calculated risk was just above the threshold of 20%, first a PSA follow-up was recommended (n=3)	- Similar to urologist	20, 21, 21
- Bladder stones increased the PSA level (n=1)	- Similar to urologist	22
- Earlier PSA test was lower, burning sensation during miction, first antibiotics (n=1)	- The urologist advised no biopsy	22
- An elevated PSA of 4.3 ng/ml for the first time (n=1)	- Similar to urologist	26
- An age of 75 years and related that to the calculated probability, a biopsy was not recommend (n=1)	- Similar to urologist	27
- Earlier PSA test 5.8 ng/ml (two months ago), probably prostatitis, first antibiotics (n=1)	- The urologist advised no biopsy	27
- First PSA, no family history of PCa and no suspicious DRE/TRUS, follow-up was indicated (n=1)	- Similar to urologist	29
- Large prostate and PSADT 105 months (2007-2010) (n=1)	- The urologist advised no biopsy	24
- Patients' anxiety for a prostate biopsy (n=1)	- Similar to urologist	66

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound; PSADT: Prostate-specific antigen doubling time

### A 'biopsy' recommendation of the risk calculator

A 'biopsy' recommendation was given to 269 patients (Figure 1). In 12 cases, the urologist and patient were non-compliant with a 'biopsy' recommendation (5%, 12/269). If urologists were non-compliant, patients were neither. Examples of reasons for non-compliance of the urologists with a 'biopsy' recommendation were comorbidity, bladder stones, a first observation of an elevated serum PSA (4.3 ng/ml), and a patient's age in combination with his calculated risk. In these cases, P(posb) was just above 20%. Patients were non-compliant with a 'biopsy' recommendation because they followed the advice of the urologist (Table 3).

Because the group of non-compliers was very small (n=12), we only report the characteristics of the patients. Patients who were compliant with the recommendation of the RC had higher PSA levels (median 7.4 vs. 6.6 ng/ml, Table 1), better physical health (mean 51 vs. 48, Table 4), more generic anxiety (mean 40 vs. 37, Table 4) and less PCa specific anxiety (mean 9 vs. 10, Table 4), less decisional conflict (mean 26 vs. 32, Table 4) and a higher P(posb) (mean 47% vs. 28%, Table 1) than patients who were non-compliant with a 'biopsy' recommendation. There were 11 of the 12 non-compliers who had a P(posb) in the range of 20%-30% (Table 3). Compliers more often made an informed choice than non-compliers (52% vs. 27%).

**Table 4.** Mean (SD) of Short Form Health Survey (SF-12), State Trait Anxiety Inventory (STAI-6), Memorial Anxiety Scale for Prostate Cancer (MAX-PC) and the Decisional Conflict Scale (DCS)

	Recommendation: NO BIOPSY*		p-value***	Recommendation: BIOPSY**	
	Compliant n=111	Non-compliant n=63		Compliant n=257	Non-compliant n=12
SF-12 Generic Health Status (Range 0-100, higher scores indicate better health)					
Physical health (PCS-12)	49 (10)	52 (6)	0.17	51 (9)	48 (13)
Mental health (MCS-12)	52 (10)	52 (10)	0.67	52 (11)	52 (14)
STAI- 6 Generic Anxiety score (Range 20-80, higher scores indicate more anxiety)	32 (10)	36 (12)	0.011	40 (11)	37 (11)
MAX-PC Subscale prostate cancer anxiety (Range 0-33, higher scores indicate more anxiety)	8 (6)	7 (7)	0.42	9 (7)	10 (6)
DCS Decision conflict Scale (Range 0-100, higher scores indicate more decisional conflict)	26 (14)	25 (13)	0.53	26 (14)	32 (8)

\* Calculated probability of having a positive prostate biopsy <20%

\*\* Calculated probability of having a positive prostate biopsy ≥20%

\*\*\* P-value for the difference between who were compliant and non-compliant with the recommendation: 'no biopsy'



**Table 5.** Knowledge scores, attitude, and the influence of the urologist and the environment on patients who have to make a decision about having a prostate biopsy or not

	Recommendation: NO BIOPSY*			Recommendation: BIOPSY**	
	Compliant n=111	Non-compliant n=63	p-value***	Compliant n=257	Non-compliant n=12
Prostate cancer knowledge (Range 0-19), mean (SD, range)	13 (3, 5-19)	13 (4, 4-19)	0.95	12 (3, 2-18)	13 (2, 9-16)
Attitude towards undergoing a prostate biopsy			0.001		
Negative attitude (%)	43 (40)	10 (16)		26 (11)	4
Positive attitude (%)	64 (60)	51 (84)		205 (89)	7
'Who has the most influence in the choice of having a prostate biopsy or not, the patient or the urologist?'			0.048		
Patient-based	11 (10)	15 (24)		43 (17)	1
Shared decision	48 (44)	22 (36)		122 (49)	5
Urologist-based	49 (46)	25 (40)		85 (34)	3
'Who has the most influence in the choice of having a prostate biopsy or not, the patient or his environment?'			0.27		
Patient-based	95 (90)	52 (84)		190 (76)	6
Shared decision	11 (10)	10 (16)		57 (23)	3
Environment-based	0	0		2 (1)	0

\* Calculated probability of having a positive prostate biopsy <20%

\*\* Calculated probability of having a positive prostate biopsy  $\geq$ 20%

\*\*\* P-value for the difference between who were compliant and non-compliant with the recommendation: 'no biopsy'.

## DISCUSSION

In the present study, we found a high compliance of urologists and patients with the recommendation of a RC for the probability of a positive prostate biopsy (83%), indicating that the outcome of the RC was acceptable to both urologists and patients. In almost all cases of a 'biopsy' recommendation, urologists and patients were compliant (96%, 257/269), but in 63 of 174 cases (36%) they were non-compliant with a 'no biopsy' recommendation. Non-compliance with a 'no biopsy' recommendation increased with higher mean P(posb) ( $p=0.001$ ). In one of the five hospitals more men were biopsied contrary to a 'no biopsy' recommendation than in the other four hospitals ( $p<0.001$ ). Overall, the most common reason of urologists to be non-compliant with a 'no biopsy' recommendation was a PSA  $\geq$ 3 ng/ml (78%, 49/63; range 3.1-10.6 ng/ml with a P(posb) <20%).

The non-compliance of urologists may be explained by the fact that the ERSPC RC not yet being validated in a clinical setting, as well as urologists preferring to use clinical guidelines advising on the indication for a prostate biopsy, which may differ between hospitals. Next to an elevated serum PSA level, these guidelines use other prebiopsy information such as age, family history, results of the DRE, PSA ratio (free/total PSA) or the PCA3 test (gene-based urinary test), which may result in recommendation opposing that of the ERSPC RC. Another reason for non-compliance with the RC recommendations of urologists may be the use of a serum PSA threshold of  $\geq 3$  ng/ml as indication for performing a biopsy, because the ERSPC showed a mortality reduction of 20-30% when using this threshold<sup>21,22</sup>. The risk of missing the disease may be also a barrier for physicians to use a prediction model<sup>9,10</sup>. Some patients will undergo additional testing, whereas the prediction tool indicated that no further investigation was necessary<sup>23</sup>. In the present study, we observed 63 cases of non-compliance with a 'no biopsy' recommendation ( $P(\text{posb}) < 20\%$ ), and only 11 of these 63 patients (17%) were diagnosed with PCa. Of these 11 men, eight men had calculated probabilities on a potentially indolent PCa in the range 45-92% according to another ERSPC RC (level 6) and one man had insufficient PCa tissue in his biopsy to assess the Gleason score, so that this RC could not be used ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com))<sup>24</sup>. These nine patients opted for active surveillance (AS) and did not change towards active treatment within the available follow-up period (mean 8.7 months, range 0-24). There were two patients ( $P(\text{posb})$  19%) who had a localized curable PCa (Gleason scores 3+4, clinical stage T1c). The need for diagnosis of potentially indolent PCa at this point in time is questionable. Overall, these findings support the threshold of  $P(\text{posb})$  of 20%. However, we recommend the need to develop a protocol for PSA follow-up in patients with a  $P(\text{posb}) < 20\%$ .

The calculated probabilities with the RC were not corrected for use in a clinical setting because the current clinical setting is comparable to the initial screening round of the ERSPC section Rotterdam, on which the RC was derived<sup>25</sup>. This may be the result of an increase in PSA testing.

We conclude that the use of guidelines may counteract the adoption of the use of the RC because of opposing recommendations. This problem should be identified and solved to allow successful implement of the RC on a larger scale. The implementation of a prediction model may succeed if physicians are able to acquire sufficient knowledge about the prediction model and its use, as well as have confidence in its utility<sup>3,26</sup>.

Non-compliance of patients with 'no biopsy' recommendations of the RC may be caused, for example, by the way in which the risk is discussed, the opinion and influence of the urologist, and the autonomy of the patient. Individual risk communication may lead to increased participation in screening, especially for patients who had higher risk percep-

tion<sup>27</sup>. Patients who were non-compliant with a 'no biopsy' recommendation, and thus opted for biopsy, reported a smaller influence of urologists than compliant patients (40% vs. 46%,  $p=0.048$ , Table 4). The non-compliant patients had higher calculated probabilities (mean 14% vs. 9%,  $p<0.001$ , Table 1) and higher levels of generic anxiety (mean 36 vs. 32,  $p=0.011$ , Table 3) than patients who were compliant with a 'no biopsy' recommendation. In most of these patients (60%, 38/63), the urologists reported that patients wanted to be certain about having PCa or not. Indeed, those patients who wanted reassurance had a higher risk perception and chose more often to undergo invasive procedures<sup>28</sup>. To enhance patient's understanding about medical information and their participation in decision-making, Epstein et al. recommended five steps to physicians; understand the patient's experience and expectations, build partnership, provide evidence, present recommendations, and check for understanding and agreement<sup>29</sup>.

The strength of the present study is that the RC was not only used as a prediction tool to inform urologists and patients on the calculated individual probability on PCa, but also as a decision tool to help make decisions on the need of a biopsy. We prespecified the threshold for when a biopsy is needed. This may be more effective than a prediction model, which provides only predicted probabilities and leaves decision-making to the physician and patient without guidance<sup>9,30</sup>.

A limitation of the present study is that the interaction of urologists and patients during the decision-making process is not known, especially in cases where patients underwent a prostate biopsy contrary to a 'no biopsy' recommendation of the RC. A standard method for informing patients about the RC was not designed. The interaction between physician and patient may influence patients to deliberate the possible attributes and consequences of options and the motivation to change behavior when deciding to undergo testing or other medical procedures<sup>31</sup>.

We recommend the need for further qualitative research aiming to investigate the communication between urologists and patients about the probability of a positive prostate biopsy, as well as with respect to the decision-making process. Further research is also necessary regarding the implementation of risk assessment tools in a urological setting and into informed decision-making of patients, i.e. sufficient knowledge and making decisions in accordance with attitude. Finally, studies are needed aiming to validate the RC in a clinical setting with a threshold of 20%.

We concluded that the recommendations of a PCa RC were followed with respect to decision-making on biopsy in most patients who were suspected of having PCa. In most cases of non-compliance with a 'no biopsy' recommendation, a PSA level  $\geq 3$  ng/ml lead to a decision to opt for biopsy. Before the implementation of the RC in urological practices on a large scale, it is important to obtain insight into the use of guidelines that may counteract the adoption of the use of the RC because of opposing recommendations.

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# Chapter 6

## The impact of a prostate cancer risk calculator on prostate biopsies taken and positive predictive value: an empirical evaluation

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## ABSTRACT

**Background:** Prostate biopsy prompted by elevated PSA levels results in high percentages of potentially unnecessary biopsies.

**Objective:** To study the impact of the implementation of a risk-based approach on the number of prostate biopsies, and the positive predictive value (PPV) i.e. how many cancers were found among those undergoing a prostate biopsy.

**Patients and Methods:** Prostate biopsies were performed based on standard clinical practice (period 1) and a risk calculator (RC, period 2) which estimates the probability on a positive biopsy (P(posb)). A biopsy was recommended for men with a P(posb)  $\geq$ 20%.

Men aged 55-75 years with PSA  $\geq$ 3 ng/ml and no prior biopsy were included from a Dutch university hospital. Patients in period 1 (2006-2007) had their P(posb) retrospectively calculated, while calculations were done prospectively in period 2 (2009-2010).

Differences in rates of biopsies and PPV were assessed using Chi-square tests.

**Results:** In period 2 more men were biopsied than in period 1 (64%, 65/102 vs. 44%, 99/227,  $p < 0.01$ ), substantially more cancer (41%, 42/102 vs. 19%, 43/227,  $p < 0.01$ ) and more important cancer were found (32%, 33/102 vs. 15%, 35/227,  $p < 0.01$ ).

The PPV with the risk-based approach was 65% (42/65) and 43% (43/99,  $p = 0.01$ ) based on clinical judgement. Between both periods there was no difference in number of biopsies cores taken ( $p = 0.06$ ).

**Conclusions:** The use of a risk calculator led to taking more appropriate biopsies in men suspected of prostate cancer and to a better selection of men at higher risk for important cancer.



## INTRODUCTION

Prostate cancer (PCa) screening using a serum prostate-specific antigen (PSA) threshold as sole indication for prostate biopsy lacks specificity and therefore results in a considerable number of false positive results<sup>1-3</sup>. To improve the specificity of PSA, multivariable prediction models have been developed<sup>4</sup>. These models estimate the probability on having a biopsy detectable PCa based on pre-biopsy information, such as age, family history, digital rectal examination (DRE), transrectal ultrasound (TRUS), previous biopsy, and prostate volume (PV). The use of multivariable prediction models may improve the identification of men being at higher risk for PCa and may hence reduce the number of unnecessary prostate biopsies<sup>1-2,5-6</sup>.

Previous studies retrospectively estimated the potential impact of basing biopsy indications on prediction models<sup>1-2,5-6</sup>. In the current study, we empirically evaluated the impact of systematically applying a prediction model in clinical practice, the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator (RC) level three ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com))<sup>7</sup>. We aimed to study the impact of a risk-based approach as compared to clinical judgement with respect to (1) the proportion of men biopsied and (2) the positive predictive value (PPV), i.e. how many PCAs were found among those undergoing a prostate biopsy.

## PATIENTS AND METHODS

### Study populations

Men were included between 55 and 75 years of age, with a PSA  $\geq 3$  ng/ml and no prior prostate biopsy in a Dutch university hospital.

A systematic database research was conducted for period 1 (2006-2007); 227 men fulfilled the inclusion criteria. In October 2008, the ERSPC RC was actively implemented in the urological practice of the same hospital<sup>8</sup>. The implementation included meetings to explain the background and use of the RC to urologists and their study nurses who supported the use of the RC in clinical practice. They were followed during 2.5 years. Evaluations were held about the use of the RC and problems that had arisen were solved. Data of 102 men were collected prospectively for period 2 (2009-2010). Data were collected on: serum PSA level, outcome of DRE and TRUS, TRUS assessed PV, biopsies and their outcome, and in case of PCa diagnosis: Gleason score.

The study was approved by the Institutional Review Board of the hospital.

## Biopsy indication

An elevated serum PSA and/or a suspicious DRE were indications for prostate biopsy before the implementation of the RC in standard clinical practice (period 1)<sup>9</sup>. An exact cut-off level for PSA was not mandated. The decision about subsequent diagnostic workup was left to the patients and their responsible physicians. After the implementation of the RC, urologists were expected to use the outcome of the RC in the discussion with their patients (period 2). The RC is based on data of 3,624 initially screened men of the ERSPC section Rotterdam and calculates the probability of a positive sextant biopsy ( $P(\text{posb})$ ) using serum PSA, outcomes of DRE and TRUS, and TRUS assessed PV.<sup>7</sup> A biopsy was recommended when the  $P(\text{posb})$  was  $\geq 20\%$ . This decision threshold is similar to the PPV of applying a cut-off of  $\text{PSA} \geq 4 \text{ ng/ml}$ <sup>8</sup>.

## Statistics

Differences in characteristics of men, proportions of prostate biopsies and PCas, and PPV were evaluated with the Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. Men who were diagnosed with PCa were considered low risk when the Prostate cancer Research International: Active Surveillance criteria were met:  $\text{PSA} \leq 10 \text{ ng/ml}$ ,  $\text{PSA density} < 0.20$ , clinical stage  $\leq \text{T2c}$ , Gleason  $\leq 3+3$ , and  $\leq 2$  positive biopsy cores<sup>10</sup>. Cancers which did not meet these criteria were considered important cancers.

The calculation of the  $P(\text{posb})$  was hampered by missing data for some characteristics in period 1. We therefore performed a single imputation procedure, which exploited the correlation between PSA values, clinical stage (18% missing), DRE (15% missing) and TRUS outcome (41% missing), TRUS assessed PV (39% missing), age and period<sup>11</sup>.

We defined the PPV as the number of diagnosed cancers divided by the number of biopsies. PPVs were compared between period 1 and period 2. We also made comparisons to population-based randomized screening studies that apply different screening algorithms. We considered the first screening rounds of the ERSPC sections Rotterdam and Sweden, and of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. In the ERSPC section Rotterdam, a biopsy was indicated in case of a serum  $\text{PSA} \geq 4 \text{ ng/ml}$  and/or a suspicious DRE and/or TRUS (1993-1996) and from 1997 a serum  $\text{PSA}$  of  $\geq 3 \text{ ng/ml}$  only; in the ERSPC section Sweden a  $\text{PSA} \geq 3 \text{ ng/ml}$  triggered a biopsy, and in the PLCO trial after a  $\text{PSA} > 4 \text{ ng/ml}$  and/or a suspicious DRE the decision to perform a prostate biopsy was left to the primary care provider<sup>12-14</sup>. Results in the PLCO trial may therefore be more reflective of clinical practice patterns with regard to PSA and DRE screening.

Analyses were performed using SPSS (version 17.0, SPSS Inc., Chicago, IL). P-values  $< 0.05$  were considered statistically significant.

## RESULTS

In period 2 as compared to period 1, more men underwent a prostate biopsy (64%, 65/102 vs. 44%, 99/227,  $p<0.01$ ), more PCas (41%, 42/102 vs. 19%, 43/227,  $p<0.01$ ) and more important cancers were found (32%, 33/102 vs. 15% (35/227),  $p<0.01$ , Table 1). In addition, more men had a suspicious TRUS (45%, 46/102 vs. 29%, 65/227,  $p<0.01$ ).

The proportion of biopsies per PSA range differed significantly between period 2 and 1, especially in the PSA range 4.0-9.9 ng/ml; 60% (42/70) and 45% (58/128,  $p<0.05$ ), and in the PSA range  $\geq 10$  ng/ml; 100% (18/18) and 60% (27/45),  $p<0.01$ , Table 1), respectively. Baseline characteristics of biopsied and not biopsied men from period 1 did not differ with respect to PV (43 ml vs. 48 ml,  $p=0.16$ ) and numbers of suspicious TRUS (26% vs. 30%,  $p=0.49$ ) in contrast to period 2 (Table 2).

**Table 1.** Characteristics of the participants in period 1 (standard clinical practice) and 2 (risk-based approach)

	Period 1: 2006-2007 n=227	Period 2: 2009-2010 n=102	p-value
Age (years), mean (range)	66 (55-75)	65 (55-75)	0.18
PSA (ng/ml), median (sd, range)	5.7 (6.3, 3-41)	6.3 (7.2, 3-50)	0.14
Number of PCa diagnosis (%)	43 (19)	42 (41)	<0.01
Number of biopsy (%)	99 (44)	65 (64)	<0.01
Number of biopsy cores, median (sd, 25-75% percentiles)	8 (2, 8-10)	10 (2, 8-11)	0.06
Percentage biopsies related to PSA range (ng/ml)			
3.0-3.9	26 (14/54)	36 (5/14)	0.47
4.0-9.9	45 (58/128)	60 (42/70)	<0.05
$\geq 10.0$	60 (27/45)	100 (18/18)	<0.01
PPV	43 (43/99)	65 (42/65)	0.01
Gleason score at biopsy			0.28
$\leq 6$	18 (42)	24 (57)	
7	18 (42)	11 (26)	
>7	7 (16)	7 (17)	
Prostate volume (ml), median (range)	45 (16-122)	50 (18-139)	0.18
No. suspicious DRE (%)	67 (30)	38 (37)	0.16
No. suspicious TRUS (%)	65 (29)	46 (45)	<0.01
Clinical T-stage based on DRE			0.54
T1c	160 (70)	64 (63)	
T2	62 (27)	35 (34)	
T3	4 (2)	2 (2)	
T4	1 (1)	1(1)	
P(posb) (%) mean (range)	33 (1-97)	37 (3-98)	0.31

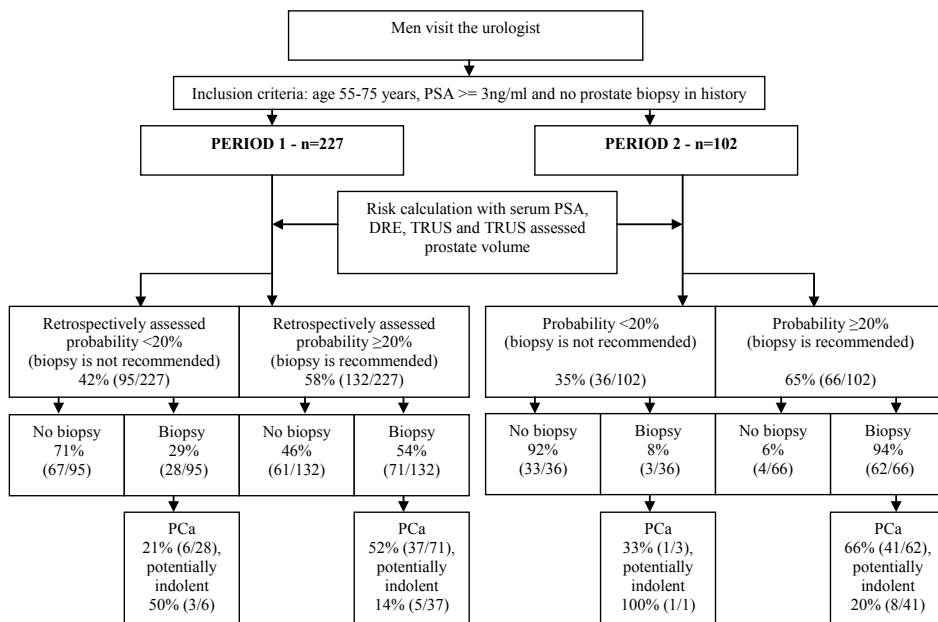
PSA; Prostate-specific antigen, PCa; Prostate cancer, PPV; Positive predictive value, DRE; Digital rectal examination, TRUS; Transrectal ultrasound, P(posb); Probability of a positive sextant prostate biopsy

**Table 2.** Baseline characteristics of men per period stratified by biopsy status

	Period 2006-2007 (standard clinical practice)			Period 2009-2010 (risk-based approach)		
	No biopsy n=128	Biopsy n=99	p-value	No biopsy n=37	Biopsy n=65	p-value
PSA ng/ml median (range)	4.9 (3.0-29.7)	6.7 (3.0-40.8)	<0.01	4.8 (3.0-8.0)	7.6 (3.3-50.0)	<0.01
Prostate volume (ml), median (range)	48 (18-123)	43 (16-95)	0.16	63 (34-139)	40 (8-99)	<0.01
PSA density, mean (range)	0.16 (0.03-1.03)	0.23 (0.05-1.05)	<0.01	0.09 (0.04-0.21)	0.24 (0.06-1.25)	<0.01
Suspicious DRE (%)	23 (29/128)	38 (38/99)	0.01	5 (2/37)	55 (36/65)	<0.01
Suspicious TRUS (%)	30 (39/128)	26 (26/99)	0.49	14 (5/37)	63 (41/65)	<0.01
P(posb) (%), mean (range)	28 (1-97)	39 (4-97)	<0.01	12 (3-34)	51 (5-98)	<0.01

PSA; Prostate-specific antigen, PCa; Prostate cancer, PPV; Positive predictive value, DRE; Digital rectal examination, TRUS; Transrectal ultrasound, P(posb); Probability of a positive sextant prostate biopsy

In period 1, 46% (61/132) did not undergo a prostate biopsy while the retrospectively assessed P(posb) was  $\geq 20\%$  (Figure 1). Compared to the biopsied men, they had less suspicious DRE outcomes than men who underwent a biopsy (33%, 20/61 versus 51%, 36/71,  $p=0.04$ , data not shown). The PPV in men biopsied with a retrospectively assessed P(posb)  $\geq 20\%$  was 52% (37/71) in period 1, while the PPV for this group in period 2 was 66% (41/62, Figure 1).



**Figure 1.** Flow chart of men included in period 1 (standard clinical practice) and period 2 (risk-based approach)

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound; PCa: Prostate cancer

When comparing men with a PSA  $\geq 4$  ng/ml of both periods with different screening settings, the risk-based approach had the highest PPV (68%, 41/60, 95% CI 0.58-0.78). In period 1 it was identical to that of the PLCO trial (both 44%, 37/85, 95% CI 0.37-0.51 and 468/1067, 95% CI 0.42-0.46, respectively), while the lowest PPV was found in ERSPC Rotterdam and Sweden, 31% (756/2408, 95% CI 0.29-0.33) and 19% (69/366, 95% CI 0.15-0.23), respectively (Table 3). The PPV was also the highest in period 2 for the PSA range 4.0-9.9 ng/ml (67%, 28/42, Table 4).

**Table 3.** Number of biopsied men, number of PCa diagnosis, and positive predictive value of period 1 (standard clinical practice), period 2 (risk-based approach), first screening rounds of the European Randomized study of Screening for Prostate Cancer (ERSPC) sections Rotterdam, Sweden and the Prostate, Lung, Colorectal and Ovarian (PLCO) trial

	Period 1: 2006-2007 n=227	Period 2: 2009-2010 n=102	ERSPC Sweden <sup>13</sup> n=661	ERSPC Rotterdam <sup>12</sup> n=2154	PLCO <sup>14</sup> N/A
PSA level $\geq 3$ ng/ml					
Men biopsied (%)	99 (44)	65 (64)	595 (90)	1850 (86)	N/A
PCa detected (%)	43 (19)	42 (42)	145 (22)	541 (25)	N/A
PPV (95% CI)	43 (43/99) (0.37-0.49)	65 (42/65) (0.56-0.74)	24 (145/595) (0.21-0.27)	29 (541/1850) (0.27-0.31)	N/A
	Period 1 n=173	Period 2 n=88	ERSPC Sweden <sup>13</sup> n=393	ERSPC Rotterdam <sup>25</sup> n=2692	PLCO <sup>**14</sup> n=2605
PSA level $\geq 4$ ng/ml					
Men biopsied (%)	85 (49)	60 (68)	366 (93)	2408 (86)	1067 (41)
PCa detected (%)	37 (21)	41 (47)	69 (18)	756 (28)	468 (18)
PPV (95% CI)	44 (37/85) (0.37-0.51)	68 (41/60) (0.58-0.78)	19 (69/366) (0.15-0.23)	31 (756/2408) (0.29-0.33)	44 (468/1067) (0.42-0.46)

\*Joint analysis of two screening protocols used in the initial screening round

\*\*PLCO PSA  $> 4$  ng/ml

PSA; Prostate-specific antigen, PCa; Prostate cancer, PPV; Positive predictive value, CI; Confidence interval, N/A; Not available

**Table 4.** Positive predictive value (number of cancer/number of biopsies) per PSA range in period 1 (standard clinical practice), period 2 (risk-based approach), first screening rounds of the European Randomized study of Screening for Prostate Cancer (ERSPC) sections Rotterdam and the Prostate, Lung, Colorectal and Ovarian (PLCO) trial

PSA range	Period 1: 2006-2007	Period 2: 2009-2010	ERSPC Sweden <sup>13</sup>	ERSPC Rotterdam <sup>25</sup>	PLCO <sup>14</sup>
3.0-3.9 ng/ml	43 (6/14)	20 (1/5)	15 (36/245)	23 (179/791)	N/A
4.0-9.9 ng/ml	38 (22/58)	67 (28/42)	22 (66/300)	26 (526/2005)	36 (297/832)
$\geq 10.0$ ng/ml	56 (15/27)	72 (13/18)	65 (43/66)	57 (230/403)	73 (171/235)

PSA; Prostate-specific antigen, N/A; Not available

## DISCUSSION

In this study, we found that a risk-based approach as compared to standard clinical practice led to more prostate biopsies; 64% vs. 44%. However, the PPV in period 2 was substantially higher, equivalent to a considerably lower proportion of negative biopsies. Not only, more cancers were found, but also more important cancers. Hence, a risk-based approach led to more appropriate biopsies and to a better selection of men at higher risk for important cancer than standard clinical practice.

The higher proportion of biopsies in period 2 might be explained by more suspicious TRUS, because in standard clinical practice a TRUS was not routinely included as part of PCa screening in contrast to the risk-based approach.

In the current study, a higher PPV was reached when applying the risk-based approach. Up till now, studies have only theoretically confirmed that a higher PPV can be reached using a 20% probability threshold with the ERSPC RC in combination with a standard screening algorithm, rather than using a screening algorithm alone<sup>2,5-6</sup>. The PPV in these studies were 23%<sup>2</sup>, 26%<sup>2</sup>, 29%<sup>6</sup> and 35%<sup>5</sup>, which increased to 35%<sup>2</sup>, 33%<sup>2</sup>, 38%<sup>6</sup> and 50%<sup>5</sup> using a 20% threshold, respectively. Consequently, these studies showed that 29-57% of prostate biopsies could be saved while only a few important PCa (1-6%) would be missed<sup>2,5-6</sup>.

When applying a biopsy threshold, it is important to weigh the benefits and harms; detecting PCa at a curable stage on one hand and performing unnecessary biopsies on the other. Various studies show that PSA thresholds alone may lead to unacceptable numbers needed to investigate and numbers needed to treat to save one life<sup>15-16</sup>. A recent study showed a number needed to investigate of 24 642 and a number needed to treat of 724 for PSA values <2.0 ng/ml. These values were slightly more favourable for PSA values 2.0 to 4.0 ng/ml (2393 and 427 respectively)<sup>15</sup>.

The PPV of period 1 (clinical judgement) agreed with the PPV of the first screening round of the PLCO trial where men with elevated PSA and/or suspicious DRE were referred to their primary care provider who made the decision whether or not to perform a biopsy<sup>14</sup>. The PLCO trial policy is comparable to that of a clinical setting, because in this setting the biopsy decision was also left to physicians.

In the ERSPC cohorts, the overall PPV was the lowest compared to both periods and the PLCO, which implicates that more unnecessary biopsies were taken. Their low PPV cannot be attributed to the number of biopsies cores taken if compared to the PLCO trial, because both in the ERSPC and PLCO studies, sextant biopsies were performed<sup>17-18</sup>. Thus, the high rates of unnecessary biopsies in the ERSPC cohorts might be caused by the fact that all men were biopsied according to a strict screening algorithm, which does not allow for interference of physicians' judgement or the use of a RC. For example, all men in the ERSPC with a PSA 4-9.9 ng/ml were biopsied. A key challenge of PSA in this range (the 'grey zone') is to discriminate between benign

prostate hyperplasia and PCa. With the risk-based approach, PSA levels are corrected for PV<sup>19-21</sup>. The use of PSA and PV (i.e. PSA density) instead of PSA alone in the diagnosis of PCa improves the diagnostic accuracy<sup>22-24</sup>. This was confirmed in a study in which 330 biopsied men were included, which showed an AUC of serum PSA for diagnosis of PCa of 0.74 while it was 0.81 for PSAD ( $p < 0.001$ )<sup>22</sup>. The current study showed that in the PSA range 4-9.9 ng/ml a considerably higher PPV (67%) was reached with the risk-based approach, including PSA and PV, compared to period 1 as well as to the screening settings in which PV was not used (PPV 38% and 22-36% respectively). In conclusion, men with increased risk for PCa with a PSA value in the 'grey zone' can best be identified by using a RC including PV.

A high proportion of men in period 1 (46%) were not biopsied while at higher risk for PCa ( $P(\text{posb}) \geq 20\%$ ). This might be explained by less suspicious DRE results in these men compared to those who were biopsied. This group of non-biopsied men with a  $P(\text{posb}) \geq 20\%$  are likely at higher risk for PCa when looking at the results of men with similar risks in the both periods; proportions of men diagnosed with PCa with a  $P(\text{posb}) \geq 20\%$  in period 1 and 2 were 52% and 66%, respectively (Figure 1).

Limitations of this study include the relatively small cohorts, the retrospective part and the non-randomized nature of the study. In period 2, fewer men were included in the study compared to period 1. The difference could not be explained by the number of men who refused to participate in the study in period 2. It could be possible that more men had an elevated PSA in that period, but were not categorized at higher risk for PCa and thus a biopsy was not considered. The difference between both periods seems not to lead to a selection bias; the distribution of men at low risk for PCa ( $P(\text{posb}) < 20\%$ ) and high risk for PCa ( $P(\text{posb}) \geq 20\%$ ) did not differ between period 1 and 2.

Also missing values may introduce a bias if men with missing values are systematically different from those without missing values. However, we used an imputation procedure for period 1 which corrects such a possible selection bias<sup>11</sup>. Furthermore, in period 2, a higher proportion of men with a PSA  $\geq 10$  ng/ml was biopsied, because they had a probability of  $\geq 20\%$  with the RC leading to a biopsy. In period 1, however, reasons for fewer biopsied men with PSA  $\geq 10$  ng/ml could be that men had a prostatitis or a benign prostate hyperplasia and therefore did not undergo a biopsy, but this was not consequently reported. There was no difference in proportion of comorbidity between both periods in this PSA range.

As far as we know, the current study is the first study evaluating the impact of a PCa RC in clinical practice and comparing the outcomes of a risk-based approach to standard clinical practice regarding the number of prostate biopsies taken and the PPV for PCa detection at prostate biopsy.

Further research is recommended to validate the threshold of the RC for biopsy indication. Because of the limitations, the results of the current study have to be interpreted

with caution and should be viewed as a finding that needs further confirmation within a larger prospective study.

In conclusion, a risk-based approach as compared to clinical judgement led to more biopsies. However, the PPV was substantially higher and thus led to a lower proportion of negative biopsies, and a higher proportion of important cancers.



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# Part 4

## **Validation of prostate cancer risk calculators calculating the probability on a positive prostate biopsy**

### Chapter 7

Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort

*European Journal of Cancer 2012*

### Chapter 8

Prediction of prostate cancer in unscreened men: External validation of a risk calculator

*European Journal of Cancer 2010*

### Chapter 9

Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators

*European Urology 2012*



# Chapter 7

## Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort

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## ABSTRACT

**Background:** Prediction models need validation to assess their value outside the development setting.

**Objective:** To assess the external validity of the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator (RC) in a contemporary clinical cohort.

**Methods:** The RC calculates the probability of a positive sextant prostate biopsy (P(posb)) using serum prostate-specific antigen (PSA), results of digital rectal examination, transrectal ultrasound (TRUS), and ultrasound assessed prostate volume. We prospectively validated the RC in 320 biopsied men (55-75 years), with no previous prostate biopsy, included in five Dutch hospitals in 2008-2011. If the P(posb) was  $\geq 20\%$  a biopsy was recommended.

The performance of the RC was tested by comparing the observed outcomes to predicted probabilities, using the area under the curve (AUC), and decision curves analyses.

**Results:** Compared to the screening cohort, men in the clinical cohort differed. They had higher PSA levels (median 6.8 versus 4.3 ng/ml,  $p < 0.01$ ), less TRUS-lesions (27% versus 34%,  $p = 0.01$ ), and more prostate cancer (PCa) at biopsy (43% versus 25%,  $p < 0.01$ ). Mainly eight biopsy cores were taken. Despite the differences between these cohorts, the mean observed probability agreed with the mean predicted probability (43% versus 40%). The RC predicted P(posb) better than a model with PSA and DRE, AUC 0.77 (95% confidence interval (CI) 0.72-0.83) and 0.71 (95% CI 0.65-0.76,  $p < 0.01$ ) respectively. This was confirmed by the decision curves analysis. Under the 20% threshold, 17% (11/63) of the biopsied men were diagnosed with PCa. Two of 11 men had an important cancer (Gleason 3+4).

**Conclusions:** The ERSPC RC performs well in a Dutch clinical cohort in men with previous PSA tests and contemporary biopsy schemes, and outperforms a PSA and DRE-based approach in the decision to perform a biopsy.

## INTRODUCTION

Serum prostate-specific antigen (PSA) screening for prostate cancer (PCa) is controversial because the test lacks specificity. This has led to the development of multivariable risk prediction tools. These tools outperform a strategy where the decision to perform a biopsy is based on the outcome of a PSA test alone<sup>1-3</sup>. However, before using a prediction tool it is important to realize its origin, i.e. the characteristics of the population on which the tool was developed. If the model is highly specific for the population from which it is derived the utility decreases. To study the general applicability of a model external validation is important<sup>4</sup>.

The European Randomized study of Screening for Prostate Cancer (ERSPC) has developed the ERSPC Risk Calculator (RC), which consists of six levels ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)). The third level was developed to calculate the probability of a positive lateralized sextant prostate biopsy (P(posb)) using serum PSA, the outcomes of digital rectal examination (DRE) and transrectal ultrasound (TRUS) investigations, i.e. the presence of hypoechoic lesions and prostate volume<sup>5</sup>. This RC has not been validated in a Dutch contemporary clinical cohort. The aim of this study was threefold (1) to compare the characteristics of the clinical cohort with the screening cohort (development cohort) (2) to prospectively validate the RC in a clinical cohort and (3) to compare the RC with the use of a model with PSA and DRE.

## MATERIALS AND METHODS

### Study population

The RC is based on 3624 biopsied men (55-75 years) from the initial screening round of the Dutch section of the ERSPC included between 1993 and 2000. A sextant biopsy indication was performed for a serum PSA  $\geq 4$  ng/ml and/or a suspicious DRE or TRUS (1993-1996) and from 1997 only a serum PSA of  $\geq 3$  ng/ml<sup>6,7</sup>.

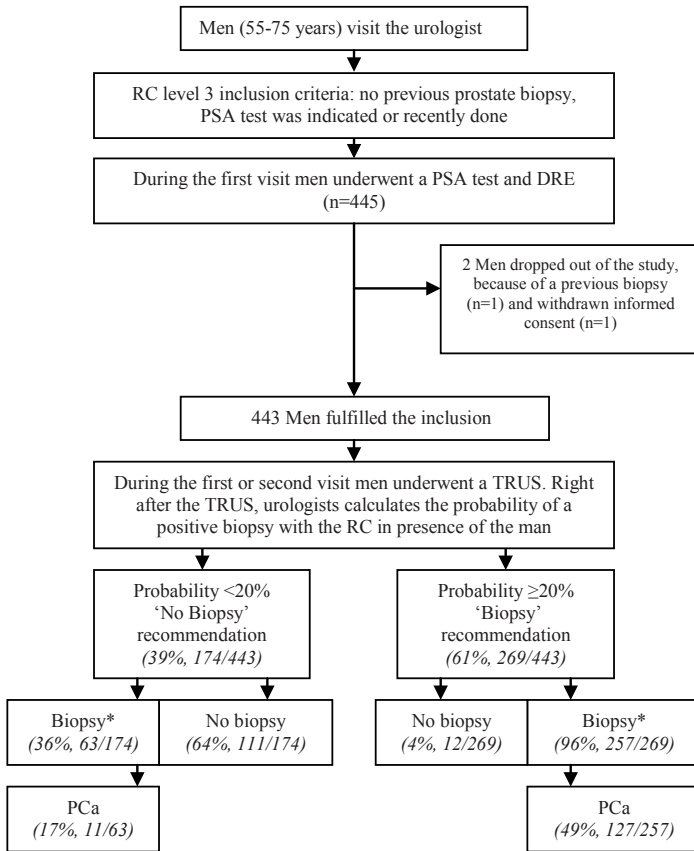
External validation of the RC was performed using prospectively collected data of men undergoing a prostate biopsy in five Dutch hospitals from October 2008 to April 2011. This cohort consisted of 320 men (55-75 years) with no previous biopsy and possibly one or more previous PSA tests.

The study was approved by the Institutional Review Board of all participating hospitals. All men provided written informed consent.

### Study procedure

Figure 1 shows the study procedure. After the PSA test, DRE and TRUS examinations, urologists calculated the P(posb) with the RC. As a decision rule a P(posb)  $\geq 20\%$  was

recommended to perform a prostate biopsy. This threshold agrees to the positive predictive value when applying a PSA  $\geq 4$  ng/ml as indication for biopsy. Often a PSA  $\geq 4$  ng/ml corresponds to a  $P(\text{posb}) \geq 20\%$  but not always, e.g. men with a 'grey zone' PSA (4-10 ng/ml) and a large prostate may have a  $P(\text{posb}) \leq 20\%$ <sup>6</sup>.



**Figure 1.** Flow chart of the participants

\* Men underwent all examinations in one day including the biopsy, one hour after taking the antibiotic, or men were asked to return for biopsy

RC: Risk calculator; PCa: Prostate cancer; PSA: prostate specific antigen; DRE: digital rectal examination; TRUS: Transrectal ultrasound

**Statistics**

The model with PSA and DRE was based on the data of the development cohort of the RC level 3 (probability =  $1/(1+\exp(-(-3.322+2.631*\log_{10}\text{psa}+1.111*\text{DRE})))$ ).

The differences between the characteristics of the two cohorts were assessed using the Chi-square test or the Mann Whitney U test. Multivariable logistic regression analysis was used to study the predictive properties of log10 transformed PSA, log10 transformed



volume, DRE and TRUS outcome with respect to biopsy results in the clinical setting. After pooling the data of the clinical cohort and the development cohort, we studied the differences in the predictive value of the predictors in the clinical cohort compared to the development cohort by adding interaction terms of the form 'cohort\*predictor'. A significant p-value for an interaction term means that the predictor had a significantly higher or lower value in the clinical cohort than in the development cohort.

The performance of the RC in the clinical setting was assessed by calibration, discrimination, and clinical usefulness.

Calibration refers to the agreement between the actual percentage of PCa diagnoses in the clinical cohort and the mean calculated probabilities with the RC. The extent of over- and underestimation relative to the observed and predicted rate was explored graphically using validation plots<sup>4</sup>. A validation plot is characterized by an intercept, which should ideally be 0 and indicates the extent that predictions are systematically too low or too high ('calibration-in-the-large'), and a calibration slope, which should ideally be equal to 1.

Discrimination refers to the ability of the RC to discriminate between men with and without PCa and is estimated by means of the area under the receiver operating characteristic curve. We compared the area under the curve (AUC) of the RC with the model using PSA and DRE using the method of DeLong et al.<sup>8</sup>. We focused on the model using PSA and DRE, because in current clinical practice the need for a prostate biopsy is often based on the PSA level and/or a suspicious DRE<sup>9</sup>.

Clinical usefulness was assessed by using decision curve analysis<sup>10</sup>. This method estimates a 'net benefit' for prediction models by summing the benefits (true-positive biopsies) and subtracting the harms (false-positive biopsies) in which the latter are weighted by a factor related to the relative harm of a missed PCa versus an unnecessary biopsy. A particular model is to be preferred if its decision curve is consistently above the decision curve for competing models over a wide range of probability thresholds. We compared the RC with the model with PSA and DRE, performing biopsy in all men and in no men, especially from the 20% threshold.

To assess tumor characteristics, especially under the 20% threshold, the inclusion criteria for a risk-based approach were used to define a potentially indolent PCa (ERSPC RC level six, [www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com))<sup>11</sup>. The RC is based on biopsy histology and calculates the probability of having indolent PCa in men who were diagnosed with PCa with a PSA <20 ng/ml, clinical stage  $\leq$ T2, <50% positive sextant biopsy cores,  $\leq$ 20 mm cancer,  $\geq$ 40 mm benign tissue and Gleason score (GS)  $\leq$ 3+3<sup>11</sup>. Cancers that do not meet these criteria were considered important cancers.

Statistical analyses were performed using SPSS software (version 17; SPSS, Inc, Chicago, Ill) and R (version 2.8.1; R foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

## RESULTS

### Study population

In the clinical cohort men had significantly higher serum PSA levels (6.8 versus 4.3 ng/ml), less TRUS-lesions (27% versus 34%), and more PCa at biopsy (43% versus 25%) than in the development cohort (Table 1). In the clinical cohort, 58% (186/320) of the men had a previous PSA test. A median number of eight biopsy cores were taken (74%, 237/320, 2.5-97.5 percentile 8-12 cores). Twenty percent of the men (63/320) were biopsied against the recommendation used in this study ( $P(\text{posb}) < 20\%$ ), and 80% (257/320) were biopsied in accordance with the recommendation ( $P(\text{posb}) \geq 20\%$ , Figure 1).

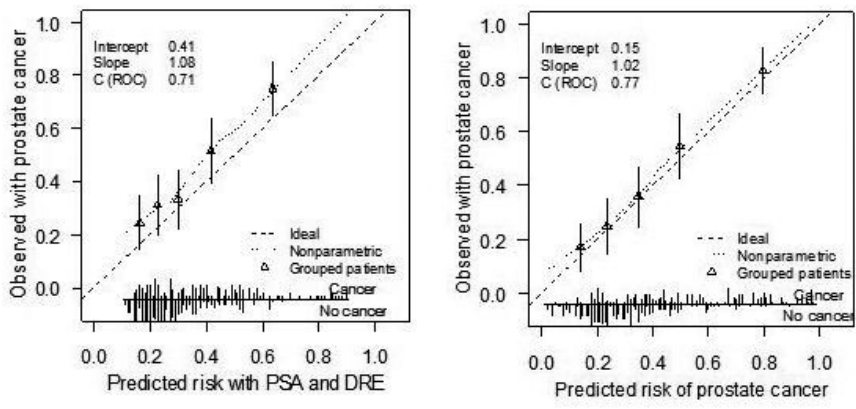
**Table 1.** Characteristics of the participants

	Clinical cohort n=320	Development cohort n=3624	p-value
Age (years)(Average, sd, range)	64.8 (5.1, 55-75)	65.5 (5.4, 55-75)	0.01
PSA ng/ml median (25-75 percentile)	6.8 (5.0-9.4)	4.3 (3.1-6.4)	<0.01
Number suspicious DRE (%) Clinical T stage DRE	104 (33)	1284 (35)	0.29
Number suspicious TRUS (%) (hypoechoogenic lesions)	87 (27)	1233 (34)	0.01
Prostate volume (ml) median (25-75 percentile)	39 (30-52)	41 (32-55)	0.02
Number prostate cancer detected on needle biopsy (%)	138 (43)	893 (25)	<0.01

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

### Calibration and discrimination

In the clinical cohort the mean observed  $P(\text{posb})$  agreed well with the mean predicted  $P(\text{posb})$ , 43% versus 40% (Table 2). The validation plot showed good calibration (Figure 2), reflected in the calibration slope of 1.02 (95% confidence interval (CI), 0.75-1.30) and the calibration-in-the-large of 0.15 (95% CI, -0.10-0.40). PSA was a relatively weak predictor (OR 16 versus 43,  $p=0.03$ ) and DRE was a stronger predictor (OR 5 versus 2,  $p=0.01$ , Table 3) in the clinical cohort than in the development cohort. Under the 20% threshold, the mean predicted  $P(\text{posb})$  was 14% and the mean observed  $P(\text{posb})$  was 17% (11/63). In the clinical cohort, the mean observed and the mean predicted  $P(\text{posb})$  disagreed for the model with PSA and DRE, 43% versus 35% (Table 2), as shown by the systematic miscalibration in the validation plot (Figure 2).



The dashed smooth curves in the calibration plots reflect the non-parametric relation between observed and predicted probability on a positive prostate biopsy. Perfect calibration is represented by the straight dotted line through the origin.

**Figure 2.** Validation plots for the prediction of the model with PSA and DRE and the risk calculator in the clinical setting (n=320)  
 PSA: Prostate-specific antigen; DRE: Digital rectal examination

Discrimination was similar among the two cohorts (Table 2). The AUC was 0.77 (95% CI 0.72-0.83) in the clinical cohort and 0.79 (95% CI 0.77-0.81) in the development cohort. For the model with PSA and DRE the AUC was 0.71 (95% CI 0.65-0.76) and 0.73 (95% CI 0.71-0.75) respectively. In the clinical cohort, the AUC of the RC was significantly higher compared to the model with PSA and DRE (p<0.01).

**Table 2.** Performance of the risk calculator and the model with PSA and DRE predicting a positive prostate biopsy in the clinical cohort and in the screening cohort of the European Randomized Study of screening for Prostate Cancer (development cohort)

	Mean predicted outcome	Mean observed outcome	Calibration-in-the-large (95% C.I.)	Calibration slope (95% C.I.)	AUC (95% C.I.)
Risk calculator: PSA, DRE, TRUS and prostate volume					
Clinical cohort	40%	43%	0.15 (-0.10-0.40)	1.02 (0.75-1.30)	0.77 (0.72-0.83)*
Development cohort	25%	25%	0 (-0.09 - 0.09)	1.0 (0.93 - 1.09)	0.79 (0.77-0.81)#
PSA with DRE					
Clinical cohort	35%	43%	0.41 (0.17-0.65)	1.08 (0.74-1.42)	0.71 (0.65-0.76)*
Development cohort	25%	25%	0 (-0.08-0.08)	1.0 (0.90-1.10)	0.73 (0.71-0.75)#

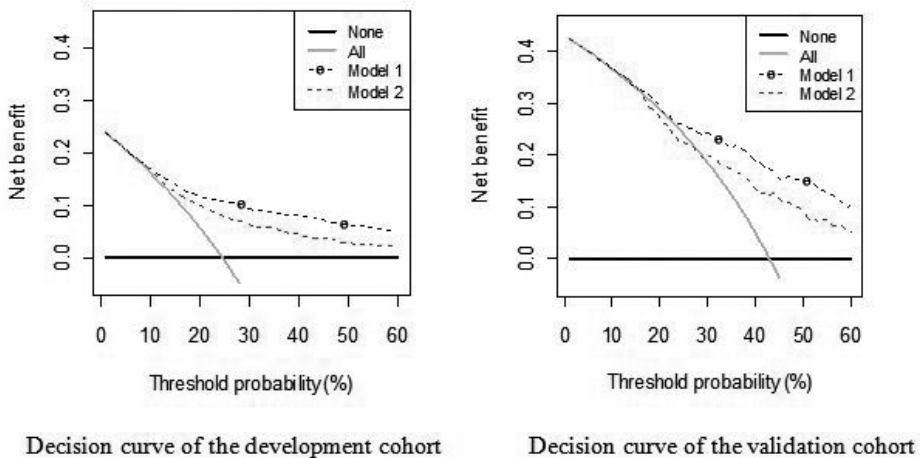
\*the difference between the AUCs was significant (p<0.01)

#the difference between the AUCs was significant (p<0.01)

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

### Clinical usefulness

The net benefit is the highest for the RC above the 20% threshold compared with the use of PSA and DRE, or biopsying all men (Figure 3), and thus the RC performed better than a model with PSA and DRE or biopsying all men. For the model with PSA and DRE, the net benefit was lower compared with the strategy to biopsy all men from a probability of approximately 15%-30%. Under the 20% P(posb) threshold, 17% (11/63) of the biopsied men were diagnosed with PCa (median P(posb) 18%, median PSA level 4.2). Two of the 11 men had important PCa (both P(posb) of 19%, GS 3+4), of which one was irradiated and one treated by radical prostatectomy. This patient had the same GS in the surgical specimen. The other cancers fulfilled the inclusion criteria for a potentially indolent PCa according to RC level six (probability range 45-92%), and in one man it was not possible to assess GS due to insufficient cancer tissue, all these men chose active surveillance.



**Figure 3.** Decision curves for the predicted probabilities in the development cohort and the clinical cohort with the risk calculator (model 1) and the model with PSA and DRE (model 2)

**Table 3.** Comparison of results of logistic regression analyses on data obtained from clinical cohort and screening cohort of the European Randomized study of Screening for Prostate Cancer (development cohort)

Variables	Clinical cohort n=320		Development cohort n=3624		Both cohorts n=3944		p-value for interaction*
	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	
LogPSA	2.75	15.61 (4.24-57.54)	3.76	42.80 (30.24-60.57)	3.70	40.59 (29.07-56.66)	0.03
Logvolume	-4.74	0.01 (0.00-0.05)	-4.21	0.02 (0.01-0.03)	-4.23	0.01 (0.01-0.03)	0.33
DRE	1.63	5.11 (2.77-9.42)	0.82	2.27 (1.88-2.73)	0.89	2.43 (2.04-2.90)	0.01
TRUS	0.68	1.97 (1.04-3.72)	0.87	2.38 (1.97-2.87)	0.85	2.34 (1.96-2.80)	0.88
Cohort					0.18	1.20 (0.91-2.80)	
Constant	4.20	66.84	2.55	12.84	2.60	13.47	

\*Significant p-value for an interaction term means that a predictor had a significantly higher or lower value in the clinical cohort than in the development cohort LogPSA: log<sub>10</sub> transformation of the serum prostate-specific antigen; Logvolume: log<sub>10</sub> transformation of the prostate volume; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

## DISCUSSION

The ERSPC RC has been validated in a clinical cohort to predict the probability of a positive sextant prostate biopsy in previously unscreened men. The model discriminates well between men with and without PCa, with an AUC of 0.77 compared to the model with PSA and DRE (AUC 0.71). Calibration of the RC was good. However under the 20% threshold there is some underestimation of the P(posb). This observation may be explained by verification bias<sup>12</sup>. This occurs when men are biopsied selectively. To avoid the verification problem all patients had to be biopsied with a PSA  $\geq 3$  ng/ml as in the development cohort (or with P(posb) < 20%).

The effect of DRE in the clinical setting was stronger than in the development cohort (Table 3). This difference may be explained by interobserver variation for DRE outcome<sup>13</sup>, and by the fact that in the clinical cohort more advanced PCa were found ( $\geq T2$ ) than in the development cohort (screening)<sup>14</sup>.

In the clinical cohort less TRUS hypoechoic lesions were found than in the development cohort. This difference may be explained by interobserver variation for TRUS outcome<sup>15</sup>. In the model an other subjective variable is included next to DRE and TRUS outcomes, i.e. TRUS assessed prostate volume<sup>7,15</sup>. Despite the three subjective variables in the model, the RC performed well in our clinical cohort in which, contrary to the development cohort mainly eight core biopsies were performed. Given the differences between the clinical and the development cohort (Table 1), it is remarkable that the predictions of the RC are in good agreement with the observations (Figure 2). A possible explanation might be the inclusion of prostate volume. In different validation studies of

the RC, prostate volume was one of the most important predictors in the model<sup>1,16,17</sup>. In particular, this plays a major role for PSA levels in the 'grey zone' (4-10 ng/ml); elevation of PSA levels in this range can be caused by PCa, but can also be due to benign prostate hyperplasia<sup>18,19</sup>. When PSA levels are corrected for prostate volume the specificity of PSA to detect PCa increases; higher PSA and a small prostate is more indicative for PCa than similar PSA and a large prostate<sup>18</sup>. An explanation for this might be that a certain tumor has a higher probability of being detected in a smaller prostate than in a large prostate due to sheer chance, assuming that the same number of biopsy cores is taken<sup>20-22</sup>. Another explanation can be sought in the reported association between lower prostate weight and higher total cancer volume<sup>23,24</sup>.

In two studies the performance of the RC was compared with the Prostate Cancer Prevention Trial (PCPT) RC. The PCPT RC uses serum PSA, family history, DRE, and having had a prior biopsy (yes or no) to calculate the P(posb), i.e. prostate volume and TRUS outcome are not included. The RC performed better than the PCPT RC in that clinical cohort, AUCs were 0.71 and 0.63<sup>1</sup>, and in a screening cohort, AUCs were 0.80 and 0.74<sup>16</sup>.

Calibration of the RC was previously assessed in clinical<sup>1</sup> and screening settings<sup>25</sup>, where the RC underestimated and overestimated the mean P(posb)s, respectively. However, in the current study, there was practically no underestimation which is against expectations since the PCa detection rates are 1.7 times higher in the clinical cohort than in the development cohort. These higher detection rates may be explained by the use of a more extended biopsy scheme and the different characteristics of the study cohort. Taking more than six cores can increase the PCa detection rate<sup>26-28</sup>.

It may be best to compare the performance of competitive RCs in a similar setting e.g. the PCPT RC<sup>1,16,29</sup>. However, this was not possible because one variable, i.e. family history was not recorded for the study population. Therefore we have limited our study to comparing the performance of the RC with a model with PSA and DRE. The decision curve analysis showed that the net benefit for the RC was the highest compared to the model with PSA and DRE or biopsying all men (Figure 2). The use of the model with PSA and DRE is less adequate than biopsying all men in the probability range of 15-30%. This may be caused by the fact that not all men were biopsied with a PSA  $\geq 3$  ng/ml<sup>12</sup>.

Limitations of this study are the small cohort and the possibility of verification bias. This bias may explain the underestimation of the probability under the 20% threshold and the lower performance of the model with PSA and DRE compared to biopsy all men from a probability of approximately 15-30%.

Strengths of our study are that the RC was validated prospectively in a Dutch clinical cohort, which is a completely different setting than its development setting, and contemporary biopsy schemes were applied. The definition of contemporary biopsy schemes used in current study is supported by the European Urology guidelines ([www.](http://www.)

uroweb.org), which prescribe that in men with a prostate volume of 30-40, at least eight biopsy cores should be sampled, >12 cores are not significantly more conclusive<sup>9,30</sup>. Furthermore, we statistically tested that there was no major centre effects which could influence the outcomes. In current study, a threshold was applied to recommend a biopsy. However, below this threshold cancers are present and these will be missed. It is therefore important that the number of these cancers is low and their tumor characteristics favourable. In this way detection at a later point in time does not imply that the window of curability is missed. From long term studies we know that men with low PSA values are at low risk to develop an important PCa in the near future<sup>31</sup>. To apply a threshold, the harms and benefits of screening thus have to be weighed<sup>32</sup>. In the development cohort, under the 20% threshold 57% (2050/3624) of the men were biopsied and 3.9% had an important PCa (Gleason >6 with no metastasis); 35 of the total 893 PCas found in the entire cohort<sup>25</sup>. In Dutch clinical practice, men with an elevated PSA would be advised to have a PSA follow-up at 3-6 months depending on the PSA level. Scientific evidence is not available on this issue. Follow-up is needed for men who did not undergo a biopsy ( $P(\text{posb}) < 20\%$ ) and those with negative biopsy results ( $P(\text{posb}) < 20\%$ ) to develop further screening recommendations.

In conclusion, the screening based ERSPC RC performed well in a Dutch clinical cohort using a contemporary biopsy scheme. A  $P(\text{posb})$  threshold  $\geq 20\%$  seems reasonable to recommend a prostate biopsy, since the majority of the PCAs detected under the 20% threshold are potentially indolent. A probability risk based approach as indication for a prostate biopsy outperformed the use of PSA and DRE-based approach.

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# Chapter 8

## Prediction of prostate cancer in unscreened men: External validation of a risk calculator

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## ABSTRACT

**Background:** Prediction models need external validation to assess their value beyond the setting where the model was derived from.

**Objective:** To assess the external validity of the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)) for the probability of having a positive prostate biopsy (P(posb)).

**Design, setting and participants:** The ERSPC risk calculator was based on data of the initial screening round of the ERSPC section Rotterdam and validated in 1825 and 531 men biopsied at the initial screening round in the Finnish and Swedish sections of the ERSPC respectively. P(posb) was calculated using serum prostate specific antigen (PSA), outcome of digital rectal examination (DRE), transrectal ultrasound and ultrasound assessed prostate volume.

**Measurements:** The external validity was assessed for the presence of cancer at biopsy by calibration (agreement between observed and predicted outcomes), discrimination (separation of those with and without cancer), and decision curves (for clinical usefulness).

**Results and limitations:** Prostate cancer was detected in 469 men (26%) of the Finnish cohort and in 124 men (23%) of the Swedish cohort. Systematic miscalibration was present in both cohorts (mean predicted probability 34% versus 26% observed, and 29% versus 23% observed, both  $p < 0.001$ ). The areas under the curves were 0.76 and 0.78, and substantially lower for the model with PSA only (0.64 and 0.68 respectively). The model proved clinically useful for any decision threshold compared with a model with PSA only, PSA and DRE, or biopsying all men. A limitation is that the model is based on sextant biopsies results.

**Conclusions:** The ERSPC risk calculator discriminated well between those with and without prostate cancer among initially screened men, but overestimated the risk of a positive biopsy. Further research is necessary to assess the performance and applicability of the ERSPC risk calculator when a clinical setting is considered rather than a screening setting.

## INTRODUCTION

Prostate cancer (PCa) screening using a prostate specific antigen (PSA) based threshold of 3–4 ng/ml as indication for prostate biopsy lacks specificity. This leads to unnecessary biopsies and missing PCa diagnosis in men with a PSA level below the threshold<sup>1,2</sup>. Risk calculators (or nomograms) for the prediction of a positive prostate biopsy have been developed to support physicians in clinical decision making with respect to the individual patient and reduce the number of unnecessary biopsies with a marginal loss of potentially aggressive PCas<sup>2-7</sup>. Risk calculators improve the diagnostic value of PSA by increasing its sensitivity and specificity by adding other potential predictive risk factors to the decisional process and provide individual risk estimation of having a biopsy-detectable PCa<sup>8</sup>. Roobol and colleagues reported that 33% fewer biopsies could be done by using a risk calculator based on a lateralised sextant biopsy, applying the PSA cut-off of  $\geq 3$  ng/ml and a calculated probability cut-off of 12.5%, compared with using PSA alone<sup>2</sup>. Another model reduced the number of biopsies with 57% using a probability cut-off of 20% compared to the model including age and PSA.<sup>6</sup> The European Randomized study of Screening for Prostate Cancer (ERSPC) section Rotterdam has developed the ERSPC risk calculator, using multivariable logistic regression analysis. This risk calculator has 6 levels (based on 6 different logistic regression models) and is internet based ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com))<sup>2</sup>. In the second level only PSA is included. The third level of this risk calculator estimates the probability of having a positive sextant biopsy in unscreened men. Next to the PSA level the results of digital rectal examination (DRE) and transrectal ultrasound (TRUS), i.e. the presence of hypoechoic lesions and prostate volume, are included in the risk calculation<sup>9</sup>.

The aim of this study was to externally validate the ERSPC risk calculator (level 3) for assessing the probability of having a positive sextant prostate biopsy in previously unscreened men, using the data of the first screening rounds of the Finnish and Swedish section of the ERSPC. We assessed the performance of the risk calculator not only for calibration and discrimination, but also for its clinical usefulness<sup>10</sup>.

## PATIENTS AND METHODS

### Study population

The risk calculator has been developed in the Dutch section of the ERSPC and is based on the data of 3624 biopsied men, in the age of 55–75. All men were evaluated between 1993 and 2000. Biopsy indication was a serum PSA  $\geq 4$  ng/ml and/or a suspicious DRE or TRUS (1993–1996) and from 1997 only a serum PSA of  $\geq 3$  ng/ml<sup>9</sup>.

External validation was performed using the data of the Finnish and Swedish section of the ERSPC. The Finnish cohort consisted of 1922 men, aged 55–67 years, from Helsinki and Tampere screened for the first time in the period 1996–2003. For validation 1825 men with a PSA  $\geq 3$  ng/ml were included, excluding 56 (3%) men due to missing values. Biopsy indications were a serum PSA  $\geq 4$  ng/ml and a PSA of 3.0–3.9 ng/ml if there is a suspicious DRE (in the period 1996–1998) or if the proportion of free PSA is  $< 0.16$  (since 1999). The Swedish cohort consisted of 661 men from Goteborg screened for the first time in period 1995–1996, 612 men were biopsied for the first time. We excluded 81 men younger than 55 years ( $n = 78$ , 13%) and those with missing values ( $n = 3$ ,  $< 1\%$ ), leaving 531 men aged 55–67 years for analysis. Men with serum PSA  $\geq 3$  ng/ml underwent a DRE, TRUS and a prostate biopsy.

### Statistics

The differences between the characteristics of the three groups were assessed by using the Chi-square test for categorical variables and the analysis of variance and the Kruskal–Wallis tests for continuous variables. Multivariable logistic regression analysis was used to refit the model combining data of all three cohorts. We compared this model with the original model, and tested for differences in predictive effect by statistical interaction tests of the form ‘cohort\*predictor’. A significant interaction term means that the relationship between a predictor and outcome varies by cohort. Comparisons were made to models with PSA only and with PSA and DRE. These models were fitted on the data of the Dutch cohort and validated in the Swedish and Finnish cohorts. These comparisons were considered relevant since these models do not require data from an invasive test (TRUS). Statistical analyses were performed using SPSS software (version 17; SPSS, Inc., Chicago, Ill) and R (version 2.8.1; R foundation for Statistical Computing, Vienna, Austria). A p-value  $< 0.05$  was considered statistically significant.

### Calibration and discrimination

Calibration, discrimination, and clinical usefulness were assessed in the 3 cohorts for the level 3 of the ERSPC risk calculator.

Calibration refers to the agreement between observed and predicted outcomes. The extent of over- or underestimation relative to the observed and predicted rate was explored graphically using validation plots<sup>11</sup>. We assessed calibration-in-the-large by fitting a logistic regression model with the model predictions as an offset variable. The intercept indicates whether predictions are systematically too low or too high, and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The area under the Receiver Operating Characteristic (ROC) curve was used to assess the

ability of the model to discriminate between those with and without PCa. We compared the area under the curve (AUC) of the model in the different cohorts with the AUC of the model using only PSA (level 2 of the ERSPC risk calculator).

### **Clinical usefulness**

Clinical usefulness was assessed by using decision curve analyses<sup>12,13</sup>. These analyses estimate a 'net benefit' for prediction models by summing the benefits (true positives biopsies) and subtracting the harms (false-positives biopsies). The latter are weighted by a factor related to the relative harm of a missed cancer versus an unnecessary biopsy. The weighting is derived from the threshold probability of PCa at which a patient would opt for biopsy. This threshold can vary from patient to patient. We concentrated on the net benefit for threshold probabilities between 10% and 40%<sup>14</sup>. This implies a weight of 9:1 for the 10% threshold, and 3:2 for the 40% threshold for missing cancer versus unnecessary biopsy.

The reduction in number of biopsies using different P(posb) in combination with the PSA cut-off value of 3.0 ng/ml was further assessed and related to the number and percentage of insignificant PCa (Gleason  $\leq 6$ ) and significant PCa (Gleason  $> 6$  and/or metastasis). We specifically studied the previously suggested 12.5% threshold<sup>2</sup>, so that the risk of missing relevant PCa was limited. The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold probability should be chosen. We compared our level 3 model with the level 2 model, which includes only PSA to predict the presence of cancer at biopsy, and with the model that includes PSA and DRE. Reference strategies were biopsying all men and biopsying no men.

## RESULTS

### Study population

Except for the number of PCa diagnosis, the men in the three cohorts differed significantly in age, PSA levels, suspicious DRE, suspicious TRUS and prostate volume (Table 1).

**Table 1.** Characteristics of the participants

	Dutch cohort n=3624	Finnish cohort n=1825	Swedish cohort n=531	p-value
Age (years) (Average, sd, range)	65.5 (5.4, 55-75)	62.3 (4.3, 55-67)	61.2 (3.1, 55-67)	<0.001
PSA ng/ml median (25-75 percentile)	4.3 (3.1-6.4)	5.6 (4.5-7.8)	4.5 (3.5-6.6)	<0.001
Number suspicious DRE (%)	1284 (35)	389 (21)	99 (19)	<0.001
Number suspicious TRUS (%) (hypoechoogenic lesions)	1233 (34)	194 (11)	151 (28)	<0.001
Prostate volume (cc) median (25-75 percentile)	41 (32-55)	37 (28-48)	40 (30-51)	<0.001
Number prostate cancer detected on needle biopsy (%)	893 (25)	469 (26)	124 (23)	0.490

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

### Calibration and discrimination

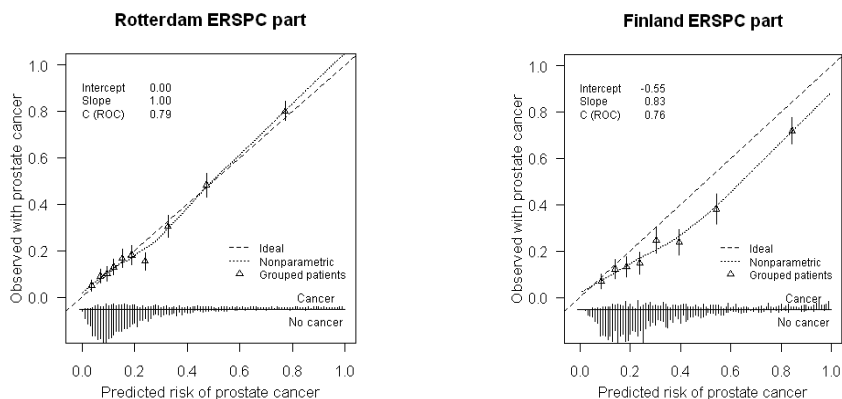
Calibration was perfect for the Dutch cohort (Figure 1), but the mean predicted outcome probability was higher than the fraction of observed outcomes for both validated cohorts (Finland: 34% versus 26% and Sweden: 29% versus 23%; both  $p < 0.001$ ) (Table 2). The effects of the predictor variables were somewhat weaker than expected in the validation cohorts, as reflected in calibration slopes of 0.83 and 0.78, respectively (Table 2). The effect of TRUS was smaller in the validation cohorts compared to the Dutch cohort ( $p < 0.001$ , Table 3)). The predictive effect of PSA was smaller in the Swedish cohort compared with the Dutch cohort ( $p < 0.001$ , Table 3). An updated version of the risk calculator is presented in the Appendix. For the updated version, the model intercept was such that calibration was on average good in the Finnish and Swedish cohort. For the model with PSA and DRE the predicted outcome was substantially higher than the fraction of observed outcomes for both validated cohorts (Finland: 49% versus 26% and Sweden: 45% versus 23%).

Discrimination was similar among the 3 cohorts (Table 2). The AUC was 0.76 and 0.78 in the validation cohorts and 0.79 in the Dutch cohort, but substantially lower for the model with PSA only (AUC 0.64, 0.68 and 0.69 respectively).

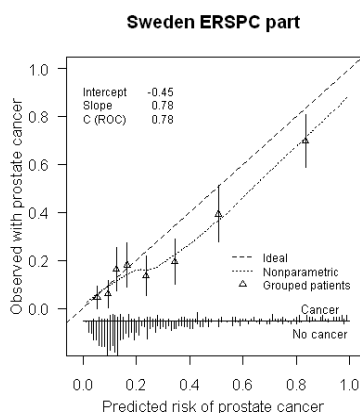


**A Development data (n=3624)**

**B Validation data (n=1825)**



**C Validation data (n=531)**



**Figure 1.** Validation plot A for the prediction of the model in the Dutch cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) (n=3624) and the validation plots B and C in the Finnish (n=1825) and Swedish cohort (n=531)

**Table 2.** Performance of the risk calculator predicting a positive prostate biopsy in the Dutch cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) and in the two validation cohorts (Finland and Sweden)

	Predicted outcome (%)	Observed outcome (%)	Calibration-in-the-Large (95% C.I.)	Calibration slope (95% C.I.)	AUC (95% C.I.)
Risk calculator: PSA, DRE, TRUS and prostate volume.					
Dutch cohort	25	25	0 (-0.09 - 0.09)	1.0 (0.93 - 1.09)	0.79 (0.77-0.81)
Finnish cohort	34	26	-0.55 (-0.67 - -0.42)	0.83 (0.73 - 0.93)	0.76 (0.74-0.79)
Swedish cohort	29	23	-0.45 (-0.69 - -0.21)	0.78 (0.61 - 0.95)	0.78 (0.73-0.83)

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

**Table 3.** Comparison of results of Logistic Regression analyses on data obtained from Dutch, Finnish, Swedish cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) and the data of all three cohorts

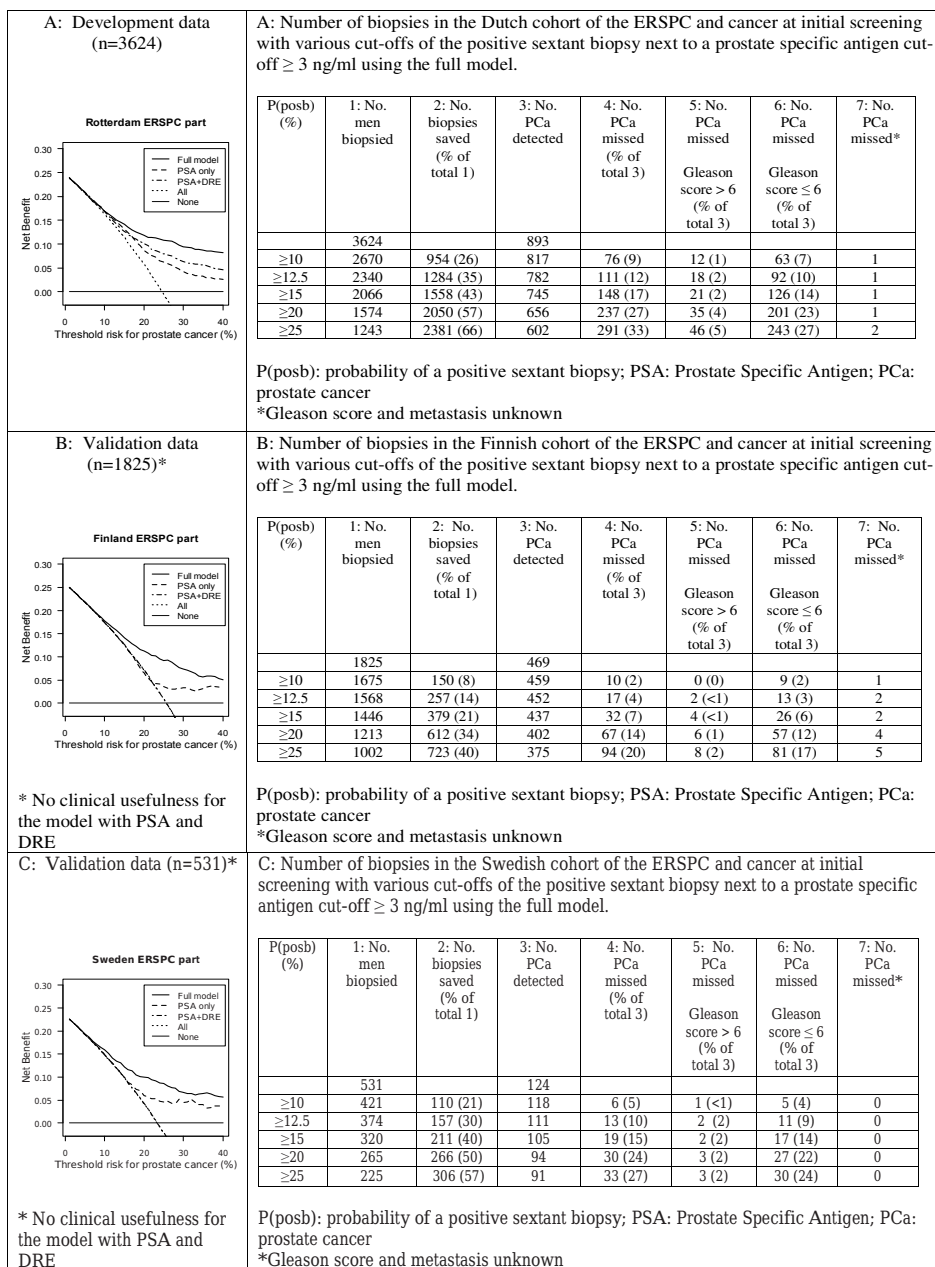
Variables	Dutch cohort n=3624		Finnish cohort n=1825		Swedish cohort n=531		All three cohorts n=5980		p-value for interaction*
	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	
LogPSA	3.76	42.80 (30.24-60.57)	2.57	13.07 (7.71-22.16)	2.68	14.63 (5.66-37.83)	3.36	28.77 (22.02-37.60)	<0.001
Logvolume	-4.21	0.02 (0.01-0.03)	-4.31	0.01 (0.01-0.03)	-4.14	0.02 (0.00-0.07)	-4.18	0.02 (0.01-0.02)	0.349
DRE	0.82	2.27 (1.88-2.73)	1.20	3.31 (2.51-4.37)	0.96	2.61 (1.48-4.59)	0.88	2.41 (2.08-2.78)	0.344
TRUS	0.87	2.38 (1.97-2.87)	0.02	1.02 (0.70-1.50)	0.34	1.40 (0.83-2.37)	0.63	1.87 (1.60-2.19)	<0.001
Finland							-0.40	0.67 (0.52-0.86)	
Sweden							-0.55	0.58 (0.49-0.68)	
Constant	2.55	12.84	3.13	22.85	2.78	16.07	2.84	17.06	

\*Significant p-value for interaction means that the relationship between the predictor and the outcome varies by cohort.

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

### Clinical usefulness

The net benefit, as shown on the y-axis, was highest for the risk calculator over the whole probability ranges in all cohorts, compared with the use of only PSA or biopsying all men or no men (Figure 2). For the model included PSA and DRE there was no net benefit in the Finnish and Swedish cohorts (Figure 2). A threshold of a calculated  $P(\text{posb}) \geq 12.5\%$  in addition to requiring  $\text{PSA} \geq 3 \text{ ng/ml}$ , would result in 35% ( $n = 1284$ ), 14% ( $n = 257$ ) and 30% ( $n = 157$ ) fewer biopsies in the Dutch, Finnish and Swedish cohort respectively (Figure 2). The price for this reduction would be that we miss 12% ( $n = 111$ ), 4% ( $n = 17$ ) and 10% ( $n = 13$ ) of the PCa respectively, with 2% ( $n = 18$ ), <1% ( $n = 2$ ) and 2% ( $n = 2$ ) with a Gleason score >6, all with no proven metastasis.



**Figure 2.** Decision curve A for the predicted probabilities in the Dutch cohort of the European Randomized study of Screening on Prostate Cancer (ERSPC) and the decision curves B and C in the Finnish and Swedish cohort of the ERSPC (validation cohorts) for the model, model with PSA and DRE, and for PSA alone. The table at each decision curve shows the number of biopsies in the different cohorts and cancers at initial screening with various probability cut-offs of a positive sextant biopsy next to a prostate-specific antigen ≥3 ng/ml  
PSA: Prostate-specific antigen; DRE: Digital rectal examination; PCa: Prostate cancer; P(posb): Probability on a positive sextant prostate biopsy

## DISCUSSION

In this study, we externally validated the ERSPC risk calculator to predict the probability of having a positive prostate biopsy in previously unscreened men in two independent screening cohorts. The model discriminated well between men with and without PCa with AUCs over 0.76. The model did overestimate the risk of a positive sextant lateralised P(posb) in the Finnish and Swedish cohorts. This may be caused by interobserver variation of pathologists of small atypical foci in prostate biopsies or adenocarcinoma, which might have led to less PCa diagnoses<sup>15,16</sup>. Furthermore, the effect of TRUS (positive for hypoechoic lesions) in these cohorts was smaller than in the Dutch cohort. This may be caused by interobserver variation of the TRUS outcome<sup>17</sup>. The performance of TRUS as a screening tool is relatively poor with only 3.5% of a biopsy of hypoechoic lesions being positive for PCa<sup>18</sup>. Furthermore, the effect of PSA was smaller in the Finnish and Swedish cohort than in the Dutch cohort, which can not readily be explained in the context of the well-controlled and standardised ERSPC study. In the Dutch cohort, the effect of PSA was greater under the 3.0 ng/ml than  $\geq 3$  ng/ml. However, if we refit the model for PSA  $\geq 3$  ng/ml, the predictive value of PSA decreased, but was still greater compared with the predictive value of PSA in the Finnish and Swedish cohort. Another reason for this risk overestimation may be caused by the effect of specific characteristics in the Finnish and Swedish cohorts which were not included in the model<sup>11</sup>.

Models predicting the probability of a positive sextant biopsy differ, because of the use of different predictors next to serum PSA, and the specifics of the studied cohorts<sup>4</sup>. External validation is therefore required for models before they can be applied in other settings. There are some other models for the prediction of PCa at initial biopsy using the sextant biopsy technique and developed in a screening setting<sup>6,19,20</sup>. The AUCs of these models were between 0.66 and 0.84<sup>6,19,20</sup>. The AUC of our risk calculator was over 0.76 in the relatively large cohorts considered for external validation. Moreover, the net benefit calculations as shown in decision curves indicated that the risk calculator was useful in taking biopsy decisions in previously unscreened men who wish to undergo PSA driven testing for PCa. Net benefit analysis gives a scientifically better founded judgement of the performance of a prediction model or nomogram than calibration and discrimination alone<sup>10,13,21</sup>. In our study, the net benefit was substantially higher for the risk calculator compared with only PSA in the model. In this net benefit calculation the burden of TRUS was not formally included. It would be difficult to determine the exact weight of the burden in balance to missing prostate cancer and unnecessary biopsy. There was no clinical usefulness with PSA and DRE in the model in the Finnish and Swedish cohort, which is explained by the substantial miscalibration of the model predictions. So, we can conclude that the optimal clinical result will be obtained by determining the indication for biopsy by use of the risk calculator, despite its problems in calibration. Another

method for validation of a model is comparison of the performance among models in different cohorts, which may be more straightforward to interpret<sup>22</sup>.

A limitation of the study is that the risk calculator relied on sextant biopsies. This procedure has been replaced by 8 to 18 core biopsies in current practice. Sextant biopsies may lead to missing PCa. Different studies have reported that when more than 6 cores are taken, for example 8 to 12 cores, this might increase the PCa detection rate in a clinical setting<sup>23-27</sup>. A possible drawback of these increased PCa detection is that not only significant PCa is detected, but also more insignificant PCa<sup>28</sup>. Schröder and colleagues concluded that most aggressive PCa which are initially missed, will be detected in a curable state with a lateralised sextant biopsy at rescreening after 4 years<sup>29</sup>. Some may however surface as interval cancers with less favourable outcomes. The question remains whether extended biopsy schemes are needed in a PCa screening setting with repeated screening. Further research is necessary to validate the risk calculator when more than 6 prostate biopsy cores are taken, and when a clinical setting is considered rather than a screening setting.

## CONCLUSIONS

In a screening setting the ERSPC risk calculator is useful to predict the probability of a positive lateralised sextant prostate biopsy and discriminates well between men with and without prostate cancer. The updated version of the ERSPC risk calculator predicts more accurately the probability in the Finnish and Swedish cohort. The risk calculator proved clinically most useful for decision thresholds between 10% and 40% compared with PSA alone or biopsied all men. Use of the risk calculator with thresholds between 10% and 25% substantially reduces doing unnecessary prostate biopsies with missing very few important prostate cancers. The risk calculator can hence support in decision making in a screening setting.

**Appendix.** Model updating

We refitted the model with the data of the three cohorts (n=5980; 4494 men without PCa and 1486 with PCa). The logistic regression formula of the refitted model for the probability of having a positive sextant prostate biopsy was  $P(\text{posb}) = 1 / (1 + \exp(-L))$ , with  $L = 2.837 + 3.359 \log\text{PSA} + -4.181 \log\text{volume} + 0.878 \text{DRE} + 0.627 \text{TRUS} + -0.403 \text{Finland} + -0.547 \text{Sweden}$

	B	S.E.	Wald	df	P-value	Exp(B)	95% C.I. for Exp(B)	
logPSA	3.359	0.136	605.742	1	<0.001	28.772	22.018	37.597
logvolume	-4.181	0.223	350.126	1	<0.001	0.015	0.010	0.024
DRE	0.878	0.075	138.583	1	<0.001	2.406	2.079	2.784
TRUS	0.627	0.079	62.389	1	<0.001	1.872	1.602	2.187
Cohortgroup			44.938	2	<0.001			
Cohortgroup (1: Finland)	-0.403	0.130	9.575	1	0.002	0.668	0.518	0.863
Cohortgroup (2: Sweden)	-0.547	0.084	42.157	1	<0.001	0.579	0.491	0.683
Constant	2.837	0.342	68.969	1	<0.001	17.059		

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound

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# Chapter 9

## Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators

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## ABSTRACT

**Background:** The European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculators (RCs) are validated tools for prostate cancer (PCa) risk assessment and include prostate volume (PV) data from transrectal ultrasound (TRUS).

**Objective:** Develop and validate an RC based on digital rectal examination (DRE) that circumvents the need for TRUS but still includes information on PV.

**Design, setting, and participants:** For development of the DRE-based RC, we studied the original ERSPC Rotterdam RC population including 3624 men (885 PCa cases) and 2896 men (547 PCa cases) detected at first and repeat screening 4 yr later, respectively. A validation cohort consisted of 322 men, screened in 2010–2011 as participants in ERSPC Rotterdam.

**Measurements:** Data on TRUS-assessed PV in the development cohorts were re-coded into three categories (25, 40, and 60 cm<sup>3</sup>) to assess the loss of information by categorization of volume information. New RCs including PSA, DRE, and PV categories (DRE-based RC) were developed for men with and without a previous negative biopsy to predict overall and clinically significant PCa (high-grade (HG) PCa) defined as T stage >T2b and/or Gleason score  $\geq 7$ . Predictive accuracy was quantified by the area under the receiver operating curve. We compared performance with the Prostate Cancer Prevention Trial (PCPT) RC in the validation study.

**Results and limitations:** Areas under the curve (AUC) of prostate-specific antigen (PSA) alone, PSA and DRE, the DRE-based RC, and the original ERSPC RC to predict PCa at initial biopsy were 0.69, 0.73, 0.77, and 0.79, respectively. The corresponding AUCs for predicting HG PCa were higher (0.74, 0.82, 0.85, and 0.86). Similar results were seen in men previously biopsied and in the validation cohort. The DRE-based RC outperformed the PCPT RC (AUC 0.69 vs 0.59;  $p = 0.0001$ ) and a model based on PSA and DRE only (AUC 0.69 vs 0.63;  $p = 0.0075$ ) in the relatively small validation cohort. Further validation is required.

**Conclusions:** An RC should contain volume estimates based either on TRUS or DRE. Replacing TRUS measurements by DRE estimates may enhance implementation in the daily practice of urologists and general practitioners.

## INTRODUCTION

It is widely recognized that too many men undergo prostate biopsy if prostate-specific antigen (PSA) alone is used for screening. Multivariable risk calculators (RCs) are essential tools for improved risk stratification. The goal is to identify men at increased risk of having a potentially life-threatening prostate cancer (PCa) as candidates for biopsy<sup>1</sup>. Based on data from the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam, a multistep PCa RC was developed ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com))<sup>2,3</sup>. The RC is meant as a decision aid for laypeople, general practitioners, and urologists that provides estimates of current risk on having a biopsy-detectable PCa based on age, family history, and urinary complaints (calculator 1), PSA level (calculator 2), and PSA in combination with digital rectal examination (DRE), transrectal ultrasound (TRUS), prostate volume (PV), and previous biopsy status (calculators 3–5). RC 6 calculates the probability of having a potentially indolent PCa and can be used to aid treatment choice.

The ERSPC RCs 3–5 require information from TRUS, including PV and the presence of hypoechoic lesions. Because the PSA level is related to PV<sup>4,5</sup>, it is reasonable to include PV in PCa prediction models. However, including parameters that require invasive procedures could limit the clinical application of the RC. DRE<sup>6,7</sup> has a reasonable ability to discriminate correctly between TRUS-assessed PV  $\pm 40$  cm<sup>3</sup> and performs well for volumes  $>50$  cm<sup>3</sup>. We aimed to develop and validate a DRE-based RC that includes information on PV but avoids the need for TRUS before biopsy.

## MATERIALS AND METHODS

ERSPC Rotterdam recruited 42 176 men (aged 55–74 yr) randomized into intervention and control arms. Of the 21 210 men randomized to the intervention arm, 19 970 were actually screened. Rescreening was scheduled every 4 yr. Details on biopsy indication are described elsewhere<sup>8</sup>. Men with a biopsy indication first underwent DRE followed by biplanar TRUS using a Bruel and Kjaer model 1846 mainframe and a 7-MHz biplanar endorectal transducer (B&K Medical Systems, Marlborough, MA, USA) in the left lateral decubitus position. The TRUS-PV was measured by planimetry by 0.5-cm step sections. Lateralized sextant biopsy was performed with an additional core for hypoechoic lesions on TRUS.

The development cohort of the ERSPC RC 3 (suitable for men not previously screened/biopsied) consisted of 3624 men who had a lateralized sextant biopsy at the first screening round of ERSPC Rotterdam. A total of 885 PCa cases were detected (24.5%)<sup>2</sup> (Table 1).

The development cohort of ERSPC RCs 4 and 5 (suitable for men previously screened (RC 4) or men with a previous negative biopsy (RC 5) consisted of 2896 men who had a

lateralized sextant biopsy at repeat screening 4 yr later, of whom 987 men (34.1%) were already biopsied at the first screening. A total of 547 PCa cases (18.9%) were detected (Table 1). Similar to RC 3, the model underlying RCs 4 and 5 includes information on PSA, PV (2-log transformed and centered), and outcome of DRE (1 if abnormal, ie, nodularity and/or induration; 0 if normal) and TRUS (1 if abnormal, ie, hypoechoic lesion; 0 if normal), as well as data on previous negative biopsy and an interaction term for previous negative biopsy and PSA.

For the development of the DRE-based RCs, data on TRUS-PV were reclassified in three categories that may be estimated during DRE: TRUS-PV  $<30\text{ cm}^3$  was coded as  $25\text{ cm}^3$ , TRUS-PV  $\geq 30\text{ cm}^3$  but  $<50\text{ cm}^3$  was coded as  $40\text{ cm}^3$ , and TRUS-PV  $\geq 50.0\text{ cm}^3$  was coded as  $60\text{ cm}^3$ . RCs were also developed to predict clinical significant PCa (high-grade (HG) PCa) defined as Gleason score  $\geq 7$  and/or T stage  $>T2b$ . Predictors entered into the model were DRE, PSA, and the three volume classes (the two latter both 2-log transformed and centered). For men previously tested or biopsied in line with the original RCs, data on previous negative biopsy and the interaction term for PSA were added.

Mean and median PSA values were calculated by PV category. New RCs predicting both the presence of PC and HG PCa in men screened for the first and second time were developed using regression coefficients from conditional logistic regression analyses. Validation was done using data from repeat screening rounds of ERSPC Rotterdam (January–July 2011) where urologists in training estimated and recorded the PV during DRE (ie, 25, 40, or  $60\text{ cm}^3$ ) before performing the TRUS volume measurement and the TRUS-guided prostate biopsy. Comparisons between DRE and TRUS-PV estimates were visualized using box-plot analysis. To assess the performance of a model including DRE-assessed PV and volume classes derived from TRUS-assessed PV, we performed two multivariable logistic regression analyses.

Predictive accuracy was quantified using the area under the curve (AUC) of the receiver operator characteristic (ROC) analysis<sup>9</sup>. We compared the AUCs of newly developed models with a model based on PSA alone, PSA in combination with DRE outcome, and the original ERSPC RCs (including TRUS-related data) using the method of DeLong et al.<sup>10</sup>.

The models were also compared with the Prostate Cancer Prevention Trial RC<sup>11</sup>, which does not include information on PV. SPSS 17.0 and Stata v.11.0 were used for analyses.

## RESULTS

Among the 885 PCa cases detected at first screening, 431 (48.7%) were classified as HG PCa using our criteria. At repeat screening, 131 (23.9%) of the 547 PCa cases were classified as HG PCa (Table 1).

PSA and DRE were both positively correlated with the presence of PCa and HG PCa. A large PV and a previous negative biopsy reduced the likelihood of a biopsy-detectable (HG) PCa (Table 2). An abnormal DRE at the initial screening was highly predictive for HG PCa (odds ratio: 6.1), a direct consequence of the definition applied because 117 of the total of 431 HG PC cases were labeled as such purely on the basis of a clinical stage >T2b (ie, Gleason score <7).

**Table 1.** Demographics of the development cohorts of risk calculator (RC) 3\* and RCs 4 and 5\*\*

	Cohort for RC 3 n=3616			Cohort for RCs 4 and 5 n=2896		
	Mean	Median	Range	Mean	Median	Range
PSA, ng/ml	6.1	4.3	0.1-316	4.8	3.8	1.0-57.0
Prostate volume, cm <sup>3</sup>	46.2	41.0	4.7-239	49.0	45.1	7.5-201
Age, yr	65.5	65.8	54.7-75.5	66.9	66.9	58.6-75.3
PSA in volume class 25 cm <sup>3</sup>	4.1	3.1	0.1-67.0	3.6	3.0	1.0-24.3
PSA in volume class 40 cm <sup>3</sup>	5.5	4.1	0.1-304	4.2	3.5	1.0-46.7
PSA in volume class 60 cm <sup>3</sup>	8.2	5.5	0.7-316	5.9	4.7	1.0-57.0
	n (%)			n (%)		
DRE abnormal	1280 (35.4)			565 (19.5)		
TRUS abnormal	1229 (34.0)			455 (15.7)		
PCa detected	885 (24.5)			547 (18.9)		
	n (% of total PCa detected: 885)			n (% of total PCA detected: 547)		
T stage >T2b	274 (30.9)			36 (6.6)		
Gleason score ≥7	313 (35.4)			115 (21.0)		
HG PCa	431 (48.7)			131 (23.9)		

\*Men screened at the initial screening round of European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam.

\*\*Men screened at the repeat screening round (4 yr later) of ERSPC Rotterdam

PSA: Prostate-specific antigen; DRE: Digital rectal examination; TRUS: Transrectal ultrasound; PCa: Prostate cancer; HG: High grade.

**Table 2.** Outcome of logistic regression analyses of four different models in men screened for the first and second time

Predictor	Initial screening (DRE-based RC 3)		Repeat screening (DRE-based RCs 4 and 5)	
	Odds ratio	95% CI	Odds ratio	95% CI
Predicting PCa				
2-log centered PSA	2.78	2.53-3.07	1.78	1.48-2.13
DRE (1/0)*	2.70	2.26-3.22	1.97	1.58-2.47
2-log centered volume classes	0.22	0.18-0.28	0.35	0.28-0.45
Previous negative biopsy (1/0)**	NA	-	0.51	0.39-0.67
Previous negative biopsy	NA	-	0.66	0.49-0.88
Constant	0.16	-	0.23	-
Predicting HG PCa				
2-log centered PSA	3.24	2.90-3.67	2.93	2.18-3.94
DRE (1/0)*	6.13	4.79-7.84	3.71	2.55-5.40
2-log centered volume classes	0.22	0.16-0.29	0.22	0.14-0.35
Previous negative biopsy (1/1)**	NA	-	0.32	0.17-0.61
Previous negative biopsy	NA	-	0.65	0.38-1.10
Constant	0.03	-	0.03	-

PCa: Prostate cancer; DRE: Digital rectal examination; NA: Not applicable; RC: Risk calculator; CI: Confidence interval; PSA: Prostate-specific antigen; HG: High grade.

\*1 is abnormal; 0 is normal

\*\* 1= yes, 0=no

Table 3 and Figure 1 show the AUC of the models based on PSA alone, PSA and DRE outcome, the DRE-based RC, and the original RC. Compared with a model solely on the basis of the PSA value, adding the outcome of the DRE to the prediction model increases discrimination significantly, which is further increased by adding information on PV. Using DRE-based information on PV reduces discrimination as compared with TRUS-based data but outperforms predictions based solely on PSA and DRE.

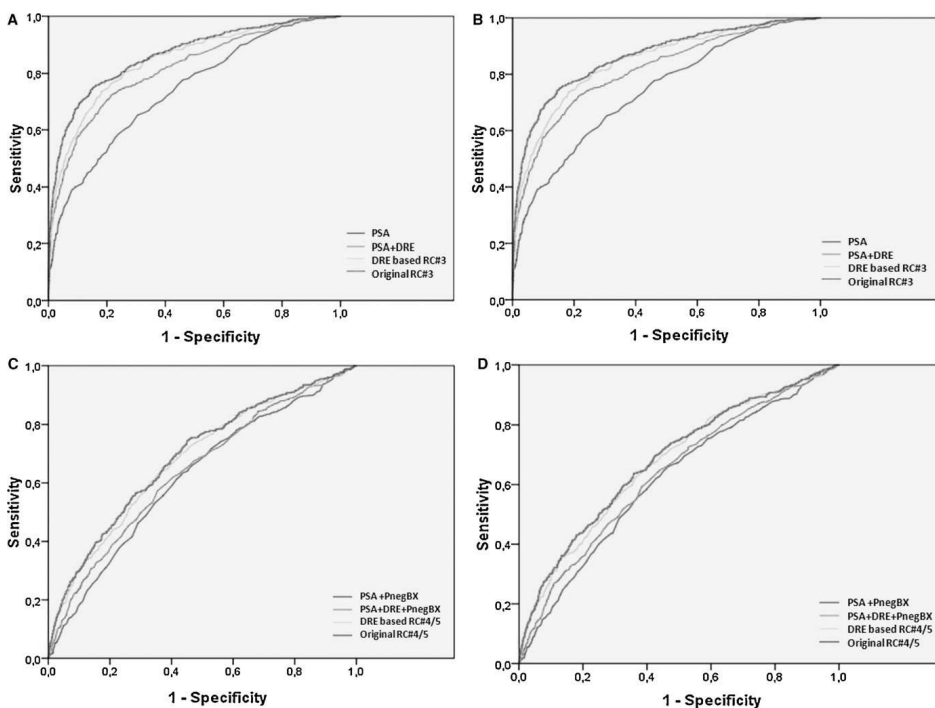
From January 2010 to September 2011, a total of 1660 men were screened for the fourth or fifth time. Of these men, 369 (22.2%) were eligible for biopsy (PSA  $\geq 3.0$ ), and 322 were actually biopsied (85.8%) with complete data on PSA, DRE outcome, and DRE-estimated PV. Mean age was 71.6 yr (66.4–75.6 yr), and PSA levels ranged from 0.7 to 32.0 ng/ml (mean: 5.0 ng/ml). A total of 76 PCa cases were detected (24 HG PCa, based on a Gleason score  $\geq 7$ , except for two cases with clinical stage  $>T2b$  detected). Of the 322 men, 137 were not previously biopsied (43 PCa detected with 17 HG PCa). Because all men in this population were previously screened, only the newly developed DRE-based RCs 4 and 5 were validated.

**Table 3.** Areas under the curve of the calculated probabilities of four different models predicting the presence of prostate cancer or high-grade prostate cancer at both initial and repeat screening

Model	Initial screening			Repeat screening*		
	AUC	95% CI	p-value	AUC	95% CI	p-value
<b>Predicting PCa</b>						
1. PSA alone	0.69	0.67-0.71	-	0.62	0.59-0.65	-
2. PSA plus DRE	0.73	0.71-0.75	Model 1 vs 2 <0.0001	0.64	0.61-0.67	Model 1 vs 2 =0.053
3. DRE-based RC	0.77	0.75-0.79	Model 2 vs 3 <0.0001	0.69	0.66-0.71	Model 2 vs 3 <0.0001
4. Original RC	0.79	0.77-0.81	Model 3 vs 4 <0.0001	0.68	0.65-0.71	Model 3 vs 4 =0.0519
<b>Predicting HG PCa</b>						
1. PSA alone	0.74	0.72-0.77	-	0.72	0.67-0.76	-
2. PSA plus DRE	0.82	0.79-0.84	Model 1 vs 2 <0.0001	0.76	0.71-0.80	Model 1 vs 2 =0.0060
3. DRE-based RC	0.85	0.82-0.87	Model 2 vs 3 =0.0001	0.81	0.78-0.85	Model 2 vs 3 =0.0015
4. Original RC	0.86	0.84-0.88	Model 3 vs 4 =0.0003	0.80	0.77-0.84	Model 3 vs 4 =0.1687

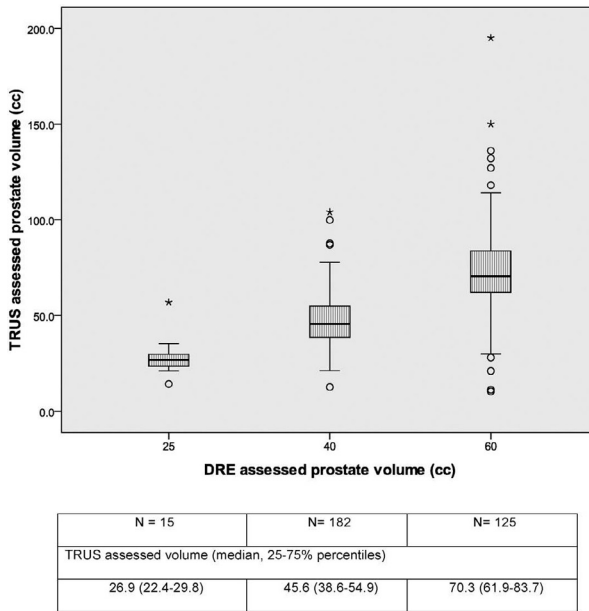
PCa: Prostate cancer; AUC: Area under the curve; CI: Confidence interval; PSA: Prostate-specific antigen; DRE: Digital rectal examination; RC: Risk calculator; HG: High grade.

\*At repeat screening all models included previous biopsy status



**Figure 1.** Areas under the curve of four different models predicting the presence of a biopsy-detectable prostate cancer (PCa) in (A) previously unscreened men, (B) a biopsy-detectable high-grade (HG) PCa in previously unscreened men, (C) the presence of a biopsy-detectable PCa in previously screened/ biopsied men, and (D) the presence of a biopsy-detectable HG PCa in previously screened/biopsied men. BX: Biopsy; DRE: Digital rectal examination; PNBx: Previous negative biopsy; PSA: Prostate-specific antigen; RC: Risk calculator.

Figure 2 shows the box plots of TRUS-PV versus DRE volume classes. Volume estimation by DRE seems to underestimate the TRUS-PV, although median values (26.9 cm<sup>3</sup>, 45.6 cm<sup>3</sup>, and 70.3 cm<sup>3</sup>) are close to the three predefined volume classes of 25 cm<sup>3</sup>, 40 cm<sup>3</sup>, and 60 cm<sup>3</sup>, respectively. Logistic regression analyses comparing the effect of using a DRE-based PV or volume classes derived from TRUS-assessed PV performed equally well with AUCs of 0.71 and 0.70, respectively.



**Figure 2.** Box plots of prostate volume assessed by transrectal ultrasound (TRUS) per digital rectal examination (DRE)-assessed prostate volume class

Results of applying both the original RCs 4 and 5 and the DRE-based RCs 4 and 5 as well as models based on PSA alone, PSA and DRE, and the Prostate Cancer Prevention Trial (PCPT) RC are shown in Table 4 and Figure 3. Models that include information on PV increase predictive accuracy considerably, and the DRE-based RC still outperforms the PCPT RC (AUC 0.69 vs 0.59; p = 0.0001) and the model based on PSA and DRE outcome (AUC 0.69 vs 0.63; p = 0.0075).

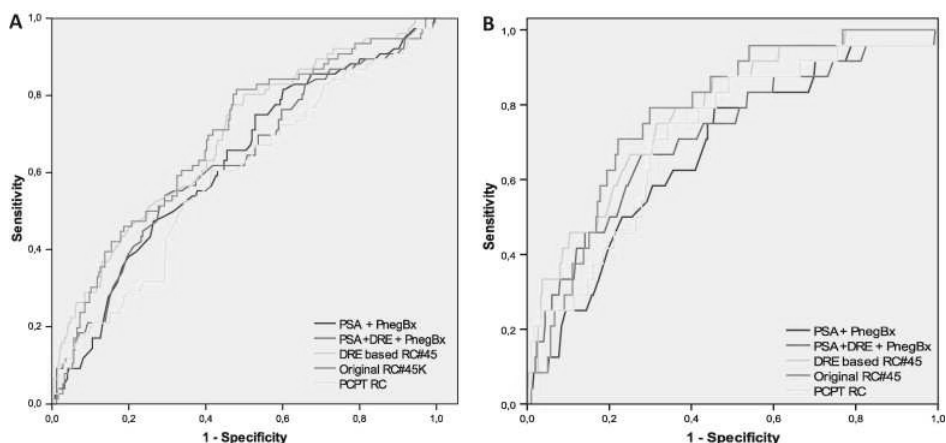


**Table 4.** Areas under the curve of the calculated probabilities of newly developed risk calculators 4 and 5 based on digital rectal examination\*

Model	Predicting the presence of PCa			Predicting the presence of HG PCa		
	AUC	95% CI	p-value	AUC	95% CI	p-value
1. PSA plus PNBx	0.62	0.55-0.70	-	0.68	0.57-0.78	-
2. PSA plus DRE PNBx	0.63	0.55-0.70	Model 1 vs 2 0.8590	0.72	0.60-0.83	Model 1 vs 2 0.2583
3. DRE-based RC	0.69	0.62-0.76	Model 2 vs 3 0.0075	0.78	0.69-0.87	Model 2 vs 3 0.0278
4. Original RC	0.70	0.63-0.76	Model 3 vs 4 0.6923	0.79	0.71-0.87	Model 3 vs 4 0.7281
5. PCPT RC	0.59	0.52-0.66	Model 3 vs 5 0.0001	0.72	0.61-0.82	Model 3 vs 5 0.0033

PCa: Prostate cancer; HG: high grade; AUC: area under the curve; CI: confidence interval; PSA: prostate-specific antigen; PNBx: Previous negative biopsy; DRE: Digital rectal examination; RC: Risk calculator; PCPT: Prostate Cancer Prevention Trial.

\*In the validation cohort consisting of 332 men biopsied at repeat screening; 137 of these men were not previously biopsied



**Figure 3.** Area under the curve (AUCs) of applying five different models on the validation set of 322 previously screened/biopsied men; (B) AUCs of models predicting the presence of a biopsy-detectable high-grade PCa in previously screened/biopsied men.

Bx: Prostate biopsy; DRE: Digital rectal examination; PCPT: Prostate Cancer Prevention Trial; PNBx: Previous negative biopsy; PSA: Prostate-specific antigen; RC: Risk calculator

## DISCUSSION

Multivariable tools have increasingly been developed and validated for use in the primary screening setting. As described earlier, our group previously developed several RCs to aid in the decision for biopsy or to predict indolent disease to help guide management<sup>2,3</sup> ([www.prostatecancer-riskcalculator.com](http://www.prostatecancer-riskcalculator.com)). These RCs have been validated in external populations and shown to have superior discrimination for the prediction of PCa as compared with the PCPT RC, which does not include PV<sup>12,13</sup>. Indeed, there is now a substantial body of evidence indicating the importance of PV and related parameters in risk assessment<sup>14</sup>.

Although DRE-estimated volume categories are a rather rough approximation for PV and prior studies have shown they are less accurate than TRUS estimates when compared with the actual weight of the radical prostatectomy specimen<sup>15</sup>, we nevertheless found that the use of DRE-estimated volume categories in the RCs did increase predictive accuracy compared with models based on PSA and DRE. The DRE-based RC still outperformed the PCPT RC on ROC analysis in the validation cohort. The inclusion of data from TRUS represents a practical limitation of the original ERSPC RCs 3–5 because TRUS is often not performed until the time of biopsy and is not done by general practitioners. The development of these new RCs including information on PV without the need for TRUS has therefore significant clinical ramifications. Their applicability in daily urologic practice is enhanced and potentially expanded to general practitioners while predictive accuracy outperforms the commonly used approach (ie, on the basis of PSA value and/or DRE outcome).

Numerous studies have shown that PSA and PV (PSA density (PSAD)) are associated with the risk of PCa on biopsy. For example, in 330 consecutive men undergoing prostate biopsy, Ghafoori et al. reported a significantly greater AUC for PSAD (0.81) compared with total PSA (0.74) for PCa detection ( $p < 0.001$ )<sup>16</sup>. With regard to disease aggressiveness, prior studies demonstrated a significant inverse relationship between PV with the presence of high-grade, non-organ-confined disease and progression<sup>17</sup>. In a landmark study from 1994, Epstein et al. reported that the best models to predict insignificant PCa at radical prostatectomy for T1c disease were a PSAD  $< 0.1$  ng/ml per gram with no adverse pathologic features or a PSAD from 0.1 to 0.15 ng/ml per gram with low-volume disease on biopsy<sup>18</sup>. This led to the inclusion of PSAD  $\leq 0.15$  among the selection criteria for contemporary active surveillance programs. In another recent study from the Johns Hopkins active surveillance program, Ko et al. reported that despite substantial intraobserver variability in TRUS volume estimation (average coefficient of variation: 0.168), in 95% of cases this did not have a sufficient enough impact on the PSAD calculation to trigger a change in clinical management<sup>19</sup>.

This study has some major limitations. The sample size of our validation cohort was small, implying that our results need to be confirmed in a larger external validation cohort before any clinical recommendations can be given with respect to replacing PV measurement by DRE instead of TRUS. It must also be noted that the validation experiment is not a true validation because data on DRE-assessed PV were not available in the development cohort but rather were mathematically derived. PV assessments in this study were performed by urologist trainees. Prior studies suggested an improved correlation between DRE and TRUS volume estimates by a trained urologist compared with junior trainees, which may affect the results<sup>20</sup>. Conversely, this might be viewed as a strength in that the predictive capability of the model was preserved.

In addition, sextant biopsies were used in our study. Numerous studies have shown a lower risk of upgrading and improved staging with a greater number of biopsy cores<sup>21,22</sup>. For this reason, we expanded our criteria for HG PCa to include clinical stage >T2b in addition to Gleason score in an attempt to avoid misclassification of aggressive PCa due to undersampling on the biopsy. Radical prostatectomy outcome showed that in men with a screen-detected clinically staged T2a/2b PCa and a biopsy Gleason score <7, the percentage of extracapsular extension (ie,  $\geq$ pT3) was approximately 15%, whereas in men with a clinically staged T2c PCa and a biopsy Gleason score <7, this percentage was 26% (ERSPC Rotterdam data not shown). Although our RC was developed in the setting of sextant biopsies, it has since been validated in multiple populations using more extended biopsy schemes, suggesting that this feature does not limit its applicability to contemporary cohorts<sup>12,13</sup>.

A final limitation of our study population is the nature and modest sample size of our validation cohort that resulted in an inability to validate the DRE-based RC for men not previously screened/biopsied and a sufficient number of HG PCa to reliably assess the performance of the DRE-based RC to predict the presence of HG PCa. Validation of the novel DRE-based RCs will be necessary in larger clinically based cohorts.

## CONCLUSIONS

Risk assessment on the basis of PSA alone is not optimal. It can be improved by adding the outcome of DRE. Additional improvement can easily be obtained, however, by adding information on PV. Realizing that invasive procedures before risk assessment are suboptimal, we developed a DRE-based prediction tool that still contains information on PV and therefore is not only more accurate in risk prediction but also easily implemented into daily urologic practice and therefore also suitable to be used by general practitioners

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# Part 5

## **Selecting men for active surveillance using a prostate cancer risk calculator and disease insight and treatment perception of men on active surveillance**

Chapter 10

Selecting men diagnosed with prostate cancer for active surveillance using a risk calculator: a prospective impact study

*BJUI 2012*

Chapter 11

Disease insight and treatment perception of men on active surveillance for early prostate cancer

*BJUI 2010*





# Chapter 10

## Selecting men diagnosed with prostate cancer for active surveillance using a risk calculator: a prospective impact study

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## ABSTRACT

**Objectives:** To assess urologists' and patients' compliance with treatment recommendations based on a prostate cancer risk calculator (RC) and the reasons for non-compliance.

To assess the difference between patients who were compliant and non-compliant with recommendations based on this RC.

**Patients and Methods:** Eight urologists from five Dutch hospitals included 240 patients with prostate cancer (PCa), aged 55-75 years, from December 2008 to February 2011.

The urologists used the European Randomized study of Screening for Prostate Cancer RC which predicts the probability of potentially indolent PCa (P(indolent)), using serum prostate-specific antigen (PSA), prostate volume and pathological findings on biopsy.

Inclusion criteria were PSA <20 ng/mL, clinical stage T1 or T2a-c disease, <50% positive sextant biopsy cores, ≤20 mm cancer tissue, ≥40 mm benign tissue and Gleason ≤3 + 3. If the P(indolent) was >70%, active surveillance (AS) was recommended, and active treatment (AT) otherwise.

After the treatment decision, patients completed a questionnaire about their treatment choice, related (dis)advantages, and validated measurements of other factors, e.g. anxiety.

**Results:** Most patients (45/55, 82%) were compliant with an AS recommendation. Another 54 chose AS despite an AT recommendation (54/185, 29%).

The most common reason for noncompliance with AT recommendations by urologists was the patient's preference for AS (n = 30). These patients most often reported the delay of physical side effects of AT as the main advantage (n = 19).

Those who complied with AT recommendations had higher mean PSA levels (8 vs 7 ng/mL, p = 0.02), higher mean amount of cancer tissue (7 vs 3 mm, p <0.001), lower mean P(indolent) (36% vs 55%, p <0.001), and higher mean generic anxiety scores (42 vs 38, p = 0.03) than those who did not comply.

**Conclusions:** AS recommendations were followed by most patients, while 29% with AT recommendations chose AS instead.

Although further research is needed to validate the RC threshold, the current version is already useful in treatment decision-making in men with localized PCa.

## INTRODUCTION

The incidence of potentially indolent prostate cancer (PCa) has risen the last two decades, mainly as a result of PSA screening<sup>1,2</sup>. Autopsy studies show a high prevalence of these small, localized, well-differentiated tumours in men dying from other causes<sup>3</sup>. Many of these cancers will remain non-harmful during a man's lifetime<sup>4,5</sup>. To avoid over-treatment they could be closely monitored with the aim of switching to active treatment (AT) with curative intent if progression occurs<sup>5</sup>. Prospective analyses of men undergoing such an active surveillance (AS) strategy show favourable 10-year PCa-specific survival rates approaching 98%<sup>4,6</sup>. Crucial for a successful AS strategy is the reliable identification of indolent PCa; however, a key problem is that it is difficult to differentiate between men with aggressive localized PCa and indolent PCa. Prediction models have been developed to support the identification of indolent PCa,<sup>7,8</sup> but the use of these models in urological practice is not standard.

We implemented levels three and six of the six levels of the risk calculator (RC) based on data from the European Randomized study of Screening for Prostate Cancer (ERSPC) in five Dutch hospitals (<http://www.prostatecancer-riskcalculator.com>). Level three calculates the probability of a positive biopsy using serum PSA, outcomes of DRE and TRUS, and TRUS-assessed prostate volume. Level six calculates the probability of a potentially indolent PCa (P(indolent)) using serum PSA level, prostate volume, mm cancer tissue, mm benign tissue, and the Gleason score at biopsy. The present study addresses level six. As a rule for treatment decision-making we decided that AS would be recommended if P(indolent) was >70%, and AT would be recommended otherwise. This 70% threshold was based on a study where an existing clinical RC was validated and adapted towards a screening setting, resulting in a 94% sensitivity (actively treating important PCa) and a 32% specificity (applying AS to potentially indolent PCa)<sup>7,8</sup>. The RC performed well in a mixed screening/clinical cohort with an area under the curve of 0.77<sup>9</sup>.

The aim of the present study was to assess: (i) urologists' and patients' compliance with treatment recommendations by the ERSPC RC level six; (ii) the reasons for non-compliance; and (iii) the difference between patients who were compliant and non-compliant with AS and AT recommendations based on a RC.

## PATIENTS AND METHODS

### Study population

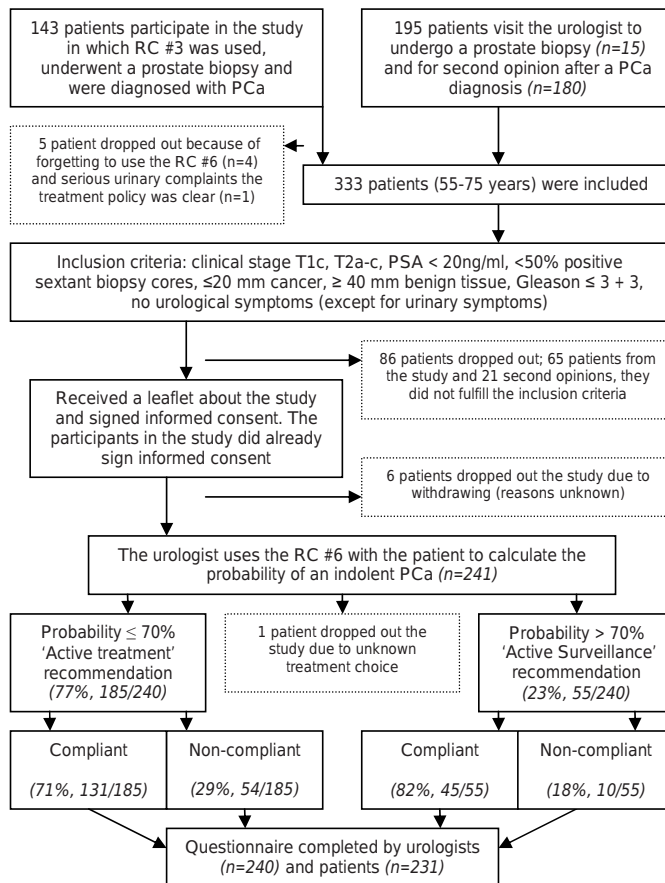
Eight urologists from five Dutch hospitals studied patients, aged 55–75 years, from December 2008 to February 2011. Before the start of the implementation project urologists

and nurses were informed about the aim, use and interpretation of the outcome of the RCs. The nurses' role was the promotion of the use of the RC and collecting data.

Patients needed to fulfill the following criteria; biopsy-confirmed PCa, PSA level <20 ng/ml, clinical stage ≤ T2c disease, <50% positive sextant biopsy cores, ≤20 mm cancer tissue, ≥40 mm benign tissue and Gleason score ≤3 + 3. These patients did not participate in a screening trial. All patients provided written informed consent. The study was approved by the Institutional Review Board of the Erasmus Medical Centre, Rotterdam.

### Study procedure

Urologists calculated P(indolent) using the RC level six and used this outcome in their treatment advice to their patients (Figure 1)<sup>8</sup>. The RC was based on sextant biopsy outcomes. When more than six biopsy cores were taken, mm cancer tissue and mm benign tissue were calculated pro rata<sup>10</sup>.



**Figure 1.** Flow chart of the study  
 RC: Risk calculator; PCa: Prostate cancer; PSA: Prostate-specific antigen

## Questionnaires

After the treatment decision was made, both urologists and patients received a questionnaire. Urologists were asked to indicate their own and patient's compliance with the recommendation by the RC and, if applicable, reasons for non-compliance. PSA level and the other necessary data for the use of the RC, the P(indolent) and the patient's final treatment choice were also recorded.

Patients were asked to indicate advantages and disadvantages of their treatment choice using open-ended items, with space for three possible responses. These were grouped and counted independently by the author (H.A.v.V.) and co-researcher (L.V.). Disagreements were resolved in consensus.

The questionnaire contained validated Dutch translations of the 12-item Short Form health survey (SF-12) to measure general health-related quality of life, the State Trait Anxiety Inventory (STAI-6) to measure generic anxiety, the Memorial Anxiety Scale for Prostate Cancer (MAX-PC), the Decisional Conflict Scale (DCS), the Center of Epidemiologic Studies Depression scale (CES-D) and the Eysenck Personality Questionnaire (EPQ)<sup>11-16</sup>. Details of the SF-12, STAI-6 and DCS scores, the attitude scale and PCa knowledge (15 items) have been described previously<sup>17,18</sup>.

The MAX-PC measures PCa-specific anxiety<sup>13</sup>. Two subscales were used; the PCa anxiety scale and the fear of recurrence scale, 50% of the total score (range 0–35) of both scales identifies patients who have clinically significant PCa anxiety<sup>19</sup>.

Depression was assessed using the CES-D, which consists of 20 items with four response options each. Total scores range from 0 to 60. Scores of  $\geq 16$  define patients as clinically depressive<sup>20</sup>.

Personality was assessed using the EPQ, which consists of 48 items with two response options each<sup>21</sup>. The EPQ consists of four personality scales; psychoticism, extraversion, neuroticism and social desirability (of questionnaire response). Scale scores range from 0 to 12.

The involvement of the urologist in the decision-making process was assessed by the question 'Who had the most influence in the treatment choice, you or your urologist?', with five response options 'you' (1), 'you/both' (2), 'both' (3), 'both/urologist' (4), and urologist (5). We recoded these options in three decision categories: patient-based (option 1 or 2), shared (option 3) and urologist-based decision (option 4 or 5). The involvement of the environment (i.e. family, friends) was assessed through a similar question.

## Statistics

We assessed the differences between those who complied and those who did not comply with treatment recommendations using the Chi-square test for categorical variables and Mann-Whitney U-test for continuous variables. We used multivariable logistic regression analyses (forward likelihood ratio) to assess the influence of P(indolent), the urologist, and levels of generic anxiety on patients' compliance with AT or AS recom-

mendations. Furthermore, we assessed the number of patients who discontinued AS and their reasons.

Analyses were performed using SPSS (version 17.0, SPSS Inc., Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

## RESULTS

### Characteristics of the study population

A total of 240 patients with a mean (sd) age of 64 (5) years were included. Study population characteristics are shown in Table 1. Based on the outcome of the RC, AT

**Table 1.** Characteristics and clinical characteristics of the patient population, stratified by treatment recommendation based on the outcome of the risk calculator

	Recommendation: AT*		p-value	Recommendation: AS **		Total n=240
	Compliant n=131	Non-compliant n=54		Compliant n=45	Non-compliant n=10	
Age (years) mean (SD, range)	64 (5, 55-75)	65 (5, 55-75)	0.25	66 (5, 55-75)	61 (3, 56-64)	64 (5, 55-75)
Marital status (%)						
Married or cohabiting	101 (81)	45 (85)	0.58	38 (86)	9 (90)	193 (84)
Single	23 (19)	8 (15)		6 (14)	1 (10)	38 (16)
Education level (%)						
Low	24 (20)	10 (20)	0.08	10 (23)	1 (10)	45 (20)
Intermediate	57 (46)	15 (29)		21 (48)	4 (40)	97 (43)
High	42 (34)	26 (51)		13 (29)	5 (50)	86 (37)
Employment status (%)						
Paid job	43 (35)	18 (34)	0.99	10 (23)	7 (70)	78 (34)
Unpaid job	13 (11)	6 (11)		6 (14)	0	25 (11)
Retired	67 (54)	29 (55)		28 (63)	3 (30)	127 (55)
Comorbidity						
Median number of conditions (range)	1.0 (0-4)	1.0 (0-4)	0.49	1.0 (0-5)	0 (0-3)	1.0 (0-5)
Clinical characteristics						
PSA ng/ml, median (SD, range)	8 (4.0, 1-20)	7 (3, 3-18)	0.02	5 (3, 1-17)	7 (3, 4-13)	7 (4, 1-20)
Mm cancer in biopsy, mean (SD, range)	7 (5, 0.2-20)	3 (3, 0.1-16)	<0.001	1 (2, 0.1-11)	1 (1, 0.4-5)	5 (5, 0.1-20)
Mm healthy tissue in biopsy, mean (SD, range)	73 (17, 40-127)	73 (19, 40-112)	0.92	86 (14, 60-126)	87 (13, 66-110)	76 (17, 40-127)
Clinical T stage DRE						
T1c	76 (58)	35 (65)	0.39	31 (69)	5 (50)	147 (61)
T2	55 (42)	19 (35)		14 (31)	5 (50)	93 (39)
P (indolent) (%)*** Mean (SD, range)	36 (17, 5-70)	55 (14, 15-70)	<0.001	81 (6, 72-97)	78 (5, 71-87)	50 (23, 5-97)

\* Probability of an indolent prostate cancer ≤70%

\*\* Probability of an indolent prostate cancer >70%

\*\*\* Range 0-100%, higher scores indicate a *higher* probability of potentially indolent PCA

AT: Active treatment; AS: Active surveillance; SD: Standard deviation; PSA: Prostate-specific antigen

was recommended in 185 patients ( $P(\text{indolent}) \leq 70\%$ ) and AS in 55 patients ( $P(\text{indolent}) > 70\%$ , Figure 1). Patients were compliant with RC recommendations in 176/240 cases (73%); 71% (131/185) were compliant with AT recommendations and 82% (45/55) with AS recommendations (Figure 1).

Of the 141 patients who eventually chose AT, 103 (73%) underwent surgery, 37 (26%) underwent radiotherapy and one underwent high-intensity focused ultrasonography (<1%).

The most frequently reported advantage of AT by patients was that AT was an appropriate way to treat PCa (68/141, 48%). The side effects of AT, such as incontinence and impotence (99/141, 70%), were cited as a disadvantage by many patients (Table 2). The most frequently reported advantage of AS included the delay of any physical side effects caused by physical damage after AT, so that quality of life/lifestyle was not altered (51/99, 52%; Table 2). Quality-of-life scores were largely similar between those who complied and those who did not.

**Table 2.** The most reported advantages and disadvantages of AS (n=99) and AT (n=141) by patients. More than one answer could be given per patient

Category	N (%)
<b>Advantages AS*</b>	
1. Delay of any physical side-effects due to physical damage after AT, so that quality of life/lifestyle is not altered	51 (52)
2. Insight in the clinical behaviour of PCa by frequent check-ups, so buying time to think to make a treatment decision	28 (28)
3. Delay of (unnecessary) AT	15 (15)
<b>Disadvantages AS*</b>	
1. Uncertainty and distress about the development of the PCa	26 (26)
2. None	23 (23)
3. Risk of unfavorable consequence, such as clinical stage progression or metastases	15 (15)
<b>Advantages AT**</b>	
1. Appropriate way to treat PCa with minimum side-effects, such as RALP and radiotherapy	68 (48)
2. Removing the PCa	55 (39)
3. Certainty about healing from PCa	21 (15)
<b>Disadvantages AT**</b>	
1. Side effects due to physical damage after active treatment, such as incontinence, impotence and bowel complaints	99 (70)
2. None	13 (9)

\* No advantage of AS was mentioned by 13% (13/99) and no disadvantages by 22% (22/99)

\*\* No advantages of AT was mentioned by 10% (14/141) and no disadvantages by 11% (15/141)

AT: Active treatment; PCa: Prostate cancer; AS: Active surveillance; PSA: Prostate-specific antigen; PCa: Prostate cancer; RALP: Robot-assisted laparoscopic prostatectomy

## AT recommendations

Active treatment was recommended to 185 patients and, of these, 71% (131/185) were compliant. Of the non-compliant patients, 48% (26/54) had a  $P(\text{indolent})$  between 60–70%. The most common reasons for urologists to be non-compliant with AT recom-

recommendations were patients' preference for AS (n = 30), patients fulfilling the inclusion criteria of the Prostate cancer Research International: Active Surveillance (PRIAS) protocol (n = 8 (PSA ≤10 ng/mL, PSA density <0.20, clinical stage ≤ T2, Gleason sum ≤3+3 and ≤2 positive biopsy cores))<sup>5</sup>, and patients having comorbid conditions (n = 8). Patients with comorbid conditions reported that their urologists also gave other treatment options, but they preferred AS. The proportion of comorbid conditions did not differ between patients (aged 65–75 years) who chose AS or AT (p = 0.14). The most reported advantage of AS according to patients was the delay of the physical side effects of AT (28/54, 52%), and the most reported disadvantages were uncertainty and distress about the development of the PCa (15/54, 28%).

Patients who complied with AT recommendations had higher mean PSA levels (8 vs 7 ng/ml, p = 0.02), a greater mean amount of cancer tissue in their biopsies (7 vs 3 mm,

**Table 3.** Mean (Standard Deviation) of Short form health survey (SF-12), State Trait Anxiety Inventory (STAI-6), Memorial Anxiety scale for Prostate Cancer (MAX-PC), the Decisional Conflict Scale (DCS), Center for Epidemiologic Studies Depression Scale (CES-D) and Eysenck Personality Questionnaire (EPQ)

	Recommendation: AT*			Recommendation: AS**	
	Compliant n=131	Non-compliant n=54	p-value	Compliant n=45	Non-compliant n=10
SF-12 Generic Health Status (Range 0-100, higher scores indicate better health)					
Physical health (PCS-12)	52 (7)	51 (8)	0.48	51 (8)	53 (4)
Mental health (MCS-12)	52 (10)	54 (10)	0.09	53 (10)	52 (12)
STAI- 6 Generic Anxiety score (Range 20-80, higher scores indicate more anxiety)					
	42 (10)	38 (10)	0.03	39 (10)	41 (16)
MAX-PC					
Subscale PCa Anxiety (Range 0-33)	10 (7)	12 (9)	0.31	13 (8)	11 (8)
Subscale Fear of Recurrence (Range 0-12)	7(2)	8 (3)	0.12	7 (2)	7 (3)
Total of both subscales (Higher scores indicate more anxiety)	17 (6)	19 (7)	0.05	20 (7)	18 (7)
DCS Decision conflict Scale (Range 0-100, higher scores indicate more decisional conflict)					
	27 (13)	26 (15)	0.80	28 (15)	25 (12)
CES-D (Range 0-60, with 60 indicate maximum depression)					
	9 (8)	8 (10)	0.03	8 (7)	9 (10)
EPQ 4 personality scales (each ranges 0-12, scores of 12 indicating the highest personality trait)					
Psychoticism	3 (2)	3 (1)	0.82	3 (1)	2 (1)
Extraversion	8 (3)	7 (3)	0.14	7 (3)	7 (3)
Neuroticism	4 (3)	3 (3)	0.38	3 (3)	3 (3)
Social Desirability	8 (3)	8 (2)	0.54	8 (3)	8 (3)

\* Probability of an indolent prostate cancer ≤70%

\*\* Probability of an indolent prostate cancer >70%

AT: Active treatment; AS: Active surveillance



$P < 0.001$ ), lower mean calculated  $P$ (indolent) (36% vs 55%,  $P < 0.001$ , Table 1), higher mean levels of generic anxiety (42 vs 38,  $p = 0.03$ , Table 3), and higher mean scores on the depression scale (9 vs 8,  $p = 0.03$ ) than those who did not comply. The proportion of compliant patients who were defined as clinical depressive (total scores of  $\geq 16$ ), however, did not differ compared with the proportion of non-compliant patients with an AT recommendation (21/120, 18% vs 10/50, 20%,  $p = 0.70$ ).

As expected, those who complied with AT recommendations had a positive attitude towards AT (91% vs 32%,  $p < 0.001$ ), and a negative attitude towards AS (87% vs 9%,  $p < 0.001$ ) more frequently than those who did not comply. The decisions of those who complied were more often patient-based than based on the urologist's opinion (30% vs 19%, Table 4) compared with those who did not comply. In multivariable analysis the strongest determinants for non-compliance were a urologist-based decision (odds ratio (OR) 5.2, 95% CI 1.5–18.6,  $p = 0.01$ ), the  $P$ (indolent)(OR 1.08 per 1% increase, 95% CI 1.0–1.1,  $p < 0.001$ ), and generic anxiety (OR 0.9, 95% CI 0.8–0.9,  $p < 0.001$ ).

**Table 4.** Knowledge scores, attitude, the influence of the urologist and the environment on patients in making their treatment decision

	Recommendation: AT*			Recommendation: AS**	
	Compliant n=131	Non-compliant n=54	p-value	Compliant n=45	Non-compliant n=10
Mean PCa knowledge (SD, range) (Range 0-15, higher scores indicate higher knowledge level)	9 (2, 2-13)	9 (2, 3-12)	0.34	9 (1, 5-11)	9 (2, 5-12)
Attitude towards AT					
Negative attitude (%)	10 (9)	32 (68)	<0.001	19 (58)	0
Positive attitude (%)	98 (91)	15 (32)		14 (42)	9 (100)
Attitude towards AS					
Negative attitude (%)	91 (87)	4 (9)	<0.001	8 (24)	8 (89)
Positive attitude (%)	14 (13)	43 (91)		26 (76)	1 (11)
'Who has the most influence in the treatment choice, the patient or the urologist?' (%)					
Patient-based	37 (30)	10 (19)	0.11	8 (18)	7 (70)
Shared decision	66 (54)	28 (53)		28 (64)	3 (30)
Urologist-based	20 (16)	15 (28)		8 (18)	0
'Who has the most influence in the treatment choice, the patient or his environment?' (%)					
Patient-based	77 (63)	38 (72)	0.44	31 (70)	8 (80)
Shared decision	45 (37)	15 (28)		11 (25)	2 (20)
Environment-based	1 (1)	0		2 (5)	0

\* Probability of an indolent prostate cancer  $\leq 70\%$

\*\* Probability of an indolent prostate cancer  $>70\%$

AT: Active treatment; AS: Active surveillance; SD: Standard deviation; PCa: Prostate cancer

### AS recommendations

Ten of 55 patients were non-compliant with an AS recommendation, resulting in limited reliability for comparisons with compliant patients (Tables 1, 3 and 4), therefore, no statistical testing was done. The most common reason for urologists to be non-compliant was that patients wanted AT ( $n = 7$ ). Reasons for patients' noncompliance included anxiety about progression of the PCa, too much stress involved in AS and undergrading of the PCa. Most patients reported removal of the PCa as the advantage of AT ( $n = 4$ ).

### Follow-up of AS patients

In the present study, 99 patients initially chose AS; 11% (11/99) were lost to follow-up and 14% (14/99) discontinued AS. The mean (range) follow-up of the 74 patients on AS was 12 (0–26) months. AS was discontinued because patients wanted AT (4/14, mean follow-up 6 months) or because of PCa progression (10/14, mean follow-up 15 months). The proportion of patients who discontinued AS below or above the 70% threshold did not differ: 16% (8/50) and 16% (6/38), respectively ( $p = 0.98$ ). Reasons for discontinuing AS did not differ between either group ( $p = 0.73$ ).

## DISCUSSION

In the present study, where the RC was actively implemented into clinical practice, urologists and patients were compliant with AS recommendations based on the RC in most cases (45/55, 82%), but AS was chosen in 54 of 185 cases (29%) where AT was recommended. These patients had relatively high calculated P(indolent), lower levels of generic anxiety, and the influence of the urologist in treatment decision-making was stronger compared with that in patients who were compliant with AT recommendations. The most common reason for urologists to opt for AS instead of AT was that patients preferred AS. This indicates that the threshold for AS of >70% may be too high for many patients. This form of non-compliance may also be explained by the fact that urologists had a preference for AS, particularly in patients who fulfilled the inclusion criteria of the PRIAS protocol (59%, 32/54, P(indolent) range 23–70%)<sup>5</sup>. Their relatively low P(indolent) was caused by a higher mean mm cancer/mm benign tissue ratio (4.1% vs 1.1%,  $p < 0.001$ ) at biopsy and a higher mean PSA density (0.15 vs 0.11,  $p < 0.001$ ) than in patients with a P(indolent) >70% and who fulfilled the PRIAS inclusion criteria (76%, 34/45). The proportion of patients who discontinued AS and their reasons for discontinuing AS, i.e. patients preferred AT or had PCa progression below or above the 70% threshold, did not differ. A reason reported by urologists for some patients' non-compliance with the AT recommendations based on the RC, was that these patients preferred AS. It may be possible that urologists had recommended

AT, but patients were not willing to undergo AT. In those cases urologists could not be denoted as being non-compliant with the AT recommendations based on the RC. Conversely, urologists gave an AT recommendation in some patients with  $P(\text{indolent}) > 70\%$ . Ultimately, it remains the patient's decision to accept or decline the AS or AT recommendation based on the RC, reflecting a personal threshold for the probability of having potentially indolent PCa.

The non-compliance of patients could be influenced by the treatment preferences of urologists, the way urologists communicate treatment options with their advantages and disadvantages, impact on quality of life, and patient's calculated  $P(\text{indolent})$ . Patients may also be influenced by information from other sources, e.g. the Internet, leaflets, family, friends and second opinions<sup>22-25</sup>. Patients who experience higher levels of generic anxiety may opt for AT rather than AS, because they have difficulties with living with untreated PCa and/or have more anxiety about PCa progression. In the present study, those who complied with AT recommendations had higher levels of generic anxiety than those who did not. This is in contrast to a previous study where anxiety has not been shown to be higher in men who have chosen initial treatment versus AS<sup>26</sup>. The present study confirmed that the most common reported advantage of choosing AS for those who did not comply with AT recommendations was the delay of physical side effects after AT, so that quality of life/lifestyle was not altered<sup>18,24</sup>.

The present study is one of the first to investigate urologists' and patients' compliance with recommendations based on a RC. Nomograms have a long track record in urology, and studying their impact on clinical practice is important. Evaluation of impact requires setting a threshold to recommend AS vs AT<sup>27</sup>. This threshold can be defined by a careful weighing of the risks and benefits in a full decision analysis<sup>28</sup>. In the present study, the 70% probability threshold was primarily motivated by a high sensitivity to actively treat potentially important PCa in a screening setting. We did not correct the probability threshold and calculated  $P(\text{indolent})$ s for use in a clinical setting. Since the introduction of the PSA test, a favourable stage shift at the time of detection has been observed. The proportion of T1c cancers at the initial screening round of the ERSPC in Rotterdam was 47.8% during the years 1994–1998, while in the control arm, reflecting the clinical setting, this proportion was 28.5% and increased during the years 2003–2006 to 50%<sup>29</sup>. In the present study the proportion of T1c tumours (61%, Table 1) bears more similarity with the screening setting in the period 1994–1998 from which the RC is derived. This increase in the proportion of T1c cancers reflects the increase of PSA testing in the clinical setting.

The results of the present implementation study showed that the RC may well be of use in treatment decision-making. The  $P(\text{indolent})$  threshold of  $>70\%$  may be suitable for AS strategies. Urologists used the RC in most eligible patients diagnosed with PCa (93%, 67/72) for whom RC level three was used previously; however, we do not know

whether urologists will continue to use the RC after the project. The best predictors of whether physicians will use a prediction rule are acquired familiarity, confidence in the usefulness of the rule and its user-friendliness<sup>30</sup>. Urologists may be more used to the inclusion criteria of an AS protocol, such as the PRIAS protocol, than the use of a RC to select men for AS or AT; however, the RC does not only support the selection of patients for AS or AT (as a decision tool), but also informs urologists and patients about the probability of a potentially indolent PCa (as a nomogram for a personal decision threshold for the risk of a potentially aggressive PCa).

Limitations of the study are that it is not clear how the motives of patients in choosing AS or AT developed, especially the patients who chose AS against the RC recommendations, and that it is not clear how the outcome of the RC affects patient's choice and the urologist in his/her counselling. Further research is needed into these topics, and a longer follow-up of patients on AS is important to improve and validate the chosen 70% threshold for indolent disease. This threshold or lower appeared to be acceptable in this Dutch clinical cohort but may not be acceptable elsewhere, reflecting factors such as cultural differences.

In conclusion, AS recommendations were followed by most patients, while 29% of patients with AT recommendations chose AS. Although further research is needed to improve the probability threshold for recommending AS over AT, the current RC proved to be useful in treatment decision-making in patients with localized PCa.

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# Chapter 11

## Disease insight and treatment perception of men on active surveillance for early prostate cancer

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## ABSTRACT

**Objective:** To investigate the levels of knowledge of prostate cancer and the perception of active surveillance (AS) in men on AS, as AS for early prostate cancer instead of radical treatment might partly solve the overtreatment dilemma in this disease, but might be experienced as a complex and contradictory strategy by patients.

**Patients and methods:** In all, 150 Dutch men recently diagnosed with early prostate cancer participating in a prospective protocol-based AS programme (PRIAS study) received questionnaires, including a 15-item measure on their general knowledge of prostate cancer, and open-ended questions on the most important disadvantages and advantages of AS, and on the specific perception of AS. We assessed knowledge scores and explored potentially associated factors, the stated (dis)advantages and specific perceptions.

**Results:** The questionnaire response rate was 86% (129/150). Participants provided correct answers to a median (interquartile range) of 13 (12–14) of 15 (87%) knowledge items. Younger and higher educated men had higher knowledge scores. In line with a priori hypotheses, the most frequently reported advantage and disadvantage of AS were the delay of side-effects and the risk of disease progression, respectively. Specific negative experiences included the feeling of losing control over treatment decisions, distress at follow-up visits, and the desire for a more active participation in disease management. No conceptually wrong understandings or expectations of AS were identified.

**Conclusions:** We found adequate knowledge of prostate cancer levels and realistic perceptions of the AS strategy in patients with early prostate cancer and on AS. These findings suggest adequate counselling by the physician or patient self-education.



## INTRODUCTION

Active surveillance (AS) is a new treatment strategy for early prostate cancer, consisting of initially withholding radical treatment. Instead, the disease is strictly monitored and active therapy with curative intent is considered as soon as progression occurs. By delaying the side-effects of surgery or radiotherapy in some, and avoiding it completely in others, AS has the potential to partly solve the overtreatment dilemma, which is mainly a result of the over-diagnosis caused by screening<sup>1,2</sup>.

Better patient knowledge and understanding of disease and treatment have been reported to be associated with better self-management and coping, with improved patient satisfaction with their care, and increased adherence<sup>3-7</sup>.

AS can be perceived as a complex or even contradictory treatment strategy by patients, especially by men with insufficient knowledge of their disease. Disease insight and perception of the treatment strategy might be underexposed but important aspects of treatment satisfaction in patients on AS.

We assessed the level of knowledge of prostate cancer and associated factors, and we explored perceived advantages and disadvantages of AS and specific perceptions of this treatment strategy in a group of patients with early prostate cancer on AS.

### Patients and methods

All patients included in the present study participated in the protocol-based AS programme of the international prospective observational Prostate cancer Research International: Active Surveillance (PRIAS) study<sup>8</sup>. Men are eligible for the PRIAS study if they have a diagnosis of adenocarcinoma of the prostate with a PSA level of  $\leq 10.0$  ng/ml, a PSA density (PSA divided by prostate volume) of  $< 0.2$  ng/ml/ml, T1c or T2 disease, and one or two positive prostate needle biopsy cores, with a Gleason score of 3+3=6 or more favourable. After the diagnosis and consultation with the urologist, a shared decision is made on the initial treatment strategy. If AS is selected and if a patient subsequently wants to participate in the PRIAS study, written informed consent is provided. The first 2 years of surveillance consist of a PSA measurement every 3 months, digital rectal examination every 6 months, and standard repeat prostate biopsies after 1 year. The Medical Ethical Committee (MEC) of the Erasmus University Medical Centre approved the PRIAS study (MEC number 2004-339), as did the MECs of the participating 12 non-university hospitals, depending on the local regulations. PRIAS is coordinated from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer<sup>9</sup>.

Between May 2007 and May 2008, all 150 Dutch men with a recent ( $\leq 6$  months) diagnosis of prostate cancer who were included in the PRIAS study, received a health and quality-of-life questionnaire by mail at their home address. If the questionnaire was not returned within 1 month, patients were reminded once by telephone. The questionnaire contained measures for psychological, demographic and other variables. A second follow-up questionnaire was sent at 9 months after diagnosis to those men who had returned the first.

### **Questionnaire measures included in the current study**

The patients' knowledge of prostate cancer was assessed using a 15-item measure with three response options each ('True', 'not true', 'don't know'). For a correctly provided answer, 1 point was added to the total 'Knowledge of prostate cancer' score. The total score range was 0–15, with 15 indicating maximum knowledge of prostate cancer. The measure was based on a 20-item 'knowledge of prostate cancer measure' that was previously used to study the effectiveness of an information leaflet on prostate cancer screening published by the Dutch Cancer Foundation ('KWF Kankerbestrijding'), from which five irrelevant questions in an AS setting were excluded. The measure was similar in size and type of questions to other knowledge of prostate cancer' measures used in other studies<sup>10-12</sup>. There was a conceptual overlap with items used in these studies in eight of the 15 items.

Advantages of AS over other treatment options as perceived by participants were assessed using one open-ended item ('Which are for you the most important advantages of AS? Start with the most important aspect.') with space for three possible responses. A similar item was included on the disadvantages of AS.

Specific perceptions of AS were extracted from the open comments section at the end of the questionnaire ('This is the end of this questionnaire. If you have any comments, please write them down below. Also, if any special personal circumstances influenced your response to the items in this questionnaire please mention these below.'). Completing this item was optional. Comments provided in the second questionnaire (9 months after diagnosis) were also included in this analysis, and was the only item from this follow-up questionnaire that was used in the current study.

Educational level was assessed using one item with six response options, and was divided into two groups defined as 'low education' (primary, secondary education, and/or high school) or 'high education' (professional education, college, and/or university). Employment status was defined as 'employed' or 'otherwise'. Civil status was defined as 'married/living together' or 'otherwise'.

## Patient specific information

Medical information (PSA level, clinical stage, number of positive biopsies, age) and hospital type were derived from the PRIAS study database. Clinical disease stage was defined as 'T1C' or 'T2'. Age was categorized into <60, 60–70, and >70 years. Hospital type was defined as 'university/specialized' if a patient was under AS in an academic or specialized oncological centre, or as 'other hospital'.

## Analysis

Scores on knowledge were assessed and related to educational level, employment status, civil status, age and hospital type. We hypothesized that men with a high educational level, employed, who were married, young, and under AS in a university hospital would have higher scores on knowledge of prostate cancer, with educational level being the strongest relationship. Variables found to be statistically significantly associated in a univariate regression analysis were entered in a multivariable model. Hypotheses on the sizes and directions of the potential relationships between these variables were based on published reports (educational level, civil status and age)<sup>12,13</sup> and on logical reasoning (employment status, hospital type) that these were potentially relevant in this patient group.

Advantages and disadvantages, and specific perceptions mentioned by participants were extracted, grouped and counted independently by two of the authors (R.C.N.vdB., M.L.E.B). We hypothesized that the most frequently reported advantage included the delay or avoidance of side-effects of radical treatment, and that the most frequently reported disadvantage included fear of disease progression. In statistical testing,  $p < 0.05$  was considered to indicate statistical significance.

## RESULTS

### Patient population

Of the 150 questionnaires sent, 129 (response rate 86%) were completed and returned at a median (interquartile range, IQR) of 2.4 (1.3–3.9) months after diagnosis. Table 1 presents the general, medical and demographic details of the 150 men. The median (IQR) age was 64.6 (60.2–70.4) years; 92% were married or living together. Information on ethnicity was not available in the study, but based on surnames of participants, we estimated our cohort to be >95% of Dutch origin.

**Table 1.** General, medical, and demographic characteristics of the 129 patients

Variable	Median (IQR) or n (%)
<b>General</b>	
Age, years	64.6 (30.2-70.4)
Months from diagnosis to completing first questionnaire	2.4 (1.3-3.9)
<b>Medical</b>	
PSA, ng/ml	5.7 (4.6-7.0)
<b>Clinical stage</b>	
T1c	91 (70.5)
T2	38 (29.5)
<b>Number of positive biopsies</b>	
1	79 (61.2)
2	50 (38.8)
<b>Demographical</b>	
<b>Education</b>	
Low	86 (67.2)
High	42 (32.8)
Missing	1
<b>Employed</b>	
Yes	50 (39.7)
No	76 (60.3)
Missing	3
<b>Hospital</b>	
University/specialized	61 (47.3)
Other	68 (52.7)
<b>Civil status</b>	
Married/living together	119 (92.2)
Other	10 (7.8)

PSA: Prostate-specific antigen

### Knowledge of prostate cancer

Table 2 presents the 15 items on prostate cancer knowledge used in the study, answers considered correct, and percentages of men answering correctly. Participants answered a median (IQR) of 13 (12–14) items correctly (87%); 11 (9%) answered all 15 items correctly. Despite overall high scores, more than half the men thought that metastasized prostate cancer is still curable while in reality this is impossible; >30% thought that prostate cancer does not recur after radical treatment while there is a relevant chance of disease recurrence, and almost 30% thought that treating early prostate cancer does not cause any urinary incontinence, while this is an important side-effect of primary treatment, or thought that prostate cancer is the second deadliest cancer, while the prognosis of prostate cancer in general is mainly favourable.

**Table 2.** Question items on prostate cancer in general, used in this study, answers considered correct, and percentage of study population answering correctly. Per correct answer, 1 point was added to the total 'Knowledge of PC' score (score range 0-15)

Question	Answer	Answered correctly (%)
1. The prostate is situated at the bottom of the abdominal cavity	True	89.1
2. The risk of being diagnosed with prostate cancer decreases with increasing age	False	94.6
3. Prostate cancer is more common in men aged 70 than in men aged 40	True	89.1
4. Prostate cancer may lead to death	True	83.7
5. Most men diagnosed with prostate cancer will not die of prostate cancer	True	82.2
6. If prostate cancer has metastasized, curative treatment is no longer possible in most cases	True	44.2
7. The treatment of early detected prostate cancer may cause unwanted incontinence	True	73.6
8. After surgery for prostate cancer, side effects may arise, such as erectile problems	True	95.3
9. Treating prostate cancer through radiation therapy does not cause any side effects	False	83.7
10. After treatment, prostate cancer stays away in all cases	False	69.0
11. A man may have prostate cancer, even though he never has symptoms	True	96.9
12. If prostate cancer is found in an early stage, it may be treated well	True	96.9
13. Prostate cancer is the second most deadly type of cancer	False	71.3
14. Urinary problems in elder men are most commonly caused by a benign enlargement of the prostate	True	85.3
15. It may occur that prostate cancer is detected that would never have caused any problems	True	87.6

Table 3 presents the univariate and multivariable regression analysis of 'knowledge of prostate cancer' score. In univariate regression analysis, higher educational level, married status and younger age were significantly ( $p < 0.05$ ) associated with a higher knowledge score. On multivariable analysis, educational level and age remained statistically significantly related with knowledge of prostate cancer, with the strongest relation for educational level ( $\beta = 0.209$ ;  $p = 0.016$ ).

**Table 3.** Univariate and multivariate analysis of factors associated with the knowledge of prostate cancer score

	Univariate		Multivariable	
	$\beta$	P-value	B	P-value
Education level (low vs. high)	.256	.004	.209	.016
Employment status (employed vs. other)	.075	.407	-	-
Civil status (married/living together vs. other)	-.176	.045	.132	.124
Age at diagnosis (<60, 60-70, >70 years)	-.235	.007	-.197	.022
Hospital type (university/specialized vs. other)	.054	.544	-	-

### Perceived advantages and disadvantages of active surveillance

Table 4 presents the advantages and disadvantages of AS mentioned by participants. A first, second and third advantage were provided by 120 (93%), 51 (40%) and 20 (16%) of the 129 respondents, respectively. Nine (7%) men did not provide any advantage of AS. A first, second and third disadvantage were provided by 103 (80%), 29 (22%) and 7 (5%) of the 129 respondents, respectively; 26 (20%) did not provide any disadvantage of AS. Significantly more men failed to provide any disadvantage than any advantage ( $p < 0.01$ ).

The most frequently reported advantage of AS included the delay or avoidance of any side-effects of radical treatment, with or without stating the specific reason for being able to continue a normal lifestyle. The most frequently reported disadvantage of AS included the potential risk of disease progression, resulting in uncertainty and distress.

**Table 4.** Advantages and disadvantages of active surveillance mentioned by participants; total number and percentage of total study cohort. (More than 1 answer could be given by a single participant)

<i>Advantages of active surveillance</i>	Number	%
- Delay of any side effects due to physical damage after radical treatment such as incontinence and impotence, so that quality of life and lifestyle are not altered	80	62
- Delay unnecessary radical treatment (no specific reason mentioned)	42	33
- Insight in the clinical behaviour of the disease by frequent checkups and by doing so buying time for the most appropriate decision on treatment	23	18
- No burden and risks of stressful treatment and hospital admission	15	12
- Better treatment options may be available in the future	2	2
- Family situation did not allow for radical treatment	1	1
- Contribution to scientific research	1	1
<hr/>		
<i>Disadvantages of active surveillance</i>		
- Risk of unfavourable consequences on disease status, such as clinical stage progression or the development of metastases	39	30
- Uncertainty and distress ( no specific reason mentioned)	25	19
- Frequent checkups, including 3 months PSAs, and yearly bothersome prostate biopsy	13	10
- Psychological burden of carrying 'untreated' prostate cancer and being a patient	13	10
- Active surveillance is merely a delay of radical treatment instead of avoidance	6	5
- Contradiction of waiting while having been diagnosed with cancer	6	5
- Active surveillance protocol may not be not adequate to timely detect progression	2	2
- Risk that nerve-sparing surgery is no longer possible in the future	1	1

No advantage was mentioned by 7%, no disadvantage was mentioned by 20% ( $p < 0.01$ )

## Patient perceptions

Out of 129 respondents, 39 (30%) provided comments in the 'open comments' section at the end of the baseline questionnaire, and 52 (49%) in the comments section of the 106 available follow-up questionnaires. No conceptually wrong perceptions were identified. Most comments could be assigned as related to the treatment decision, to prostate cancer as a disease, and to AS as a treatment strategy. Table 5 presents the specific illustrative statements of 17 different patients.

**Table 5.** Statements made by 17 men with early prostate cancer on active surveillance (AS) related to treatment decision, to prostate cancer as a disease, or to active surveillance as a treatment strategy, and patient details

Statements	Age (years)	Education	Times from diagnosis
TREATMENT DECISION-RELATED			
Confidence in putting the treatment decision in the hands of the physician:			
-'Because I am a layman only, my choice for active surveillance is mainly based on my confidence in my treating urologist, the decisions he makes, and the (active surveillance) follow-up protocol.'	57	High	4 months
Feeling of losing control over treatment decision:			
-'I received little to no advice on the treatment-options for my disease; the choice for active surveillance had actually already been made by my urologist.'	55	Low	19 days
-'Living with prostate cancer is something you have to learn. I feel I am handed over to the medical world. Due to a lack of knowledge, it is very hard for me to make decisions on my own.'	55	Low	9 months
Important role of a patient's spouse:			
-'At part 1 of the questionnaire, WE felt unable to give an adequate answer.'	62	Low	8 months
PROSTATE CANCER-RELATED			
Varying levels of anxiety and distress due to the diagnosis early PC:			
-'I am not sure whether I am a 'real' cancer patient, as my PSA fluctuates somewhere around 6 and only a few malignant cells have been found.'	75	High	9 months
-'It doesn't help to worry about these things. So we just continue on the path we have chosen.'	70	Low	9 months
-'I am depressed, and I am using medication. I am afraid of having cancer at other sites in my body as well, in my abdomen etc.'	49	Low	9 days
Unexpected side effects of the diagnosis:			
-'In general, the knowledge of having prostate cancer isn't causing too much (of) trouble, however, unintentionally, it does influence my sexual interest, which seems to have decreased since the diagnosis.'	57	Low	9 months
Other events overshadowing the impact of the diagnosis PC:			
-'(my experience of prostate cancer) is strongly influenced by the fact that I have lost my wife recently due to the results of pancreatic cancer.'	71	High	4 months

ACTIVE SURVEILLANCE STRATEGY RELATED			
Wish to be in control over the disease:			
-'Because my PSA kept rising during the last three measurements, I am thinking of getting a PSA test earlier than scheduled according to the active surveillance protocol.'	61	Low	9 months
-'Whenever the PSA level will reach 10.0 ng/ml, I will quit active surveillance and switch to radical treatment.'	64	High	9 months
Difficulties in monitoring PC during AS:			
-'I do not understand why PSA values vary so much, could this be related to dietary or lifestyle factors?'	60	High	9 months
The possibility of changing from AS to other treatment options:			
-'I feel well, also physically. Life is still a challenge for me. My religion plays a major role in this. The thought of being under close surveillance for my disease with the possibility of switching to radical treatment when this is necessary is very comforting.'	76	Low	8 months
The rise or fall of the PSA values:			
-'Because the PSA value has been rising over the last three measurements, I am increasingly worried.'	55	Low	1 month
-'As the last 2 measurements clearly showed a lower PSA value, I have become more positive on expectant management, although deep inside the anxiety remains.'	55	Low	1 month
-'Every time my PSA is measured, I am very stressed.'	63	Unknown	9 months
Burden of the intensive follow-up regimen:			
-'The prostate biopsies are painful investigations and have side effects afterwards. I am reluctant to undergo this again, especially since the PSA value is not rising.'	62	Low	3 months

PC: Prostate cancer; PSA: Prostate-specific antigen; AS: Active surveillance

## DISCUSSION

We found an adequate knowledge of prostate cancer and a realistic perception of the treatment strategy of AS in a group of men with early prostate cancer participating in a prospective AS study, with highly educated and especially younger men having highest knowledge scores. Only a few deficiencies in comprehension of background and treatment of prostate cancer, and in the treatment strategy of AS, were identified.

To our knowledge, this is the first study to measure knowledge of prostate cancer in men on AS, and that explored specific patients' expectations and perceptions of this treatment strategy. The median knowledge score of 13 of a maximum of 15 might be considered as adequate, although there is no reference for what constitutes 'adequate knowledge' and our study design did not allow for direct comparisons with other patient cohorts receiving other treatments. The incorrectly answered questions suggest that these patients might expect somewhat too much of the possibilities and results of radical prostate cancer treatments. Besides the lack of any association of knowledge with employment status or hospital type, the size and direction of correlations of factors with knowledge were in line with a priori hypotheses.



The most frequently mentioned advantages and disadvantages of AS by participants were also in line with the authors' hypotheses. Our finding that significantly more men provided any advantage of AS than any disadvantage, could be caused by the fact that the advantages of AS might be more emphasized than disadvantages in patient-physician discussions at the moment of treatment decision or in the patient information provided, that these are simply remembered better by patients, or that this is a result of a selection bias. Men who more intensively experience the disadvantages of AS might tend to choose another treatment option earlier. No conceptually wrong (dis)advantages were reported, although 'Better treatment options may be available in the future' might not be a realistic consideration.

Various patient-specific positive and negative perceptions of the treatment decision, the diagnosis of early prostate cancer, and the treatment strategy of AS were identified. Again, no conceptually wrong ideas or expectations were identified.

We previously found no evidence for an association of anxiety and distress levels with disease knowledge in men on AS<sup>14</sup>. However, men with less knowledge of prostate cancer might be more confused by the treatment strategy of AS. Other factors such as physician attitude and advice might be more decisive in the eventual choice for and perception of AS<sup>15,16</sup>. We believe that especially in this specific patient group that is living with 'untreated' cancer, adequate knowledge of prostate cancer and the treatment strategy of AS is essential to understand the advantages and disadvantages of expectant management when compared to radical therapies for localized prostate cancer, such as surgery or radiotherapy. Reasons for the adequate knowledge of prostate cancer and realistic perceptions of AS found in our study (even with the same protocol being applied in different hospitals) remain unknown, but might include counselling by the physician, patient self-education, or a selection bias of men with adequate knowledge choosing AS earlier than men with less knowledge.

Various groups have measured knowledge of prostate cancer in different cohorts<sup>10-12,17-19</sup>. Disease knowledge levels were found to be associated with important decisions such as participation in screening programmes<sup>10</sup>. Our finding that younger and better educated men had higher knowledge of prostate cancer scores is in line with other reports<sup>12,17</sup>. Socio-economic group and ethnicity have also been reported to be associated with knowledge levels<sup>18,19</sup>, but our study design did not allow for analysis of these variables.

Denberg et al., after interviewing 20 men, found that treatment decisions in men with localized prostate cancer were not uncommonly based on misconceptions and anecdotes, instead of on realistic deliberations on survival and the risk of side-effects<sup>20</sup>. This is in contrast with our findings.

Limitations of the present study include the use of an unvalidated measure of prostate cancer knowledge. Attempts to develop a reliable and valid questionnaire to test prostate cancer knowledge have been reported, but the use of these measures seems limited<sup>21</sup>. A recent study by Deibert et al. used a self-designed measure, as was done in our study<sup>12</sup>. Second, our study design did not include other patient cohorts receiving other treatments for prostate cancer, making comparisons impossible. Third, the optional type of items we included on (dis)advantages and on specific perceptions might have limited the value of the response.

A strength of the study is that it is the first to evaluate disease knowledge and (dis)advantages of AS, and potential misunderstandings about AS in men with early prostate cancer on AS. Furthermore, extensive questionnaires were used, with a high response rate, completed with no help from the study team. Finally, the study was conducted within the controlled environment of the prospective PRIAS study.

Future research should further clarify the role of knowledge of their disease in men with prostate cancer, and its relation with decisions to stop AS that are not based on the protocol should be investigated longitudinally<sup>22</sup>. The development of a standardized and validated knowledge of prostate cancer measure might also be useful.

In conclusion, this is one of the first studies to provide an insight into the thoughts and feelings of patients on AS for early prostate cancer. Patients recently diagnosed with early prostate cancer who participated in a prospective AS programme had an adequate knowledge of their disease and reported realistic expectations of AS. Although true misconceptions on prostate cancer or on AS were not identified, various factors that influence the personal perception of AS were reported. Our findings suggest counseling by the physician or patient self-education was adequate.

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# Part 6

## General discussion

Chapter 12

General discussion



# Chapter 12

General discussion





## INTRODUCTION

PSA screening according to a strict protocol leads to a significant prostate cancer-specific mortality reduction<sup>1,2</sup>. Current PSA screening practice also causes two important unwanted side effects; firstly, screening induces many unnecessary prostate biopsies; biopsies with a negative outcome, and secondly, it leads to overdiagnosis and overtreatment of clinically insignificant cancers<sup>1,3-4</sup>. In order to reduce these effects, it was hypothesized in this thesis that the use of prediction models supports the identification of men with an increased risk of having a biopsy detectable prostate cancer and the distinction of potentially indolent cancer from cancer that is relevant and needs treatment. The key findings of testing a decision aid and applying risk-based strategies were described in previous chapters will be the subject of this general discussion.

## INFORMED DECISION-MAKING ABOUT PSA TESTING USING A DECISION AID

The results described in Chapter 4 show that a leaflet with information about prostate cancer and the pros and cons of PSA screening, as well as including a risk calculator increased the individual knowledge on prostate cancer and pros and cons of PSA screening, improved informed decision making, and most men reported no decisional conflict about having a PSA test or not. The intention to have a PSA test increased. The preference of men to undergo a PSA test was associated with higher calculated probabilities on prostate cancer as calculated by the risk calculator. The study described in Chapter 5 demonstrates a comparable result in case of a biopsy decision. Men, who were non-compliant with 'no biopsy' recommendations of a risk calculator, and thus opted for a prostate biopsy, had higher calculated probabilities of prostate cancer than men who were compliant. Both outcomes are in line with literature that shows that a higher risk perception may lead to increased participation in screening and willingness to undergo invasive procedures<sup>5-6</sup>.

Randomized controlled studies vary on the outcome of the effect of decision aids on men's preference for a PSA test<sup>7-12</sup>, and show comparable results with the outcomes in Chapter 4 such as decision aids increase informed decision making, individual's knowledge about the pros and cons of PSA screening and reduce decisional conflict<sup>13</sup>. As a result, we recommend the use of a decision aid to support informed decision making about PSA testing and shared decision making in which both, physicians and patients, participate in decision making. Beside the discussion about the pros and cons of PSA testing, the literature shows that physicians also have to consider patients' individual risk factors and life expectancy in the decision making process about PSA screening<sup>14</sup>. In the discussion about the pros and cons, however, physicians tend to emphasize the

pros more often than the cons<sup>15</sup>. Using decision aids might prevent that patients receive unbalanced information about the pros and cons. However, the use of decision aids is not part of daily practice<sup>16</sup>. Two strategies can stimulate the use of decision aids. The first strategy is dissemination of evidence based knowledge about the relevance of decision aids, such as they help to educate patients about pros and cons of PSA screening, might alleviate the time burden on clinicians and increase informed decision making<sup>17</sup>. Publications, postgraduate trainings and presentations at congresses may be helpful to disseminate the scientific knowledge<sup>18</sup>. The second strategy, which can also be an application to the first strategy, is active implementation of decision aids in general practice. Implementation can be supported by educating physicians in the use and benefits of the decision aid and solves misconceptions, supports them to get insight into possible barriers to use decision aids and solve these problems together<sup>18</sup>. In Chapter 5, we recommended that before the implementation of risk calculators, it is important to pay extra attention to existing guidelines in clinical practice, because that might limit the adoption of these tools. During the implementation process of prostate cancer risk calculators, we found that our support in the use of these risk calculators and in solving problems stimulated physicians to use these tools. In addition, nurses had an important role to remind physicians to use prostate cancer risk calculators during their consultations with patients.

Limitations of the study described in Chapter 4 include the non-randomized design, the fact that the effect of a risk estimation on attitude towards individuals' own participation in screening (and thus not on general attitude towards PSA screening) could not be assessed, and lack of data about whether men actually had a PSA test. Further research is needed, preferably in a randomized controlled study design including two groups of which one will receive a leaflet and the other a leaflet with risk calculator. We recommend to assess the effect of the intervention on attitude towards individuals' own' participation in screening and on the uptake of PSA testing.

## **PROSTATE CANCER RISK CALCULATORS IN THE DECISION MAKING ABOUT THE NEED OF A PROSTATE BIOPSY AND ABOUT PROSTATE CANCER TREATMENT**

The European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator was actively implemented in urological practice of five Dutch hospitals in 2008 with the support of study nurses. The results described in Chapter 5 show a high compliance of urologists and patients with biopsy recommendations by this risk calculator (83%). In most non-compliant cases, urologists and men did not comply with 'no biopsy' recommendations; the main reason to do so for urologists was an elevated PSA. Existing guidelines appear to counteract the adoption of a risk calculator, for example a PSA

threshold of  $\geq 3$  ng/ml (and/or a suspicious DRE)<sup>1,19</sup>. However, this was mainly the case in one hospital.

Data in Chapter 10 show comparable results with respect to treatment recommendations of the ERSPC risk calculator level six (since May 2012 level five). Firstly, compliance with treatment recommendations of the ERSPC risk calculator was also high in Dutch clinical practice (73%). In cases of non-compliance, mainly active treatment recommendations were ignored, thus active surveillance was chosen instead. In both studies, it showed that when urologists were non-compliant, patients were neither. Secondly, the results are comparable with Chapter 5 because a 'guideline' also reduced the adoption of the outcome of the risk calculator in cases of active treatment recommendations. One of the most important reasons for urologists to be non-compliant was that patients fulfilled the Prostate cancer Research International: Active Surveillance (PRIAS) inclusion criteria<sup>20</sup>. Both studies suggest that traditional guidelines may reduce the adoption of the advice coming from the risk calculators in urological clinical practice.

Previous evidence showed that a risk-based approach outperforms the use of PSA alone and a model with PSA and DRE in the decision whether or not to take a biopsy<sup>21-23</sup>. Results described in Chapter 7, 8 and 9 confirm the outcomes of this previous evidence. In the studies in Chapter 7, 8 and 9, the validity of a risk calculator was tested and compared to a model with PSA and DRE in clinical and screening settings. A risk calculator better discriminates men with and without prostate cancer than a model with PSA alone and a model that includes PSA and outcome of DRE. In Chapter 6, the results of using a risk-based approach compared to standard clinical practice (an elevated PSA and/or a suspicious DRE) are shown. A risk-based approach led to a higher positive predictive value (number of cancers divided by the number of biopsies) compared to the clinical approach (68% and 44%, respectively), and more significant cancers were found (34% and 15%, respectively). This study has limitations, such as the small cohorts and the retrospective part that may have caused a selection bias. Results therefore have to be interpreted with caution and should be viewed as a finding that needs further confirmation within a prospective study design, preferably in a large randomized controlled trial.

Both strategies, the PRIAS inclusion criteria and the ERSPC risk calculator, are supportive in the differentiation of potentially indolent cancers and significant cancers. Significant cancers were also called important or high grade cancer in the articles of this thesis. Evidence is lacking about which strategy better differentiates and thus leads to best health outcome for men. Ideally, men with significant cancers are treated and men with indolent cancers are not treated. Since we cannot fully separate these two groups, actively monitoring according to a protocol of potentially indolent cancers will be necessary. The strategies differ from each other in the combination of predictors and the use of cut-offs. Cut-offs per predictor are applied in the PRIAS criteria in contrast

with a risk calculator; where a cut-off is applied only after calculation of a probability including multiple, possibly continuous, predictors.

Future research is needed to assess and compare the effect of both strategies on the frequency of indolent disease at radical prostatectomy. Through retrospective research short-term outcomes can be studied. Selection strategies can possibly be improved by the addition of (new) parameters such as the life-expectancy; age and comorbidity, and new markers. Secondly, other endpoints may be used instead of indolent disease at radical prostatectomy. More relevant endpoints are clinical progression or mortality.

### **Compliance of patients**

Data in Chapter 5 show that the main reported reason for patients to be non-compliant with 'no biopsy' recommendations was that they wanted to be certain about having prostate cancer or not. In cases of a 'biopsy' recommendation almost all patients were compliant. Data in Chapter 10 show that the main reason for patients to be non-compliant with active treatment recommendations of the risk calculator was their preference for active surveillance. Almost all patients were compliant with active surveillance recommendations of the risk calculator. The threshold of 70% for indolent disease or lower appears to be acceptable for patients in a Dutch cohort. They most often reported the delay of side-effects after active treatment so that quality of life is not altered as advantage of active surveillance, and uncertainty and distress about progression of the disease as disadvantage. Chapter 11 presents the results of a questionnaire-based study in patients on active surveillance. This study confirmed that the delay of side-effects after active treatment was the most reported advantage in men on active surveillance; the risk of unfavourable outcomes of the disease, such as clinical stage progression or the development of metastases was an important reported disadvantage. Furthermore, the study shows that men had adequate knowledge about prostate cancer and realistic expectations of active surveillance. These results seem to support the idea that men who chose for active surveillance against the recommendation of the risk calculator (Chapter 10) were able to make a 'conscious' choice after considering both the advantages and disadvantages of expectant management.

A limitation of both studies described in Chapter 5 and 10 is that it is unknown how motives developed in patients to be non-compliant with 'no biopsy' recommendations and active treatment recommendations. Furthermore, a guideline about how to communicate probabilities related to the threshold is not yet developed. Although it may be difficult to realize, it could be of additional value in decision making. Qualitative research into factors that influence non-compliance of physicians and patients, and into how physicians communicate risks with their patients is needed. Research techniques could be videotaping of conversations, in-depth-interviews and focus groups.

## Risk communication

For men it may be difficult to interpret the meaning of a probability on prostate cancer. Some men regard a probability of 1-5% as too high, despite of the explanation about the 20% probability threshold by urologists. This might be a reason for men who opted for biopsy against the recommendation of the risk calculator, next to the fact that they wanted reassurance (Chapter 5).

Patients often tend to have a dichotomous understanding of risk rather than understanding risk as a continuum. The risk calculators level three and six provide both risks. A threshold has been set to provide dichotomous understanding; a biopsy was indicated when the threshold was  $\geq 20\%$  and active surveillance was recommended when the threshold was  $>70\%$  (Chapter 5 and 10, respectively). On the website of the risk calculator a biopsy advice was not given. Recently, a recommendation for prostate biopsy is given which might support patients and physicians in decision making (Table 1)<sup>21</sup>. Furthermore, physicians should in cases of a biopsy decision not only communicate the probability on overall prostate cancer risk, but also the probability of a significant cancer, i.e. a cancer which needs treatment<sup>24-25</sup>.

**Table 1.** Prostate biopsy advice at ERSPC risk calculator level three

Chance of having a positive biopsy	Action
< 12.5%	No prostate biopsy
12.5% - 20.0%	Consider biopsy depending on co-morbidity and more than average risk on high grade prostate cancer (> 4%)
$\geq 20.0\%$	Prostate biopsy

To further improve patients' understanding of the risk on prostate cancer or indolent disease, probabilistic information in graphical format should be presented in addition to numerical format<sup>26-27</sup>. Other possibilities are not to communicate the probability on prostate cancer, but the probability of not having prostate cancer, or communicate relative risk instead of /or in addition to absolute risk<sup>17</sup>. Prospective studies are needed to assess the effect of different methods or combinations of methods to effectively communicate the risk on prostate cancer with patients.

## THE USE OF THE RISK CALCULATOR LEVEL THREE

The inclusion of TRUS in the risk calculator, which could be considered as an invasive procedure, could limit the clinical application. Chapter 9 describes the development and validation of a new risk calculator, the DRE based risk calculator, that includes information on prostate volume based on DRE and thus avoid the need for a TRUS. The

practical applicability of this novel risk calculator is expected to be higher for physicians and general practitioners, because less invasive procedures are needed. This reduces the time that is needed for use of the risk calculator. This new risk calculator performs well. Validation results in six cohorts, screening as well as clinical cohorts, showed moderate to good performance<sup>28</sup>. Furthermore, it was shown that this risk calculator outperforms the use of a model with only PSA and DRE and confirms that a PSA based risk calculator should contain some estimate of prostate volume, either based on TRUS or DRE.

### **VALIDATION OF THE RISK CALCULATOR LEVEL THREE**

The risk calculator developed in a Dutch initial screening setting was externally validated in different settings, i.e. in a Dutch clinical cohort and two initial screening cohorts of the ERSPC. The results in these cohorts were somewhat different. Chapter 7 presents the results of testing the validity of the risk calculator in a Dutch contemporary clinical cohort. The risk calculator performed well and showed good calibration and discrimination in a cohort with previous PSA tests and contemporary biopsy schemes. Limitations of the study were the small cohort, and the possibility of verification bias which could cause underprediction of the prostate cancer risk, because not every man under the 20% threshold was biopsied. Furthermore, follow-up of men on the development of prostate cancer is needed to draw conclusion for future screening. The study should be repeated in a larger cohort. It is however not ethical to biopsy all men under the threshold probability of 20% to assess performance of the risk calculator. In this low risk group, large numbers of biopsies would be unnecessary and mainly indolent disease would be detected<sup>21,29-30</sup>. A future improvement may be the possibility to use of a risk calculator for individual future risk estimation of a biopsy detectable prostate cancer, categorized into no cancer, low risk, and significant cancer in clinical setting. This should also provide a risk-based screening algorithm for PSA testing and biopsy in case of a negative biopsy<sup>31</sup>. In current Dutch clinical practice, men with an elevated PSA are advised to have a PSA follow-up at 3-6 months depending on the PSA level. Scientific knowledge is insufficiently available on this issue and also on the follow-up of men with a negative prostate biopsy.

The validity of the risk calculator in two screening cohorts of the ERSPC in Sweden and Finland (Chapter 8) was in contrast with the good performance of the risk calculator in a Dutch clinical setting. In both Scandinavian cohorts, the risk calculator discriminates well, but systematically underestimated the prostate cancer risk. The study in Chapter 8 and other studies<sup>22,32-33</sup> show that in different populations the risk calculator may need to be recalibrated before it can be used safely for predicting the probability on a positive biopsy.

In both studies (Chapter 7 and 8), a decision curve analysis showed that the optimal clinical result will be obtained by determining the biopsy indication using the risk calculator instead of using a model with PSA and DRE as is routinely used in current clinical practice. A benefit of this relative new analysis is that it integrates outcomes of discrimination and calibration<sup>34-35</sup>. For example, in case a model has superior discrimination but poorer calibration than the other model, which model should then be used in clinical practice? The results of the decision curve analysis indicate which of the different models would lead to better biopsy decisions if used in the validation setting. However, the risk calculator should be corrected for future applications in cases of miscalibration or physicians have to take into account the miscalibration.

It is possible to implement the use of risk calculators as addition to a general guideline when good instructions are included about the use of these tools. In guidelines have to be note, that before using a prediction model it is important to realize its origin, i.e. the characteristics of the population in which the tool was developed. If the model is highly specific for the population from which it is derived the utility decreases. For example, the calculations of the ERSPC risk calculator level three do not currently apply to men of African descent because insufficient men were included in the development cohort of the risk calculator to obtain meaningful data. This group of men has a genetically higher risk on prostate cancer. The risk calculator can be used, but with caution, especially if the risk is low or the PSA is between 2 and 10 ng/ml (PSA in 'grey area') or another risk calculator can be used in which men of African descent were included in the development cohort. When a prediction model is validated in an other setting than the development setting, it provides the best evidence about the performance of a prediction model in that setting. We recommend that references of studies about external validation of prediction models are added to a guideline.

If validation shows good performance and evidence shows that a prediction model outperforms the use of a model with PSA alone and a model with PSA and DRE, the confidence of physicians in the usefulness of the model in decision making will increase<sup>36</sup>, and consequently this might increase compliance of physicians with recommendations derived from a risk calculator. We recommend to educate physicians not only in the use of a risk calculator and the risks of using a risk calculator, but also to assess which risk calculator is the best to use in relation to the characteristics of their patients.

## **REDUCING THE NUMBER OF UNNECESSARY BIOPSIES WITH A PROSTATE CANCER RISK CALCULATOR**

Data in Chapter 6 show that with a risk-based approach a higher positive predictive value is reached compared to standard clinical practice, thus more appropriate biopsies

are taken. Besides this also more significant cancers are found with the risk-based approach. Results in Chapter 7 show that the 20% threshold seems reasonable, because under the 20% threshold mainly potentially indolent prostate cancers are detected in biopsied men. Data in Chapter 8 show that using the ERSPC risk calculator with a threshold probability of  $\geq 20\%$  next to a PSA  $\geq 3$  ng/ml substantially reduces the number of biopsies (34-50%) while missing very few significant cancers (2-4% of the total cancers detected) for which diagnosis at a later point in time might be too late for treatment with curative intent, however, depending on the moment of PSA follow-up. Also the detection of potentially indolent cancers decreased (12-23%), which is important because the focus should be on the detection of significant cancers as indication for biopsy. These cancers pose the highest risk of morbidity and mortality; whereas insignificant cancers by definition do not cause any harm during patients' lifetime. The chance of dying from prostate cancer decreases with increasing comorbidity<sup>37</sup>. Recently, models have been developed predicting significant cancer with a DRE-based risk calculator and the ERSPC risk calculator level three which may be useful in the identification of these cancers (Chapter 9). The study in Chapter 9 shows a good performance of these risk calculators. The risk calculators are developed in a screening setting and need further validation in screening and clinical cohorts.

When applying a biopsy threshold, it is important to weigh the benefits and harms; detecting prostate cancer at a curable stage on the one hand and performing unnecessary biopsies on the other<sup>38-39</sup>. Various studies show that PSA thresholds may lead to unacceptable numbers needed to investigate and numbers needed to treat to save one life<sup>38-39</sup>. A recent study showed a NNI (number needed to investigate) of 24 642 and a NNT (number needed to treat) of 724 for PSA values  $< 2.0$  ng/ml and; NNI of 2393 and a NNT of 427 for PSA values 2.0 to 4.0 ng/ml<sup>38</sup>. The probability threshold of  $\geq 20\%$  to perform a biopsy seems acceptable to urologists. However, cancers are present under this threshold and these will be missed. Ideally, the number of these cancers should be low and their tumor characteristics favourable.

Further improvements to better identify men at higher risk on significant prostate cancer are: firstly, updating risk algorithms with new biomarkers and risk factors and validate them in an external cohort. Secondly, the development of new markers that are suitable to detect only the significant, which is a major challenge. Thirdly, new imaging technologies, such as multiparametric magnetic resonance imaging (MRI) that is likely to be of aid in identifying significant disease and might avoid biopsies in men with insignificant disease<sup>40</sup>.



## CONCLUSIONS

In order to reduce two important negative side-effects of PSA screening; the large numbers of unnecessary biopsies, and overdiagnosis and overtreatment of prostate cancer, it was hypothesized in this thesis that the use of prediction models supports the identification of men with an elevated risk of having a biopsy detectable prostate cancers and distinguishes potentially indolent disease in cases of a prostate cancer diagnosis. The key findings of testing a decision aid and applying risk-based strategies are:

- *Decision aid*

A leaflet with individual risk estimation and information about the pros and cons of PSA screening supported informed decision making and may be a useful tool for shared decision making.

- *The use of risk calculators*

- Is efficient; the number of unnecessary biopsies and also the detection of potentially indolent disease reduce using a risk calculator which calculates the probability on prostate cancers.
- Is effective; more significant cancers were detected with the risk calculator compared to clinical judgement and these are the cancers that should be treated. Recently, the risk calculator provides also the risk on significant cancer which might improve the identification of these cancers.
- Supports the identification of men with potentially indolent disease in case of a prostate cancers diagnosis and has the potential to prevent overtreatment of these tumours.
- Performs better in the identification of prostate cancer than a model with only PSA or a model with PSA and DRE.
- Can be cost-effective by reducing the number of unnecessary biopsies and active treatment in cases of a potentially indolent prostate cancer.
- Is useful in prostate biopsy decision making, and treatment decision making in men with localized prostate cancer. The best ways to communicate probabilities have to be investigated.

- *Compliance with risk calculators*

Overall compliance of physicians and patients with recommendations of a risk calculator was high after active implementation. The use of guidelines or protocols may counteract the adoption of recommendations of a risk calculator. In general, the use of a risk calculator in clinical practice is limited. To improve the use and compliance, physicians need to have acquired a state of familiarity with the risk calculators, need to have confidence in the usefulness which will be positively influence by proven good performance, and need to have confidence in its user-friendliness. If validation of the risk calculator shows good performance, the confidence of physicians in the

usefulness of the model in decision making will increase. Active implementation of risk calculators will support the use and compliance; interactively physicians are informed about the use of the risk calculator and its performance, and their misconceptions can be solved. Furthermore, with the new DRE-based risk calculator it is likely that the use will increase, because TRUS is replaced by DRE estimates.

- *Validity of risk calculator predicting the risk on prostate cancer*

Overall the risk calculator level three performs well in a Dutch clinical cohort. The threshold probability of 20% seems reasonable, since the majority of the cancers found under this threshold are potentially indolent. However, there is a lack of follow-up. The risk calculator discriminates well in two other initial screening cohorts in Sweden and Finland, but overestimates the risk of a positive biopsy. In such cases, a risk calculator has to be updated to provide reliable risk estimates. This is important to make safe decisions based on the risk calculator.

## OVERALL LIMITATIONS OF A RISK CALCULATOR

- It is not possible to use safely in every setting, thus external validation and continuous updating to changing circumstances is needed.
- Below each probability threshold, prostate cancers are present and may be missed. This number should be low and their characteristics favourable. To apply a threshold, the harms and benefits of screening have to be weighed. Longer follow-up of larger cohort of patients, ideally, in a prospective study design is needed. Short term results can be provided by retrospective research. Future improvements in the detection of prostate cancer, especially significant cancers, are updating prediction models with new markers, developing new models, identification of new biomarkers, and imaging will be supportive to selectively screen men at risk.

## RECOMMENDATIONS REGARDING A DECISION AID AND PREDICTION MODELS

- We recommend to physicians the use of decision aids about the pros and cons of PSA testing and, based on the literature, to consider patients' preference, individual risk factors for prostate cancer and life expectancy in shared decision making with their patients about the need of a PSA test.
- Prediction models should not be the sole factor determining the need of a prostate biopsy or treatment in men with prostate cancer. These decisions benefit from risk estimation, but should also be based on life expectancy (age and comorbidity), physicians' judgment and experience, patients' opinion, and individual risk factors

for prostate cancer in case of a biopsy decision and side effects in case of a treatment choice. In conclusion, all these factors have to be considered in shared decision making with patients.

- Implementation of the new DRE-based risk calculator in general practice is recommended, because this risk calculator may improve the gatekeeper function of general practitioners. If general practitioners are better enabled to refer patients to urologists with a biopsy indication based on the recommendation of a risk calculator instead of referrals based on an elevated PSA and/or suspicious DRE can this prevent unnecessary referrals.
- The development of recommendations for the follow-up of patients with an elevated PSA who either opted for no biopsy or had a negative biopsy. A future risk calculator might be promising.
- The development of a protocol to communicate risks with patients in line with best evidence.

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# Part 7

## Appendices

Summary

Samenvatting (Dutch)

Curriculum Vitae

List of publications

Dankwoord

PhD Portfolio





## SUMMARY

The first part of this thesis includes a general introduction on different aspects of the prostate, prostate cancer and prostate cancer treatment (**Chapter 1**). Subsequently, **Chapter 2** is a review about PSA screening, incidence and mortality rates of prostate cancer, and the benefits and harms of PSA screening. Based on the outcome of the review, we concluded that PSA screening reduces the prostate cancer-specific mortality. However, PSA screening leads to two important unwanted side effects; firstly, screening induces many unnecessary prostate biopsies, and secondly, it leads to overdiagnosis and overtreatment of prostate cancer. The balance between the benefits and harms of PSA screening has yet to be determined. So, at this moment a population-based PSA screening programme is not attractive as healthcare policy. Various organizations developed guidelines about recommendations on individual PSA testing. Most guidelines stress the importance of individuals having to make an informed decision regarding PSA testing after being informed about the pros and cons of PSA screening. The scope of this thesis is outlined in **Chapter 3**. In order to reduce the two important side effects of PSA testing, it was hypothesized that the use of prediction models supports the identification of men with an elevated risk of having a biopsy detectable prostate cancer and the identification of potentially indolent disease. The scope of this thesis was to test a decision aid and the application of prediction models in urological clinical practice.

**In Chapter 4** (part two of this thesis), an intervention study was performed. In 601 men, the effect of providing a leaflet including individual risk estimation on informed decision making about PSA testing was assessed, i.e. knowledge about prostate cancer and PSA screening, attitude towards undergoing a PSA test and intention to have a PSA test. This risk calculator uses information about family history, age and urinary symptoms to calculate a rough estimation on prostate cancer. Men filled in two questionnaires; before and after receiving the leaflet. After the second assessment more men met the requirement of informed decision, more men had relevant knowledge on prostate cancer and PSA screening, and most men reported no decisional conflict about having a PSA test or not.

The third part of this thesis (Chapter 5 and 6) focuses on the use of the recommendation of a prostate cancer risk calculator in decision making regarding the need of a prostate biopsy. **Chapter 5** shows the results of an implementation study about compliance of urologists and patients with biopsy recommendations in five Dutch hospitals. The recommendations were obtained from the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator level three. This risk calculator estimates the probability of a positive lateralized sextant prostate biopsy using serum PSA, the out-

comes of digital rectal examination (DRE) and transrectal ultrasound (TRUS) investigations, i.e. the presence of hypoechoic lesions and prostate volume. A prostate biopsy was recommended if the probability was  $\geq 20\%$ . Biopsy recommendations of the risk calculator were followed in almost all patients. However, 36% of the patients with a 'no biopsy' recommendation underwent a prostate biopsy. In most of these cases, urologists opted for biopsy because of an elevated PSA ( $\geq 3$  ng/ml) and patients preferred a biopsy because they wanted certainty. Patients who were compliant with a 'no biopsy' recommendation made less often an informed decision, had lower mean probabilities on prostate cancer and lower levels of generic anxiety than non-compliant patients. Before a risk calculator can be implemented, it is important to obtain insight into guidelines that might counteract the adoption of the use of a risk calculator as a result of opposing recommendations. In **Chapter 6**, using the risk calculator led to more biopsies, but more appropriate prostate biopsies compared to clinical judgement that includes serum PSA and/or a suspicious DRE in the decision making, translating into a higher positive predictive value (number of cancers/number of biopsies, 64% versus 44%, respectively) and the detection of a more significant cancers (34% versus 15%, respectively). This study has limitations, such as the relatively small cohorts and the retrospective part of the study.

In the fourth part of this thesis (Chapter 7, 8 and 9), we aimed to validate prostate cancer risk calculators in other settings to assess their value beyond the development setting. The ERSPC risk calculator level three was prospectively validated in a contemporary Dutch clinical setting (**Chapter 7**). The risk calculator performed well using contemporary biopsy schemes; it discriminates men with and without prostate cancer well (area under the curve (AUC) 0.79) and the actual percentage of prostate cancer diagnoses agreed with the mean calculated probabilities with the risk calculator. A threshold  $\geq 20\%$  seems reasonable to recommend a prostate biopsy, since the majority of the prostate cancers detected under this threshold were potentially indolent. The risk calculator performed significantly better than a model with only PSA and DRE in the selection of men at higher risk on prostate cancer.

The risk calculator was also validated in two initial screening settings of the ERSPC section Finland and Sweden (**Chapter 8**). The risk calculator discriminated well between men with and without prostate cancer (AUC 0.76 and 0.78, respectively), but overestimated the probability of a positive prostate biopsy. Also, this study showed that a risk calculator as indication for a prostate biopsy outperformed the use of model with only PSA and DRE. Using a probability threshold of  $\geq 20\%$  next to a PSA  $\geq 3$  ng/ml substantially reduced unnecessary prostate biopsies while a few significant cancers were missed. The inclusion of TRUS in the risk calculator, which could be considered as an invasive procedure, could limit the clinical application. However, a new risk calculator, the DRE-based

risk calculator, has been developed and validated that includes information on prostate volume based on DRE and thus avoids the need for a TRUS before biopsy (**Chapter 9**). This risk calculator performs well with a slight impact on performance compared to risk calculator level three. For both risk calculators, the ERSPC risk calculator level three and the novel DRE-based calculator, the calculation of the probability of significant cancer has been developed next to the calculation of the overall probability of prostate cancer. These models discriminate well between men with and without significant disease.

In the fifth part of this thesis, we studied the selection of men for active surveillance using a prostate cancer risk calculator (Chapter 10) and disease insight and treatment of men on active surveillance (Chapter 11). **Chapter 10** shows that active surveillance recommendations based on the ERSPC risk calculator level six were followed in 82% of the patients. Another 29% chose for active surveillance despite an active treatment recommendation. This indicated that the 70% threshold may be too high for urologists and patients. In these cases which were non-compliant with active treatment recommendations, most reported reasons for urologists were that patients preferred active surveillance and that patients fulfilled the Prostate cancer Research International: Active Surveillance (PRIAS) criteria. The most reported reason for patients was the delay of side-effects of active treatment so that the quality of life/lifestyle is not altered. Patients who chose active surveillance against the recommendation of the risk calculator reported a greater influence of the urologist, had lower PSA levels and lower generic anxiety levels than men who complied with an active treatment recommendation. A questionnaire-based study was performed in 129 men on active surveillance (**Chapter 11**). Men had adequate knowledge of prostate cancer and realistic perceptions of the active surveillance strategy. The most reported advantage and disadvantage of men on active surveillance were the delay of side-effects of active treatment and the risk of disease progression, respectively.

The studies described in the previous chapters are discussed in **Chapter 12** (part six) and summarized in part seven of this thesis.



## SAMENVATTING

In het eerste deel van dit proefschrift wordt een algemene introductie gegeven over verschillende aspecten van de prostaat, prostaatkanker en de behandeling van prostaatkanker (**Hoofdstuk 1**). Vervolgens wordt een literatuuroverzicht gegeven van studies naar het effect van PSA screening, prostaatkanker incidentie en sterfte, en de voor- en nadelen van PSA screening (**Hoofdstuk 2**). Op basis van het literatuuroverzicht wordt geconcludeerd dat PSA screening leidt tot een afname van de prostaatkanker specifieke sterfte. Echter, PSA screening leidt ook tot twee belangrijke negatieve effecten. Ten eerste leidt PSA screening tot een grote hoeveelheid onnodige prostaatbiopsies en ten tweede tot overdiagnose en overbehandeling van prostaatkanker. De balans tussen de voor- en nadelen van PSA screening moet nog worden bepaald. Zodoende kan er geen prostaatkanker screening op bevolkingsniveau worden geadviseerd. Verschillende organisaties ontwikkelden richtlijnen met betrekking tot het aanbevelen van individuele PSA screening. De meeste richtlijnen benadrukken het belang van individuen om een geïnformeerde keuze te maken over het al dan niet ondergaan van een PSA test, nadat zij informatie hebben ontvangen over de voor- en nadelen van PSA screening. In **Hoofdstuk 3** wordt het doel van dit proefschrift beschreven, het bepalen van het effect van een informatiefolder met risicowijzer op het maken van een geïnformeerde keuze over PSA screening door mannen en de toepassing van predictie modellen in de urologische praktijk.

In **Hoofdstuk 4** (deel twee van dit proefschrift) is een interventie studie beschreven. Het effect van een informatiefolder over prostaatkanker en PSA screening inclusief een risicowijzer op het maken van een geïnformeerde keuze over individuele PSA screening werd bepaald. Een geïnformeerde keuze is een keuze die gebaseerd is op het hebben van relevante kennis en consistent is met de waarden van de beslisser. De risicowijzer berekent de kans op prostaatkanker en in die berekening wordt informatie over de familiegeschiedenis, leeftijd en plasklachten meegenomen. Zeshonderd en één mannen vulden twee vragenlijsten in; voor en na het ontvangen van de informatiefolder met een risicowijzer. Na de tweede meting maakten meer mannen een geïnformeerde keuze over het al dan niet ondergaan van een PSA test, meer mannen hadden relevante kennis over prostaatkanker en PSA screening, en de meeste mannen hadden geen probleem in het nemen van een beslissing ten aanzien van PSA screening.

Het derde deel van dit proefschrift richt zich op het gebruik van een prostaatkanker risicowijzer in de besluitvorming om al dan niet een prostaatbiopsie te doen. **Hoofdstuk 5** beschrijft de compliance van urologen en patiënten met de biopsie aanbeveling die voortkwam uit het gebruik van de European Randomized study of Screening for

Prostate Cancer (ERSPC) risicowijzer drie. Deze wijzer berekent de kans op een positieve sextant prostaatbiopsie bij niet eerder gescreeende mannen. Voor deze berekening worden de uitkomsten van de serum PSA test, DRE, TRUS (hypoechoogene laesie ja/nee) en het transrectaal echografische prostaatvolume gebruikt. Een prostaatbiopsie werd aanbevolen als de kans op een positieve prostaatbiopsie  $\geq 20\%$  was. In bijna alle cases werd de aanbeveling voortgekomen uit het gebruik van de risicowijzer opgevolgd door zowel urologen als patiënten. Echter 36% van de patiënten met een 'niet bioteren' aanbeveling ondergingen een prostaatbiopsie. De belangrijkste reden voor urologen om tegen het advies van de risicowijzer te bioteren was een verhoogd PSA ( $\geq 3$  ng/ml) en voor patiënten de voorkeur voor een biopsie omdat zij zekerheid wilden over het al dan niet aanwezig zijn van prostaatkanker. Patiënten die compliant waren met een 'niet bioteren' aanbeveling, maakte minder vaak een geïnformeerde keuze, hadden gemiddeld een lagere kans op prostaatkanker volgens de uitkomst van de risicowijzer, en gemiddeld minder algemene angst in vergelijking tot patiënten die zich lieten bioteren tegen de aanbeveling. Voordat een risicowijzer kan worden geïmplementeerd in de klinische praktijk is het belangrijk om inzicht te hebben in huidige richtlijnen die worden gebruikt. Deze kunnen invloed hebben op de acceptatie van de risicowijzer, indien tegenovergestelde adviezen worden gegeven. In **Hoofdstuk 6** wordt het effect beschreven van de implementatie van de ERSPC risicowijzer drie in vergelijking met het klinisch oordeel van urologen op basis van PSA en DRE uitkomsten op het percentage prostaatbiopsieën die zijn afgenomen en de positief voorspellende waarde (het aantal positieve prostaatbiopsieën gedeeld door het aantal prostaatbiopsieën). Het gebruik van een risicowijzer leidt tot meer prostaatbiopsieën, maar ook tot een aanzienlijk hoger percentage prostaatkanker diagnoses en significante tumoren, in vergelijking tot het klinische oordeel van urologen. De beperkingen van deze studie waren de kleine cohorten en het retrospectieve deel van de studie.

In het vierde deel van dit proefschrift worden drie studies gepresenteerd. In deze studies wordt de validiteit van prostaatkanker risicowijzers onderzocht in andere settings dan waarin zij zijn ontwikkeld. In **Hoofdstuk 7** is de validiteit van de ERSPC risicowijzer drie in een 'hedendaags' klinische cohort bepaald, namelijk in de urologische praktijk van vijf Nederlandse ziekenhuizen. Driehonderd twintig mannen werden geïnccludeerd. De studie toonde aan dat de risicowijzer goed de kans op een positieve prostaatbiopsie voorspelde en eveneens goed mannen zonder en met prostaatkanker kon onderscheiden, in een cohort waarin meer dan zes prostaatbiopsies werden afgenomen en een groot deel van de mannen in de voorgeschiedenis een PSA test ondergingen. De resultaten toonden eveneens aan dat de risicowijzer beter presteert dan een model met alleen PSA en DRE voor de selectie van mannen met een verhoogd risico op prostaatkanker. De aanbeveling van een prostaatbiopsie bij een kans op een positieve prostaatbiopsie

$\geq 20\%$  lijkt acceptabel, omdat bij gebiopteerde mannen met een kans onder de 20% hoofdzakelijk potentiële indolente tumoren werden gediagnosticeerd.

De ERSPC risicowijzer drie werd ook gevalideerd in twee screening cohorts van de ERSPC, de eerste screeningsronde in Finland en Zweden (**Hoofdstuk 8**). De risicowijzer onderscheidde mannen met en zonder prostaatkanker goed, maar overschatte de kans op een positieve biopsie. Eveneens werd ook in deze studie aangetoond dat het gebruik van een risicowijzer leidde tot een betere selectie van mannen met een verhoogd risico op prostaatkanker, dan het gebruik van alleen de uitkomsten van PSA en DRE. Het gebruik van de 20% cut-off met de risicowijzer naast een PSA  $\geq 3$  ng/ml als screening algoritme leidde tot aanzienlijk minder onnodige prostaatbiopsieën, terwijl enkele significante tumoren werden gemist.

Voor het kunnen gebruiken van de ERSPC risicowijzer drie is het noodzakelijk om een extra invasieve procedure te doen, de TRUS, dit kan de klinische toepasbaarheid van de wijzer beperken. Een nieuwe risicowijzer werd daarom ontwikkeld en gevalideerd. Deze wijzer includeert prostaatvolume bepaald tijdens een DRE in de berekening van de kans op een positieve prostaatbiopsie, en hierdoor kan een TRUS worden vermeden (**Hoofdstuk 9**). De risicowijzer onderscheidt mannen met en zonder prostaatkanker bijna even goed als de ERSPC risicowijzer drie. In deze studie werden deze beide risicowijzers uitgebreid met de berekening van de kans op een significante tumor naast de berekening van de kans op een positieve prostaatbiopsie. Deze wijzers presteren goed in het onderscheiden van mannen met en zonder een significante tumor.

In het vijfde deel van dit proefschrift worden twee studies gepresenteerd. In de eerste studie is de selectie van mannen voor een actief afwachtend beleid met behulp van een prostaatkanker risicowijzer onderzocht, en in de tweede studie het ziekte-inzicht en inzicht in de behandeling van mannen die een actief afwachtend beleid volgen. In **Hoofdstuk 10** werd de compliance bepaald van urologen en patiënten met de uitkomst van de ERSPC risicowijzer zes. Deze wijzer berekent de kans op een indolente tumor. Een actief afwachtend beleid werd aanbevolen als de kans op een indolente prostaatkanker  $>70\%$  was, en actieve behandeling indien de kans  $\leq 70\%$  was. De aanbeveling voortgekomen uit het gebruik van de risicowijzer werd opgevolgd in 82% van de patiënten. Negenentwintig procent van de patiënten kozen voor een actief afwachtend beleid, ondanks dat een actieve behandeling werd aanbevolen. Dit betekent dat de 70% grens misschien te hoog is voor zowel urologen als patiënten. De meest genoemde redenen door urologen om de aanbeveling van een actieve behandeling niet op te volgen waren: de voorkeur van patiënten voor een actief afwachtend beleid en patiënten voldeden aan de Prostate cancer Research International: Active Surveillance (PRIAS) criteria. Patiënten vonden een belangrijk voordeel van een actief afwachtend beleid het uitstellen van complicaties als gevolg van een actieve behandeling, zodat kwaliteit van leven gehandhaafd blijft.

In **Hoofdstuk 11** worden de uitkomsten beschreven van een vragenlijstonderzoek onder 129 mannen die een actief afwachtend beleid volgen. Bij de meeste mannen was de kennis over prostaatkanker voldoende en hadden zij realistische percepties over de strategie van een actief afwachtend beleid. Het meest gerapporteerde voordeel van een actief afwachtend beleid door mannen was ook in deze studie het uitstellen van complicaties als gevolg van een actieve behandeling, en het meest gerapporteerde nadeel was de kans op progressie van de prostaatkanker.

In deel zes van dit proefschrift worden de resultaten van de voorgaande hoofdstukken bediscussieerd (**Hoofdstuk 12**) en samengevat in deel zeven.



## CURRICULUM VITAE



Heidi van Vugt is geboren op 23 juli 1969 te Mijdrecht. Nadat zij haar HAVO diploma behaalde aan het Veenlanden College in Mijdrecht, verhuisde zij in 1987 naar Utrecht en begon aldaar de verpleegkundige-A opleiding in het Diaconessenhuis. Na het behalen van haar diploma werkte ze kortdurend op de afdeling neurologie. Tijdens die periode volgde zij de management opleiding aan de Hogeschool Midden Nederland te Leusden en aansluitend in 1994 kon zij beginnen als leidinggevende op de afdeling orthopedie en urologie. In 1996 startte zij op de Intensive Care en Hartbewaking en rondde na anderhalf jaar de opleiding Intensive Care en Hartbewaking af. Na 12 jaar werken in het Diaconessenhuis te Utrecht ging zij in 1998 aan het werk in het Universitair Medisch Centrum Utrecht als Intensive Care verpleegkundige. In 2007 rondde zij de studie Algemene Gezondheidswetenschappen afstudeerrichting Management en Innovatie af aan de Universiteit Utrecht. Na deze studie kon zij beginnen als promovenda in augustus 2008 bij de afdeling Urologie en Public Health van het Erasmus Medisch Centrum te Rotterdam, onder leiding van Professor Chris Bangma, Professor Ewout Steyerberg, Monique Roobol en Ida Korfage.



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The impact of a prostate cancer risk calculator on biopsies taken and positive predictive value: an empirical evaluation. van Vugt HA, Steyerberg EW, Bul M, Bangma CH, Roobol M. Submitted

## DANKWOORD

In 2008 kreeg ik de kans om bij de afdelingen Urologie en Maatschappelijk gezondheidszorg onderzoek te mogen doen. Een nieuwe wereld die ik graag wilde ontdekken en dat is gelukt. Ik heb veel mogen leren en ben uitgedaagd om tot het uiterste te gaan. Ik heb zoveel mensen mogen meemaken, die allemaal een belangrijk aandeel hebben gehad in het kunnen bereiken van dit eindresultaat. Die mensen wil ik graag bedanken.

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Heidi van Vugt  
Juli 2012

## PHD PORTFOLIO

Name PhD student	Heidi A. van Vugt
Erasmus MC Department	Urology
PhD period	2008-2012
Promotors	Chris H. Bangma Ewout W. Steyerberg
Supervisors	Monique J. Roobol Ida J. Korfage

### Phd training

	Year	Workload (ECTS)
<b>Courses</b>		
Biomedical English Writing and Communication	2009	2
Classic Methods for Data-analysis	2009	5.6
Modern statistics methods	2009	4.3
Clinical Decision Analysis	2009	0.7
Planning and Evaluation of Screening	2010	1.4
<b>Seminars and workshops</b>		
Phd meeting	2008-2011	1
Seminars/journal club/symposia	2008-2011	2
<b>Presentations</b>		
Urology Amphia Hospital Breda	2009	0.5
ZonMw Utrecht	2009	1
Phd meeting Erasmus MC Rotterdam	2010	0.5
Integraal cancer center Rotterdam	2011	1
Regio avond Noord Nederland UMCG Groningen	2011	1
Symposium Cancer center UMCG Groningen	2011	1
Deskundigheidsbevordering Huisartsen Breda e.o Amphia Hospital Breda	2011	1
NVU Hengelo	2011	0.5
NVU 's-Hertogenbosch	2012	0.5
<b>(Inter)national conferences</b>		
Visits and oral or poster presentations at (ERSPC meeting 2010, EAU 2011, ERSPC meeting 2011, AUA 2011, ISDM 2011, AS 2012, EAU 2012, AUA 2012)	2010-2012	6
<b>Total ECTS</b>		<b>30</b>

ZonMw Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie

UMCG Universitair Medical Center Groningen

NVU Nederlandse Vereniging voor Urologie

ERSPC European Randomized study of Screening for Prostate Cancer

EAU European Association of Urology

AUA American Urological Association

ISDM International Shared Decision Making

AS Active Surveillance