# POPULATION BASED SCREENING FOR PROSTATE CANCER:

# TUMOR CHARACTERISTICS

## POPULATIE ONDERZOEK SCREENING NAAR PROSTAAT KANKER: TUMOR KARAKTERISTIEKEN

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## Contents

## List of abbreveations

| | |
|---|---|
| BPH | Benign Prostate Hyperplasia |
| DRE | Digital Rectal Examination |
| ERSPC | European Randomized study of Screening for Prostate Cancer |
| F/T PSA | Ratio between Free Prostate Specific Antigen and Total Prostate Specific Antigen |
| GP | General Practitionar |
| hK2 | Human Glandular Kallikrein 2 |
| LUTS | Lower Urinary Tract Symptoms |
| PALGA | Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (the nationwide network and registry of histo- and cytopathology in the Netherlands) |
| PCPT | Prostate Cancer Prevention Trial |
| PLCO | Prostate Lung Colorectal Ovarian cancer screening trial |
| PPV | Positive Predictive Value |
| PSA | Prostate Specific Antigen |
| PSA-D | Prostate Specific Antigen Density |
| PSA-V | Prostate Specific Antigen Velocity |
| SEER | Surveillance, Epidemiology and End Results program |
| THvdK | Prof.dr. T.H. van der Kwast |
| TRUS | Trans Rectal Ultra Sonography |

# Introduction

## Foreword

The fact that prostate cancer can be detected at an early stage, before the occurrence of symptoms, does not mean that screening for prostate cancer will be beneficial. The introduction of serum PSA measurements into medical practice has led to dramatic changes in the incidence of prostate cancer, i.e. increased detection rates and a stage reduction at the time of detection. However with respect to mortality reduction and quality-of life effects the value of screening for prostate cancer is still uncertain. At this time randomized controlled trials are being performed to assess the impact of screening and early intervention on the morbidity and mortality of prostate cancer. In the mean time the improvement of the specificity, sensitivity and accuracy of screening methods is important for both the large randomized studies and for screening upon request. Not only is it necessary to improve specificity for the reduction of unnecessary biopsies, but also more accurate staging and grading of prostate cancer at the time of diagnosis will enable the selection of patients that need treatment and those that can be followed through active surveillance. At this moment there is no conclusive evidence for a beneficial effect of screening for prostate cancer, hence we have to wait for the outcome of randomized controlled trials to determine a place for prostate cancer screening in public health.

The present thesis intends to contribute to the understanding of the procedures applied to early detection of prostate cancer within the European Randomized Study of Screening for Prostate Cancer (ERSPC). The parameters under study, which include tumor characteristics and interval cancers as a measure of the appropriateness of the screening interval, will help to design the most adequate way of testing for prostate cancer once ERSPC has been completed. If the outcome of the study is positive, the data will contribute to the design of the best screening regiment that can be recommended to health care providers around the world. In case of a negative outcome, it is likely that men will remain attracted to the idea of early detection of a potentially lethal disease. In that case the results will be useful to help to determine the best way of opportunistic screening.

## Scope of the thesis

The European Randomized study of Screening for Prostate Cancer is a multi-centre randomized controlled trial to examine whether screening for prostate cancer has an effect on prostate cancer mortality. The total study cohort consists of 268.000 men in eight different European Countries. In the Netherlands the study is being conducted in the region of Rotterdam by the study group of the Erasmus Medical Centre Rotterdam. Between 1993 and 2000 a total of 42,376 men (21,210 in the screen arm and 21,166 in the control arm) aged 55-74 years were randomized to the ERSPC, section Rotterdam. In the screen arm screening consisted of PSA measurement, rectal examination and trans-rectal ultrasound. From December 1993 to February 1997 the Rotterdam screening regimen called for lateralized sextant trans-rectal biopsy if the PSA level was equal to or higher than 4.0 ng/mL, and if DRE and/or TRUS were suspicious for cancer at low PSA values (0.0 – 3.9 ng/mL). The biopsy procedure was performed in a second visit. From December 1993 to October 1996 an early recall visit (after one year) was performed for those men who had a biopsy indication in the prevalence screen but a negative biopsy outcome. These men were invited again for PSA, DRE, TRUS and sextant biopsy. From February 1997 onwards, a PSA of $\geq$ 3.0 ng/mL became the sole biopsy indication. The ERSPC, section Rotterdam applies a re-screening interval of 4 years. Men in the control arm were not offered PSA measurement or screening. They received general medical health care.

This thesis focuses on the tumor characteristics of the prostate cancers and whether the current screening procedure is correct or might be improved. The down-staging and grading seen in the prostate cancers detected in the screen arm compared to the control arm and the subsequent screening rounds show that prostate cancer can be detected at an earlier possibly curable stage. These results are intermediate endpoints in an ongoing trial and do not necessarily predict the true outcome in time. They can however help to improve the specificity, sensitivity and the accuracy of the screening methods used, and to identify the optimum interval for screening. The tumor characteristics of the advanced prostate cancers detected in the various screening rounds will help to recognize the prognostic factors, necessary to identify the cancers that need to be treated. Furthermore the impact of contamination in the control arm has been investigated and depends strongly on the definition of contamination. Contamination in this thesis is the rate of PSA measurements resulting in prostate biopsy in the control arm of the trial. A high contamination rate would lead to more and earlier detection of prostate cancers in the control arm and a shift in the overall composition of the tumor difference between screened and non-screened groups regarding tumor characteristics and numbers. This

could seriously affect the power of the trial. Finally the rate of the interval cancers has been established. Interval cancers are prostate cancers detected in the inter-screening interval after a fully completed first screening round. A high rate of interval cancers would mean that the screening interval is too long or that the screening methods used were not effective.

This thesis therefore discusses a number of questions:

1. Is the current screening interval correct?
2. Is the method of screening correct with regard to the intermediate endpoints, that is tumor characteristics?
3. Does the current contamination in ERSPC influence the characteristics of the tumors found?
4. Do the tumor characteristics provide prognostic factors that are needed to recognize prostate cancer that requires treatment?

In chapter 1 of the thesis the tumor characteristics detected in the first round of screening are compared with the tumor characteristics of the prostate cancers found in the control arm. In chapter 2 the impact of contamination in the control arm is described. In chapter 3 the tumor characteristics of the prostate cancers detected in the first and subsequent screening rounds are analyzed. In chapter 4 the tumor characteristics of the interval cancers were analyzed and described.

## General introduction and description of screening tools

An apparent rise in prostate cancer incidence is seen: in many industrialized countries prostate cancer has become the most common cancer diagnosed and the second most common cause of cancer deaths in men [1]. Extensive efforts have been made on secondary (to detect prostate cancer at a curable stage) and tertiary prevention (to prevent metastasis or recurrence of the cancer). At this moment the most realistic opportunity for cure is the detection of prostate cancer at an early stage. Different screening methods i.e. digital rectal examination (DRE), transrectal ultrasound (TRUS), different forms of prostate specific antigen (PSA) and TRUS-guided biopsies are available. Although we are technically able now to screen for prostate cancer, screening remains a debatable issue. The value of screening is still uncertain with respect to mortality reduction and quality-of life effects. The effectiveness of screening is assessed by randomized, controlled trials such as the European Randomized study of Screening for Prostate Cancer (ERSPC) [2-4] and the Prostate, Lung, Colon and Ovarian cancer (PLCO) trial [5] in the United States. However, different screening methods for early detection of prostate cancer are being used at this moment. The most effective method still has to be established.

### *Incidence*

The importance and aggressiveness of prostate cancer and its impact on public health is illustrated by incidence and mortality rates. In 1998 the Netherlands Cancer Registry shows a crude rate of prostate cancer incidence of 85.0 cases per 100,000 person-years. The mortality (crude) rate is 33 cases per 100,000 person-years. Between the ages of 40 – 60 years the overall incidence rate for prostate cancer is 5.5% and the mortality rate is 2.2%. Both rates keep rising above the age of 60 [6]. In the European Community it was estimated that in 1980 prostate cancer was the second most common form of cancer in men after lung cancer. The incidence is still rising and overall; it appears that prostate cancer is increasing more rapidly in southern Europe (25% every 5 years) than elsewhere in Europe. The European standardized rate for prostate cancer incidence is 87.2 cases per 100,000 person-years and for mortality 34.1 per 100,000 person-years [7]. In the United States the incidence of clinical prostate cancer differs widely with large ethnic and international differences. Caucasian men in the United States have a lower lifetime risk of developing prostate cancer or dying from the disease than Afro-Americans (156 per 100,000 person-years and 243 per 100,000 person-years versus 26.7 per 100,000 person-years and 65.1 per 100,000 person-years respectively). Another feature of prostate cancer is the association between incidence (and mortality) rates and age, which rises dramatically from men in their forties (2.59%) to peak during their eighties (13.83%). The life time probability of being diagnosed with prostate cancer in the USA is 17.12% [1].

## Diagnostic tools

The value of different diagnostic tools used in screening for prostate cancer is usually expressed in terms of sensitivity, specificity and positive predictive value (PPV). In order to calculate the true sensitivity the underlying prevalence of the disease in the population must be known. This is not known for prostate cancer. Therefore prevalence and subsequently sensitivity are based on the number of positive biopsies in the screened population. Screened means, who underwent PSA test alone or combined with DRE. Sensitivity defined in this way is termed 'relative sensitivity' [8].

| | | disease | | | |
|---|---|---|---|---|---|
| | | + | - | | |
| test | + | True Positive (TP) | False Positive (FP) | All with positive test TP + FP | Positive Predictive Value TP / (TP+FP) |
| | - | False Negative (FN) | True Negative (TN) | All with negative test FN + TN | Negative Predictive Value TN / (FN + TN) |
| | | All with disease | All without disease | Everyone TP + FP + FN + TN | |
| | | Sensitivity | Specificity | Pre-test probability | |

### *Digital rectal examination*

Digital rectal examination (DRE) has always been the primary method for evaluating the prostate. It is easy to perform, causes little discomfort to the patient and it is inexpensive. However Smith et al [9] showed that DRE is investigator dependent and has a great interexaminer variability. The usefulness of DRE in screening is subject to several studies. In a case-control study Jacobsen et al [10] reported an effect of DRE in screening for prostate cancer; men screened with DRE were less likely to die from prostate cancer and screening may have prevented as many as 50% to 70% of prostate cancer deaths. However both the studies from Friedman et al [11], a case-control study with a case group of patients with metastatic disease and Chodak et al [12] reporting a substantial clinical under staging compared to pathologic stages of radical prostatectomy specimens, showed little or no additional beneficial effect of DRE in a screening program.

It is thought that DRE can have an additional value in the detection of clinically significant cancers especially in the low 'normal' ranges of PSA (< 4.0 ng/ml). Babaian et al [13] biopsied 436 men. They found a statistically significant difference favoring the PPV of the combination DRE and PSA compared tot that of TRUS and PSA or PSA alone. The current American Cancer Society guidelines recommend that both a DRE and a serum PSA measurement be offered annually with periodic health examinations in men over the age of 50 years who have a life expectancy of at least 10 years [14]. However studies from Schröder et al [15] and Beemsterboer et al [16] are doubtful about the efficacy of DRE since DRE shows a poor performance, especially in the lower PSA ranges. Tumors often are too small to be detected by DRE and the tumors that will be found might not be clinically significant cancers. Data addressing the issue of serendipity (change findings) conclude that more than 50% of positive DRE in that range may be false positive and cancers are found by chance at different locations [17]. Recently Gosselaar et all [18] reviewed the prevalence and tumor characteristics of prostate cancers detected at low PSA levels and concludes that the favorable characteristics of the tumors detectable at very low PSA levels seem to justify the conclusion that an unknown but sizeable proportion of the cancers found at biopsy are clinically insignificant. Thompson et all [19,20] in the PCPT trial reported that as many as 15% of men with a PSA value less than 4.0 ng/ml have prostate cancer and that 15% of these cancers are high grade. Predictive for high grade disease is the PSA level, abnormal DRE result, older age at biopsy and African American race, and a previous negative biopsy reduced the risk. Although DRE is still used as a method for detecting prostate cancer, its additional value as a screening tool in healthy men remains limited.

### *Trans-rectal ultrasound*

Trans-rectal ultrasound (TRUS) is widely available for numerous physicians, easy to handle in an outpatient clinic and less expensive than for example MR imaging. TRUS has become the most commonly used imaging modality for the prostate. However there are many questions about the interpretation of ultrasound images and its place in prostate cancer detection. TRUS can detect cancers as a hypo-echoic lesion [21]. However the finding of a hypo-echoic lesion is not specific for prostate cancer because benign processes, such as prostatitis or infarction [21], can also appear as a hypo-echoic lesion. When a hypo-echoic lesion causes an irregular bulge or disruption of the capsule, extra-capsular extension is suspected and the lesion should be biopsied; the presence of extra-prostatic tumor growth obviously alters treatment choices.

To analyze the accuracy of TRUS and more recently advanced imaging methods like MRI in the detection and staging of prostate cancer Rifkin et al [22] compared MRI and TRUS results in patients with apparent clinically localized prostate cancer. MRI correctly staged 77% of cases of advanced disease and 57% of cases of localized disease; the corresponding figures for TRUS were 66% and 46%. In detecting and localizing lesions MRI identified 60% of all tumors more than 5mm and TRUS identified 59%. These figures illustrate that neither TRUS nor MRI are highly accurate in the detection and staging of prostate cancer. More recently Anastasiadis et all [23] showed that MRI guided transrectal biopsy of the prostate has the potential to improve cancer detection in men with previous negative TRUS-guided biopsies. Smith JA Jr et al [24] investigated the accuracy of TRUS versus DRE. TRUS and DRE results were compared with the pathology results after radical prostatectomy. Neither TRUS nor DRE proved to be superior for staging local extend of the tumor. No imaging modality that is currently available is likely to have a high degree of accuracy in the detection and staging of prostate cancer.

So far no consensus exists regarding the use of imaging for evaluating primary prostate cancers [25]. TRUS is mainly used for biopsy guidance and brachytherapy seed placement. Endorectal magnetic resonance (MR) imaging is helpful for evaluating local tumor extent, and MR spectroscopic imaging can improve this evaluation while providing information about tumor aggressiveness. MR imaging with superparamagnetic nanoparticles has high sensitivity and specificity in depicting lymph node metastases, but guidelines have not yet been developed for its use, which remains restricted to the research setting. Computed tomography (CT) is reserved for the evaluation of advanced disease. The use of combined positron emission tomography/CT is limited in the assessment of primary disease but is gaining acceptance in prostate cancer treatment follow-up. A more precise stratification of patients in clinical trials (population based), closer monitoring of progress in patients with watchful waiting and better assessment of local prostate cancer therapies may become possible [25]. In the search for new and more technically advanced imaging modalities the clinical usefulness and cost-effectiveness should be taken into regard.

### *Biopsy procedure*

Although TRUS is not efficient in cancer detection, it has become indispensable for taking biopsies of the prostate. Since the use of TRUS guided transrectal biopsies, biopsies are easier to perform, require no anaesthesia and severe complications have become rare with the use of antibiotic prophylaxis. Haemorrhagic complications such as hematospermia and hematuria are most frequently seen. The most feared complications are febrile reaction with prostatitis and septicaemia. Severe complications such as gross

rectal blood loss, septicaemia and even death are extremely rare [26]. In a cohort of 5,802 biopsied men within the ERSPC Raaijmakers et al [27] reported mild complications such as hematospermia in 50.4% and hematuria in 22.6%, low grade fever in 3.5%, urinary retention in 0.4% and hospital admission in 0.5%. Quite similar figures were reported by other studies from Gustafsson et al [28], who found hematuria and hematospermia in 2/3 of patients and five hospital admissions in 145 men biopsied , and Desmond et al [29], where in 670 men biopsied 2.1% of patients reported mild morbidity and four patients needed hospitalization. All three studies motivate the use of antibiotic prophylaxis to reduce the morbidity rate and keep the procedure as safe as possible.

### *Number of biopsies*

The classical way to perform prostate biopsies is random sextant biopsies. In 1997 Eskew et al [30] stated that the use of the 5 region technique with more lateralized biopsies significantly increases the diagnostic yield of detecting prostate cancer. For a long period of time lateralised sextant biopsies were taken to limit the proportion of missed cancers. However in recent years the sextant biopsies are considered to be obsolete. There is an evolution ongoing from the sextant biopsy method to more extended biopsy protocols. These protocols are used to improve the diagnostic accuracy and the use of anaesthetics and antibiotics add to the acceptability of the method [31]. Increasing the number of biopsies and prostate cancers detected will increase the risk off overdiagnosis and the detection of clinical insignificant cancer. To minimize this risk Remzi et all [32] conducted a trial to validate a newly developed nomogram that defines the optimal number of biopsy cores required for prostate cancer detection, based on age and total prostate volume. Using that nomogram cancer detection rates improve and economically make systematic repeat biopsies unnecessary. Vashi et all [33] determined a model for the number of cores per prostate biopsy based on patient age and prostate gland volume. Younger men and men with larger prostate glands require more than 6 cores to ensure the detection of life threatening prostate cancer. Older men may require less than 6 cores biopsy to prevent overdetection. Whether maximisation of biopsy procedures is desirable, is at this moment an unanswered question unless one wishes to maximise prostate cancer detection. And although there is a trend towards more biopsies taken an optimum biopsy procedure has not yet been established [34].

## Prostate specific antigen

Prostate specific antigen (PSA) is a protein, which is almost exclusively produced by the prostatic epithelium. There is information of low concentrations of PSA produced by the endometrium [35], breast tissue [36], adrenal and renal carcinomas [37], and measurable amounts were found in female serum [36], but for clinical practice PSA is sufficiently specific for the prostate gland. Although PSA is organ specific, it is not cancer specific. Benign diseases of the prostate, such as benign prostatic hyperplasia (BPH) can also cause serum PSA to rise [38]. A substantial overlap between PSA values for prostate cancer and BPH is seen. Furthermore PSA values can be influenced by prostate manipulation, such as DRE, TRUS or cystoscopy and to a variable degree acute prostatitis and urinary retention can effect the PSA value as well [39].

The introduction of PSA in the late 1980s has revolutionized the detection, staging and management of prostate cancer. Prostate cancer detection rates increased substantially due to PSA based early detection programs and a remarkable shift towards earlier stage and more organ confined tumors on detection is established [40]. Catalona et al [41] investigated the usefulness of PSA in the detection and staging of prostate cancer by comparing two groups of men above 50 years old. One group with a PSA above 4.0 ng/ml and an abnormal DRE and/or TRUS and one group with symptoms and/or an abnormal DRE. PSA proved to have the lowest error rate of the tests and PSA and DRE had the lowest error rate of the two-test combination. In a multi-centre study by Crawford et al [42] 31,953 men aged 50-93 years were tested by both DRE and PSA (cut off of 4.0 ng/ml). The cancer detection rate was 3.6% for PSA, 3.0% for DRE and 4,7% for the combination of DRE/PSA. The PPV for PSA above 4.0 ng/ml was 31.6% and for DRE 25.5%. PSA appeared to be the strongest predictor for prostate cancer. Even though we know that by using a cut off of 4.0 ng/ml up to 33% of cancers can be missed [43]. The predictive value of PSA can possibly be improved by using another threshold value. Using different cut off values for PSA in a series of 1,002 men between 45 and 80 years old Labrie et al [44] reported an optimal threshold of 3.0 ng/ml. Sensitivity and specificity figures for a PSA cut off of 3.0 ng/ml were 81% and 85% respectively. Lodding et al [45] reported that an increase in cancer detection by 30% was achieved by lowering the PSA cut off from 4.0 to 3.0 ng/ml and also concluded that the majority of these cancers were clinically significant cancers. At this moment a PSA threshold value of 3.0 ng/ml as a direct biopsy indicator is being used in most ERSPC centres [3,15,16]. If proven effective a major step is taken towards a better understanding of the use of PSA as a screening test.

The clinical significance of tumors detected with a PSA below 4.0 ng/ml is still uncertain. Schröder et al [46] reported that more than half of the cancers missed by DRE had aggressive characteristics (Gleason score 7 or greater, Gleason 4-5 components) and were organ confined. Therefore an unknown proportion of prostate cancers detected with PSA levels below 4.0 ng/ml may well be significant cancers which require surgical treatment. The value of rectal examination as a screening tool for prostate cancer at low PSA (0.0-3.9 ng/ml) was determined by Vis et al [47]. In two study populations, one with and one without DRE as an initial screening test, the tumor characteristics of the prostate cancers detected were analyzed. Prostate cancers were detected by DRE only in 26.6% of the cases. Almost all of these cancers corresponded with the prostate cancers detected using a PSA above 3.0 ng/ml as a sole biopsy indication. 60% of these cases were assessed as clinically significant. Thompson et al [20] showed that 15% of the men with a PSA < 4.0 ng/ml have prostate cancer and 15% of these cancers are high grade. Furthermore Thompson et al [48] stated that there is no such thing as a normal PSA . There is a continuum risk and no clearly defined PSA cut point at which to recommend biopsy. This could possibly explain the discrepancy between the rate of PSA screening and the prostate cancer mortality change in the past decades and may even account for the high risk (35%) of recurrence after radical prostatectomy. However lowering the cut point of PSA to detect these high risk cancers, would inevitably lead to an increase in the detection of clinically insignificant cancers. Caution is warranted.

Most stage T1C cancers (normal DRE/TRUS, PSA level >= 4.0 ng/ml) are considered to be clinically significant cancers. Scardino et al [49] reported that these T1C cancers are clinically significant in the majority of cases and clearly different from the insignificant cancers found in autopsy series. Partin et al [50] reported that only 60% of stage T1C cancers prove to be pathologically organ confined, indicating that a substantial number of T1C cancers are significant. To predict the insignificant cancers statistical models have been proposed. Steyerberg et al [51] validated and updated model predictions for a screening setting using a cohort of men diagnosed with T1C or T2a prostate cancer. Predictive characteristics were PSA, TRUS volume, clinical stage, biopsy Gleason grade, and the total length of cancer and non-cancer in the tissue samples. Indolent cancer was defined as organ confined cancer, less than 0,5 cc in volume and without poorly differentiated elements. The prostate cancers identified in the screening setting seem to have a higher probability of being indolent than the proposed nomogram predicted. Another study from Kattan et al [52] showed a nomogram predicting the presence of indolent cancer using the same prostate cancer characteristics and proved a discrimination with a rise in the AUC of 0.64 to 0.79. Correct discrimination between significant and insignificant prostate cancers can help to establish the best choice of treatment for the patient.

Further research is needed to determine the value of different screening modalities in these areas with potentially significant cancers. To improve the clinical usefulness of serum PSA with regard to sensitivity, specificity and the reduction of prostate biopsies, four methods have been investigated: PSA density, PSA velocity, age-related reference ranges and the free/total ratio of PSA.

### *PSA density*

The overlap in PSA ranges for benign prostate hyperplasia (BPH) and prostate cancer is one of the major problems in PSA based prostate cancer detection [38]. In an attempt to alleviate this problem PSA density (PSAD), PSA (ng/ml) divided by prostate volume (cc), was assessed. Especially in the range from 4.0 to 10.0 ng/ml PSAD should better differentiate between prostate cancer and BPH. A PSAD cutoff point of 0.15 ng/ml/cc can result in a better PPV and specificity, but will lower the relative sensitivity [53]. Ohori et al [54] reported a beneficial effect of PSAD only when PSA levels were above 10.0 ng/ml, which would make PSAD unnecessary in clinical practice. In a study by Ohi et all [55] the diagnostic significance of PSA density adjusted by transition zone volume in males with PSA levels between 2 and 4 ng/ml was investigated. The use of PSA transition zone density cut offs (0,28 in the PSA range 3.3-4.0 ng/ml) as a biopsy indication may reduce many unnecessary biopsies without missing significant prostate cancers. A factor in the evaluation of the clinical use of PSAD is the need for TRUS measurement, which is costly and time consuming. Keetch et al [56] reported a possible application for PSAD for men with persistently high PSA levels after prior negative prostate biopsies. However Roobol et all [57] showed that the screening tests used in the initial screening round might not be suitable at re-screening, because the populations are essentially different. Even when the same screening test would be applied, both patients with stage T1C prostate cancer and those without prostate cancer had a larger prostate volume. Using an extensive biopsy scheme rather than PSAD is more likely to increase the sensitivity in patient with large prostates. Radwan et al [58] investigated whether PSAD could be a predictor for adverse pathologic findings instead of being used as a screening tool. They demonstrated that PSAD is a strong predictor for advanced pathologic features and biochemical failure after radical prostatectomy. PSAD should therefore be included in a prognostic nomogram.

### *PSA velocity*

PSA velocity (PSAV) is the change of a PSA value in time, based on longitudinal measurements of PSA levels. At least 3 measurements should be obtained during a 2-year period or at least 12 to 18 months apart to obtain maximal benefit using PSAV. In 1992 Carter et all [59] suggested a PSAV cut-off point of 0.75 ng/ml/yr in men with a total

PSA between 4.0 and 10.0 ng/ml. A PSAV exceeding 0.75 ng/ml/yr is supposedly a strong prediction for prostate cancer [59]. The predictive value of PSAV varies with patient's age and inital PSA level. A cut-off point of 0.75 ng/ml might not be sufficient for younger men (< 60 years) as it is for older men (> 70 years). Loeb et all [60] determined whether PSAV could be useful in men younger than 60 years. In a retrospective study 6,844 men younger than 60 years and with a PSA history sufficient for PSAV calculations were analysed. 346 (5%) of the men were diagnosed with prostate cancer. The mean PSAV was 0.84 ng/ml/yr in men diagnosed with cancer compared to 0.094 ng/ml/yr in men who were not ($p < 0.0001$). In the multivariate analysis age, total PSA, race and family history were included. The use of PSAV increased the AUC by 0.03 using a PSAV greater than 0.4 ng/ml/yr in men younger than 60 years with a total PSA less than 4.0 ng/ml. They recommend the use of a PSAV cut-off of 0.4 ng/ml/yr in men younger than 60 years. Raaijmakers et al [61] calculated a mean PSAV of 0.62 ng/ml/yr for men with prostate cancer in a re-screened population. Although the PSAV differed significantly between men with and without prostate cancer, PSAV was of limited value in predicting prostate cancer on the biopsy results. A lower cut-off point for PSAV may also be of use in men with low PSA (< 4.0 ng/ml) as is suggested by Fang et al [62]. In prostate cancer detection a sensitivity of 81% and a specificity of 50% could be reached using a PSAV cut-off of 0.1 ng/ml/yr. However in a study by Roobol et al [63] PSAV was calculated for 774 men who underwent prostate biopsy in the second screening round of the ERSPC. In the univariate and multivariate logistic regression analysis PSAV did not appear to be a useful tool for the identification of prostate cancers in the low PSA ranges. Total PSA, prostate volume, TRUS, DRE and age are statistically significant predictors for the outcome of a biopsy, but an increase in PSAV is not. Different from the Baltimore Longitudinal Study of Aging [59], in the ERSPC prostate cancers are detected through screening without the use of DRE. Taking into account the lead time in prostate cancer this might explain the fact that PSAV is not useful in prostate cancer detection.

Limitations to the use of PSAV are difficulties in calculating PSAV, dependency on different PSA assays, possible verification bias when biopsy information is not available, lead time and variable predictive values due to patient age and initial PSA level [62,63]. The role for PSAV in prostate cancer detection is not clarified yet. It may be of use in younger men, men with a total PSA below 4.0 ng/ml or it may even be a parameter for the aggressiveness of prostate cancer [64]. In an extended review performed by the group of Thompson [65] PSAV proves to be at best a weak predictor of high risk disease. This association between PSAV and disease specific survival does not necessarily imply that PSAV will be a useful screening tool. In the PCPT trial Thompson et al [19] already showed that PSAV did not contribute to the independent prognostic information and in the PCPT trial all men were biopsied. The use of PSAV remains limited.

### *Age-specific reference ranges*

To improve prostate cancer detection sensitivity in younger men and the specificity in older men, Oesterling et al [66] suggested the use of age-specific reference ranges: 2.5 ng/ml, 3.5 ng/ml, 4.5 ng/ml and 6.5 ng/ml for men in their forties, fifties, sixties and seventies respectively. Crawford et al [67] analyzed the diagnostic efficiency of PSA and DRE testing when using either 4.0 ng/ml or an age-specific reference range as an abnormal cutoff PSA value. Although using an age-specific reference range cut-off value suggested higher PPVs and fewer unnecessary biopsies, lower sensitivities resulted in fewer cancers detected. They still recommend the combination of DRE and PSA with a general cut-off value of 4.0 ng/ml. Bassler et al [68] evaluated the efficacy of age-specific reference ranges in men between the ages of 60 to 69 years and reported a significant loss in sensitivity if the upper limit of normal PSA would be raised to 4.5 ng/ml in this age group. A standard PSA cut-off value of 4.0 ng/ml for all ages therefore remains the most effective and least costly method for screening for the time being. This obviously could change if cancers detected at lower PSA ranges would have significant impact on prostate cancer mortality.

### *Free/total ratio of PSA (percent free PSA)*

PSA circulates in the serum as complexed (bound) and uncomplexed (free or unbound) forms [68]. Usually total PSA is measured, which comprises the bound and unbound forms. When the free PSA percentage decreases, the probability of having prostate cancer increases [69]. The free-to-total PSA ratio or percent free PSA therefore is expected to improve the specificity and sensitivity of cancer detection especially in the lower ranges of total PSA. Bangma et al [70] analyzed the value of f/t PSA ratio for a PSA of 4.0 to 10.0 ng/ml in a screened population. With a cut-off of 0.20 or less the f/t PSA ratio could avoid 44% of biopsies with 19% of cancers not detected. When using in combination with DRE 35% of biopsies could be avoided and only 12% of cancers would be missed. In the PSA range between 4.0 and 10.0 ng/ml the f/t PSA ratio improves the specificity of tPSA significantly. Veltri et al [71] evaluated the ability of free PSA (fPSA), PSA (tPSA) and the free/total ratio (f/t ratio) to differentiate between BPH and prostate cancer for both a tPSA range between 2 to 10 ng/ml and 2 to 20 ng/ml. Both fPSA and f/t PSA ratio improved the differentiation between BPH and prostate cancer, but the f/t PSA ratio performed best. The predictive value of the f/t ratio improves further as tPSA levels increase and is best when the tPSA is greater than 6 to 8 ng/ml. The use of f/t PSA therefore can give the patient a more realistic answer of his true risk of having prostate cancer. Rydén et al [72] retrospectively analyzed the cancer detection rate in men with different levels of tPSA and different f/t PSA ratios in a series of men. In the group of men with a tPSA of < 4.0 ng/ml, the risk of having prostate cancer increased considerably with a low PSA ratio.

Pannek et al [73] investigated the usefulness of percent free PSA for staging of clinically localized prostate cancer. Total PSA and free PSA were measured preoperatively in 263 men undergoing radical prostatectomy for clinically localized prostate cancer. A cut-off value of 12% free PSA provided a PPV of 72% and a negative predictive value (NPV) of 52% for organ confined disease. A cutoff value of 15% free PSA provided a PPV of 76% and a NPV of 53% respectively. An important advantage using this method is the fact that it only needs one blood test and no TRUS. However there are still some questions that remain to be answered in the clinical usefulness of percent free PSA. For example what sensitivity level will be acceptable in clinical practice? At which cut-off value of total PSA should we use percent free PSA? And can percent free PSA improve the prediction of pathological stage [74]. The cut-off value for percent free PSA still has to be established, but despite substantial differences between study designs, percent free PSA seems to add to the clinical specificity of cancer detection in the PSA range from 4 to 10 ng/ml.

## Stage and grade of prostate cancer and the risk of treatment failure

The time from preclinical onset to diagnosis of prostate cancer can be relatively long. Usually prostate cancers are slow growing, locally minimally symptomatic and with low potential for systemic spread [75]. Many prostate cancers even will never cause any symptoms and prove to be clinically insignificant. Autopsy data show that approximately one out of three men over 50 and nearly two out of three over 70 have asymptomatic not clinically significant prostate cancer [76]. This makes prostate cancer a unique malignancy with a very high prevalence of histological identifiable tumors but relatively mild clinical manifestation. The risk of detecting insignificant disease which could lead to overdiagnosis and overtreatment of prostate cancer is apparent. Epstein et al [75] reported that the best model predicting insignificant disease, with an accurate prediction of 73% of insignificant cancers, was a PSAD of less than 0.1 and no adverse pathological finding on needle biopsy or a PSAD of 0.1 to 0.15 with less than 3 mm low to intermediate grade cancer on only 1 needle biopsy core. When preoperatively insignificant disease is expected a conservative approach may be warranted in older individuals. For younger men a more aggressive treatment may still be the best choice, because of the risk of tumor growth and progression. Tumors don't always need to reach large volumes before they become poorly differentiated and develop a less favorable prognosis [75].

The multifocal and heterogeneous nature of prostate cancer makes it difficult to assess the extent of the disease. PSA is not specific and sensitive enough for the prediction of

clinical and pathological stage. Using variables such as Gleason score, clinical stage and prostate-specific antigen level nomograms are developed for the predicted probability of pathologically organ-confined disease, extraprostatic extention, seminal vesical invasion, or lymph node involvement [76].

The Gleason grading system is the most commonly used grading system and is used to place patients in prognostic groups to determine the best choice of treatment [76]. Needle biopsies are difficult to grade because different Gleason patterns may be present within one cancerous prostate. Undergrading therefore is common. One of the problems is that fewer patterns of Gleason 3 or 4 are recognized and furthermore a sampling error could be explained by the fact that both lowest (Gleason 2) and highest (Gleason 10) lesions can only be obtained with a single predominant pattern of 1 and 5, respectively, which is relatively rare [77].

To estimate tumor volume, the length of biopsy core involvement can be measured. A correlation between a large degree of tumor involvement and high-stage disease might be expected. However a considerable overlap between grades has been reported. Low volume tumors (less than 1.0 cc) were found with Gleason sums of 2 through 8. Higher volume tumors (more than 10.0 cc) had Gleason sums of 4 to 9. Only a modest correlation between grade and tumor volume is present [78, 79]. Hence focal cancer on the needle biopsy is not automatically a guarantee for an insignificant cancer. In a retrospective study by Postma et al [80] they analysed whether clinical preoperative variables and focal carcinoma found at sextant biopsy could predict minimal carcinoma in radical prostatectomy specimens or disease progression in the watchful waiting group. The incidence of focal carcinoma increased significantly to almost 30% of all cancers detected in the second screening round of the ERSPC (Rotterdam). The positive predictive value of focal disease for a minimal tumor in the radical prostatectomy group was 94% using a PSA density cut-off value of =< 0.1 ng/ml/cm$^3$. Patients with focal carcinoma on biopsy have a small risk of PSA progression after radical prostatectomy (4,6%). Delayed therapy with curative intent after a watchful waiting policy in patients with focal disease may be an acceptable option.

Clinical staging depends on the pre-operative PSA measurement, clinical T stage, Gleason score and percentage of cancer on needle biopsy. After radical prostatectomy for clinically organ confined cancer, the cancer pathologically often proves to be extra-capsular. In the lower ranges of Gleason score 5-6 the rate of organ confined disease is reported to be 73% [76]. More poorly differentiated tumors are associated with increasing rates of extra-capsular disease, seminal vesicle invasion and lymph node metastases. A study on 104 patients who underwent systematic sextant biopsy prior to radical prostatectomy reported that the risk of extra capsular extension was 8% and 14% on sides containing

no or one of three positive biopsies, whereas it was 37% and 43% in sides containing two or three positive biopsies, respectively [81]. In a cohort of 157 men undergoing radical prostatectomy for a clinically T1C tumor Epstein et al [75] reported 37% advanced tumors with capsular penetration with a Gleason sum of 7 or more, positive margins, positive seminal vesicles or positive lymph nodes.

To estimate the risk of treatment failure an accurate assessment of tumor grade and stage is important. If prostate cancer is organ confined the prognosis after radical prostatectomy is very good. Ohori et al [82] reported only 16% of patients with a Gleason grade 4 or 5 cancer on radical prostatectomy with progression after 5 years if the tumor was organ confined and 28% of patients with extra-capsular extension and/or positive margins with progression after 5 years. Huland et al [83] reported that with respect to biochemical recurrence, patients with fewer than three positive biopsies and a Gleason score less than 7 were at a low risk to recur irrespective of preoperative PSA levels (14% risk with a mean follow-up of 2 years). Vis et al [84] stated that the stage and grade shift of currently diagnosed prostate cancer has led to a diminished prognostic power of the Gleason score system. They investigated the predictive value of the amount of high-grade cancer (Gleason growth pattern 4-5) in the biopsy for biochemical and clinical relapse after radical prostatectomy. The amount of high-grade cancer proved to be superior to the Gleason grading system in predicting patients outcome. They propose that the amount of growth patterns 4-5 should be mentioned in the pathology report.

At this moment serum PSA, PSA density and needle biopsy pathological results seem to provide the best estimation of tumor extent. Impalpable tumors detected through screening don't seem to differ from tumors diagnosed in clinical practice and can be seen as significant cancers [76, 83]. Improvements in local staging and risk assessment are still ongoing and hopefully will result in better prognostic information.

## Comment

The introduction of serum PSA measurements into medical practice has led to a substantial increase in the incidence of prostate cancer. Since 1992 however a decline in incidence rates of prostate cancer and a decrease in prostate cancer mortality rates in those areas served by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Registry Program is seen [85-87]. Evaluation of these data is complex and questions arise about possible mislabelling (as dying of prostate cancer) of cases [86] and about the opinions on lead time, which question the very short period between the start

of PSA based screening and the decline in mortality rates [87]. More recent data from the SEER program show a transient increase in prostate cancer incidence since 1986 and the age –adjusted prostate cancer mortality rates have dropped below the rate in 1986 since 1995 for white men and since 1997 for black men. The incidence based mortality rates show that the recent declines were due to declines in distant mortality, more specifically to a decline in distant disease incidence and not to improved survival of patients with distant disease [88]. The use of PSA may explain the increased detection of organ confined prostate cancer and the decrease in prostate cancer mortality. The first trial claiming a mortality reduction due to screening for prostate cancer is reported by Labrie et al [89]. The Quebec Prospective Randomized Controlled Trial aimed at assessing the impact of prostate cancer screening on cause-specific death. They used PSA measurements at a cut-off level of 3.0 ng/ml and a DRE to screen for prostate cancer. A 69% decrease in the incidence of deaths due to prostate cancer was found in the screened compared to the unscreened population. The study has been criticized heavily, because the methods of analysis used in this trial are seriously biased. A randomized controlled trial should be analysed in an intention-to-screen analysis with the total population in the screening arm compared to the control arm. If done in this way, no mortality reduction could be shown [90, 91]. The trial is very small-scale, and only 23% of invited men were actually screened. An update on the Quebec Prospective Randomized Controlled trial [92] confirmed a decrease in prostate cancer mortality of 62% in favour of prostate cancer screening using the same methods of analysis. Despite these biases the results of this trial are interesting and important data in the understanding of prostate cancer screening, but the Quebec trial does not provide sufficient evidence for mortality reduction in screening for prostate cancer.

At this moment randomized controlled trials are being performed to assess the impact of screening and early intervention on the morbidity and mortality of prostate cancer. Priorities are set to improve the sensitivity, specificity and accuracy of screening methods. To improve the detection of prostate cancer the major breakthrough should come in the field of imaging of the prostate and in the field of more sensitive and specific markers for prostate carcinoma or a combination of the several factors. So far PSA remains the best marker in use. The search for new and better tumor markers is ongoing and studies have been published regarding measurement of free and conjugated forms of prostate specific antigen, the development of monoclonal antibodies specific to human glandular kallikrein (hK2) and the precursor isoforms of PSA (proPSA), PSA-ACT, PSA-A2m and more [74]. Both hK2 and proPSA are thought to discriminate better between large-volume BPH and prostate cancer. However the clinical effect of using proPSA and hK2 remains limited.

More recently hK2 and other serum variables are identified as a possible marker of poorly differentiated and non-organ confined prostate cancer. Further studies are ongoing. The development of these prognostic factors is of major importance [93,94]. We have to wait for the outcomes of these studies to see if and when new effective screening methods will become available.

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# CHAPTER 1

# Comparison of screen detected and clinically diagnosed prostate cancer in the European Randomized study of Screening For Prostate Cancer, section Rotterdam

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## Abstract

### *Purpose*

This report provides a comparison of characteristics detected in the screening and the control arm of the European Randomized study of Screening for Prostate Cancer, section Rotterdam.

### *Materials and Methods*

Between December 1993 and January 1999 a total of 35,148 men, aged 55 to 74 years, were randomized to ERSPC Rotterdam (17,635 in the screen arm and 17,513 in the control arm). PSA testing, digital rectal examination, transrectal ultrasound and sextant biopsies were offered to all participants in the screen arm according to 2 algorithms. All screening detected cancers and cancers found in the control arm are evaluated at the same cut off point January 1, 2003. To identify cases with prostate cancer in the control arm yearly linkage was performed with the Rotterdam Cancer Registry database. Follow up information was collected by chart review.

### *Results*

By January 1, 2003 1,269 cancers were detected in the screening arm and 336 were detected in the control arm. A shift to more favorable clinical stages and histological grades on biopsy is seen in the screening arm of the trial. T1C and T2 cancers are 5.8 and 6.2 times more often diagnosed, respectively, in the screening arm than in the control arm of the trial. Only 4.6% of control arm cancers were found through opportunistic screening.

### *Conclusion*

Although a favorable shift of prognostic factors is seen for the screening arm of the trial, these results do not provide evidence that prostate cancer screening has an effect on prostate cancer mortality.

## Introduction

The introduction of serum PSA measurements into medical practice has led to dramatic changes in the incidence of prostate cancer. However the fact that prostate cancer can be detected at an early stage, before the occurrence of symptoms, does not imply that screening for prostate cancer is beneficial. With respect to mortality decrease and quality of life effects the value of screening for prostate cancer is still uncertain. At this time randomized, controlled trials are being performed to assess the impact of screening and early intervention on the morbidity and mortality of prostate cancer. The European Randomized study of Screening for Prostate Cancer (ERSPC) is a large, multicenter, randomized, controlled trial that aims to show or exclude a decrease in prostate cancer mortality of at least 20% in men randomized to a screening arm compared to men in the control arm. It has been calculated that about 100.000 men in the age group 55 – 69 years are to be randomized to screening (with 100.000 men in the control group) with 10 years of follow-up to provide 80% statistical power to detect this 20% difference [1]. ERSPC is closely associated with the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) trial of the National Cancer Institute (NCI), and a combined analysis is planned [2].

We compared prognostic factors at the diagnosis of cancer found in the screening and control arms. Effective screening must lead to a shift toward more favorable tumor characteristics. If this shift does not occur, it must be assumed that test procedures are not effective or excessive testing occurs in the control group. In this sense the findings presented may anticipate the proper end point of the study, that is prostate cancer mortality.

## Patients and Methods

Data on men randomized between December 1, 1993 and January 1, 1999 are included. During this period 35,148 men, aged 55 to 74 years were randomized to the Rotterdam section of the ERSPC, including 17,635 in the screening arm and 17,513 in the control arm. All screening detected cancers, the interval carcinomas and the cancers found in the control arm in this cohort are evaluated at the same cut off point in time January 1, 2003. This end point was chosen because it allowed the comparison of detection in the screening arm and of cancer accumulation in the control arm for an identical time period.

All men randomized to screening were offered blood sampling. This sample is taken prior

to digital rectal examination (DRE) and transrectal ultrasound (TRUS), so that physical examination would be performed blinded to PSA.

From December 1, 1993 to February 1, 1997 the Rotterdam screening regimen called for sextant transrectal biopsy if the PSA level was equal to or greater than 4.0 ng/mL, and if DRE and/or TRUS were suspicious for cancer at low PSA values (0.0 – 3.9 ng/mL). The biopsy procedure was performed during a second visit. From December 1, 1993 to October 15, 1996 an early recall visit was performed by men who had a biopsy indication on prevalence screening but a negative biopsy outcome. One year after the prevalence screen men were invited again for PSA, DRE, TRUS and sextant biopsy. From February 1997 and thereafter PSA $\geq$ 3.0 ng/mL became the only biopsy indication. Around the same time lateralized sextant biopsies were introduced. From this time on DRE and TRUS were no longer applied as initial screening tests. Four years after initial prostate cancer screening all men in the screen group were invited to undergo repeat screening. Another four years after the second screening all men in the screen group were invited for a third round of screening. The conditions and algorithm of the screening regimen of ERSPC are described in greater detail elsewhere [3-5].

Patients in the ERSPC control arm received standard medical care, which means that the evaluation of symptoms, and the diagnosis and management of prostate cancer were provided by regional urologists, including those at the coordinating center. Men in the control arm were not offered PSA measurement at randomization. To identify cases of prostate cancer in the control arm yearly linkage was performed with the Rotterdam Cancer Registry database. These data were provided up to 1 year before the actual calendar date. Men diagnosed with prostate cancer, and those known to have died were identified and data were returned to the ERSPC.

At the cut off point of January 1, 2003 prostate cancer was detected in 818 men at the prevalence screening, while 63 cancers at the early recall screening after one year, 336 were detected at the second screening and 8 were detected at the third round of screening. Also, 44 cancers were detected in the interscreening interval. Interval cancers are defined as cancer detected in the screening arm of the trial between fully completed screening visits and in the 55 to 74-year-old age group. At the same cut off point 336 cancers were diagnosed in the control arm. In the 2 arms all data related to prostate cancer detection and management were obtained by a review of the patient charts at the local hospitals and stored in a comprehensive database.

For all prostate cancers detected in the screening group, a single genitourinary pathologist (THvdK) assessed Gleason score prospectively in each case. After the identification of men with prostate cancer in the control group the histological slides with prostate cancer were retrieved from the pathologic storage facilities of the local hospitals and Gleason scores

were reviewed by the same pathologist (THvdK). All tumors were staged according to the 1992 TNM system.

## Statistics

Statistics are purely descriptive. Testing for significance is performed by SPSS for Windows, version 10.0 software (SPSS, Chicago, Illinois). The independent samples t test was used to compare mean PSA values in the screening and control arms. The chi-square test was used to compare the number of nonadvanced (T1 and T2) and advanced (T3 and T4) tumors, biopsy Gleason scores (below 7 and 7 or higher), the number of lymph node metastases and the number of distant metastases in each arm of the trial.

## Results

Tables 1 to 6 list the findings of the comparison between prostate cancers detected in the ERSPC screening and control groups. **Table 1** shows the number of men randomized and prostate cancers detected in the prevalence screen, early recall and second screening, the third round of screening, interval carcinomas and cancers detected in the control arm. Data on the number of biopsies or the cancer detection rate were not available on interval carcinomas or the control arm. The cancer detection rate was high in the first round of screening (4.9%) and it decreases to 3.5% and 2.7%, respectively, at the subsequent rounds.

**Table 1:** Men randomized between October 1993 and December 31, 1998 in ERSPC screening and control arms. This cohort was followed until January 1, 2003.

| | | No. Men randomized | No. Prostate cancer detected | No. Biopsies | Cancer detection rate (%) |
|---|---|---|---|---|---|
| Screen arm | Visit 1 | 17,635 | 818 | 3,480 | 4.9 |
| | Early recall | 1,218 | 63 | 509 | 5.6 |
| | Visit 2 | 9,926 | 336 | 1,694 | 3.5 |
| | Visit 3 | 293 | 8 | 39 | 2.7 |
| | Interval cancer | | 44 | Not available | Not available |
| Control arm | | 17,513 | 336 | Not available | Not available |

**Table 2:** PSA distribution in the trial screening arm.

| *PSA (ng/ml)* | *Screen arm* | | | | | | |
|---|---|---|---|---|---|---|---|
| | ***Total number of men randomized to screen N (%)*** | *Screen detected Prostate Cancers* | | | | | |
| | | **Initial visit** | **Follow up visits** | | | Interval Cancers **N** (%) | ***Total number of cancers detected in the screen arm N (%)*** |
| | | Visit 1 **N** (%) | Early recall **N** (%) | Visit 2 **N** (%) | Visit 3 **N** (%) | | |
| 0.0 - 0.9 | 5,936 (35.9) | **4** (0.5) | - | - | - | - | **4** (0.3) |
| 1.0 - 1.9 | 5,1589 (31.2) | **45** (5.5) | **7** (11.1) | - | - | **1** (2.3) | **53** (4.2) |
| 2.0 - 2.9 | 2,069 (12.5) | **30** (3.7) | **2** (3.2) | - | - | **4** (9.1) | **36** (2.8) |
| 3.0 - 3.9 | 1,193 (7.2) | **132** (16.1) | **4** (6.3) | **133** (39.6) | **4** (50.0) | **2** (4.5) | **275** (21.7) |
| 4.0 - 9.9 | 1,821 (11.0) | **422** (51.6) | **38** (60.3) | **179** (53.3) | **4** (50.0) | **14** (31.8) | **657** (51.8) |
| > 10.0 | 369 (2.2) | **185** (22.6) | **12** (19.0) | **24** (7.1) | - | **16** (36.4) | **237** (18.7) |
| Missing | 1,088 * | - | - | | - | 7 (15.9) # | 7 (0.6) |
| **N = Total** | **17,635** (100.0) | **818** (100.0) | **63** (100.0) | **336** (100.0) | **8** (100.0) | **44** (100.0) | **1,269** (100.0) |
| Range | 0.0 – 315.7 | 0.3 – 315.7 | 1.0 – 24.8 | 3.0 – 59.0 | 3.0 – 7.4 | 1.6 – 803.0 | 0.3 – 803.0 |
| Mean PSA | 2.3 | 10.5 | 6.5 | 5.7 | 4.5 | 31.4 | 9.6 |
| Median PSA | 1.3 | 5.7 | 5.4 | 4.3 | 4.0 | 8.0 | 5.2 |

* No blood sample taken
\# Follow up data pending

**Table 2** shows the PSA distribution at diagnosis for prostate cancers in the screening arm. At the prevalence screening half of the cancers were detected in the range of 4.0 to 10.0 ng/ml, almost a quarter of the cancers had a PSA greater than 10.0 ng/ml and mean PSA was 10.5 ng/ml. At the subsequent screening rounds the proportion of cancers with higher PSA values (greater than 10.0 ng/ml) decreases drastically. The mean PSA decreases from 10.5 to 4.5 ng/ml. Table 3 shows the PSA distribution of cancers in the screening arm compared with those in the control arm are shown. PSA at diagnosis was higher in the control arm of the trial. In the screening arm about half of the cancers (51.8%) were detected at the PSA range 4.0 – 10.0 ng/ml, whereas in the control arm about half of the cancers (52.7%) are detected in the PSA range of greater than 10.0 ng/ml. Also, mean and median PSA was 7.7 ng/ml which was 2.2 times higher than in the control arm. **Table 3** is incomplete because of pending data in the control arm followup. The 7.7-fold difference in mean PSA in the control arm compared with the screening arm was statistically significant ($p < 0.001$).

**Table 3:** PSA distribution for prostate cancers detected in screening versus control arm.

| | ***Screen arm*** | ***Control arm*** |
|---|---|---|
| *PSA (ng/ml)* | *Screen detected prostate cancers* ***N*** *(%)* | *Prostate cancers diagnosed* ***N*** *(%)* |
| 0.0 - 0.9 | **4** (0.3) | **3** (0.9) |
| 1.0 - 1.9 | **53** (4.2) | **7** (2.1) |
| 2.0 - 2.9 | **36** (2.8) | **8** (2.4) |
| 3.0 - 3.9 | **275** (21.7) | **7** (2.1) |
| 4.0 - 9.9 | **657** (51.8) | **97** (28.9) |
| > 10.0 | **237** (18.7) | **157** (46.7) |
| Missing * | **7** (0.6) | **57** (17.0) |
| **N = Total** | **1,269** (100.0) | **336** (100.0) |
| Range | 0.3 – 803.0 | 0.3 – 2,970.0 |
| Mean PSA | 9.6 | 73.8 |
| Median PSA | 5.2 | 11.6 |

* Follow up data pending

**Table 4**: TNM tumor characteristics in screening and control arms.

| | ***TNM CLASSIFICATION*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***SCREEN ARM*** | | | | | | | ***CONTROL ARM*** | |
| | *PROSTATE CANCER (PC)* | | | | | | *Number of PC / Number of men randomized (%)* | *Total number of prostate cancers N (%)* | *Number of PC / Number of men randomized (%)* |
| Clinical T-stage | *Visit 1 N (%)* | *Early recall N (%)* | *Visit 2 N (%)* | *Visit 3 N (%)* | *Interval Cancers N (%)* | *Total screen arm N (%)* | | | |
| T1A-B | - | - | - | - | 10 (22.7) | **10** (0.8) | **0.06** | **24** (7.1) | **0.1** |
| T1C | 252 (30.8) | 29 (46.0) | 203 (59.8) | 6 (75.0) | 15 (34.1) | **505** (39.8) | **2.9** | **90** (26.8) | **0.5** |
| T2A-C | 391 (47.8) | 30 (47.6) | 120 (35.7) | 1 (12.5) | 11 (25.0) | **553** (43.6) | **3.1** | **84** (25.0) | **0.5** |
| T3A-B | 131 (16.0) | 4 (6.4) | 10 (3.0) | 1 (12.5) | 2 (4.5) | **148** (11.7) | **0.8** | **57** (17.0) | **0.3** |
| T3C | 33 (4.0) | - | 3 (0.9) | - | - | **36** (2.8) | **0.2** | **7** (2.1) | **0.04** |
| T4A-B | 11 (1.3) | - | - | - | 2 (4.5) | **13** (1.0) | **0.07** | **13** (3.9) | **0.07** |
| Missing * | - | - | - | - | 4 | **4** (0.3) | | **61** (18.2) | |
| **Total** | **818** (100.0) | **63** (100.0) | **336** (100.0) | **8** (100.0) | **44** (100.0) | **1,269** (100.0) | **17,635** | **336** (100.0) | **17,513** |
| Lymph node metastasis | 9 (1.1) | 0 | 0 | 0 | 0 | **9 (0.7)** | **0.05** | **12 (3.6)** | **0.07** |
| Distant metastasis | 5 (0.6) | 0 | 1 (0.3) | 0 | 1 (2.3) | **7 (0.6)** | **0.04** | **27 (8.0)** | **0.2** |

* Follow up data pending.

**Table 4** lists the TNM classification for the 2 arms. A large proportion of cancers detected in each arm were classified as T1 and T2, that is 84.2% after screening and 58,9% in the control arm. Overall a more favorable stage distribution in the screening versus the control arm was noted. This difference between the number of nonadvanced (T1 and T2) and advanced tumors (T3 and T4) was statistically significant in favor of the screen arm ($p < 0.001$). Considering the total number of men randomized T1C cancers are diagnosed 5.8 times more often in the screening arm of the trial compared with the control arm (2.9% vs 0.5% of all men randomized, $p = 0.001$). Only 44 of the 1,269 screen detected cancers (3.5%) were detected as interval cancer. About 82% of these cancers were classified as T1 and T2 without distant metastasis. Most striking was the fact that the absolute number (27 and 7) and the proportion (8.0% and 0.6%) of men with distant metastatic disease were higher in the control arm than in the screening arm, respectively. Also, in relation to the total number of men randomized distant metastases were 5.0 times more frequent in the control arm. This was a statistically significant difference in favor of the screen arm ($p < 0.001$).

In addition to the clinical stage shift, a more favorable distribution of biopsy Gleason scores was also seen between the screening and control groups in favor of screening (**table 5**). At the first round of screening 36.2% of cancers had a biopsy Gleason score of 7 or higher. At subsequent screening rounds the proportion of Gleason scores 7 or higher decreased to 22.3% and 12.5% respectively ($p = 0.001$). In the control arm about 55% of cancers had a Gleason score 7 or higher, which was a significantly higher difference than in the screening arm of the trial ($p < 0.001$). Gleason scores of the interval cancers are pending, but tended to be low.

**Table 5:** Biopsy Gleason scores in cancers detected in screening and control arms.

| Biopsy Gleason score | *Screen Arm* | | | | | | *Control Arm* |
|---|---|---|---|---|---|---|---|
| | *Screen detected Prostate Cancer* | | | | | Total Screen arm N (%) | Control arm N (%) |
| | Visit 1 N (%) | Early recall N (%) | Visit 2 N (%) | Visit 3 N (%) | Interval cancers N (%) | | |
| 2 - 4 | **43** (5.3) | **5** (7.9) | **3** (0.9) | - | - | **51** (4.0) | **9** (2.7) |
| 5 - 6 | **472** (58.4) | **43** (68.3) | **258** (76.8) | **7** (87.5) | **6** (13.0) | **786** (61.9) | **126** (37.5) |
| 7 | **216** (26.8) | **13** (20.6) | **62** (18.5) | **1** (12.5) | **2** (4.3) | **294** (23.2) | **92** (27.4) |
| 8-10 | **76** (9.4) | **2** (3.2) | **13** (3.9) | - | - | **91** (7.2) | **75** (22.3) |
| missing | 11# | - | - | - | 36 * | 47 | 34 (10.1) # |
| **Total** | **818** (100.0) | **63** (100.0) | **336** (100.0) | **8** (100.0) | **44** (100.0) | **1,269** (100.0) | **336** (100.0) |

* Follow up data pending.
\# Data not available.

**Table 6** shows detailed data on detection mechanisms in the control arm. Although due to pending followup data this table is incomplete, there was a consistent referral pattern. Almost half of the men (43.9%) consulted a urologist because of prostatism complaints with or without a suspicious DRE, as assessed by their general practitioner. Lower urinary tract symptoms possibly also related to prostatism with increased PSA was the reason for 25.9% of the men. Opportunistic screening was established in only about 5% of men with prostate cancer.

The use of 5 α-reductase inhibitors at randomization was recorded in the database. A total of 101 men in the screening arm (0.6%) and 92 men in the control arm (0.5%) were receiving 5 α-reductase inhibitors at the time of inclusion.

**Table 6:** Reasons for referral to urologist in control arm.

| Reason for referral | Number of men | Percentages % |
|---|---|---|
| Prostatism complaints with/without suspicious DRE # | **134** | **43.9** |
| LUTS * with increased PSA | **79** | **25.9** |
| Opportunistic screening | **14** | **4.6** |
| Other | **78** | **25.6** |
| Subtotal | 305 | 100 |
| Pending § | 31 | |
| Total | 336 | |

# DRE = digital rectal examination.
* LUTS = lower urinary tract symptoms.
§ Follow up data pending.

## Discussion

This report shows a shift to more favorable prognostic stages and grades in the screening arm of this population based, randomized trial. This is in line with observations of others [6,7]. The prevalence rates of prognostic factors were calculated in relation to reported cancers and in the whole study population. An important stage shift is evident. Most impressively the absolute number of men with metastatic disease was lower in the screened population compared to the total number of men diagnosed with prostate cancer, i.e. 0.6% (7 of 1,269) of men in the screening arm and 8.0% (27 of 336) of men in the control group ($p = 0.001$). Also related to the number of men randomized a 5.0 fold difference is noticed. The proportion of men presenting with distant metastatic disease in the control group was remarkably lower than that reported in historical controls (i.e. 20 to 25%) [8]. The data reveal a significant stage shift (table 3 and 4). A statistically

significant difference was found for lower mean PSA, less advanced tumors (T3 and T4), less metastatic disease and biopsy Gleason score below 7 in favor of the screen arm of the trial ($p < 0.001$). Time will show whether this difference persists as the rate of cancers in the control arm increases.

In population based screening trials the occurrence of opportunistic screening (contamination) is unavoidable. A high contamination rate seriously affects the end points of the trial. The proportion of T1C cancers is an indication of opportunistic screening in the control arm. In our study the rate of T1C disease in cancers in the screening arm was 39.8% and in the control arm 26.8%, which is a 1.5-fold difference. Related to the number of men randomized, the rate of T1C disease in the screening arm is a 5.8-fold higher. The results show that about 70% of T1C cancers in the control arm were diagnosed due to prostatism or lower urinary tract symptoms in general (table 6). A previous study of PSA contamination in ERSPC Rotterdam revealed a rate of 7.6% of yearly PSA testing in the control arm vs 3.3% in the screening arm [9]. The fraction of men in the control arm with PSA 3.0 ng/ml or greater, followed by biopsy and prostate cancer was 7% to 8% and 3%, and it was 3% and 0.4% to 0.6% in the screening arm, respectively. Thus, effective contamination within ERSPC Rotterdam is low and close to the assumption made in the sample size calculation [10]. Further support for this observation comes from the incidence figures. In the control arm of the trial prostate cancer incidence is 350/100.000 man-years. Compared with the general population in the Netherlands the incidence of prostate cancer in 1997 is 292.5/100.000 man-years for the same age group [11]. The similarity of these figures suggests that opportunistic screening does not seem to have an important role in ERSPC Rotterdam to date.

The use of 5α-reductase inhibitors could influence prostate cancer detection and outcome. The group was satisfied that the number of men on this drug was small and balanced between the arms.

The detection of presumably clinically insignificant disease (cancers that would never lead to any signs and symptoms) is unavoidable in prostate cancer screening. In our study the ratio of cancer incidence between the screening and control arms was 3.7 (1,269:336) during the 4-year recruitment period. Many cancers found by screening would probably not be diagnosed during the lifetime of these men (over diagnosis). Indeed, available studies suggest that over diagnosis occurs in 35 to 100% of screening detected cases [12, 13, 14].

The rate of interval carcinomas depends strongly on the definition of interval cancers. In our study 44 interval cancers were detected between fully completed screening rounds and in the 55 to 74-year-old age group. Interval cancers account for a low rate of only 3.5%

of screening detected cancers and 13.1% of control group cancers. This is in line with 2003 data from our group [15].

## Conclusion

A favorable shift of prognostic factors is seen favoring the screening arm of the trial. The data shown confirm that the screening procedure is effective but they provide no evidence that prostate cancer screening decreases the mortality of the disease. The data must be considered preliminary because of the slower accumulation of cases in the control arm.

Wilma Roobol, Conja Franken, Ellen de Bilde, Lakshmi Hariharan, Stijn de Vries MD, René Raaijmakers MD and Renske Postma MD, Rotterdam Screening Bureau proveded assistance and Professor Dr. T. van der Kwast established and reviewed all Gleason scores.

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# CHAPTER 2

# Effective PSA Contamination in the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer

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## Abstract

The extent of effective PSA contamination in the Rotterdam section of the ongoing European Randomized Study of Screening for Prostate Cancer (ERSPC) trial was evaluated and defined as when opportunistic PSA testing of ≥3.0 ng/ml was followed by biopsy, similar to the regular procedure within the trial. Records of participants aged 55-74 years at entry were linked to the regional database of the General Practitioner (GP) Laboratory, to obtain PSA tests requested by GPs in the period July 1, 1997 - May 31, 2000 (2.9 years), and to the national pathology database, to quantify the number of biopsies. All men randomized were included, only those with prostate cancer screen-detected or clinically diagnosed before July 1997 were omitted from the analyses. 2,895 Out of the 14,349 men (20.2%) in the control arm and 1,981 out of the 14,052 men (14.1%) in the screening arm were PSA tested, at an average annual rate of 73 and 52 per 1000 person-years, respectively. These rates were higher than those recorded at the national and regional levels, 33 and 38 per 1,000 person-years, respectively. Opportunistic PSA testing in the control arm reached a peak within the first months of randomization, after which it decreased to around 70 per 1,000 person-years. An opposite pattern was observed in the screening arm, where participants already had received the scheduled screening within the trial. The proportion of men in the control arm with PSA ≥3.0 ng/ml followed by biopsy and prostate cancer was 7-8% and 3%, respectively (3% and 0.4-0.6% in the screening arm) over the whole study period. Over a 4-year re-screening interval, the average PSA and effective contamination amount approximately 28% and 10%, respectively. PSA testing in the control arm in the Rotterdam ERSPC section is high, but was not followed by a substantial increase in prostate biopsies. Although the reasons for ordering PSA test or indicating biopsy are unknown, effective PSA contamination in the Rotterdam ERSPC section is low and not likely to jeopardize the power of the trial.

## Introduction

There is still much controversy on the benefit of early detection of prostate cancer using prostate-specific antigen (PSA). An important shift in stages at diagnosis to more localized confined cancers has been reported. However, with respect to reduction of prostate cancer mortality, no conclusion can be drawn yet on the beneficial effects of PSA screening, either from analyses of international trends[1] or from the first results of the Quebec trial for prostate cancer detection [2]. The Tyrol mass screening project has shown promising results, but is not a randomized control trial [3]. Presently, 2 large-scale randomized screening trials are ongoing, the European Randomized Study of Screening for Prostate Cancer (ERSPC) in Europe and the Prostate, Lung, Colorectal and Ovary cancer (PLCO) trial in the United States, to assess the effectiveness of PSA screening (and two different screening algorithms, ERSPC) on the reduction of prostate cancer mortality [4]. Meanwhile, in the United States and several Western countries, PSA testing in asymptomatic men is increasing, mainly due to the simplicity and noninvasiveness of the test as a screening tool. This implies that PSA testing may occur in some men randomized to the control arm or, outside the protocol procedures, in men from the screening arm.
In these trials, PSA contamination, *i.e.* testing of asymptomatic men in the control arm of the trial for whatever reason, must be closely monitored. The rate of contamination in the control arm may adversely affect the power of the trial [4]. This is particularly so if a routine PSA examination is followed by biopsy, as indicated in the regular screening programs, *i.e.* effective opportunistic PSA testing. However, before making inferences on the extent of opportunistic PSA testing in the control arm, the underlying PSA testing practice, background incidence, should be taken into account. A PSA test in the control arm could be the result of diagnostic testing or follow-up in men treated for prostate cancer. Previously, Beemsterboer et al [5] evaluated opportunistic PSA testing in the first 1.5 year of the trial in the Rotterdam section. They reported that after randomization, approximately 8% of the men in the control arm received one or more PSA tests each year.
In the present study the extent of opportunistic PSA testing in the trial population was further studied by linkage with the regional GP laboratory. Moreover, the number of histological examinations of the prostate was quantified in both trial arms and in these men with opportunistic PSA determinations, to evaluate the effective PSA contamination rate in the Rotterdam section of the ERSPC-trial.

## Material and Methods

### *Study population*

The ERSPC trial is conducted in 8 different European countries, including the Netherlands [4]. In the Rotterdam center, 42,376 men aged 55-74 years were randomized between June 1994 and March 2000; 21,210 into the screening and 21,166 into the control arm (the core age group in the ERSPC as a whole is 55-69 years). Participants were recruited from the city of Rotterdam and 12 neighboring municipalities, identified through the corresponding population registries. All men in the age group 55-74 years received an invitation by letter to participate and were aware that, if randomized into the screening arm they would be offered PSA testing. After receipt of a full written informed consent, the men were randomized to either the screening or control arm. In the Rotterdam section of ERSPC, a rescreening interval of 4 years is used after the prevalence screening round. Since the protocol change in February 1997 [6], the initial and follow-up screenings in this center are based on PSA testing with a cutoff level of 3.0 ng/ml as only referral for biopsy. Currently, the first screening round is completed and the second is ongoing.

### *PSA testing*

Data on all PSA tests performed in the period of July 1, 1997 through May 31, 2000 were obtained from the General Practitioner Laboratory (GP laboratory) in Rotterdam. This regional laboratory covers, besides the municipality of Rotterdam, 7 of the 12 neighboring municipalities from which the trial participants were recruited. Only 11 out of a total of 32,321 PSA tests (0.04%) performed in the GP laboratory were residents from the other 5 trial municipalities, lying outside the working area of this laboratory. Hence, in the calculations of PSA rates, the participants in these 5 municipalities were not considered as population at risk (and not included in the denominator) and the 11 PSA tests mentioned above were not included in the numerator.

In the Dutch healthcare system, the GP is the gatekeeper for the specialized medical care, which is accessible only after a referral by the GP. Published data on referral for PSA test by GPs participating in the Dutch Sentinel Practice Network were used for the evaluation of the background rate of PSA testing at national level [5,7]. The PSA assay used in the GP laboratory was the PSA-2 (Bayer Diagnostics, Tarrytown, NY); in the ERSPC trial laboratory the Access of Hybritech (Beckman-Coulter Inc., San Diego,CA).

By linking the trial records to the PSA database of the GP laboratory, the number and outcome of PSA tests requested by the GPs in both the control and screening arms were obtained. The linkage procedure has been described previously [5], but was slightly modified in the current study in order to obtain all PSA tests (and not random ones)

of the respective participants. Briefly, one 9- and two 8-character keys consisting of a combination of the first initials plus characters from the subject's last name and the date of birth (ddmmyyyy) were made for each record in both the trial and the PSA database of the GP laboratory. In the first step of the linkage procedure, the 9-character linkage-key (first initial+ first and last character of the last name) was applied to retrieve the trial participants from the PSA database. In the next steps of the linkage the two other 8-character variables, with the first + last character of the last name and first initial + first character of the last name respectively, were used to trace the subjects whose initials were missing or whose names were misspelled. In order to correct for possible mismatched records, each matched record was manually checked for the complete last names and the postal codes to verify whether it really concerned a trial participant [8].

### *Histological examinations*

To quantify the number of histological examinations in the control arm and in the screening arm with the exception of those performed within the scheduled screening in the trial, we used the Dutch National Database for Pathology (PALGA). In this database, all excerpts of diagnostic (and screening) histological and cytological examinations on cell material and tissues performed in pathology laboratories across the country (100% coverage) are registered together with the conclusion formulated by the pathologists. This conclusion is also stored as a diagnosis text phrase composed of various diagnosis expressions coded by PALGA using the SNOMED classification system.

Request for linkage was done for all histological examinations of the prostate performed in the participants of the trial between 1 July 1997 and 31 December 2000 in the pathology laboratories within and adjacent to the area of Rotterdam. After submission of trial data, linkage to the pathology database was done according to the standard PALGA procedures based upon the first four characters of the last name, first initial, date of birth (yyyymmdd) and gender. By using these identifiers the possibility existed that examinations of one subject was merged with the records of another subject with exactly the same identifiers. Correctness of these records was manually verified by comparing the first initial and the place of residence reported by PALGA with those registered in the trial database [8]. Thereafter, all examinations (biopsies, lymph node resections and prostatectomies) in the screening arm that appeared to have been carried out in connection with the regular screening procedures in the trial were discarded. External second revisions of already reported histological examinations as well as post mortem examinations were deleted from the data set.

### *Linkage of PSA test and biopsies*

The corrected and verified PSA and histological data were then combined. For each matched record the dates of PSA test and pathology examination were compared. Only those histological examinations done within three and six months after the PSA test are presented here. This time limit was chosen because we assume that an interval longer than 6 months may indicate that the currently retrieved biopsy was not a consequence of the linked PSA tests.

All prostate cancer cases screen-detected (screening arm) or clinically diagnosed (control arm) before 1July 1997 were excluded from the calculations, because a PSA test retrieved would indicate rather a follow-up test than a screening test. For men in whom prostate cancer was screen-detected or clinically diagnosed within the study period, their follow-up ended at the time of diagnosis and any PSA test performed after that date was discarded from analyses. All men randomized before 1July 1997 were at risk throughout the follow-up period and those men randomized after that date, the person-years were calculated from the date of randomization to 31 May 2000. However, for all men, the follow-up time ended when the subject was diagnosed with prostate cancer. The period of 4 year after randomization is, in part, covered for each subject, as recruitment was from June 1994 till March 2000.

Rates were calculated per 1,000 person-years at risk that each man contributes to the follow-up period and standardized to the European standard population [9]. Results are presented for the age group 55-74 years at entry. Differences in rates between groups were analyzed statistically using the Chi-square test. Students t-test analysis was performed to compare the continuous variables (PSA level and age at time of testing) between the two arms.

## Results

### *PSA testing*

In the follow-up period of almost 3 years, 2,895 out of the 14,349 men (20.2%) in the control arm, and living within the working area of the GP laboratory, had 1 or more PSA tests (39,859.35 person-years). In the screening arm, 1,981 out of the 14,052 men (14.1%) were tested (38,535.28 person-years). Most men undergoing PSA testing have had only 1 PSA test throughout the follow-up period, 72.8% in the control and 76.1% in the screening arm. Ninety-four percent of those men in the screening arm who had a test outside the trial, were men who had already been tested as part of the study. The remaining 6% were nonattenders (n=113) and men who were tested after randomization but before the date

of their first screening appointment (n=12).

**Figure 1** shows the age-standardized rate of PSA testing outside the regular screening program in men aged 55-74 at entry (Fig. 1*a* includes first visits only and fig. 1*b* all visits) in the screening and control arm and in the Sentinel Practices and GP laboratory (excluding data of the trial participants). The latter two rates give an impression of PSA testing on the national and the regional level, respectively, and were lower than those observed in the trial arms (overall annual rates 32.9 and 37.8 per 1,000 person-years, respectively, and statistical significantly different). Generally, there was an upward trend in the PSA testing rate in the screening arm, the region of Rotterdam and across the country (Fig. 1*a*), in contrast to the rates in the control arm. However, except for year 2000, the rates of opportunistic PSA testing in the control arm were significantly higher than in the screening arm (overall annual rates 72.7 and 51.8 per 1,000 person-years, respectively, and statistically significant different). In 2000, the PSA testing rate in the control arm (60.6 per 1,000 person-years) dropped and had reached a comparable level as seen in the screening arm (57.7 per 1,000 person-years). Calculation of the PSA rates including all PSA tests per person showed an increase in both trial arms. However, this rise was more pronounced in the screening arm, from 51.1 in 1997 to 83.6 per 1,000 person-years in 2000 and from 96.1 to 113.6per 1,000 person-years in 2000 in the control arm.

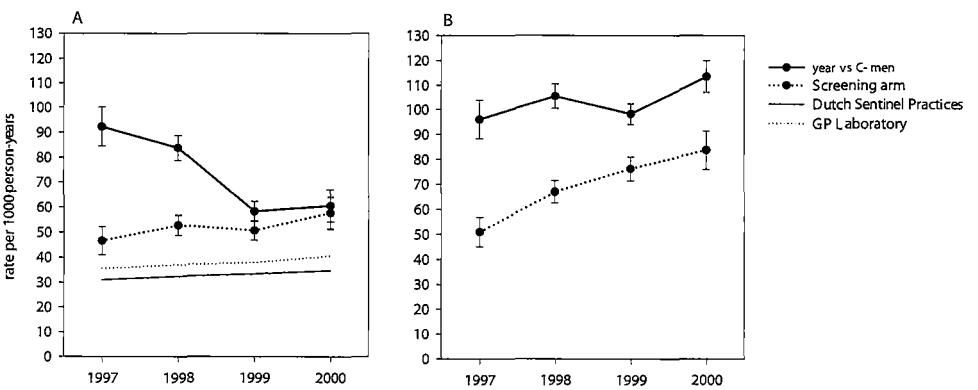


**Figure 1:** Age-standardized rate of opportunistic PSA testing by calendar year, 1997-2000, in the trial arms of the ERSPC-Rotterdam, the Sentinel Practices and the regional GP laboratory, age group 55-74. Data of the two trial arms were excluded from those of the GP laboratory in order to present the background PSA testing in the region. In (A), PSA rates in the trial arms were calculated based on the number of men tested, first visit, in respective years, whereas in (B) all PSA performed in respective years, not only the first one, were included in the calculations.

**Figure 2** describes the opportunistic PSA testing over time since randomization in men aged 55-74 at entry (rates are age-standardized). The overall rates observed before randomization in the control and the screening arm, 65.3 and 66.9 per 1,000 person-years, were higher than those seen at the national and regional level. In the first month after randomization, a relatively large number of men in the control arm had their PSA tested through the GP. Thereafter, the rate declined and approached the level observed before randomization. An opposite pattern was seen in the first months after randomization for the men in the screening arm. In the first 4 months of randomization, the PSA testing rate dropped to a level substantially below the pre-randomization level and started to increase gradually again thereafter. At 51 months after randomization, which corresponded with the end of the first 4-year screening interval, the number of men having one or more PSA tests declined again in the screening arm (Fig. 2). Men who were randomized prior to July 1, 1997 determined the tail of the curves in this figure.

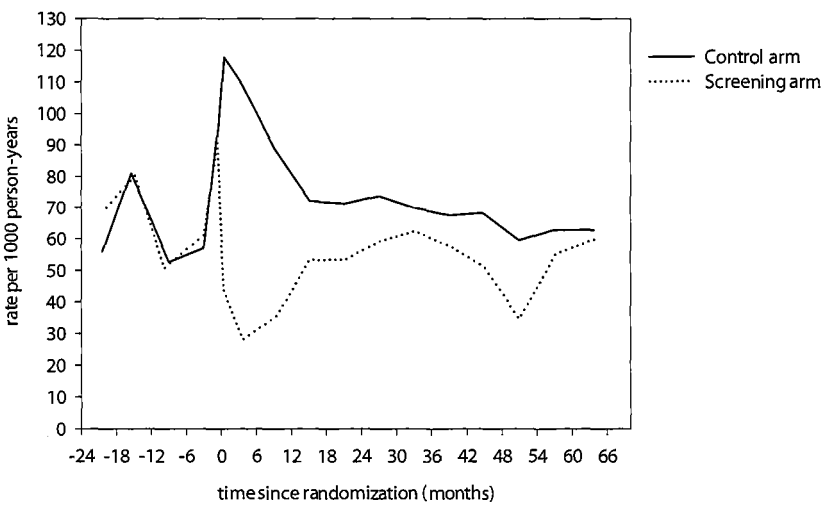


**Figure 2:** Age-standardized rate of opportunistic PSA testing over time since randomization in the screening and control arm of the Rotterdam section of ERSPC, age group 55-74 years at entry. The intervals before and after randomization were calculated as within 1 month and consecutively by 6-month intervals; the x-axis denotes the average of each interval for both trial arms.
For sake of clarity, standard errors were omitted and given below for both arms separately (± s.e.) with the respective point on the x-axis between brackets:
control arm: 32 *(-20)*, 35 *(-15)*, 28 *(-9)*, 17 *(-3)*, 39 *(-0.5)*, 41 *(0.5)*, 15 *()*, 11 *(9)*, 9 *(15)*, 8 *(21)*, 7 *(27)*, 7 *(33)*, 7 *(39)*, 9 *(45)*, 9/7 *(51)*, 11 *(57)*, 13 *(64)*.
screening arm: 36 *(-20)*, 35 *(-15)*, 28 *(-9)*, 18 *(-3)*, 37 *(-0.5)*, 25 *(0.5)*, 8 *(3)*, 7 *(9)*, 8 *(15)*, 7 *(21)*, 7 *(27)*, 7 *(33)*, 7 *(39)*, 8 *(45)*, 7 *(51)*, 11 *(57)*, 13 *(64)*.

**Table 1:** Frequency distribution of the PSA levels of screenings outside the trial and the initial screenings within the trial.

| | PSA ng/ml[1] | | | | | | | | | | PSA ng/ml | | age[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤2.9 | age[3] | 3.0-3.9 | age[3] | 4.0-9.9 | age[3] | ≥10 | age[3] | n.c[2] | age[3] | mean | median | |
| | % | yrs | % | yrs | % | yrs | % | yrs | % | yrs | | | yrs |
| *outside the trial* | | | | | | | | | | | | | |
| Control arm | | | | | | | | | | | | | |
| (n= 2895) | 73.3 | 65.6 | 7.4 | 67.7 | 15.3 | 68.3 | 4.0 | 71.1 | 0.1 | 70.2 | 3.7 | *1.5* | 66.4 |
| Screening arm | | | | | | | | | | | | | |
| (n= 1981) | 74.6 | 66.0 | 8.0 | 68.7[4] | 13.6 | 69.1 | 3.5 | 71.7 | 0.3 | 65.0 | 2.6[5] | *1.4* | 66.8 |
| *within the trial* | | | | | | | | | | | | | |
| Initial screenings | | | | | | | | | | | | | |
| (n= 19,970) | 79.4 | 62.3[56] | 7.1 | 65.7[56] | 11.2 | 66.5[56] | 2.3 | 68.8[56] | | | 2.3[5] | *1.3* | 63.2[46] |

[1] only first visits (PSA assay used in the GP laboratory was PSA-2, BayerDiagnostics, USA, and in the ERSPC trial laboratory was Access, Hybritech, Beckman Coulter, USA, used).
[2] not categorized: PSA values of 3 subjects in the control arm and 5 in the screening arm could not be classified, because of wrong annotation (not numerical).
[3] median age at the time of testing
[4] differed significantly from the control arm ($p<0.05$, t-test)
[5] differed significantly from the control arm ($p<0.001$, t-test)
[6] differed significantly from the screening arm ($p<0.001$, t-test)

**Table 1** presents the distribution of PSA levels (only first visits) measured in the GP laboratory compared to the outcome of the initial screenings in the trial. The mean PSA level in the control arm, 3.7 ng/ml, was significantly higher in comparison to the screening arm, 2.6 ng/ml, and the initial screenings within the trial, 2.3 ng/ml. The median ages at time of PSA testing in both trial arms were comparable (66.4 years and 66.8 years), but were significantly higher than the median age at the initially scheduled screenings. According to the current screening protocol of the trial, PSA cutoff value of 3.0 ng/ml, 26.7% (n=770) of the men in the control arm and 25.1% (n=498) in the screening arm would have been referred for biopsy, compared to 20.6 in the trial.

### *Biopsies*

The histological examinations done outside the trial in men aged 55-74 years at entry, living in all municipalities where recruitment took place, included a total of 1,018 biopsies. These were performed in 305 men in the screening arm (353 biopsies) and 652 men in the control arm (760 biopsies), during 45,874.2 and 47,767.7 person-years, respectively. As shown in **Figure 3**, both the control and the screening arm had increased biopsy rates between 1997 and 2000. The rate of prostate cancers also went up in the two trial arms in this period. From 2.6 to 5.7 per 1,000 person-years (overall, 4.2 per 1,000 person-years) in the control arm and from 0.7 to 1.8 per 1,000 person-years in the screening arm (overall, 1.1 per 1,000 person-years; significantly lower than the control arm).

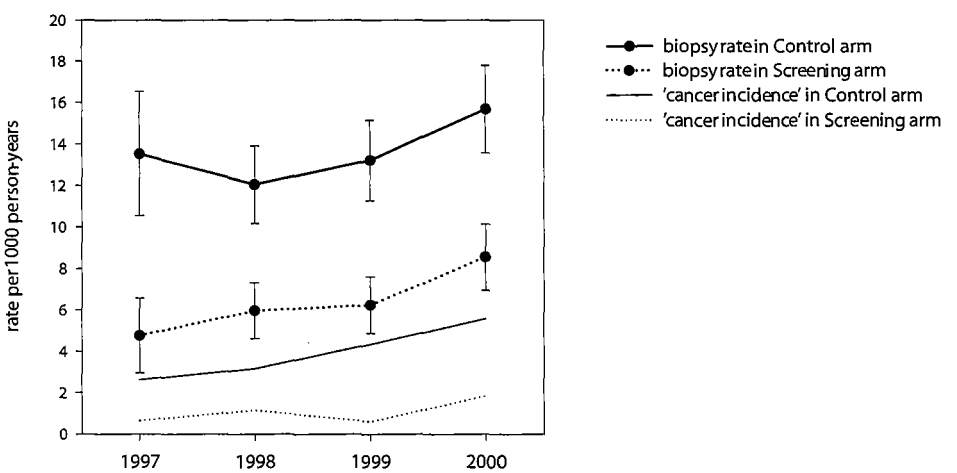


**Figure 3:** Age-standardized rate of biopsy and the crude incidence rate of prostate cancers diagnosed outside the regular screening program, age group 55-74 at entry.

**Table 2:** Biopsies and cancers diagnosed within 3-6 months of the PSA testing date in the control arm, A, and in the screening arm, B (all ages at entry).

Control arm

| | | *following PSA test within* | | | |
|---|---|---|---|---|---|
| | | **0-3 months** | | **0-6 months** | |
| **PSA level** | **Men[1]** | **biopsies** | **cancers** | **biopsies** | **cancers** |
| **ng/mL** | **n** | **n (%)[2]** | **n (%)[2]** | **n (%)[2]** | **n (%)[2]** |
| ≤1.9 | 1728 | 91 (5.3) | 28 (1.6) | 107 (6.2) | 33 (1.9) |
| 2.0 – 2.9 | 394 | 19 (4.8) | 7 (1.8) | 21 (5.3) | 9 (2.3) |
| ***<3.0*** | ***2122*** | ***110 (5.2)*** | ***35 (1.6)*** | ***128 (6.0)*** | ***42 (2.0)*** |
| 3.0 – 3.9 | 213 | 15 (7.0) | 7 (3.3) | 18 (8.5) | 8 (3.8) |
| 4.0 - 9.9 | 442 | 28 (6.3) | 13 (2.9) | 34 (7.7) | 13 (2.9) |
| 10 – 19.9 | 75 | 5 (6.7) | 2 (2.7) | 5 (6.7) | 2 (2.7) |
| ≥20 | 40 | 2 (5.0) | 2 (5.0) | 2 (5.0) | 2 (5.0) |
| ***≥3.0*** | ***770*** | ***50 (6.5)*** | ***24 (3.1)*** | ***59 (7.7)*** | ***25 (3.2)*** |
| total[2 3] | 2895 | 160 (5.5) | 59 (2.0) | 187 (6.5) | 67 (2.3) |

Screening arm

| | | *following PSA test within* | | | |
|---|---|---|---|---|---|
| | | **0-3 months** | | **0-6 months** | |
| **PSA level** | **Men[1]** | **biopsies** | **cancers** | **biopsies** | **cancers** |
| **ng/mL** | **n** | **n (%)[2]** | **n (%)[2]** | **n (%)[2]** | **n (%)[2]** |
| ≤1.9 | 1227 | 25 (2.0) | 5 (0.4) | 36 (2.9) | 5 (0.4) |
| 2.0 – 2.9 | 251 | 9 (3.6) | 1 (0.4) | 9 (3.6) | 1 (0.4) |
| ***<3.0*** | ***1478*** | ***34 (2.3)*** | ***6 (0.4)*** | ***45 (3.0)*** | ***6 (0.4)*** |
| 3.0 – 3.9 | 158 | 1 (0.6) | 0 | 3 (1.9) | 1 (0.6) |
| 4.0 - 9.9 | 270 | 12 (4.4) | 2 (0.7) | 13 (4.8) | 2 (0.7) |
| 10 – 19.9 | 59 | 1 (1.7) | 0 | 1 (1.7) | 0 |
| ≥20 | 11 | 0 | 0 | 0 | 0 |
| ***≥3.0*** | ***498*** | ***14 (2.8)*** | ***2 (0.4)*** | ***17 (3.4)*** | ***3 (0.6)*** |
| total[2 3] | 1981 | 48 (2.4) | 8 (0.4) | 62 (3.1) | 9 (0.5) |

[1] sum of column does not equal the total, because of wrong annotation (not numerical) of the PSA value of 3 men in the control arm and 5 in the screening arm could not included; no biopsies were found for the respective subjects.

[2] proportion of the number of men who had one or more PSA

**Table 2** shows the results of the linkage of the PSA and biopsy data conducted within 3 and 6 months of the PSA testing date. The delay of 3 to 6 months had more impact on the number of biopsies than on the number of cancers diagnosed. In general, more biopsies were performed in men with an outcome ≥3.0 ng/ml, particularly in the control arm. Correspondingly, the number of prostate cancers diagnosed was also higher in this PSA range, approximately 1.5-2 times higher than in the low PSA range (3.1% and 1.6% within 3 months and 3.2 and 2.0 % within 6 months of PSA testing date, respectively). Nevertheless, regardless of the interval between date of PSA testing and biopsy, prostate cancer was diagnosed in 3% of the men with a PSA outcome ≥3.0 ng/ml. In the screening arm, lower cancer percentages were found, 0.4-0.6% of the men was diagnosed with prostate cancer after a PSA outcome ≥3.0 ng/ml. However, similar figures were also found at the lower range.

## Discussion

In the present study, the extent of effective PSA contamination was estimated in the ongoing randomized prostate cancer screening trial within the Rotterdam section of the ERSPC trial. Effective PSA contamination was defined as when opportunistic PSA testing of ≥3.0 ng/ml was followed by biopsy, similar to the regular procedure within the trial.
It has been suggested that the excessive incidence of prostate cancer in the control arm should be considered as effective PSA contamination. However, it is difficult to obtain figures on the background prostate cancer incidence in this PSA era against which the rate in control arm should be compared [10].
The results of the study indicated that 20% of men in the control arm had had their PSA tested at least once, in the 3 years of follow-up. Immediately in the first month after being randomized, men in the control arm were increasingly tested by their GPs. This probably results from arousal of their curiosity or disappointment of not being randomized to receive screening. As time after randomization went on, men in the control arm were seemingly no longer inclined to get their PSA tested, at least not more than prior to randomization. Therefore, it is very likely that the proportion of men in the control arm undergoing PSA screening will not exceed the annual rate of 7% (73 per 1,000 person-years) in the following years, as recruitment in the Rotterdam section of the ERSPC has already been completed.
Screening is assumed to prevent prostate cancer deaths because of early diagnosis and treatment. Therefore, if active screening occurs in the control arm, the final analysis of the main study endpoint would not be between a real unscreened and a screened group,

something that consequently will affect the power of the study. This contamination will reduce the difference in early treatments and prostate cancer mortality expected. In the recent evaluation of the sample size of the ERSPC trial as a whole, power calculations assumed a contamination rate of 20% [11]. However, to have a real effect on the trial, PSA contamination has to be effective, in that men in the control arm with PSA value of ≥3.0 ng/ml should undergo biopsy similar to the regular procedure within the ERSPC trial. We found that 7-8% of the men in the control arm with PSA ≥3.0 ng/ml underwent biopsy and in less than half of this cases (3%) were prostate cancer diagnosed. This observation indicates that the effective PSA contamination in the control arm is low and that its rate in the recent power was overestimated.

A limitation of our study is that not all PSA tests performed outside the trial could be traced, since the regional GP laboratory did not cover all municipalities in which recruitment was carried out. Furthermore, no tests done in hospital laboratories were quantified. So, we have no evidence of PSA testing carried out by urologists in the regional hospitals, however, in the Dutch health care system a specialist sees patients only after referral by their GPs, implying that these men were most likely symptomatic and a PSA test ordered would rather be diagnostic than opportunistic testing. In the United Kingdom, by contrast, at least 50-80% of patients were reported to have been already tested by the GP before referral to the urologist [12]. Opportunistic PSA testing occurred not only in the control arm, but in the screening arm as well. Fourteen percent of men in this trial arm had had their PSA tested between 1997 and 2000. The vast majority (93%) were men who had already had their prevalent screen as part of the trial, which explains the low prostate cancer rate due to these opportunistic screenings (0.4-0.5%). This non-compliance in the screening arm has been reported previously by Beemsterboer et al [5], when PSA contamination in the first years of the Rotterdam section was evaluated. Their finding, that screening outside the regular screening program increases continuously within this trial arm, was confirmed by the present longer-term evaluation. This increase may possibly be a result of aging, since this follow-up was conducted on average 4 years (range 0.4-6.6 years) after the men were randomized into the trial. It may also arise from a need for self-reassurance between two screening invitations, as men likely experience the 4-year interval as long. The latter is underlined by the observation that the opportunistic PSA testing had declined as the second screening round got closer.

In both the control and the screening arm, the overall pre-randomization PSA rate was higher than that observed for the general male population of the same age group in the Rotterdam area. It is not clear whether this results from selection during recruitment. There is the concern that men volunteering to participate in the trial may form a self-selected group of the general male population [13]. This issue, therefore, is presently

being investigated in the Rotterdam section of ERSPC.

The frequency of biopsy following a PSA test within 3 or 6 months did not considerably differ between low and high PSA ranges. This is not consistent with the general observation that increasing PSA levels will lead to higher numbers of biopsies. Moreover, this resulted in high positive predictive value (42-48%) in comparison to that arising from the scheduled screenings within the trial (24.3%) [14]. No medical charts were reviewed and none of the trial participants were approached in connection with this study. Consequently, the intent of the GP for ordering a PSA test (screening, diagnostic or follow-up) is not known, the same is true for the biopsy indication, another limitation of our study [15]. An explanation for the low biopsy rates at PSA outcome ≥3.0 ng/ml is not obvious. The result of rectal examination may play a role. However, GPs may also have reservation in advising biopsies, because of the lack of evidence on the effectiveness of screening, as stated recently by Páez et al [16]. In their study, on the PSA use in an area in Spain, more than half of the patients with PSA outcome ≥ 4.0 ng/ml was not biopsied, because they were simply not referred to the urologist.

Despite the limitations, our results suggest that presently the effective PSA contamination in the Rotterdam section of the ERSPC trial is low and is likely not to jeopardize the power of the study. The latter will depend upon figures from the other European ERSPC centers and the PLCO trial as well.

## Acknowledgement

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# CHAPTER 3

# Tumorcharacteristics and prognostic factors in two subsequent screeningrounds with a four year interval within the prostate cancer screening trial, ERSPC Rotterdam

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## Abstract

### *Introduction*

To evaluate tumor characteristics and prognostic factors in screen-detected prostate cancers in two successive screening rounds with a 4-year screening interval in the European Randomized study of Screening for Prostate Cancer, section Rotterdam.

### *Methods*

From 1993 to 2000 42,376 men (21,210 in the screening arm and 21,166 in the control arm) were randomized and screened. PSA testing, digital rectal examination, transrectal ultrasonography and sextant biopsies were offered to the participants in the screen arm. A total of 1,218 men with a biopsy indication at the first screen received an additional screening after one year (early recall). By 2004, all men had received their second screening. Interval carcinomas were defined as cancers detected during the screening interval and are identified by linkage with the Cancer Registry.

### *Results*

In the first round, 1,014 prostate cancers were detected – 24 in the men noncompliant to screening, 63 at the early recall screening, and 433 in the second round of screening. Also, 62 interval carcinomas were diagnosed. In the second screening round, the mean PSA value was lower (5.6 versus 11.1 ng/ml), advanced clinical stage T3/T4 was 7.1-fold less common and 76.4% versus 61.5% of biopsy Gleason scores were less than 7. In the first screening round,13 regional and 9 distant metastasis were detected; in the second round, 2 cases with distant metastasis were found.

### *Conclusion*

Overall, a shift to more favorable tumor characteristics was seen for the second round of screening. These results support the screening methods used and the inter-screening interval of 4 years.

## Introduction

The possibility of detecting prostate cancer at an early stage through PSA-based screening has an important impact on prostate cancer incidence and management. PSA testing has become a widespread phenomenon. Large randomized trials on PSA based screening for prostate cancer are ongoing. The European Randomized study of Screening for Prostate Cancer (ERSPC) is a multi-center randomized controlled trial. The screening methods, tumor characteristics and prognostic factors are being evaluated and the quality-of-life effects and health costs are analyzed. The ERSPC is similar to the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) trial of the National Cancer Institute of the USA, and a combined analysis is planned [1,2].

The main endpoint of ERSPC is prostate cancer mortality. Recently a decrease in prostate cancer mortality in the United States was seen [3]. It is not clear whether PSA-based screening is responsible for this decrease. Some studies have claimed a reduction in prostate cancer mortality through PSA-based screening, but undisputed evidence is not available [4-6]. It is hoped that the large randomized trials will answer this question in the future.

In this report, we describe the tumor characteristics and prognostic factors at diagnosis of screen-detected prostate cancers in two subsequent screening rounds of the ERSPC, section Rotterdam. The interscreening interval was four years. More favorable tumor characteristics, specifically a down staging and grading of prostate cancers in the second round of screening were expected [7,8].

## Material and Methods

A total of 42,376 men (21,210 in the screening arm and 21,166 in the control arm) aged 55-74 years were randomized to the ERSPC, section Rotterdam. From December 1993 to May 2000 all men in the screen arm underwent their initial screen. The ERSPC, section Rotterdam, includes a rescreening interval of 4 years, and by March 2004, the second screen was completed.

Screening consisted of a PSA measurement before rectal examination (DRE) and trans-rectal ultrasound (TRUS). The physical examination was performed without knowledge of the PSA value. From December 1993 to February 1997 the Rotterdam screening regimen called for lateralized sextant trans-rectal biopsy if the PSA level was 4.0 ng/mL or greater and if DRE and/or TRUS findings were suspicious for cancer at low PSA values (0.0 – 3.9 ng/mL). The biopsy procedure was performed at a second visit. From December 1993 to

October 1996 an early recall visit (after one year) was performed for those men who had a biopsy indication in the prevalence screen but a negative biopsy outcome. These men were invited again for PSA, DRE, TRUS and sextant biopsy. From February 1997 onwards, a PSA of 3.0 ng/mL or more became the sole biopsy indication. The conditions and algorithm of the screening regimen of ERSPC are described in greater detail elsewhere [9-11].

Interval cancers were defined as cancers detected in the interscreening interval after a completed first screening round. To identify the interval cancers, a yearly linkage is performed with the database of the Rotterdam Cancer Registry. A total of 62 cancers were considered interval cancers.

All data related to prostate cancer detection and management were obtained by a patient charts review and stored in a comprehensive database. For all prostate cancers detected a single genital-urinary pathologist (THvdK) assessed the Gleason score prospectively for each case. All tumors were staged according to the 1992 TNM system.

## Statistical analysis

The statistics are purely descriptive. Testing for significance was performed by Statistical Package for Social Sciences (SPSS, Chicago, Illinois) for Windows, version 10.0 software. The nonparametric Mann Whitney U test was used to compare the mean PSA values in the screening and the control arms. The chi-square test was used to compare the number of nonadvanced (T1 and T2) and advanced tumors (T3 and T4) and the biopsy Gleason scores (less than 7 and 7 or more).

## Results

An ERSPC consort diagram is shown in **Figure 1**. A total of 1,038 prostate cancers were diagnosed in the first round of screening; 1,014 in the first screening round and 24 in men who were randomized to screen but were never screened (noncompliant randomized-to-screen group). At the early recall screen, 63 cancers were detected, and in the second screening round,433 cancers were detected. All 433 cancers in the second round were detected using the protocol with a sole biopsy indication of PSA 3.0 ng/ml or more.

In the second round, 12,483 (62%) of the 20,108 eligible men were rescreened. Of the remainder, 3,370 men were too old, 714 had died, 718 had moved away, 290 had severe health problems, 807 refused and 1,726 were otherwise lost.

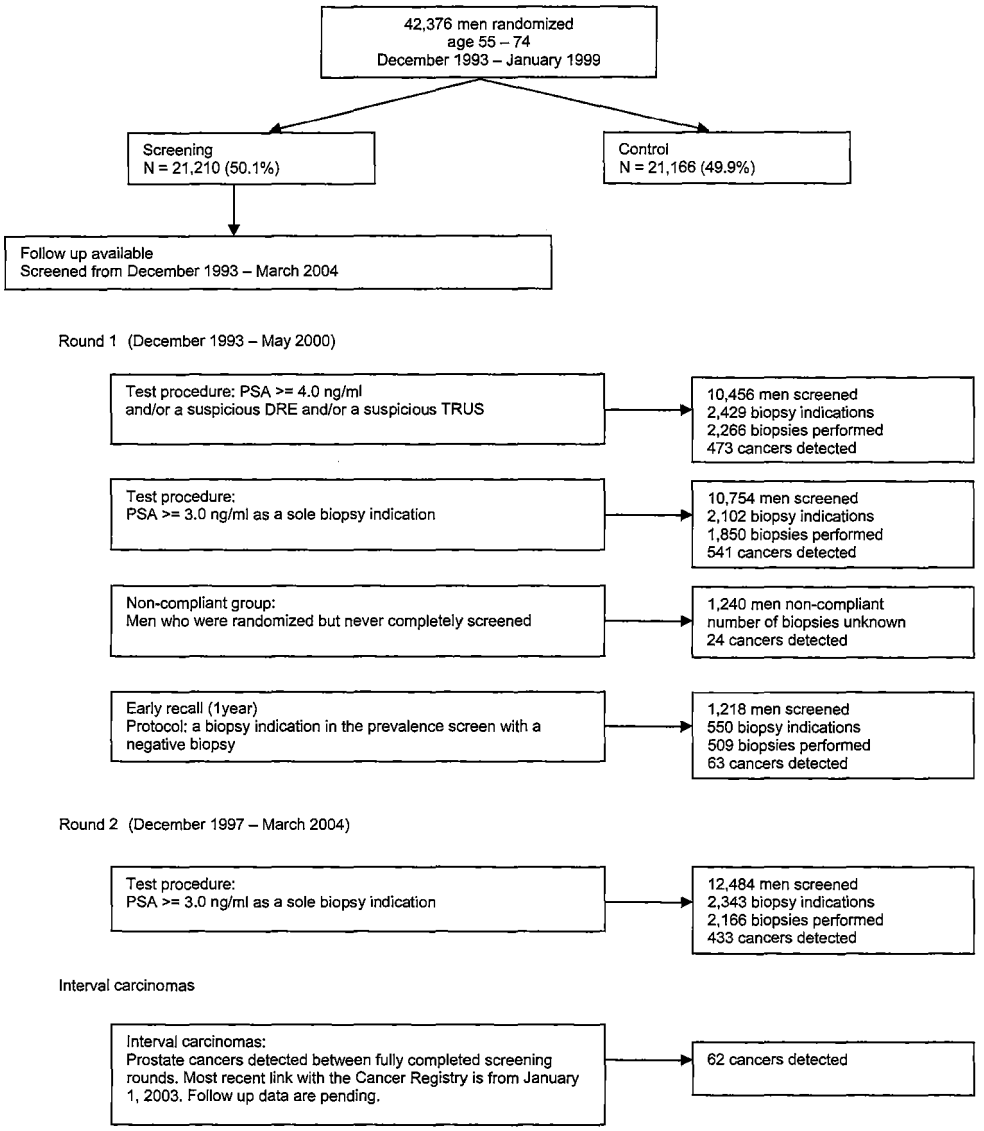


**Figure 1:** ERSPC Consort diagram

At diagnosis in round 1 the mean and median age was 66.4 and 66.8 respectively. At diagnosis in round 2 the mean and median age was 67.1 and 67.0 respectively ($p = 0.065$). In **table 1**, the PSA distribution for all men randomized to screen is shown. In the second round, a decrease was seen in the PSA levels greater than 4.0 ng/ml. The mean and median values of PSA were not significantly different between both rounds.

**Table 1:** PSA distribution in all men randomized to screen for round 1 and 2 (four years later).

| | *Total number of men randomized to screen* | | | |
|---|---|---|---|---|
| | *Visit 1* | | *Visit 2* | |
| **PSA (ng/ml)** | **N** | **%** | **N** | **%** |
| 000 – 0.9 | 7,139 | *35.8* | 4,304 | *34.5* |
| 1.0 – 1.9 | 6,205 | *31.1* | 3,863 | *30.9* |
| 2.0 – 2.9 | 2,508 | *12.6* | 1,850 | *14.8* |
| 3.0 – 3.9 | 1,426 | *7.1* | 946 | *7.6* |
| 4.0 – 9.9 | 2,235 | *11.2* | 1,343 | *10.8* |
| => 10 | 456 | *2.3* | 177 | *1.4* |
| Subtotal | 19,969 | *100.0* | 12,483 | *100.0* |
| Not screened * | 1,241 | | 7,625 | |
| Total # | 21,210 | | 20,108 | |
| | | | | |
| Range | 0.0 – 315.7 | | 0.0 – 59.0 | |
| Mean | 2.4 | | 2,1 | |
| Median | 1.3 | | 1.4 | |

# Total number of men for visit 2 21,210 – number of cancers detected (1,014 + 63 + 24) = 20,108
* Not screened for visit 1included men noncompliant randomised to screening; not screened for visit 2 included men not eligible for rescreening, lost to follow up, who refused rescreening or who had died.

In **table 2**, the PSA distribution at the diagnosis of prostate cancer is shown. In round 2, PSA values greater than 10.0 ng/ml were rare, and almost 40% of the detected cancers had a PSA level of 3.0 - 3.9 ng/ml. The positive predictive value for PSA 3.0 – 3.9 ng/ml was 19.9%. The cancer detection rate was 3.5% compared with 4.9% in the first round. The difference in mean and median PSA values in men with prostate cancer was more pronounced at the diagnosis of prostate cancer than for all men randomized (11.1 versus 5.6 and 2.4 versus 2.1 for the mean PSA value) resulting in greater PSA values at diagnosis. The mean and median PSA values at diagnosis were lower in the second round ($p < 0.01$). If only those cancers detected with a PSA level of 4.0 ng/ml or greater were compared, the mean and median PSA value in the second round remained lower (7.0 and 5.4 ng/ml for round 2 versus 13.0 and 7.0 ng/ml for round 1; $p < 0.01$).
The early recall data show 550 biopsy indications and 63 cancers detected. Of these, 50 cancers were detected with PSA values of 4.0 ng/ml or more; 363 men (66.0%) did not have a biopsy indication confirmed in round 2.

**Table 2:** PSA distribution at the time of diagnosis of prostate cancer for round 1, early recall after one year, and round 2.

| | *Visit 1* | *Early recall (1 year)* | *Visit 2* |
|---|---|---|---|
| **PSA (ng/ml)** | **N (%)** | **N (%)** | **N (%)** |
| 000 – 0.9 | **4** (0.4) | - | - |
| 1.0 – 1.9 | **45** (4.3) | **7** (11.1) | - |
| 2.0 – 2.9 | **31** (3.0) | **2** (3.2) | - |
| 3.0 – 3.9 | **179** (17.2) | **4** (6.3) | **172** (39.7) |
| 4.0 – 9.9 | **531** (51.1) | **38** (60.3) | **230** (53.1) |
| => 10 | **247** (23.8) | **12** (19.0) | **31** (7.2) |
| Missing * | **1** (0.1) | - | - |
| Total # | **1,038** (100.0) | **63** (100.0) | **433** (100.0) |
| Range | **0.3 – 550.0** | **1.0 – 24.8** | **3.0 – 59.0** |
| Mean | **11.1** | **6.5** | **5.6** |
| median | **5.8** | **5.4** | **4.4** |

# Total number of prostate cancers is 1,038; 1,014 cancers detected in round 1 plus 24 cancers detected in the noncompliant group.
* For 1 case of the noncompliant group cancers PSA is not available.

**Table 3** shows the tumor characteristics of the prostate cancers detected. An obvious shift was seen towards more stage T1C cancers in the second round (58.9% versus 35.1%). Advanced clinical T stages (T3-T4) was 7.1-fold less common in round 2 ($p < 0.001$) and 21.9% of cancers had a Gleason score of 7 or more in the second round versus 35.2% in the first round ($p < 0.001$). Half way through the first screening round, the PSA threshold was lowered and DRE omitted. Even when comparing those cancers detected in the first and the second round using the same protocol, the marked shift towards less advanced stage and grade remained. With DRE as a screening tool, 1,079 men had suspicious DRE findings. Of the 1,079 men, 265 had cancer and 83 of these 265 men had a PSA level of less than 4.0 ng/ml. Of these 83 men, 34 had a PSA level between 3.0 and 4.0 ng/ml. Only 49 (83 minus 34) of the 1,079 men (4.5%) with suspicious DRE findings would have been missed using a sole biopsy indication of a PSA level of 3.0 ng/ml or greater.
The early recall protocol also found less advanced cancers, with biopsy Gleason scores more favorable than in the first screening round ($p < 0.001$). In the first screening round, 13 regional (lymph node) and 9 distant (bone) metastasis were detected. In the second round, 2 cases of distant metastasis were detected.

**Table 3:** Tumor characteristics of prostate cancers detected at Visit 1, early recall after one year, and Visit 2.

| | ***Biopsy indication*** | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Visit 1* | | | *Early recall (1 year)* | | | *Visit 2* |
| ***Biopsy indication*** | PSA >= 4.0 ng/ml and/or suspicious DRE/TRUS N (%) | PSA >= 3.0 ng/ml N (%) | **Total N (%)** | PSA >= 4.0 ng/ml and/or suspicious DRE/TRUS N (%) | PSA >= 3.0 ng/ml N (%) | **Total N (%)** | **PSA >= 3.0 ng/ml Total N (%)** |
| ***Clinical T stage*** | | | | | | | |
| T1A-B | 1 (0.2) | 2 (0.4) | **3 (0.3)** | - | - | - | - |
| T1C | 124 (25.8) | 240 (43.1) | **364 (35.1)** | 18 (37.5) | 11 (73.4) | **29 (46.0)** | **255 (58.9)** |
| T2 | 249 (51.8) | 228 (40.9) | **477 (46.0)** | 28 (58.3) | 2 (13.3) | **30 (47.6)** | **163 (37.6)** |
| T3-T4 | 107 (22.2) | 87 (15.6) | **194 (18.7)** | 2 (4.2) | 2 (13.3) | **4 (6.3)** | **15 (3.5)** |
| Total | 481 (100.0) | 557 (100.0) | **1,038 (100.0)** | 48 (100.0) | 15 (100.0) | **63 (100.0)** | **433 (100.0)** |
| ***Biopsy Gleason score*** | | | | | | | |
| Below 7 | 284 (59.0) | 354 (63.6) | **638 (61.5)** | 34 (70.8) | 14 (93.3) | **48 (76.2)** | **331 (76.4)** |
| 7 | 122 (25.4) | 155 (27.8) | **277 (26.7)** | 12 (25.0) | 1 (6.7) | **13 (20.6)** | **79 (18.2)** |
| Above 7 | 56 (11.6) | 32 (5.7) | **88 (8.5)** | 2 (4.2) | - | **2 (3.2)** | **16 (3.7)** |
| Missing * | 19 (4.0) | 16 (2.9) | **35 (3.4)** | - | - | - | **7 (1.6)** |
| Total | 481 (100.0) | 557 (100.0) | **1,038 (100.0)** | 48 (100.0) | 15 (100.0) | **63 (100.0)** | **433 (100.0)** |

* Data not available in the follow-up.

## Discussion

In ERSPC, Rotterdam, an overall shift toward less-advanced tumor characteristics and prognostic factors was seen in the second screening round. The prognostic factors are described in relation to the prostate cancers detected and the whole study population. Because the same cohort was followed during the interscreening interval of 4 years, the stage and grade shift could be reliably evaluated. A marked shift to less-advanced clinical T stages and an obvious decrease in biopsy Gleason scores was present in the second screening round. These observations were influenced by lowering the PSA threshold to 3.0 ng/ml. However, one half of the men screened in round 1 were screened with PSA level of 3.0 ng/ml or more as the sole biopsy indication. Comparing the tumor characteristics of those cancers with the characteristics found in round 2, the stage and grade shift remained obvious. This trend toward a less-advanced stage and grade seemed to be progressing in round 3, the findings of which were previously by our group [12]. These observations are similar to the data described by other ERSPC partners. The Finnish trial also showed an early and marked shift toward more favorable prognostic factors [8,13]. The subsequent screening rounds showed most tumors had stage T1C, Gleason score 3 + 3 and a PSA level less than 10.0 ng/ml. Their detection rate in the first round was 2.2% compared with 4.9% in our trial. Because of a different recruitment regimen the stage and grade shift in the Finnish trial was not as obvious as that seen in our trial. The nonattenders from the first screening round participated as first-time screeners in the second screening round, resulting in more aggressive cancers detected in later screening rounds.
The Swedish trial also showed a remarkable stage and grade shift [7,14]. However, in the Swedish trial, the first round in which an individual participated was treated as his first screening round, regardless of whether this individual had been invited to participate in previous screening rounds. Therefore every cohort consisted of participants at varying rounds of screening. This affected the prostate cancer incidence rates and the presence of advanced tumors in later screening rounds. Furthermore, because of a difference in age distribution (men aged 50-55 were included), the PSA levels were lower in the Swedish trial. In the first round of screening, only 7.6 % of the PSA values were 4.0 ng/ml or more compared with 13.5% in our trial.

The detection of presumably clinically insignificant disease (cancers that would never lead to any signs and symptoms) is unavoidable in prostate cancer screening. In a previous study, we described a ratio of prostate cancer incidence between the screening and control arm of 3.7 during the 4-year recruitment period. Many cancers found by screening would probably not be diagnosed during the lifetime of these men (overdiagnosis). Available data have suggested that overdiagnosis occurs in 35-100% of screen-detected cases [15].

At present, what the optimum screening interval should be is not clear. The American Cancer Society has recommended annual PSA testing for men 50 years or older. The ERSPC Rotterdam included a rescreening interval of 4 years. Only a few advanced cancers were detected in the second screening, suggesting that the 4-year interval might not be too long to prevent detection of prostate cancer at a curable phase. These findings are in line with data published by Hoedemaeker et all [16]. Their results strongly suggest that even during a screening interval of 4 years, no evidence was found of unfavorable changes in the characteristics of detected carcinomas in the subsequent screening rounds.

The rate of interval carcinomas depends strongly on the definition of interval cancers. In our study, 62 interval cancers were detected in the screening arm between screening rounds and within the age group 55 to 74 years. The interval cancers accounted for a low rate of 6.0% (62 of 1,038) of screen-detected cancers. This finding is in line with data published from our group in 2003 [17]. We have no reason to believe the interval cancers would have a profound effect on the data we describe here.

## Conclusion

When comparing the first and second round of screening, a strong reduction in advanced cancers in stage and grade is seen. These results confirm and add to the screening methods used and the inter-screening interval of 4 years. However, they provide no evidence that PSA based screening will decrease prostate cancer mortality.

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# CHAPTER 4

# Intervalcarcinomas in the European randomised study of screening for prostate cancer (ERSPC) - section Rotterdam

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## Abstract

### *Background*

The interval cancer rate is an important parameter for the determination of the sensitivity of the screening procedure and the screening interval. We evaluated the time and mechanism of detection and the stage distribution of prostate cancers diagnosed during a four-year screening interval.

### *Methods*

We determined the rate of interval cancers and the sensitivity of the screening protocol (involving prostate-specific antigen, digital rectal and transrectal ultrasound examinations) in a cohort of 17,226 men (8350 on the screened arm, 8876 on the control arm) enrolled consecutively on the European Randomized study of Screening for Prostate Cancer – Rotterdam. Men on the screened arm received a first screen between October 1993 and December 1996 and a scheduled second screen 4 years later. Prostate cancers detected in men enrolled on the control arm over the same 4-year period and, between screens, in men on the screened arm, were identified by linkage to the Dutch national cancer registry.

### *Results*

During the first screen, 412 prostate cancers were detected. During the 4-year period 135 cancers were diagnosed in the control arm and 25 cancers were diagnosed in men in the screened arm. Seven of the 25 cancers were diagnosed in men who had refused a recommended biopsy at their initial screen. Of the remaining 18 cancers, all were classified as stage T1A-C or T2A and none were poorly differentiated or metastatic. The rate of interval cancers relative to the number of cancers in the control group was 18.5% (25/135) or 13.3% (18/135), if the seven who refused an initial biopsy were excluded. The sensitivity of the screening protocol was 79.8% when considering all 25 interval cancers and 85.5% when considering 18 interval cancers.

### *Conclusions*

The interval cancer rate with a 4-year interval was low, confirming that the screening procedure has a high sensitivity and that the 4-year screening interval is reasonable.

## Introduction

The quality and effectiveness of a screening program cannot be evaluated on the basis of the results from the initial screening round. Instead, these properties must be evaluated with consideration for crucial indicators, such as detection rates from subsequent rounds, the interval cancer rates, underlying cancer incidence and tumor characteristics.
It will be several years before the outcomes, including effects on cancer-related mortality, of population based randomized trials – such as the European Randomized study of Screening for Prostate Cancer (ERSPC) [1] and the Prostate, Lung, Colorectal an Ovarian (PLCO) trial [2] – will be available. In the meantime intermediate endpoint analyses are important indicators for the quality of the screening procedures. One such intermediate endpoint for prostate cancer screening is the rate of interval cancers, i.e., cancers detected in the screened population between screening rounds and outside screening trials. Because the rate of interval cancers reflects the number of and the time needed for new cancers to surface clinically, it is an important parameter for determining the sensitivity of the screening procedure and the proper screening interval. The sensitivity of the screening procedure in the ERSPC, which included collection of sextant biopsy specimens, was estimated to be approximately 70% [3,4]. In this study, we evaluated the time and mechanism of detection and the stage distribution of prostate cancers diagnosed during a 4-year screening interval in a subgroup of the ERSPC study population.

## Patients and Methods

We studied a cohort of 17,226 men aged 55 – 74 years (8350 men in the intervention arm and 8876 men in the control arm) (Fig. 1) enrolled on ERSPC – Rotterdam. All men in the intervention arm had their first screen between October 1993 and December 1996. ERSPC – Rotterdam uses a 4-year screening interval. The second screen was completed by the end of December 2000. This allowed a full 4-year period for the study of interval cancers. All men in the control arm were enrolled simultaneously.
At the first screen, all participants in the intervention arm were offered a prostate-specific antigen (PSA) level measurement, digital rectal examination (DRE) and transrectal ultrasound (TRUS). Individuals who had PSA levels equal to or higher than 4.0 ng/mL or who had PSA levels of 0-3.9 ng/ml and suspicious DRE and/or TRUS results were then recommended to have lateral sextant transrectal biopsies, as stated for the Rotterdam screening regimen. All participants received extensive information about potential benefits and harms of screening for prostate cancer as part of the informed consent

procedure.

To identify individuals with prostate cancer in each study arm, including interval carcinomas in individuals in the intervention arm, a database from the local Rotterdam Comprehensive Cancer Registry was checked annually. For men diagnosed with prostate cancer and those known to have died from other causes, data regarding the diagnosis of prostate cancer were collected and entered into the ERSPC database. All data related to prostate cancer staging and management were obtained by reviewing the patients' medical records at the regional hospitals.

For individuals identified with interval carcinomas, histological slides of sections of prostate cancer biopsy specimens were retrieved from the pathologic storage facilities of the local hospitals. All diagnosis and Gleason scores were reviewed by one of the authors (T.H. van der Kwast). If discrepancies occurred among the diagnoses and Gleason scores from the patients´ medical records and those assigned after review, blinded re-grading by the reference pathologies was used. The pathologic features of the cancers, including the extent of the cancers and Gleason scores, in men who had undergone radical prostatectomy were obtained in the same way as those of the biopsy specimens to collect a maximum amount of reliable prognostic information. All tumors were staged according to the 1992 Tumor-Node-Metastasis (TNM) System [5]. All men diagnosed with prostate cancer, regardless of study arm, received standard medical care, which meant that the evaluation of symptoms and diagnosis and management of the prostate cancer were provided by local urologists not associated with the study. The study was approved by the Minister of Health of The Netherlands (via letters dated 15 August 1997 and 05 February 2001 from Dr. E. Borst-Eilers, the Hague). Written informed consent was obtained from each participant.

## Statistical Analysis

The rate of interval cancer was calculated as the ratio of the number of interval cancers to the number of cancers found in the control group during the same time period. Sensitivity was calculated according to the proportional incidence method (6).

## Results

The ERSPC – Rotterdam recruited 42 375 participants randomly assigned them to either the intervention arm (21 210 men) or the control arm (21 166 men) (**Fig. 1**). For the purpose

of this study we used a cohort of 17226 men (8350 screen arm and 8876 control arm) who were consecutively enrolled on the ERSPC – Rotterdam. Men in the intervention arm had their first screen between October 1993 and December 1996. At the end of December 2000, all participants in the intervention arm had been followed to the completion of their scheduled second screen, a 4-year follow-up period.

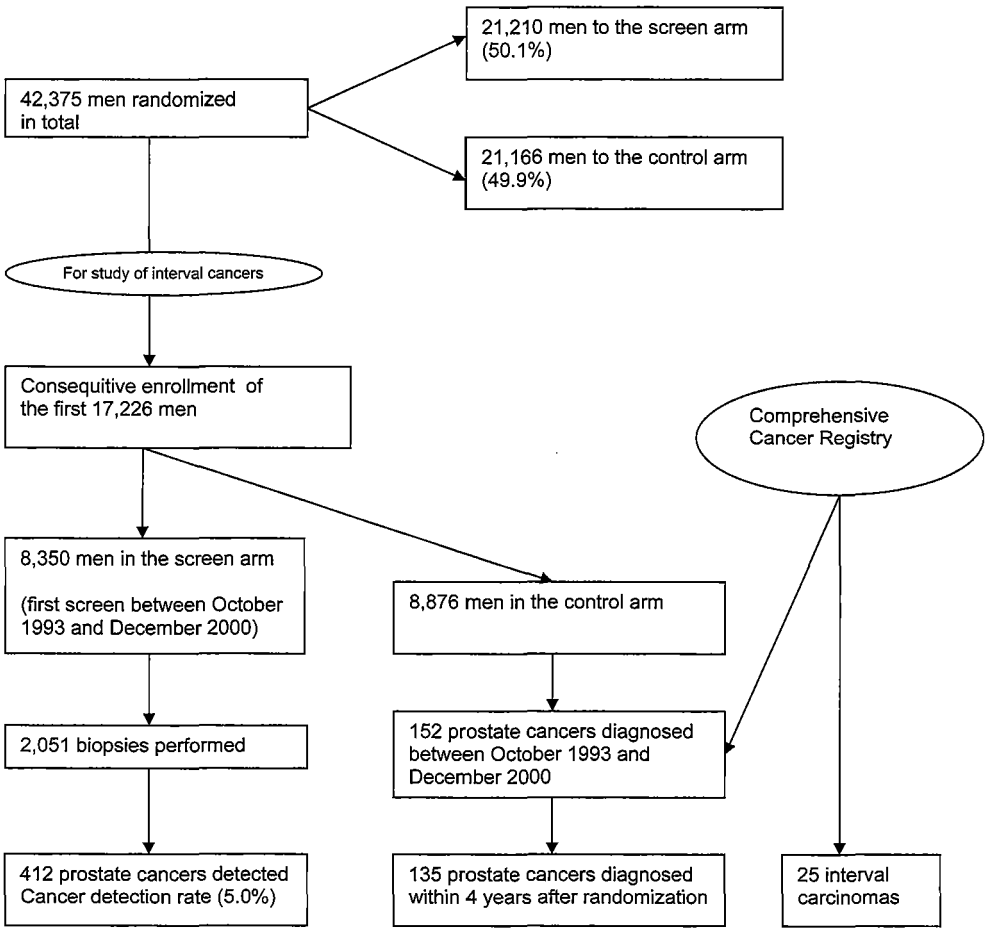


**Figure 1:** ERSPC Consort Diagram relating to interval cancers

Of the 152 prostate cancers diagnosed among individuals in the control arm, 135 were diagnosed within 4 years of randomization. Among individuals in the intervention arm, 25 prostate cancers were not diagnosed as a result of screening but were diagnosed outside the trial and within 4 years of randomization. The prognostic characteristics of

the 25 cancers are described in Tables 1-4. Twenty-two of the 25 cancers were classified as early-stage (T1A, T1B, T1C, or T2A). None of the cancers were poorly differentiated or metastatic (N+ or M+).

Of the 25 cancers, seven were diagnosed among men who had a biopsy indication initially but who refused a recommended biopsy at the initial screen. Three of the seven cancers were advanced cancers, with a T3 or worse tumor stage. None of these seven men had metastatic disease. Five of the seven cancers were detected within 1 year of the initial screening examination (**Table 1**).

**Table 1:** Tumorcharacteristics of interval cancers among men enrolled in the European Randomized study of Screening for Prostate Cancer – Rotterdam who refused a recommended biopsy at the initial screen and their therapy choices (n = 7)*.

| | INITIAL SCREEN | | | | | | DIAGNOSIS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PSA (ng/ml) | DRE | TRUS | biopsy | Interval Mo & | Age y | PSA (ng/ml) | Tstage § | biopsy Gleason | Therapy | pTstage § | RP Gleason score |
| 1 | 6.6 | B | B | N | 44 | 62 | 8.8 | T1C | 6 | Radical prostatectomy | PT2C | 5 |
| 2 | 7.1 | B | B | N | 25 | 67 | 9.6 | T1C | 6 | Radiotherapy | | |
| 3 | 16.0 | - | - | N | 8 | 73 | 18.7 | T1C | 8 | Radiotherapy | | |
| 4 | 21.0 | - | - | N | 0 | 61 | 21.0 | T1C | 7 | Radical prostatectomy | PT2A | 6 |
| 5 | 62 | T2C | T2C | N | 5 | 71 | 65.0 | T3A | 9 | Radiotherapy | | |
| 6 | 2.8 | T2C | B | N | 3 | 68 | 2.8 | T3B | 6 | Radiotherapy | | |
| 7 | 19.1 | - | - | N | 4 | 72 | 19.1 | T4 | 7 | Endocrine therapy | | |

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; TURP = transurethral resection of the prostate (for apparently benign disease); B = benign; N = not done; Y = yes, biopsy performed.
& Interval refers to the number of months between the first screen and a prostate cancer diagnosis.
§ T stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor-Node-Metastasis System of 1992. No lymph nodal or distant metastases were found.

Of the remaining 18 men diagnosed with an interval prostate cancer, four were aged 75 years or older. In three of the four men, the cancers were carcinomas diagnosed by transurethral resection of the prostate (TURP), which was done for what was thought to be benign disease. These three cancers are considered incidental cancers (**Table 2**). The remaining 14 cancers were diagnosed clinically, as indicated in Tables 3 and 4. Five of the cancers were diagnosed by cystoprostatectomy for bladder cancer, and two were diagnosed by TURP for benign disease. The other seven cancers were diagnosed because of increasing PSA levels or complaints of prostatism.

**Table 2:** Tumorcharacteristics of interval cancers among men enrolled in the European Randomized study of Screening for Prostate Cancer – Rotterdam who were not eligible for rescreening because of age (older than 75 years) and their therapy choices (n = 4)*.

| INITIAL SCREEN | | | | | | | | DIAGNOSIS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PSA (ng/ml) | DRE | TRUS | Biopsy | histology | Interval Mo & | Age y | PSA (ng/ml) | Tstage § | TURP/ Biopsy Gleason | Therapy |
| 8 | 1.4 | B | B | N | N | 44 | 76 | 1.0 | T1A | | Watchful waiting |
| 9 | 2.8 | B | T2 | Y | Y Chronic prostatitis | 46 | 78 | 3.2 | T1B | 4 | Watchful waiting |
| 10 | 4.0 | B | B | Y | Y No malignancy | 33 | 76 | 6.0 | T1B | 4 | Watchful waiting |
| 11 | 2.4 | B | B | N | N | 48 | 77 | 5.3 | T1C | 6 | Radiotherapy |

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; TURP = transurethral resection of the prostate (for apparently benign disease); B = benign; N = not done; Y = yes, biopsy performed.
& Interval refers to the number of months between the first screen and a prostate cancer diagnosis.
§ T stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor-Node-Metastasis System of 1992. No lymph nodal or distant metastases were found.

During the initial screen, 412 prostate cancers were diagnosed. Thus, the proportion of interval cancers among all cancers diagnosed in men in the screening arm was 6.1% (25/412). The proportion of interval cancers in men in the screened arm, relative to cancers diagnosed in men in the control arm during the 4-year period after randomization was 18.5% (25/135). If the seven men who a biopsy after their initial screen are not included among the interval cancers, then the proportion of interval cancers relative to the control arm would be 13.3% (18/135). Other definitions of interval cancer rates can easily be applied using the information provided in the tables.

The incidence of prostate cancer was 21 per 1000 person-years among men in the screened arm and 3.9 per 1000 person years among men in the control arm. The number of screen-negative men in our cohort is 7938, which represents men who actually had a negative screen (7798), men from whom a biopsy specimen could not be taken because they used anticoagulants (48), and men who were non-attenders (92). The expected number of cancers in the screen-negative men would be 123.8 (7938 * 3.9/1000 * 4 years of follow up). Sensitivity was calculated according to the proportional incidence method [6] and was estimated to be 79,8% ((123.8 – 25) / 123.8). If the seven men who refused a biopsy during the first screen were not considered among the interval cancers, then the sensitivity was estimated to be 85.5%.

## Discussion

This is the first report on interval carcinomas in prostate cancer screening from the ERSPC. The rate of interval cancers was low and reflects the usefulness of a screening interval of at least 4 years. In general, cancers not detected in the initial screening visit may be detected as interval cancer, may be detected in the second screening round, or may remain occult during the lifetime of their carriers. The occurrence of interval carcinomas may be the result of a lack of sensitivity of the screening test or an interscreening interval that is too long. Increased sensitivity (and a lower proportion of interval cancers) can be reached by more aggressive screening strategies but such an approach would increase the rate of overdiagnosis, a problem that is inherent in screening for prostate cancer.

### *Characterization of Interval Cancers*

In our study, interval cancers were defined as prostate cancers detected during 4 years after randomization in the screened population but outside the screening protocol. Because the first screening round is complete only if men who are recommended to have a biopsy did in fact do so, the cancers found in the seven patients listed in Table 1 who refused to have a prostate biopsy may not represent true interval cancers. The information regarding classification of the interval cancers in the tables is purely descriptive and does not contain any judgments on what may be a clinically relevant or irrelevant cancer. Some cancers are diagnosed as so-called "incidental prostate cancers" (i.e., T1A and T1B cancers). Their high prevalence of approximately 30% at autopsy is well established in men aged 50-60 years [7]. Some incidental prostate cancers were found during treatment for other diseases, such as during cystoprostatectomy for bladder cancer (cases 12-16) and during transurethral resection for obstructive benign prostatic hyperplasia (cases 17 and 18). Four cases (11, 19, 20, and 21), all stage T1C, were found through opportunistic screening. By definition, a T1C cancer can be diagnosed only on the basis of an elevated PSA level.

### *Potential biases*

It is unclear why interval cancers are rarely mentioned in the prostate cancer screening literature. One reason may be that interval cancers do not occur because of the short intervals that are in general use (6-12 months) and are recommended in the United States [8]. ERSPC chose a 4-year screening interval in light of the limited evidence available regarding lead time in prostate cancer [9-11] during the ERSPC protocol development phase (1992 through 1994). The Swedish center of ERSPC uses a screening interval of 2 years and has described nine interval cancers that were found over a 4-year period [12]. Their data cannot be compared with ours because the difference in screening intervals

will bias the determination of rates of interval cancers.

Several factors could have influenced the results of this study by either raising or lowering the number of interval cancers or their rate relative to prostate cancer incidence in the control group. These factors include the frequency of screening, the screening procedures used, the age group screened, and the underlying incidence. It is well known that collecting more biopsy specimens will detect more cancer [13-15]. This knowledge has led to a change in clinical practice in several ERSPC countries but not in The Netherlands. However, 49 cancers were detected at temporary early rescreens performed on men in ERSPC – Rotterdam who had a negative biopsy during the first screening round [16]. These cancers are part of the first round detection rate and therefore are likely to have decreased the number of interval cancers.

The prevalence of opportunistic screening, defined as screening of participants outside the study, in the intervention and the control arms could be another important source of bias. Opportunistic screening was therefore subject to continuous monitoring. The preliminary results of opportunistic screening in the ERSPC have been published [17,18]. The data show that effective screening, which involved a PSA test combined with a biopsy according to indication, occurred in about 10% of men in the control arm over a 4-year period [18]. The proportion of men who were classified as T1C and, by definition, were diagnosed by PSA-driven screening is presently under investigation.

Our results could also be biased by incomplete incidence data obtained from the cancer registry. However, all Dutch cancer registries are maintained according to one countrywide protocol; one regional comprehensive cancer center that follows the protocol evaluated the completeness of cancer registration and found that 96.2% of the eligible malignancies were included in the registry [19]. Thus, it is reasonable to expect that the completeness of the data obtained from the Rotterdam Cancer Registry is similar. ERSPC procedures include a double check of the incidence data obtained from the registry. This additional check has rarely led to corrections of the cancer registry database.

### *Lead time*

Lead time is an important codeterminant of the sensitivity of a screening procedure. Determinations of lead time [9-11] were made on the basis of clinical diagnoses of prostate cancer associated with archived serum samples used during follow-up periods of 10-15 years. Gann et al. [11] point out that lead time is not a parameter that depends exclusively on test characteristics but a parameter that depends also on prognostic factors such as stage at the time of diagnosis, tumor aggressiveness, patient age, and other disease-related factors. Factors associated with a worse outcome are likely to be associated with a shorter lead time than those associated with clinical cancers. The ERSPC has made two

attempts to model lead time.

Auvinen et al. [20] estimated a lead time of 5-7 years on the basis of the duration of follow-up that was needed to accrue the same expected number of incident prostate cancer cases in the absence of screening as were detected in the initial screening round. These estimates vary from those found by Draisma et al. [21] who, using the MISCAN technique, found that for a group of men aged 55-75 years and a screening interval of 4 years, lead time was 10.3 years (range = 9.9-11-2 years). Lead times were age-dependent [21]. This information also confirmes the choice of a long screening interval in the ERSPC.

Sensitivity of PSA-based screening was estimated by Hakama et al.[22], who used follow-up and PSA determinations from archived serum samples. They studied 21,387 men in whom 104 prostate cancers were detected clinically. The sensitivity of the PSA test was 86% for cancers that were diagnosed within 5 years of collecting the blood sample. This estimate is in line with our sensitivity results of 79.85-85.5%. However, it should be noted that we used PSA, DRE, and TRUS in our screening protocol.

### *Clinical Importance of Interval Cancers*

If we had detected a large number of interval cancers and/or interval cancers with advanced stage or otherwise poor prognostic factors, it would have indicated that the screening protocol had a low sensitivity. However, all interval cancers were detected at a locally confined stage, and only three had an unfavorable Gleason score of 7, one in **Table 3** and two in **Table 4**, not counting those in Table 1 (these are the case patients who refused biopsy). The preponderance of low Gleason scores is in line with the fact that many of the cancers were detected by transurethral resection for benign prostatic hyperplasia and as incidental findings of cystoprostatectomy. T stage and Gleason score have poor intra-and interobserver reproducibility and poor correlation with definitive findings in radical prostatectomy specimens and often result in understaging. Future screening tests and screening intervals will have to consider these difficulties and aim to identify aggressive cancers in time for curative management.

**Table 3:** Tumorcharacteristics of interval cancers among men enrolled in the European Randomized study of Screening for Prostate Cancer – Rotterdam who were diagnosed with cancer by cystoprostatectomy or transurethral resection of the prostate (TURP; for apparently benign disease) and their therapy choices (n = 7)*.

| INITIAL SCREEN | | | | | | DIAGNOSIS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PSA (ng/ml) | DRE | TRUS | biopsy | Histology | Interval Mo & | Age y | PSA (ng/ml) | Tstage § | Therapy | pT stage § | RCP/ TURP Gleason score |
| 12 | 1.6 | B | B | N | | 43 | 74 | - | | Cystoprostatectomy | PT2C | 7 |
| 13 | 1.7 | B | B | N | | 38 | 73 | 2.4 | | Cystoprostatectomy | PT2A | 4 |
| 14 | 1.8 | B | B | N | | 10 | 65 | 2.4 | | Cystoprostatectomy | PT3A | 5 |
| 15 | 1.8 | B | B | N | | 32 | 70 | 2.5 | | Cystoprostatectomy | PT2A | 6 |
| 16 | 7.2 | B | B | Y | Hyperplasia | 10 | 71 | 8.0 | | Cystoprostatectomy | PTX | 6 |
| 17 | 2.2 | T2A | T2A | Y | No malignancy | 4 | 67 | 3.1 | T1A | Watchfull waiting | | 5 |
| 18 | 4.9 | B | B | Y | No malignancy | 28 | 68 | 6.0 | T1B | Watchfull waiting | | 3 |

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; TURP = transurethral resection of the prostate (for apparently benign disease); B = benign; N = not done; Y = yes, biopsy performed.
& Interval refers to the number of months between the first screen and a prostate cancer diagnosis.
§ T stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor-Node-Metastasis System of 1992. No lymph nodal or distant metastases were found.

**Table 4:** Tumorcharacteristics of interval cancers among men enrolled in the European Randomized study of Screening for Prostate Cancer – Rotterdam who were clinically diagnosed with cancer and their therapy choices (n = 7)*.

| INITIAL SCREEN | | | | | | DIAGNOSIS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PSA (ng/ml) | DRE | TRUS | biopsy | Histology | Interval Mo & | Age y | PSA (ng/ml) | Tstage § | biopsy Gleason score | Therapy | pT stage § | RP Gleason score |
| 19 | 3.0 | B | B | N | | 26 | 63 | 5.3 | T1C | 6 | Watchful waiting | | |
| 20 | 3.6 | B | B | N | | 30 | 68 | 5.4 | T1C | 6 | Watchful waiting | | |
| 21 | 2.6 | B | B | N | | 26 | 73 | 6.4 | T1C | 6 | Radiotherapy | | |
| 22 | 3.0 | B | B | N | | 31 | 74 | 5.3 | T2A | 7 | Radiotherapy | | |
| 23 | 3.4 | B | B | N | | 28 | 72 | 6.9 | T2A | 6 | Radiotherapy | | |
| 24 | 18.2 | B | B | Y | Prostatitis | 21 | 67 | 15.4 | T2A | 7 | Radical prostatectomy | PT3a | 6 |
| 25 | 20.2 | T2C | T2A | Y | No malignancy | 28 | 69 | 25.0 | T2A | 6 | Radical prostatectomy | pT2A | 6 |

*PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound examination; TURP = transurethral resection of the prostate (for apparently benign disease); B = benign; N = not done; Y = yes, biopsy performed.
& Interval refers to the number of months between the first screen and a prostate cancer diagnosis.
§ T stage = tumor extent determined before and after excision of the prostate. All tumors were staged according to the Tumor-Node-Metastasis System of 1992. No lymph nodal or distant metastases were found.

## Conclusion

The rate of interval cancers found within ERSPC – Rotterdam with a 4-year screening period was exceedingly low. The interval cancers were associated with favorable prognostic factors. The data confirm a high sensitivity of the screening procedure and the usefulness of a 4-year screening interval. The resulting estimates of lead time are in agreement with the findings of others. [9-11,21] and with the long natural history of the disease. The results confirm that very few, if any, aggressive prostate cancers escape screening with the procedures used within the ERSPC.

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# General discussion and conclusions

The introduction of PSA measurements into medical practice has led to increased detection rates and a stage reduction at the time of diagnosis of prostate cancer. The increase in detection rates is seen in industrialized countries and prostate cancer has become the most common cancer diagnosed and the second most common cause of cancer deaths [1]. In the Netherlands a crude rate of prostate cancer incidence is seen of 85 cases per 100,000 person years. The mortality crude rate is 33 cases per 100,000 person years [2]. In the United States incidence differs widely with large ethnic and international differences. Caucasian men have a lower lifetime risk of developing prostate cancer or dying from the disease than Afro-American men (156 per 100,000 person-years and 243 per 100,000 person-years versus 26.7 per 100,000 person-years and 65.1 per 100,000 person-years, respectively) [1]. In 1999 the SEER data of the National Cancer Institute showed a decline in prostate cancer incidence and a decrease in prostate cancer mortality rates since 1992 [3]. However more recent data from the SEER database show a transient increase in prostate cancers incidence since the use of PSA in 1986. The age-adjusted prostate cancer mortality rates have dropped below the rate in 1986 since 1995 for white men and since 1997 for black men. The incidence based mortality rates show that the recent declines were due to declines in distant mortality, more specifically to a decline in distant disease incidence and not to improved survival of patients with distant disease [4]. Labrie et al [5,6] provided the first data claiming a reduction in prostate cancer mortality due to screening for prostate cancer. However this study has been criticized heavily because of the small-scale size of the trial and flaws in the methods of analysis [7,8]. Evidence of prostate cancer mortality reduction due to screening is not available, but until the effect of screening becomes clear data from randomized trials are important for the understanding of prostate cancer management.

The impact of screening and early intervention on prostate cancer morbidity and mortality is being assessed by large randomized trials such as the European Randomized study of Screening for Prostate Cancer (ERSPC). Furthermore the improvement of specificity of screening test for the reduction of unnecessary biopsies, and more accurate staging and grading of prostate cancer at the time of diagnosis will enable the selection of patients that need treatment and those that can be followed by watchful waiting. In this thesis these issues and the tumor characteristics of prostate cancers detected in two successive screening rounds and in the control arm are discussed.

## Results

In **chapter 1** a comparison is made between screen detected prostate cancers and clinically diagnosed cancers in a cohort of men from the ERSPC, section Rotterdam. In the screen arm of the trial 1,269 prostate cancers were detected, 818 in the first round, 63 at early recall, 336 in the second round, 8 in round three and 44 as interval carcinomas. The cancer detection rate is 4.9% in the first round and drops to 3.5% and 2.7% in the subsequent rounds. In the control arm 336 prostate cancers were detected. The PSA values at the time of diagnosis of prostate cancer differ largely between the different screening rounds. In the subsequent screening rounds the higher PSA values (> 10.0 ng/ml) disappear. Compared to the screen arm the mean and median PSA values are 7.7 respectively 2.2 times higher in the control arm. Due to the fact that the first screening round is a prevalence round the proportion of advanced cancers (T3-T4) in the first screening round is relatively high, but they become rare in the subsequent screening rounds. Compared to the control arm there is a statistically significant difference in advanced cancers in favour of the screen arm. The results of the biopsy Gleason scores can be described in the same way. In the prevalence round the biopsy Gleason score is relatively high, decreases in the subsequent screening rounds and compared to the control arm the biopsy Gleason score shows a statistically significant difference in favor of the screen arm. The most remarkable observation is the fact that the absolute number of distant metastatic disease is lower in the screened population than in the control arm (7/27) and compared to all men diagnosed with prostate cancer (0.6%/8.0%) and even compared to all men randomized (0.04%/0.2%). The proportion of men with metastatic disease in the control arm was much lower than reported in historical controls [9]. The down-staging and grading seen in screen detected prostate cancers shows that screening for prostate cancer will lead to the detection of prostate cancers in an earlier possibly curable stage.

In **chapter 3** the tumor characteristics of cancers detected in the completed first, the early recall and the second screening round are discussed. In the first round 1,038 cancers are detected; 1,014 screen detected and 24 cancers in men in the non-compliant men randomized to the screening group. At the early recall screen 63 cancers were detected and in the second round 433. A marked shift towards less advanced clinical T stages and an obvious decrease in biopsy Gleason score is seen in the early recall and the second screening round. There was a protocol change during the trial to a PSA cut off of 3.0 ng/ml as a sole biopsy indication, instead of a PSA cut off point of 4.0 ng/ml and/or a suspect DRE [10]. The results are split up by the different protocols and even then the stage shift to more favourable tumor characteristics in the second screening round remains obvious. In our study 83 of the 1,079 men with a PSA < 4.0 ng/ml but a suspicious DRE

were diagnosed with prostate cancer. 34 of these 83 men had a PSA between 3.0 and 4.0 ng/ml. This means that 49 (83-34) of the 1,079 cancers (4.5%) would have been missed if a sole biopsy indication of a PSA of >= 3.0 ng/ml would have been used. The low positive predictive value of DRE in the lower PSA ranges was the main reason for our group to omit DRE from the screening procedure.

The stage shift to more favorable tumor characteristics in subsequent screening round is also present in other studies. In the Finnish trial [11] the subsequent screening rounds show a majority of tumors with stage T1C, Gleason score 3 + 3 and a PSA < 10.0 ng/ml. However the stage and grade shift in the Finnish trial is not as obvious because the non-attenders from the first screening round participated as first time screeners in the second screening round, resulting in more aggressive cancers detected in later screening rounds. The Swedish trial also showed a remarkable stage and grade shift [12] regardless of the fact that every cohort in time consisted of participants in various rounds of screening and thus the presence of advanced tumors in later screening rounds. Furthermore due to a difference in age distribution (age 50-55 included) the PSA levels are lower in the Swedish trial. In the first round of screening only 7.6 % of the PSA values is 4.0 ng/ml or higher, in contrast to 13.5% in our trial.

### *Number of biopsies*

We recognize the fact that the sextant biopsies are considered to be obsolete. Whether maximisation of biopsy procedures is desirable, is at this moment an unanswered question unless one wishes to maximise prostate cancer detection. We did not perform classical sextant biopsies but lateralised sextant biopsies, which should limit the proportion of missed cancers. Eskew et all [13] stated that the use of the 5 region technique with more lateralized biopsies significantly increases the diagnostic yield of detecting prostate cancer. Increasing the number of biopsies and prostate cancers detected will increase the risk off over-diagnosis and the detection of clinical insignificant cancer. Although there is a trend towards more biopsies to be taken an optimal biopsy procedure has not yet been established [14]. Given the first analysis of the interval carcinomas (chapter 4) we do not have the impression that we are missing potentially aggressive cancers to a serious extend.

### *Contamination*

The subject of contamination is addressed to in **chapter 2**. Contamination means the measurement of PSA outside the screening protocol, either during the screening interval or in the control arm as a whole. Effective contamination is defined by a PSA measurement followed by biopsy if the PSA is 3.0 ng/ml or higher. Because of a high general awareness

in the population and ignorance of the fact that the value of screening is still uncertain more and more men are having their PSA measured. In population based screening trials the occurrence of opportunistic screening (contamination) therefore is unavoidable. A high contamination rate could seriously affect the endpoints of the trial. The proportion of T1C cancers is an indication of opportunistic screening in the control arm. The rate of T1C disease in cancers in the screen arm is 39.8% and in the control arm 26.8%, which is a 1.5 fold difference. Related to the number of men randomized the rate of T1C disease in the screening arm is a 5.8 fold higher. About 70% of T1C cancers in the control arm are diagnosed due to prostatism or lower urinary tract symptoms in general and not because of opportunistic screening.

The rate of PSA contamination in the ERSPC, section Rotterdam is established. Data on all PSA tests performed in the general practitioners laboratory in the Rotterdam area over a period of three years were obtained. The data on biopsy results were obtained from the Dutch National Database for Pathology (PALGA). During the follow up period of three years 20.2% of the men in the control arm and 14.1% of the men in the screen arm were tested, with an annual rate of 73 and 52 per 1000 person years respectively. The fraction of men in the control arm with PSA >= 3.0 ng/ml followed by biopsy and prostate cancer was 7-8% and 3% respectively and 3% and 0.4-0.6% in the screening arm. These data confirm the figures on a previous study concerning PSA contamination within ERSPC Rotterdam where a rate of 7.6% of yearly PSA testing in the control arm versus 3.3% in the screen arm was seen [15]. Thus the effective contamination within ERSPC Rotterdam is low and close to the assumption made in the sample size calculation which was 10% or less [16]. Further support for this observation comes from the incidence figures. In the control arm of the trial prostate cancer incidence is 350/100.000 man-years. Compared to the general population in the Netherlands the incidence of prostate cancer in 1997 is 292.5/100.000 man-years for the same age group [2]. The similarities of these figures suggest that opportunistic screening does not seem to play an important role so far in ERSPC Rotterdam. Páez et al [17] analyzed the PSA testing rate in the Madrid area. In the general population the PSA testing rate was 21.6 per 1000 person years. In the age group 55-69 years the rate was 86.8 per 1000 person years. However few men with a PSA >= 4.0 ng/ml were referred to an urologist and the overall detection rate of prostate cancer is 1.76%. This study also shows a rather high rate of PSA measurement, but the effective PSA contamination (PSA measurement leading to biopsy) is low.

### *Tumor characteristics of the Interval carcinomas*

The rate of interval carcinomas depends strongly on the definition of interval cancers. In this thesis the interval cancers are defined as cancers detected in between fully completed

screening rounds and within the age-group 55-74 years. In chapter 1 a cohort of men is followed and a comparison is made between the screen and the control arm. 44 cancers detected in this cohort were marked as an interval cancer. The interval cancers account for a low rate of 3.5% (44/1,269) of the screen detected cancers and 13.1% (44/336) of the control group cancers. In chapter 3 two completed subsequent screening rounds are analyzed allowing a full four year follow up of the cohort. In the screening interval 62 interval cancers were detected. The interval cancers account for a low rate of 6.0% (62/1,038) of screen detected cancers. To determine the rate of interval cancers and the sensitivity of the screening protocol a separate study was performed. The data are described in **chapter 4**. We studied a cohort of 17,226 men aged 55-75 years enrolled in the ERSPC, section Rotterdam. This cohort was followed during the full four years of the screening interval. During the first screen 412 prostate cancers were detected, 135 cancers were diagnosed in the control arm and 25 as interval cancers. Seven of the 25 cancers were diagnosed in men who refused a biopsy despite a clear biopsy indication. The remaining 18 cancers all had favorable tumor characteristics; no advanced cancers, biopsy Gleason score of 7 or below and no distant metastasis. Related to the number of cancers in the screen arm the interval cancer rate was 6.1% (25/412) and related to the number of cancers in the control arm the rate was 18.5% (25/135) or 13.3% (18/135) depending on definition. The sensitivity of the screening protocol was 79.8% (with 25 interval cancers) or 85.5% (with 18 interval cancers). There is little literature on interval cancers in prostate cancer screening. Hugosson et all [18] described 9 interval cancers during a 4-year period. However because of the difference in the screening interval (2 years) these data are not comparable. In time when more data on prostate cancers in the control arm and on the interval cancers become available, a better understanding of the characteristics of interval cancers and the sensitivity of screening procedure will be reached.

### *Screening interval and tumor characteristics*

At the present time it is not clear what the optimum screening interval should be. The American Cancer Society recommends annual PSA testing for men 50 years or older. The ERSPC Rotterdam utilizes a re-screening interval of 4 years. Only few advanced cancers are detected in the second screen, suggesting that the 4 year interval may not be too long to prevent detection of prostate cancer in a curable phase. These findings are in line with data published by Hoedemaeker et al [19]. Their results strongly suggest that even over a screening interval of 4 years there is no evidence of unfavorable changes in the characteristics of detected carcinomas in the subsequent screening rounds. As described earlier other ERSPC centres also show favorable tumor characteristics in their subsequent screening rounds (with a 2 year screening interval) as well [11,12].

### *Lead time and over-detection*

The detection of presumably clinically insignificant disease (cancers that would never lead to any signs and symptoms) is unavoidable in prostate cancer screening. The analysis of tumor characteristics of the prostate cancers detected in the subsequent screening rounds will help to recognize the characteristics of clinically insignificant disease. In this thesis the ratio of cancer incidence between the screen and control arm was 3.7 (1,269/336) during the 4 year recruitment period (chapter 1). Many cancers found by screening would probably not be diagnosed during the lifetime of these men (over-diagnosis). Available studies suggest that over-diagnosis occurs in 35-100% of screen detected cases [20,21,22]. Draisma et al [22] revealed that mean lead times and rates of over-detection depended on a man's age at screening and the test procedures used. For a single screening test at age 55, the estimated mean lead time was 12.3 years (range = 11.6-14.1 years) and the overdetection rate was 27% (range = 24%-37%); at age 75, the estimates were 6.0 years (range = 5.8-6.3 years) and 56% (range = 53%-61%), respectively. For a screening program with a 4-year screening interval from age 55 to 67, the estimated mean lead time was 11.2 years (range = 10.8-12.1 years), and the overdetection rate was 48% (range = 44%-55%).

## Conclusions

The analysis of the tumor characteristics provide us with the answers to the questions posed in the scope of the thesis.

1. *Is the current screening interval correct?*
   The ERSPC, section Rotterdam constitutes a re-screening interval of 4 years. The rate of interval cancers found within 4 years was exceedingly low. Moreover the interval cancers showed favorable prognostic factors. These data confirm the usefulness of a four-year re-screening interval.

2. *Is the method of screening correct with regard to the intermediate endpoints that are tumor characteristics?*
   These data clearly show a down staging and grading of prostate cancers detected in the subsequent screening rounds of the trial. The data confirm a high sensitivity of the screening procedure resulting in more favorable stage and grade of the prostate cancers at the time of diagnosis, which may enable the selection of patients that need treatment and those that can be followed through active surveillance.

3. *Does the current contamination in ERSPC influence the characteristics of the tumors found?*
   If active screening occurs in the control arm, the analysis of the tumor characteristics would not be between a real unscreened and a screened group, which will affect the power of the study. This contamination will reduce the difference in early treatments and prostate cancer mortality expected. However the effective contamination within ERSPC Rotterdam is low and close to the assumption made in the sample size calculation which was 10% or less. It is therefore unlikely that this contamination rate will affect the power of the trial.

4. *Do the tumor characteristics provide prognostic factors that are needed to recognize unfavorable prostate cancer?*
   Advanced cancers in the subsequent screening rounds are rare. The tumor characteristics of the advanced prostate cancers that were detected in the various screening rounds greatly resemble the findings well known from other prostate cancer screening studies. These findings may help us to recognize the prognostic factors, necessary to identify the cancers that need to be treated.

PSA based screening for prostate cancer shows a strong reduction in advanced cancers in stage and grade in favour of the screen arm of the trial. The data must be considered preliminary because of the slower accumulation of cases in the control arm. Although at this time there is no evidence that PSA based screening will decrease prostate cancer mortality, screening for prostate cancer will lead to the detection of prostate cancers at an earlier possibly curable stage.

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# Summary

## Introduction

Despite all the knowledge on prostate cancer screening and detection that has become available through the years, screening still remains a debatable issue. Prostate cancer incidence is rising and prostate cancer has become the most common cancer diagnosed and the second most common cause of cancer deaths in men. We are technically able to screen for prostate cancers using different forms of PSA, digital rectal examination, trans-rectal ultrasound en TRUS-guided biopsies. Total PSA is the best tumor marker available, but PSA based screening results in a substantial amount of overdiagnosis and overtreatment. In this chapter the diagnostic tools used in prostate cancer screening are discussed. The role of digital rectal examination in prostate cancer screening is limited. Although the American Cancer Society Guidelines still recommend the use of PSA and DRE, DRE shows a poor performance especially in the lower PSA ranges. Trans-rectal ultrasound has become the most commonly used imaging modality for the prostate. Although TRUS plays no role in prostate cancer screening, it is indispensable in guiding prostate biopsies. The classical way to perform prostate biopsies is random sextant biopsies. Recently there is a trend towards using more extensive biopsy protocols. Maximisation of biopsies leads to maximisation of prostate cancer detection, overdiagnosis of prostate cancer is imminent. An optimum biopsy procedure has not been established. Prostate specific antigen is organ specific, but not cancer specific. A substantial overlap between prostate cancer and benign conditions of the prostate is seen in the high ranges of PSA. The PPV for a PSA between 4.0 and 10.0 ng/ml lies between 20 and 30%. To improve the clinical usefulness of serum PSA four methods have been investigated: PSA density, PSA velocity, age-related reference ranges and the free/total ratio of PSA. All of these methods have there advantages and disadvantages, but none of these methods resulted in an undisputable improvement. The multifocal and heterogeneous nature of prostate cancer makes it difficult to assess the clinical and pathological stage of the disease. An accurate assessment on tumor extent and progression is important to estimate the risk of treatment failure. In the United States a transient rise in incidence of prostate cancer has been seen over the past decades and the mortality rates are decreasing for both white and black men. The declines in prostate cancer mortality are due to a decline in distant disease incidence and not to improved survival of patient with distant disease. PSA based screening might explain the increased detection of organ confined disease and the decrease in prostate cancer mortality. So far none of the ongoing randomized controlled trials provided sufficient evidence for mortality reduction in prostate cancer screening.

## Chapter 1

In chapter 1 a comparison is made between screen-detected prostate cancers and clinically diagnosed cancers in a cohort of men from the ERSPC, section Rotterdam. In the screen arm of the trial 1,269 prostate cancers were detected, 818 in the first round, 63 at early recall, 336 in the second round, 8 in round three and 44 as interval carcinomas. The cancer detection rate is 4.9% in the first round and drops to 3.5% and 2.7% in the subsequent rounds. In the control arm 336 prostate cancers were detected. The PSA values at the time of diagnosis of prostate cancer differ largely between the different screening rounds. In the subsequent screening rounds the higher PSA values (> 10.0 ng/ml) disappear. Compared to the screen arm the mean and median PSA values are 7.7 respectively 2.2 times higher in the control arm. Due to the fact that the first screening round is a prevalence round the proportion of advanced cancers (T3-T4) in the first screening round is relatively high, but they become rare in the subsequent screening rounds. Compared to the control arm there is a statistically significant difference in advanced cancers in favour of the screen arm. The results of the biopsy Gleason scores can be described in the same way. In the prevalence round the biopsy Gleason score is relatively high, decreases in the subsequent screening rounds, and compared to the control arm the biopsy Gleason score shows a statistically significant difference in favor of the screen arm. The most remarkable observation is the fact that the absolute number of cases with distant metastatic disease is lower in the screened population than in the control arm (7/27) and compared to all men diagnosed with prostate cancer (0.6%/8.0%) and even compared to all men randomized (0.04%/0.2%). The proportion of men with metastatic disease in the control arm was much lower than reported in historical controls.

## Chapter 2

The subject of contamination is addressed to in chapter 2. Contamination means the measurement of PSA outside the screening protocol, either during the screening interval or in the control arm as a whole. Effective contamination is defined by a PSA measurement followed by biopsy if the PSA is 3.0 ng/ml or higher. Because of a high general awareness in the population and ignorance of the fact that the value of screening is still uncertain more and more men are having their PSA measured. In population based screening trials the occurrence of opportunistic screening (contamination) therefore is unavoidable. A high contamination rate could seriously affect the endpoints of the trial. The proportion of T1C cancers is an indication of opportunistic screening in the control arm. In chapter 1

the rate of T1C disease in cancers in the screen arm is 39.8% and in the control arm 26.8%, which is a 1.5 fold difference. Related to the number of men randomized the rate of T1C disease in the screening arm is a 5.8 fold higher. About 70% of T1C cancers in the control arm are diagnosed due to prostatism or lower urinary tract symptoms in general and not because of opportunistic screening.

To establish the effective PSA contamination within the ERSPC Rotterdam data on all PSA tests performed in the general practitioners laboratory in the Rotterdam area over a period of three years were obtained. The data on biopsy results were obtained from the Dutch National Database for Pathology (PALGA). During the follow up period of three years 20.2% of the men in the control arm and 14.1% of the men in the screen arm were tested, with an annual rate of 73 and 52 per 1000 person years respectively. The fraction of men in the control arm with PSA >= 3.0 ng/ml followed by biopsy and prostate cancer was 7-8% and 3% respectively and 3% and 0.4-0.6% in the screening arm. These data confirm the figures on a previous study concerning PSA contamination within ERSPC Rotterdam were a rate of 7.6% of yearly PSA testing in the control arm versus 3.3% in the screen arm was seen. Thus the effective contamination within ERSPC Rotterdam is low and close to the assumption made in the sample size calculation.

## Chapter 3

In chapter 3 the tumor characteristics of cancers detected in the completed first, the early recall and the second screening round are discussed. In the first round 1,038 cancers are detected; 1,014 screen detected and 24 cancers in the non-compliant men randomized to the screening group. At the early recall screen 63 cancers were detected and in the second round 433. A marked shift towards less advanced clinical T stages and an obvious decrease in biopsy Gleason score is seen in the early recall and the second screening round. There was a protocol change during the trial to a PSA cut off of 3.0 ng/ml as a sole biopsy indication, instead of a PSA cut off point of 4.0 ng/ml and/or a suspect DRE. The results in chapter 3 are split up by the different protocols and even then the stage shift to more favourable tumor characteristics in the second screening round remains obvious. In our study 83 of the 1,079 men with a PSA < 4.0 ng/ml but a suspicious DRE were diagnosed with prostate cancer. 34 of these 83 men had a PSA between 3.0 and 4.0 ng/ml. This means that 49 (83-34) of the 1,079 cancers (4.5%) would have been missed if a sole biopsy indication of a PSA of >= 3.0 ng/ml would have been used. The low positive predictive value of DRE in the lower PSA ranges was the main reason for our group to omit DRE from the screening procedure.

## Chapter 4

The rate of interval carcinomas depends strongly on their definition of interval cancers. In this thesis the interval cancers are defined as cancers detected in between fully completed screening rounds and within the age-group 55-74 years. In chapter 1 a cohort of men is followed and a comparison is made between the screen and the control arm. 44 cancers detected in this cohort were marked as an interval cancer. The interval cancers account for a low rate of 3.5% (44/1,269) of screen detected cancers and 13.1% (44/336) of control group cancers. In chapter 3 two completed subsequent screening rounds are analyzed allowing a full four year follow up of the cohort. In the screening interval 62 interval cancers were detected. The interval cancers account for a low rate of 6.0% (62/1,038) of screen detected cancers. To determine the rate of interval cancers and the sensitivity of the screening protocol a separate study was performed. The data are described in chapter 4. We studied a cohort of 17,226 men aged 55-75 years enrolled in the ERSPC, section Rotterdam. This cohort was followed during the full four years of the screening interval. During the first screen 412 prostate cancers were detected, 135 cancers were diagnosed in the control arm and 25 interval cancers. Seven of the 25 cancers were diagnosed in men who refused a biopsy despite a clear biopsy indication. The remaining 18 cancers all had favorable tumor characteristics; no advanced cancers, biopsy Gleason score of 7 or below and no distant metastasis. Related to the number of cancers in the screen arm the interval cancer rate was 6.1% (25/412) and related to the number of cancers in the control arm the rate was 18.5% (25/135) or 13.3% (18/135) depending on definition. The sensitivity of the screening protocol was 79.8% (with 25 interval cancers) or 85.5% (with 18 interval cancers). There is little literature on interval cancers in prostate cancer screening.

## General discussion and conclusions

The introduction of PSA measurements into medical practice has led to increased detection rates and a stage reduction at the time of diagnosis of prostate cancer. The increase in detection rates is seen in industrialized countries and prostate cancer has become the most common cancer diagnosed and the second most common cause of cancer deaths. In 1999 the SEER data of the National Cancer Institute showed a decline in prostate cancer incidence and a decrease in prostate cancer mortality rates since 1992. However more recent data from the SEER database show a transient increase in prostate cancers incidence since the introduction of PSA in 1986. The age-adjusted prostate cancer mortality rates have dropped below the rate in 1986 since 1995 for white men and since

1997 for black men. The incidence based mortality rates show that the recent declines were due to declines in distant mortality, more specifically to a decline in distant disease incidence and not to improved survival of patients with distant disease. Evidence of prostate cancer mortality reduction due to screening is not yet available, but until the effect of screening becomes clear data from randomized trials are important for the understanding of prostate cancer management. Improvement of the specificity of the screening test for the reduction of unnecessary biopsies, and more accurate staging and grading of prostate cancer at the time of diagnosis will enable the selection of patients who need treatment and those who can be followed by watchful waiting.

Comparing the screen detected prostate cancers to the clinically diagnosed prostate cancers in the control arm, the down-staging and grading seen in screen-detected prostate cancers shows that screening for prostate cancer will lead to the detection of prostate cancers in an earlier, possibly curable stage.

The tumor characteristics of the cancers detected in the completed first, the early recall and the second screening round show a marked shift towards less advanced clinical T stages and an obvious decrease in biopsy Gleason score in the early recall and the second screening round. The stage shift to more favorable tumor characteristics in subsequent screening round is also present in other studies. In the Finnish trial the subsequent screening rounds show a majority of tumors with stage T1C, Gleason score 3 + 3 and a PSA < 10.0 ng/ml. However the stage and grade shift in the Finnish trial is not as obvious because the non-attenders from the first screening round participated as first time screeners in the second screening round, resulting in more aggressive cancers detected in later screening rounds. The Swedish trial also showed a remarkable stage and grade shift regardless of the fact that every cohort in time consisted of participants in various rounds of screening and thus the presence of advanced tumors in later screening rounds. Furthermore due to a difference in age distribution (age 50-55 included) the PSA levels are lower in the Swedish trial. In the first round of screening only 7.6 % of the PSA values is 4.0 ng/ml or higher, in contrast to 13.5% in our trial.

The sextant biopsies are considered to be obsolete. Whether maximisation of biopsy procedures is desirable, is at this moment an unanswered question unless one wishes to maximise prostate cancer detection. Increasing the number of biopsies and prostate cancers detected will increase the risk off over-diagnosis and the detection of clinical insignificant cancer. Although there is a trend towards more biopsies to be taken an optimal biopsy procedure has not yet been established.

Effective contamination is defined by a PSA measurement followed by biopsy if the PSA is 3.0 ng/ml or higher. The effective contamination within ERSPC Rotterdam is low and close to the assumption made in the sample size calculation which was 10% or less. Further support for this observation comes from the incidence figures. In the control arm of the trial prostate cancer incidence is 350/100.000 man-years. Compared to the general population in the Netherlands the incidence of prostate cancer in the period 1989 to 2003 is 365.5/100.000 man-years for the same age group [Siesling et al. Ned Tijdschr Geneesk, 2006,150(45)]. The similarities of these figures suggest that opportunistic screening does not seem to play an important role so far in ERSPC Rotterdam.

The interval cancers are defined as cancers detected in between fully completed screening rounds and within the age-group 55-74 years. Related to the number of cancers in the screen arm the interval cancer rate was 6.1% and related to the number of cancers in the control arm the rate was 18.5%. In the Swedish trial 9 interval cancers were described during a 4-year period. However because of the difference in the screening interval (2 years) these data are not comparable. In time when more data on prostate cancers in the control arm and on the interval cancers become available, a better understanding of the characteristics of interval cancers and the sensitivity of screening procedure will be reached.

At the present time it is not clear what the optimum screening interval should be. The American Cancer Society recommends annual PSA testing for men 50 years or older. The ERSPC Rotterdam utilizes a re-screening interval of 4 years. Only few advanced cancers are detected in the second screen, suggesting that the 4 year interval may not be too long to prevent detection of prostate cancer in a curable phase. As described earlier other ERSPC centres also show favorable tumor characteristics in their subsequent screening rounds (with a 2 year screening interval) as well.

The detection of presumably clinically insignificant disease (cancers that would never lead to any signs and symptoms) is unavoidable in prostate cancer screening. The analysis of tumor characteristics of the prostate cancers detected in the subsequent screening rounds will help to recognize the characteristics of clinically insignificant disease. In this thesis the ratio of cancer incidence between the screen and control arm was 3.7 (1,269/336) during the 4 year recruitment period. Many cancers found by screening would probably not be diagnosed during the lifetime of these men (over-diagnosis). Available studies suggest that over-diagnosis occurs in 35-100% of screen detected cases. The mean lead times and rates of over-detection depended on a man's age at screening and the test procedures

used. For a single screening test at age 55, the estimated mean lead time was 12.3 years and the overdetection rate was 27%; at age 75, the estimates were 6.0 years and 56%, respectively. For a screening program with a 4-year screening interval from age 55 to 67, the estimated mean lead time was 11.2 years, and the overdetection rate was 48%.

## Conclusions

The impact of screening and early intervention on prostate cancer morbidity and mortality is still uncertain. PSA based screening for prostate cancer shows a strong reduction in advanced cancers in stage and grade in favour of the screen arm of the trial. The data must be considered preliminary because of the slower accumulation of cases in the control arm. The rate of interval cancers found within 4 years was exceedingly low. The interval cancers showed favorable prognostic factors. The data confirm a high sensitivity of the screening procedure and the usefulness of a four-year re-screening interval. Improvement of the specificity leads to the reduction of unnecessary biopsies, but also more accurate staging and grading of prostate cancer at the time of diagnosis enables the selection of patients that need treatment and those that can be followed through active surveillance. Although at this time there is no evidence that PSA based screening will decrease prostate cancer mortality, screening for prostate cancer will lead to the detection of prostate cancers at an earlier possibly curable stage.

# Samenvatting

## Introductie

De incidentie van prostaat kanker in de geïndustrialiseerde landen stijgt en prostaat kanker is inmiddels de meest voorkomende vorm van kanker en de op één na meest voorkomende doodsoorzaak door kanker voor mannen. De laatste jaren is er veel onderzoek gedaan naar de mogelijkheid van een screeningsmethode voor de vroegopsporing van prostaat kanker. Het is echter niet bewezen dat screening op prostaat kanker zal leiden tot een afname van de morbiditeit en mortaliteit. Het is technisch mogelijk om te screenen naar prostaat kanker met behulp van de verschillende vormen van PSA, rectaal toucher, transrectale echografie en echo geleide biopten. PSA is op dit moment de beste tumormarker die we hebben, echter een op PSA gebaseerde screeningsprocedure resulteert in een aanzienlijk aantal gevallen van overdiagnose en overbehandeling.

In dit hoofdstuk worden de verschillende screening methodes besproken. De waarde van het rectaal toucher in prostaat kanker screening is beperkt. Het rectaal toucher heeft een lage voorspellende waarde in de lage waarden van PSA. De American Cancer Society Guidelines adviseren nog steeds het gebruik van PSA én het rectaal toucher. Transrectale echografie is de meest gebruikte beeldvormende techniek voor de prostaat. Hoewel transrectale echografie geen rol speelt in prostaat kanker screening, is de echografie onmisbaar bij het nemen van prostaat biopsiëen. De klassieke methode om prostaat biopten te nemen is een zestal biopten verspreid door de perifere zone van de prostaat. Sinds enige tijd is er een trend zichtbaar naar het nemen van meer biopten. Echter maximalisering van het aantal biopten leidt tot een toename van het aantal gedetecteerde prostaat kankers en overdiagnose ligt op de loer. Een optimale biopsie procedure is nog niet vastgesteld.

PSA is orgaan specifiek, echter niet kanker specifiek. In de hoge PSA waarden wordt een substantiële overlap gezien tussen prostaat kanker en benigne aandoeningen van de prostaat. De PPV voor een PSA tussen de 4.0 en de 10.0 ng/ml ligt tussen de 20 en 30%. Om het gebruik van PSA in de praktijk te verbeteren zijn er 4 verschillende vormen van PSA onderzocht: PSA density, PSA velocity, leeftijdsafhankelijke referentie waarden en de free/total ratio van PSA. Al deze methoden hebben hun voor en nadelen, maar geen van deze vormen van PSA leidt tot een substantiële verbetering. Het multifocale en heterogene karakter van prostaat kanker maakt het moeilijk het klinische en het pathologische stadium van prostaat kanker op waarde te schatten. Een precieze bepaling van het tumor volume en de tumor progressie is belangrijk om de prognose en de beste behandeling in te schatten. In de USA is in de laatste 10 jaar een geleidelijke stijging in de incidentie van prostaat kanker waargenomen en het mortaliteitscijfer is dalende voor zowel de blanke als de zwarte man. De daling van de prostaat kanker mortaliteit cijfers

wordt veroorzaakt door een daling in het aantal gevallen van gemetastaseerde ziekte en niet door een verbeterde survival van mannen met gemetastaseerde ziekte. Mogelijk zorgt een op PSA gebaseerde screeningsprocedure voor een stijging van organ confined prostaat kanker en daardoor een daling van de prostaat kanker mortaliteit. Tot op heden heeft geen van de gerandomiseerde trials voldoende bewijs geleverd om een mortaliteits reductie aan te tonen.

## Hoofdstuk 1

In hoofdstuk 1 is een vergelijking gemaakt tussen de door screening gedetecteerde prostaat kankers en de klinisch gediagnostiseerde prostaat kankers in een cohort van deelnemers van de ERSPC, Rotterdam. In de screen arm van de trial zijn 1,269 prostaat kankerscancers gedetecteerd, 818 in de eerste ronde, 63 na 1 jaar (early recall), 336 in de tweede ronde, 8 in de derde ronde en 44 als interval kanker. De kanker detectie fractie is 4.9% in de eerste ronde en daalt naar 3.5% en 2.7% in de opeenvolgende rondes. In de controle arm zijn 336 prostaat kankers gedetecteerd. De PSA waardes op het moment van diagnose van prostaat kanker verschillen enorm tussen de verschillende screening rondes. In de latere screening rondes komen de hogere PSA waarden (> 10.0 ng/ml) niet meer voor. Vergeleken met de screen arm zijn de gemiddelde en de mediane PSA waarden in de controle arm 7.7 respectievelijk 2.2 keer hoger. Vanwege het feit dat de eerste screening ronde een prevalentie ronde is, is de proportie van gevorderde kankers (T3-T4) in de eerste ronde relatief hoog, maar gevorderde kankers zijn zeldzaam in de opeenvolgende screening rondes. Vergeleken met de controle arm is er een statistisch significant verschil in gevorderde kankers in het voordeel van de screen arm. De resultaten van de biopsie Gleason scores zijn op dezelfde wijze verdeeld. In de prevalente ronde zijn de Gleason scores relatief hoog en deze dalen in de latere rondes. Vergeleken met de controle arm laten de Gleason scores in de screen arm een statistisch significant verschil zien in het voordeel van de screen arm. Opmerkelijk is het feit dat het absolute aantal van gemetastaseerde ziekte in de screen arm lager is dan in de controle arm (7/27), ook in vergelijking met alle mannen gediagnostiseerd met prostaat kanker (0.6/0.8%) en zelfs vergeleken met alle gerandomiseerde mannen (0.04%/0.2%). De proportie van mannen met gemetastaseerde ziekte in de controle arm is veel lager dan gerapporteerd werd in eerdere studies naar het natuurlijk beloop van prostaat kanker.

## Hoofdstuk 2

In hoofdstuk 2 wordt het onderwerp contaminatie bestudeerd. Contaminatie betekent het buiten het screening protocol om laten bepalen van PSA tijdens het screening interval of in de controle arm. Effectieve contaminatie is gedefineerd als een PSA bepaling gevolgd door prostaat biopsiëen bij een PSA van 3.0 ng/ml of hoger. Door de bekendheid van de PSA bepaling en de bijbehorende verhoogde kans op prostaatkanker en de onwetendheid over het gebrek aan bewijs voor de waarde hiervan laten steeds meer mannen hun PSA bepalen. In op populatie gebaseerde screening studies is het voorkomen van contaminatie (opportunistische screening) daarom onafwendbaar. Een hoge mate van contaminatie kan de eindpunten van de studie negatief beïnvloeden. Het aantal T1C kankers is een indicatie voor de mate van opportunistische screening in de controle arm. In hoofdstuk 1 is het percentage T1C kankers in de controle arm 26.8% en in de screen arm 39.8%, dit is 1,5 keer zo veel. Gerelateerd aan het totaal aantal gerandomiseerde mannen komt T1C kanker 5.8 keer zo vaak voor in de screen arm. Ongeveer 70% van de T1C kankers in de controle arm zijn gediagnostiseerd naar aanleiding van LUTS en 5% door opportunistische screening. Om de mate van effectieve PSA contaminatie binnen de ERSPC na te gaan werden de gegevens met betrekking tot PSA van de laboratoria in de regio Rotterdam over een periode van 3 jaar verzameld. Gegevens met betrekking tot de biopsie resultaten werden verzameld met behulp van de nationale databank voor de pathologie (PALGA). Gedurende de follow up periode van 3 jaar hebben 20.2% van de mannen in de controle arm en 14.1% van de mannen in de screen arm hun PSA laten testen met een jaarlijks percentage van respectievelijk 73 en 52 per 1000 persoonsjaren. Het percentage van mannen in de controle arm met een PSA >= 3.0 ng/ml gevolgd door biopsie en de diagnose prostaat kanker is 7-8% en 3% en respectievelijk 3% en 0.4-0.6% in de screen arm. Deze data bevestigen de cijfers van een eerdere studie aangaande PSA contaminatie binnen de ERSPC, waarbij een jaarlijks percentage van 7.6% in de controle arm en 3.3% in de screen arm werd gezien. Effectieve PSA contaminatie binnen de ERSPC, Rotterdam komt weinig voor en blijft onder de aanname van 10% in de sample size berekeningen.

## Hoofdstuk 3

In hoofdstuk 3 worden de tumorkarakteristieken die gedetecteerd zijn in de gehele eerste ronde, de herhalingsronde na 1 jaar en de tweede screening ronde besproken. In de eerste ronde zijn 1,038 kankers gedetecteerd; 1,014 in de screen arm en 24 in de groep non-compliant randomized to screen. Bij de herhalingsoproep na 1 jaar zijn 63 kankers

gedetecteerd en in de tweede ronde 433. Er is een evidente trend zichtbaar naar lagere minder uitgebreide klinische stadia en een eneneens evidente daling van de biopsie Gleason score in de herhalings groep en in de tweede ronde. Tijdens de study is er een verandering van het protocol geweest waardoor een PSA van 3.0 ng/ml of hoger de enige biopsie indicatie werd, in plaats van een PSA van 4.0 ng/ml of hoger en/of een afwijkend rectaal toucher. De resultaten in hoofdstuk 3 zijn opgesplitst per protocol en zelfs dan is de verschuiving naar meer gunstige tumorkarakteristieken in de tweede ronde duidelijk aanwezig. In onze studie bleken 83 van de 1,079 mannen met een PSA < 4.0 ng/ml, maar een verdacht rectaal toucher prostaat kanker te hebben. 34 van deze 83 mannen hadden een PSA tussen de 3.0 en 4.0 ng/ml. Dit betekent dat 49 (83-34) van de 1,079 kankers (4.5%) gemist zouden zijn indien een PSA van 3,0 ng/ml of hoger als enige biopsie indicatie zou zijn gebruikt. De lage PPV van het rectaal toucher in de lagere PSA waarden was de belangrijkste reden voor onze groep om het rectaal toucher te verwijderen uit de screening procedure.

## Hoofdstuk 4

Het is de definitie van interval carcinomen, die het percentage interval carcinomen bepaalt. In dit proefschrift worden de interval kankers gedefinieerd als kankers die gediagnosticeerd zijn in de periode tussen twee volledige screening rondes en binnen de leeftijdsgroep van 55-74 jaar. In hoofdstuk 1 wordt een cohort van mannen gevolgd en de data van de screen arm en de controle arm worden met elkaar vergeleken. In dit cohort zijn 44 kankers aangemerkt als interval kankers. De interval kankers maken slechts 3.5% (44/1,269) uit van de door screening gedetecteerde kankers en 13.1% (44/336) van de controle groep kankers. In hoofdstuk 3 worden twee complete opeenvolgende screening rondes met elkaar vergeleken, hierdoor is er een volledige follow up van 4 jaar beschikbaar. In het screening interval zijn 62 interval kankers gediagnostiseerd. De interval kankers maken slechts een klein deel uit van het totaal aantal door screening gevonden kankers, nl. 6.0% (62/1,038). Om het aantal interval carcinomen en de sensitiviteit van het screening protocol te bepalen is een aparte studie verricht. De data staan beschreven in hoofdstuk 4. Een cohort van 17,226 mannen tussen de 55-75 jaar is geevalueerd. Het cohort is vervolgd tijdens het volledige screening interval van 4 jaar. In de eerste screening ronde werden 412 prostaat kankers gedetecteerd, in de controle arm 135 kankers en een totaal van 25 interval kankers werd gevonden. Van deze 25 interval kankers hadden 7 mannen een duidelijke indicatie voor biopsie in de eerste ronde, echter zij hebben een biopsie geweigerd. De overige 18 kankers hadden gunstige tumor

karakteristieken; geen gevorderde stadia, een biopsie Gleason score van 7 of minder en geen aanwijzingen voor metastasen. Vergeleken met het aantal kankers in de screen arm was het percentage interval kankers 6.1% (25/412) en vergeleken met het aantal kankers in de controle arm was het percentage 18.5% (25/135) of 13.3% (18/135) afhankelijk van de definitie. De sensitiviteit van het screening protocol was 79.8% (met 25 interval kankers) of 85.5% (met 18 interval kankers). Er is weinig literatuur bekend over interval kankers in prostaat kanker screening.

## Algemene discussie en conclusies

De introductie van PSA bepalingen in de medische praktijk heeft geleid tot een verhoging van het aantal gedecteerde prostaat kankers en tot de detectie van prostaat kankers in een lager stadium op het moment van diagnose. De verhoogde detectie fractie wordt gezien in alle geïndustrialiseerde landen. Prostaat kanker is de meest voorkomende vorm van kanker en de op een na meest voorkomende doodsoorzaak door kanker. In 1999 lieten de SEER data van de National Cancer Institute een daling zien in de incidentie van prostaat kanker en sinds 1992 een daling in de prostaat kanker mortaliteit. Echter meer recente data van de SEER database laten een geleidelijke stijging zien in het aantal prostaat kankers sinds het gebruik van PSA als een screening methode in 1986. De leeftijds afhankelijke prostaat kanker mortaliteit voor blanke mannen is sinds 1992 gedaald tot onder het niveau van 1986 en sinds 1997 voor zwarte mannen. Nadere analyse van de mortaliteits cijfers laten zien dat de meest recente dalingen toe te schrijven zijn aan een afname van mortaliteit door gemestastaseerde ziekte, meer specifiek een afname van de incidentie van metastasen en niet door een verbeterde overleving van patiënten met gemetastaseerde ziekte. Er is nog geen bewijs dat screening leidt tot lagere mortaliteits cijfers aan prostaat kanker, maar door de gerandomiseerde trials wordt het effect van screening naar prostaat kanker duidelijk en deze data zijn belangrijk voor de diagnose en het beleid van prostaat kanker. Door verbetering van de specificiteit van de screening methode kan het aantal onnodige biopsieën worden gereduceerd en kan een meer adequate stadiëring en gradering van prostaat kanker worden bepaald. Hierdoor wordt het mogelijk te selecteren tussen patienten die behandeld moeten worden en diegenen die gevolgd kunnen worden door active surveillance.

Vergeleken met de klinisch gediagnosticeerde prostaat kankers in de controle arm en de door screening gedecteerde prostaat kankers laten de door screening gedetecteerde kankers een gunstigere stadiëring en gradering zien.

De tumor karakteristieken van de kankers gedetecteerd in de eerste ronde, de

herhalingsronde na 1 jaar en de tweede screening ronde laten een duidelijke verschuiving zien naar lagere T stadia en een duidelijke daling in de biopsie Gleason score in de opeenvolgende screening rondes. De verchuiving van de T stadia naar meer gunstige tumor karakteristieken in de opeenvolgende rondes is ook te zien in andere screening studies. In de Finse trial laten de opeenvolgende screening rondes zien dat de meeste tumoren een stadium T1C hebben met een Gleason score van 3 + 3 en een PSA < 10.0 ng/ml. De verschuiving in stadium en gradering in de Finse trial is niet zo uitgesproken, omdat de niet-komers van de eerste screening ronde als prevalente screeners participeerden in de tweede ronde, waardoor een hoger percentage aggressieve kankers is gedetecteerd in de latere screening rondes. De Zweedse trial liet ook een duidelijke verschuiving zien naar meer gunstige tumor karakteristieken ongeacht het feit dat in ieder gescreened cohort deelnemers zaten uit verschillende screening rondes, waardoor er ook in de latere rondes gevorderde kankers werden gedetecteerd. Bovendien zijn de PSA waarden in de Zweedse trial lager, omdat er een leeftijds verschil is in de gescreende mannen, in de Zweedse trial zijn ook mannen geïncludeerd tussen de 50 en de 55. In de eerste ronde is slechts 7.6 % van de PSA waarden 4.0 ng/ml of hoger, ten opzichte van 13.5% in onze trial.

Het nemen van zes biopsieën is obsoleet. Echter of maximalisatie van de biopsie procedure wenselijk is, is op dit moment niet zeker, tenzij men de detectie van prostaat kanker wil maximaliseren. Een stijging van het aantal biopsieën en van het aantal gedetecteerde prostaat kankers zal het risico van overdiagnose en de detectie van klinische insignificante tumoren verhogen. Hoewel er een trend is naar het nemen van meer biopsieën, is een optimale biopsie procedure nog niet vastgesteld.

Effective contaminatie is gedefinieerd als een PSA bepaling gevolgd door een biopsie als de PSA 3.0 ng/ml of hoger is. De effectieve contaminatie binnen de ERSPC Rotterdam is laag en net onder de aanname in de powerberekening, nl. 10% of minder. Deze observatie wordt bevestigd door de incidentie getallen. In de controle arm van de trial is de incidentie van prostaat kanker 350/100.000 persoonsjaren. Bekeken over de hele Nederlands populatie in de periode 1989 – 2003 is de incidentie 365,5/100.000 persoonjaren in dezelfd leeftijdsgroep [Siesling et al. Ned Tijdschr Geneesk 2006, 150 (45)]. De overeenkomsten van deze getallen suggereren dat opportunistische screening niet een hele grote rol speelt in de ERSPC Rotterdam.

De interval kankers zijn gedefinieerd als kankers gediagnostiseerd tussen twee volledige screening rondes en binnen de leeftijdsgroep 55-74 jaar. Afgezet tegen het aantal kankers

in de screen arm is het percentage interval carcinomen 6.1% en afgezet tegen het aantal kankers in de controle arm is het percentage 18.5%. In de Zweedse trial zijn 9 interval kankers geschreven gedurende 4 jaar. Deze aantallen zijn echter niet vergelijkbaar, omdat de screeningintervallen verschillend zijn (2 jaar in Zweden). Als er meer gegevens over interval kankers bekend worden, zal een beter begrip van de tumor karakteristieken van de interval kankers kunnen leiden tot een verbetering van de sensitiviteit van de screening procedure.

Op dit moment is nog niet duidelijk wat het optimale screening interval zou moeten zijn. De Amerikaanse Kanker Vereniging (the American Cancer Society) raad een jaarlijkse PSA test aan voor mannen van 50 jaar en ouder. De ERSPC Rotterdam houdt vast aan een re-screening interval van 4 jaar. Slechts een enkele gevorderde kanker is gediagnosticeerd in de tweede ronde, suggererend dat een interval van 4 jaar niet te lang is om kanker in een geneesbare fase te ontdekken. Zoals eerder beschreven laten de ander centra van de ERSPC ook gunstige tumor karakteristieken zien in door screening ontdekte kankers (hoewel met een twee-jaarlijks interval).

De ontdekking van klinisch insignificante ziekte (kanker die nooit tot symptomen en klachten zou leiden) is onvermijdelijk in prostaat kanker screening. De analyse van tumor karakteristieken van prostaat kanker ontdekt in de opeenvolgende screening rondes zal ons helpen de karakteristieken van insignificante tumoren te herkennen. In dit proefschrift is de ratio tussen de kanker incidentie van de screen arm en de controle arm 3.7 (1,269/336) gedurende de 4 jaar periode. Veel kankers gedetecteerd door screening zouden waarschijnlijk niet zijn ontdekt gedurende het leven van deze mannen (overdiagnose). Literatuur studies laten zien dat overdiagnose voorkomt in 35-100% van door screening gedetecteerde kankers. De gemiddelde lead time en het percentage overdetectie is afhankelijk van de leeftijd van de man ten tijde van screening en de gebruikte screening methode. Voor een enkele screening test op de leeftijd van 55 jaar, is de geschatte lead time 12,3 jaar en het percentage over-diagnose 27%; op de leeftijd van 75 is dat respectievelijk 6.0 jaar en 56%. Voor een screening programma met een 4-jaarlijkse screening interval in de leeftijd van 55 en 67, is de geschatte gemiddelde lead time 11.2 jaar, en het percentage over-diagnose 48%.

## Conclusie

De impact van screening en vroeg opsporing op de morbiditeit en de mortaliteit van prostaat kanker is nog steeds onzeker. Op PSA gebaseerde screening trials laten een sterke reductie zien in het aantal gevorderde kankers ten faveure van de screen arm. De data moeten als onvolledig worden beschouwd, omdat het aantal mannen met prostaat kanker in de controle arm langzamer accumuleerd. Het percentage interval kankers gediagnostiseerd binnen de 4 jaar is extreem laag. De interval kankers laten gunstige tumor karakteristieke zien. De data laten een hoge sensitiviteit zien van de screening procedure en een verantwoord gebruik van een 4 jarig screening interval. Verbetering van de specificiteit leidt tot een reductie van onnodige biopsieën, maar ook tot een betere stadiëring en gradering van de prostaat kanker op het moment van diagnose. Hierdoor kunnen we beter selecteren tussen die patienten die behandeling nodig hebben en diegenen die gevolgd kunnen worden door active surveillance. Alhoewel screening naar prostaat kanker leidt tot de detectie van prostaat kanker in een vroeger mogelijk te cureren stadium, is er op dit moment geen bewijs dat op PSA gebaseerd screening naar prostaat kanker zorgt voor een daling in de prostaat kanker mortaliteit.

# Appendix

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| | |
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## Lijst van Presentaties

1998 – 2002: Halfjaarlijks internationale presentaties studievoortgang ERSPC tijdens het overleg met de Europese partners en jaarlijks met de partner in de Verenigde Staten (PLCO trial).

2001: NVU voorjaarsvergadering
Presentaties
- 'Prognostisch gunstige tumorkarakteristieken bij herscreening voor prostaatkanker 4 jaar na de initiële screening'
- 'Evaluatie van bij screening gedetecteerd prostaatkanker en klinisch gediagnosticeerd prostaatkanker in een gerandomiseerde trial'.

2002: arts assistenten wetenschapsdag in het Academisch Ziekenhuis Rotterdam
Prof.Dr. J.C. Birkenhäger award
2e prijs met presentatie: 'European Randomized study of Screening for Prostate Cancer': vergelijking van door screening gedetecteerde en klinisch gediagnosticeerde prostaatkankers.

2002: NVU najaarsvergadering
presentatie
'Opportunistische PSA screening buiten de European Randomized study of Screening for Prostate Cancer: Effectieve PSA contaminatie of niet?'

2002: American Urological Association, the 2002 annual meeting
moderated poster session en persconferentie
'Comparison of screen detected and clinically diagnosed prostate cancer in the 'European Randomized study of Screening for Prostate Cancer'.

2003: American Urological Association, the 2003 annual meeting
unmoderated poster session
'Intervalcarcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC) - section Rotterdam'.

2003: NVU najaarsvergadering:
Presentatie
'Intervalcarcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC) – section Rotterdam.'

2004: NVU najaarsvergadering
Presentatie
'Prognostisch gunstige tumorkarakteristieken voor de door screening gedetecteerde prostaatkankers in de prostaatkanker screening trial.'

2008: European Association of Urology, the 2008 annual meeting
moderated poster session
'Tumor characteristics within the European Randomized study of Screening for Prostate Cancer, section Rotterdam.'
Best poster presentation of the session.

## Onderscheidingen

2004: Vlietstra prijs
Beste presentatie NVU najaarsvergadering 2003

2004: EAU Best paper on clinical research
The European Association of Urology voor het artikel: Intervalcarcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC) - section Rotterdam.

2006: Urology Second Place Award 2006 Resident/fellow essay contest voor het artikel:
Tumorcharacteristics and prognostic factors in two subsequent screeningrounds with a four year interval within the prostate cancer screening trial, ERSPC Rotterdam.

## Curriculum Vitae

Op 12 oktober 1968 ben ik geboren in Zutphen. De winter die daarop volgde, was een van de laatste winters met een meter sneeuw, waar mijn moeder de kinderwagen met trots doorheen duwde.
Mijn lagere schooltijd heb ik doorgebracht in zuid Limburg, maar weinigen zullen dit nog herkennen.
In 1986 haalde ik het VWO diploma in een dorpje aan de Maas genaamd Cuijk.
Nadat ik werd uitgeloot voor geneeskunde ben ik een jaar biologie gaan studeren aan de Landbouw Universiteit Wageningen.
In 1988 kon ik dan toch starten met de studie geneeskunde aan de Katholieke Universiteit St. Radboud in Nijmegen, tegenwoordig het Universitair Medisch Centrum St. Radboud Nijmegen.
In 1993 heb ik geduldig een jaartje gewacht voor ik met mijn co-schappen kon beginnen en in 1996 heb ik het artsexamen behaald.
Na een jaar AGNIO urologie te zijn geweest in het Virga Jesse Ziekenhuis in Hasselt te België, kon ik in 1998 kennis maken met het medisch wetenschappelijk ondezoek bij prof. Schröder in het Erasmus MC in Rotterdam. De kennismaking groeide uit tot 4 jaren full time onderzoek voor de ERSPC in Rotterdam en uiteindelijk tot dit boekje.
In 2003 ben ik begonnen met de vooropleiding chirurgie in de Isala Klinieken, locatie Weezenlanden in Zwolle. In 2005 startte mijn perifere opleiding tot uroloog in diezelfde kliniek.
Sinds 2007 ben ik werkzaam in het Universitair Medisch Centrum Groningen voor het academische deel van de opleiding. In april 2009 zal mijn opleiding tot uroloog afgerond zijn.

In het dorpje aan de Maas heb ik de man ontmoet, die mij al die jaren gesteund heeft en gevolgd is. Wij zijn inmiddels de trotse ouders van 3 fantastische zonen: Noud van 9 jaar, Teun van 7 jaar en Jurre van bijna 2 jaar oud.

## Dankwoord

Er zijn geen woorden die het proces van het schrijven van een proefschrift recht doen. Er is ongeloof, zou ik dit wel kunnen? Er is volharding, omdat ik dit nou eenmaal besloten hebt. Er is ongeduld, het gaat niet snel genoeg. Er is teleurstelling, vanwege afgewezen stukken. Er is blijdschap, bij een behaald succes. Er is nederigheid, bij de echte grote wetenschappers. Er is wanhoop, dit gaat me nooit lukken. En er is trots, het is af.

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De tweede persoon die ik wil bedanken is Monique Roobol. Alhoewel men aanvankelijk bang was dat we elkaar de tent uit zouden vechten, is er uit onze samenwerking een diepe vriendschap ontstaan. We hebben samen veel beleefd in het kippenhok op de poli urologie, tijdens congressen en op de ERSPC meetings. We hebben vooral veel lol gehad. Ik ben er trots op met je samengewerkt te hebben en ik hoop dat we elkaar nog regelmatig zien.

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