Prostate cancer screening

Tests and algorithms

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SCREENING FOR PROSTATE CANCER

Tests and algorithms

VROEGOPSPORING VAN PROSTAATKANKER

Testen en algoritmen

Proefschrift

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List of abbreviations.

ANN	Artificial Neural Network
APPA	A Priori Prevalence Assessment
BPH	Benign Prostate Hyperplasia
CDR	Cancer Detection Rate
cPSA	Complex Prostate Specific Antigen
DRE	Digital Rectal Examination
ERSPC	European Randomised study of Screening for Prostate Cancer
F/T PSA	Ratio between Free Prostate Specific Antigen and Total Prostate Specific Antigen
hK2	Human Glandular Kallikrein 2
OR	Odds Ratio
Pca	Prostate Cancer
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-DT	Prostate Specific Antigen Doubling Time
PSADV	Prostate Specific Antigen Density Velocity
PSA-V	Prostate Specific Antigen Velocity
RRP	Radical Retropubic Prostatectomy
SIR	Standardized Incidence Rate
TRUS	Trans Rectal Ultra Sonography

Part I

1.0
Introduction and scope of the thesis

1.0 Introduction:

"Detect prostate cancer early, it offers a better chance of cure and will reduce cancer specific mortality". The concept speaks for itself and seems convincing. Yet, prostate cancer screening is perhaps the most debated and controversial topic in the urological world at the moment. Just typing the words prostate, cancer and screening in PubMed, the online search engine of the National Library of Medicine, results in a listing of more than 24,000 scientific papers.

Since the early nineties there have been two mainstreams of thinking about prostate cancer screening. One extreme is represented by those who are definitely against screening for prostate cancer and consider it as unethical [1,2]; the opposite view is represented by those investigators who argue that men should not be denied the opportunity of early detection and treatment [3,4].
In the past 10 years no consensus has emerged and prostate cancer screening is still a controversial issue [5,6,7,8,9], resulting in very different screening policies in different countries, varying from very aggressive screening protocols, where men are screened every 6 to 12 months starting as early as the age of 40, to no screening at all. [11,12,13,14].

What causes these great differences of opinion between specialists in the field? Apart from the lack of convincing evidence that early detection indeed will reduce prostate cancer mortality, arguments against early detection of prostate cancer are basically based on the lack of a specific screening test, the poor understanding of the natural history of screen detected prostate cancer and doubt over the effectiveness of the different treatment possibilities of prostate cancer.
Although serum PSA testing is now widely used as a screening test for prostate cancer it is commonly known that PSA is not specific for prostate cancer, and that there is considerable overlap between serum PSA levels in men with normal prostates, benign prostatic hyperplasia (BPH) and those with clinically localized prostate cancer. The major reason for the wide spread use of PSA as a screening test is not its higher specificity but the fact that PSA was more sensitive as a first line screening test for prostate cancer compared to a digital rectal examination (DRE) [15].
In general, prostate cancer is a slow growing tumor in elderly men. The median age at onset of clinically apparent disease is 72 years, and median age at death is 79 years [16]. The question is whether early detection and available treatment, with related morbidity, will reduce prostate cancer mortality.
Any attempt to detect cancer early implies some degree of overdiagnosis, i.e. the identification of cancer which, in absence of screening, would never have reached the threshold of clinical diagnosis, as the subject would have died of some other disease before the cancer could become symptomatic. This is more likely in a cancer with a low average growth rate, a long preclinical detectable phase for which sensitive tests are available, and which affects subjects with a relatively low life expectancy, as is the case in prostate cancer. It has been estimated that for a 50-year-old man with a life expectancy of 25 years, there is a 42% lifetime risk of having microscopic cancer, a 9.5% risk of

having clinically evident cancer, and a 2.9% risk of dying from prostate cancer [17]. Clearly, more men will die with prostate cancer than of it.

An important argument in favor of early detection is the fact that more than 30% of men with clinically diagnosed prostate cancer have locally advanced or metastatic disease [18,19]. Prostate cancer diagnosed at this stage has a poor prognosis; in some men the disease kills the patient within a year after diagnosis. It has been estimated that men with clinically diagnosed prostate cancer will lose an average of 40 % of their life expectancy compared to an age matched control group without prostate cancer [20,21]; therefore the disease should be detected at an earlier, more curable stage. Data from Swedish studies showed that the life expectancy of men with clinically diagnosed, organ confined disease exceeded 10 years and that the cancer specific mortality at 15 and 20 years was high. [18,22,23].

The majority of cases detected by screening are organ confined and well differentiated and thus eligible for curative treatment [24, 25] by radical prostatectomy [26] or radiotherapy [27]. For any medical treatment, informed decisions about treatment choice can only be made if unbiased, representative data on outcomes, i.e. from a randomized controlled trial, are available. Recently a prospective randomized trial of 695 Scandinavian men randomised to observation or radical prostatectomy showed a clear improvement in disease specific and overall survival in patients who underwent radical prostatectomy compared with those in the observation arm [28].

The only scientifically valid way to determine whether early detection has an effect on prostate cancer mortality is by means of a randomized controlled trial with prostate cancer death as the main endpoint. Two large trials are ongoing namely the European Randomised Study of Screening for Prostate Cancer (ERSPC) [29] and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [30] from which an answer can be expected within the next five years.
The ERSPC was initiated in 1993 and has app. 205,000 men randomized in eight different centers in Europe. The PLCO was initiated in 1993 and has included app. 74,000 men randomized to the prostate arm of the trial [31]. Conditions for a possible common analysis of ERSPC and PLCO were defined and described in 1996 [32].

1.1 Scope of the thesis:

Apart from the lack of evidence that early detection of prostate cancer will indeed reduce prostate cancer mortality the differences of opinion about prostate cancer screening are based on two issues relating to specificity. The first is the lack of a screening test or combination of tests that can efficiently identify men with an elevated risk of having prostate cancer in an asymptomatic population in order to avoid unnecessary testing and secondly the lack of knowledge about which prostate cancers are life threatening, and need to be detected, and which are not.
This thesis concentrates not on the debate whether prostate cancer screening should be common practice or not, nor on which prostate cancers should be detected or not, these decisions can only be made after completion of the ongoing randomized trials. Whatever the outcome of these randomized trials will be, it is unrealistic to think that prostate cancer screening can be stopped at this point in time. This makes an acceptable and efficient screening algorithm much-needed.
This thesis focuses specifically on the value of the available screening tests, and their algorithm, in identifying men with an elevated risk of having prostate cancer in an asymptomatic population in the ERSPC (section Rotterdam).

The first part of this thesis consists of some background information on the prostate, prostate cancer, screening and a general description of available diagnostic tests and statistical techniques used. Furthermore the different screening algorithms used in the Dutch center of ERSPC are discussed. The second part discusses possible changes in the screening algorithm and the value of different diagnostic tests both at initial and subsequent screening rounds. Data coming from the first four pilot studies are included. This offers the opportunity to discuss results with respect to the final outcome of the ERSPC trial. Finally the results are summarized and other (new) possible predictors for biopsy outcome are discussed.

2.0

Prostate, Prostate Cancer, Screening and Statistics.

2.0 Prostate, Prostate Cancer, Screening and Statistics.

2.0 The prostate:

The prostate is situated at a low level in the true pelvis, behind the inferior border of the symphysis pubis and the pubic arch, and anterior to the rectum, through the wall of which it may be palpated (Figure 1). It is somewhat conical in shape, resembling a chestnut, and thus presents for examination a base or vesical aspect, an apex, and posterior, anterior and two posterolateral surfaces. The prostate consists of groups of exocrine glands that are packed in dense fibromuscular tissue. The glandular tissue can be divided into two main zones, the transition zone (central and surrounding the urethra) and the peripheral zone (laterally located). The glands in the transition zone are the main sites for the development of benign prostate hyperplasia (BPH), while glands in the peripheral zone are more prone to malignant transformation [33,34].
Together with the seminal vesicles, the prostate produces proteins and enzymes that control the liquidity of the semen.

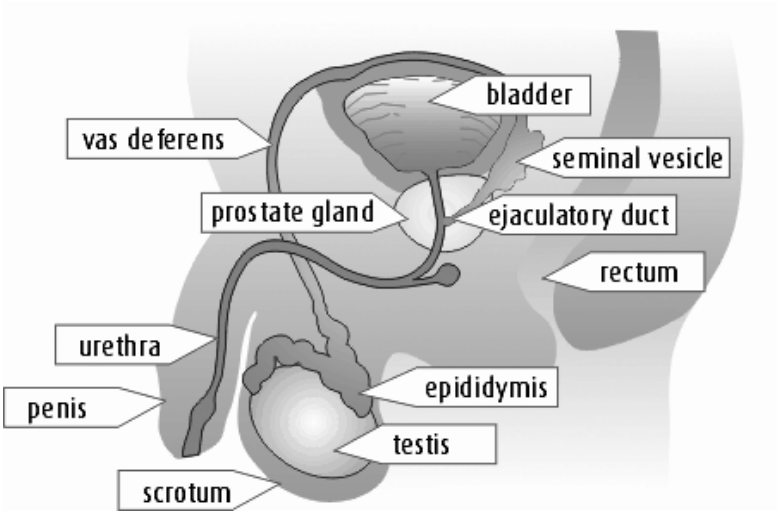

Figure 1: Position of the prostate

2.1 Prostate cancer:

As a man ages, the epithelial cells and the stroma of the transition zone of the prostatic gland become hyperplastic and the gland increases in size. This relatively common condition is called “benign prostatic hyperplasia” (BPH). Prostate cancer appears to begin as a small focus or several foci within the peripheral zone (stage T0). In most men, these small cancers remain dormant for a long time and may be found only at autopsy or not at all. When the dormant focus becomes active and grows into a prostatic nodule, the tumor is in stage T2. This nodule is palpable and most men presenting with a nodule at this stage may fail to receive proper treatment. As the prostatic nodule grows, eventually it perforates the prostatic capsule (stage T3). At this stage, there may be partial or complete obstruction of the urethra or one or both ureters

the seminal vesicles and the pelvic lymph nodes. Once these nodes are involved (N+) the chances of cure are greatly reduced [35]. Unfortunately, even in this stage, the disease may not be recognized and the symptoms blamed on other age related factors resulting in the presence of metastases (M+) at diagnosis.

2.2 Prostate cancer epidemiology:

Prostate cancer is the sixth most common cancer in the world (in the number of new cases) and the third most common cancer in men. In 2002, the number of new cases was estimated at 679,000 worldwide [36] and accounted for 11.7% of all cancers in men (19.0% in developed countries and 5.3% in developing countries). In Europe, prostate cancer incidence is lower in the southern part (Mediterranean countries) than in Northern Europe. In the Netherlands 6900 new cases emerged in the year 2000, being the most common cancer in men (19% of all cancers in men). The cumulative risk for prostate cancer in men 0-74 years in The Netherlands is 7.03 % [37]. The highest incidence rates are found in the United States (33% of all newly diagnosed malignancies among men, with a cumulative risk of 16%), Canada and Scandinavia, though the lowest rates are found in China and other parts of Asia [38]. A recent study reports a trend towards an increasing incidence of prostate cancer in Asia [39]. The differences in incidence are caused by genetic susceptibility, exposure to unknown external risk factors, differences in health care and cancer registration, or a combination of these factors [40].

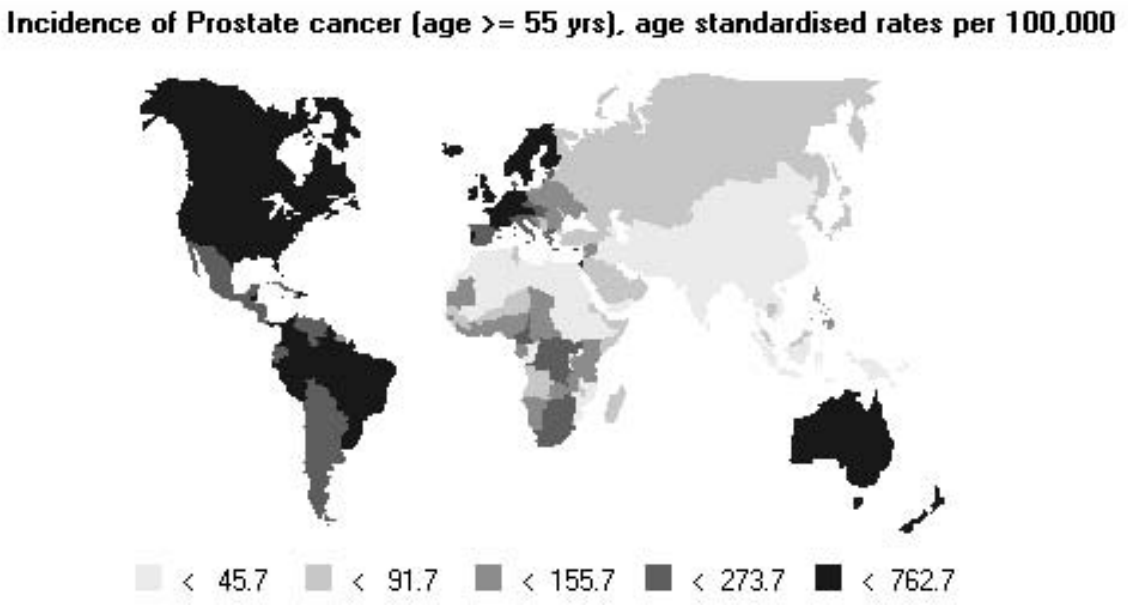

Figure 2: Incidence of prostate cancer (age >= 55-yrs), age standardized rates per 100,000 men

Prostate cancer mortality also varies worldwide. The highest rates are reported in the Caribbean and Scandinavia and the lowest rates in China, Japan, and countries of the former Soviet Union [41,42,43].

Few cancers vary as widely in incidence and mortality between and within countries as prostate cancer. So far no single risk factor for prostate cancer has been identified with sufficient certainty to advocate its use in a primary prevention regimen. Secondary prevention through screening is therefore the only population-based approach available.
Approximately 85% of all cases of prostate cancer are diagnosed in men older than 65 years. The number of men >= 65 years is expected to increase 4-fold worldwide between the years 2000 and 2050, representing an increase from 12.4% of the total population in 2000 to 19.6% in 2030 [44, 45]. This increase in male longevity will lead to a substantial increase in the number of men who will be diagnosed with prostate cancer and who will require treatment for their malignancy.

2.3 Clinical staging.

Multifocality of prostate cancer has been known for many years [46]. As many as five separate tumors may be found in the same prostate. Most frequently, one dominant tumor can be identified and associated with one or more microscopic small independent lesions. The dominant or largest tumor can be considered the primary, clinically most important, or best detectable tumor. The 1992 TNM classification [47], used in this thesis, translates the extent of the tumor (T), and reflects its state of progression (N,M). (See table I). T1 represents incidental carcinoma found upon a trans urethral resection of the prostate (TURP) or needle biopsy; T2 corresponds to organ confined while non-organ-confined disease can be divided into (a) capsular penetration only with extraprostatic extension (T3a-T3b), (b) extension into adjacent organs i.e. seminal vesicles (T3c) and bladder (T4a), and (c) distant metastases (T4b).
Metastases to lymph nodes are separately staged (N).

2.4 Histologic grading.

The degree of differentiation of malignant tumors, being the degree in which tumors show features similar to the benign tissue from which they arise, is often highly predictive of their biologic behavior. The Gleason score method [48, 49] is the most commonly used grading system in the world. In the Gleason score system growth patterns are divided into five categories by the degree of glandular differentiation. The total score is obtained by adding the growth pattern of the most dominant pattern to that of the second most dominant pattern. If only one pattern is present, that grade is multiplied by two. The Gleason scores therefore range from 2 to 10.

The determination of a clinical stage and grade provides a systematic way to describe the amount, extent and degree of differentiation of the tumor. The extent and degree of differentiation of the tumor strongly predicts its natural course. In combination with patient characteristics such as age and

comorbidity the knowledge of stage and grade strongly influence therapeutic decisions.

T0	No pathologic evidence of tumor (note that clinical stage T0 does not exist)
T1	No clinical evidence of tumor. Tumor is an “incidental finding” (note that a pathologic stage pT1 does not exist)
T1a	Tumor found incidentally at transurethral resection in <= 5% of tissue.
T1b	Tumor found incidentally at transurethral resection in > 5% of tissue.
T1c	Tumor found incidentally at needle biopsy.
T2	Tumor is confined to the prostatic gland
T2a	Tumor in one side of the prostate, smaller than half a lobe.
T2b	Tumor in one side of the prostate, larger than half a lobe.
T2c	Tumor in both sides of the prostate.
T3	Extraprotatic extension
T3a	Tumor extends into the periprostatic tissue on one side.
T3b	Tumor extends into the periprostatic tissue on both sides.
T3c	Seminal vesicle invasion on one or both sides.
T4	Invasion of other organs…
T4a	Bladder neck or rectal wall invasion.
T4b	Levator musculature or pelvic wall invasion.
N	Invasion of regional lymph nodes.
NX	Regional lymph node invasion cannot be assessed.
N0	No regional lymph node invasion.
N1	Metastasis in a single regional lymph node <= 2 cm in diameter.
N2	Metastasis in a single regional lymph node > 2 cm in diameter.
N3	Metastasis in regional lymph nodes, either multiple or > 5 cm.
M	Presence of distant metastasis
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph nodes
M1b	Bone metastasis
M1c	Metastasis to other site

Table I: the 1992 version of the TNM system for prostate cancer.

2.5 Screening.

Screening differs from the clinical use of tests in several important ways. In the clinical situation patients consult their physician about complaints or problems resulting in testing to confirm or exclude a diagnosis. Because the patient requests help, the risk and expense of the tests are usually deemed acceptable by the patient. Screening however, engages apparently healthy individuals who are not seeking medical help. Consequently the medical and ethical standards justifying a screening programme must be of a higher level than those related to a diagnostic process in the hope of avoiding any adverse effect of screening.
Even after a disease is determined to be suitable for screening and a valid test becomes available, it does not necessarily follow that a widespread screening program should be implemented. Evaluation of a potential screening program involves consideration of three main issues, namely feasibility, effectiveness and costs. Feasibility will depend on how easy it is to organize the population to attend for screening, whether the screening test is acceptable, and whether facilities and resourses exist to carry out the necessary further tests and treatment following screening. Effectiveness is evaluated by the extent to which implementing a screening program affects the subsequent outcomes. This is difficult to measure because of a number of biases that affect most of the study designs used:

a. Selection bias - people who participate in screening programs often differ from those who do not with respect to the parameters which may be important for the outcome of the study.
b. Lead time bias - because screening identifies disease that would otherwise be identified at a later stage there may be an apparent improvement in the length of survival resulting from screening and thus earlier diagnosis.
c. Length time bias - as some tumors develop more slowly, they have a longer pre clinical stage and are more likely to be detected at that stage. They may also have a more favorable prognosis leading to the false conclusion that screening is beneficial in prolonging life in those who test positive.

These biases can be avoided by performing a randomized controlled trial with disease specific mortality as the endpoint, as is done in the ongoing prostate cancer screening trials, of the ERSPC and PLCO [29, 30].

The cost of screening programs is also important. There will always be competition for the resources for health care. The relative cost-effectiveness of a screening program compared with other forms of healthcare should therefore be considered. Costs relate not just to the implementation of the screening program but also to the additional diagnostic tests and the subsequent cost of treatment. On the other hand, in the absence of screening, costs will be generated later by the diagnosis and treatment of patients in more advanced stages of the disease.

Screening studies also have to live up to the usual pre-requirements of all randomised trials: the experimental group must have a realistic chance of a better outcome than the control group. This is of particular importance because screening will always cause some initial mental and physical damage and because of the fact that overdiagnosis (and treatment) is immanent to screening.

2.6 Screening tests:

For a screening test to be useful, certain conditions must be met: firstly the screening test must be valid. The validity is measured by its ability to distinguish between subjects with the condition and those without. The validity of a screening test is determined by its sensitivity and specificity. These vary with the screening test, not the population. A good screening test preferably will have a high sensitivity and specificity and must be rapid, simple and ideally noninvasive and acceptable for the population screened. Sensitivity is defined as the proportion of men with a positive test result of those who truly have the disease. Specificity is defined as the proportion of men with a negative test result of those patients who are known to be free of the disease. A positivity criterion can influence the sensitivity and specificity of a test. If the positivity criterion is moved up (e.g. a PSA cut-off value for the indication of prostate biopsy) the specificity increases but the sensitivity decreases. The number of false-positives would decrease, but the number of false-negatives (those with the disease, but missed by the given test) increases. Also to be considered in the evaluation of a screening test is the positive predictive value (PPV), which reflects the possibility that if the test is positive, the patient has the disease in question. To calculate the true sensitivity the underlying prevalence of the disease should be known. This is not the case for prostate cancer. Therefore, sensitivity is based on the number of positive biopsies in the screened population as a “gold standard”. Sensitivity defined in this way is termed “relative sensitivity” [50]. Next to the sensitivity of a screening test the specificity is of great importance in a population based screening program, simply because all those with a positive screening test(s) need further workup (i.e. prostate biopsy), which may cause unnecessary damage, mental stress and costs.

In the prostate cancer screening trial in Rotterdam three tests serve(d) as indicators for the need of further testing, the digital rectal examination (DRE), transrectal ultrasonography (TRUS) and the serum prostate specific antigen (PSA) level.

2.7 Digital rectal examination of the prostate (DRE).

As the name says DRE is an examination of the prostate with the digit (index finger) via the rectum. Performing a DRE gives the physician information on the size of the prostate and the character of the prostate tissue (hard -> weak). There is a tendency to detect larger tumors with DRE, and the risk of detecting clinically insignificant tumors with DRE is low. On the other hand, small multi focal lesions with an aggressive biologic potential may not be detected with DRE alone. The general belief is that DRE is highly subjective. The findings within the same prostate on the same day by two different examiners are often divergent [51], although there is one study [52] that found a good correlation between different observations of examiners when assessing the prostate in a systematic way.
In a screening algorithm the result of a DRE is mostly given as abnormal (i.e feeling a hard nodule) or normal. In the case of an abnormal finding the corresponding clinical stage is determined by DRE and recorded (see TNM 1992,[47]).
The inter examiner variation makes the DRE less suitable in population based screening programs. Several studies have already questioned the use of DRE in screening programs [53, 54, 55] and found little or no additional beneficial effect of a DRE in men with PSA levels >= 4.0 ng/ml. The value of DRE in detecting (clinically significant) cancer in men with a low “normal” range of PSA (< 4.0 ng/ml or < 3.0 ng/ml) remains controversial [56, 57, 58, 59].
Data of the Dutch part of ERSPC [60, 61, 62, 63], have shown that on average, in men with a PSA level < 3.0 ng/ml, 96 DRE’s are needed to diagnose one prostate cancer.
The controversy about the value of DRE as a screening test (at low PSA levels) is a topic of ongoing studies.

2.8 Transrectal ultrasonography of the prostate (TRUS).

With TRUS, an ultrasound probe is inserted into the rectum. It emits sound waves that bounce off the prostate gland, producing echoes that a computer uses to create a picture of the prostate. This picture, called a sonogram, can show abnormal areas (hypo echoic areas), including tumors, within the prostate [64]. As with the DRE the interpretation of TRUS is highly dependent on the investigator which makes it less suitable as a screening test. Furthermore it has been shown that hypo-echoic lesions are not specific for prostate cancer [65] and that cancers can have ultrasonic characteristics ranging from non hypo echoic to hypo echoic and to hyper echoic [66, 67].
It is recognised that the value of TRUS as a screening test is limited [68, 69, 70, 71,72]. It is now generally accepted that TRUS is not useful as a screening test but is indispensable for guiding prostatic biopsies and assessing prostatic volume.

2.9 The serum prostate Specific Antigen (PSA).

PSA is a glycoprotein, encoded by the KLK3 gene that is almost exclusively produced by the epithelial cells of the prostate, and is perhaps more a specific organ marker rather than a tumor marker [73]. In the normal prostate most of the PSA produced will be excreted into the semen where it acts as an androgen related serine protease (controlling the liquidity of the semen fluid). It is speculated that, due to tumor development, the tissue architecture is altered by the disruption of the basal cell layer and basement membrane causing leakage of PSA into the blood stream [74]. PSA can be measured reliably either by a monoclonal immuno radiometric assay or by a polyclonal radioimmunoassay [75]. The calculated half-life of serum PSA ranges from 2.2 to 3.2 days.
Digital rectal examination, cystoscopy and prostate biopsy all can cause spurious elevations of the serum PSA level. Conditions such as bacterial prostatitis and acute urinary retention can also elevate the serum PSA level. There is also a considerable overlap in PSA levels between patients with organ-confined cancer and those with benign prostatic hyperplasia (BPH). As a result, approximately 38% to 48% of the patients with organ confined prostate cancer, the candidates for curative therapy; show no elevation of serum PSA [76].
The problem with PSA testing is the choice of a cut off value for the decision to continue with more invasive examinations such as the prostate biopsy.
Important positive characteristics of PSA determination for screening are the high acceptance of a blood test by the general population, and the fact that the result is objective and the test is easy to perform.
Choosing a PSA cut off level in a screening setting will thus be a trade off between sensitivity and specificity. There have been several attempts to improve the specificity of total PSA including the use of PSA density (relating the serum PSA value with the volume of the prostate), PSA velocity (changes in serum PSA level over time), PSA doubling time (the time that is needed to double its value, expressed in years) and the use of other molecular forms of PSA as tumor markers. The value of these forms of PSA, as predictor for biopsy outcome will be discussed.

2.10 Prostatic biopsy.

Screening tests are used to identify men with an elevated risk of having prostate cancer. This suspicion must however be confirmed. The gold standard to prove the presence or absence of prostate cancer is the surgical removal of the entire prostate followed by a histological analysis of the entire gland. Next to this clinically and ethically impossible maneuvre, there is no superior method to prove the presence or absence of prostate cancer than a prostate biopsy, recognising that prostate cancers may be missed with this procedure [77,78,79].
Historically, the diagnosis of prostate cancer has been limited to a DRE and a digitally directed biopsy (taking a tissue sample of the palpable nodule). With the increasing use of PSA as a screening test the systematic sextant biopsy

performed under ultrasound guidance was introduced [80]. With the original sextant technique six sites were biopsied; the apex, middle and base of the prostate in the mid plane of each lobe of the prostate. The sextant technique was more effective in detecting prostate cancer than the digitally directed technique. Several years later, the sextant technique was modified in that sextant biopsies were taken laterally to the mid plane in the peripheral zone where most prostate cancers are located (figure 3) [81,82,83]. This latter technique is used within ERSPC (section Rotterdam).

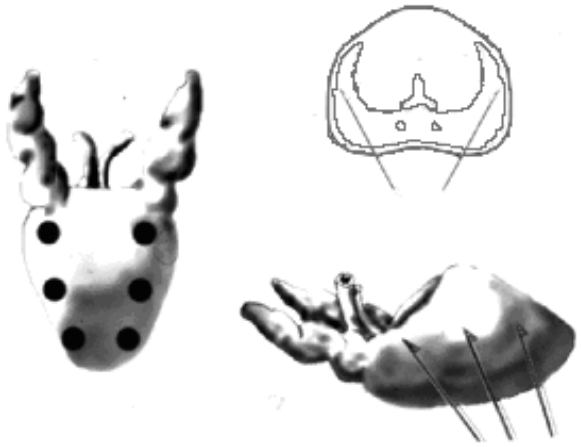

Figure 3: Schematic sextant transrectal biopsy. Left: dorsal view, upper right: transverse view, lower right sagittal view.

Prostatic biopsy is in general a safe procedure though some local pain with or without urethral or rectal bleeding and haematospermia is common. In order to avoid infectious complications an antibiotic prophylaxis is usually given. The most feared complications are febrile reaction with prostatitis, septicemia and gross rectal blood loss. These severe complications are rare. There are however several case reports of death as a possible complication of a prostate biopsy [84,85,86].
Within ERSPC the rate and type of complications after prostate biopsy have been studied. In a cohort of 1687 biopsied men within the ERSPC Rietbergen et al. [87] reported mild complications such as haematospermia in 45.4% and haematuria in 23.6% of the men. This was later on confirmed by Raaijmakers et al. in a study were complications after 5802 biopsies done in ERSPC (section Rotterdam) were reviewed [88]. Although severe complications are rare these can lead to a negative effect and considerable costs since many men are involved in a population based screening setting.

In addition to the three tests mentioned above; DRE, TRUS, PSA (and PSA-D and PSA-V) additional information known before the actual performance of the sextant biopsy can be of help in determining the probability of detecting prostate cancer, e.g. age, prostate volume (determined at TRUS), results of earlier screening visits and family history of prostate cancer.
The value of all the predictors mentioned above is measured against the used standard for the detection of prostate cancer within ERSPC, section

Rotterdam, namely the TRUS guided lateral sextant prostate biopsy described above. Recognizing the fact that all sampling procedures, such as the prostate biopsy, incur the risk of being falsely negative (i.e. cancer is present but missed by the biopsies), the calculation of statistical performance characteristics of the screening tests are inherently incorrect and biased.

2.11 Assessing the predictive value of a screening test for the presence or absence of prostate cancer.

As mentioned above part of this thesis concentrates on the ability of a screening test to identify men with an elevated risk on having prostate cancer (assessed by a sextant prostate biopsy!) in an asymptomatic population.
Predictive modeling in medicine entails making predictions about patient outcomes based on available parameters such as clinical and pathologic variables. Rarely does any single variable provide sufficient predictive value to be a definitive predictor of an outcome of interest. To improve the predictive value of a single clinical parameter it is often helpful to consider it in combination with other variables in a multivariate analysis.
A regression analysis makes it possible to predict the value of a dependent variable with using one or more independent variables. To assess the predictive value of an independent variable (i.e. result of screening test) to a dichotomous dependent variable (having cancer yes or no) the use of a logistic regression model is the correct choice [89].
A logistic regression model gives probabilities that an individual, for whom results of different screening tests are known, e.g PSA value, outcome of DRE and outcome of TRUS, belongs in group 1 (e.g. having cancer) or group 0 (no cancer).

In two of the following chapters this technique is used and in order to understand the outcomes of such analyses an example of a logistic regression analysis will be discussed.
Before that it is necessary to clarify the following terms:

- Probability: the chance, in % terms, of an event occurring: 20/100 = 20%.
- Odds: the probability of an event occurring divided by the probability of it not occurring: 20% / 80 % = 0.25.
- Odds ratio: the ratio of two sets of odds (e.g. positive test versus negative test): 1.0 /0.25 = 4.0

The odds ratio (OR) is a measure of the association between two variables. An OR of 1 means there is no association, odds are equal. An OR < 1 means that the odds of an event occurring decreases by moving between values of the explaining variable. An OR > 1 means that the odds of an event occurring increases by moving between values of the explaining variable. For example if the outcome variable is having grey hair or not, and the OR for age is > 1, this means that with higher age the odds of having grey hair increases.
The OR is however asymmetrical, the lower bound is fractionally above zero and there is no upper bound. For modeling purposes this is problematic and therefore the OR is transformed by taking the natural logarithm, the OR is

transformed to the logit. This purely mathematical procedure has one goal namely that the logit has symmetrical properties, zero means no association and negative values means odds decrease and positive values means odds increase. It is however hard to think with values such as the natural log of the OR. Therefore the logit is transformed back to an OR. This so called exp (B) is the output in statistical packages such as SPSS (version 10.0, Chicago, Illinois, USA), used in this thesis.
Exp (B) gives us the percentage increase or decrease in the odds. When the OR > 1, the % increase in odds is "OR – 1". When the OR < 1, the % decrease in odds is "1 – OR".
For example, an OR = 3 means an increase of the odds by 200 % (3 – 1). An OR of 0.42 implies a decrease in odds of (0.42 – 1) = 58%.

In order to explain the interpretation of a logistic regression analysis the following example is used:

Some men hate soccer, other men love soccer. A researcher, for some reason, wants to examine the determinants of such behavior. Hence, a sample of men is asked whether they hate or like soccer. The height, weight, age, and wage of these individuals are also assessed. An extract of the data is displayed in the following table.

Order	**Height**	**Weight**	**Age**	**Wage**
Hate	192	71	21	34,509
Hate	184	84	34	29,500
Like	203	92	42	41,600
Hate	185	63	27	38,456
Like	191	84	41	48,670
Hate	194	81	55	29,698
Like	173	64	44	49,569
..	..	..	..	..
..	..	..	..	..
Hate	162	87	23	58,598

Presumably, the researcher could undertake a series of t-tests to ascertain whether or not the age, height, weight, and wage of individuals differs between individuals who hate or like soccer. The outcomes that arise from these analyses are summarized in the table below.

Measure	Average if hate soccer	Average if like soccer	T-value	P-value
Height	191	173	4.92	0.001
Weight	67	61	4.84	0.001
Age	45	32	6.03	0.001
Wage	39,658	31,483	5.85	0.001

In this instance, all of the measures clearly differentiate the two groups. Nevertheless, these t-tests do not provide a comprehensive account of the data. In particular, these analyses do not indicate whether or not each measure differs between the two groups after controlling the other measures. In other words, these analyses do not demonstrate that each measure would differ between groups that are equivalent on the other measures. For example, weight might not differ between individuals who hate or like soccer if these groups were equal in height. That is, weight might not differ between the two groups after controlling for height, age, and wage.

Logistic regression provides a means to explore these issues. Specifically, logistic regression determines whether or not the two groups differ from one another on each measure after controlling the other variables. Logistic regression is applicable only when the researcher compares two groups (0 = hate soccer and 1 = like soccer).

After a logistic regression analysis is executed, the above mentioned exp(B) and its significance (Sig) is displayed (B = estimated effect on the logit (natural log of the odds), S.E its standard error).

	B	S.E	Sig.	Exp(B)
Height	-0.47	0.24	0.03	0.62
Weight	0.37	0.20	0.05	1.44
Age	0.16	0.32	0.61	1.17
Wage	0.11	0.23	0.64	1.12
Constant	2.12	1.68	0.10	16.04

In this example, two of the p values are less than or equal to 0.05. These p values reflect measures that differ significantly between the two groups, after controlling the other variables. In this instance:

Height depends on whether individuals hate or like soccer, after controlling weight, age, and wage (p=0.03).

Weight depends on whether individuals hate or like soccer, after controlling height, age, and wage (p=0.05).

Neither age nor wage depends on whether individuals hate or like soccer after controlling the other measures (p= 0.61 and p=0.64).

These p values, however, do not indicate which group generated greater height and weight.

The column labeled Beta (B) can be utilized to determine the direction of any significant effects. In this instance, the Beta value associated with height is negative. This negative value indicates that height is inversely correlated with the grouping variable. Recall that 0 reflects hating soccer and 1 reflects liking soccer. Accordingly, the negative Beta value indicates that individuals who are taller are more likely to hate soccer.

In contrast, the Beta value associated with weight is positive. This positive Beta value suggests that individuals who are heavier are more likely to like soccer.

The Beta values can also be utilized to predict the group to which individuals belong from their measures alone. That is, in this example, whether individuals hate or like soccer can be predicted from their height, weight, age, and wage. To predict group membership, the Beta values can be substituted into the following formula:

Probability the individual is in group 1 = $e^{(\text{Constant} + B1 \times \text{Var1} + B2 \times \text{Var2...})}/(1 - e^{(\text{Constant} + B1 \times \text{Var1} + B2 \times \text{Var2...})})$

This formula may appear to be complex, but is actually reasonably straightforward to use. Specifically, e refers to the base of natural logarithms and approximates 2.7. 'Constant' denotes the Beta value in the row labeled 'Constant' and represents the intercept of the fitted hyper plane. 'B1' refers to the beta value associated with the first measure, and so forth. Hence, when the Beta values that were derived earlier are substituted into this equation, the following formula emerges:

Probability the individual is in group 1 = $e^{(2.12-0.47 \times \text{Height} + 0.37 \times \text{Weight} + 0.16 \times \text{Age} + 0.11 \times \text{Wage})}$ divided by $(1 - e^{(2.12-0.47 \times \text{Height} + 0.37 \times \text{Weight} + 0.16 \times \text{Age} + 0.11 \times \text{Wage})})$

To illustrate this formula, consider an individual who is 173 cm tall, 78 kg in weight, 37 years old, and earns € 76,000. These values can be entered into the equation. Suppose this equation yields an answer of 0.78. This finding indicates that such an individual is more likely to pertain to group 1, who likes soccer. Specifically, the probability this individual likes soccer rather than hate it is 0.78.

The Beta values also provide some insight into the extent to which the measures differentiate the groups. Specifically, the column labeled ‘Exp (B)' equals e (i.e. 2.7) to the power of each Beta value. These values give some insight into the magnitude of each effect. The column ‘Exp (B)' presents the extent to which the corresponding measure influences this odds ratio. In particular, this value represents the extent to which raising the corresponding measure by one unit influences the odds ratio. For example, the Exp (B)

value associated with Weight is 1.44. Hence, when weight is raised by one unit, the odds ratio is 1.44 times as large. Specifically, when weight is raised by one kilogram, individuals become 1.44 more times as likely to like soccer.

Examples of logistic regression models in prostate cancer research are the Partin tables [90]. The Partin tables were developed to predict pathologic stage in men undergoing radical prostatectomy for clinically localized cancer. Other models have been developed to predict outcomes such as disease recurrence and prostate cancer survival [91,92]. The logistic regression analysis is widely used and is available in most statistical packages.

Another, newer and more complicated way to retrieve a model which can be used to estimate the probability that an individual belongs to group 1 or group 0, is an artificial neural network (ANN). ANNs represent a relatively new methodology for predictive modeling in medicine. ANNs are computer software constructs based on concepts in neural anatomy and physiology designed to mimic the way the brain learns. In contrast with traditional statistical techniques, ANNs are capable of automatically resolving relationships between variables without the need for a priori assumptions about the nature of the interactions. Although promising, ANNs have inherent limitations and are not free of controversy in medical applications [93,94,95]. The primary disadvantage of an ANN is its “black box” quality, that is, without extra effort, it is difficult if not impossible to gain insight into a problem based on an ANN model. Regression techniques allow the user to sequentially eliminate possible independent variables that do not contribute to the fit of the model and thus allow hypothesis testing regarding both the univariate and multivariate association between each independent variable and the outcome of interest. These features are not as standards available for ANN. Additional drawbacks of ANN included the computational resources required and the lack of standard software. Many authors have analyzed the same data set by using both approaches, with the outcomes of these comparisons varying as much as the data sets them selves. A review of 28 studies concluded that ANN should not replace a standard statistical approach. Both methods should be continued to be used and explored [96].

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3.0

Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam)

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Abstract:

OBJECTIVE
To describe the preliminary results of the Dutch section of a large multicentre study of screening for prostate cancer, the European Randomized study of Screening for Prostate Cancer (ERSPC), initiated in the Netherlands and Belgium in 1991.
MATERIALS AND METHODS
After a series of five pilot studies which started in 1991, full-capacity screening started in 1994 with the use of a serum prostate-specific antigen (PSA) determination, a digital rectal examination (DRE) and transrectal ultrasonography (TRUS) as screening tests. Depending on the results and the screening protocol used, men were referred for further examination by sextant biopsies (extended with a seventh biopsy if TRUS showed abnormality). The protocols used, efficiency of the different screening tests, number of cancers detected in the pilot studies, initial screening round and preliminary results of the second screening round are described.
RESULTS
After the pilot studies it became clear that a study of prostate cancer screening was feasible in the Rotterdam area. The screening protocol was workable and the recruitment rate acceptable (39.5%). An inventory of the population registries of Rotterdam and surrounding municipalities, and the known recruitment rate, made it clear that a contribution of 40 000 men (aged 55–74 years) from the Dutch centre to the ERSPC was feasible. The initial screening round started in December 1993 and lasted until December 1999 (protocol 5–10). In all, 42 376 men were randomized and 1014 cancers detected (5.1%). During this screening the protocol was simplified. After evaluating the different screening tests abnormal results of the DRE and TRUS were omitted as an indication for a sextant biopsy. Only a serum PSA level of ≥ 3.0 ng/mL is now used as the indication. The second screening round started in December 1997 and continues. To December 2002, 9920 men were screened for the second time, 4 years after their initial screening visit. To date 446 cancers have been detected (4.5%); this round will last to December 2003. Further evaluation of the screening regimen and characteristics of the cancers detected are constantly assessed within the Dutch ERSPC. Meanwhile a third screening round has also been initiated, which will last to December 2007.
CONCLUSION
A prostate cancer screening study of the projected magnitude is feasible in Rotterdam; the recruitment rate is acceptable and the screening tests well tolerated. The study has generated many scientific publications and will be of great value in determining whether prostate cancer screening should be part of general healthcare.

Introduction:

In the 1980's carcinoma of the prostate was (and still is) the second leading cause of cancer deaths among men in the European community [1]. From 1979 to 1988 the number of deaths due to prostate cancer in The Netherlands had increased by 2% annually over the past 10 years [2]. During the same period the identification of prostate specific antigen (PSA) had increased the number of methods available (adding toDRE and TRUS) for the early detection of prostate cancer [3,4]. With the increasing incidence and mortality on one hand, and the availability of several very promising detection techniques on the other hand, the question arose whether early detection or screening for prostate cancer would be feasible and effective in reducing prostate cancer mortality. That a cancer can be detected earlier in its natural history is no guarantee that benefits will follow. Numerous studies (case-finding, retrospective and prospective) were already undertaken to determine the efficacy of cancer screening. However there are three important biases (Lead-time, length- and selection) pertinent to many of these studies, causing serious problems with interpreting the study results. The most elegant way to account for these biases is a randomized controlled trial with cancer specific mortality as the main endpoint [5].

In 1990 Schröder et al. [6,7] started to pursue the idea of a randomized study of screening for prostate cancer. From the start it was clear that it would be impossible to conduct such a costly trial in one European country; international cooperation was necessary. Based on institutional investments and a grant by the European Community program "Europe against Cancer" it was possible to initiate randomized pilot studies in Belgium (Antwerp, 1992-1993) and the Netherlands (Rotterdam, 1991-1994) [8]. At the same time the contours of the European Randomized study of Screening for Prostate Cancer (ERSPC) emerged [6,9].

Material and Methods.

ERSPC Rotterdam started with a series of 5 pilot studies in October 1991 which served to obtain an impression of the logistics involved in setting up a screening study of the projected magnitude. Full capacity screening started in June 1994.
Apart from the main endpoint (prostate cancer mortality) the Dutch centre also assessed the efficiency of the different screening tests, pathological features of the cancers detected, treatments applied and quality-of-life related issues. With the use of MISCAN computer program the screening process is being modelled.
The first part of this paper describes the results of the pilot studies and the initial screening round of the Dutch center located in Rotterdam.
The second part describes the preliminary results of the ongoing second screening round 4 years after the initial screening, a screening interval that was chosen on the basis of the ratio between prevalence in the first pilot screening and the incidence in the general population [8].

1. The pilot studies (1991-1993).

Men aged 55-74 years of age, selected from the population registry of Rotterdam were invited for screening. The only exclusion criterion was a previous diagnosis of prostate cancer. Men who responded by returning the intake questionnaire and who provided a signed informed consent were randomized and notified of the outcome. The screening protocol consisted of three tests, i.e. serum PSA determination, a DRE and TRUS. The findings of these three tests resulted in a re-screening visit after 1 or 4 years, or a sextant biopsy, depending on the used protocol. Men with a benign biopsy result were re-invited after 1 year.
During the first four pilot studies the logistical and screening procedures were tested and optimized to a workable and acceptable protocol, which was finally tested in the fifth pilot study.
The characteristics of all protocols used are shown in Table I. The first protocol started in October 1991. A total of 1186 men were randomized in a period of 15 months. The most important characteristic in this first pilot study was the randomization after PSA testing. No further screening tests were done if the serum PSA level was >= 10.0 ng/ml; these men were directly referred to their GP. The protocol changed in January 1993; men were randomized before PSA testing, meaning that only men randomized to the screening arm were PSA tested. Protocol 2 was used until March 1993 (256 men).

In March 1993 the screening procedure after blood sampling was changed. If possible the biopsy was performed directly after the DRE and TRUS. Protocol 3 lasted until May 1993 (297 men). Protocols 4 and 5 had some minor changes in logistic procedures and the indication for sextant biopsy was simplified and became partly PSA driven (Table I).

The mean recruitment rate (Table I) over the five pilot studies was 39.5%. Recruitment procedures proved to be relevant for establishing higher participation rates. Eliminating the need for the control group to visit the study centre introduced with protocol 2 led to an increase of the recruitment rates (Table I). The screening tests were well accepted and tolerated [10].

As noted, PSA driven biopsies were not taken in pilot study 1 and were rare in pilot study 2 and 3 (biopsy was indicated at a PSA of >= 20.0 ng/ml). This resulted in a detection rate of app. 9% in men with a PSA of 4.0 – 10.0 ng/ml. In pilot study 4 and 5 (biopsy indicated if PSA was >= 4.0 ng/ml, irrespective of DRE and TRUS results) the detection rate increased to 24%. This finding was one reason to decide on a PSA-driven screening protocol, i.e. a PSA threshold of >= 4.0 ng/ml, in the future. Furthermore the rate of false positive findings (i.e. unnecessary sextant biopsies) was extremely high in protocols 5 and 6 (76 biopsies to detect two cancers) in men with PSA levels of < 2.0 ng/ml. Further analysis showed that the proportion of false-positive TRUS (24%) was about twice that of false-positive DRE (13%) in men with PSA levels of < 4.0 ng/ml. If both tests had been omitted in the group of men with a PSA of < 2.0 ng/ml, 69.3% of the study population, only two prostate cancers would have been missed. These findings showed that the role of the three

available tests in prostate cancer screening was still to be determined for their predictive value and, obviously also with respect to the final study outcome, preventing death from prostate cancer [8].

Protocol number	Period	Recruit-ment rate (%)	Men (n)	Biopsy indication used
1	10/'91 - 01/'93	35.6	1186	DRE and/or TRUS abnormal with lesion >= 8 mm. PSA done in all men.
2	01/'93 - 03/'93	36.5	256	DRE and/or TRUS abnormal with lesion >= 8 mm or PSA >= 20.0 ng/ml.
3	03/'93 - 05/'93	42.4	297	DRE and/or TRUS abnormal with lesion >= 8 mm or PSA >= 20.0 ng/ml.
4	05/'93 - 11/'93	42.4	679	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml.
5	12/'93 - 05/'94	40.6	450	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml.
6	06/'94 - 11/'95	43.4	8642	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml.
7	11/'95 - 01/'96 03/'96 - 10/'96	53.9	4147	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml. No screening if PSA < 1.0 ng/ml.
8	01/'96 - 03/'96	52.8	1404	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml. No screening if PSA < 1.0 ng/ml.
9	10/'96 - 04/'97	50.7	6000	DRE and/or TRUS abnormal or PSA >= 4.0 ng/ml. No screening if PSA < 1.0 ng/ml.
10	05/'97 - 12/'99	48.0	21733	PSA >= 3.0 ng/ml. No screening if PSA < 3.0 ng/ml.
Total	Protocol 5-10		**42376**	

Table I: Characteristics of the screening protocols 1 – 10.

Evaluating all procedures related to recruitment of participants, to applying the screening tests and to data collection during the pilot studies resulted in an infrastructure as shown in fig 1. (section A).
An inventory of the population registries of Rotterdam and surrounding municipalities and a known recruitment rate of app. 40% made it clear that a contribution of 40,000 men (aged 55-74 years), from the Dutch centre to ERSPC, was feasible.

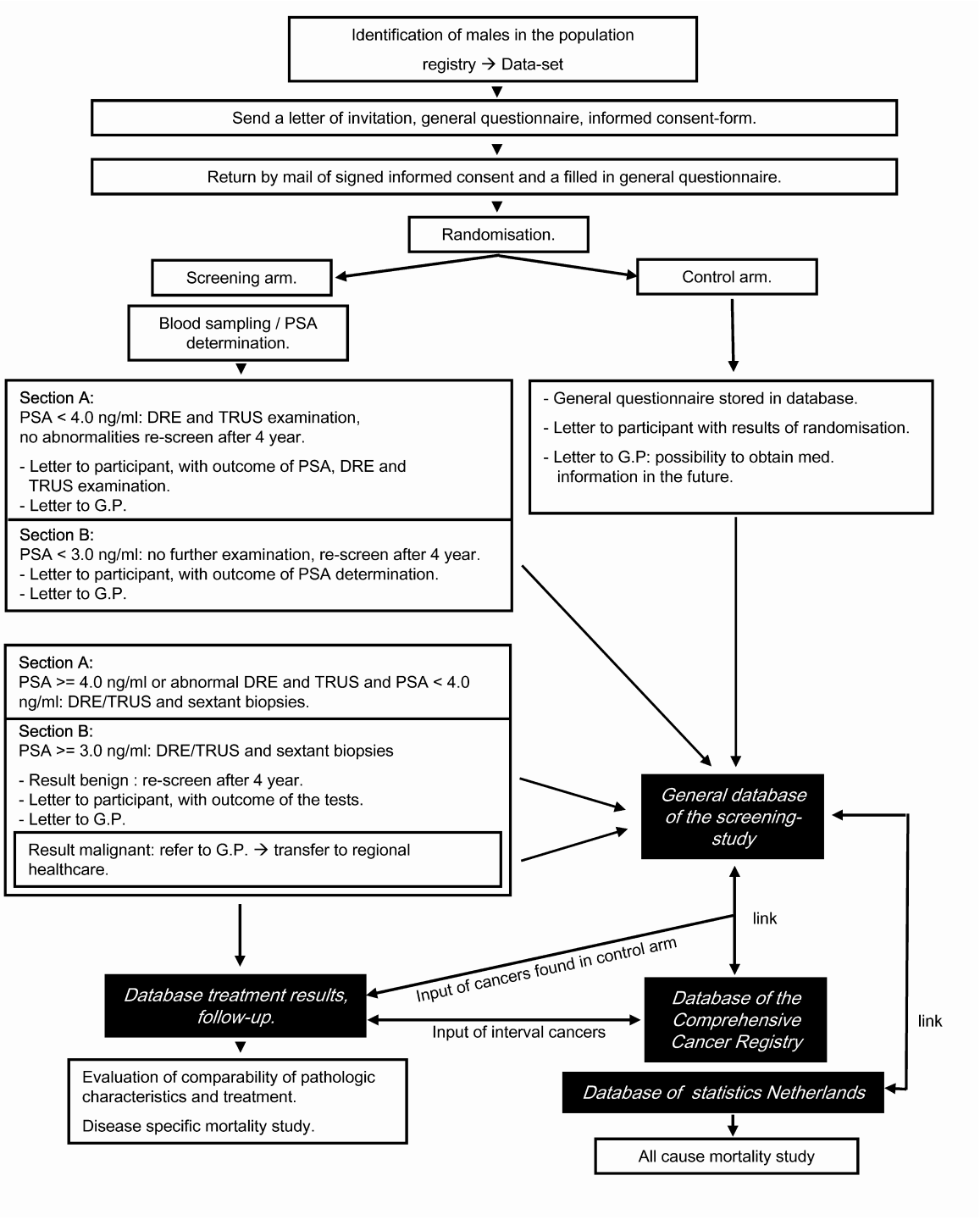

Fig. 1. The ERSPC, section Rotterdam. Infrastructure of the screening process.

2. The initial screening round (1994 – 2000).

In June 1994 protocol 6 started (Table I). This protocol was used until November 1995 and consisted of 8642 men. During this period again the value of PSA, DRE and TRUS was assessed to identify possible improvements in the accuracy of the screening procedures. Bangma et al [11,12] studied the use of the ratio between free and total PSA (F/T ratio), age specific reference ranges and PSA density and the possibility to improve the specificity of total PSA, DRE and TRUS in prostate cancer screening. These studies resulted in positive findings for all three items. Using of these detection techniques could reduce the number of biopsies with app. 35%, with a reduction in cancer detection of 11%. The most cost-effective screening protocol was pre-screening with total serum PSA and exclusion of DRE and TRUS at PSA values of <= 2.0 ng/ml.

Rietbergen et al [13] also found that total PSA was the most powerful tool for predicting biopsy outcome in a group of 3963 men (981 sextant biopsies taken and 172 cancers found). In that study it became clear that most cancers were found within the PSA range of >= 4.0 ng/ml and that within this PSA range 3.6 biopsies had to be taken to detect one case of prostate cancer. At PSA levels of < 4.0 ng/ml 14.2 biopsies were necessary to find one cancer. In the PSA range 0.0 – 1.0 ng/ml, 43 sextant biopsies were taken to detect one case of prostate cancer. Furthermore it became clear that the cancers that were found through a positive DRE or TRUS findings alone (at PSA levels of < 4.0 ng/ml) only amounted to respectively 8.1% and 7% of the cancers detected. If PSA had not been used as a screening test, DRE would have detected 47.1% and TRUS 45.3% of all cancers. Calculations on the use of a PSA threshold value to avoid unnecessary prostate biopsies resulted in an optimal PSA threshold value of 1.7 ng/ml. When using this value 33.9% of the biopsies would have been avoided at the expense of 5.3% of the prostate cancer detected. As there were relatively few cancers detected at PSA levels of < 4.0 ng/ml, on which these calculations were based, it was decided to change the protocol to a pre-screen PSA threshold of 1.0 ng/ml, meaning that men with a PSA level of < 1.0 ng/ml were not screened further and directly scheduled for their next screening visit after 4 years.

Another reason for changing the protocol was related to the fact that men invited for ERSPC at that time lived in surrounding municipalities. To maintain a good recruitment rate it was necessary to reduce the number of visits to the University Hospital. Therefore it was decided that blood samples should be taken in the municipality and, if necessary, subsequent screening tests (DRE, TRUS and sextant biopsy) were to be performed at the University Hospital in Rotterdam. Doing so, only app. 20% of the participants had to travel to the University Hospital. Protocol 7- 9 were conducted accordingly, with some minor changes in the logistic procedures after PSA testing. Protocol 7- 9 were used from November 1995 until April 1997 (a total of 11,551 men). This change in the screening procedure resulted in a considerable increase of the recruitment rate (Table I).

During protocol 6 - 8 a study was done to evaluate the value of a 1-year re-screening after a benign biopsy result. Rietbergen et al. [14] found that biopsy

at repeat screening diagnosed prostate cancer in 11% of the men biopsied (442 men biopsied, 49 cancers detected). Of the 984 men who were eligible for repeat screening after one year only 442 men were actually biopsied. A large proportion of the men (42.2%) had PSA levels of < 4.0 ng/ml and abnormalities found at initial screening could not be reproduced, or serum PSA was below the cut-off value of 1.0 ng/ml. Furthermore, the clinical characteristics of the tumors detected after repeat screening were more favourable, with an increased proportion of stage T1C tumours, than those detected at initial screening.
In October 1996, having available more results of a re-screening after 1 year, it was decided to stop the re-screening procedure after 1 year. With the start of Protocol 9 this change was implemented. (Table I). Men with a benign biopsy result were re-invited after 4 years.
Since deciding to take a sextant biopsy in participants with PSA values of <= 4.0 ng/ml (from pilot 4), the DRE was the mainstay of early diagnosis at lower PSA ranges.
As noted [13], the DRE as a screening test at low PSA levels (i.e. PSA <= 4.0 ng/ml) performed very poor (only 8.7% of all cancers detected were detected by DRE), so a further evaluation was indicated.
Schröder et al. [15] studied the value of DRE as a screening tool at low PSA ranges in a screening population consisting of 10,523 men. The data confirmed that DRE has a low predictive value in men with low PSA levels. When PSA levels were < 3.0 ng/ml, 11 biopsies were necessary to detect one cancer. Beemsterboer et al. [16] used a logistic regression model in order to predict the number of cancers for PSA of <= 4.0 ng/ml if all men were biopsied (so called Predictive Index) [17]. The effects of a change in PSA threshold on the outcomes of screening were explored in a group of 8600 men. Applying a DRE and TRUS only in the PSA-range 1.5 – 3.9 ng/ml and 2.0 – 3.9 ng/ml to indicate that a biopsy was required, would result in a decrease of biopsies by 29% - 36%, respectively, and a decrease in cancers detected of 5% - 8% respectively. In addition DRE and TRUS are difficult to reproduce because they are investigator-dependent. A protocol with only PSA of >= 3.0 ng/ml as a direct biopsy indication resulted in a decrease of biopsies by 12% and a decrease of detected cancers by 7.6% and above all a much more simple screening procedure.

A protocol change which permits to miss otherwise detectable tumors, could in theory result in missing those cancers with the largest potential to contribute to the reduction in disease specific-mortality. In a study by Hoedemaeker et al. [18] the group of tumors detected by DRE and/or TRUS below a PSA level of 4.0 ng/ml was examined. This group had low pathological stages with a considerable fraction (43%) meeting the criteria for a ‘minimal tumor’ (one < 0.5 ml, lacking Gleason pattern 4 or 5 and being confined to the prostate); 86% had a tumour volume of < 0.5 ml. Men with low PSA levels are therefore most likely to harbor clinically insignificant tumors. These findings were confirmed by Vis et al [19], who also showed that the DRE as screening test at low PSA values (i.e. <= 3.0 ng/ml) was inefficient; 289 DREs were needed to find one case of clinically significant disease and 96 DREs were needed to diagnose a prostate cancer of any size, grade or stage. These data indicated that a change in protocol where DRE and TRUS are omitted in lower PSA-ranges was likely not to result in significant loss in potential mortality reduction, providing that re-screening was used after an adequate interval. In addition,

the sextant biopsy procedure is bothersome and not without danger for the participants. On the basis of the data noted a final protocol change took place in May 1997 (protocol 10, table I). From this point all men with PSA of < 3.0 ng/ml were not screened further and men with PSA of >= 3.0 ng/ml were invited for further examination (DRE, TRUS and sextant biopsies, fig 1, section B).

During the period of screening according to protocol 10 (table I) there was a validation study of the effects of the change in protocol [20]. In this study the cancer detection rates and tumor characteristics of the cancers detected in the “old protocols”, (protocol 6 – 9), and the “new protocol (protocol 10)” were compared. The cancer detection rates were similar in the two screening regimens, because there were many more prostate cancer cases per biopsy in the PSA range 3.0 – 3.9 ng/ml in protocol 10. The positive predictive value of the PSA range 3.0 – 3.9 ng/ml was 6.4% in the “old protocols” and 18.0% in the “new protocol”.

Prostate cancers detected with the new screening regimen had a similar distribution of Gleason scores but a larger proportion of confined disease. Final conclusion of this validation study was that the overall characteristics of the cases detected at PSA threshold of 3.0 ng/ml differed very little from those detected with the regimen based on PSA, DRE and TRUS.

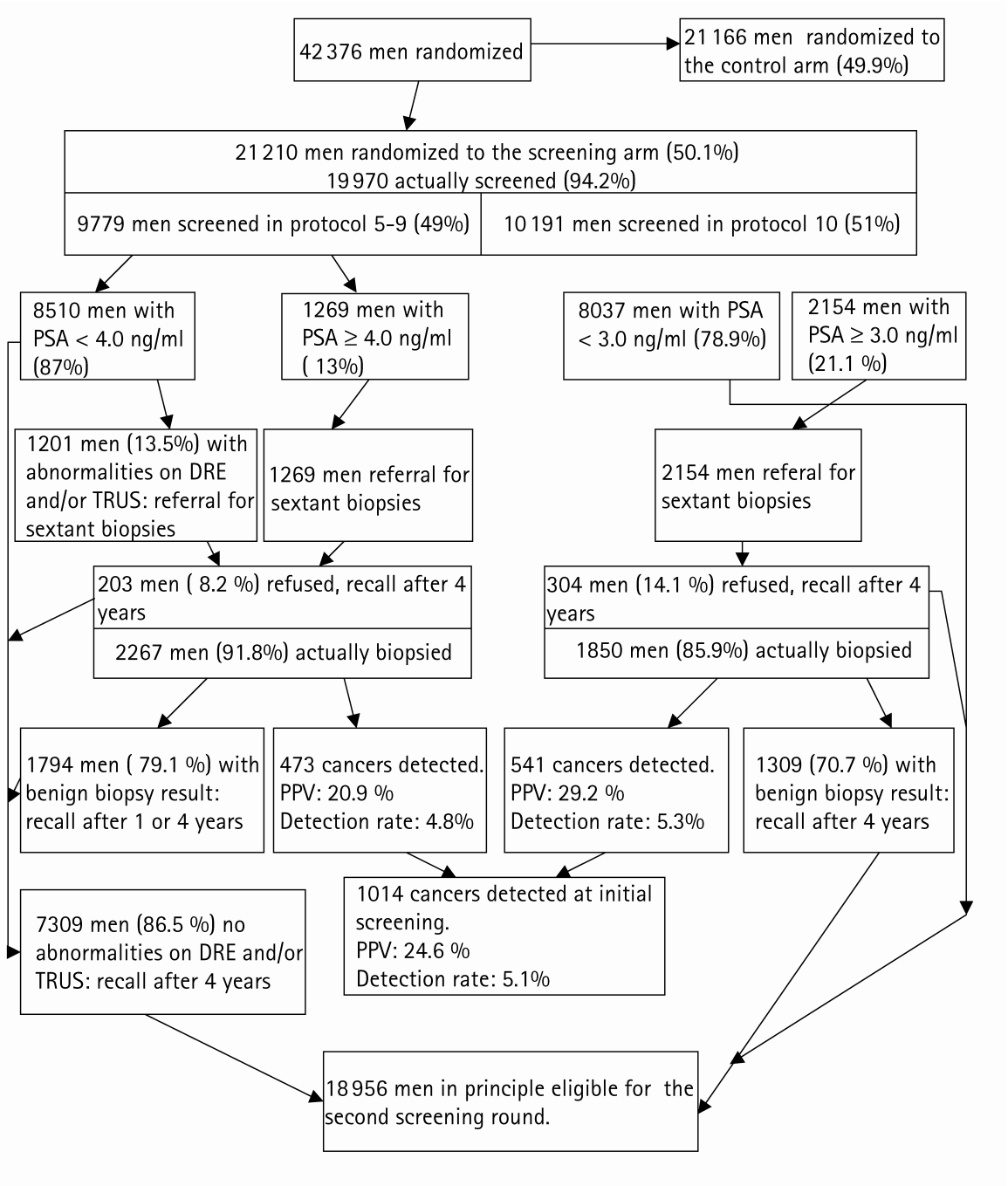

Fig. 2: *Results of the initial screening round ERSPC, Rotterdam section, from November 1993 (pilot 5) through December 1999 (protocol 10). Numbers are not definite.*

Recruitment and randomization lasted until December 1999. Fig 2 shows the final data (number randomized, actually screened, biopsied and cancers detected) of protocols 5 – 10. These data became part of the central data set administered at the central database of ERSPC in Edinburgh (from July 2003, London).

3. The second screening round.

For the second screening round we address three important questions: what will be the compliance and the detection rate at the subsequent screening round and what has happened during the chosen 4-year interval with regard to interval cancers?
In December 1997 the second screening round started (according to protocol 10) for men initially screened in protocol 5 – 10. Until December 2002, 14695 men were eligible for a second screening visit. Men who had reached the age of 75 years or died within the 4-year interval (2455men, 16.7 %) were not invited for re-screening. This resulted in 12240 men who were actually invited. 9920 responded to the invitation and were invited for blood sampling. The response in the second screening round so far is thus high, at 81.0 %.
The main reasons for non-response were bad health (5.4%), moving out of the region (5.8 %) and unknown in 7.8 % of the men invited. Figure 3 shows preliminary results (number of men screened, number of men biopsied and cancers detected) in the second screening round.

Through linkage with the Cancer Registry (fig 1) and active medical record follow-up the Dutch centre is also able to assess the number and characteristics of the clinically diagnosed cancers found elsewhere in the population randomized.
The number of these “interval cancers” gives an indication on the effectiveness of the screening tests used and of the correctness of the chosen screening interval. At present the definitions of interval cancers are being established and data on interval cases obtained through linkage with the Cancer Registry are being evaluated. Although data on the complete 4-year interval were not yet available the available data show a very low number of interval cancers [21].

Through linkage, not only the number interval cancers can be assessed, but also the number of clinically detected cancers in the control arm during the screening period. Comparing the tumor characteristics of screen-detected and a clinically detected cancer is an important intermediate endpoint of the ERSPC. Results show a favorable prognostic shift for the screen-detected cancers [22].

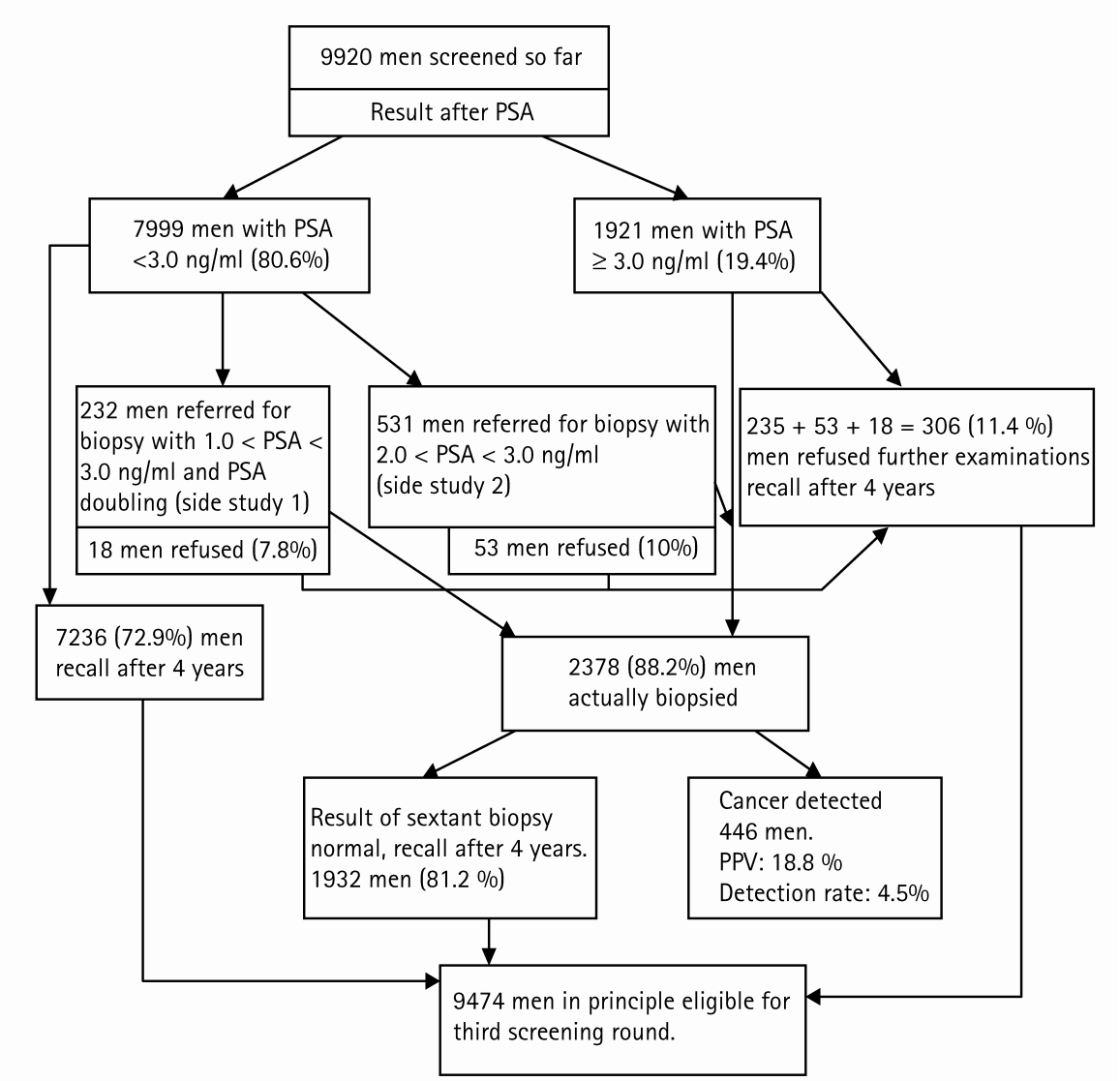

Fig. 3: Preliminary results of the second screening round ERSPC, Rotterdam section, from November 1997 through December 2002. Numbers are not definite.

Using a second screening round also enables the validation of more predictors of biopsy outcome, e.g. PSA velocity, defined as the difference between the PSA value at initial screening and the PSA value at subsequent screening divided by the number of interval years, and new serum markers such as pro-PSA and hK2. Data from the initial screening round already showed that a considerable proportion of the cancers that can be detected by screening are in men with low PSA levels [23] and that a part of these cancers have potentially aggressive characteristics, are organ confined, and thus suitable for treatment. As mentioned above DRE and TRUS were not very efficient as screening tools in these low PSA ranges. In order to investigate the possibilities for effective screening at low PSA ranges, two side studies were initiated during the second screening round.

The first side study (fig 3, side study 1) ordered after review of our protocol by one of the review committees, was set up in order to evaluate the value of PSA velocity as a predictor for biopsy outcome at low PSA levels. During the

period December 1997 and April 2001 men with a PSA level of 1.0 - 3.0 ng/ml and a doubling of their PSA level within the 4-year interval were also biopsied. In this side study 214 men were biopsied and 34 cancers were detected. The final evaluation of this study is in detail in chapter 5 [24].

The second side study (fig 3, side study 2) focused on the value of free-PSA and hK2 as predictor of biopsy outcome at low PSA levels (2.0 – 4.0 ng/ml). However, a more important goal of this study is however not only to establish their value as predictor for biopsy outcome but also their value as predictors of the aggressiveness of screen detected-tumours. This side- study lasted from April 2001 until October 2002. In the PSA range 2.0 – 4.0 ng/ml 734, men were biopsied and serum free-PSA and hK2 were determined. Together with the data of the radical prostatectomy specimen of the cancers detected the value of free-PSA and hK2 as screening tests was determined [25].

Another point of interest at a subsequent screening round are those men with a negative biopsy result at initial screening and a biopsy indication, based on an elevated PSA level, at the second screening round. As the PSA level is also strongly related with BPH, it is possible that men with persistently elevated PSA levels will be biopsied at every screening round. The cancer detection rate, PPV and tumor characteristics of cancers detected in men with elevated PSA levels biopsied at the second screening round were assessed with a further evaluation of predictors for biopsy outcome in this particular group of men, chapter 7 [26].

The second screening round will last to December 2003. Further evaluation of the screening regimen and characteristics of the cancers detected are the subjects of constant attention within the Dutch center of ERSPC. In the mean time a third screening round is also initiated which will last to December 2007.

Conclusion.

Setting up a prostate cancer screening study of the projected magnitude is feasible in Rotterdam. International cooperation was established and a central database containing all data of ERSPC set up. The recruitment rate is acceptable and the screening tests used well tolerated. Data of this study have so far led to at least 93 scientific publications from the Dutch center and app. 175 scientific publications from all ERSPC centers together. This study will certainly be of great value in determining whether prostate cancer screening should be part of general health care.

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Part II

4.0 Prostate-specific antigen-based early detection of prostate cancer-validation of screening without rectal examination.

5.0 Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of the second screening round of ERSPC (Rotterdam).

6.0 Is additional testing necessary in men with PSA levels <= 1.0 ng/ml in a population based screening setting? (ERSPC, Rotterdam)

7.0 No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/ml or greater (ERSPC, Rotterdam).

8.0 A comparison of first and repeat (4 years later) prostate cancer screening in a randomized cohort of a-symptomatic men aged 55-75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC-Rotterdam).

9.0 Rotterdam randomized pilot studies of screening for prostate cancer — an overview after 10 years.

4.0

Prostate-specific antigen-based early detection of prostate cancer-validation of screening without rectal examination.

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Abstract:

Objectives.
The evaluation of the screening procedures for prostate cancer (Pca) was a part of the protocol of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, The Netherlands. We sought to establish an improved strategy for the early detection of Pca using a prostate specific antigen (PSA) cut off of 3.0 ng/mL or greater as the only indication for prostate biopsy with omission of the digital rectal examination (DRE).
Methods.
In June 1996, 8612 men, 55 to 74 years old, were randomized to screening and were screened within the ERSPC Rotterdam by a PSA level of 4.0 ng/mL or greater or positive DRE or transrectal ultrasound findings as the indication for biopsy. Four hundred thirty men had Pca. Those treated by radical prostatectomy provided the tumor characteristics considered essential for a change in the screening strategies. Various options were evaluated and predictions made by logistic regression analyses. The protocol change was implemented in May 1997. Another 7943 men were screened according to the new protocol (PSA 3.0 ng/mL or greater). The resulting data were used to compare the two protocols.
Results.
The detection rate (proportion of Pca in those screened) turned out to be very similar, with rates of 5.0 and 4.7 at a PSA cut off of 4.0 ng/mL or greater and 3.0 ng/mL or greater, respectively. This was due to a much larger number of cases of Pca per biopsy in the PSA range of 3.0 to 3.9 ng/mL than expected. The positive predictive value of the PSA range 3.0 to 3.9 ng/mL in the two protocols was 6.4 % and 18.0%, respectively. Tumor characteristics were studied on radical prostatectomy specimens from the original protocol. Pca detected with the new screening regimen had a similar distribution of Gleason scores but a larger proportion of confined disease. Tumor volumes were smaller in patients with PSA levels of less than 2.9 ng/mL; the proportion of “minimal disease” in that group was 50% compared with 28% in the group with a PSA level between 3.0 and 3.9 ng/mL.
Conclusions.
Lowering the biopsy indication to a PSA cut off of 3.0 ng/mL or greater without a DRE improved the positive predictive value from 18.2% to 24.3%. The number of biopsies necessary to detect 1 case of Pca accordingly changed from 5.2 to 3.4. The overall characteristics of the cases detected at that PSA cut off differed very little from those detected with the regimen based on PSA, DRE, and transrectal ultrasound.

Introduction.

Screening for prostate cancer (Pca) is controversial at this time because it has not been shown to decrease Pca mortality. Regimens for early detection have been widely applied in large studies, such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) and in screening on request (opportunistic screening).
Optimization of the screening tests is warranted. More definite screening regimens for Pca can only be identified after completion of randomized studies as the algorithm that maximizes potential advantages in Pca mortality or overall survival. Unfortunately, such data are not yet known. However, the application of screening regimens within large scale studies and with screening by request in urologic practices warrants a preliminary optimization of the available strategies. Within the ERSPC, section Rotterdam, we evaluated the PSA cut off level of 4.0 ng/mL or greater and positive digital rectal examination (DRE) and/or transrectal ultrasound (TRUS) findings as an indication for biopsy according to protocol since June 1, 1994. The first evaluation showed that 4 of 5 men underwent an unnecessary biopsy. This rate was in part due to the very low positive predictive value (PPV) of only 2% in the PSA range 0 to 0.9 ng/mL and led to a change in the protocol in 1996, the details of which were reported by Beemsterboer *et al.*[1] Modification of the screening procedure according to PSA level had already been suggested in 1992 by Labrie *et al.* [2] to maximize the relative sensitivity and specificity of the screening procedure. Within the European study, the Swedish group has used a PSA cutoff of greater than 3.0 ng/mL as the only screening parameter since December 1994.[3] The European study group did not accept this procedure as general policy because the impact on the detection rates, PPV, and tumor characteristics was not known at that time; however, they have recently been described for data resulting from the ERSPC. [4,5] The parameters of aggressiveness, especially tumor volume, and the proportion of potentially non-aggressive (minimal) disease correlated with the PSA values. A major change in the screening regimen was implemented in May 1997 on the basis of the results of the logistic regression estimates performed in June 1996. [1,5] Here, we report the results of a prospective validation study of the effects of the change in the protocol. Important lessons for clinical routine can be learned with respect to the use of the DRE and the biopsy indications in men with low PSA values who undergo screening on request in urologic practice.

Material and Methods.

THE ERSPC

The ERSPC is a large randomized screening study conducted in seven European countries (Belgium, Finland, Italy, The Netherlands, Portugal, Spain, and Sweden) since 1994 and has a close association with the Pca arm of the Prostate, Lung, Colon, and Ovary Screening Study of the National Cancer Institute of the United States.[6] The ERSPC aims to show or exclude a difference in Pca mortality between screening and control arms of 20% with

a power of 90%. To achieve this, 191,000 men will have to be randomized to screening versus control and followed up for 10 years. This sample size accommodates a contamination rate by opportunistic screening of 10%. By March 2000, more than 180,000 men had been randomized in Europe. Within the ERSPC, re-screening intervals of 2 and 4 years are used. A central database and an effective committee structure have been established. The ERSPC is supervised by an independent Data Monitoring Committee. The individual national contributions are approved by the respective ethical committees and national rules for population based screening studies are applied. Other recent reports related to the ERSPC give more details on the method and background. [4-9]

ERSPC ROTTERDAM

The screening procedure and the numbers of participants are detailed in Figure 1. Men 55 to 74 years old were identified in the population registry and invited to participate. After receipt of full written informed consent, the men were randomized to the screening group or control group. After a number of pilot studies,[7] the ERSPC Rotterdam started in June 1994.

An evaluation of the screening tests was part of the Rotterdam protocol and, on the basis of the data produced and reported here, the European study group decided in February 1997 to screen using PSA determination only and to biopsy all men with PSA values of 3.0 ng/mL or greater. This group decision was based on the results obtained after screening 8612 men for whom the biopsy indication was a PSA value greater than 4.0 ng/mL and positive DRE and/or TRUS findings and the results of estimates based on logistic regression analysis of the numbers of Pca detectable in men with PSA values of 3.0 to 3.9 ng/mL.[1,5]

All participants were screened only once and for the first time (prevalence screen). The evaluation also included the results of a detailed study of the histopathologic features determined from radical prostatectomy specimens, which allowed an estimate of the aggressiveness of the cases of Pca missed with the change of protocol and those detected with the change in the biopsy indication.[4] In the text and Figure 1, protocols 5 to 9 and protocol 10 are referred to as “PSA 4.0 ng/mL or greater” and “PSA 3.0 ng/mL or greater” or the “old” and “new” protocols, respectively.
The prospective validation of the change in the biopsy indication is based on the population of 8726 men randomized to screening after May 1997.

Men age 55-74

↓

Letter of invitation (N = 77,182)

↓

Written informed consent (38,297, 49.6%)

↓

Randomization

↓

	Screening		Control
Protocol	5-9* ("OLD")	10** ("NEW")	5-10
A. Randomized N	10,450	8,726	19,121
B. Screened N (%)	9,776 (93.6)	7,943 (91.0)	Follow-up through
C. Cancers N (% of B)	474 (4.9)	377 (4.7)	Cancer Registry

* Biopsy if PSA ≥ 4.0 ng/ml or DRE and/or TRUS suspicious

** Biopsy if PSA ≥ 3.0 ng/ml

Median ages in the "old" and "new" protocols are 63.17 and 63.20 years respectively

Fig 1: Consort diagram of ERSPC Rotterdam old protocol (biopsy indication PSA 4.0 ng/mL or greater and/or abnormal DRE and/or TRUS findings) (June 1994 to January 1997) and the new protocol (biopsy indication PSA 3.0 ng/mL or greater) (May 1997 to May 1999).

The numbers and proportions of biopsy indications, biopsies performed, and Pca cases found overall, as well as in the relevant PSA ranges, were compared between the original protocol (PSA 4.0 ng/mL or greater) and the new protocol (PSA-driven biopsy indication with a PSA cutoff of 3.0 ng/mL or greater) and the a priori prevalence assessment (APPA) estimates made in June 1996. Lateral sextant biopsies were carried out in diverting from the original recommendation of Stamey [9] and in line with the later recommendations of Eskew *et al.*[10] A seventh biopsy was taken of visible (hypoechogenic) lesions. Some of the data are inconsistent because of two factors: (a) the omission of DRE and TRUS in January 1996 in men with a PSA level of less than 1.0 ng/mL because an interim evaluation revealed that in 1702 screened men, 183 biopsies were necessary to find four tumors,[11,12] and (b) a delay in putting into effect the protocol change from June 1996 to February 1997, affecting the statistics on the characteristics, and small errors in group assignment.

PATHOLOGIC FINDINGS

The evaluation of the histopathologic parameters included the number of positive biopsies, location of the positive biopsies, proportion of individual cores with Pca, grade of differentiation, tumor volume determined in radical prostatectomy specimens, Gleason grade of the radical prostatectomy specimens, determination of positive margins, and other parameters according to a previously agreed protocol. These procedures and an arbitrary classification model that considers PSA, radical retropubic prostatectomy-based Gleason score, and tumor volume to assign the categories of minimal, moderate, and advanced disease are described in greater detail by Hoedemaeker *et al.*[11] Tumor volume was determined in 4-mm step sections and by morphometry.

STATISTICAL ANALYSIS

The number of Pca cases per biopsy found in the original protocol were compared with the number of Pca cases per biopsy detected in the new protocol, in which a biopsy was indicated irrespective of the DRE and TRUS findings (ie, PSA 3 ng/mL or greater). The calculation of the *P* values was based on the comparison of the proportions of independent samples. Fisher's exact test was used in the comparisons. The results and method of the logistic regression analysis are described elsewhere [5].

Results.

The evaluation leading to the major protocol change of using a PSA cut off of 3.0 ng/mL or greater as the indication for biopsy was performed on the basis of the results of the logistic regression estimates in June 1996. After this, the old protocol continued to be active until a group consensus could be reached in November 1996 and until the necessary administrative steps were taken to change the protocol and obtain approval from the ethical committees. In this report, the data obtained in June 1996 are presented in Table I (8612 men were screened and 430 Pca cases found). The data on the tumor characteristics (Table II) were updated to the situation in February 1997 when a total of 474 Pca cases had been detected in 10,450 men randomized to screening. Figure 1 reveals a loss of participants in the screening arms after randomization. In the original protocol and in the new protocol, 6.4% and 9%, respectively, of randomized men did not undergo screening for various reasons (see the following section).

Table I presents a comparison of the results of the biopsies in the original and the validation sample (new protocol). In June 1996, 8612 men had been screened; 7.5% had a PSA level between 3 and 3.9 ng/mL and 21.1% had a PSA value of 3.0 ng/mL or greater. A total of 430 Pca cases were found, compatible with a detection rate of 5.0%. Of these, 41 were diagnosed by DRE and/or TRUS in the PSA range of 3 to 3.9 ng/mL (6.4% of all cases). The validation sample consisted of 7943 men screened between May 1997 and May 1999. Of these, 1552 men (19.5%) had a PSA level of 3.0 ng/mL or greater and should have undergone biopsy; 250 of these men (16.1%) did not undergo biopsy. The detection rate was 4.7%, similar to that for the original protocol (5.0%). The rate of Pca detection with a PSA cut off of 3.0 ng/mL or greater per number of indicated biopsies was 24.3% as opposed to 18.2% with a PSA cut off of 4.0 ng/mL or greater (old protocol) (Table I) and a

detection rate of 29.0% in those who in fact underwent biopsy compared with 19.1% at a PSA cut off of 4.0 ng/mL or greater (Table I).

In Table II, the characteristics of the 166 cases of Pca detected by biopsy in men with a PSA value of 4.0 ng/mL or greater or positive DRE and/or TRUS findings are described. The cases of Pca with a PSA between 3.0 and 3.9 ng/mL were detected by DRE and TRUS. In the original screening protocol, the rate was only 9.2% of all Pca cases; in the new protocol, to date 25.5% of all Pca cases detected were found in this PSA range.

	DRE or TRUS + PSA ≥4.0 ng/mL (June 1994 to June 1996) (Original Protocol)	PSA ≥3.0 ng/mL (May 1997 to May 1999) (Validation or New Protocol)	*P* Value*
A. Screened (n)	8612	7943	
B. DRE + TRUS performed			
Total (n)	8612	1302	
Percentage	100	16.4 (15.6–17.2)	<0.001
C. PSA 3–3.9 ng/mL			
Total (n)	642	534	
Percentage	7.5 (6.9–8.0)	6.7 (6.2–7.3)	0.07
D. Biopsies PSA 3–3.9 ng/mL			
Total (n)	160	446	
Done (percentage of A)	1.8 (1.6–2.2)	5.6 (5.1–6.1)	<0.001
E. Biopsies indicated (all)			
Total† (n)	2365	1552	
Percentage of A	27.4 (26.5–28.4)	19.5 (18.7–20.4)	<0.001
F. Biopsies done			
Total† (n)	2250	1302	
Percentage of A	26.1 (25.1–22.6)	16.4 (15.6–17.2)	<0.001
G. PCa found, PSA 3–3.9 ng/mL			
Total (n)	41	96	
Percentage of C	6.4 (4.6–8.6)	18.0 (14.8–21.5)	0.32
H. PCa			
Total† (n)	430	377	
Percentage of A = detection rate	5.0 (4.5–5.5)	4.7 (4.3–5.2)	0.47
I. PPV			
H/E (%)	18.2 (16.6–19.8)	24.3 (22.2–26.5)	<0.001
K. PCa/biopsy			
H/F (%)	19.1 (17.5–20.8)	29.0 (26.5–31.5)	<0.001
L. False-positive biopsy indication			
(F−H)/H (%)	80.9 (79.2–82.5)	71.0 (68.5–73.5)	0.001

Key: PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound; PCa = prostate cancer.

Numbers in parentheses are the 95% confidence intervals.
*Fishers exact test
† By extrapolation from 183 men who underwent biopsy with a PSA level of 0.0 – 0.9 ng/ml, to 3045 men in the same PSA range without DRE/TRUS, 5 cases of Pca and 327 biopsies were added.

Table I: Biopsy indications and cancer detection with PSA, DRE, and TRUS (n= 8612) vs. PSA-driven screening (biopsy with PSA >3.0 ng/mL) without DRE or TRUS (n = 7943)

The PPVs of the DRE and TRUS findings are about equal.[4] The histologic features of the radical prostatectomy specimens from the new protocol will be reported elsewhere.
In both protocols, the proportion of Stage cT2 or lower tumors was rather similar at approximately 80%. The proportion of moderately differentiated Pca did not vary very much between the different PSA ranges but was lower for a PSA level less than 3.0 ng/ml.
Poorly differentiated disease with Gleason score 8–10 only occurred in men with PSA values greater than 4.0 ng/mL. The tumor volumes were low and the proportion of minimal disease was high in those cases of Pca detected at a

low PSA. Relatively large proportions of advanced disease were present in all subgroups. With PSA-based screening and a biopsy cut off of 3.0 ng/mL or greater, 13% minimal disease and 28% of cases beyond the reach of cure were seen (on the basis of DRE/TRUS-detected tumors and their characteristics).

	Biopsy Indications (DRE and/or TRUS Positive)			
Characteristics	All Cancers	PSA ≤2.9 ng/mL (n)	PSA 3–3.9 ng/mL (n)	PSA ≥3.0 ng/mL (n)
PCa detected	474 (100)	79 (16.7)	44 (9.3)	395 (83.3)
RRP	166 (35.0)	32 (40.5)	18 (40.5)	134 (33.9)
Gleason score				
2–4 (pG1)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.7)
5–6 (pG2)	50 (43.1)	17 (53.1)	9 (50.0)	59 (44.0)
7 (pG2)	60 (51.7)	15 (46.9)	9 (50.0)	69 (51.5)
8–10 (pG3)	5 (4.3)	0 (0.0)	0 (0.0)	5 (3.7)
pT ≤2	102 (61.4)	26 (81.3)	16 (88.9)	76 (56.7)
Tumor volume (mL)				
<0.2	11 (9.5)	11 (34.4)	3 (16.7)	14 (10.4)
0.2–0.49	17 (14.7)	13 (40.6)	6 (33.3)	23 (17.2)
≥0.5	88 (75.9)	8 (25.0)	9 (50.0)	97 (72.4)
Minimal disease	34 20.5	16 50.0	5 27.8	18 13.4
Moderate disease	88 53.0	10 31.2	12 66.7	78 58.2
Advanced disease	44 26.5	6 18.8	1 5.5	38 28.4

KEY: Abbreviations as in Table I.
Numbers in parentheses are percentages.
In the new protocol (PSA cutoff ≥3.0 ng/mL), PCa detection was 96 (25.5%) of 377 cases of PCa; in the original protocol, this rate was 26.6% for cases in the PSA range of 0–3.9 ng/mL.

Numbers in parentheses are percentages

Table II: Characterization of 166 cases detected by biopsy in men with >4.0 ng/mL PSA or positive DRE and/or TRUS (June 1994 to January 1997) treated by radical prostatectomy

In Table III, the proportion of biopsy indications, biopsies done, and cases found within the two different protocols are directly compared. It is evident that with the new protocol (PSA of 3.0 ng/mL or greater), more men failed to undergo biopsy than in the old one, which included the DRE and TRUS findings. Overall, 16.1% of men in the new protocol failed to accept the biopsy recommendation. The failure to undergo biopsy was about equally distributed among the PSA ranges indicated in Table III. The percentage of Pca detected in men with PSA values greater than 4 ng/mL in relation to the number of men screened (detection rate) was about equal in both protocols (27.7% versus 27.6%). This comparison obviously could not take into account the 250 men who failed to undergo biopsy in the new protocol when a biopsy was indicated. Their inclusion would increase the detection rate further to about 32%.

Original Protocol				
PSA (ng/mL)	Screened (n) A*	Biopsy Indicated (n) B (B/A)*	Biopsy Done (n) C (C/B)*	PCa Detection Rate (n) D (D/A)*
<1.0	3556	509† (14.3)	376‡ (73.9)	9‡ (0.3)
1–1.9	3051	556 (18.2)	511 (91.9)	45 (1.5)
2–2.9	1199	238 (19.8)	221 (92.9)	30 (2.5)
3–3.9	701	182 (26.0)	174 (95.6)	44 (6.3)
≥4.0	1269	1269 (100)	1176 (92.7)	351 (27.7)
Total	9776	2754 (28.2)	2458 (89.3)	479† (4.9)

New Protocol				
PSA (ng/mL)	Screened (N) E*	Biopsy Indicated (n) F (F/E)*	Biopsy Done (n) G (G/F)*	PCa Detection Rate (n) H (H/E)*
<1.0	2843	—	1	—
1–1.9	2500	—	—	—
2–2.9	1048	—	—	—
3–3.9	534	534	446 (83.5)	96 (18.0)
≥4.0	1018	1018	855 (84.0)	281 (27.6)
Total	7943	1552 (19.5)	1302 (83.9)	377 (4.7)

Numbers in parentheses are percentages.
* See table 1 for explination
‡ Extra polated from 244 biopsy indications in 1702 men.
† Extra polated from 180 biopsies in 1702 men with 4 cases of PCh, resulting in 376 biopsies and 9 cases of Pca

Table III: Biopsies and Pca detection per PSA range in the original protocol and new protocol.

Discussion.

In several ways, it was premature to write this report. A conclusive evaluation of the value of the screening tests for Pca will only be possible after the conclusion of randomized screening studies in which a difference in Pca mortality is shown. Meanwhile, the problem remains that the sensitivity of the tests cannot be calculated because the underlying prevalence remains unknown and a proper definition is missing. Eventually, the screening procedure will have to be adjusted to the appropriate “window of opportunity,” the type of cancer that can be associated with an effect on Pca mortality. This will lead to identification and eventually to a reduction of what might be called “overdiagnosis” in terms of identifying Pca that for whatever reason does not pose a threat to the life of the patient and avoiding treatment or, preferably, diagnosis. Still, since screening algorithms are used in opportunistic screening that occurs on a large scale in current clinical practice and in large case-finding and randomized screening studies, it is appropriate to use current knowledge, especially with respect to the prognostic factors, to streamline the screening procedure in such a way that unnecessary biopsies and unnecessary treatment are avoided through the screening procedure itself.

Prediction by a priori prevalence assessment

Logistic regression analysis was used to predict the number of tumors that would have been found if every participant in each of the PSA ranges had undergone biopsy. The methodologic details and results of this exercise have been described elsewhere. [1,5]

This resulted in the estimate of what might be called “study sensitivity,” the proportion of Pca per total number of participants that would have been found if every participant had undergone a sextant biopsy.
This would have resulted in a detection rate of 7.2% in the original as opposed to the empirically found 4.9%, indicating that, overall, 31% of Pca was missed by the current procedures. This figure was found to amount to more than 60% in men presenting with PSA values of 0 to 4.0 ng/mL.[5,7] The results were used to change the screening procedure within the ERSPC after a comparative evaluation was performed together with the Swedish study group who performed biopsies without prior knowledge of the tumor characteristics in every man presenting with a PSA level greater than 3.0 ng/mL. The results were confirmatory [5].

Validation
In the present report, a prospective validation of screening with PSA only (biopsy with PSA of 3.0 ng/mL or greater) without DRE (new protocol) was carried out by using a sample of 7943 screened men in whom 1302 biopsies detected 377 tumors. The relevant data with respect to biopsy indications, biopsies performed, Pca found, and derived parameters are given in Tables I and III. The validation study found similar detection rates and a more favorable PPV for screening with PSA alone at a cut off value of 3.0 ng/mL or greater. It is obvious from Table I that avoidance of DRE and TRUS in 78.9% of participants can be considered a great potential advantage of the new protocol in terms of cost and invasiveness. It turned out, however, that in the validation study of the 1552 men with a PSA value of 3.0 ng/mL or greater and thus a biopsy indication, only 1302 men underwent biopsy. The proportion of men not undergoing a biopsy for various reasons in the old protocol was only 10.7% compared with 16.1% in the new protocol (Table III). The reasons include a delay in biopsy processing in the new protocol before the cutoff date of this evaluation. However, other factors such as direct contact with a urologist at the time of the DRE may play a role, which did not occur in the validation (new) protocol. As Table I indicates, the proportion of Pca found in the range of PSA 3 to 3.9 ng/mL was very high. The proportion of Pca found in this range was 6.4% with the old protocol and 18.0% with the validation study (Table I). If all 534 men in the new protocol with a PSA value between 3 and 3.9 ng/mL had undergone biopsy (instead of the 446 men who did), the number of tumors detected would have been 115 (instead of 96) (Table III). This would have led to a detection rate (or PPV) in this PSA range of 21.5% (instead of 18.0%). This unexpected high detection rate (and PPV) overcompensates for the loss of Pca cases by not doing a DRE and TRUS with PSA values between 1 and 2.9 ng/mL, as shown in Table III. No other confounding factors, such as age, regional variation in incidence, or changes in biopsy procedures, can be identified to explain this difference. It is evident from Figure 1 that another group of men drop out of the study after randomization, those who were randomized but did not show up for screening (6.4% in the old protocol and 9% in the new protocol). Also, this group was not taken into account in the 1996 estimates. This dropout rate may be less important in daily practice, since it may be assumed that men who present for opportunistic screening will usually undergo all the necessary procedures.

Tumor characteristics

A complete comparison of the characteristics of the biopsies in terms of the numbers of cores involved, the proportion of all cores involved, and the Gleason scores was performed between the old and new protocols (Table II). It was, however, elected to present these data together with the characterization of the radical prostatectomy specimens done within the new protocol in a separate report. The attempt to characterize Pca, Pca expected to be missed by omitting DRE and TRUS at a PSA level of less than 2.9 ng/mL, Pca expected to be found in the PSA range of 3 to 3.9 ng/mL, and Pca expected to be found using the new protocol by biopsying everyone with a PSA level of 3.0 ng/mL or greater is entirely based on the findings related to 166 radical prostatectomies performed within the old protocol (PSA of 4.0 ng/mL or greater). These data have previously been used to evaluate the efficacy of DRE [4] and to evaluate the characteristics of Pca detected at low PSA ranges.[12] In the latter report, the characteristics of DRE findings positive and negative for tumors were also compared. The figures on the DRE findings in the validation study were not reported; these were biased by knowledge of the PSA at the time of the DRE. A number of investigators [12,13–18] have dealt with this issue in previous publications. Agreement has been reached on the following: screen detected Pca, even in the low PSA ranges, is most frequently moderately differentiated (Gleason score 5–7), 20% to 30% of non palpable tumors are classified as minimal according to criteria by Hoedemaeker [11] adapted from those described by Epstein *et al.*, [13] and the proportion of Pca that has a volume of less than 0.02 mL and may be compatible with the frequently found autopsy tumors is very low. The only report giving detailed information on the characteristics of Pca detected in the PSA range of 3 to 4 ng/mL comes from the ERSPC, section Göteborg, Sweden. [3] That group found that 32 (23.4%) of 137 tumors detected by sextant biopsy taken because of PSA values of 3.0 ng/mL or greater in men, 50 to 65 years old, fell into the PSA range of 3 to 3.9 ng/mL. The detection rate in total during the first round of screening was 137 (2.3%) of 5859 men, 50 to 65 years old, who agreed to undergo screening. Fourteen of these men underwent radical prostatectomy. Eight (57%) of these 14 men had histologically organ-confined disease (Stage pT2 or lower). Of the 14 tumors, 13 were classified as Gleason score 5–7 and 3 as Gleason score 7.3 As one would expect, the proportion of histologically organ-confined tumors was slightly lower in men with PSA values of 3.0 ng/mL or greater than in the original protocol, which included all cases found with low PSA values (0.0 to 2.9 ng/mL). The proportion of minimal disease was 13.4% in Pca detected at a PSA level of 3.0 ng/mL or greater; the proportion of minimal disease was 50% in Pca found at a PSA level of 0 to 2.9 ng/mL. With the new regimen, 79 (16.7%) of 447 cancers would have been missed, as estimated by the logistic regression model. [5] One half of these cases were classified as either moderate or advanced disease. The uncertainty concerning the possible impact of these cases on the improvement of Pca mortality in this randomized study represents a considerable risk taken by the study group. We acknowledge that the number of biopsies needed to detect one case of Pca may be influenced by other (time-dependent) factors. Such influences cannot be evaluated within the existing database. “Contamination” by opportunistic screening has increased only slightly, from about 9% to about 13%.[19]

Comparison of biopsy indications and biobsy outcome between original and new protocols

Table III gives a comparison of the biopsy indications, biopsies that were done, and Pca detection per PSA range in the original and new protocols. Table III shows that in all PSA ranges and in both protocols, some men did not follow the advice to have a biopsy. This proportion was highest in men with PSA values less than 1.0 ng/mL in the original protocol. This is understandable, since the outcome of screening is known to the participants who often consult with their family physician for further advice. The low prevalence of biopsy-detectable Pca in this PSA range is general knowledge and is documented in Table III. The proportion of men who for some reason did not undergo an indicated biopsy, however, was much larger if screening by PSA only was used. In that case, numbers did not relate to the PSA levels and remain unexplained. Table III also shows that the large differences seen using the PSA cutoff of 3.0 ng/mL or greater for screening with respect to the detection rate, PPV, false-positive rate of biopsy indications, and proportion of biopsies per Pca detected were not due to men with PSA values of 4.0 ng/mL or greater.

Conclusions.

The data presented illustrate the effect of a major change in the screening procedures within the ERSPC. The data establish the value of a PSA cutoff of 3.0 ng/mL or greater as an indicator for biopsy in the early detection of Pca. The PPV and false-positive biopsy rates improved significantly at equal detection rates compared with the previously used standard regimens. However, 75 (16.0%) of 470 cancers were missed in the PSA range of 1.0 to 2.9. A comparison of tumor characteristics revealed that the proposed regimen avoids many of the cases classified as “minimal” that are found with lower PSA values. The avoidance of DRE and TRUS in about 80% of cases is advantageous for population- based screening but not to the same degree for clinical practice, where a DRE is often done before knowing the PSA value and not for the sole purpose of diagnosing Pca. The results of this study demonstrated that the characteristics of Pca with PSA values between 3.0 and 3.9 ng/mL may be expected to be similar to those of standard regimens. The need to diagnose Pca at PSA values of less than 3.0 ng/mL is debatable. The improvement of the screening procedure by the addition of other parameters is especially desirable in the PSA range of 2 to 2.9 ng/mL. On the basis of this validation study, the decision to change the screening regimen within the ERSPC to performing biopsies in all men with PSA values of 3.0 ng/mL or greater is considered justified.

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5.0

Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: results of the second screening round of ERSPC (Rotterdam).

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Abstract.

Objectives.
To study retrospectively whether the prostate-specific antigen (PSA) velocity, that is, the change in PSA level over time, might serve as a screening tool in this PSA range. It is estimated that 40% of detectable prostate cancers are present in men with a PSA level of 4.0 ng/mL or less. Digital rectal examination and/or transrectal ultrasonography have been used as screening tools at these low PSA levels, but this approach is not very efficient.
Methods.
The possible predictors (including PSA velocity) for biopsy outcome were studied using univariate and multivariate logistic regression analysis in 774 men who underwent biopsy between November 1997 and January 2002 in the second screening round of the European Randomised Study of Screening for Prostate Cancer (ERSPC). The clinical stage of the tumors was determined, and the Gleason scores of the biopsies were studied.
Results.
A total of 149 cancers were found (positive predictive value 19.2%). The odds ratio for the PSA velocity determined by univariate logistic regression analysis was 2.2 (95% confidence interval 0.7 to 6.9, P = 0.19) and was 0.73 (95% confidence interval 0.20 to 2.6, P = 0.64) by multivariate analysis. The distribution of the clinical stage of the detected tumors was 64.4% T1c, 32.2% T2, and 3.4% T3. The biopsy Gleason score was 6 in 84.5%, 7 in 14.2%, and 8 in 1.3%.
Conclusions.
The number of cancers detected in this study and the distribution of clinical stage and biopsy Gleason score confirmed that a relatively large proportion of potentially curable cancers can be found in the low PSA ranges. The PSA velocity did not appear to be a useful screening tool for the identification of these cancers.

Introduction.

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in Western Europe and the United States.[1,2] Most prostate cancer is found in men with a prostate-specific antigen (PSA) level greater than 4.0 ng/ mL. It has been estimated, however, that roughly 40% of all detectable cancers are in men with a low PSA level (less than 4.0 ng/mL).[3] A considerable proportion of these cancers have potentially aggressive characteristics and are organ confined and thus suitable for treatment. Digital rectal examination (DRE) and/or transrectal ultrasonography (TRUS) may be used as screening tools at these low PSA levels; however, this approach is not very efficient.[4–6] For example, at the initial screening visit of the European Randomised Study of Screening for Prostate Cancer (ERSPC), Section Rotterdam, in the PSA range between 1.0 and 4.0 ng/mL, 102 cancers were detected in 822 biopsies indicated on the basis of suspicious DRE and/or TRUS findings in 4398 men. A logistic regression model using PSA level and prostate volume, in addition to DRE and TRUS findings as predictors for biopsy outcome, estimated that 254 cancers would have been found if all 4398 men had undergone biopsy (39.6% of all those detectable by sextant biopsy).[7] It has been recently suggested that the rate of change of PSA (PSA velocity) may be of use to detect prostate cancer more efficiently at low PSA values.[8] Using data from the ERSPC, we retrospectively studied this hypothesis.

Material and methods.

Between November 1997 and January 1, 2002, 1681 of 7570 men underwent biopsy in the second screening round of the ERSPC, 4 years after the initial screening visit. The ERSPC was approved by the institutional review board of the Erasmus Medical Centre and by a national board (required by Dutch law for population screening studies). All participants provided written informed consent. Of the 1681 men who underwent biopsy, 894 (53%) had a PSA level of less than 4.0 ng/mL. Of these 894 men, 777 (87%) did not undergo biopsy at the initial screening visit. At the initial screening visit, biopsies were only indicated for a PSA level of less than 4.0 ng/mL if the DRE and/or TRUS findings were suspicious. The biopsy indication applied in the second screening round of the ERSPC varied according to the PSA range (Fig. 1). Biopsy was indicated for all men with a PSA level greater than 3.0 ng/mL (n = 367). Biopsy was indicated for participants with a PSA level in the range of 2.0 and 3.0 ng/mL who participated in a sub-study that investigated the utility of human kallikrein 2 in prostate cancer screening or in a sub-study after PSA doubling with respect to the initial screening visit (n = 294). Biopsy was indicated for participants with PSA in the range between 1.0 and 2.0 ng/mL who participated in a sub-study after PSA doubling with respect to the initial screening value (n = 113). For PSA values lower than 1.0 ng/mL, no biopsies were done. Neither the DRE nor TRUS findings influenced the biopsy indication.

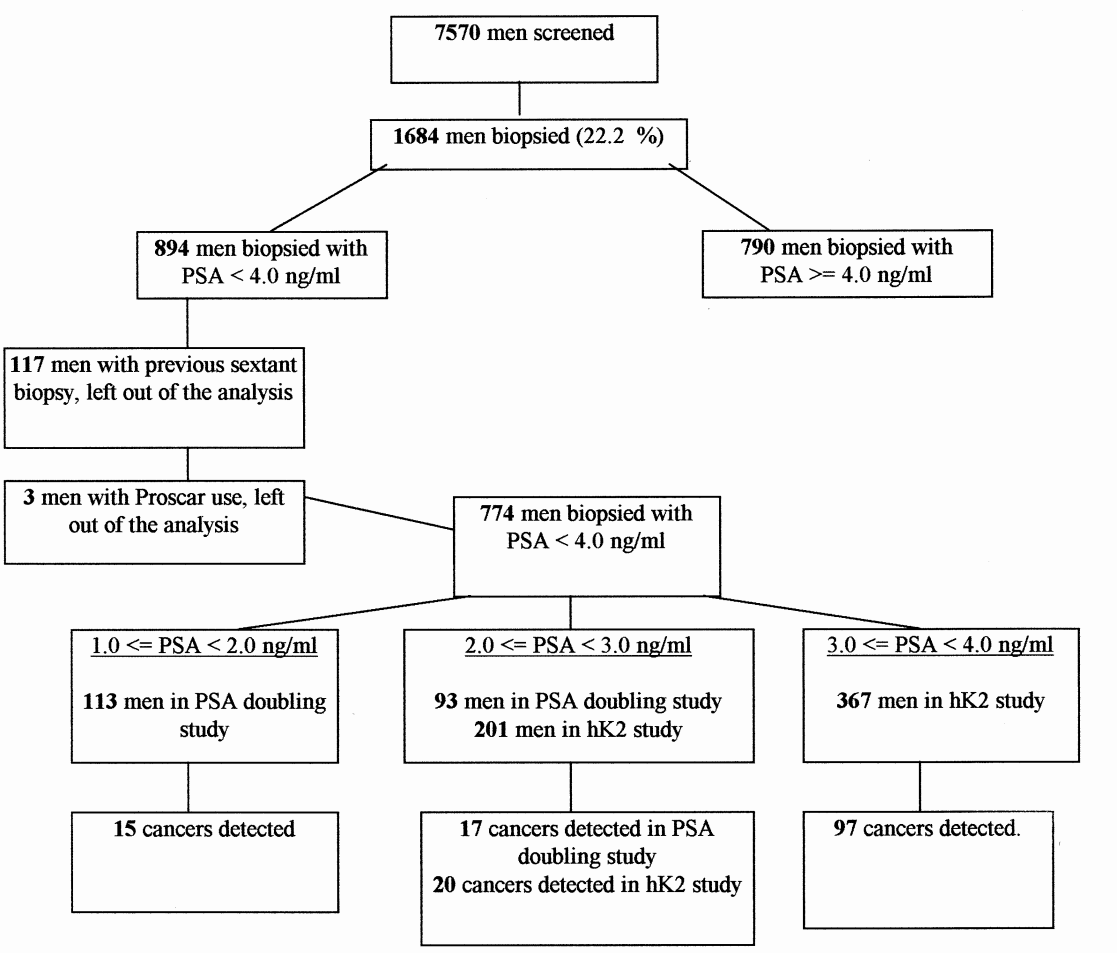

Fig1: Consort diagram of screening procedure of second screening round, November 1997 through December 2001. Study population consisted of 774 biopsied men with PSA less than 4.0 ng/mL.

PSA ASSAYS AND BIOPSY PROCEDURE

From November 1993 to October 1994, the IMX (Abbott) assay was used for PSA determination. From November 1994 to the time of this report, the Hybritech Tandem E/Access assay was used. We standardized the PSA values on the Hybritech Tandem E assay by adding 8% to the Abbott IMXdetermined PSA values, because these values were on average 8% lower than those determined by the Hybritech Tandem E assay for the same sample.[9] Lateralized sextant biopsies (augmented with a seventh biopsy directed toward a hypoechoic lesion if present) were taken. Three men who took Proscar were excluded from the study.

STATISTICAL ANALYSIS

Summary statistics for the 774 men who underwent biopsy and met the above mentioned inclusion criteria were calculated for the TRUS-assessed prostate volume, DRE outcome, TRUS outcome, PSA level at the second screening round, PSA velocity, and PSA density stratified for the PSA ranges of 1.0 to 1.9, 2.0 to 2.9, and 3.0 to 3.9 ng/mL. The positive predictive value, defined as the number of cancers detected divided by the number of biopsies done, was calculated per PSA range.
PSA density was calculated as the PSA value divided by the TRUS-estimated prostate volume in the second round. The PSA velocity was calculated as the (second PSA value minus the first PSA value) divided by the calculated delay in months between the first and second screening visits. We calculated the relative sensitivity (those diagnosed as sick among all those sick) and the relative specificity (those diagnosed as healthy among all those healthy) as a function of the PSA velocity cutoff (using cutoff values of 0.1, 0.2, and 0.3 ng/mL per year). These relative sensitivities and specificities differ from the true sensitivity and specificity because a negative sextant biopsy will not rule out the presence of prostate cancer. A univariate logistic regression analysis using the presence of cancer as a dichotomous dependent variable (true or false) and the PSA velocity as the sole independent variable (the predictor) was performed. Multivariate logistic regression analysis was used to study the predictive value of PSA velocity, controlling for age, prostate volume, and DRE and TRUS findings suspicious for prostate cancer with respect to the same dependent variable. Suspicious DRE and TRUS findings were coded as 0 if no abnormalities were found and 1 if otherwise. The continuous variables PSA velocity and prostate volume were first categorized according to the quartiles of their distribution. The multinomial variables thus obtained were coded in the regression analysis using dummy variables. A backward deletion procedure based on the likelihood ratio test was applied to select a final model, which included the most important predictors for the outcome of a biopsy. The outcomes of the logistic regression models are reported in terms of odds ratios.[10] Interaction terms were not removed from the model if the main effect terms involved were still included.

The clinical stage (TNM 1992) of the tumor and the Gleason scores of the biopsies were studied.

Predictor	PSA Range (ng/mL)			
	1–2	2–3	3–4	1–4
Screened (n)	2397	1013	532	3942
Biopsied (n)	113	294	367	774
Cancer (n)	15	51	83	149
PPV (%)	13.3	17.3	22.6	19.3
DRE suspicious	20	37	67	124
TRUS suspicious	16	30	55	101
PSA velocity (ng/mL/yr)				
Median	0.21	0.24	0.27	0.25
25–75%	0.17–0.24	0.12–0.32	0.15–0.38	0.15–0.35
PSA density (PSA/vol)				
Median	0.049	0.067	0.081	0.069
25–75%	0.037–0.061	0.054–0.080	0.065–0.099	0.057–0.088
Prostate volume (cm^3)				
Median	28.7	36.3	42.2	37.5
25–75%	24.0–36.7	29.1–44.3	34.6–50.8	29.6–46.8
Age				
Median (yr)	64.40	65.54	66.31	65.68
25–75%	60.73–68.30	61.38–69.73	61.92–70.17	61.55–69.77

Table I: Descriptive statistics of selection of predictors for outcome of biopsy in second screening round, stratified by PSA range.

Results.

The summary statistics of the 774 biopsied men in the second screening round of the ERSPC (Rotterdam) are given in Table I; 159 cancers were found (positive predictive value 19.2%). The PSA velocity varied widely, with a modest, but statistically significant, correlation with the absolute PSA level (0.279, *P* <0.001, Spearman's rank correlation). The prostate volume correlated positively with the PSA levels (0.317, *P* < 0.001, Spearman's rank correlation). Table II displays the different sensitivities and specificities of the PSA velocity for several cut-off values in the second round of the ERSPC, Rotterdam. The odds ratio for PSA velocity as determined by the univariate logistic regression analysis was 2.2 (95% confidence interval 0.7 to 6.9, *P* = 0.19, not statistically significant). No odds ratios that were significantly different from 1 were found for the PSA ranges of 1 to 2, 2 to 3, and 3 to 4 ng/mL. In the multivariate regression analysis, no interactions between the different predictors were found. The odds ratios for the main effects are given in Table III. The clinical stage was T1c in 96 men (64.4%), T2 in 48 men (32.2%), and T3 in 5 men (3.4%).
The biopsy Gleason score was 3 + 3 in 126 men (84.5%), 3 + 4 in 21 men (14.2%), and 4 + 4 in 2 men (1.3%).

PSA Velocity	Total Subjects (n)	Cancers Found (n)	Relative Sensitivity* (%)	Relative Specificity (%)
≤0.1	134	22		
>0.1	640	127	85.2	17.9
≤0.2	308	53		
>0.2	466	96	64.4	40.8
≤0.3	509	58		
>0.3	265	91	38.9	66.9

* All biopsy detected prostate cancers (n=149) were the denominator in "relative sensitivity"

Table II: Sensitivity and specificity of PSA velocity for several cut off values in second round of ERSPC, Rotterdam

Comment.

On the basis of the data from the Baltimore Longitudinal Study on Aging (BLSA), it was recently suggested that the PSA velocity may be of use to detect prostate cancer in men with low PSA values. [8] The reported sensitivity and specificity of the PSA velocity using a cut off value of 0.1 ng/mL per year was 81% and 50%, respectively. We studied the application of the suggested biopsy strategy (i.e. biopsy for all men with a PSA velocity of 0.1 ng/mL or greater) using data from the ongoing ERSPC, as well as some alternative biopsy strategies. The distribution of the clinical stage of the detected tumors and the biopsy Gleason scores confirmed that a relatively large proportion of potentially curable cancers could be found in men with low PSA ranges.

In general, any test may be of use as a screening tool for prostate cancer if its outcome adds information with respect to the presence of prostate cancer in a subsequent biopsy compared with the situation in which all men undergo biopsy. For example, greater PSA values are associated with a greater probability of detecting cancer during prostate biopsy.[11–13] The outcome of the univariate logistic regression analysis for PSA velocity was, however, not very convincing in this respect. Although the odds ratio was greater than 1 (odds ratio 2.2), the associated *P* value was only 0.19 (not statistically significant).

Parameter	Odds Ratio (95% Confidence Inverval)
PSA*	1.72 (1.31–2.28)†
PSA velocity	0.73 (0.21–2.67)‡
Prostate volume*	0.96 (0.94–0.98)†
TRUS*	2.15 (1.30–3.54)†
DRE*	1.58 (0.98–2.55)‡
Age*	1.06 (1.02–1.11)†

* as determined in second screening round
† P < 0.05, two sided
‡ Not statistically significant

Table III: Odds ratios for predictors for presence of cancer studied by multivariate logistic regression analysis.

Univariate analysis does not take into account all the other factors that may affect the outcome of a biopsy and that are known before the biopsy. We, therefore, studied the value of the absolute PSA levels, prostate volume, TRUS and DRE outcomes (suspicious or not), and age in the second screening round in this respect using a multivariate logistic regression analysis. The data in Table III demonstrate that the PSA velocity was not an important predictor for the presence of cancer. In fact, the backward deletion procedure excluded only the PSA velocity; all other predictors remained in the model. Therefore, despite the sensitivity of PSA velocity (using a cut off value of 0.1 ng/mL; Table I), the PSA velocity per se is not an important predictor of the presence of prostate cancer in a sextant biopsy in men who had been previously screened. The interpretation of the univariate and the multivariate analyses may be that the detection of prostate cancer is conditionally independent of the PSA velocity (i.e. if only the PSA velocity is known [as in the univariate analysis], the prostate cancer risk will depend on the PSA velocity, although not significantly in our data set). However, if other factors are also known, the information concerning the presence of cancer provided by knowing the PSA velocity is completely overwhelmed by the information present in the other variables (in this case, primarily the PSA level and prostate volume).

It is important to note the differences between the BLSA and ERSPC. The PSA velocity was 0.1 ng/mL per year or greater in nearly all men who underwent biopsy in the ERSPC, Rotterdam with a PSA level less than 4 ng/mL (83%). In the BLSA study, 42% of the men had a PSA velocity of 0.1 ng/mL per year or greater. Such an observed difference for a PSA level of 1 to 2 ng/mL is easy to explain because in the ERSPC only men with a PSA doubling in this PSA range underwent biopsy. This explanation did not hold for the 3 to 4 ng/mL PSA range in which all men underwent biopsy in the ERSPC. Even in this range, the percentage of men with a PSA velocity of 0.1 ng/mL per year or greater was 82.6%. Possible explanations for the observed 40.6% difference (82.6% - 42%) in the proportion of men with a PSA velocity of 0.1 ng/mL per year or greater include the effects of processing stored samples for those men in whom cancer was detected before 1991 in the BLSA or the use of different PSA assays (we standardized our PSA values to Hybritech Tandem E). Another explanation may be that the age range in which the PSA velocity was determined was completely different in both studies.

Table II of the BLSA report provided some information on the age distribution. In the ERSPC, Rotterdam, all men were between 59 and 75 years old (about evenly distributed) at the time of the second screening biopsy. In the BLSA, some PSA samples from very young men (41.2 years) and very old men (87.3 years) were included. Another difference was that although the reference standard for the presence of cancer in the BLSA study was the biopsy outcome, the type of biopsy was not specified and may very well have been different from the procedure used in the ERSPC in which systematic sextant biopsies were taken. Most importantly, in the BLSA, an increased PSA velocity was not an indication for biopsy. The hypothesized merits of the use of PSA velocity were based on a retrospective study. The real value of the PSA velocity can only be tested by actually using it as a biopsy indication, such as was (at least in part) done in the present study. To assess the discrepancy between the ideal situation in this respect (biopsy on the basis of a PSA velocity of 0.1 ng/mL per year or greater) and the approach in the present study, the following calculation may be informative.
Of the 3942 men who, between November 1997 and January 2002, had a PSA value greater than 1.0 but less than 4.0 ng/mL, 1683 (82.7%) had a PSA velocity of greater than 0.1 ng/mL per year. In this retrospective study, approximately 40% of these men actually underwent biopsy. In contrast, 134 men with a PSA velocity less that 0.1 ng/mL per year were biopsied. Finally, neither in the BLSA study nor in the present work, was the value of the PSA velocity assessed with respect to the outcome of an initial biopsy in an individual. In the BLSA, this was not done, because no PSA velocity-based biopsy indication was used. In the present work, a considerable number of men underwent biopsy at the initial screening round of the ERSPC and the value of the PSA velocity was assessed between the initial screening round (in which some men with cancer were filtered out) and the second screening round.

Conclusions.

The risk of biopsy-detectable prostate cancer in the second round of the ERSPC, Rotterdam even for those with a PSA value less than 4.0 ng/mL was high (positive predictive value 19.3%). In the current study, prostate volume, TRUS findings, age and PSA level were statistically significant predictors for the outcome of a biopsy, but an increased PSA velocity was not. Because several different parameters apparently provide independent information with respect to the outcome of a biopsy, it makes sense to derive a biopsy strategy on the basis of a mixture of parameters (e.g. PSA level, prostate volume, and DRE and TRUS findings). The predicted cancer probability determined using the multivariate logistic regression model presented in this study might serve this purpose.

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6.0

Is further testing necessary in men with PSA levels <= 1.0 ng/ml in a population based screening setting? (ERSPC, Rotterdam)

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Abstract:

Objectives.
Currently, several prostate cancer re-screening intervals are in use in different countries worldwide, varying from 1 to 4 years. Recently, it has been proposed to determine the re-screening interval relative to the initial prostate-specific antigen (PSA) level and possibly to extend the re-screening interval up to 5 years.
Methods.
We evaluated the screening results of two subsequent screening visits (4-year interval) of 1703 men aged 55 to 65 years with an initial PSA level of 1.0 ng/mL or less within a randomized screening trial. We assessed the PSA values, numbers of men biopsied (biopsy indication: PSA level of 3.0 ng/mL or greater), and numbers of cancers detected at the second and third screening visits.
Results.
A total of 1327 men (79.3%) attended the second screening visit. Of these men, 13 (0.98%) had a PSA level of 3.0 ng/mL or greater, and three cancers were detected (cancer detection rate 0.23%). At the third screening visit, 1017 men (76.8%) attended, 34 men (3.3%) had a PSA level of 3.0 ng/mL or greater, and five cancers were detected (cancer detection rate 0.49%). The 2344 subsequent PSA determinations in an 8-year period after the initial screening resulted in eight cancers detected, for an overall cancer detection rate of 0.47%. Through linkage of all men with the cancer registry, no additional cancers were found.
Conclusions.
A strategy of PSA screening every 8 years for men with a PSA level of 1.0 ng/mL or less will lead to a considerable decrease in the number of screening visits (with the associated costs and stress), with a minimal risk of missing aggressive cancer at a curable stage.

Introduction.

Although the introduction of serum prostate-specific antigen (PSA) determination has led to a favorable stage migration, allowing for early treatment, prostate cancer screening in asymptomatic men is still controversial. To solve uncertainties regarding screening for prostate cancer, prospective randomized controlled trials are currently ongoing in the United States (Prostate Lung Colorectal Ovarian Cancer Screening Trial)[1] and Europe (European Randomized study of Screening for Prostate Cancer [ERSPC]).[2] An optimal screening algorithm will be crucial in the evaluation of population-based prostate cancer screening programs, not only in terms of decreasing the prostate cancer mortality rate, but also for cost-effectiveness evaluations. Currently, several re-screening intervals are in use in different countries worldwide, varying from 1 to 4 years.[3–6] The choice of a re-screening interval was made with the knowledge of the lead-time based on serum banks used for PSA determinations and the subsequent diagnosis of clinical cancer. In 1997, Carter *et al.*[7] suggested that re-screening intervals should be linked to the baseline PSA level and that a re-screening interval longer than 1 year could be used for men with low PSA levels. Recent studies have proposed extending the re-screening intervals to up to more than 4 years. [4,8,9] We evaluated the screening results of two subsequent screening visits, each at a 4-year interval, of men with an initial PSA level of 1.0 ng/mL or less in the Dutch part of the ERSPC.

Material and Methods.

The total screening cohort of ERSPC (section Rotterdam) consisted of 21,210 men (aged 55 to 74 years), of whom 19,970 men were actually screened. Of these men, 8036 (40.2%) presented with a PSA value of 0.1 to 1.0 ng/mL. The study population consisted of all men (n = 1703) aged 55 to 65 years with a PSA level of 1.0 ng/mL or less who were screened between October 1991 and March 1996 (initial screening visit). This period and age selection was made to get a cohort of eligible men for two subsequent screening visits, each with an interval of 4 years. We assessed the PSA values (Beckman-Hybritech), number of men biopsied and number of cancers detected at the second (October 1995 to March 2000) and third (October 1999 to March 2004) screening visits.

During the second screening visit, the indication for biopsy changed. Up to May 1997, the biopsy indication was a PSA level of 4.0 ng/mL or greater or a lower PSA level (1.0 ng/mL or greater) with abnormal digital rectal examination and/or transrectal ultrasound findings. From May 1997 to date, the indication for biopsy has been a PSA level of 3.0 ng/mL or greater. The tumor and screening characteristics of the cancers detected at the subsequent screening visits were examined. Through linkage of all men with a PSA level of 1.0 ng/mL or less (n = 8036) with the Cancer Registry, we obtained information on possible interval cancers or cancers detected in men who refused further screening after attending the initial screening visit. The institutional review board of the Erasmus Medical Center and a national board (required by Dutch law for population- screening studies) approved the ERSPC. All participants provided written informed consent.

Results.

The 1703 screened men had a mean PSA level of 0.63 ng/mL at the initial screening. The mean PSA value at the second screening visit was 0.87 ng/mL (range 0.1 to 6.2 ng/mL) and was 1.09 ng/mL (range 0.1 to 11.0 ng/mL) at the third screening visit. Table I shows the PSA distribution of men at initial screening and the number and PSA distribution of men attending the second and third screening. Of the eligible 1703 men, 1327 (79%) attended the second screening visit. Loss was owing to death (3.3%), comorbidity (5.1%), moved from the region (5.1%), and refusal (10.1%). Of the 1327 men, 13 men (0.98%) had a PSA level of 3.0 ng/mL or greater, 10 men actually underwent biopsy, and three cancers were detected (positive predictive value 30%, cancer detection rate 0.23%). At the third screening visit, 1017 (76.8%) of the 1324 eligible men attended, and 34 (3.3%) had a PSA level of 3.0 ng/mL or greater, 30 actually underwent biopsy, and five cancers were detected (positive predictive value 16.7%, cancer detection rate 0.49%).
At the second screening visit, the clinical stage of the three cancers detected was T1c in 2 cases and T3a in 1 case. One of the three cancers detected (clinical Stage T3a, Gleason score 3 + 4) showed a rapid rise in the PSA level during the 4-year interval (1.38 ng/mL/yr). At the third screening visit, the clinical stage distribution was 3 cases of T1c and 2 cases of T2c. In two of the five cancers detected (both T2c, Gleason score 4 + 4 and 4 + 5), the PSA level increased rapidly in the second 4-year interval (PSA velocity 2.4 ng/mL/yr and 1.9 ng/mL/yr.
Through linkage of all 8036 men with the Cancer Registry, no additional cancers were found (data complete to January 2003).

Comment.

The determination of an optimal re-screening interval in a population-based screening setting is important for many reasons. Shorter intervals are preferable to avoid the risk of missing prostate cancers that might be of influence to the main endpoint, decreasing prostate cancer-specific mortality. Longer screening intervals, however, are preferable to avoid over-diagnosis, which is substantial in prostate cancer screening,[10] and to reduce costs. The latter will be a key factor in decision making for population-based screening programs. In this study, we evaluated the screening results of two subsequent screening visits, each with a 4-year interval, of men with a baseline PSA level of 1.0 ng/mL or less, representing 42% of the total screening population aged 55 to 65 years.
The data showed that the total of 2344 (1327 + 1017) subsequent PSA determinations resulted in 41 sextant biopsies and 8 cancers detected; an overall cancer detection rate of 0.47% (8 of 1703) at 8 years. In 5 (0.7%) of the 672 men with a baseline PSA level of 0.5 ng/mL or less (39.5% of the study cohort), the PSA level increased to 3.0 ng/mL or greater and one cancer was detected. These findings are in line with those of Ito *et al.*[9] in their study of 4794 men with a baseline PSA level of 1.0 ng/mL or less, a total of four

cancers (0.08%) were found after a mean follow-up of 4 years. Two patients had had a rapid PSA increase 5 and 9 years after the baseline PSA measurement. Therefore, PSA measurements were recommended every 4 or 5 years. Hugosson *et al.*[4] found that in a cohort of 5267 men screened two times at an interval of 2 years (PSA cutoff 3.0 ng/mL), 3 of the 111 cancers detected were detected in men with baseline PSA levels less than 1.5 ng/mL. None of the 2950 men with a PSA level less than 1.0 ng/mL at the initial screening had a PSA increase above the cutoff level used. Hugosson *et al.* [4] concluded that men with a PSA level of less than 1.0 ng/mL did not need to be screened yearly and probably not as often as every second year. Recently, Candas *et al.* [11] published a study of 5387 men (Laval University Cancer Screening Program) with an initial PSA level of less than 3.0 ng/mL and a median number of seven annual follow-up visits. They concluded that compared with annual screening visits, the number of screening visits could be reduced by 45% in men with a PSA level less than 3.0 ng/mL, with almost the same cancer detection rate after a median follow-up of 7 years (range 1 to 14 years). Our current data, with a follow-up of 8 years, have shown that after this relatively long period, the number of cancers detected was very limited. No screening policy for any cancer is capable of avoiding all related mortality. A longer screening interval or perhaps even a single screening visit might be possible in men with these low PSA levels, without missing substantial cancer diagnoses, which could influence the effectiveness of a population-based screening program. Finally, it is an unresolved issue whether it is possible to identify the cancer cases detected at subsequent screening visits at the initial screening to avoid unnecessary testing in a large group of men.

Of the 8 cancer cases detected, 3 at second round screening and 5 at the third screening visit, all, except 1, had an initial PSA level greater than 0.5 ng/mL. Also, 3 of the 8 cases, detected at a more advanced stage, showed a rapid PSA increase in the 4-year interval before diagnosis. However, the baseline PSA levels of the cancer cases at the third screening visit were not indicative of the presence of prostate cancer. At the time of detection, the digital rectal examination findings were abnormal in 3 cases and not suspicious in 5. Digital rectal examination might have detected additional cancers during the first and subsequent round. Arguments for omitting digital rectal examination as a screening test in exchange for biopsying every man with a PSA level of 3.0 ng/mL or greater have been presented elsewhere. [12,13] The numbers of prostate cancers missed are likely to have been very small, considering the previous reported positive predictive value of 2%.[14]

TABLE I. *Distribution of PSA levels at second and third screening (screening interval 4 years) of 1703 men with initial PSA ≤1.0 ng/mL*

Initial Screen		Second Screen						Third Screen					
PSA (ng/mL)	Men (A)	Lost (% of A)	Men (B)	PSA2 ≤1.0 ng/mL (% of B)	PSA2 1.1–2.9 ng/mL (% of B)	PSA2 ≥3.0 ng/mL (% of B)	PC (n)	Lost (% of B)	Men (C)	PSA3 ≤1.0 ng/mL (% of C)	PSA3 1.1–2.9 ng/mL (% of C)	PSA3 ≥3.0 (% of C)	PC (n)
0.1	29 (1.7)	7 (24.1)	22	21 (95.5)	1 (4.5)	—		4 (18.2)	18	17 (94.4)	1 (5.6)	—	
0.2	69 (4.1)	10 (14.5)	59	55 (93.2)	4 (6.8)	—		18 (30.5)	41	36 (87.8)	5 (12.2)	—	
0.3	145 (8.5)	30 (20.7)	115	111 (96.5)	4 (3.5)	—		20 (17.4)	95	86 (90.5)	8 (8.4)	1 (1.1)	
0.4	199 (11.7)	41 (20.6)	158	142 (89.9)	16 (10.1)	—		40 (25.3)	118	99 (83.9)	18 (15.3)	1 (0.8)	
0.5	230 (13.5)	46 (20.0)	184	161 (87.5)	22 (12.0)	1 (0.5)		38 (20.6)	146	106 (72.6)	38 (26.0)	2 (1.4)	1
0.6	238 (14.0)	54 (22.7)	184	153 (83.2)	30 (16.3)	1 (0.5)		41 (22.3)	143	106 (74.1)	33 (23.1)	4 (2.8)	1
0.7	208 (12.2)	43 (20.7)	165	127 (77.0)	37 (22.4)	1 (0.6)	1	33 (20.0)	131	82 (62.6)	46 (35.1)	3 (2.3)	1
0.8	209 (12.3)	49 (23.4)	160	104 (65.0)	53 (33.1)	3 (1.9)		46 (28.8)	114	52 (45.6)	60 (52.6)	2 (1.8)	
0.9	184 (10.8)	44 (23.9)	140	62 (44.3)	76 (54.3)	2 (1.4)		34 (24.3)	106	29 (27.4)	64 (60.4)	13 (12.2)	
1.0	192 (11.3)	52 (27.1)	140	40 (28.6)	95 (67.9)	5 (3.5)	2	33 (23.6)	105	20 (19.1)	77 (73.3)	8 (7.6)	2
Total	1703 (100.0)	376 (22.1)	1327	976 (73.5)	338 (25.5)	13 (1.0)	3	307 (23.1)	1017	633 (62.2)	350 (34.4)	34 (3.4)	5

KEY: PSA = prostate-specific antigen; PC = prostate cancer.
Data presented as number of men, with percentages in parentheses.

The rapid rise in PSA levels could point toward the possible use of the PSA velocity for detecting these cancers. The PSA velocity of the cancers detected at repeat screening was 1.38, 0.50, and 0.63 ng/mL/yr. The cancers detected at the third screening had a PSA velocity (calculated as the mean PSA velocity of the two intervals[15] of 0.41, 1.30, 0.31, 0.35, and 1.03 ng/mL/yr. The PSA velocity of the 3 advanced cases was 1.38, 1.30, and 1.03 ng/mL/yr. These data, although based on a very small sample, showed a wide distribution in PSA velocity values. This will make it difficult to use PSA velocity, in population-based setting, as an indicator for the presence of prostate cancer at low PSA levels. This becomes even more evident if we consider the PSA velocity values of the men with a PSA level of 3.0 ng/mL or greater who underwent biopsy at the second screening (n = 7) or third screening (n = 25) in whom no cancer was detected. The PSA velocity values varied from 0.53 to 1.27 ng/mL/yr (mean 0.86) for men biopsied at the second screening (of whom 4 men who attended the third screening again had no cancer found). For men who underwent biopsy at the third screening with a PSA value of 3.0 ng/mL or greater with no cancer detected, the PSA velocity values varied from - 0.27 to 1.43 ng/mL/yr (mean 0.52). The rapid rise in PSA in the 4-year interval in the more advanced cancer cases is in line with the findings of Carter *et al.,*[16] in which an exponential rise in PSA level was found 4 to 5 years before clinical diagnosis.
In men who did not reach the PSA threshold value of 3.0 ng/mL during the 8-year period, the PSA velocity values varied from - 0.29 to 0.56 ng/ mL/yr (mean 0.004). Other parameters known at initial screening, such as age, family history, prostate volume, and PSA density showed no remarkable differences between the cancer and non-cancer cases. Statistical testing was not done because of the very small number of cancer cases.

Conclusion.

The numbers of cancers detected after 8 years of follow-up with two subsequent screening visits were very low in men with a PSA level of 1.0 ng/mL or less, which represented 42% of men screened in the age range of 55 to 65 years in our study. In a population-based screening setting, a trade off is always present between the specificity (ie, unnecessary screening) and sensitivity (i.e, number of cancers detected). A strategy of PSA screening every 8 years for men with a PSA level of 1.0 ng/mL or less will lead to a considerable decrease in the number of screening visits (with the associated costs and stress) with a minimal risk of missing aggressive cancers at a curable stage.

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7.0

No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/ml or greater (ERSPC, Rotterdam).

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Abstract.

Objectives.
In the early detection of prostate cancer (Pca) uncertainty exists concerning the most appropriate biopsy procedure. Within the European Randomized Study of Screening for Prostate Cancer (ERSPC) lateralized sextant biopsies are used. False-negative results of sextant biopsies have led to the extensive use of procedures using 12 or more biopsy cores. The ERSPC offers the opportunity to study the yield of repeat biopsies after 4 years in men who had negative sextant biopsies and a prostate-specific antigen (PSA) level of 4.0 mg/mL or more at the first screening round.
Methods.
Between August 1996 and May 1998, a total of 6876 men (age 55 to 74 years) were randomized to the screening arm and actually underwent screening. The numbers and levels of biopsy indicators, as well as possible predictors for biopsy outcome, in the second screening round, such as prostate volume, volume change over time, prostate-specific antigen density (PSAD), PSA velocity, and age, were calculated and compared for participants with positive and negative biopsies in round 2. The positive predictive value (PPV) and detection rates, as well as parameters of aggressiveness, were evaluated for second-round biopsy detected and interval Pca cases.
Results.
Of the 728 men with a PSA level of 4.0 mg/mL or more who underwent biopsy at initial screening, 553 were eligible for a second screening visit after 4 years. Of these, 272 (49.2%) actually underwent screening. Eighteen Pca cases were detected with 217 biopsies, indicated by a PSA level of 3.0 ng/mL or more (PPV 8.3%). Eight interval cases were identified by linking to the Cancer Registry. These 26 cases would have increased the PPV and detection rate of the initial screening round from 36.1% to 39.7% and from 3.8% to 4.2%, respectively. Most of these cases (23 of 26 or 88.5%) were organ confined and amenable to potentially curative treatment.
Conclusions.
Although the results of this study may have been biased by the low rate of availability/eligibility of participants for re-screening (after 4 years), the proportion of cancers detected after a previous lateral sextant biopsy indicated by a PSA value of 4.0 mg/mL or more (PPV 8.3%) fell far short of the overall PPV at re-screening (PPV 20%). The features of most cancers that were possibly missed during the first round allowed a potentially curative approach. The ERSPC study group found no reason to change the ERSPC protocol.

Introduction.

Since Hodge *et al.* [1] demonstrated that the ultrasound-guided transrectal sextant prostate biopsy is superior to digital guidance; this technique has become the most commonly used procedure for diagnosing prostate cancer (Pca), in both clinical and screening settings. However, some recent studies have suggested that the sextant prostate biopsy may underestimate the presence of Pca. The false-negative rate of the standard sextant biopsy has been reported to be as high as 15% to 31%. [2–7] Several series have shown that additional biopsy samples or lateralization of the sextant biopsies may increase the diagnostic yield by 30% to 35%. Repeated sextant biopsies or more extended systematic sampling in men in whom screening findings are suspicious for Pca (such as an elevated prostate-specific antigen [PSA] level) and a prior negative prostate biopsy have, therefore, been recommended in several studies.[8–13]

Using a more extensive biopsy regimen will most certainly lead to an increased Pca detection rate. It is, however, known that most Pca develops slowly in elderly men. This results in a substantial risk that cancer will be detected for which treatment cannot bring any benefit. Over-detection or over-diagnosis is a considerable problem in Pca screening. [14–16] Whether an increased cancer detection rate through early detection will influence Pca mortality remains uncertain. The critical question is which of the cancer cases detected by early detection are clinically significant and need to be detected at this stage or later during the life of the host, or at all.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC, Rotterdam), additional biopsies are only performed in the case of a high-grade prostatic intraepithelial neoplasia lesion or a “suspicious for malignancy” diagnosis. Men with a normal biopsy result do not undergo immediate repeat biopsy irrespective of the PSA level and/or suspicious digital rectal examination (DRE) and/or transrectal ultrasound (TRUS) findings. Their next screening visit is scheduled 4 years after the initial screening visit. This screening regimen was fixed at the start of the study, and, unless convincing evidence becomes available that makes it necessary to change the screening regimen, it will continue, preferably unadjusted, to remain consistent over time within the established, multinational approach.

In this study, we focused on the repeat screening results of those participants who underwent biopsy at the initial screening (PSA level of 4.0 mg/mL or more) but in whom the biopsy result was benign.

Material and Methods.

STUDY POPULATION AND SCREENING ALGORITHM

Our study population consisted of 6876 men, aged 54 to 74 years, who were randomized to screening and underwent screening between August 1996 and May 1998. At the initial screening visit, until May 1997, a PSA value of 4.0 mg/mL or more and/or suspicious DRE findings and/or suspicious TRUS findings were used as biopsy indications. After May 1997, sextant biopsies were suggested in all men who had a PSA value of 3.0 ng/mL or more, and

DRE and TRUS were no longer used as screening tests.[17] Men who had undergone biopsy after May 1997, with a PSA value between 3.0 and 4.0 ng/mL at initial screening, were not included in this study. The period of August 1996 until May 1998 was chosen to obtain a homogeneous sample with respect to the re-screening interval and to obtain the group of participants who were eligible for the second screening round 4 years later between August 2000 and May 2002. A total of 816 men (11.9%) had a PSA level of 4.0 mg/mL or more. Men in whom no Pca was detected at initial screening were eligible for second-round screening (PSA cut off 3.0 ng/mL or greater). Details of the study population are given in Figure 1. A permit for conducting this study was obtained from the institutional review board of the Erasmus Medical Centre and the Dutch Health Council Committee.

BIOPSY TECHNIQUE

Lateralized sextant biopsies were obtained using a Bard 18- gauge biopsy needle. In the case of a hypoechogenic lesion, one extra biopsy was taken toward the suspicious lesion. Needle biopsy diagnoses of normal prostate, benign prostatic hyperplasia, atrophy, prostatitis, atypical adenomatous hyperplasia, and low-grade prostatic intraepithelial neoplasia were categorized as benign and those participants were invited or their next screening visit after 4 years.

STATISTICAL ANALYSIS

For all the participants who underwent biopsy at repeat screening, the positive predictive value (PPV; number of cancers detected divided by number of biopsies done) and cancer detection rate (number of cancers detected divided by number of men screened) were calculated. The association between the categorical variables (DRE and TRUS, coded as 0 [benign] or 1 [suspicious]) and diagnostic groups (cancer or no cancer detected at repeat screening) was tested by the chi-square test. Distinction was made between the DRE and TRUS results of the initial and repeat screening. Differences in the continious numeric variables (i.e, total PSA [visit 1 and visit 2], PSA velocity [PSAV; PSA level of visit 2 - PSA level of visit 1 divided by 4], prostate volume [visit 1 and visit 2], prostate volume velocity [prostate volume at visit 2 - prostate volume at visit 1], PSA density [PSAD; PSA divided by prostate volume], and PSAD velocity [PSADV; PSAD of visit 2 - PSAD of visit 1], and age [visit 2]) were tested by the Mann-Whitney *U* test.

Data on the clinical stage, Gleason score, and treatment applied to the cancers detected at repeat screening were assessed. Through linkage with the National Cancer Registry, possible interval cancers within the 4-year period were identified for all men with a PSA level of 4.0 mg/mL or more and no cancer detected at initial screening.

Results.

Of the 6876 participants at the initial screening, 816 men had a PSA level of 4.0 mg/mL or more (11.9%), 728 men underwent biopsy (89.2%), and 263 cancers were detected (PPV 36.1%, cancer detection rate 3.8%). In total, 272 (49.1%) of the 553 men who were eligible for second screening were screened, and 217 men (39.2%) underwent biopsy (Fig. 1). In the 217 men who underwent biopsy, 18 cancers were detected (PPV 8.3%). Table I shows the distribution of possible indicators for a positive or negative result for these 217 men. Table I separates the 199 participants who had a negative biopsy from the 18 with cancer detected at the second screening. The numeric distributions of abnormal DRE or TRUS findings during the first and second visits, as well as the average values and ranges for PSA, prostate volume, volume change over time, PSAV, PSAD, PSADV, and age distribution (only visit 2) between the first and second visit were compared. The P values relate to these comparisons and were probably influenced by the very small numbers of cancers detected in round 2. The PSA level was not significantly different between the cancer and non-cancer cases; statistically significant differences were found for PSAV and PSADV. Although not displayed in Table I, the mean prostate volume of men with Pca detected at a second screening visit with abnormal DRE findings was 45.5 cm3. This was substantially lower than the 60.1 cm3 in men with Stage T1c Pca detected at second screening.
The clinical stage distribution of the 18 cancers detected was T1c in 8, T2 in 9, and T3c in 1. The Gleason scores were as follows: 3 + 3 in 16 and Gleason 3 +4 in 2 cases. Fifteen men had one positive biopsy core. All men were treated with curative intent, five radical prostatectomy, six radiotherapy, one brachytherapy and six by watchful waiting.

Through linkage with the Cancer Registry (data complete until June 2002), 8 cases of cancer were identified within the 312 men who were not screened in the second round (Fig. 1). These cancers were detected at either the Erasmus Medical Centre or hospitals within the region where, at least until 2002, sextant biopsies were used. Six cases were found in men who were too old to attend their second screening visit, of whom three had refused biopsy at the initial screening. In men eligible for the second screening visit, two interval cancer cases were detected. In 1 of those 2 cases, biopsy had been indicated but was not performed at initial screening (refusal). The available data on clinical stage showed that most Pca cases were organ confined: T1a in 1, T1b in 1, T2a in 3, T3a in 1, and T3c in 1 case. Most Pca cases were treated with curative intent (radiotherapy in 4, radical prostatectomy in 1, watchful waiting in 1); the 2 patients with non-organ-confined Pca underwent hormonal therapy.

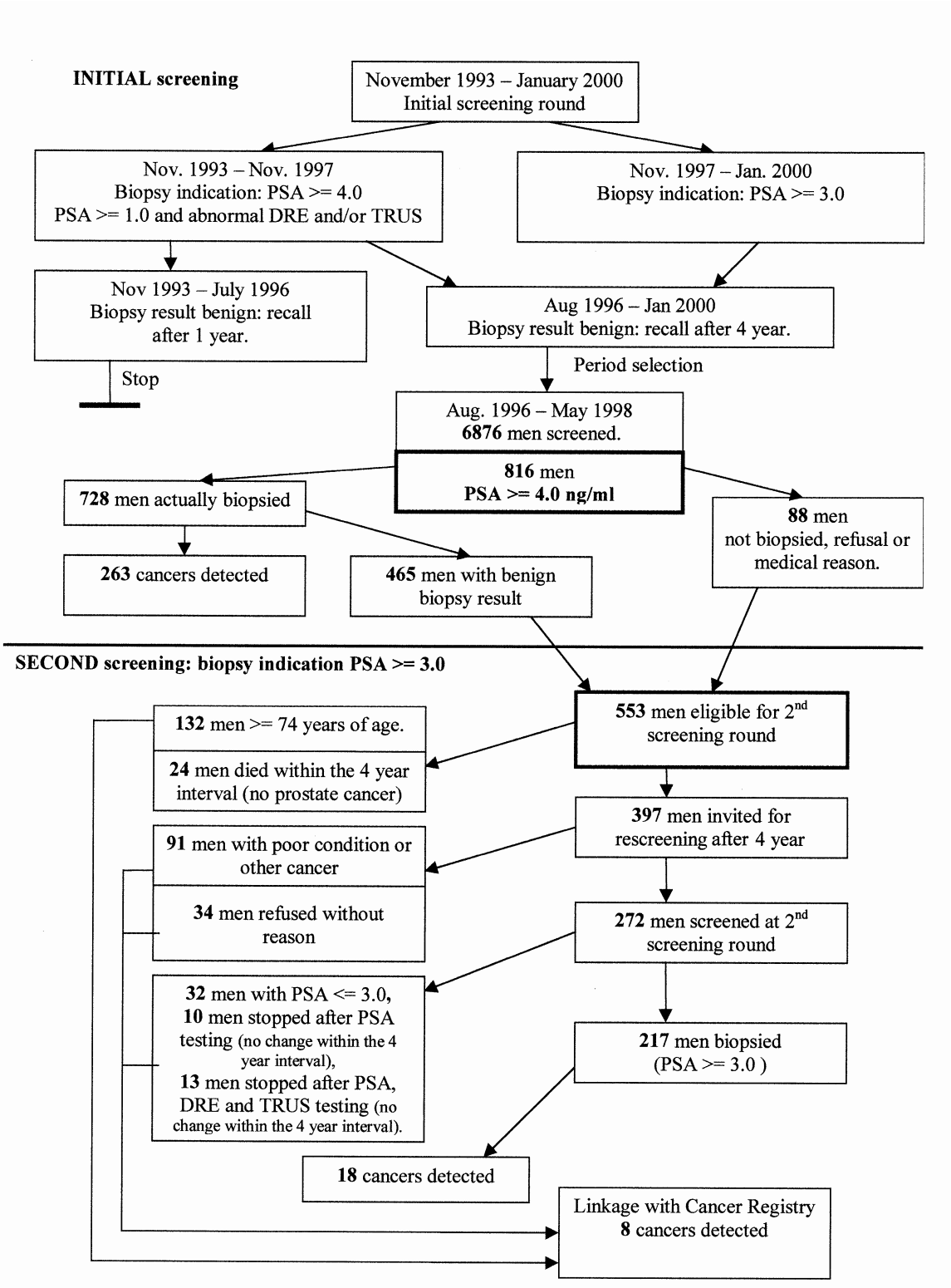

Fig 1. Consortdiagram of study population.

Parameter	No Cancer Detected at Visit 2 (n = 199)	Cancer Detected at Visit 2 (n = 18)	*P* Value
Visit 1			
DRE abnormal (%)	44 (22.9)	3 (17.6)	0.619
TRUS abnormal (%)	46 (24.0)	4 (23.5)	0.968
Visit 2			
DRE abnormal (%)	50 (26)	8 (47.1)	0.064
TRUS abnormal (%)	39 (20.3)	6 (35.3)	0.150
Mean PSA (ng/mL)			
Visit 1	6.72 (4.1–40.1)	5.90 (4.0–11.8)	0.293
Visit 2	8.80 (2.0–57.0)	12.44 (4.5–46.7)	0.149
Mean prostate volume (cm^3)			
Visit 1	54.69 (24.9–103.0)	47.66 (24.9–103.0)	0.076
Visit 2	64.36 (23.1–181.2)	53.20 (13.8–154.0)	0.028
Mean VolV (cm^3)	9.66 (−42.1–74.7)	5.54 (−89.0–65.9)	0.456*
Mean PSAD (ng/mL^2)			
Visit 1	0.13 (0.05–0.63)	0.14 (0.06–0.34)	0.741
Visit 2	0.15 (0.05–0.90)	0.34 (0.07–1.45)	0.013
Mean PSAV (ng/mL)	0.52 (−4.57–6.88)	1.64 (0.08–8.73)	0.014†
Mean PSADV (ng/mL^2)	0.014 (−0.31–0.55)	0.199 (−0.05–1.11)	0.003†
Mean age (yr), visit 2	68.0 (59.2–74)	68.2 (59.8–74)	0.838

Data in parentheses are ranges (minimum to maximum), unless noted otherwise.
* Test result remained statistically insignificant (P = 0.562) if men with VolV < - 20.0 (n = 15) are excluded from analysis.
† Test result remained significant (P = 0.017 and P = 0.009, respectively) if men with VolV < -20.0 (n = 15) are excluded from analysis.

Table I: Patient characteristics of 217 men who underwent biopsy at second screening visit

Comment.

Performing lateral sextant biopsies at repeat screening (4-year interval) in men with a previous benign biopsy and an elevated PSA level (4.0 mg/mL or more) resulted in the detection of 18 cases in 217 biopsied men (overall PPV and cancer detection rate at repeat screening 20.0% and 4.1%, respectively). Through linkage with the Cancer Registry, 8 additional cases of Pca were identified. Most cancers were organ confined and were treated with curative intent. The diagnosis of these 26 Pca cases, if added to the PPV and detection rate in round 1 increased these values by only 3.6% for the PPV (36.1% to 39.7%) and 0.4% for the cancer detection rate (3.8% to 4.2%). These findings do not correspond with the findings of other studies. Roehl *et al.* [2] found a cancer detection rate of 18% at a second series of prostate biopsies in men with a PSA level of 4.0 mg/mL or more after an initial cancer detection rate of 30%. This difference can be explained by the use of quadrant biopsies at the start of the study that was later changed to the use of sextant biopsies and the composition of the study population. Part of their study population consisted of men who were considered to be at high risk of Pca.
The results presented here may have been adversely influenced by the low compliance rate at repeat screening. Only 272 (49.2%) of the 553 men invited underwent screening and only 217 men underwent biopsy (39.2%). Considering the men who did not respond, one can argue the benefit of an additional sextant biopsy. Other than the men who died within the 4-year interval, 132 men were older than 74 years and 91 men did not participate because of poor physical condition or cancer diagnosed elsewhere. General agreement has been reached that screening does not make sense for men

with a life expectancy of less than 10 years.[18] In older men or those with serious comorbid conditions, a competing hazard is much more likely to result in morbidity or death than Pca. Furthermore, it was found that side effects after Pca treatment (eg, incontinence, impotence) are also greater in older men.[19] Removing these men (24 dead, 132 too old to participate, and 91 with comorbidity) from the calculation resulted in a compliance rate of 70.9% (217 of 306). Therefore, taking into account that early detection is done to have some benefit during a patient's lifetime, the ERSPC decision to not change the biopsy protocol was made from a compliance rate of 71% combined with a linkage procedure that included all eligible men.

The linkage with the Cancer Registry resulted in another 8 Pca cases. This number is certainly not negligible. Six cases surfaced in men older than 74 years during the interval before their second screening visit. Three had refused biopsy and three had been missed. It is unknown what benefit would have been achieved if the detection had been 1 or 2 years earlier through screening. One of the other two clinically detected cancers would probably have been detected at the initial screening if the patient had not refused at that time, leaving a total of 4 Pca cases that were most probably missed at the initial screening, of which 3 were detected in men already older than 74 years. These findings, together with the low cancer detection rate at the second screening visit, caused us to determine that a change in the biopsy protocol within the ERSPC is not required for participants with a previous benign biopsy result. More important was the evaluation of the characteristics of the screen-detected cancers missed at initial screening and identifying possible reasons for a missed diagnosis.

Uzzo *et al.* [20] and Karakiewicz *et al.* [21] showed that the yield of the sextant biopsy decreases with increasing prostate volume. Our data and those published by Feneley *et al.* [22] showed that patients with Stage T1c Pca and those without Pca had a larger prostate volume. Although the latter study was not a detection study, but a retrospective analysis of radical prostatectomy specimens, its conclusion was that using PSA testing (as done in our screening setting) results in a selection of men with larger prostates owing to the effect of benign prostatic hyperplasia on the serum PSA level. Combining the results of Uzzo *et al.,* [20] Karakiewicz *et al.,* [21] and Feneley *et al.* [22] suggests that the group of men in our study in whom no Pca was detected at the second screening visit consisted, in part, of men who already did have Pca. Increasing the number of biopsy cores in men with prostate volumes greater than 50 cm3, as suggested by Uzzo *et al.* [20] could, therefore, be an option. However, this would mean that men with benign prostatic hyperplasia and an elevated PSA level would also have to undergo this extensive biopsy scheme at successive screening visits.

Our data showed that the screening test used (PSA level) is not a very powerful discriminator between malignant and benign disease in this particular group of men at repeat screening (PSA 4.0 mg/mL or more). Also DRE and TRUS examinations showed no statistically significant differences in the risk of a second-round positive biopsy. This implies that the tests used to predict the biopsy outcome at initial screening are not suitable at repeat screening. Finding suitable markers for the further refinement of the re-screening algorithm and, perhaps more important, finding markers for the detection of aggressive forms of Pca will, therefore, be indispensable to avoid unnecessary biopsies. Although the biopsy procedure is relatively harmless and well accepted, [23–25] applying prostate biopsies to large populations

may still result in a considerable absolute number of complications. Our data suggest that PSAV and the PSADV can perhaps help in this matter. The statistically significant difference in the PSADV between the Pca and non-Pca cases in this group of men could indicate that the rise in PSA level within the 4-year interval was greater in the Pca cases than what would be expected by normal prostate growth due to aging. Additional studies, in a multivariate setting, will be required to determine the value of these changes as biopsy indicators at repeat screening. Although not mentioned in this report, free PSA has been shown to be a powerful predictor of the presence of Pca in several studies. [26–28] Free PSA determinations are, however, not standard procedure within the ERSPC, Rotterdam, and the value of free PSA in this particular group of men remains unclear.

Conclusions.

The results of this study did not provide a reason to adjust the screening protocol with regard to repeat biopsies in men with an elevated PSA level (4.0 mg/mL or more) and benign biopsy result. The PPV of the second screening visit in men (age younger than 74 years) with a negative biopsy at the first screening round was low (8.3%). Through linkage of all eligible men, only one additional Pca case (probably missed at initial screening in a man younger than 74 years) was found. The screening tests used (PSA, DRE, and TRUS) were not useful in predicting the biopsy outcome at repeat screening.
Additional refinement of the indication for biopsy at repeat screening, particularly in this group of men, is necessary. Perhaps the use of PSAV and PSADV can be useful. However, at present, the number of cancers detected at repeat screening was too small to reach definite conclusions concerning the possible use of these predictors for biopsy outcome after 4 years in men with an initial PSA level of 4.0 ng/mL or greater and a benign biopsy result.

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8.0

A comparison of first and repeat (4 years later) prostate cancer screening in a randomized cohort of a-symptomatic men aged 55-75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC-Rotterdam).

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Prostate 2005.

Abstract.

Introduction.
The identification of predictors for prostate biopsy outcome at two screening rounds using a PSA >= 3.0 ng/ml as biopsy indication.
Materials and Methods.
We compared predictors by means of descriptive statistics and logistic regression analysis in men (55 - 75 years) biopsied in either the 1st or 2nd screening round of ERSPC Rotterdam (interval 4 years).
Results.
Positive predictors for biopsy outcome in both screening rounds were an increased PSA level in the absence of a previous negative biopsy (PrevNB), DRE and TRUS suspicious and a positive family history (PFH). A higher than median prostate volume was a consistent negative predictor. Having had a PrevNB at initial screening strongly reduced the chance of cancer detection at repeat screening and in addition canceled the predictive potential of PSA.
Conclusion.
If “detecting prostate cancer efficiently” were the aim, this study indicates that a “PSA only based biopsy threshold” may be replaced by another criterion incorporating e.g. DRE, TRUS and prostate volume in men who were biopsied in the preceding 4 year interval.

Introduction.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) [1] was designed to show if a 20% or higher prostate cancer specific mortality reduction may be achieved by early detection and treatment of the disease. In Rotterdam a cohort of over 40,000 men aged 55-75 years was randomized to either the screening or the control arm of the study. Prior to randomization all men signed an informed consent. Men randomized to the screening arm have been invited to be screened every four years, men randomized to the control arm were informed of that fact only. The control arm will be used in the future as a reference cohort to study the effect of screening. Screening is a two step procedure. First men with a perceived elevated prostate cancer risk are identified. This step necessitates at least one visit to the screening center. Within ERSPC Rotterdam this pre-selection step is a serum PSA measurement. In men with a biopsy indication (PSA greater than or equal to (>=) 3.0 ng/ml) a DRE, TRUS and biopsy is scheduled (lateral sextant biopsy) at a 2nd visit (usually within two weeks of the initial visit).

At present we have screened a large cohort of men twice (1st and 2nd screening round, 4-year interval) using an identical biopsy indication (PSA >= 3.0 ng/ml).

The topic of this paper is the predictive value of information that is available before a biopsy is taken with respect to its outcome (“cancer” or “no cancer”) Due to the study design (identical biopsy indication at initial and repeat screening) we are able to study the possible differences in predictive potential in the initial and repeat screen of pre-biopsy available source of information. Additionally, the availability of second screening round biopsy data in addition to first screening round data allows the study of the predictive potential of a change in information with respect to biopsy outcome. We focus on the value of a change in PSA levels. In addition, we study the impact of “having had a previous negative biopsy at the initial screening” on the probability to detect the disease at the repeat screen.

Materials and Methods.

The total ERSPC Rotterdam study cohort (N = 42,376 men; screening arm 21,210 men and control arm 21,166 men) and screening algorithm has been described previously [2]. The cohort of men for this study (Fig. 1) comprises 10191 asymptomatic men aged 55-75 year consecutively screened from May 1997 until December 1999 for the first time using a PSA >= 3.0 ng/ml as biopsy indication (no further testing was done in men with PSA lower than (<) 3.0 ng/ml).

ERSPC has been approved by the IRB of the Erasmus Medical Center and by a national board (required by Dutch law for population screening studies). All participants signed an informed consent.

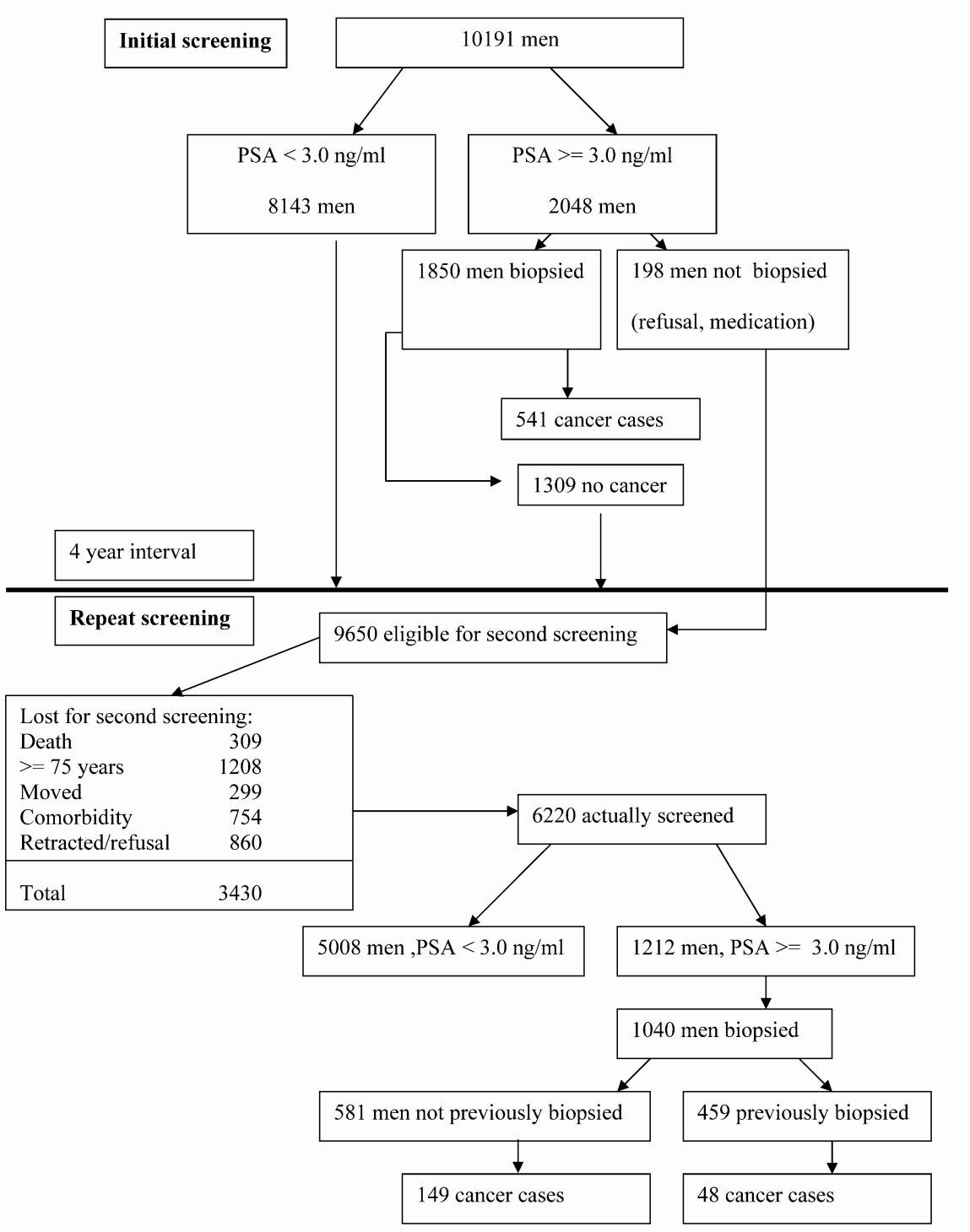

Figure 1: Consort diagram of study population at initial screening (May.1997-Dec. 1999) and repeat screening (May. 2001 -Dec 2003).

In the period May 2001 - December 2003 a consecutive cohort of 6220 of these men were screened for the second time using the same screening protocol (men in whom cancer was detected were not invited for the second round screen). Of the 10191 men screened in the first round, 1850 men were biopsied because of PSA >= 3.0 ng/ml. Of the 6220 men screened in the 2nd screening round 1040 men were biopsied using the same biopsy indication. Of these 1040 men 459 men were also biopsied in the first round (no cancer was found on that occasion).

The predictors for biopsy outcome studied in this paper included: PSA level, change in PSA level over time (for 2nd round biopsies only), TRUS estimated prostate volume, age, DRE and TRUS outcomes, self reported prostate cancer family history and "having had a 1st screen (negative) biopsy" (for 2nd round biopsies only).

For the first and second screening round for those men who were biopsied the distributions of the predictors and their changes between the initial and second screening round were calculated.

In addition two databases were created. The first database (based on 1st screening round data only) contained:

- PSA level >= median PSA level (0 = 'false'/1 = 'true')
- estimated prostate volume >= median prostate volume (0/1)
- age >= median age (0/1)
- DRE outcome (0 (i.e. non suspicious)/1(i.e. suspicious))
- TRUS outcomes (0/1)
- self (i.e. by the participant) reported prostate cancer family history (0 (i.e. no Pca in family)/1 (i.e. father and/or brother with Pca))
- biopsy outcome (0 (i.e. no cancer detected)/1 (i.e. cancer detected))

The second database (with only information on men who were biopsied in the 2nd screening round) contained:

- PSA as measured in the second screening round >= median PSA measured in the first screening round (0/1)
- increase in PSA level between the first and 2nd screening round >= median increase in PSA level (0/1)
- 2nd screening round prostate volume >= median 2nd screening round prostate volume (0/1)
- 2nd screening round DRE outcome (0/1)
- 2nd screening round TRUS outcome (0/1)
- 2nd screening round age >= median 2nd screening round age (0/1)
- having had a previous negative biopsy (in the first screening round) (0 (i.e. no previous negative biopsy) /1 (i.e. previous negative biopsy))
- the self reported prostate cancer family history (0/1)
- Biopsy outcome (0/1)

Two multivariate logistic regression analyses [3] using a backwards deletion procedure were carried out (one for the 1st round biopsy data and one for the 2nd round biopsy data). In the analysis for the 2nd round data interaction terms between the predictors and having had a previous negative biopsy were included into the model. The backwards deletion procedure used a parameter rejection threshold p-value of 0.2.
To facilitate the study of the predictive potential of PSA levels for both the first and 2nd round biopsy data PSA levels were categorized into high and low levels compared to the median of PSA levels in the first screening round. In order to focus specifically on PSA levels and changes in PSA levels for 2nd round biopsy data only they were (separately) categorized as either high or low with respect to the median 2nd round levels for men with a comparable biopsy history.
All p-values listed in the paper refer to 2-sided 5% probability thresholds. Stata software was used for all analyses.

Results.

In 2048 of 10191 men entered into the study for the first screening round PSA was >= 3.0 ng/ml, in 1850 men a biopsy was actually done (compliance is 86%). Some men refused to undergo a biopsy others took e.g. anti coagulant medication that could not be stopped. Twelvehundred and twelve (1212) of 6220 men screened in the 2nd round had a PSA >= 3.0 ng/ml of whom 1040 men were actually biopsied (compliance 86%). In the first screening round 541 cancers were detected in 1850 biopsies (PPV = 0.29), in the 2nd screening round 197 cancers were found with 1040 biopsies (PPV = 0.19). The 2nd screening round data can be stratified in 581 biopsies in men not previously biopsied (149 cancers detected, PPV = 0.26) and 459 biopsies in men previously biopsied (48 cancers detected, PPV = 0.10). A quarter (48 out of 197) of all the cancers that were detected in the 2nd screening round was detected in men who had a previous negative biopsy (Fig.1).
At first screening PSA values ranged from 3.0 ng/ml to 218.0 ng/ml, 1038 men (56 %) had a PSA level between 3.0 and 5.0 ng/ml. At repeat screening PSA values ranged from 3.0 ng/ml to 59.0 ng/ml. The percentage of men with a PSA level between 3.0 and 5.0 ng/ml was 82.8 % in men not previously biopsied and 39.4 % in men previously biopsied respectively. Mean prostate volume of men biopsied at initial screening was 49.7 ml (95%CI: 48.6 – 50.7 ml). At repeat screening the mean prostate volume of men not previously biopsied was 47.4 ml (95%CI: 36.8 – 58.1 ml) and 50.6 ml (95% CI: 48.7 - 52.4 ml) for men previously biopsied.

Distributions of parameters studied	Parameter	N Valid	Suspicious or positive change(1)	Cancers detected	Negative change (-1)	Cancers detected	PPV
Biopsied first screening round, 541 cancers found	DRE	1850	489	238	NA		0.49
	TRUS	1850	446	239	NA		0.54
	Fam	1850	156	62	NA		0.40
Biopsied 2nd screening round, 197 cancers found	DRE	1040	220	65	NA		0.30
	TRUS	1040	169	43	NA		0.25
	Fam	1040	74	20	NA		0.27
Biopsied 2nd screening round only, 149 cancers found	DRE	581	124	49	NA		0.40
	TRUS	581	93	30	NA		0.32
	Fam	581	43	15	NA		0.35
Biopsied in first and second screening round, 48 cancers found	DRE	459	96	16	NA		0.17
	DRE change	459	58	11	49	4	0.19
	TRUS	459	76	13	NA		0.17
	TRUS change	459	61	13	56	4	0.21
	Fam	459	31	5	NA		0.16

Table I. Overview of binomial predictors for biopsy outcome. Positive and negative changes refer to second round screening when compared to first round screening. Eg. A positive change (1) occurs if the initial round investigation was normal and the second round finding suspicious.

Table I gives information for the categorical variables DRE, TRUS, prostate cancer family history and the changes in DRE and TRUS. For all these parameters the PPV is listed in the last column.
Roughly 50% of the men biopsied in the 2nd screening round had a previous negative biopsy at the initial screen. Only a quarter of the 2nd round cancers were found in these men.

Table II lists the outcomes of the multivariate logistic regression analyses (using a backward deletion strategy). The odds ratios (OR) of the parameters for 1st and 2nd round screening are in consecutive rows to allow an easy comparison. The OR's show that a positive DRE and TRUS and a positive family history are positive predictors for biopsy outcome. The "age parameter" does not reach statistical significance for the 2nd screening round data but age is a positive predictor for the 1st screening round. Prostate volume is a consistent negative predictor for biopsy outcome. Having had a previous negative biopsy is a strong negative predictor for biopsy outcome in the 2nd screening round. PSA is strong positive predictor in the first screening round. In the 2nd screening round PSA is a strong predictor only for those men who were not biopsied before due to the significant interaction term (interaction with "having had a previous negative biopsy"). The OR for PSA for men without a previous negative biopsy is 6.9, it is 6.9 * 0.13 (the interaction term) = 0.9 (which is non-significantly different from 1) for men with a previous negative biopsy.

Parameter	Screening round	Odds ratio	95% CI odds ratio	p-value
PSA1 >= med PSA 1	1	2.3	1.8 - 2.9	< 0.001
PSA2 >= med PSA1	2	6.9	1.2 - 39.5	0.003
Previous negative biopsy	2	0.5	0.3 - 0.7	0.001
Interaction between PSA2 >= med PSA1 and having had a previous negative biopsy	2	0.1	0.0 - 0.8	0.03
Vol1 >= median Vol1	1	0.4	0.3 - 0.5	< 0.001
Vol2 >= median Vol2	2	0.5	0.3 - 0.7	< 0.001
Age1 >= median Age1		1.2	1.0 - 1.5	0.10
DRE and TRUS suspicious	1	6.0	4.4 - 8.1	< 0.001
DRE and TRUS suspicious	2	2.8	1.7 - 4.7	< 0.001
Positive family history	1	1.7	1.2 - 2.4	0.006
Positive family History	2	1.8	1.0 - 3.2	0.004

Table II. Outcomes of the multivariate logistic regression analysis of 1st and 2nd round biopsy data.

Table III illustrates the relative unimportance of PSA and changes in PSA levels for predicting the outcomes of 2nd round biopsies, when compared to biopsy status (i.e. being biopsied for the first time in the 2nd screening round or having had a previous negative biopsy at the initial screening). Having had a previous negative biopsy reduces the PPV by a factor 2.5 which is considerably more than the 20-25% changes in PPV related to changes in PSA level or “changes in PSA” level. With respect to PSA the presence of an interaction between PSA levels and having had a previous negative biopsy is illustrated by the absence of a predictive potential of high PSA levels for men who had a previous negative biopsy.

	No previous biopsy		Previous biopsy		Row totals	
	PSA2 < median PSA2	Change in PSA < median change in PSA	PSA2 < median PSA2	Change in PSA < median change in PSA	PSA2 < median PSA2	Change in PSA < median change in PSA
Cancers detected (n)	62	71	24	20	86	91
Biopsies done (n)	274	284	224	225	498	509
PPV	0.23	0.25	0.11	0.09	0.17	0.18
	PSA2 >= median PSA2	Change in PSA >= median change in PSA	PSA2 >= median PSA2	Change in PSA >= median change in PSA	PSA2 >= median PSA2	Change in PSA >= median change in PSA
Cancers detected (n)	87	78	24	28	111	106
Biopsies done (n)	307	297	235	234	542	469
PPV	0.28	0.33	0.10	0.12	0.20	0.23
Column totals						
Cancers detected (n)	149		48		197	
Biopsies done (n)	581		459		1040	
PPV	0.26		0.10		0.19	

The table illustrates three facts

1) having had a previous negative biopsy is a much more important predictor for biopsy outcome in the 2nd screening round than having either a relatively high PSA level or having a relatively high change in PSA levels.
2) Having a relatively high PSA level and having a relatively high change in PSA level carry almost identical information with respect to biopsy outcome if the previous biopsy variable is given.
3) The predictive effect of having a high PSA level is affected (reduced) on biopsy outcome by having had a previous negative biopsy (interaction).

Ad 1) Having had a previous negative biopsy reduces the PPV more than twofold (0.26 to 0.10).
Ad 2) Having a relatively high PSA level in the 2nd screening round increases the PPV (relatively marginally) from 23 to 28 %. Having a relatively high change in PSA levels increases the PPV from 0.25 to 0.33 (again relatively marginally when compared to the effect of having a previous negative biopsy). The increase in PPV of having a high change in PSA over time is proportionally smaller in men with a previous negative biopsy (0.09 to 0.12).
Ad 3) The predictive effect of having a relatively high PSA level is absent in men who had a previous negative biopsy (0.11 to 0.10 i.e. hardly any effect).

Table III. Contingency table of PSA level and PSA change in men with and without a previous negative biopsy.

Discussion.

We have studied a consecutive cohort of men who were biopsied in ERSPC Rotterdam in either the initial screening round or the 2nd screening round 4 years later. The indication for a sextant biopsy was identical in both screening rounds (PSA was greater than or equal to 3.0 ng/ml). The compliance to the biopsy indication was equally good (86%) in both the first and second screening round.

The observation that more than half of the men who were biopsied have a PSA level between 3.0 – 5.0 ng/ml illustrates the importance of the right skewedness of the PSA distribution of the general population (i.e. the longest tail of the distribution is towards larger PSA values) in relation to the workload generated by a given PSA based biopsy indication. Lowering the PSA cut-off leads to a larger than proportional increase in the number of men with a biopsy indication.
Higher PSA levels are more prevalent in the 1st screening round. Apparently the men who were removed from the cohort in the first screening round with high PSA values (because cancer was detected) were not replaced in the intervening 4 year period by other men with lower PSA levels at the initial screen and high PSA velocities during the interval. Another possible explanation for the absence of higher PSA levels in the 2nd round might have

been that men with high PSA velocities were clinically detected in the 4 year interval (interval cancers). Considering the reported low number of interval cancers in ERSPC Rotterdam [4] this latter assumption is very unlikely.

The PSA distribution of men biopsied for the 1st time in the 2nd screening round is shifted towards lower PSA values when compared to the PSA distribution of men with a previous negative biopsy. Prostate volumes are lower in men biopsied in the first screening round when compared to prostate volumes in men biopsied in the 2nd screening round. In the group of men who were biopsied for the 2nd time the mean change in prostate volume over a four year period was 10 ml, st.dev. 13 ml (N = 459). Prostate volumes in men who were biopsied twice were considerably larger than prostate volumes in the other men who were biospied in the 2nd screening round. This in combination with the low PPV in the former group supports the view that these men have high PSA levels primarily related to their large prostate volumes (Benign Prostatic Hyperplasia) [5].

Table I shows that both DRE and TRUS have a relatively high PPV but a low NPV, both tests miss many cancers that can be detected by means of a biopsy (between 50-80% depending on screening round and having had a previous negative biopsy). Family history has a slightly lower PPV and an even lower NPV.

The outcomes of the logistic regression analysis (Table II) shows that the predictor that was used to select men for a biopsy in the first screening round (a PSA >= 3.0 ng/ml) is not an effective predictor for biopsy outcome in the 2nd screening round if men were biopsied in the first screening round. Its positive predictive properties with respect to biopsy outcome persist (at least qualitatively) if a man was not biopsied in the first screening round. Given the large spread in confidence interval we doubt whether the difference in OR between first and 2nd round PSA parameters (2.3 vs 6.9, Table II) signifies a real difference.
Apparently first round biopsies effectively removed many cancers that were related to high PSA levels. These cancers were not or to a very limited extent replaced by “new” cancers with relatively high PSA levels in the 4 year screening interval. Were this not the case PSA level would have been an important predictor for biopsy outcome in the second screening round in men previously biopsied.

Interestingly high “increases in PSA with respect to the first screening round PSA levels (PSA velocity)” are not a strong predictor for biopsy outcome in the 2nd screening round (irrespective if a man was biopsied in the 1st screening round). This can be appreciated from the logistic regression analysis (Table II, increase in PSA is not listed as its p-value was > 0.2 and so it was removed in the backwards deletion procedure). This Table highlights the relative unimportance of PSA levels and PSA velocity with respect to repeat screen biopsy outcome when compared to being biopsied before. In short “PSA increase over time” is certainly not a strong predictor for biopsy outcome in this pre screened cohort of men.

This contrasts strongly with some reports on the issue [6, 7, 8]. The discrepancy may be explained by differences in study setups. Most studies

reporting the predictive value of PSA velocity (i.e. PSA2 – PSA1) are based on a retrospective analysis of serum bank data and clinically detected cancers. In such a setup not all men are biopsied, and amongst men who are biopsied the indications for doing so very likely differ considerably. The setup of the present study is completely different. All men were biopsied on the condition of PSA >= 3.0 ng/ml, i.e. the study is a prospective one. Another possible and likely explanation has to do with the type of statistical analysis that was used. From Table III it may be concluded that PSA2 – PSA1 is a (rather weak) predictor for biopsy outcome, at least in men who were not biopsied before. But in appreciating the independent value of PSA velocity we must also take into consideration the predictive value that other parameters have given a specific PSA velocity value. One such parameter is the PSA level measured at the 2nd screening round (this parameter shows a comparably weak predictive effect as PSA velocity in men without a previous negative biopsy). If this parameter (i.e. PSA level) and the other parameters (previous biopsy, volume, DRE, TRUS etc) are jointly taken into consideration (as was done in the logistic regression analysis) the predictive value of PSA velocity is virtually reduced to zero. Maybe the explanation for the discrepancy is simply related to the fact that the studies reporting the effect of PSA velocity did not analyze the data in a multivariate fashion. Still another possible explanation for the fact that PSA velocity is no predictor for biopsy outcome in an early detection setting is related to the pathological characteristics of the cancers detected in this study. Postma et al. [9] found that 29% of the cancers detected at repeat screening can be classified as focal cancers. Their detection is most probably many years before they might become clinically detectable (lead time). Carter et al. [6,10] using data from the Baltimore Longitudinal Study of Aging (BLSA) found that a cancer specific exponential rise in PSA is observed at the time of the first symptoms, i.e. close to the time of clinical detection. Since the cancers detected at repeat screening in the ERSPC are in general many years before this stage [11] this can be an explanation for the fact that the range of PSA velocity values of the cancers detected is comparable to the range of PSA velocity values of men with a benign biopsy result.
If this 3rd explanation holds, PSA velocity is of no additional use in identifying men with an elevated risk of having prostate cancer in an early detection program but there is the possibility that it may be a valuable tool in identifying cancers with possible aggressive characteristics. Within ERSPC-Rotterdam studies to confirm this putative relationship between PSA velocity and adverse pathological characteristics of the cancers found are ongoing.

Although a direct comparison between the outcomes as reported in this paper for the 1st screening round data is not possible a recent paper on the same subject yielded qualitatively comparable results [12]. We note in this respect that the positive predictive properties of a high PSA level combined with the negative predictive properties of a high volume equate to a high positive predictive value of PSA density (PSA/Volume).

Conclusions.

In this study we have found that the predictive value of PSA that is a dominant predictor for biopsy outcome in men biopsied for the first time loses its predictive value in repeat screening in the subgroup of men who were biopsied at the initial screening. The PPV in these men is 10% which may be considered high or low depending on one's point of view. It is definitely true that having had a previous negative biopsy four years before does not rule out the detection of prostate cancer at repeat screening. On the other hand it strongly reduces this probability when compared to men who are biopsied using the same PSA related biopsy threshold and who were not biopsied before.

The present analysis indicates the following:

1) prostate cancer is a common disease (many cancers can be found, even at relatively low PSA values and even after a previous negative biopsy)
2) It is hard to detect all cancers by means of one screening test. In repeat screening cancers are even harder to detect by means of one screening test than at the initial screen.
3) If finding prostate cancer efficiently were the aim the analysis of the predictors for biopsy outcome in repeat screens indicates that it may make sense to include "having had a previous negative biopsy" and e.g. estimated prostate volume, DRE and TRUS outcomes and positive family history in the indication for a repeat screen biopsy. Such a modified biopsy criterion would very likely detect quite a few other cancers than the ones presently detected with fewer biopsies. Other cancers (those that are currently detected at low PPV's) will be missed.

Here it must be kept in mind that the conclusions drawn above extend to a PSA range that was not studied in this paper (biopsies done in men with a PSA <= 3.0 ng/ml). Whether or not a man with a PSA level between 2.0 – 3.0 ng/ml, a small prostate volume and a suspicious DRE and TRUS is indeed more likely to have prostate cancer than a man with a PSA level of eg. 6.0 ng/ml, a normal prostate volume and a previous negative biopsy remains to be shown.

In view of the above mentioned future biopsy protocols may instead of being PSA- threshold based, "detection probability based". Such protocols would minimize the number of negative biopsies at a given PPV (which is the probability threshold used). The use of such a biopsy protocol requires that in addition to PSA, prostate volume, DRE and TRUS have to be determined for every man. Alternatively the following hybrid approach is feasible: In men without a previous negative biopsy PSA >=3.0 ng/ml is used as a biopsy indication. In men with a previous negative biopsy and a PSA >= 3.0 ng/ml the probability of cancer detection is calculated and a probability threshold based biopsy indication is used. It seems logical to set this threshold equal to the PPV of the PSA >= 3 ng/ml biopsy indication (which is roughly 20%). At present a nomogram is being developed to aid in the calculation the prostate cancer detection probability (as an easy to use alternative for the logistic regression model that is presented in this paper).

Until the ongoing randomized studies have finished the analysis of the primary study endpoint (the achievement of a significant prostate cancer mortality reduction by screening) we will not know for sure whether, and if so, which cancers may be missed or need to be found. In the future knowledge of predictors for biopsy outcome may however be of value to optimize screening procedures. Especially for prostate cancer such optimization seems particularly important as at present it is evident that many more cancers will be detected by screening than expected on the basis of pre PSA screening prostate cancer incidence statistics (overdiagnosis).

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9.0

Rotterdam randomized pilot studies of screening for prostate cancer — an overview after 10 years.

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Introduction.
Four pilot studies were conducted in Rotterdam, The Netherlands, prior to the initiation of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The main purpose of these studies was to establish the feasibility of randomization and of the testing procedures. The pilot studies were not part of the ERSPC, and they were not carried out according to a predesigned evaluation plan. Here, we present the data from these trials in an effort to prevent publication bias.

Material and Methods.
The four pilot studies were conducted from October 24, 1991, to November 30, 1993; a total of 2367 men aged 55 – 75 years were identified in the population registry, invited to participate, and, after providing written informed consent, randomly assigned to receive screening for prostate cancer or no screening (control group). Screening procedures varied among the four pilot studies and are reported in detail elsewhere [1]. All protocols were approved by the local medical ethical committee. Men who reported that they had been diagnosed with prostate cancer were excluded. Men who were randomly assigned to screening were tested by determination of their serum level of prostate- specific antigen (PSA), a digital rectal examination, and transrectal ultrasonography. Biopsy indications differed among the four pilot studies.

Results.
A total of 2367 (38%) of the 6229 invited men agreed to be randomly assigned, and 94.5% of men who had an indication for biopsy underwent the procedure. This proportion varied only slightly between the initial screening and rescreening, which took place at 4-year intervals. Rectal examination and transrectal ultrasonography were not used in the second and third rounds of screening; instead, participants were offered lateralized sextant biopsies if their serum PSA value was 3.0 ng/mL or higher [2,3]. Selected data are shown in Table 1 . Of the 111 prostate cancers found in men who were randomly assigned to screening, 16 were interval cancers, six occurred in men who were not compliant with biopsy indications during the second or third rounds of screening, and 89 were detected by screening. Interval cancers were defined as cancers found during the screening intervals or within the 4 years after men who had complied with the screening protocol had passed the 75-year age limit. The 16 interval cancers were equally distributed over the approximately 10 years of the total study period.
This follow-up period is the same as that envisaged for the ERSPC as a whole.

Study arm	No. of men randomly assigned	No. of men diagnosed with prostate cancer	No. of men who underwent treatment†				No. of deaths from any cause (%)	No. of deaths with prostate cancer	No. of deaths from prostate cancer‡
			RP	RT	ET	WW			
Screening	1163	111	43	35	8	20	223 (19.2)	23	3
Control	1204	71	12	22	12	12	252 (20.9)	23	12

*ERSPC = European Randomized Study of Screening for Prostate Cancer; RP = radical prostatectomy; RT = external beam radiotherapy; ET = endocrine treatment; WW = watchful waiting.

†Type of treatment was not known for five men in the screening arm and 13 men in the control arm.

‡Verified by an independent committee.

*Table I: Results of pilot studies 1 – 4 of ERSPC, Rotterdam, with median and average follow-ups of 11.1 years and 9.9 years, respectively **

Diagnoses of prostate cancer among men in the control arm were based on cancer registry data and were confirmed by chart review. The differences in treatment between the screening and control arms reflect, in large part, the different stage distributions of prostate cancers in the two arms. The death rate from any cause was not statistically significantly different between the screening and control arms. Prostate cancer deaths were verified by an independent committee whose members were blinded with respect to the randomization assignment. There were 12 verified prostate cancer deaths in the control arm and three in the screening arm. In each of the arms, one patient is still alive with clinically diagnosed metastatic disease. Statistical testing was not applied to the reported data because of the obvious lack of statistical power.

Conclusion.

Nonetheless, these data support the continuation of the European Randomized Study of Screening for Prostate Cancer [4] by international study groups in eight European countries in the hope that it will ultimately prove the efficacy of prostate cancer screening and establish a useful preventive regimen for men at risk of this disease.

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Part III

10.0

General Disussion

Population based screening for prostate cancer has not been adopted in most health care systems because of the uncertainty regarding its efficacy in decreasing prostate cancer specific mortality at an acceptable effect on quality of life and cost. Several studies have been undertaken to determine the validity of mass screening [1, 2, 3, 4]. One of these studies is the “European Randomized study of Screening for Prostate Cancer (ERSPC) which apart from addressing the main endpoint (prostate cancer mortality), aims to improve the test procedures used for early detection of prostate cancer.
In a population based setting, where many participants and considerable amounts of money are involved, specificity is a crucial issue. This thesis focuses on the ability of the available screening tests in ERSPC (section Rotterdam) to discriminate between men with or without an elevated risk of having prostate cancer and upon their screening algorithm.

Chapter 2 provides an overview of problems and controversies of screening for prostate cancer, the anatomy of the prostate, certain aspects of prostate cancer (epidemiology, staging and grading), and available screening tests and applicable statistical techniques.

Chapter 3 describes the different screening protocols and the first round screening results of ERSPC (section Rotterdam).
At initial screening the cancer detection rate and PPV increased with increasing PSA level. In other words PSA is a positive predictor for the frequency of a positive biopsy outcome. In fact PSA was the best positive predictor for biopsy outcome (cancer yes or no) in men screened for the first time [5, 6, 7] when comparing DRE, TRUS and serum PSA level. This is also confirmed in other studies [8, 9]. The PPV of the sextant biopsy in men with PSA levels above 4.0 ng/ml was acceptable (3.6 biopsies to detect one case of prostate cancer) Using PSA derivatives improved the specificity to some degree, but, as specificity and sensitivity are generally inversely related, always resulted in a more complicated screening algorithm and a loss of detectable cancers [10, 11].
The positive predictive value of the sextant biopsy at low PSA levels was also a topic of several studies at the initial screening round (1991 – 1999). Already in 1993/1994 it became clear that DRE and/or TRUS had very low PPV’s in men with PSA levels < 2.0 ng/ml [12]. By the end of the year 1995, when data of app. 11,500 men were available it became evident that screening with DRE and/or TRUS in men with PSA levels < 1.0 ng/ml was very inefficient (43 sextant biopsies were necessary to detect one prostate cancer). From that point in time men with PSA levels < 1.0 ng/ml were not screened any further and were reinvited four years later [5]. This resulted in many less DRE/TRUS examinations and biopsy procedures and, as mentioned earlier, in a considerable increase in the recruitment rate.
A major change in the screening algorithm was introduced in May 1997 after studies were completed on the effect of changing the PSA threshold for biopsy indication. The high PPV of the sextant biopsy at the PSA range 3.0 – 3.9 ng/ml, the overall cancer detection rate and the favourable tumor characteristics of cancers found by DRE at low PSA levels were the justifications for the change [7, 13, 14, 15, 16]. DRE and TRUS were omitted as screening tests and the PSA threshold was lowered to a cut off of 3.0 ng/ml.

If a screening program is applied to the whole population a basic requirement is of course an acceptable participation rate. This will be measured against the costs involved in setting up such a program. The participation rate in ERSPC Rotterdam was 47.9% which may give rise to concern about the feasibility of a population based screening program. It must however be kept in mind that this participation rate is the result of a recruitment procedure where it is obligatory by law to obtain informed consent before randomization. In other ERSPC centers where this is not a requirement participation rates in men allocated to screening are considerably higher (60.0 - 70.1 %)[1]. The latter type of recruitment is more comparable to a situation where prostate cancer screening becomes population based.
The motives for attending or not attending the screening study [17, 18] were evaluated. Urological complaints as a reason for attending or not were part of the motives and men recruited for the trial turned out to be healthier than men in the target population [19].
Therefore although the data of the trial may not be automatically generalizable to the whole population, they may be considered representative of those who readily participate in a population based screening program [20]. If prostate cancer will become population based a good health education of the general population with regard to having urological complaints and attending screening will be of great importance.

It is obvious from the Rotterdam data that participation rates are influenced not only by the randomization procedure and screening tests offered but also by the screening algorithm. Minimizing the number of visits to a screening centre by using peripheral screening locations and making the screening algorithm a stepwise procedure resulted in a considerable increase of the recruitment rate. Obviously the knowledge that one may belong to a group in whom no further testing is necessary at this point in time lowers the barrier to participate in a screening program.

Chapter 4 describes the comparison of cancer detection rates of the “old screening protocol” (DRE and/or TRUS as screening test at PSA <= 4.0 ng/ml) and the “new screening protocol” (PSA cut off >= 3.0 ng/ml, data of 7,943 men). As predicted in the studies mentioned above the overall detection rate remained almost unchanged (5.0 % vs. 4.7% in the new screening protocol). In the old protocol 6.4% of all cancers detected were found (with DRE/TRUS) in the PSA range 3.0 – 3.9 ng/ml. In the new protocol this percentage was 18%, an almost threefold increase.
After completion of the first screening round (December 1999) the complete numbers were respectively: 10191 men screened according to the new protocol, with an overall cancer detection rate of 5.3%. The PPV of the PSA range 3.0 – 3.9 ng/ml was 21.8%. Twenty five percent of all cancers detected in this new protocol were detected in the PSA range 3.0 – 3.9 ng/ml. Omitting DRE and TRUS as screening tests and lowering the PSA cut off level did not result in detecting fewer prostate cancers, in fact the overall cancer detection rate increased as more cancers were found at the relatively low PSA values of 3.0 – 3.9 ng/ml.
A point of concern within the new protocol was the increase in men refusing the biopsy procedure. In the old screening protocol 10.7 % of the men eligible for biopsy refused. In the new screening protocol this percentage increased to

16.1%. However, complete data of the initial screening round, and thus eliminating the effect of a delay in biopsy processing, showed a refusal rate of 12.0 %, comparable to the rate at the old screening protocol.
A protocol change which permits the missing of otherwise detectable tumors must be carefully monitored, because it could result in missing cancers with the potential to contribute to the reduction in disease specific mortality.
Vis et al. [21] compared tumor characteristics of cancers found with and without rectal examination at low PSA levels. The tumors were categorized according to a predictive model, which included pathological tumor stage, tumor volume and the proportion of high grade cancer [22]. In this model minimal tumors were defined as small (< 0.5 ml), organ-confined, without Gleason pattern 4 and 5, whereas advanced cancers were tumors invading adjacent organs , cancers of >= 1.0 ml in tumor volume extending through the prostatic capsule and/or tumors containing large amounts (>= 0.5 ml) of poorly differentiated cancer (Gleason pattern 4 or 5). All cancers with tumor characteristics in between were classified as moderate (i.e. potentially aggressive and curable) disease. Subsequently moderate and advanced cases were classified as clinically significant. Vis found that when DRE and TRUS were used as initial screening tests at low PSA levels the proportion of cancers detected with any poorly differentiated components (i.e. Gleason scores 7 to 10) in the biopsy specimen, increased from 0% in men with PSA levels between 0.0 – 1.0 ng/ml, 18.6% in the PSA range 1.0 -1.9 ng/ml, to 37% in the PSA range 2.0 – 2.9 ng/ml and even 44.2% in the PSA range 3.0 – 3.9 ng/ml.
A suspicious DRE and/or TRUS led to the detection of significantly more moderately and poorly differentiated cancers (as determined on the biopsy) than PSA based screening. This conclusion was based on the comparison of the two different screening protocols in the PSA range 3.0 – 3.9 ng/ml. The percentage of cancers detected with Gleason score 7 to 10 in the old protocol (biopsy DRE and/or TRUS driven) was as noted 44.2 % compared to 18.2% in the PSA driven biopsy protocol.
A low rate of aggressive cancers was also seen in a side study done during the second screening round [23]. During a period of 20 months, men with a PSA level between 2.0 – 2.9 ng/ml (n= 576) were also systematically biopsied. This resulted in the detection of 75 cancers (cancer detection rate 13.0 %) of which only 6.7 % had a Gleason score of 7 or more.
The percentages of clinically significant cancers mentioned above however do not reflect the number of men screened necessary to detect these clinically significant cancers. Relating the number of cancers to the total number of men screened in these low PSA ranges results in the following numbers: In the PSA range 1.0 – 1.9 ng/ml 3051 men were screened with DRE/TRUS, 511 men were biopsied (335 men had abnormal DRE), 43 cancers were diagnosed of which 8 had a Gleason score of >= 7. This implies that the cancer detection rate of clinically significant cancers found with DRE and/or TRUS is 8/3051 = 0.26 % in men with PSA levels between 1.0 – 1.9 ng/ml. For the PSA ranges 2.0 – 2.9 ng/ml and 3.0 – 3.9 ng/ml this figure is res. 0.83 % and 3.0 %.
These studies show that clinically significant cancers are present at low PSA ranges (especially in the PSA range 3.0 – 3.9 ng/ml) but when DRE was used as biopsy indication; the ability to detect these potentially aggressive tumors was extremely low (289 rectal examinations were required to detect one case of clinically significant disease).

These findings are comparable to a study of Carvalhal et al [24]. This group examined biopsy results of 1905 men with a PSA <= 4.0 ng/ml and a suspicious DRE. 244 cancers were detected (13%); all cases were clinically localized and 62% had moderately differentiated biopsy Gleason scores (5-7). 3% of the cancer cases were poorly differentiated (Gleason scores of 8-10). The PPV of the DRE increased with increasing PSA levels from 5% in the PSA range 0.0 – 1.0 ng/ml to 14.2% in the PSA range 1.1 – 2.5 ng/ml. They conclude that DRE may detect tumors that have histopathological features of clinically important and still curable disease in men with low PSA levels. The PPV of the DRE is considered sufficiently high at PSA levels > 1.0 ng/ml to continue the use of DRE with PSA testing for the early detection of prostate cancer.
Additional evidence of the presence of clinically significant prostate cancers at low PSA levels came from a study of Thompson et al [25]. In a side-study of the Prostate Cancer Prevention Trial (PCPT) they considered the prevalence of prostate cancer among 2950 men randomized to the placebo group. These participants had a PSA < 3.0 ng/ml at entry and during the seven-year study period never had a PSA value =>4.0 ng/ml or an abnormal DRE (measured and examined annually). At the end of the study all these men underwent prostate biopsy (sextant biopsy technique). Prostate cancer was diagnosed in 15.2% of the participants, of whom 14.9% had a Gleason score >=7. The prevalence of prostate cancer increased with the PSA level (from 7% at PSA <= 0.5 ng/ml to 27% at PSA 3.1-4.0 ng/ml). The prevalence of high-grade cancers also increased with the PSA level from 12.5% (PSA <= 0.5 ng/ml) to 25.0% (PSA 3.1 to 4.0 ng/ml).
It was concluded that biopsy-detected prostate cancer, including high-grade cancer, is not rare among men with PSA value <= 4.0 ng/ml and even in men with PSA values below 2.0 ng/ml. However it is important to relate the number of high grade cancers to the total number of men in the different PSA ranges. In the PSA range < 0.5 ng/ml, 4 high grade cancers were found in a total of 486 men (0.82%) and in the PSA range 3.1 – 4.0 ng/ml this percentage was 6.7% (13/193).
Within ERSPC Rotterdam 69% of the men had a PSA <= 2.0 ng/ml. Knowing that approximately 44-83% of men in the age range 55 – 79 years have latent prostate cancer [26] it is very possible that these small cancers, even if they are Gleason grade >= 7, can be detected later in time still in a curable stage (chapter 6).
Data on detection rates and tumor characteristics of cancers detected in the second round (4 years later) or perhaps even better in the third round of screening (8 years later) differentiating between the two different initial protocols will give more answers on the effect of omitting DRE as a screening test at low PSA levels. So far results show no increased interval cancer rate, nor an increase in poorly differentiated cancers detected at repeat screening when comparing men screened during the initial round with the “old protocol” and the “new protocol” [27].

The question remains why these cancers do not cause an elevated PSA level. A study by Sokoloff et al. [28] showed that prostatectomy specimens of men with a pre-operative PSA < 4.0 ng/ml or PSA > 4.0 ng/ml were impossible to differentiate on immunohistological staining for tissue-PSA. The intensity of PSA staining in the radical prostatectomy specimens was identical, implying

that tissue-PSA production was comparable. Why then are the serum PSA levels different?
In men with normal prostates only small amounts of serum PSA are detectable. However, for men with prostatic disease serum PSA is often elevated. On average normal prostatic epithelium contributes 0.1 ng/ml/gm tissue to serum PSA. Corresponding figures for BPH tissue and cancer tissue have been estimated to be 0.3 and 3.5 ng/ml/gm respectively. Furthermore it is known that tissue PSA (being 10^6 times as high as serum PSA levels) decreases and serum PSA increases with increasing tumor volume and cytological grade [29,30].
Using tissue from fine needle biopsies Stege et al. [31] also found this negative association between serum PSA and tissue PSA and concluded that serum PSA values mainly reflect the degree of leakage from the tumor tissue rather than the intracellular concentration of PSA. Factors such as tumor volume, gland structure, and vascularization may thus be more important than the production of PSA in the prostatic tissue. It is very possible that a small high graded tumor causes no serum PSA elevation simply because the gland structure is not (yet) disrupted by tumor growth. This latter observation was confirmed by comparing tumor volumes and serum PSA levels in radical prostatectomy specimens of cancers detected at the initial and repeat screening visits in ERSPC Rotterdam [32]. This study showed a significant relationship between PSA level at diagnosis and tumor volume in the radical prostatectomy specimen. At a PSA level of 3.0 ng/ml the mean tumor volume was 0.32 ml while at a PSA level of 10.0 ng/ml or higher the mean tumor volume was 1.06 ml (data from initial screening).

The observer dependent character of the DRE and low PPV at low PSA levels, together with the knowledge that prostate cancers amenable for curable treatment are present in this PSA range [14] makes a more specific and objective screening test desirable. Fang et al [33] suggested that the PSA velocity could be of use in men with low PSA levels.

Chapter 5 is the result of two side studies done during the second screening round of ERSPC (Rotterdam). The value of the PSA velocity (calculated with the PSA levels of the initial and second screening) as a predictor for biopsy outcome in men with low PSA levels was retrospectively assessed. This study again showed that the risk of biopsy detectable prostate cancer in these low PSA ranges (PSA < 4.0 ng/ml) was high, with an overall PPV of 19.3%. PSA velocity however was, in this dataset, not a significant predictor for biopsy outcome. When using a PSA velocity cut-off of > 0.1 ng/ml/yr the relative sensitivity would have been 85.2% with a relative specificity of only 17.9%. These observations were confirmed by a study of the rate of four year PSA progression from an initial value < 3.0 ng/ml towards the cut off point of 3.0 ng/ml (Schröder et al. [34]). From this study it became clear that the most pronounced PSA increase e.g. from 0.0 – 0.9 to > 3.0 ng/ml in the 4-year interval was not associated with a higher PPV.
Our observations on PSA velocity are not in line with the observations by Carter et al. and Fang [33, 35] from the Baltimore Longitudinal Study of Aging (BLSA). The most plausible explanation for this difference is the difference in the two study populations. Cancer cases in the ERSPC study were detected by a PSA driven protocol (n= 149), whereas the cancer cases in the BLSA study (n= 21) were either clinically detected or detected by an abnormal DRE.

Prostate cancer is a disease with a relatively long pre clinical detectable phase. This is the time between the first detectable patho-physiologic change (e.g. an elevation of the serum PSA level) and the first symptoms and or signs (e.g. a palpable nodule). Using data from the Finnish arm of the ERSPC the mean duration of the pre clinical detectable phase was estimated to be 10-14 years [36].
Data from the Baltimore Longitudinal Study of Aging (BLSA) showed that men with BPH have a linear or moderate exponential increase in PSA level with time, whereas patients with prostate cancer have a similar linear or moderate exponential increase with a subsequent exponential increase in PSA level at the time of the first symptoms i.e. the time of clinical detection [37,38]. PSA based early detection results in an advance of the diagnosis by many years. This so called lead time is on average at least half of the time of the preclinical detectable phase or less than one half because more easily diagnoseable larger tumors are likely to occur toward the end of this period. Its estimations vary from 5 – 7 years [36,39] to 11 years [40], depending on the histological grade of the tumor and age of the patient at time of diagnosis. This would mean that the cancers detected by screening are on average detected before the exponential, cancer specific, increase of the PSA level. (figure 4)
This hypothesis is further confirmed by a univariate analysis of the Rotterdam data where the outcome variable was not cancer yes or no, but no cancer versus cancer stage T2C or higher and/or Gleason score 7 or higher (where it is assumed that the latter group reflects a more clinical situation). In this analysis, PSA velocity had an odds ratio > 1.0 and was significant. This significance is however lost in a multivariate setting (unpublished results).

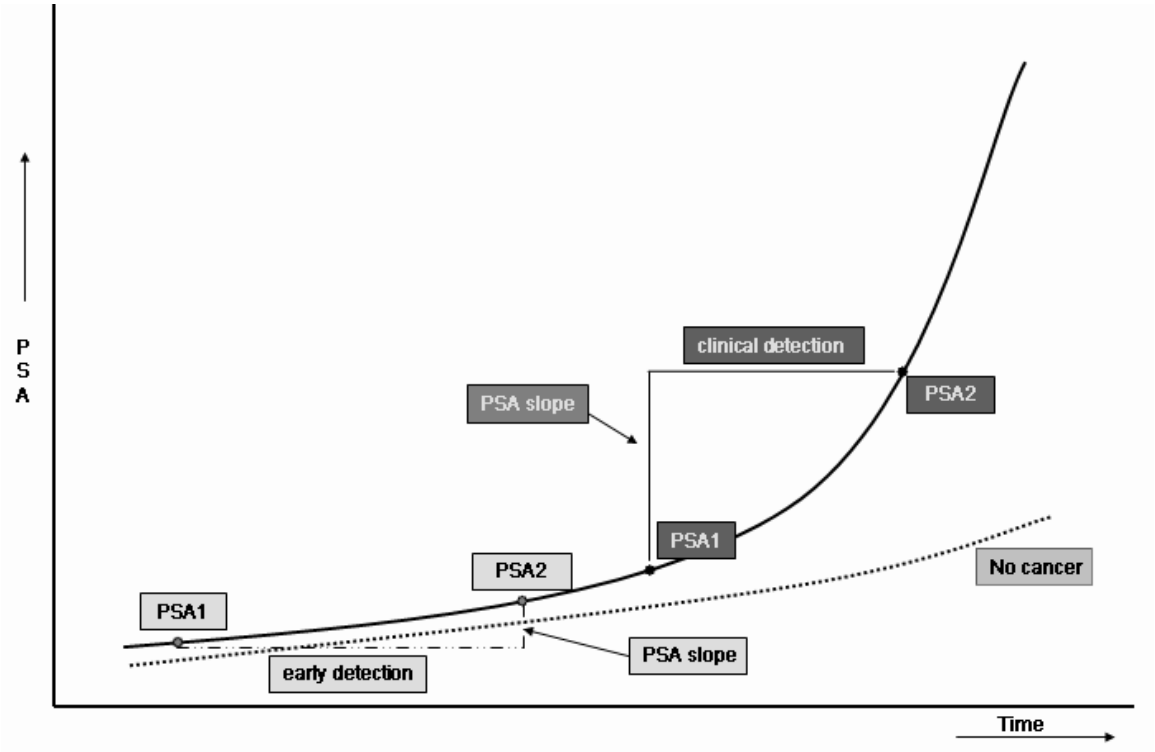

Figure 4: PSA course in prostate cancer and BPH

These findings together with the considerable intra individual biological variation [41, 42, 43, 44], resulting in the necessity of long term sampling and preferably three consecutive measurements for a reliable calculation of the PSA velocity [43] makes PSA velocity less suitable as a screening test for prostate cancer in a population based setting.
It must however be noted that the proper way to assess the value of PSA velocity in identifying men with an elevated risk of having prostate cancer is to use a PSA velocity cut off as the indication for biopsy in an unscreened population preferably starting at a younger age.
PSA velocity or doubling time was shown to be of value in men already diagnosed with prostate cancer and treated with radical prostatectomy or expectant management. In the first case DÁmico et al. [45] reported that the preoperative PSA velocity predicts the risk of dying of prostate cancer after radical prostatectomy and that this measurement may be used to enhance the identification of aggressive prostate cancer. Expectant management of localized prostate cancer has evolved during the last decade as a treatment option because screening and biopsy sampling strategies were shown to lead to a large amount of overdiagnosis. PSA velocity or PSA doubling time may improve the identification of men who are likely to have a low rate of progression at repeat biopsy and rendering them eligible for continuing expectant management [46].

The omission of further screening in men with PSA levels < 1.0 ng/ml was a protocol change that could have resulted in missing cancers that can be life threatening when not detected whilst in an organ confined state.

Chapter 6 describes the results of screening of men with a PSA level <= 1.0 ng/ml at initial screening after an 8 year follow-up period (n = 1703). In two subsequent screening visits 47 men had a PSA increase above the cut off level of 3.0 ng/ml (2.8%) and 8 cancers were detected (0.47%). More importantly no additional clinically detected cancer arose during the 8 years. Omitting further screening, at least for 8 years, in men with PSA levels <= 1.0 ng/ml implies a minimal risk of missing aggressive cancers in a curable state. This study again confirms the observations mentioned earlier: PSA progression in men with very low PSA levels is rare, but cancer and clinically significant cancer is, although in low percentages, present at these low PSA ranges. PSA velocity is of no additional value in this cohort of men.
Delaying the biopsy procedure until PSA increases to a certain cut off value, saves a lot of unnecessary biopsies, but does not seem to lead to an increase in the detection of incurable prostate cancer cases. Searching for effective prostate cancer screening tests, especially in men with these very low PSA levels (which represent 42% of the screening cohort!), is important. Testing should in the future become more selective for those cancers with aggressive features to further decrease the rate of biopsies, their complications and over diagnosis. One can estimate that the lifetime risk for prostate cancer would be even greater than the present 16 % in the US, if all men with a PSA > 1.0 ng/ml were biopsied [47].
These data together with the data presented in the PSA progression paper [34] suggest that the ERSPC can give an answer to the issue of detection of cancers with aggressive patterns as seen in the end of study biopsies done in the placebo arm of the PCPT [25]. The available data suggest that it is an option to observe men with very low PSA values until they reach a biopsy threshold of 3.0 ng/ml.

Another concern within a prostate cancer screening program are those men who fulfill the criteria for further investigation (in this case an elevated PSA level) and are actually biopsied, but have a benign biopsy result. Knowing that the sextant biopsy procedure is not 100% sensitive, one must consider the appropriateness of the sextant technique and the dilemma of re-biopsying.
Many studies have dealt with these topics. Computerized biopsy simulations on a series of radical prostatectomy specimens showed that the chance of missing a cancer by sextant biopsy is about 25% [48]. This knowledge resulted in the development of refinements to the sextant biopsy technique. Biopsies should be directed more laterally [49, 50], perhaps with eight [51], thirteen [52] or even 18 or more cores [53,54,55,56].
Prostate volume became an issue in determining the adequate number of cores, as the relative amount of gland that is sampled is determined by the size of the prostate. Two groups [57,58] retrospectively found that the systematic sextant biopsy in larger prostates detected significantly fewer tumors than in smaller prostates. Computer generated models and nomograms were developed to predict the appropriate number of biopsies for a given volume [59,60].
While midline biopsy cores have been shown to be the least frequently affected by prostate cancer, lateral biopsies, directed towards apex and base combined with standard sextant biopsies are currently used by most urological centers.

If, despite the number of biopsy cores taken, the result of the biopsy is still benign there is always the option of repeating the biopsy session. Several studies have addressed this topic [61, 62, 63, 64, 65, 66, 67]. Overall, between 10 and 34% of men (depending on the particular features of the patient and type of biopsy) are found to have cancer on a second TRUS biopsy after an initially negative biopsy. A third and fourth sequential biopsy identified 5% additional cancers [68].
All studies have drawn a more or less similar conclusion: increasing the number of biopsy cores and biopsy sessions increases the cancer detection. The critical question is whether the cancers detected with increasing number of cores or sessions are clinically significant and need to be detected at this point in time, later or at all.
ERSPC data have the potential to investigate the effect of not taking more cores and not performing immediate repeat biopsy procedures, since the protocol with regard to the number of cores and the indication for repeat biopsy (dubious malignant or high grade PIN) has not changed since the start of the study.

This issue of repeat biopsy sessions is addressed in **Chapter 7** which reports on a cohort of men (n = 272) biopsied for the second time after a benign biopsy result four years earlier (sextant technique). If the technique of lateralized sextant biopsies and the policy of not performing an immediate re-biopsy would be ineffective this should result in a considerable number of (advanced) interval cancers or an increased detection rate and/or more advanced cancers at repeat screening four years later. The PPV at 4-year repeat screening was 8.3 % (all cancers detected, except one, were organ confined). The number of interval cancers was certainly not negligible (8 cases in 312 men = 2.6%) but they were mainly found in men older than 74 years of age and in men who had refused biopsy at initial screening.
The data confirm the importance of prostate volume as a negative predictor. Men with a benign biopsy result had significantly larger prostate volumes which could indicate that the sextant technique misses cancer in this cohort of men. However making decisions on more biopsy cores or repeated biopsies based on an elevated PSA level and prostate volume will also imply more unnessecary biopsy sessions in a group of men with a persistently elevated PSA level caused by BPH.
Again refinement of the screening algorithm is desirable and data presented in chapter 7 (based on low numbers) show the possible use of PSA velocity, but perhaps even more specific for this particular cohort of men, the PSA density velocity.
With the completion of the second screening round in December 2003 more data became available. Analysis of a data set of 434 men with an initial PSA >= 4.0 ng/ml and a benign biopsy result and a biopsy indication at second round screening resulted in the detection of 46 cancers (PPV = 10.6%). The change in PSA values (PSA velocity, ng/ml/yr) and PSA density values (PSAD velocity, $ng/ml^2/yr$) in the 4 year interval were significantly different res. p= 0.037 and 0.038 (Mann-Whitney U test). Between the first and second screen however the overlap in values between cancer and non-cancer cases was considerable. These data indicate that PSA, PSA velocity and PSAD velocity, despite the significant differences shown, have no real discriminating effect between cancer or no cancer (determined by a lateralized sextant biopsy) in

this particular cohort of men (unpublished results). These results are similar to an earlier published study of Hayek et al [69].
As mentioned it was not possible to evaluate free PSA as a possible predictor for biopsy outcome.

The free/total PSA ratio (F/T ratio) to discriminate BPH from cancer is a concept extensively investigated in the past few years. Total PSA consists of Complex PSA (cPSA) and Free PSA (fPSA). cPSA is serum PSA that is bound to circulating proteins, usually alpha-1-antichymotrypsin. The remainder is classified as fPSA. It has been shown that the proportion of circulating cPSA is higher in patients with carcinoma than in those with BPH [70]. Studies comparing the diagnostic efficacy of cPSA with total PSA and the free to total (F/T) ratio report diverging results. Superior performance for cPSA over total PSA or the F/T ratio [71, 72], superiority of cPSA over total PSA, but not over the F/T ratio [73], equivalence of cPSA with total PSA and the F/T ratio [74], as well as equivalence of cPSA with total PSA but superiority of the F/T ratio over cPSA [75] have all been reported.
Within ERSPC the value of the F/T ratio was also been examined during a certain period. Bangma et al. [11] found that with the application of a threshold of 0.20 the number of biopsies would have increased substantially, especially in the PSA range below 4.0 ng/ml. The use of an F/T ratio for men with a total PSA of 4.0 ng/ml or higher would miss 11% of the cancers and reduce the number of biopsies by 37%. The Swiss group of ERSPC looked at men with PSA levels between 1-3 ng/ml and a F/T ratio of 0.20 or less. They found an almost identical F/T ratio in men with or without cancer [76]. Hugosson et al. [77] found that in a cohort of men with a PSA level >= 3.0 ng/ml, the use of a F/T ratio < 0.22 cut off level decreased the number of unnecessary biopsies 31%.
The Italian center of ERSPC [78] concluded, on the basis of their screening data, that the F/T ratio was not a reliable predictor for biopsy outcome. Using different F/T ratio cut-off values indeed could reduce the number of benign biopsies but as a result would lead to missing a comparable percentage of prostate cancer cases. In the Dutch center free PSA was also measured during a certain time period at repeat screening in men with total PSA values of 2.0 – 3.9 ng/ml. This study [79] suggested a moderate role for the F/T ratio in avoiding benign biopsies but confirmed that the F/T ratio was predictive in assessing tumor aggressiveness. This observation is similar to the study of Khan et al [46].

Also the F/T ratio may be of use in men with a previous negative biopsy. Catalona et al. [80] concluded that using a free PSA cut-off of less than 25%, twenty percent of unnecessary biopsies could be prevented with a loss of 5% of detectable cancers. Djavan et al. [81] used a cut-off of 30% and could eliminate 50% of the biopsies while detecting 90% of the cancers.
In addition to the very divergent results in prostate cancer screening the concept of F/T ratio has several other flaws. Pre-analytical and clinical factors may influence the F/T ratio, e.g. instability of free PSA both at 4°C and at room temperature, assay characteristics, and a dilution effect in large prostates due to concomitant BPH.
Processing of free PSA to complex PSA is different during the release of PSA from benign and malignant tissue [82, 83]. This makes a specific

determination of various forms of free PSA in serum a potential way to improve the specificity of prostate cancer detection. So far assays for the different forms of free PSA are not generally available and are thus not suited for a population based screening setting at this point in time.

Human glandular kallikrein 2 (hK2) and PSA (human kallikrein 3), belong to the human tissue kallikrein family. It has been reported that hk2 expression increases incrementally during the change from benign prostatic epithelium to primary cancer and lymph node metastasis [84]. Several studies have been done to establish the value of hk2 in prostate cancer detection. Kwiatkowski and Recker reported a significant difference in hk2 level between prostate cancer cases (0.135 ng/ml) and BPH (0.09 ng/ml) in men with PSA levels of 4.0 – 10.0 ng/ml. Also specificity of the ratio of hk2 to free PSA was significantly better compared with the F/T PSA ratio and total PSA [85,86]. One flaw of these studies was the fact that sextant prostate biopsies were not performed routinely, thus leaving the possibility of an attribution bias.
On the other hand Partin and Bangma [87,88] found, that the utility of hK2 was limited.
Because the serum concentrations of hK2 are 50-100 fold lower than those of PSA, determination of hK2 is quite demanding. Variable results in various studies may thus be caused by differences in assay performance.
Though hk2 or derivates of hk2 might contribute to improvements in the accuracy of prostate cancer detection a standardized test will be needed before hK2 could be used in a population based setting.

The observation that the predictive value of serum PSA in men previously biopsied is lost at the second screening round makes the use of a simple PSA cut –off as an indication for biopsy in this particular cohort of men debatable.

Chapter 8 studies the phenomenon of a changing relation between PSA levels and prostate cancer detection in a multivariate setting including men who had a previous negative biopsy at initial screening.
These data show that the cohort of men screened for the second time in fact consists of two groups where predictors for biopsy outcome act completely differently. Analyzing these men together will thus lead to false conclusions with regard to the value of the different predictors. The key finding is that in men not previously biopsied predictors for biopsy outcome are comparable to those at initial screening. The cohort of men previously biopsied is clearly different; PSA lost its predictive value completely, increasing the relative importance of other predictors (DRE, TRUS and prostate volume). PSA kinetics do not contribute to the prediction of biopsy outcome at repeat screening.
The above mentioned data suggest that the decision to perform a prostate biopsy based on an algorithm could be more efficient than performing a biopsy based on one predictor, especially in men who already had a negative biopsy procedure.
The estimated cancer detection probability can be used as a biopsy indication instead of the present PSA threshold. In that case prostate volume, DRE and TRUS have to be determined for every man. Alternatively the following approach is feasible: In men without a previous negative biopsy PSA >=3.0 ng/ml is used as a biopsy indication. In men with a previous negative biopsy

and a PSA >= 3.0 ng/ml the probability of cancer detection is calculated. A biopsy is indicated if the calculated probability is higher than a certain threshold. E.g. 215 men with a previous negative biopsy and a PSA >= 3.0 ng/ml (46.8 % of cohort under study) have an estimated cancer detection risk of < 8% in the presented data set. In these men only 13 cancers were detected (6.5 % of the cancers detected in the 2nd screening round).

The loss of the predictive value of PSA in the detection of prostate cancer has also been observed in the United States in areas where screening is prevalent. Stamey et al [89] claim that the PSA era is over and that PSA was related to the presence of prostate cancer 20 years ago, but at present is only related to BPH. This observation is however based on data coming from an area where screening has been common practice for many years (with relatively short intervals and aggressive screening algorithms) and the data relating to the present time are thus most likely based on a heavily pre-screened cohort.
Even the 4-year interval of the ERSPC is too short for the remaining cancers to re-grow to the same volume as the cancers detected at initial screening that caused the positive correlation between the chance of cancer detection (PPV) and PSA level. This will certainly be the case in the United States where screening intervals are much shorter and men with very low PSA levels are biopsied.
The concept that the era of PSA is over therefore needs some specification, PSA is still a valuable tool in the early detection of prostate cancer on a population based level and is related to the presence of prostate cancer, especially in men screened/biopsied for the first time. Due to PSA increase over time it was shown that the (arbitrary) cut-off value of PSA in second round screening has a PPV of 20-25% as in round 1 [34].

Also used in the multivariate analyses in this thesis, is a positive family history (i.e. brother(s) and/or father with prostate cancer).
At the initial screening round in Rotterdam, men with a positive family history had a relative risk (RR) of 1.59 for detecting prostate cancer as compared to men with a negative family history. This conclusion was based on 19,815 filled in questionnaires in which 1,364 men reported a positive family history. At repeat screening the relative risk for men with a positive family history was 1.30 [90,91]. These data are comparable to a large cohort study of 5,496 sons of Swedish men found to have prostate cancer between 1959 and 1963. A significantly increased overall standardized incidence ratio (SIR) of 1.70 (95% confidence interval, 1.51-1.90) was seen for prostate cancer in this cohort [92]. Selective screening of this subgroup would increase the specificity of the screening program, but will result in a very low sensitivity because only a small proportion of the men eligible have a positive family history.
A positive family history was not associated with prognostic indicators such as Gleason score and clinical stage in our data set [93]. This latter observation is confirmed by other studies [94,95,96]. Longer follow up will give more insight into the prognostic impact of the tumour characteristics of men with a positive family history. This will be important to decide whether a more intensive screening algorithm in this group of men possibly starting at an earlier age is necessary.

Opposite findings with regard to having had a negative biopsy are also found within the ERSPC [97]. Mäkinen et al. found that a PSA level >= 4.0 ng/ml and

having had a negative biopsy at initial screening was associated with an up to 9-fold risk of cancer in re-screening relative to those with lower PSA levels at baseline (and therefore not biopsied at initial screening).These differences however can be explained by the differences in the screening algorithm used at initial screening and the fact that calculations are based on groups of men with different percentages of men actually biopsied, as is explained in an editorial [98]. Data shown here make it clear that the PPV in men previously biopsied is lower than that of men biopsied for the first time (i.e. men whose PSA raises above the cut-off level of 3.0 ng/ml in the 4-year interval).

It is clear that the current methods used to diagnose prostate cancer have their limitations, resulting not only in missed cases of prostate cancer, but also in the diagnosis of cancers whose natural history is not likely to be life-threatening. Extensive research is ongoing to refine the current tools, and to develop new, more reliable tests.
In recent years, pro PSA has been investigated as a means to better differentiate prostate cancer from BPH. Pro PSA represented approximatively 3% of total PSA when measured in malignant tissue, while it was detected only in minimal amounts in benign tissue. Moreover, the truncated (-2) pro PSA form accounts for 25–95% of the free PSA in the serum of prostate cancer patients, but only for 6–19% of free PSA in the serum of patients without prostate cancer. Recently, some clinical studies have suggested that the use of pro PSA could improve the detection rate of prostate cancer. Sokoll et al. [98] evaluated the impact of pro PSA on the detection of prostate cancer in men with a total PSA between 2.5 and 4 ng/ml. Archival serum samples from 119 men (non-cancer 88, cancer 31), obtained before biopsy, were assayed for total PSA, fPSA, and pro PSA. Pro PSA was defined as the sum of the (-2), (-4), and (-7) pro PSA forms, and %pPSA as proPSA/fPSA. Total PSA and %fPSA values were similar between the non-cancer and the cancer groups. Although %pPSA tended to be higher in the cancer group (50.1% versus 35.5%), this difference was not statistically significant ($p = 0.07$). On the other hand, at a fixed sensitivity of 75%, the specificity was significantly greater for %pPSA compared with %fPSA (59% versus 33%, $p < 0.0001$).

The hK11 protein is encoded by the *KLK11* gene, which belongs to the human kallikrein family along with PSA (hK3) and other kallikrein. In a study were the serum hk11 level was compared between men with prostate cancer and BPH showed that the hK11: total PSA ratio and percentage of free PSA were much stronger predictors of the presence of prostate cancer than total PSA. These preliminary data suggest that the hK11: total PSA ratio could be a useful tumor marker and could be combined with percentage of PSA to further reduce the number of unnecessary prostatic biopsies [100].
Insulin-like growth factor-1 (IGF-1) and IGF bindingprotein- 3 (IGFBP-3) play an important role in the regulation of prostate cancer cell growth. However, whether these molecules represent tumour markers or aetiological factors has been a subject of debate. In a study done within the ERSPC section Rotterdam the measurement of serum IGF-I and/or IGFBP-3 concentrations in addition to PSA did not improve the identification of men at high risk to develop early stages of prostate cancer. In addition, the results indicated that the endocrine IGF-I system is not directly involved in the growth of the early stages of prostate cancer [101,102].

The diagnostic potential of somatic changes that occur in prostate cancer cells should not be forgotten, with changes becoming more common as the disease progresses. Of particular note is differential display code 3 (DD3PCA3), which is highly over expressed in prostate cancer tumours, but is not expressed in normal human tissue. DD3PCA3 could potentially play an important role in the early identification of malignancy, although this is not yet tested in an asymptomatic population. Use of a new molecular urine assay test to detect prostate cancer based on the presence of urinary DD3PCA3 showed a sensitivity of the assay of 67%. Furthermore, a negative predictive value of 90% was calculated (tested in men with a PSA level > 3.0 ng/ml) [103].
Other markers under investigation are, Neuroendocrine tumor markers i.e. chromogranin A (CgA) and estrogen inducible pS2 protein [104, 105], Prostate stem cell antigen (PSCA) and transient receptor potential p8 (trp-p8) [106,107,108] and Prostate-specific membrane antigen [PSMA, 109, 110].

The diagnostic tools discussed so far have mainly relied on the use of established scientific approaches. However, the latest technology—gene chips (DNA microarrays) and proteomics [111]—has opened up completely new diagnostic avenues. These powerful tools are likely to accelerate identification of new molecular diagnostic and therapeutic targets. Gene chip analysis allows the pattern of gene expression in tumours to be profiled, with thousands of genes monitored simultaneously. This technique can be used to compare the level and types of genes expressed in tumours compared with normal tissue, and to follow changes in prostate cancer cells during disease progression.
One important new gene has been identified using gene chip analysis; this is a-methylacyl-CoA racemase (AMACR). AMACR is up regulated in prostate cancer and has been shown to increase confidence in the diagnosis of malignant disease [112,113].
The definite need of more specific biomarkers for prostate cancer is underlined by the start of the so-called P-mark project [114].
In the P-Mark project, several recently developed; promising markers will be evaluated using clinically well defined bio repositories. Following successful evaluation, these markers will be validated on a sample set derived from two large, European, prostate cancer studies and used for the identification of special risk groups in the general population.

Chapter 9 describes the results of the first four pilot studies of ERSPC. These pilot studies are not included into the European Randomized Study of Screening for Prostate Cancer (ERSPC). The results of these pilot studies cannot replace the final outcome of ERSPC because of a drastic lack of power. The data may however serve as an encouragement to continue the ERSPC and at the same time as a trigger to start thinking about the future of prostate cancer screening. As said before it is unrealistic to think that prostate cancer screening will be discontinued, even if the ERSPC shows no significant mortality reduction. In that case screening almost certainly will not lead to national, population based, screening programs, but opportunistic screening will probably continue. If however the ERSPC shows a significant mortality reduction the impact of this message will be important. Many men will search for a possibility to be screened, making an effective screening

algorithm a first priority. It must however be kept in mind that this possible prostate cancer specific mortality reduction will be the result of a major effort with respect to the number of necessary screening tests. Also perhaps more importantly a considerable amount over-diagnosis and subsequent over-treatment will result. It is therefore of great importance that research continues using available data of the ERSPC. The value of screening tests, tumor characteristics, treatment, mortality and not least the serum and tissue repositories will be invaluable in developing an acceptable and effective screening algorithm which either drastically decreases over diagnosis or identifies with an acceptable degree of certainty those patients which are preferably managed by watchful waiting.

Conclusions:

Based on the data presented in this thesis the following conclusions can be drawn:
Population based screening for prostate cancer is feasible, participation rates are acceptable and the screening tests well tolerated.
Screening with the use of total PSA is at this moment the most efficient approach in unscreened populations.
PSA kinetics are of no additional value in the early detection of prostate cancer at least as long as cut-off values are used as biopsy indications.
Screening in men with low PSA values is sub optimal because of low PPV's of the sextant biopsy.
The role of DRE at low PSA values needs further investigation.
New markers, to improve specificity, are urgently needed in the low PSA range, which represent a large proportion of men eligible for prostate cancer screening.
Longer screening intervals are possible men with PSA levels <= 1.0 ng/ml.
Men with a previous benign biopsy result form a separate group and a screening test which is able to discriminate between BPH and prostate cancer is needed.
A screening algorithm, especially at repeat screening, should be more "tailored" to the individual using a combination of several (new) predictors.
It must however be kept in mind that whenever a test or combination of tests for diagnosing prostate cancer approaches 100% sensitivity and specificity, there is the concern that insignificant cases of prostate cancer may be diagnosed. The development of a method to determine which cancers are clinically relevant and need to be detected at an early stage would represent an important breakthrough in prostate cancer research. After that the optimal biopsy technique and screening interval could also be evaluated further.
The data from the initial and repeat screening visits in ERSPC, the established serum and tissue repositories as well as the clinical follow-up of the cancers diagnosed will provide valuable data with respect to the above mentioned needs.
Until these data from the ongoing randomized trial become available the guideline in prostate cancer screening should be "less is more" and men who wish to be screened should be properly informed to enable them to evaluate the possible harms and benefits of prostate cancer screening.

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Summary

Although the concept of early detection of cancer sounds intuitively logical it is not automatically so in the case of prostate cancer despite the fact that the data on incidence and mortality show that it is an important health problem. The fact that prostate cancer is in general a slow growing tumor mainly in elderly men raises the question whether early detection and available treatment (with related morbidity) will improve prostate cancer specific survival. The identification of PSA as a diagnostic tool, and an increased awareness of the disease by patients and doctors resulted in an increase in incidence of prostate cancer. Whether such early detection and treatment of prostate cancer will save lives can only be answered by a well performed randomized controlled trial. The European Randomized study of Screening for Prostate Cancer (ERSPC) is a multi centre study that has the power to investigate the impact of screening for prostate cancer on disease specific mortality. The ERSPC also provides a means to study the performance of screening tests in identifying men with an elevated risk of having prostate cancer in an asymptomatic population. This thesis concentrates on this subject (chapter 1).
Chapter 2 gives background information on the prostate, prostate cancer, screening and the statistical methods used in this thesis.
Chapter 3 describes the history of the ERSPC (section Rotterdam) trial. During the course of the study it was shown that the initially chosen screening algorithm based on the available knowledge at that time, was not optimal. The evaluation of the screening data that became available identified groups of men in which the screening algorithm primarily chosen was not very effective. Two major changes were put into effect: screening was omitted in men with PSA values < 1.0 ng/ml and the use of DRE and TRUS as screening tests together with the lowering of the PSA cut-off value from 4.0 ng/ml to 3.0 ng/ml as an indication for sextant biopsy. The changes in the screening algorithm led to a more efficient screening procedure (with regard to unnecessary visits and biopsy procedures) and also increased the participation rate.
In Chapter 4 the two different screening algorithms are compared with regard to cancer detection rate and tumor characteristics of the cancers detected. Omitting DRE and TRUS as screening tests and lowering the PSA cut off level did not result in detecting fewer prostate cancers. In fact the overall cancer detection rate increased as cancers previously missed were found at the relatively low PSA values of 3.0 – 3.9 ng/ml. Furthermore it was found that the overall characteristics of the cases detected at the lowered PSA cut-off differed very little from those detected with the algorithm based on PSA, DRE, and TRUS.
In chapter 5 the value of PSA velocity as a predictor for biopsy outcome in the low PSA ranges (PSA < 4.0 ng/ml) is evaluated in both a univariate and multivariate setting. Data from a side study at the second screening round were used. In this side study men with a PSA above 2.0 ng/ml or a doubling of the PSA value within the 4-year interval were biopsied. The study confirmed the relatively high prevalence of biopsy detectable prostate cancer (PPV = 19.3 %) at these low PSA ranges and showed that both in the univariate and multivariate setting an increased PSA velocity was no significant predictor for biopsy outcome.
Chapter 6 evaluates the effect of a protocol change implemented 8 years earlier. As mentioned in chapter 3 it was decided to stop further screening with DRE, TRUS and sextant biopsy in men with a PSA level < 1.0 ng/ml. The omission of further screening this particular cohort of men is again a protocol

change that can lead to missing cancers that can be life threatening if not detected in an organ confined state. The conclusion of this study was that delaying the biopsy procedure until PSA increases to a certain cut off value (in this case 3.0 ng/ml), and thus saving a lot of unnecessary biopsies, does not seem to lead to an increase in the detection of incurable prostate cancer cases. In fact prolonging the screening interval to e.g. 8 years will lead to a considerable decrease of screening visits with a minimal risk of missing aggressive cancers in a curable stage.

Chapter 7 evaluates the results of re-screening in men with a PSA >= 4.0 ng/ml and a benign biopsy result at initial screening. If the sextant biopsy technique and the policy of not performing an immediate re- biopsy would be ineffective this could result in a considerable number of (advanced) interval cancers or an increased detection rate and/or more advanced cancers at repeat screening four years later. It turned out that the PPV at repeat screening was 8.3 % (overall PPV at repeat screening was 18.9 %). The number of interval cancers was certainly not negligible (8 cases in 312 men = 2.6%) but they were mainly found in men older than 74 years of age and in men who refused biopsy at initial screening. The results of this study did not provide a reason to adjust the screening protocol with regard to repeat biopsies in men with an elevated PSA level (4.0 mg/mL or more) and a benign biopsy result.

Chapter 8 studies the change of the predictive value of information known before a biopsy is taken in a multivariate setting by comparing the value of the available predictors for biopsy outcome at initial and repeat screening. The data show that the cohort of men screened for the second time in fact consists of two groups where predictors for biopsy outcome act completely differently. Analyzing these men together will thus lead to false conclusions with regard to the value of the different predictors at repeat screening. The key finding of this study is that in men not previously biopsied predictors for biopsy outcome are comparable to those at initial screening. The cohort of men previously biopsied is clearly different; PSA loses its predictive value completely. Finally chapter 9 gives possibly a glimpse to the future. The results after a mean follow-up period of 9.9 years show a considerable decrease in prostate cancer mortality in the screening arm compared to the control arm. It must be noted that the screening algorithm used in the pilot studies reported is definitely not comparable with the screening algorithms used in the whole of ERSPC. It is however not unthinkable that, when analysing the data from ERSPC as a whole, a significant mortality reduction will be achieved within a few years based on earlier detection and effective treatment of aggressive cancers. This certainly will not mean the end of our investigations; to the contrary test evaluation must continue. This possible mortality reduction will be the result of a major effort with respect to the number of necessary screening tests. Also perhaps more importantly a considerable amount of over-diagnosis and subsequent over-treatment will result. Information coming from the ERSPC on the value of screening tests, tumor characteristics, treatment, mortality and not in the least the serum and tissue repositories will be invaluable in developing an acceptable and effective (in the context of both cancer detection and costs) screening algorithm. Until these data from the ongoing randomized trial become available the guideline in prostate cancer screening should be “less is more”and men who wish to be screened should be properly informed to enable them to evaluate the possible harms and benefits of prostate cancer screening.

11.0

Summary (Dutch)

Het concept van vroege opsporing lijkt voor de hand liggend, een vroege diagnose leidt tot een betere kans op genezing. Dit is echter niet altijd het geval bij de diagnose van prostaatkanker. De reden hiervoor is niet omdat de ziekte zo weinig voorkomt, in tegendeel, de incidentie- en mortaliteitscijfers tonen aan dat prostaatkanker een veel voorkomende aandoening is. Het feit dat prostaatkanker een tumor is die vaak langzaam groeit en voornamelijk voorkomt bij de wat oudere man, is aanleiding tot het zetten van vraagtekens bij de waarde van vroege opsporing. Het is namelijk zeer de vraag of een vroege opsporing en behandeling, die gepaard kan gaan met vervelende bijwerkingen, de sterfte aan prostaatkanker zal verminderen. Ondanks deze onduidelijkheden over de waarde van vroege opsporing van prostaatkanker is de incidentie de laatste jaren toegenomen. Dit niet in de laatste plaats als gevolg van de ontdekking van het prostaat specifieke antigeen (PSA) en de toegenomen bekendheid van prostaatkanker onder de bevolking en bij medisch specialisten.
De vraag of de vroege opsporing van prostaatkanker levens kan redden, kan alleen beantwoord worden door middel van een correct uitgevoerd gerandomiseerd onderzoek. De European Randomized study of Screening for Prostate Cancer (ERSPC) is een gerandomiseerde studie die wordt uitgevoerd in verschillende Europese centra. De studie heeft als hoofddoel het effect van vroege opsporing op de prostaatkankerspecifieke sterfte te onderzoeken. Daarnaast kunnen de resultaten ook inzicht geven in de waarde van verschillende screeningtesten en van waarde zijn in het identificeren van mannen met een verhoogde kans op prostaatkanker uit een populatie zonder specifieke klachten. Dit proefschrift richt zich op het laatstgenoemde onderwerp
(hoofdstuk 1).

Hoofdstuk 2 geeft algemene informatie over de prostaat, prostaatkanker en het fenomeen van vroege opsporing of screening. Tevens worden de statistische technieken, gebruikt in dit proefschrift, besproken.
Hoofdstuk 3 geeft een overzicht van de screeningresultaten van het Nederlandse deel van de ERSPC. De screeningtesten en het algoritme, gekozen bij de start van de studie, zijn gedurende het verloop van de studie geëvalueerd. Dit heeft geleid tot twee belangrijke veranderingen in het screeningalgoritme. Al vrij snel na de start van de studie werd bij mannen met een serum PSA waarde van minder dan 1.0 ng/ml afgezien van verder onderzoek. De tweede verandering in het screeningalgoritme betrof het verlagen van de drempelwaarde van het PSA die leidt tot het doen van een prostaatbiopsie. Halverwege de studie werd deze drempelwaarde verlaagd van 4.0 ng/ml naar 3.0 ng/ml. Bovendien werd bij mannen met een PSA lager dan 3.0 ng/ml afgezien van verder onderzoek. De veranderingen in het screeningalgoritme leidden tot een vermindering van het aantal benodigde bezoeken aan het screeningbureau en tot een meer efficiënte identificatie van mannen met een mogelijk verhoogd risico op prostaatkanker. Dit resulteerde in een vermindering van het aantal onnodige biopsieën en tevens een hogere opkomst.
In hoofdstuk 4 wordt het originele screeningalgoritme, een prostaatbiopsie bij een serum PSA waarde van 4.0 ng/ml of hoger, of bij een lagere serum PSA waarde een afwijkend rectaal toucher en/of echo, vergeleken met het nieuwe screeningalgoritme (alleen een prostaatbiopsie bij een serum PSA waarde van 3.0 ng/ml of hoger). Er werd gekeken naar het aantal gevonden kankers

en hun karakteristieken. Het bleek dat de verandering van screeningalgoritme niet leidde tot de detectie van minder kankers, ondanks het feit dat bij mannen met een serum PSA waarde lager dan 3.0 ng/ml geen verder onderzoek plaats vond. Het aantal diagnoses nam zelfs toe doordat er veel meer kankers werden gevonden in de mannen met een serum PSA waarde tussen de 3.0 en 3.9 ng/ml. De karakteristieken van de gevonden kankers in de twee verschillende screeningalgoritmen waren vergelijkbaar.

Hoofdstuk 5 beschrijft een onderzoek naar de waarde van de verandering van het serum PSA over tijd in het voorspellen van de uitkomst van een prostaatbiopsie. De studie richt zich met name op mannen met relatief lage serum PSA waarden. De benodigde gegevens voor deze studie kwamen uit een zijstudie, gedaan tijdens de tweede screening ronde. In deze zijstudie zijn tijdelijk alle mannen met een serum PSA waarde van 2.0 ng/ml of hoger of mannen die een verdubbeling van hun PSA waarde hadden gedurende de periode tussen de twee screeningbezoeken, gebiopteerd. De resultaten tonen aan dat ook bij lage serum PSA waarden prostaatkanker niet zeldzaam is en dat de verandering van het serum PSA over tijd geen goede voorspeller was voor de uitkomst van de prostaatbiopsie.

Hoofdstuk 6 evalueert de mogelijke gevolgen van de eerste protocolverandering, namelijk geen verder onderzoek bij mannen met een serum PSA lager dan 1.0 ng/ml. Het niet verder onderzoeken van een bepaalde groep mannen kan leiden tot het missen van diagnoses, die op hun beurt weer een effect kunnen hebben op de prostaatkankerspecifieke sterfte. Voor deze studie werd een cohort van mannen gebruikt die al aan drie screeningronden hadden deelgenomen en die bij hun eerste screeningbezoek een serum PSA gehalte hadden van 1.0 ng/ml of lager. Het aantal mannen, wiens PSA na 8 jaar boven de drempelwaarde voor een biopsie was gestegen bleek na analyse van de data heel laag te zijn. Het zou dus mogelijk zijn om de tijd tussen twee screeningbezoeken in deze groep mannen te verlengen met enkele jaren, zonder dat er een grote kans bestaat dat de diagnose, van nog te genezen kanker, te laat zou zijn.

Hoofdstuk 7 richt zich op een andere groep mannen binnen de screening-populatie, namelijk mannen met een serum PSA waarde hoger of gelijk aan 4.0 ng/ml en een eerdere prostaatbiopsie met een goedaardig resultaat. Het zou kunnen zijn dat de gebruikte sextant biopsietechniek, of het niet direct herhalen van de biopsie, niet toereikend is voor de tijdige diagnose van prostaatkanker. Dit zou dan leiden tot een verhoogd aantal diagnoses van, mogelijk vergevorderde, prostaatkankergevallen in het screeninginterval of bij het tweede screening-bezoek. Biopsieresultaten van de tweede ronde van deze groep mannen toonden aan dat het aantal diagnoses van prostaatkanker relatief laag was (8.3%). Het aantal klinisch gevonden prostaatkankers in het 4 jaar interval was zeker niet laag. Deze prostaatkankergevallen werden echter wel gevonden in mannen die een biopsie hadden geweigerd bij hun eerste screeningbezoek, of die ouder waren dan de leeftijd waarop een vroege diagnose nog zinvol wordt geacht. Conclusie van deze studie is dan ook dat er geen aanleiding is om het aantal biopten per biopsieprocedure te verhogen of om de biopsieprocedure binnen korte tijd te herhalen.

In hoofdstuk 8 worden de voorspellers voor de uitkomst van een biopsie in eerste en tweede ronde bestudeerd en vergeleken. Uit deze studie blijkt dat het cohort mannen dat voor de tweede keer wordt onderzocht in feite uit twee verschillende groepen bestaat. De eerste groep bestaat uit mannen die nog

niet eerder gebiopteerd zijn en de tweede groep bevat mannen met een eerder goedaardig biopsieresultaat. Tussen deze twee groepen is de voorspellende waarde van de verschillende screeningtesten geheel verschillend. Het gezamenlijk analyseren van alle mannen in een tweede screening ronde kan dus leiden tot verkeerde conclusies met betrekking tot de voorspellende waarde van de verschillende screeningtesten. Het blijkt dat de voorspellende waarde van de screeningtesten in mannen die niet eerder gebiopteerd zijn, vergelijkbaar is met die in mannen die voor het eerst gescreend worden. In de groep mannen met een eerder negatief biopt verliest het serum PSA zijn voorspellende waarde.

Hoofdstuk 9 beschrijft de resultaten van de eerste 4 pilotstudies gedaan in de periode 1991 – 1993. Na een vervolgperiode van gemiddeld 9,9 jaar blijkt er een aanzienlijke daling in de prostaatkankersterfte in de screeninggroep te zijn. Ondanks het feit dat de manier van screenen in deze vier pilotstudies niet te vergelijken is met het uiteindelijk gekozen screeningalgoritme, kan de uitkomst van deze pilotstudies ons toch een idee geven over de uiteindelijke uitkomst van de gehele ERSPC studie. Het is niet ondenkbaar dat vroege opsporing van prostaatkanker uiteindelijk leidt tot een vermindering van de prostaatkanker-specifieke sterfte. Dit betekent echter niet dat het onderzoek gestopt kan worden. Deze eventuele daling van de prostaatkankersterfte is dan het resultaat van een enorm aantal screeningbezoeken en een aanzienlijke hoeveelheid overdiagnose en overbehandeling.

De data van de ERSPC, en dan met name de gegevens over de waarde van de verschillende screeningtesten, de karakteristieken van de gevonden tumoren, resultaten van behandeling- en sterftecijfers en niet te vergeten de opgebouwde serum- en weefselbank, zullen van grote waarde zijn voor het verdere ontwikkelen van een acceptabel en betaalbaar screeningprogramma.

Tot de tijd dat deze data gecompleteerd en geanalyseerd zijn dient het aanbeveling om terughoudend te zijn met betrekking tot de vroege opsporing van prostaatkanker. Mannen die er voor kiezen om gescreend te worden dienen goed geïnformeerd te worden over de megelijke risico's en voordelen die de vroege diagnose van prostaatkanker met zich meebrengt.

Part IV

13.0

List of co-authors

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14.0

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15.0

Curriculum vitae

Ik ben geboren op een zonnige zondagochtend, 22 oktober 1961, vlak naast het Feyenoord stadion (Clara ziekenhuis). Met mijn ouders, twee zussen en twee broers ben ik opgegroeid in Rotterdam Alexanderpolder. In 1979 behaalde ik het HAVO diploma aan de scholengemeenschap Prins Alexander te Rotterdam. Hierna volgde ik de HBO analisten opleiding (botanische studie richting) te Delft. Het diploma behaalde ik in 1982. Aangezien het vinden van een baan in die tijd iets heel bijzonders was besloot ik door te stromen naar de HLS (Hogere Landbouw School) te Dordrecht. Na een jaar ploegen, lassen, zaaien en koeien melken bleek dat ook in deze studie richting werk alleen te vinden was voor degene met een boerenbedrijf in de familie.
Een ommezwaai was dus nodig wilde er ooit brood op de plank komen. Van 1983 tot 1985 heb ik daarom de opleiding tot apothekersassistente gevolgd. Tijdens deze opleiding vond ik in februari 1985 werk als research analist en wel op de afdeling Immunologie van het Erasmus MC. In 1987 ben ik getrouwd met Wouter Roobol en op 9 april 1991 werd Stefan geboren. Hierdoor ontstond de wens om part time te gaan werken en ben ik als datamanager begonnen bij de afdeling Urologie (september 1991). Op 11 februari 1994 werd Dennis geboren. Mijn loopbaan binnen Urologie moge duidelijk zijn; na het opzetten en praktisch uitvoeren van het Nederlandse deel van de “European Randomised study of Screening for prostate Cancer (ERSPC)” werd het analyseren en interpreteren van de data steeds interessanter. In 1998 schreef ik mijn eerste abstract en al snel daarna kwam de mogelijkheid om promotie onderzoek te doen ter sprake. Aangezien een universitaire graad in mijn cv ontbrak, heb ik in de zomer van 2003 mijn Masters Degree in de Epidemiologie gehaald. Het promotieonderzoek is nu afgerond en dit boekje is het resultaat. Na mijn promotie blijf ik werken op de afdeling Urologie en zal mij voornamelijk bezig houden met het voltooien van het rotterdamse deel van de ERSPC.

16.0

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