# SCREENING FOR PROSTATE CANCER

## Digital rectal examination: outdated or still valuable?

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Screening for prostate cancer; digital rectal examination: outdated or still valuable?

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# Screening for Prostate Cancer

## Digital rectal examination: outdated or still valuable?

# Vroegopsporing van prostaatkanker

## Het rectaal toucher: ouderwets of nog steeds waardevol?

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Een wijze uil is toch ook ooit eens gewoon als een uilskuiken begonnen. *Wiel Oehlen*

Voor Wies en Pelle

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# Part I

## General Introduction

# Chapter 1

## The European Randomized Study of Screening for Prostate Cancer

Prostate cancer is a major public health problem in the Western world; it is the most common type of cancer and the second leading cause of cancer deaths in men[1]. In the early 1990s evidence emerged that prostate-specific antigen (PSA), a glycoprotein produced practically exclusively by the prostate gland, could be used for the early detection of prostate cancer[2-4].

In Belgium and the Netherlands plans originated for conducting a randomised screening study in order to evaluate whether population-based screening for prostate cancer is effective in decreasing prostate cancer mortality at an acceptable price in terms of quality of life and costs[5]. Screening aims to detect prostate cancers at an early stage, when these are still curable. After conducting two pilot studies to test the feasibility of such a large prospective randomised controlled trial[6, 7], in December 1993 the European Randomized Study of Screening for Prostate Cancer (ERSPC) started. In total, more than 200,000 men have been recruited in eight European countries. A comparable screening trial is carried out in the United States: the Prostate, Lung, Colorectal and Ovary (PLCO) cancer trial[8]. The answer to the question whether screening for prostate cancer reduces prostate cancer mortality will probably be available in 2010. In the meanwhile, the evaluation of screening algorithms and tests used is ongoing and will form the basis of a possible national prostate cancer screening program.

In Rotterdam, the ERSPC study centre of the Netherlands, more than 40,000 men aged 55-75 years were randomised to either the screening or control arm of the study. Participants in the screening arm were screened every 4 years by means of a serum PSA measurement, a digital rectal examination (DRE) and a transrectal ultrasonography (TRUS).

Until May 1997, a man with a PSA level of 4.0 ng/ml or higher or an abnormal result on DRE or TRUS was offered a lateralised sextant biopsy. TRUS was not shown to be a valuable test for the early detection of prostate cancer in a screening programme[9-11]. The value of DRE in the early detection of prostate cancer remained more controversial[12-16]. For this reason, DRE and TRUS were discontinued as an indication for biopsy and simultaneously the PSA threshold as a biopsy indication was lowered to 3.0 ng/ml[9, 14]. This change resulted in an overall 10% decrease in the rate of biopsies and in a very similar detection rate of 4.7% using the PSA 3.0 ng/ml cut-off instead of the 5.0% rate using PSA>4.0 ng/ml and DRE/TRUS[14]. At the moment, 14 years after the ERSPC was launched, the fourth screening round is in progress.

# Chapter 2

## Introduction

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## SCREENING FOR PROSTATE CANCER

Before discussing the main subject of this thesis, the digital rectal examination, the prevalence of prostate cancer and prostate cancer screening in general are addressed. The benefits and limitations of PSA, the most important screening test, are evaluated and several suggestions for improving prostate cancer screening are mentioned.

### The background - latent prostate cancer

Latent prostate cancer is defined as cancer not diagnosed during lifetime but found at autopsy or during the examination of the complete prostate, removed as a part of a cystoprostatectomy specimen for the treatment of bladder cancer.

Data available in literature provide background information about the prevalence of prostate cancer in the age groups concerned. The reported autopsy studies have been carried out over a large period of time, the first one by Franks[17] was reported in 1954, the most recent ones by Sakr in 1993[18]. This latter study included victims of traffic accidents and showed that already in the fourth and fifth decade of life small foci of prostate cancer could be discovered in 27% and 34% of those autopsy cases.

The prevalence of prostate cancer is strongly dependent on age and, obviously, on preparative techniques. Table 1 gives a review of literature data. The number of cases autopsied as well as the number and percentage of prostate cancers identified are indicated in decades of age. The data average out to 15%, 21%, and 26% in the sixth, seventh and eight decade. However, it may not be acceptable to calculate these averages, considering the great differences in preparative techniques that have been applied between these either prospective or clinical routine studies. Probably, data reported by Franks are most reliable because the most extensive examination of the removed prostates has been applied. He reported prevalence rates of 29% to 40% for the age groups 50 to 79. Most of the tumours identified in autopsy series are described as well-differentiated and small. The applied methods of histological grading are not comparable.

**Table 1:** Prevalence of prostate cancer at autopsy in men age 50-79 years and in men of all ages, including ages below 50 and above 79 (given in the column 'total').

| | Age 50-59 | | Age 60-69 | | Age 70-79 | | Total (all ages) | |
|---|---|---|---|---|---|---|---|---|
| | N autopsy | N PC (%) | N autopsy | N PC (%) | N autopsy | N PC (%) | N autopsy | N PC (%) |
| Franks[17] | 38 | 11 (29) | 53 | 16 (30) | 70 | 28 (40) | 210 | 69 (38) |
| Edwards *et al.*[87] | 31 | 3 (10) | 54 | 10 (19) | 48 | 12 (25) | 173 | 29 (17) |
| Andrews *et al.*[88] | 38 | 2 (5) | 39 | 7 (18) | 22 | 7 (32) | 142 | 17 (12) |
| Moore[89] | 56 | 9 (14) | 77 | 18 (23) | 63 | 13 (21) | 304 | 51 (17) |
| Holund[90] | 23 | 2 (9) | 56 | 7 (13) | 93 | 24 (26) | 223 | 50 (22) |
| Totals | 186 | 27 (15) | 279 | 58 (21) | 296 | 77 (26) | 1,052 | 216 (21) |

Contrary to the age-dependence seen in table 1, Breslow and co-workers found no age-dependence in 350 latent, focal carcinomas identified in 1,327 autopsy cases in seven different areas of the world. The frequency of small focal lesions amounted to about 12% and did not vary between areas of high and low incidence of prostate cancer[19].

More precise information on currently applied prognostic factors such as tumour volume and Gleason grading is available from series of prostates removed with radical cystoprostatectomy specimens. Such data are summarised in table 2.

**Table 2:** Prevalence and characteristics of prostate cancer incidentally found in radical cystoprostatectomy specimens (after Gosselaar *et al.*[91]).

| | Stamey *et al.*[92] | Montie *et al.*[93] | Ohori *et al.*[94] | Kabalin *et al.*[95] | Ward *et al.**[96] | Montironi *et al.*[97] |
|---|---|---|---|---|---|---|
| Age (years) Mean, median (range) | 66, 65 (31-84) | 62, 64 (34-80) | ? | 66, 66 (31-82) | 69, 69 (44-92) | mean 61 (45-73) |
| Prostate cancers N (% of specimens) | 55 (40) | 72 (46) | 90 (?) | 25 (38) | 30 (23) | 55 (42) |
| Gleason scores | | | | | | |
| <7 % | - | 63 | 89 | 100 | 93 | 71 |
| ≥7 % | - | 37 | 11 | - | 7 | 29 |
| Tumour volume ≤0.2 ml % | 74 | - | 83 (≤0.5 ml) | 87 | 73 | - |

* case selection: PSA<2.0 prior to cystectomy



It can be seen that the age ranges are comparable to those of the autopsy data. Probably due to more careful and prospectively planned reviews of the entire prostatic specimens the prevalence numbers are high and are in the range of those reported by Franks. Sixty-three to 100% of the cancers identified have been assigned Gleason scores below 7. Up to 37% have more aggressive features. Seventy-three to 87% of the described cases have total tumour volumes of less than 0.2 or 0.5 ml, classifying them as clinically unimportant or minimal disease (in case of confinement to the prostate and Gleason score <7) according to Epstein[20].

From these data a number of clinically relevant conclusions can be drawn. Firstly, the prostate contains a large pool of cancers of which the majority can be classified as small and well-differentiated in line with definitions of clinically insignificant or minimal disease. Secondly, the prevalence figures produced from autopsy studies and from prostates removed with radical cystoprostatectomy specimens can be compared to lifetime incidence and lifetime mortality data. For the US such figures applying to the year of 2005 have been estimated by Jemal *et al.*[1]. The lifetime risk of being diagnosed with prostate cancer amounts to 17.8% and the chance of dying of the disease to less than 3.5%. The number of new prostate cancer cases was estimated on 232,090. Prostate cancer was with 30,350 deaths the second leading cancer death cause in 2005[1]. Autopsy and cystoprostatectomy prevalence figures exceed the lifetime risk of death from prostate cancer by at least 10-fold.

The number of cancers diagnosed by screening exceeds the risk of dying of the disease by at least by a factor of 5. These data suggest that present diagnostic techniques are capable of diagnosing many of the cancers found in autopsy and cytoprostatectomy specimens. In 1990, prior to the more general use of PSA-driven screening in North America and Western European countries, the ratio of the incidence and dying of prostate cancer was roughly 2:1. The changes induced by PSA- driven screening can also be visualised by comparing incidence and mortality in different areas of the world. Table 3 shows selected data from the Globocan 2002 website. In Eastern Asia, where screening is still uncommon, the ratio of incidence and mortality still amounts to about 2:1 as used to be the case in the US and in Western Europe. Whether mortality decreased due to screening in a significant fashion remains to be shown by the ongoing randomised controlled trials of screening for prostate cancer.

**Table 3:** Incidence and mortality of prostate cancer in different areas of the world (Globocan 2002).

| | Incidence | | Mortality | | Ratio |
|---|---|---|---|---|---|
| | Cases (N) | Crude rate | Deaths (N) | Crude rate | Incid/mort |
| World | 679,023 | 21.7 | 221,002 | 7.1 | 3.1 |
| Southern Africa | 4,778 | 19.3 | 2,648 | 10.7 | 1.8 |
| Eastern Asia | 29,472 | 3.9 | 14,535 | 1.9 | 2.1 |
| Western Europe | 98,083 | 109.2 | 29,382 | 32.7 | 3.3 |
| Northern America | 257,943 | 163.7 | 36,447 | 23.1 | 7.1 |

www-dep.iarc.fr

### Does PSA-driven screening detect clinically insignificant (autopsy) cancers?

The epidemiological and pathological data presented strongly suggest that this is indeed the case. Cumulative detection rates from screening studies add further evidence.

In table 4 data on detection rates resulting from systematic screening are summarised (cut-off date July 2007). In seven centres participating in the European Randomized Study of Screening for Prostate Cancer (ERSPC) men age 50–74 are randomised to a screening or a control group. The screening interval is 4 years except for Sweden and Belgium where the population is rescreened every two, respectively seven years. The detection rates reported relate to the number of men randomised, which is usually higher than the number of men who are actually screened. Also, test procedures are slightly different from centre to centre. All centres, however, utilised sextant biopsies, mostly lateralised, in men who had a PSA level above 3 or 4 ng/ml. It is important to differentiate, in this context, the cancer detection rate (CDR), which relates to the total number of cancers found in all men randomised or screened from the positive predictive value (PPV), which indicates the proportion of cancers in those who have a biopsy indication. The average detection rate in all ERSPC centres was 3.8% in 2003[21] and has increased to 5.7% in July 2007. There is a variation in CDRs between the dif-

**Table 4:** Prevalence of prostate cancer in randomised studies. Detection rates are given (ERSPC meeting Antwerp, Belgium, October 2007).

| | Randomised to screen (excluding deaths before randomisation) | PCs detected at 1st screen N (% of men randomised) | PCs detected at follow-up screens N | Total cancers detected N (% of men randomised) |
|---|---|---|---|---|
| ERSPC: cut-off date July 2007 | | | | |
| Belgium | 5,188 | 116 (2.2) | 98 | 214 (4.1) |
| Finland | 31,970 | 658 (2.1) | 832 | 1,429 (4.5) |
| Italy | 7,499 | 98 (1.3) | 75 | 173 (2.3) |
| Netherlands | 21,206 | 1,014 (4.8) | 769 | 1,783 (8.4) |
| Spain | 2,416 | 40 (1.7) | 40 | 80 (3.3) |
| Sweden | 9,957 | 209 (2.1) | 580 | 789 (7.9) |
| Switzerland | 5,156 | 159 (3.1) | 121 | 280 (5.4) |
| Total | 83,392 | 2,294 (2.8) | 2,515 | 4,748 (5.7) |
| PLCO[22, 23] | 38,350 | ± 537 (1.4) | - | 537 (1.4) |
| PCPT[24]* | 4,692 | - | - | 571 (12.2) |

* for cause biopsies, 7-year period.

ferent ERSPC study centres. For Rotterdam, the CDR was 8.4% in July 2007 (table 4, related to the number of men randomised).

In the similar PLCO trial which utilises the same age distribution but yearly screening by means of PSA and rectal examination (DRE) over a 5-year period, the detection rate in 2005 was 1.4%[22, 23]. This CDR contrasts with the other studies mentioned in table 4, and concerns only the initial screening round of the PLCO. Furthermore, the biopsy rate of participants with an abnormal PSA level or DRE result are lower than in the ERSPC due to the study design of the PLCO.

The last line in table 4 refers to the placebo control arm of the Prostate Cancer Prevention Trial (PCPT)[24]. In this trial 9,459 men of age 55 or older (median age 62 years) presenting without prostate cancer and a PSA value of less than 3.0 ng/ml were randomised to placebo. The participants were followed for seven years. Men who developed an abnormal rectal examination or a PSA value above 4.0 ng/ml were offered biopsy. This was applicable to 4,692 men in whom 571 cancers were detected by 1,934 biopsies. This resulted in a PPV (the number of cancers detected divided by the number of men biopsied*100%) of 29.5% and a very high CDR (the number of cancers detected divided by the number of men screened*100%) of 12.2%. In line with the protocol, independent of their PSA or rectal examination, the remaining men were recommended to undergo biopsy after a 7-year participation period in this study. This resulted in a total, cumulative detection rate of 24.4% in the placebo group. Next to the fact that this rate approaches the prevalence rate seen at autopsy, the data also show that the 7 year routine screening procedure missed almost exactly 50% of all cancers which were diagnosed by predominantly sextant biopsies in this population at the end of the seven year period (12.2 of 24.4%). This contrasts with the detection rate of 9.1% in the period until

January 2008 in the ERSPC Rotterdam. As already mentioned, the CDR of the Rotterdam study centre is higher compared to the average CDR of the ERSPC (table 4). Furthermore, a CDR concerns the number of cancers detected divided by the number of men screened. In table 4 the denominater is formed by the number of men randomised to screen, which is usually higher than the number of men actually screened.

Present PSA-driven early detection measures for prostate cancer are capable of diagnosing a substantial proportion of those cancers found in autopsy studies. The question is if screen-detected cancers match the properties of indolent or autopsy cancers (matching the current definitions[20]). Unfortunately, current series of prostate cancer cases treated by either radical prostatectomy or radiotherapy are not very suitable for comparison with autopsy series because they will usually represent a mixture of clinically and screen-detected cases.

The problem of detecting possibly indolent cancer by screening was recognised in an editorial by Carroll[25] which urged the urological community to identify cases with a pattern compatible with a minimal risk of disease progression and to apply active surveillance regimens to this group in order to reduce overtreatment.

## PSA as an indicator for biopsy

### *Initial screening*

Prostate-specific antigen (PSA) has been and remains one of the corner stones of early detection of prostate cancer. Catalona *et al.*[2] used a PSA cut-off value of 4 ng/ml as a biopsy indication in a group of 1,653 men in age groups at risk. Thirty-seven cancers (2.3%) were detected. Sixteen of the 37 cancers would have been missed by rectal examination alone. Screening based on PSA identified men with prostate cancer who had a significantly increased proportion of organ-confined tumours compared with those detected through evaluation for an abnormal DRE alone[26]. Catalona and co-workers[13] evaluated the 4.0 ng/ml cut-off value in conjunction with rectal examination in a multicentre setting and found a cancer detection

**Table 5:** PSA distribution and the diagnosis of prostate cancer in the first screening in 9,779 men aged 55-74 years.

| PSA ng/ml | Randomised to screen N | Biopsied N (% of men randomised) | Cancers per PSA range N (% of total number PCs) | PPV % | CDR % |
|---|---|---|---|---|---|
| 0-2.9 | 7,808 | 915 (11.7) | 79 (16.7) | 8.6 | 1.0 |
| 3-3.9 | 702 | 174 (24.8) | 44 (9.3) | 25.3 | 6.3 |
| 4-10 | 1,063 | 985 (92.7) | 241 (51.0) | 24.5 | 22.7 |
| ≥10 | 206 | 193 (93.7) | 109 (23.0) | 56.5 | 52.9 |
| Total | 9,779 | 2,267 (23.2) | 473 (100.0) | 20.9 | 4.8 |

The study population was randomised to screening; the biopsy indication was PSA≥4.0 ng/ml and/or an abnormal DRE/TRUS (ERSPC Rotterdam).

PPV= the number of cancers detected divided by the number of men biopsied*100%

CDR= the number of cancers detected divided by the number of men screened*100%

rate of 3.2% for DRE and 4.6% for PSA alone. Prostate cancer was detected in 10% of the men biopsied for an abnormal DRE and a PSA<4.0 ng/ml.

Later, lower cut-off values were used. Catalona and co-workers suggested to biopsy everyone with a PSA>2.5 ng/ml or in case of an abnormal DRE[27]. Within the ERSPC a PSA value of 3.0 ng/ml (without DRE as a screening test) nowadays is used after validation of this procedure[14].

Table 5 and 6 show the PSA distribution and the diagnosis of prostate cancer in respectively 9,779 and 10,191 men age 55–74 who were randomised to screening according to respectively the old and new protocol. Biopsy was recommended if PSA was ≥4.0 ng/ml and/or an abnormal DRE/TRUS (old protocol, table 5) or if PSA was ≥3.0 ng/ml (new protocol, table 6, DRE was not a screening tool). In the PSA range 3.0–3.9 ng/ml the old regimen missed about two thirds of the cancers (CDR 6.3% compared to 18.6%) compared to the new protocol.

**Table 6:** PSA distribution and the diagnosis of prostate cancer in the first screening in 10,191 men aged 55-74 years.

| PSA ng/ml | Randomised to screen N | Biopsied N (% of men randomised) | Cancers per PSA range N (% of total number PCs) | PPV % | CDR % |
|---|---|---|---|---|---|
| 0-2.9 | 8,044 | - | - | | |
| 3-3.9 | 724 | 618 (85.4) | 135 (24.9) | 21.8 | 18.6 |
| 4-10 | 1,172 | 1,021 (87.1) | 285 (52.7) | 27.9 | 24.3 |
| ≥10 | 251 | 210 (83.7) | 121 (22.4) | 57.6 | 48.2 |
| Total | 10,191 | 1,850 (18.2) | 541 (100.0) | 29.2 | 5.3 |

The study population was randomised to screening; the biopsy indication was PSA≥3.0 ng/ml (ERSPC Rotterdam).

PPV= the number of cancers detected divided by the number of men biopsied*100%

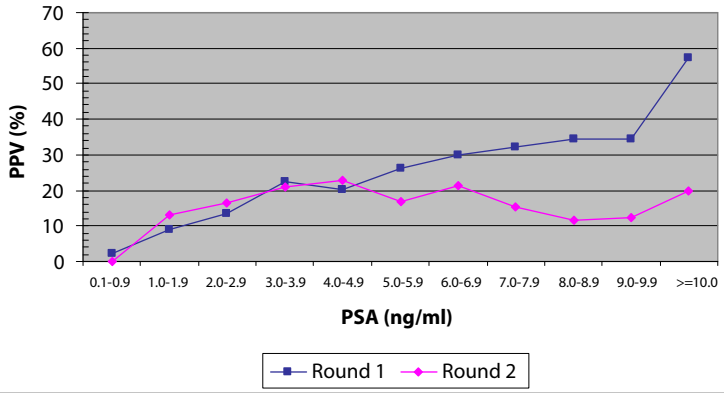
CDR= the number of cancers detected divided by the number of men screened*100%

*Rescreening*

Increasing evidence has recently accumulated showing that the detection characteristics change drastically if PSA has been used in a previous screening procedure. This has been documented by comparing the results of first and second round screening 4 years later in the ERSPC[28]. Figure 1 shows the relationships between the PPVs and PSA levels in the first and second round. As can be seen in figure 1, above the cut-off values of 3 and 4 ng/ml, which were used in the 21,210 men randomised to screening, PSA maintains its predictive value of about 20% in round 2. The rise of PPV associated with higher PSA levels in round 1 is lost in round 2.

A possible explanation for this finding is that an elevated PSA level in previously biopsied men mainly correlates with the prostatic volume. This is confirmed by observations made by Stamey *et al.*[29], which show that in areas where screening has been prevalent for years, elevated PSA levels do not correlate with index prostate cancer volume but mainly with the

**Figure 1:** The positive predictive value (PPV) of PSA-driven screening in relation to serum PSA in the 1st round of screening and the 2nd 4 years later (ERSPC, section Rotterdam[28]).




size of benign prostatic hyperplasia. This finding is also demonstrated within the ERSPC in a study of 1,040 men who underwent biopsy in second round screening for PSA values above 3.0 ng/ml. The PPV was 19.0%. In a multivariate analysis age, PSA, DRE, family history, a previous negative biopsy, prostatic volume, and a suspicion of cancer by transrectal ultrasonography (TRUS) were included. Prostatic volume equal to or greater than the median volume of the population and a previous negative biopsy were significant negative predictors (for both: OR 0.5, 95% CI 0.3-0.7)[30].

The cut-off of 3 ng/ml derives its unchanged PPV from cancers that have progressed to PSA levels >3 ng/ml and from those cancers that have potentially been missed in a previous screening round. Further details on the characteristics of PSA as a second round screening test are given in a paper written by Schröder *et al.*[31]. A summary is given in table 7. Obviously, using an absolute cut-off value in second round screening will include biopsy indications in all those men who have elevated PSA values because of an enlarged prostate.

**Table 7:** PSA progression 4 years after screening (N=5,771, age 55-74, PSA round 1 <3.0 ng/ml) after Schröder *et al.* 2005[31].

| **Round 1** | | **Round 2** | | | |
|---|---|---|---|---|---|
| Initial PSA distribution | N (%) | PSA≥3.0 ng/ml | Biopsies | PC | PPV |
| ng/ml | | N (%) | N (%) | N | % |
| <1.0 | 2,622 (45.4) | 23 (0.9) | 21 (91.3) | 4 | 19.0 |
| 1.0-1.9 | 2,268 (39.3) | 211 (9.3) | 181 (85,8) | 43 | 23.8 |
| 2.0-2.9 | 881 (15.3) | 428 (48.6) | 376 (87.9) | 105 | 27.9 |
| Total | 5,771 | 662 (11.5) | 578 (87.3) | 152 | 26.3 |

Differences in PPVs are not significant (Fisher's exact test).

PPV= the number of cancers detected divided by the number of men biopsied*100%

Available data show that in men presenting with PSA values <1.0 ng/ml rescreening can safely be delayed by at least 8 years[32].

An algorithm for detection of cancer in second round screening, which utilises prostatic volume as a negative predictor has been developed as the 'prostate risk indicator', available at www.uroweb.org.

At this time, it can be stated that the best way of utilising PSA in diagnosing prostate cancer in previously screened populations is not fully understood. However, as table 7 shows, the cut-off value of 3.0 ng/ml relates to PPVs of 19–28% depending on PSA 4 years earlier. The use of this (arbitrary) cut-off value resulted in biopsying only 10% of all 5,771 men.

More doubts about the use of PSA cut-off values in secondary screening come from data of the PCPT[24, 33]. The end of study biopsies carried out in the placebo control arm of this randomised trial also offer a unique opportunity to study the test characteristics of PSA below the customary cut-off values of 2.5 and 3.0 ng/ml. Another important feature of this series is that this group of 3,820 men has been heavily prescreened by yearly PSA determinations and rectal examinations utilised as biopsy indications. In spite of the rigid preselection and heavy prescreening 15.1% of men undergoing the end of study biopsies (576 of 3,820) turned out to have prostate cancer.



*PSA is a continuous marker*

Further analysis reported by Thompson *et al.*[33] revealed that PSA is not capable of differentiating in the presence or absence of cancer. No single cut-off could be identified that simultaneously yielded a high relative sensitivity and relative specificity of testing. It seems that the role of PSA in diagnosing prostate cancer is more uncertain than ever before. The term relative sensitivity is used instead of sensitivity, which indicates the proportion of correct positive tests to the total number of cancers that could have been diagnosed in a given population. The total number of cancers remains however unknown, as the only way to determine this number is to investigate the radical prostatectomy specimens of all participants[34].

While lowering PSA cut-off levels leads to a higher detection rate of prostate cancer, it also leads to an increase of the diagnosis of cancers, which might otherwise never bother their carrier (indolent, clinically insignificant, potentially overdiagnosed cancers)[35]. In addition, potentially aggressive cancers as defined by Gleason scores of 7 or higher cannot be identified by appropriate PSA cut-off levels. Even with PSA values below 3.0 ng/ml a considerable number of cancers detected have been shown to have aggressive features. The high rate of overdiagnosis makes strategies desirable, which identify aggressive but still curable cancers with an acceptable accuracy.

### Can PSA cut-offs be replaced by PSA kinetics?

As there is no PSA level at which prostate cancers cannot be detected and as potentially aggressive prostate cancers cannot be identified by appropriate PSA cut-off levels, the use of PSA kinetics (PSA changes over time) is being evaluated.

The increase of PSA over time can be described as PSA doubling-time (PSADT) or PSA velocity (PSAV), the yearly increase of PSA. Both expressions of PSA kinetics require several observations of serum PSA with observation periods of preferably one year, in order to compensate for the biological variation of this marker[36-38].

The yearly increase in PSA over time was first utilised by Carter *et al.*[39] in a case study related to the Baltimore's Longitudinal Study of Ageing (BLSA). The study compared 16 men recruited to a normal control group, 20 to a group of BPH cases and 18 with histologically diagnosed prostate cancer. Multiple PSA determinations were available for time periods between 7 and 25 years prior to the histologic diagnosis or the exclusion of prostatic disease. The evaluation allowed a comparison between loco-regional and metastatic cancer and the control groups. Up to 5 years before diagnosis of cancer, the PSA did not differ between cancer and control subjects. After diagnosis of clinical disease an exponential increase of PSA velocity was noticed. It was shown that a rate of change of 0.75 ng/ml/year was significantly related to the prostate cancer cases.

In 1994 Smith *et al.*[40] evaluated 982 serially screened men who were initially all negative for cancer. Subsequently, all men had at least one PSA value >4.0 ng/ml and underwent biopsy. A PSA velocity cut-off point of 0.75 ng/ml/year or more maximised the prediction of cancer with an odds ratio of 7.20 with respect to those who had a PSAV of less than 0.75.

In a more recent study Fang *et al.*[41] described that in 21 men with mostly clinically diagnosed prostate cancer mostly and 68 controls, a PSAV of 0.5 ng/ml/year was associated with a relative risk of prostate cancer of 6.53 with respect to those who had a lower PSAV. This difference in relative risk was statistically significant. Also the cumulative probability of being free of cancer progression correlated strongly with this cut-off point of PSAV. Later, Loeb and co-workers concluded that PSAV is significantly associated with detection of prostate cancer in men with a total PSA<4.0 ng/ml[42].

These studies are unfortunately subject to verification bias. The wrong assumption is made that men with low PSA levels (below biopsy threshold) do not have cancer. The impact of this mistake has been demonstrated by Roobol[43-45].

Large studies derived from second round screening in the ERSPC section Rotterdam[46] and the PCPT[47] did not confirm the value of PSAV in second round prostate cancer detection, in spite of attempting to imitate the selection criteria used by Fang[30]. The observation that PSAV plays no additional role was confirmed in a commentary by Etzioni and co-workers[48].

### Why are findings with respect to the value of PSAV in diagnosing prostate cancer contradictory?

The most likely explanation lies in the fact that in second round screening most cancers are detected in the pre-clinical detectable phase[46], the period of linear increase where controls cannot be differentiated from cancers as shown by Carter[39], except that the pre-clinical detectable phase in a screening setting is likely to be much longer. The fact that in Carter's original observation PSAV increased when prostate cancer became 'clinical' suggests that PSAV may be a marker of aggressiveness rather than a diagnostic marker[46].

This notion is confirmed by observations showing that high PSA velocity and short PSA doubling times are related to very aggressive disease[49, 50]. Obviously, more information with respect to the potential use of PSA kinetics as diagnostic tools and as parameters that may help to determine tumour aggressiveness prior to treatment are necessary.

Recently, Wolters *et al.* concluded that the use of PSAV as a biopsy indicator would miss a large number of clinically significant PC cases with increasing PSAV cut-offs. In their study, PSAV was not an independent predictor of a positive biopsy in general or significant PC on biopsy. Therefore, they concluded that PSAV does not improve the ERSPC screening algorithm[51].

Active surveillance regimens are likely to greatly benefit from increasing knowledge about PSA kinetics considering the fact that in the series of observational treatment of Choo *et al.* PSA doubling times vary between <2 and >50 years with a median PSADT of 7 years and 42% of men showing a doubling time of >10 years[38].



### Can we selectively identify aggressive cancers?

Considering what has been said so far it is evident that the problem in diagnosing prostate cancer cannot be resolved by maximising the relative sensitivity of biopsy indications. This would lead (as the data of the PCPT show) to the diagnosis of about half of those cancers that can be identified at autopsy and/or prostates removed by radical cystoprostatectomy. Every step in the direction of maximising cancer detection would lead to an increase in lifetime risk of a prostate cancer diagnosis, which was estimated by Draisma *et al.*[52] to be in the range of 300% (an increase from 8% to 36%).

The real problem and future task for our profession will be to identify those cancers that are aggressive and to make screening more selective in this respect. The PCPT data[24] and ERSPC data[53] shown in table 8 illustrate the problem. Assuming that cancers with a Gleason score of ≥7 will be the target of future detection strategies then, according to the PCPT data, 67 cancers must be identified by biopsying 2,950 men. Such a procedure would have a PPV of 2.3%, 44 biopsies would be necessary to find one of these cases. The rate of diagnosis of high Gleason score cancers in the control arm of the PCPT overall amounts to 4.1% (237 of 5,754*100%). Of the cancers found in the biopsies performed for indication (PSA≥4.0 ng/ml or abnormal DRE) during the 7-year study period 29.4% were classified as having Gleason scores of ≥7 as opposed to 15.8% in the end of study biopsies. Of all men analysed in the

**Table 8:** Detection of prostate cancer in men with PSA values <4.0 ng/ml.

| | Thompson *et al.*[24] | | | Raaijmakers *et al.*[53] | | |
|---|---|---|---|---|---|---|
| PSA ng/ml | Biopsied N | PC N (%) | Gleason ≥7 (%) | Biopsied N | PC N (%) | Gleason ≥7 (%) |
| ≤ 0.5 | 486 | 32 (6.6) | 4 (12.5) | - | | - |
| 0.6-1.0 | 791 | 80 (10.1) | 8 (10.0) | - | | - |
| 1.1-2.0 | 998 | 170 (17.0) | 20 (11.8) | - | | - |
| 2.1-3.0 | 482 | 115 (23.9) | 22 (19.1) | 478 | 75 (15.6) | 6 (8.0) |
| 3.1-4.0 | 193 | 52 (26.9) | 13 (25.0) | 258 | 51 (19.8) | 12 (23.5) |
| Total | 2,950 | 449 (15.2) | 67 (14.9) | 736 | 126 (17.1) | 18 (14.3) |

placebo arm who underwent biopsy for indication during the 7-year period 3.2% had cancers with Gleason scores of 7 or higher (148/4,692*100%).

At present the selective identification of PCs with Gleason scores of ≥7 is not possible unless very large numbers of negative biopsies are accepted. In the ERSPC 80.5% and 68.1% of men had PSA values <3.0 and <2.0 ng/ml and were therefore excluded from biopsy.

A more promising approach might be to identify potentially indolent cancers and consider the remaining ones as potentially aggressive[54].

### Transrectal ultrasonography as biopsy indication

It has been recognised that the value of a TRUS of the prostate is limited as a screening test for prostate cancer[9, 11, 55, 56]. TRUS is highly investigator-dependent and mainly for this reason not suitable as a screening test. Furthermore, hypoechoic lesions are not specific for prostate cancer[57]. Next to hypoechoic lesions, prostate cancers may have iso-echoic or hyperechoic characteristics[58-60]. Nevertheless, TRUS is very useful in performing systematic prostate biopsies. For this reason the TRUS-guided systematic prostate biopsy is the gold standard in obtaining prostatic tissue in men indicated for prostate biopsy.

### Digital rectal examination as biopsy indication

With the common use of PSA cut-off points of 2.5, 3.0 or 4.0 ng/ml as biopsy indications, the domain of rectal examination has been limited to PSA values below these cut-offs. Only one in ten suspicious rectal examinations is likely to reveal prostate cancer at biopsy at PSA levels below 4.0 ng/ml[13].

As already discussed, rectal examination has been eliminated as a screening test from the ERSPC and its limited value has been confirmed in a validation study[14]. Still, without rectal examination a certain fraction of clinically diagnosable prostate cancers will be missed and the question of their later detection with elevated PSA values in a state of curability is unresolved.

DRE is a basic element of urological practice and will obviously continue to play this role. Clinicians should however realise that with low PSA values 9 of 10 biopsies indicated by rectal examination will be negative for prostate cancer.

### Aggressiveness of cancers detected by DRE

Several studies suggest that prostate cancer detected by rectal examination may have more aggressive characteristics than tumours detected on the basis of elevated PSA levels only[47, 61-63].

Any pre-treatment procedure or finding that would enhance the selectivity of screening and help in an efficient way to differentiate between less aggressive and aggressive cancers should be highly welcomed and pursued. What is the evidence that DRE is helpful in this respect?

In the multicentre case finding study of 6,630 men older than 50 years reported by Catalona *et al.*[13] a PSA value of 4.0 ng/ml was a biopsy indication, which was met by 14.8% of the population. A number of 5,647 men (85.2%) had PSA levels of 0–4 ng/ml. This finding is very similar to data reported in table 5 for the ERSPC Rotterdam. Presumably, all cases included in Catalona's series were not previously screened. In this study 481 men were biopsied indicated by a positive rectal examination as only biopsy indicator (8.6%). In these men 48 prostate cancers were detected resulting in a PPV of 10%. Of these, 3% were poorly differentiated.

During the first 4 years of the initial screening round of the ERSPC Rotterdam 86.6% of 4,190 men had PSA values <4.0 ng/ml. Of these 3,629 men 142 (3.9%) were biopsied purely on the basis of an abnormal rectal examination. Seventeen cancers were found resulting in a PPV of 12% and a detection rate of 0.5%[9]. During the first round of the ERSPC Rotterdam, roughly half of the 21,210 men randomised to screening were screened by use of rectal examination in the PSA range 0–3.9 ng/ml. The other half was screened without rectal examination recommending biopsy in all participants with a PSA of 3.0–3.9 ng/ml. In this latter PSA range routine PSA-driven biopsy discovered almost three times as many prostate cancers as rectal examination (121 versus 43). However, the prevalence of Gleason score 7 or higher cancers amounted to 44% in the group screened by DRE versus 18% in the group screened without DRE. This difference seems to indicate selectiveness of DRE for detection of Gleason 7 or higher cancers. However, if one relates the number of Gleason 7 or higher cancers to the total number of men with PSA values below 4 in both groups, detection rates of 0.75% and 0.78% result[62].

Recently, Borden *et al.* concluded that an abnormal DRE was significantly associated with an increased risk of high-grade (Gleason score ≥7) prostate cancer in a cohort of 790 referred men, using a multivariate logistic regression analysis that corrected, amongst others, for the PSA level[61]. Thompson *et al.* drew the same conclusion in a study including 5,519 men within the placebo arm of the PCPT[47]. Nevertheless, a substantial number of prostate cancers would

be missed using DRE as biopsy indicator, of which it is not known if these can safely be left undiagnosed.

### Future

The best way of using PSA for diagnosing prostate cancer in the future and its role in differentiating between aggressive and less aggressive tumours seems uncertain at the moment.

For the time being, arbitrary cut-off levels will remain an important option even in repeat screening, despite the resulting high rate of overdiagnosis of more than 50% achieved by systematic screening of non-clinical populations[64]. Utilising a PSA cut-off of 4 or 3 ng/ml will eliminate the need for prostatic biopsy in respectively 87% and 79% of all men in the age groups at risk.

An alternative for a PSA cut-off is to determine the risk of prostate cancer for an individual using a risk calculator[65, 66] to decide whether or not to undergo a biopsy. On the website www.uroweb.org the 'prostate risk indicator', based on the results of the ERSPC screening study so far can be viewed.

There are momentarily several ways to deal with the problem of unnecessary biopsies and the many malignancies that are detected by screening but would most probably not have caused any symptoms during a man's lifetime if they had remained undiagnosed (overdiagnosis).

Firstly, screening intervals can be individualised. If a PSA test shows a value below the cut-off level, the rescreening interval should be adapted to the first PSA value. Strong evidence exists that a PSA level between 0 and 1 will not necessitate a repeat screening for periods of 8 years or longer (in men older than 55 years)[32, 67].

Although several studies[14, 16, 68] indicate that DRE is not useful as a screening test due to its limited PPV at low PSA levels, recent findings that DRE detects high-grade disease selectively[47, 61, 63] should be further investigated. Probably, DRE can play a role in the more selective detection of high-grade PCs. Another possibility would be the implementation of DRE in individual screening algorithms (e.g. modification of the screening interval) or in a risk calculator as mentioned above. Investigating these applications of DRE is one of the objectives of this thesis.

Secondly, in order to prevent that overdiagnosis results in overtreatment, i.e. subjecting men to unnecessary costly and invasive treatment with the risk of important side-effects[69, 70], initial active treatment can be replaced by active surveillance. Active surveillance entails a strategy by which selected men are managed expectantly with the intention to apply potentially curative treatment if signs of progression occur. Men who are diagnosed with prostate cancer and who present with 'minimal' or 'indolent' disease as defined in literature[71-77] can safely be included into active surveillance regimens with a minimal chance of unnoticed progression to an incurable state. The Rotterdam section of the ERSPC and the Department of Urology of the Erasmus Medical Center in Rotterdam have initiated the prospective, observa-

tional Prostate cancer Research International: Active Surveillance (PRIAS, www.prias-project.org) study to validate the management of prostate cancer with active surveillance[78, 79].

Thirdly, in order to prevent men from unnecessary biopsies the recently discovered prostate cancer antigen 3 (PCA3) is a promising prostate cancer marker. Furthermore, urinary PSA has been shown to be helpful.

PCA3 is the most prostate cancer-specific gene described to date[80, 81]. It concerns prostate-specific non-coding mRNA that is highly overexpressed in more than 95% of primary prostate cancer specimens and prostate cancer metastases[80, 81]. A PCA3 gene-based urine test was analysed in men with PSA levels of 3.0 ng/ml or higher and has shown to improve the specificity of prostate cancer diagnosis and to reduce the number of unnecessary biopsies in the serum PSA grey zone between 3 and 15 ng/ml[82, 83]. Currently, the PCA3 urine test is being evaluated within the ERSPC Rotterdam screening arm as an indicator for prostate biopsy independent of the PSA value.

Recently has been shown that urinary PSA seems to be a useful marker in a prospective study in 170 men for the differential diagnosis of prostate cancer and BPH, especially when serum PSA is between 2.5 ng/ml and 10 ng/ml. Low urinary PSA and urinary/serum PSA ratios point toward prostate cancer. Urinary PSA threshold of >150 ng/ml may be used to decrease the number of prostate biopsies.

Eventually, it will hopefully be possible to determine what should be called 'aggressive disease' on the basis of pre-treatment criteria in the near future. Molecular markers may resolve the problem in the future but are unavailable at present for the differentiation between aggressive and less aggressive cancers. However, the recent discovery of the TMPRSS2-gene fusions to the ERG-gene in prostate cancer have been shown to allow stratification of prostate cancer into distinct survival categories and to be promising in more exactly distinguishing the future clinical behaviour of prostate cancers, especially in the large group Gleason 6 and 7 cancers[84]. Recent reports on this subject show that a combined test for PCA3 and TMPRSS2:ERG expression in urine[85] or a multiplex biomarker analysis in urine (including several biomarkers among which PCA3 and TMPRSS2:ERG)[86] outperformed serum PSA and PCA3 alone for the detection of prostate cancer.

# Chapter 3

## Scope of the thesis |

Whether screening for prostate cancer has a beneficial effect on prostate cancer mortality is still unclear. For the answer to this important question we have to await the final outcomes of the two ongoing randomised early detection trials: the ERSPC in Europe and the PLCO in the United States of America[8].

PSA is the most commonly applied screening test in these trials, but also in daily clinical practice. As it is known that PSA is not a specific test for prostate cancer, but an overlap in PSA levels exists between men with normal prostates, benign prostate hyperplasia and localised PC, overdiagnosis and overtreatment have emerged as important side-effects of screening.

Basic research endeavours momentarily focus on the development of new, more specific markers for the detection of prostate cancer, or preferably, for the detection of aggressive, potential life-threatening disease. Unfortunately, such markers have not yet become available. Until that time PSA remains one of the corner stones of prostate cancer screening.

As described in chapter 1, DRE and TRUS have been omitted as screening test to indicate biopsy during the initial screening round of the ERSPC Rotterdam[9, 14]. From then on, the reason for undergoing a prostate biopsy in the largest part of the trial has been based on solely a PSA cut-off of 3.0 ng/ml. However, in all men who underwent biopsy still a DRE and TRUS were performed as part of the screening procedure.

If population-based screening for prostate cancer will indeed prove to be beneficial in terms of prostate cancer mortality reduction, the first question that arises will be what the appropriate screening algorithm should be.

This thesis focuses on the role of DRE in screening for prostate cancer. It aims to evaluate whether the omission of the digital rectal examination in 1997 in the ERSPC Rotterdam is still justified several screenings later by analysing the consequences. It is essential to know if screening without DRE has possibly led to the detection of relatively more advanced cancers at subsequent screenings or more cancers presenting clinically in between subsequent screenings as interval cancers.

Another focus of this thesis is to investigate if DRE is valuable in other applications than as a sole biopsy indicator. For example, is DRE useful in predicting prostate cancer in addition to an elevated PSA level as biopsy indication or for selectively detecting aggressive prostate cancers?

Since DRE is subjective, the interobserver variability can play a role in its value as a screening test. For this reason the interobserver variability within the ERSPC Rotterdam is evaluated.

# Part II

## Prostate cancer screening at low PSA levels: what kind of prostate cancers do we find?

**Chapter 4**

Prevalence and characteristics of screen-detected prostate carcinomas at low prostate-specific antigen levels: aggressive or insignificant?

*BJU Int. 2005 Feb;95(2):231-7*

# Chapter 4

## Prevalence and characteristics of screen-detected prostate carcinomas at low prostate-specific antigen levels: aggressive or insignificant?

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## SUMMARY

Screening for prostate cancer at low prostate-specific antigen (PSA) levels (≤4.0 ng/ml) risks detecting clinically insignificant cancers, which are of no threat to the man. In this review we evaluate the prevalence and tumour characteristics of prostate cancer detected at low PSA levels, comparing screening studies, cystoprostatectomy series and autopsy data. The favourable characteristics of tumours detectable at very low PSA levels seem to justify the conclusion that an unknown but sizeable proportion of the cancers found at biopsy are clinically insignificant.

## INTRODUCTION

Prostate cancer is a large public health problem[87]; it is currently the most common neoplasm and the second leading cause of cancer death in Western men[1]. Prostate cancer is unique among the potentially lethal malignancies in the wide discrepancy between the high prevalence of histological changes recognisable as cancer and the much lower prevalence of clinical disease. A common goal in research is to detect prostate cancer at an early, curable stage and to selectively detect those cancers which are aggressive.

'Clinically insignificant' prostate cancers, often called autopsy, latent, incidental or histological cancers, are thought not to be of immediate threat to the life or well-being of the host. Because of the slow progression of these prostate cancers, the often advanced age at diagnosis and comorbidity of the patient, it is not unlikely that the patient dies from other causes (intercurrent disease) before a prostatic tumour becomes aggressive. The estimated life-time risk of developing prostate cancer for a 50-year-old American man is ≈42% (based on autopsy data), yet the lifetime risk that he will have a clinically detected prostate cancer is ≈9.5% and the risk that he will die from the disease is only 2.9%[88, 89].

While not decisive in discriminating the malignant potential of a tumour, pathological features indicate which carcinomas are likely to be clinically insignificant, as such cancers tend to be of small volume (<0.5 ml according to Stamey *et al.*[90]), well differentiated and not invasive[89]. Epstein *et al.*[20] classified tumours as clinically insignificant if they were <0.2 ml, confined to the prostate and had a Gleason score (GS) of <7.

A concern about PSA-based screening is that it might detect many clinically insignificant prostate cancers that would not pose a clinical threat to the patient (overdiagnosis). The optimum threshold PSA value that indicates prostate biopsy remains unknown and is difficult to determine. The use of a higher PSA threshold risks missing an important cancer which is still curable, whereas the use of a lower threshold increases not only the number of unnecessary biopsies but also the number of clinically insignificant cases.

Thompson *et al.*[91] reported, in a side-study of the Prostate Cancer Prevention Trial (PCPT), the prevalence of prostate cancer among 2,950 men (median age 69.4 years, range 62–91). This side-study was carried out in participants in the placebo group; the selected participants, during the 7-year study period, never had a PSA value of ≥4.0 ng/ml or an abnormal DRE (measured and examined annually). At the end of the study all these men had a prostate biopsy (sextant technique). Prostate cancer was diagnosed in 15.2% of them, of whom 14.9% had a GS of ≥7. The prevalence of prostate cancer increased with the PSA level (from 7% at ≤0.5 ng/ml to 27% at 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% (PSA 3.1–4.0 ng/ml). Therefore, it was concluded that biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of ≤4.0 ng/ml and even in men with PSA values of <2.0 ng/ml. Carter[92] already suggested in an editorial that the prostate cancers found in the PCPT resemble autopsy cancers, with no clinical relevance.

In the following sections we discuss the question of whether systematic screening for prostate cancer at low PSA levels leads to the detection of clinically insignificant carcinomas, tumours which may normally never be diagnosed during a man's lifetime. The aim of the review is to compare the prevalence and tumour characteristics of prostate cancers found at end of study biopsy in the PCPT at PSA levels of ≤4.0 ng/ml with those found in the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam section, and in cystoprostatectomy series and autopsy studies. Prostate cancers found in cystoprostatectomy specimens (surgery for bladder cancer) and prostate cancers found at autopsy are considered incidental, being without symptoms or otherwise clinically significant before detection. We refer to the biopsy results of the ERSPC because of their similarity at PSA levels of 2.1–4.0 ng/ml and because of the available model predictions at 0–2.0 ng/ml. Variables of tumour aggressiveness of prostate cancers in the selected series are also compared.



## PREVALENCE OF PROSTATE CANCERS DETECTED AT LOW PSA LEVELS

We compared the positive predictive value (PPV, the number of prostate cancers divided by the number of men who had a biopsy in a given PSA range) or the prevalence of prostate cancers of the PCPT with the PPV or prevalence of the ERSPC, autopsy studies and cystoprostatectomy series.

### Comparison of the PCPT with ERSPC

In the first round (biopsy indication for PSA≥3.0 ng/ml) of the ERSPC[14], the PPV at a PSA of 3.1–4.0 ng/ml was 21.4%, comparable with the 26.9% found in the PCPT in the same range (the PSA range of the data concerned[14] was modified using the ERSPC database for optimum comparison with the PCPT). In this round of the ERSPC, 680 men had a PSA of 3.1–4.0 ng/ml,

**Table 1** An estimate of the number of prostate cancers in the ERSPC (if all men in the screening arm had a biopsy)[55], corrected for underestimation at a PSA of 2.1-3.0 and 3.1-4.0 ng/ml with data of round 1 and 2 of the ERSPC. The PPV of the ERSPC is compared with that from the Prostate Cancer Prevention Trial (PCPT).

| | ERSPC[14, 53] | | | | | Estimated[55] | | | Corrected | | PCPT[101] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PSA range (ng/ml) | N | Bx | PC | CDR (%) | PPV (%) | N | ePC | ePPV (%) | cPC | cPPV (%) | PPV (%) |
| 0-1.0 | | | | | | 3,045 | 34 | 1.1 | 34 | 1.1 | 8.8 |
| 1.1-2.0 | | | | | | 2,663 | 96 | 3.6 | 96 | 3.6 | 17.0 |
| 2.1-3.0 | 543 | 456 | 73 | 13.4 | 16.0 | 1,093 | 81 | 7.4 | 175* | 16.0 | 23.9 |
| 3.1-4.0 | 680 | 584 | 125 | 18.4 | 21.4 | 642 | 77 | 12.0 | 137** | 21.4 | 26.9 |
| overall | | | | | | 7,443 | 288 | 288/7,443 =3.9 | 442 | 442/7,443 =5.9 | 449/2,950 =15.2 |

N, number of men screened; Bx, number of men biopsied; PC, number of prostate cancers found; ePC, estimated number of prostate cancers (if all men in screening arm were biopsied); ePPV, estimated PPV (if all men were biopsied); cPC, estimated number of prostate cancers after correcting for underestimation; cPPV, estimated PPV after correction for underestimation

*1093 x 0.16 (PPV ERSPC side study) = 175

**642 x 0.214 (PPV ERSPC round 1) = 137

of which 85.9% (584 men) had a biopsy and 125 had prostate cancer; 99% of these men had never had a biopsy before (first screening round) (table 1)[14, 53, 55, 91].

However, at a PSA of 2.1–3.0 ng/ml the PPV in round two of the ERSPC (side study[53], biopsy indicated at a PSA of ≥2.0 ng/ml, 94% never biopsied before, and again the PSA range was modified) was 16% (73/456), considerably lower than the PPV of 23.9% from the PCPT[91].

For the other PSA ranges at <4.0 ng/ml, Kranse *et al.*[55] calculated the PPV by logistic regression (estimated PPV). A shortcoming in using this estimate is that cases with an abnormal DRE were not excluded. They estimated an overall PPV of 3.9%, with a PPV of 7.4% and 12% at a PSA of 2.1–3.0 and 3.1–4.0 ng/ml, respectively (table 1). The previously mentioned data gave higher PPVs (16.0% and 21.4%) so Kranse *et al.* underestimated by about half. Correcting for this underestimate at a PSA of 2.1–4.0 ng/ml, a new overall PPV of 442/7,443, or 5.9%, was calculated, which remained lower than that of 15.2% in the PCPT (the number of participants per PSA group was similar in both series). If the 50% underestimate is used to correct the other PSA ranges (0–1.0 and 1.1–2.0 ng/ml), the overall PPV becomes 507/7,443, or 6.8%, which is still dissimilar to the 15.2% in the PCPT.

So, at low PSA levels (0–4.0 ng/ml), the PPV in the PCPT is considerably higher than in the ERSPC (15.2% and 6.8%, respectively). In only one PSA range were the PPVs comparable (21.4% and 26.9% at 3.1–4.0 ng/ml). The most striking difference is in the PPVs for <1.0 ng/ml (respectively 8.7% and 1.1%) and 1.1–2.0 ng/ml (respectively 17.0% and 3.6%). This can at least partly be explained in that Kranse *et al.* used calculations based on the number of cancers found from an abnormal DRE. It is known that the PPV of a DRE decreases with de-

creasing PSA levels. Data from the first screening round of the ERSPC gave a PPV of 2.3% for a PSA of 0–1.0 ng/ml and 5.3% for 1.1–2.0 ng/ml[56]. So the underestimate here may be much more than half.

Another explanation is that the participants in the PCPT were older (median 69.4 years, range 62–91) than those in the first round of the ERSPC (PSA 3.1–4.0 ng/ml, median 65.7 years, mean 65.5, range 55–74) and in the side-study in round two (PSA 2.1–3.0 ng/ml, median 66.2, mean 66.6, range 58.5–74). It is possible that in these very low (<2.0 ng/ml) PSA ranges the participants were the oldest in the PCPT. A third explanation for this difference could be that Thompson *et al.* obtained more samples per biopsy than were assumed by Kranse *et al.* in their model. However, Thompson *et al.* stated that there was no significant difference in PPV for subjects who had a sextant biopsy (84.5% of participants) and those in whom more samples were obtained.

### Comparison of the PCPT with autopsy studies

Franks[17] is often cited for his autopsy study in which he found a prevalence of 37.7% for incidental prostate cancer, ranging from 29% at age 50–59 years to all men of ≥90 years. At

**Table 2** Incidence of latent prostate cancers in different age groups (autopsy studies).

| | Cancer detected per age group, as % (n cancers/n cases assessed, unless <≈20) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Age group, years | Franks[17] | Hirst[103] | Edwards[87] | Andrews[88] | Moore[89] | Holund[90] | Sakr *et al.*[18]* | Sakr *et al.*[104]* | Sanchez-Chapado *et al.*[105]** |
| 10-19 | | | | | | | 0/2 | | |
| 20-29 | 0/4 | | | | 0/24 | | 0/7 | 8 | 4 |
| 30-39 | 0/8 | | | | 0/28 | 0/3 | 30 (7/23) | 31 | 9 |
| 40-49 | 0/18 | | 4 (1/23) | 5 (1/22) | 17 (4/23) | 1/8 | 32 (7/22) | 37 | 14 |
| 50-59 | 29 (11/38) | | 10 (3/31) | 5 (2/38) | 14 (9/65) | 9 (2/23) | | 44 | 24 |
| 60-69 | 30 (16/53) | | 19 (10/54) | 18 (7/39) | 23 (18/77) | 13 (7/56) | | 65 | 32 |
| 70-79 | 40 (28/70) | | 25 (12/48) | 32 (7/22) | 21 (13/63) | 26 (24/93) | | 83 | 33 |
| 80-89 | 12/17 | 48 (16/33) | 3/17 | | 29 (7/24) | 37 (13/35) | | | |
| 90+ | 2/2 | 5/6 | | | | 60 (3/5) | | | |
| Totals | 38 (69/210) | 54 (21/39) | 17 (29/173) | 12 (17/142) | 17 (51/304) | 22 (50/223) | 26 (14/54) | N = 211 | 19 (27/146) |

N, no. of examined prostates

*Only Caucasian population mentioned in table

**Study in Caucasian Mediterranean men who are thought to have a lower prevalence of prostate cancer

the time Franks studied the prostate specimens (1954) there was no uniformity in the grading of prostatic malignancy. Local spread of these tumours was frequent; there was infiltration of the capsule in 52 of the 69 cases, and generally accompanied by invasion of periprostatic tissues. In other autopsy studies before 1955, the incidence of prostate cancer at autopsy was 12–54%[93-96] (table 2)[17, 18, 93-99]. The incidence in one study[95] was very high because the study population comprised men aged ≥80 years.

The frequency of finding small prostate cancers depends on the completeness of the histological examination and accurate studies require complete embedding of the gland. In all the cited studies a similar method was used (step sectioning) to examine the complete embedded prostate at intervals of 4 mm; in theory, any lesion of ≥4 mm would be detected. Most of the studies comprised older patients. Autopsy studies carried out more recently included more patients in the younger groups and showed a higher prostate cancer incidence in younger men than did the earlier studies[18, 98, 99] (table 2).

The prevalence of prostate cancer in autopsy studies (12–54%) is similar to or higher than the prevalence in the PCPT (15.2%), despite younger groups being included in several such studies. An explanation is that the whole prostate was examined in the autopsy series, compared to detection by biopsy, by which a tumour can easily be missed, in the PCPT.

**Table 3** Gleason score and tumour volume of prostate cancers detected in cystoprostatectomy series compared with Gleason scores detected in the Prostate Cancer Prevention Trial (PCPT).

| Variable | Montie *et al.*[93] | Kabalin *et al.*[95] | Ohori *et al.*[94] | Ward *et al.*[96]* | Stamey *et al.*[92] | Thompson *et al.*[101] (PCPT) |
|---|---|---|---|---|---|---|
| Mean, median (range) age, years | 62, 64 (34-80) | 66, 66 (31-82) | NA** | 68.5, 69 (44-92) | 66, 65 (31-84) | 69.4 (median) (62-91) |
| Specimen derived by | CP | CP | CP | CP | CP | Biopsy at end of study |
| N prostate cancers | 72 | 25 | 90 | 30 | 55 | 449 |
| Prevalence, % | 46 | 38 | NA** | 23 | 40 | 15.2 |
| GS 2-4, % | | 3 | <7: 89 | 0 | | 2.7 |
| GS 5-6, % | <6, 29 ≥6, 17 | 97 | | 93 | | 77.7 |
| GS, % | | 0 | 11 | 7 | | 14.9 |
| TV ≤0.2 ml, % | | 87 | 83 (≤0.5 ml) | 73 | 74 | |

CP, cystoprostatectomy; NA, not applicable

*PSA range ≤2.0 ng/ml

**CP specimens were used for comparison with RP specimens for pathological findings. All CP specimens used contained prostate cancer; patient age was not mentioned

### Comparison of the PCPT with cystoprostatectomy series

Cystoprostatectomy specimens obtained from men with a normal DRE undergoing surgery for bladder cancer potentially represent the closest approximation possible to an autopsy series for assessing incidental adenocarcinoma of the prostate. Men operated for bladder cancer with a normal DRE are not likely to have elevated (≥4.0 ng/ml) PSA levels; that 90% of men aged 50–90 years have PSA values of ≤4.0 ng/ml[9, 100-102] supports this assumption. Therefore, the prevalence and tumour characteristics (discussed later) found in these studies can be compared with the PCPT results.

The prevalence of unsuspected prostate cancer in different cystoprostatectomy series was 23–46%[90, 103-106] (table 3), i.e. higher than the prevalence in the PCPT (15%), and matching that of autopsy-detected cancer of 30–40% in men aged 50–80 years[17]. Again, this difference can be explained in that the PCPT concerned biopsy-detected prostate cancers.

## TUMOUR CHARACTERISTICS OF PROSTATE CANCERS DETECTED AT LOW PSA LEVELS

### Aggressiveness

In a simplified way, prostate cancers can be classified as clinically important (i.e. threatening the life or well-being of the patient within his remaining life expectancy) or clinically insignificant (i.e. a latent cancer of no threat to the man). It is unclear at this time which small screen-detected prostate cancers will progress rapidly, slowly or possibly not at all. Also, the lifetime risk of a clinical diagnosis is co-determined by age and comorbidity. Tumour volume (TV), Gleason grade and invasiveness are variables that can help to distinguish clinically important from insignificant prostate cancers[88].



### The Gleason score

In the GS the most prominent pattern of growth, ranging from 1 (well differentiated) to 5 (undifferentiated), is combined with the second most common growth pattern as a criterion of overall grade. The total score, of 2–10, is obtained by adding the two most prominent patterns[107].

In 2000, Epstein[108] discussed the detection of low-grade prostate cancer on needle biopsy, suggesting that a GS of 2–4 should not be assigned to adenocarcinoma on needle biopsy, because this initially leads to undergrading, its reproducibility is poor and thus it can adversely affect patient care. This leads to the identification of three prognostic groups by biopsy, i.e. men with GS 6, 7 and 8–10 (all lower scores being included in 6). If reported, the biopsy GS of 2–4 should be interpreted cautiously; GS 6 and 7 are the most prevalent scores on prostatic needle biopsy.

A problem of a GS based on prostate biopsy is undergrading; this is reported in about half of the biopsy GS of <7[109, 110]. Thus patients with a biopsy GS of <7 are upgraded after examining the radical prostatectomy (RP) specimen in almost half of the cases, to a higher GS (≥7).

In the ERSPC, a biopsy GS of <7 was undergraded in 26% (Postma R, van der Kwast T. unpublished data); this reduction in undergrading in a screening situation is probably the result of a better biopsy technique and the few poorly differentiated tumours in prescreened populations.

When comparing biopsy GS (PCPT) with pathological GS (as in autopsy studies or cystoprostatectomy series) in this review, 20–50% of GS≥7 cancers should be added to biopsy-detected prostate cancers to correct for undergrading. Verifying these estimates using sufficiently many carefully studied RP specimens of PCPT cases is desirable and would resolve the problem of diagnosing indolent cancers.

### Tumour volume

TV is an important predictor of clinical progression; the probability of histological progression, i.e. capsular penetration, seminal vesicle invasion and microscopic metastases to the pelvic lymph nodes, is related directly to intracapsular cancer volume[90, 111, 112].

Stamey *et al.*[113] concluded that TV was an independent predictor of progression after RP in a series of 379 RP specimens. However, in multivariate analyses TV appeared not to be a significant independent predictor of prognosis[114, 115].

Prostate cancers are considered insignificant if they are confined to the prostate and have a TV of <0.2 ml and a GS of <7. These tumours are thought not to progress within the normal life expectancy of the man[20, 89]. In contrast, Stamey *et al.*[90] determined a threshold TV of 0.5 ml for clinical insignificance. However, Stamey reconsidered this value of 0.5 ml in a recent editorial, because it is not a clinical variable (it requires RP to measure the cancer). Furthermore, he suggested that what constitutes an insignificant cancer remains unknown, but it is likely to be >0.5 ml[116].

### Comparison of the PCPT with ERSPC

In a side-study (biopsy indication PSA≥2.0 ng/ml[53]) in the second round of the ERSPC[53], 14.3% of the prostate cancers at a PSA of 2.0–3.9 ng/ml had a GS of ≥7 (GS were determined from the ERSPC database), which is similar to the proportion of poorly differentiated tumours in the PCPT (table 4)[53, 91, 109, 117, 118]. However, this side-study included only PSA levels of 2.0–3.9 ng/ml, whereas the PCPT included 0–4.0 ng/ml. Specifically, in that lowest range (0–1.9 ng/ml) fewer aggressive tumours would be expected and would therefore, if included in the ERSPC, lower the detection rate of 14.3%.

Hoedemaeker *et al.*[68] showed that prostate cancers found at a PSA level of <4.0 ng/ml and with an abnormal DRE/TRUS had more favourable tumour characteristics in the RP specimen than those with a PSA of ≥4.0 ng/ml and a normal DRE/TRUS, or those at a PSA of ≥4.0 ng/ml

**Table 4** Biopsy-derived Gleason score of prostate cancers detected in clinical studies at low PSA levels in comparison with Gleason scores detected in the Prostate Cancer Prevention Trial (PCPT).

| | Catalona *et al.*[111] | Catalona *et al.*[119]* | Lodding *et al.*[120] | Raaijmakers *et al.*[53] | Thompson *et al.*[101] (PCPT) |
|---|---|---|---|---|---|
| Biopsy GS 2-4, % | | 12.3 | 25 | | 2.7 |
| Biopsy GS 5-6, % | ≤5, 13 =6, 77 | 79.4 | 68.8 | 85.7 | 77.7 |
| Biopsy GS 7-10, % | =7, 7 8-10, 4 | 8.2 | 6.3 | 14.3 | 14.9 |
| N prostate cancers | 224 | 73 | 32 | 126 | 449 |
| Prevalence | Retrospective | 22 | 13.2 | 17.1** | 15.2 |
| Age, years (range) | Median 64 | Mean 62 (50-90) | Mean 59 (50-66) | Mean 66 (55-74) | Median 69 (62-91) |
| PSA range, ng/ml | 2.0-4.0 | 2.6-4.0 | 3.0-4.0 | 2.0-3.9 | 0.0-4.0 |

*Only 36% of study population underwent the recommended biopsy

**PPV, 126/736 = 0.171

and abnormal DRE/TRUS. Despite 57% of the prostate cancers in the first group having a GS of 7, 43% met the criteria of minimal cancer and 21% were insignificant (in the other groups no insignificant prostate cancers were found). A substantial proportion of these tumours were detected on the basis of a false-positive DRE/TRUS, and thus by accident. These findings are confirmed by recent data on TVs of cancers detected at repeat screening in the ERSPC (biopsy indication PSA≥3.0 ng/ml, and almost half of the cancers detected had a PSA level of 3.0–4.0[119]). The median TV of these cancers was 0.48 ml in the first and 0.43 ml in the second round. The mean volumes in both rounds also differed significantly but were much higher, indicating that the PSA-related volume distributions are strongly skewed 'to the left'. This indicates a preponderance of low-volume cancers which are often ≤0.2 ml, which according to several studies are compatible with insignificant 'autopsy cancers'[20]. These results indicate that screening at low PSA levels seems to detect more insignificant tumours, which can lead to overdiagnosis and overtreatment.

The distribution of a biopsy GS of ≥7 in several other studies was 6.3–11%; these prostate cancers were detected at a PSA of 2.0–4.0 ng/ml (table 4). Unfortunately, for a PSA of 0.0–2.0 ng/ml no comparable series were found and therefore it is difficult to compare these results with the PCPT. Another problem is that in one of the cited series[117], 85% of the men were previously screened, and in another[109] only 36% of the participants had the recommended biopsy and no information on DRE was available.

In the series of Lodding *et al.*[118] (biopsy indication PSA≥3.0 ng/ml, 66% normal DRE, 93% had the recommended biopsy) all detected tumours for which RP data were available had a TV of >0.2 ml and 21.4% of these tumours had a RP GS of 7 (biopsy GS of 7 in 6.3%). Based on RP specimens, 21.4% of these tumours were clinically important.

It is not surprising that series in which the PSA 3.0–4.0 ng/ml is included contain many clinically significant tumours. It is, among others, for this reason that a PSA level of 3.0 ng/ml has been proposed recently as the threshold value for screening[16].

### Comparison of the PCPT with autopsy studies

In 1980 Holund[97] described the differentiation of latent prostate cancer, varying from well differentiated to anaplastic, in six stages. In his study, 223 prostates were removed at consecutive autopsies. If translated into GS groups, Holund found a similar percentage of poorly to undifferentiated prostate cancers as did Thompson *et al.*[91] (16% and 14.9%, respectively, table 5[91, 97, 99]). Translating Holund's grading system into GS cannot be done with any restriction, but it still seems useful for comparison.

Sanchez-Chapado *et al.*[99] examined 27 prostates at autopsy and found only one prostate cancer with a GS of 7 (table 5). This tumour was a diffuse neoplasm extending outside the prostate, in an 80-year-old. As a result of the few prostates included in the study it is difficult to compare the results with the findings of Thompson *et al.*[91].

Because of the period in which the reviewed studies were performed and the heterogeneity in study methods, it is not possible to draw any conclusions from comparing the PCPT GS and autopsy study results. In none of the reviewed studies was TV measured and only one autopsy study[97] described a similar number of poorly to undifferentiated prostate cancers, which suggests a resemblance of prostate cancers found in the PCPT with autopsy tumours (that are thought to be clinically insignificant).

**Table 5** Gleason score of prostate cancers detected in autopsy studies compared with Gleason scores detected in the Prostate Cancer Prevention Trial (PCPT).

| | Holund[90] | Sanchez-Chapado *et al.*[105] | Thompson *et al.* [101] (PCPT) |
|---|---|---|---|
| Age, years (range) | (36-94) | Mean 48.5 (20-80) | Median 69.4 (62-91) |
| Specimen derived by | autopsy | autopsy | End of study biopsy |
| N prostate cancers | 50 | 27 | 449 |
| Prevalence, % | 22 | 18.5* | 15.2 |
| GS 2-4, % | 36 | 37 | 2.7 |
| GS 5-6, % | 48 | 59 | 77.7 |
| GS 7-10, % | 16 | 4 | 14.9 |

*Study in Caucasian Mediterranean men who are thought to have a lower prevalence of prostate cancer

### Comparison of the PCPT with cystoprostatectomy series

In the reviewed cystoprostatectomy studies (incidental prostate cancers in men with a normal DRE), high-grade cancer (GS≥7) was found in 0–11%[103, 105, 106] (table 3). One study reported prostate cancers with a GS of ≥6 in 17% of men[104]. About 15% of the detected prostate cancers in this study were considered morphologically significant (defined as invasion or penetration

of the capsule and GS≥6). Notably, the study in which none of the tumours was poorly differentiated had few subjects, by which the findings are probably distorted[103].

TV was significant in 13–27% of the detected prostate cancers in the cited series[90, 103, 106] (table 3). In one series 17% of the detected cancers had a TV>0.5 ml[105].

Recently, Ward *et al.*[106] assessed the pathological characteristics of incidentally discovered prostate cancers at a PSA of 0–2.0 ng/ml in patients with a normal DRE. Of the 129 patients, 30 (23%) had prostate cancer, of whom two (7%) had Gleason pattern 4 (versus 11% with GS≥7 at a PSA of 0–2.0 ng/ml in the PCPT). Only one patient had extraprostatic extension. Defining clinical significance as a GS of ≥7 and TV of >0.2 ml, only one tumour was clinically significant.

In summary, in only one series[105] was there a similar percentage of poorly differentiated tumours (11%) as in the PCPT. However, these prostate cancers were mainly small and confined to the prostate, and therefore resemble autopsy cancers. TV and confinement to the prostate of cancers in the PCPT are unknown (biopsy-detected cancers), but may be similar because these cancers are also unsuspected in men with no complaints or an abnormal DRE or PSA findings. TV was clinically significant (>0.2 ml) in 13–27% of the detected prostate cancers. However, it is not possible to claim clinical significance of a tumour on the basis of TV alone[114, 115]. Thus the expected number of clinically significant tumours is lower than this. Taking other tumour characteristics into account, Ward *et al.*[106] detected, at a low PSA level, only one clinically significant prostate cancer, which contradicts the hypothesis that high-grade prostate cancers are not rare at low PSA levels.



## CONCLUSION

Thompson *et al.*[91] concluded that biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with a PSA level of ≤4.0 ng/ml and even in men with PSA values of <2.0 ng/ml. Because of the variability in reporting and execution of studies, it is difficult to compare the prevalence and aggressiveness of prostate cancers detected at low PSA levels. Nevertheless, the reviewed studies for which comparison was possible generally contradict the findings of the PCPT. The favourable characteristics of tumours detectable at very low PSA levels[68, 103, 105, 106] seem to justify the conclusion that an unknown but sizeable proportion of the cancers found at routine biopsy in apparently normal men are clinically unimportant but compatible with autopsy cancers.

In summary, the higher prevalence of indolent cases, as compared to the significant and possibly life-threatening cases, put the value of screening in men with these low PSA levels (<3.0 ng/ml) in question. A PSA threshold of 3.0 ng/ml produced a good balance between an acceptable PPV of the test and detecting clinically significant tumours[16].

# Part III

## Evaluation of omitting the digital rectal examination as a screening test

**Chapter 5**
Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam.
*The Prostate. 2006 May 1;66(6):625-31*

**Chapter 6**
Screening for prostate cancer at low PSA range: the impact of digital rectal examination on tumour incidence and tumour characteristics.
*The Prostate. 2007 Feb 1;67(2):154-61*

# Chapter 5

## Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam.

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*The Prostate. 2006 May 1;66(6):625-31*

## ABSTRACT

### Background

Omission of DRE/TRUS as biopsy indication results in fewer unnecessary biopsies, but may increase the risk of missing potentially aggressive prostate cancers. In 1997, the biopsy indication within the ERSPC was changed from a PSA cut-off of 4.0 ng/ml and/or abnormal DRE/TRUS (group-1) to solely a PSA cut-off of 3.0 ng/ml (group-2). We estimated the effect of omitting DRE/TRUS by comparing the results of a rescreening 4 years after initial screening to the original policy.

### Methods

We compared rate and characteristics of detected prostate cancers in the second round in men initially screened in group-1 (N=5,957) or group-2 (N=8,044). Additionally, we compared the rate of interval cancers after screening with and without DRE/TRUS.

### Results

There was no significant difference in second round cancer detection rates (group-1, 3.0%; group-2, 2.7%), positive predictive values (group-1, 23.9%; group-2, 26.3%) and number of poorly differentiated tumours (group-1, 2.6%; group-2, 3.8%). Most prostate cancers were clinically confined to the prostate. Eleven interval cancers were detected in each group (0.18 and 0.14%).

### Conclusions

Omitting DRE/TRUS did not result in an increased interval cancer or prostate cancer detection. However, considering the natural history of prostate cancer, the 4-year follow-up may be too short to draw a definitive conclusion.

## INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC) aims to show whether prostate cancer (PC) mortality differs significantly between the screening and control arms. Its set-up also enables us to evaluate the screening tests used, such as digital rectal examination (DRE), transrectal ultrasound (TRUS) and prostate-specific antigen (PSA)[120].

It is generally assumed that TRUS is not a valuable test for the early detection of PC in a screening program[9-11]. The value of DRE as a screening test for the early detection of PC remains controversial. For this reason, in May 1997 both test procedures were discontinued as an indication for sextant biopsy (at PSA levels <4.0 ng/ml) in the Rotterdam section of the ERSPC. At the same time, the PSA threshold as a biopsy indication was reduced from 4.0 to 3.0 ng/ml[9, 14].

Due to the omission of DRE/TRUS, and therefore the omission of biopsies at PSA<3.0 ng/ml, there is a risk of missing potentially aggressive tumours at these low PSA levels which could surface as interval cancers (ICs), i.e. PCs detected between the two screening rounds. Another possibility is that these cancers are detected at a subsequent screening when the PSA level has risen to a value above the threshold of 3.0, probably expressing more aggressive tumour characteristics. This may lead to more PC-specific deaths, and therefore can have an effect on the outcome of the study by decreasing a potential difference in PC-specific mortality.

The number of missed cases with potentially aggressive tumour characteristics depends both on the prevalence below the threshold value for biopsy, and on the effectiveness of the screening tests used to detect these cases. To evaluate this, we compared prognostic factors of tumours found in the second screening between two groups of men who had been initially screened either with DRE/TRUS (group-1) or without these tests (group-2). In the second round, both groups were biopsied if PSA was above the threshold value of 3.0 ng/ml (PSA as the sole biopsy indication). In order to make these two screening protocols more comparable, only men with a PSA level <3.0 ng/ml at first screening were included. In this way, DRE/TRUS were the sole tests that could indicate a sextant biopsy in round 1 in group-1 and there was no indication for biopsy in group-2.

The difference in prevalence of aggressive cancers in round 2 between men initially screened with or without DRE/TRUS should relate directly to the value of DRE and TRUS. The same applies to the rate of ICs.

## MATERIALS AND METHODS

### Study population

In the Rotterdam area, all men in the age group 55-75 years were identified by the population registry and asked to participate in a randomised screening study for PC. Men who

responded by returning the intake questionnaire and a signed informed consent form were randomised. Men randomised to the screening arm were screened by means of a serum PSA determination and, depending on the screening protocol, DRE and TRUS were carried out. Sextant biopsy was proposed if indicated. A more detailed description of the study design has been published previously[120].

Before May 1997, the screening protocol determined that participants with a PSA≥4.0 ng/ml and/or a suspicious DRE/TRUS finding at a low PSA value (0.0-3.9 ng/ml) were to undergo sextant prostate biopsy (referred to as 'screening with DRE/TRUS', group-1, in this paper). It should be noted that in November 1995 the omission of DRE/TRUS was already implemented for participants who presented with a PSA level <1.0 ng/ml[9, 56]. These participants were excluded from the present study.

After May 1997, a major protocol change was implemented in the ERSPC. Biopsies were taken exclusively from men with a PSA≥3.0 ng/ml. Men with a PSA<3.0 ng/ml were directly rescheduled for their next screening visit 4 years later ('screening without DRE/TRUS', group-2, in this paper). Thus, in round 1 (1993-1999) the biopsy indication based on a PSA cut-off of 4.0 ng/ml and/or abnormal DRE/TRUS (group-1) was changed to a PSA cut-off of 3.0 ng/ml as the sole biopsy indication (group-2). All men included in this study had an initial PSA<3.0 ng/ml in order to make the screening protocols comparable. Rescreening without DRE/TRUS (1997-2003) was offered after 4 years in the second screening round (figure 1).

Positive predictive value (PPV, the proportion PCs/number of biopsied men), cancer detection rate (CDR, the proportion PCs in screened men), number of ICs and tumour characteristics (clinical stage, pathological stage, Gleason score (GS)) of PCs detected at rescreening were compared between the initial two protocols.



### Techniques

Screening entailed a determination of serum PSA concentration (Beckman-Coulter Hybritech Tandem-E Assay; San Diego, California). Blood samples were drawn before the other tests were performed. DRE and TRUS were performed by a resident urologist or an ultrasound technician. Nodularity and induration were considered abnormal on DRE. TRUS was performed using a Bruel & Kjaer® model 1,846 mainframe and a 7 MHz biplanar endorectal transducer, with the subject in the left lateral decubitus position. Hypoechoic lesions were considered suspicious. Lateral sextant transrectal prostate biopsy was performed, in line with the findings of Eskew *et al.*[121], using a Bard (C.R. Bard, Convington, GA) spring-loaded biopsy gun and an 18-gauge biopsy needle. Additional biopsies were taken from suspicious areas on TRUS. Palpable lesions were not a reason for an additional, lesion directed biopsy, so in the second round a suspicious DRE was not an indication for biopsy at all. At the time of performing DRE/TRUS, the members of the screening team were not aware of the current PSA value (round 1). At the second screening, the screening team knew that the PSA value was ≥3.0 ng/ml, but was not aware of the exact value or previous screening results.

### Pathologic examination

Biopsy specimens were histopathologically analysed by a single pathologist (TvdK). PC was graded according to the GS system. All radical prostatectomy (RP) specimens (n=75, second screening round) were fixed, totally embedded, and processed. For these tumours, a RP GS was determined and the tumour was staged according to the 1992 UICC TNM classification[122].

### Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS 10.1.0; SPSS Incorporated, Chicago, IL). Statistical testing was done by the Fisher's exact two-sided test. Statistical significance was defined as a p-value <0.05.

## RESULTS

### First screening round

At their first visit, all men included had a PSA<3.0 ng/ml. In this initial screening round (prevalence screen), 5,957 (4,249+1,708) men were screened according to the protocol with DRE/TRUS (group-1, December 1993-April 1997), and 8,044 participants were screened according to the protocol without DRE/TRUS (group-2, May 1997-December 1999).

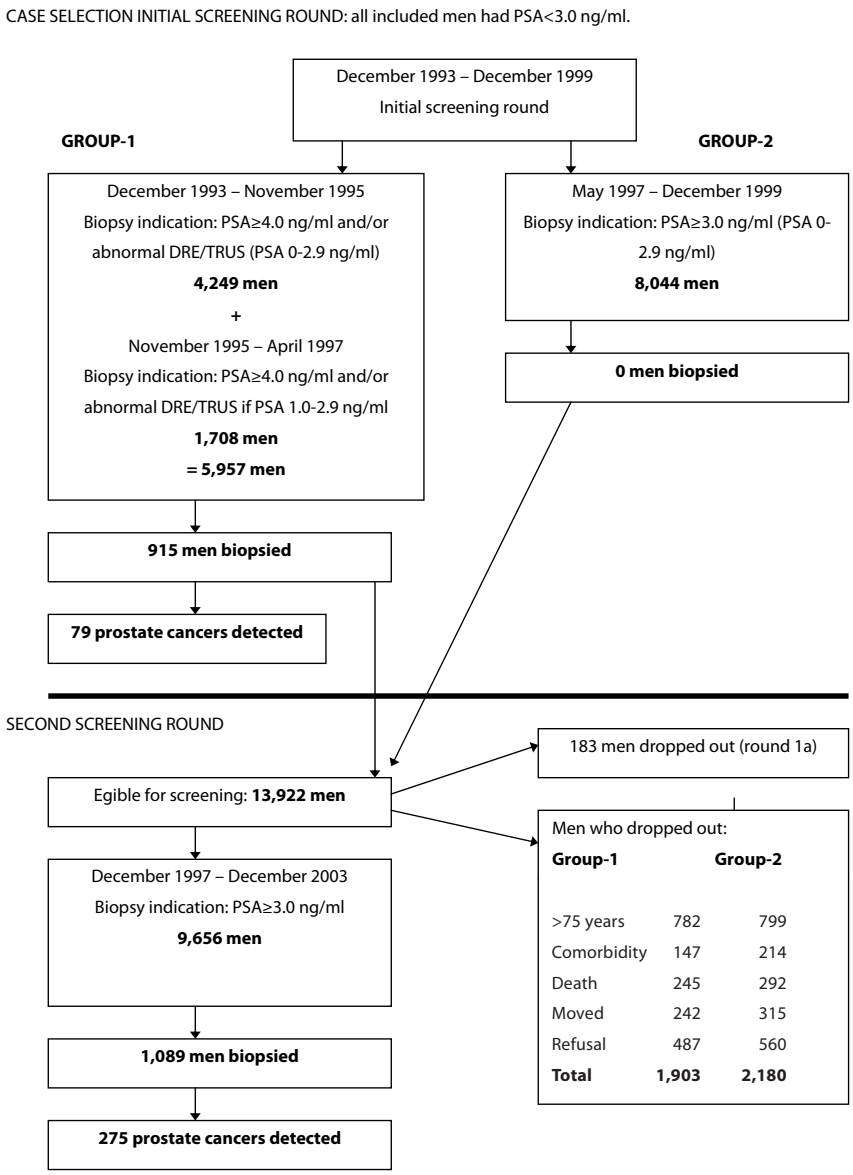
At the first screening visit, 79 PCs were detected (biopsy indication was an abnormal DRE in 30 cases, an abnormal TRUS in 30 cases and both tests abnormal in 19 cases). These tumours had in 89.9% clinical stage T2 and in 10.1% T3a and a biopsy GS<7 in 77.2%, 7 in 17.7% and >7 in 5.1%. Thirty-nine men underwent RP, of whom 82.1% had a pathologically organ confined tumour, 77.0% had a pathological GS<7 and 20.5% a GS=7 (1 GS missing) (figure 1, table 1).

### Second screening round

After 4 years, 3,792 (64%) men from group-1 were rescreened, and 5,864 (73%) men from group-2. Rescreening was carried out without DRE/TRUS (December 1997-December 2003, table 1). The loss of participants in the second round was ascribed to old age (>74 years) (782 men for group-1 and 799 men for group-2), co-morbidity (147 and 214, respectively), death (245 and 292), removal from the Rotterdam region (242 and 315) or refusal (487 and 560) (figure 1). Of the participants initially screened according to the protocol with DRE/TRUS (group-1), 183 had already dropped out before the second screening round due to rescreening after one year in a side-study (round 1a).

The mean age in years of the participants at the first screening visit was 63.4 (median 62.8) in group-1 and 63.1 (median 62.3) in group-2. At the second visit, the mean age in these groups was 65.8 (median 65.4) and 66.0 (median 65.4).

**Figure 1:** Flow chart ERSPC Rotterdam. The second screening round was carried out 4 years after the first screening visit.




In round 2, there was no significant difference between the two protocols in CDR (group-1, 3.0%; group-2, 2.7%, p=0.381) and PPV (group-1, 23.9%; group-2 26.3%, p=0.399) (table 1). Table 2 shows that most of these cancers were clinically confined to the prostate in both groups (group-1, 95.6%; group-2, 96.3%). There was no significant difference in the percentage poorly differentiated tumours (biopsy GS>7) between the two groups (2.6% of the PCs detected in group-1 and 3.8% in group-2, p=0.384). Two PCs with GS=9 (clinical stage T2b and

**Table 1:** First and subsequent second screening round after 4 years. Group-1 is initially (first round) screened according to the protocol with DRE/TRUS , group-2 to the protocol without DRE/TRUS. All men had initially PSA values <3.0 ng/ml.

| **Initial screening** | | | | | | **Second screening after 4 years** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PSA (ng/ml) | N men (%) | Bx (N) | N PC | PPV (%) | CDR (%) | N men | Bx (N) | N PC | PPV (%) | CDR (%) |
| **Group-1: screened with DRE/TRUS** | | | | | | **Group-1: PSA≥3.0 ng/ml is biopsy indication** | | | | |
| <1.0 | 1,708 (28.7) | 183 | 4 | 2.2 | 0.23 | 1,137 | 17 | 1 | 5.88 | 0.088 |
| 1.0 – 1.9 | 3,051 (51.2) | 511 | 45 | 8.8 | 1.47 | 1,967 | 168 | 38 | 22.62 | 1.93 |
| 2.0 – 2.9 | 1,198 (20.1) | 221 | 30 | 13.6 | 2.50 | 688 | 296 | 76 | 25.68 | 11.05 |
| Total | 5,957 (100) | 915 | 79 | 8.6 | 1.33 | 3,792 | 481 | 115 | 23.91 | 3.03 |
| **Group-2: no further screening (PSA<3.0 ng/ml)** | | | | | | **Group-2: PSA≥3.0 ng/ml is biopsy indication** | | | | |
| < 1.0 | 3,580 (44.5) | - | - | - | - | 2,659 | 22 | 5 | 22.73 | 0.19 |
| 1.0 – 1.9 | 3,154 (39.2) | - | - | - | - | 2,296 | 186 | 44 | 23.65 | 1.92 |
| 2.0 – 2.9 | 1,310 (16.3) | - | - | - | - | 909 | 401 | 111 | 27.68 | 12.21 |
| Total | 8,044 (100) | - | - | - | - | 5,864 | 608 | 160 | 26.32 | 2.73 |

PPV, positive predictive value, the proportion PCs/number of biopsied men; CDR, cancer detection rate, the proportion PCs/number of screened men; Bx, biopsied men; DRE, digital rectal examination; TRUS, transrectal ultrasound; PSA, prostate-specific antigen.

T3c) and one with GS=10 (T2a) were detected in group-2, while all 115 PCs in group-1 had a GS≤8. If the detected tumours were grouped into two prognostic GS categories (GS<7 and GS≥7), men in group-2 had in 26.3% tumours with a GS≥7, and in group-1 19.1% (p=0.19).

### Radical prostatectomy

Of the 275 men diagnosed with PC at the second screening, 75 (42 in group-1 and 33 in group-2) underwent RP at our hospital. The surgical specimens showed organ confinement (pathological stage T2) in 90.5% (38/42) in group-1 and in 70.0% (23/33) in group-2 (p=0.035). The percentage of poorly differentiated tumours (RP GS>7) did not differ significantly between the two groups. One out of 40 RP specimens in group-1 (2.5%, 2 GS missing) and 2/32=6.2% (1 GS missing) for group-2 had a GS>7 (p=0.290). If RP specimens were grouped into two prognostic GS categories (GS<7 and GS≥7), men in group-1 had in 35.0% tumours with a GS≥7, and in group-2 53.1% (p=0.154).There were no lymph node metastases in 93% in group-1 and in 88% in group-2 (p=0.692, regional lymph node stage unknown in 7% (group-1) and in 12% (group-2)).

**Table 2:** Second screening round: clinical stage and biopsy Gleason score of the screen detected prostate cancers (N=115 for screening with DRE/TRUS and N=160 for screening without DRE/TRUS). The screening group with DRE/TRUS consisted of 3,792 men, the screening group without DRE/TRUS of 5,864 men.

| | Screening regimen in the first screening round | | | |
|---|---|---|---|---|
| | **DRE/TRUS** | | **No DRE/TRUS** | |
| Clinical stage | N prostate cancers (% of total N prostate cancers) | % of men screened | N prostate cancers (% of total N prostate cancers) | % of men screened |
| T1c | 66 (57.4) | 1.7 | 99 (61.9) | 1.7 |
| T2a | 27 (23.5) | 0.71 | 40 (25.0) | 0.68 |
| T2b | 11 (9.6) | 0.29 | 9 (5.6) | 0.15 |
| T2c | 6 (5.2) | 0.16 | 6 (3.8) | 0.10 |
| T3a | 4 (3.5) | 0.11 | 4 (2.5) | 0.068 |
| T3b | - | - | 1 (0.6) | 0.017 |
| T3c | 1 (0.9) | 0.03 | 1 (0.6) | 0.017 |
| Total | 115 (100.0) | 115/3,792 = 3.0 | 160 (100.0) | 160/5,867 = 2.7 |
| Confined to prostate | 110 (95.6) | 2.9 | 154 (96.3) | 2.6 |
| Biopsy Gleason score | N prostate cancers (% of total N prostate cancers)* | % of men screened | N prostate cancers (% of total N prostate cancers)* | % of men screened |
| <7 | 93 (80.9) | 2.5 | 118 (73.8) | 2.0 |
| 7 | 19 (16.5) | 0.50 | 36 (22.5) | 0.61 |
| >7 | 3 (2.6) | 0.079 | 6 (3.8) | 0.10 |
| Total | 115 (100.0) | 115/3,792 = 3.0 | 160 (100.0) | 160/5,867 = 2.7 |

*p=0.384 (Fisher's exact 2-sided)




### Interval cancers

In group-1, 11 ICs were reported in 5,957 screened men (0.18%), in group-2, there were also 11 ICs, in 8,044 men (0.14%, p=0.522) (table 3). In group-1, 11 ICs were clinically organ confined, in group-2, 1 IC showed invasion of other organs (T4) and the stage was unknown in four cases. The biopsy GS of these tumours and the initial PSA of patients with an IC are listed in table 3.

## DISCUSSION

As described in a previous paper, our decision to discontinue DRE and TRUS as screening tests and to use a PSA threshold as the sole biopsy indication was based on an investigation of the value of DRE in 10,523 consecutive men in the screening arm[16], 7,055 of whom were found to have a PSA value <4.0 ng/ml. At these PSA levels, DRE should be useful, whereas the PSA value is so low that it was considered not to discriminate between a man with cancer or without. However, in the referred study the PPV (average 12.8% at PSA 0-3.9 ng/ml)

**Table 3:** Clinical stage and biopsy Gleason score of the interval cancers in the group initially screened with DRE/TRUS (N=11) and without DRE/TRUS (N=11).

| | Screening regimen in the first screening round | |
|---|---|---|
| **Interval Cancers** | **DRE/TRUS** | **No DRE/TRUS** |
| Clinical stage | N (% of men screened) | N (% of men screened) |
| T1a | 3 | 2 |
| T1b | 1 | - |
| T1c | 6 | 2 |
| T2b | 1 | 1 |
| T2c | - | 1 |
| T4x | - | 1 |
| unknown | - | 4 |
| Total | 11 (11/5,957 = 0.18) | 11 (11/8,044 = 0.14) |
| Biopsy Gleason score | N (% of men screened) | N (% of men screened) |
| <7 | 5 | 3 |
| 7 | 1 | 1 |
| unknown | 5 | 7 |
| Total | 11 (0.18) | 11 (0.14) |
| PSA in first round (ng/ml) | N (% of men screened) | N (% of men screened) |
| <1.0 | - | 1 |
| 1.0 – 1.9 | 6 | 3 |
| 2.0 – 2.9 | 5 | 7 |
| Total | 11 (0.18) | 11 (0.14) |

PSA, prostate-specific antigen

and sensitivity (14-39%, calculated by using the estimated underlying prevalence of PC) of DRE were low. If DRE had been omitted at a PSA<3.0 ng/ml, 47 of the 473 cancers actually detected (9.9%) would have been missed[16]. Conversely, another study on PC detection at low PSA levels (PSA<4.0 ng/ml) estimated that if every man with PSA 3.0-3.9 ng/ml (N=734) had a biopsy (instead of only the men with an abnormal DRE/TRUS), 43 (48.3%) more PCs would have been detected[15]. In addition, it was demonstrated that a substantial proportion of the tumours at PSA≤4.0 ng/ml were detected on the basis of a false-positive DRE/TRUS, and thus by accident[68, 123]. These findings were confirmed by another study[62], that demonstrated the inefficiency of DRE at low PSA levels (<3.0 ng/ml) by comparing the same two protocols as we do in our current study: 289 DREs were necessary to find one clinically significant PC (tumour not confined to the prostate, tumour volume ≥0.5 ml or Gleason pattern 4 or 5); and 96 DREs were needed to diagnose one PC irrespective of tumour characteristics. Nevertheless, in the 3.0-3.9 ng/ml PSA range, an abnormal DRE detected significantly more biopsy GS 7-10 cancers than PSA-based screening[62].

On the basis of a validation study in 7,943 men in the screening arm carried out previously[14], the new screening regimen in the ERSPC was considered justified. By using the new

protocol, the CDR remained similar (CDR 5.0 and 4.7 at PSA cut-off of ≥4.0 and ≥3.0 ng/ml, respectively) while the PPV became higher in PSA range 3.0-3.9 ng/ml (from 6.4% in the old protocol to 18% in the new one). At the same time, the number of men who had to undergo a biopsy decreased[14]. In the validation study, PCs detected with the new regimen had a similar distribution of GS, but a larger proportion of confined disease[14].

In contrast, in a multicentre clinical trial, Catalona *et al.*[13] concluded that DRE in conjunction with PSA enhanced early PC detection (biopsy indication PSA≥4.0 ng/ml and/or suspicious DRE). DRE in men with PSA values ≤4.0 ng/ml had a PPV of 10.0%, which is similar to our study (PPV of DRE/TRUS of 8.6% at PSA<3.0 ng/ml, table 1). In another series[12], they found an overall PPV of suspicious DRE of 13%. This means that approximately eight biopsies are necessary to find one PC. The majority of DRE-detected cancers had features of clinically important and potentially curable disease, which are strong arguments in favour of performing DRE (in patients with PSA>1.0 ng/ml and ≤4.0 ng/ml) together with PSA testing in screening programs[12].

Recently, Han *et al.*[124] evaluated 235 PCs of men diagnosed by a suspicious DRE and a PSA level <2.6 ng/ml, who underwent an RP. They found that 1/3 of these men had a tumour with GS≥7 or pathologic T3 stage, with a high risk of progression following RP. The actuarial 5- and 10-year biochemical progression-free survivals (PSA<0.3 ng/ml) were 86% and 59% for this high-risk group, in contrast with 97% and 90% for the low risk group (GS<7 and pathologic T2). On the basis of these findings they suggested that DRE and serum PSA level should both be incorporated into in prostate screening programs so as to salvage men with higher grade or higher stage tumours. The PPV going with these data is not given, leaving unclear how many biopsies were needed to find one cancer. Also, it remains undetermined how many of these cancers progress to a higher PSA value and might still be curable after a next screen.

Our present study aims at further elucidation of the value of DRE in detecting preferably poorly differentiated PCs by using data derived from the second screening round.

Screening without DRE/TRUS (biopsy indication PSA≥3.0 ng/ml) resulted 4 years later in a PC detection rate similar to that in the group initially screened with DRE/TRUS (table 1). Clinical stage and differentiation grade did not differ in a statistically significant way between these protocols. Neither the GS of the 75 RP specimens differed significantly. In contrast, pathological stage of these 75 specimens showed more extraprostatic extension (T3 or more) in the group initially screened without DRE/TRUS (group-2, p=0.035). Although this conclusion is based on a small number of RP specimens and the difference is just significant (p=0.035), this is an observation to which we have to pay attention during further follow-up.

The rate of ICs is an important parameter to determine the sensitivity of the screening procedure[125]. The number of ICs was identical in the two groups (N=11). Also the percentage ICs of those at risk in group-1 and 2 (0.18 and 0.14%) was comparable. As far as we can judge on the basis of these low numbers, IC characteristics seemed to remain similar after the protocol change in this study, although one IC had a T4 clinical stage in group-2.

Even if a high risk group existed amongst the cancers found by DRE at low PSA levels (<2.6 ng/ml) as described by Han *et al.*[124], PSA-based screening should find these tumours in a consecutive screening round when the PSA has risen to a level higher than the threshold value for biopsy. If these aggressive tumours were missed in the first round of this study due to the omission of DRE/TRUS, we would find aggressive, poorly differentiated PCs in the second round or many PCs would be clinically detected between the two screening rounds, as ICs.

However, we did find three PCs with a biopsy GS≥9 in group-2 (round 2). Such highly de-differentiated tumours should not be missed in a screening program. If we assume that these PCs had a palpable or visible lesion in round 1, 8,044 men had had to undergo DRE/TRUS at that time. A screening program will never be able to find all cancers in a group, but intends to find a balance between the number of detected, clinically significant cancers and the burden to the screened individual. A trade-off has to be made between finding all PCs examining 8,000 more men by DRE/TRUS and biopsy those with an abnormal result, or to miss these three cancers, bothering fewer men with invasive tests.

Due to the omission of DRE/TRUS, we may have missed PCs in group-2 in the first screening round, which we did find in group-1 (79 PCs in round 1). These 79 PCs were mainly confined to the prostate and had a GS<7, and were therefore curable. There are three possibilities for the PCs we missed after the protocol change. Firstly, they were detected 4 years later in the subsequent screening, which is acceptable because most cancers we detected in the second round were still curable. Secondly, they were detected as ICs. This is not likely, because we detected an equal number and proportion of ICs in both groups. Based on this finding, a screening interval of 4 years seems plausible, because group-2 did not reveal more ICs or screen-detected PCs in the second round. Also the omission of DRE in favour of lowering the PSA cut-off level seems justified. Thirdly, they remain undetected in spite of our follow-up of 4 years.

## CONCLUSIONS

Omitting DRE and TRUS in the screening protocol did not result in an increased interval cancer rate or an increased prostate cancer detection after 4 years. Screening without DRE/TRUS did not lead to the detection of more aggressive prostate cancers after 4 years (similar tumour characteristics were seen in both groups). So far, the interval cancers also seem to have similar tumour characteristics in both protocols. Therefore, the risk of screening without DRE/TRUS seems acceptable. However, considering the naturally slow growth of prostate cancer, the 4-year follow-up in this study may be too short to draw a definitive conclusion. A conclusive evaluation of the omission of DRE/TRUS will be possible only after the conclusion of the randomised study.

# Chapter 6

## Screening for prostate cancer at low PSA range: the impact of digital rectal examination on tumour incidence and tumour characteristics.

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## ABSTRACT

### Objectives

To compare tumour characteristics of screen-detected prostate cancers either by digital rectal examination (DRE) or by prostate-specific antigen (PSA) as biopsy indication at low PSA.

### Methods

Two populations with PSA between 2.0-3.9 ng/ml were studied. Group-1 was biopsied if DRE was suspicious (1st screening-round, N=1,877). In group-2 all men were offered biopsy, regardless of DRE result (side-study in 2nd screening-round, N=801). We compared cancer detection rates and tumour characteristics.

### Results

In group-1 abnormal DRE prompted biopsy in 253 (13.5%) men (236 (93.3%) actually biopsied). Forty-nine prostate cancers were detected, resulting in a cancer detection rate of 49/1,877=2.6%. In group-2 we found 120 cancers in 666 (83.1%) men actually biopsied, cancer detection rate=120/801=15.0%. Of all cancers detected, organ confinement (clinical T2) was found in 77.5% (group-1) and 96.6% (group-2; of which 99 T1c). Of all prostate cancers 46.9% in group-1 and 15.0% in group-2 had biopsy Gleason score ≥7. In the latter, 15.2% of T1cs were classified as Gleason score ≥7. Considering only prostate cancers with organ confinement or Gleason score ≥7 for each group, cancer detection rates amounted to 2.0% versus 14.5% and 1.2% versus 2.3% for group-1 and group-2, respectively.

### Conclusions

PSA-based screening detected a considerable amount (15.2%) of potentially aggressive tumours as T1cs, but in addition large numbers of possibly insignificant cancers (T1c, Gleason score 6) were diagnosed. DRE seemed to detect more selectively high-grade cancers, but also missed many of these. Considering both populations and the need to detect aggressive but confined cancers, PSA as biopsy indication outperformed DRE at the price of more biopsies (13.5% versus 100% if all would comply).

## INTRODUCTION

Screening for prostate cancer (PC) has become common in Western Europe and the United States. In the United States, approximately 75% of the men aged 50 years or older underwent a prostate-specific antigen (PSA) test at least once[126, 127].

In screening and early detection programs for PC, the value of digital rectal examination (DRE) remains controversial due to its variable performance and subjectivity. The current use of PSA cut-off points such as 2.6[117, 128], 3.0[14, 62] or 4.0 ng/ml[129] as a biopsy indication, limits the domain of DRE to PSA levels below these points. It has been shown that at PSA levels <4.0 ng/ml, approximately nine out of ten biopsies indicated by a suspicious DRE are negative for the diagnosis of PC[13, 16]. The PSA range <2.0 ng/ml is mainly credit to this large number of cancer-negative prostate biopsies. Schröder *et al.* found that DRE had a low predictive value in men with low PSA levels. Performance of DRE was strongly dependent on PSA levels and was poorest when the PSA level was less than 3.0 ng/ml, an area that is considered the domain of DRE[16]. As a consequence of this low predictive value and of the favourable characteristics of most detected PCs, rectal examination has been omitted as a screening test from the European Randomized Study of Screening for Prostate Cancer (ERSPC)[9, 14, 55].

However, a protocol change which permits the missing of potentially life threatening cancers, here defined as cancers with Gleason score (GS) 7 or higher, must be carefully monitored. In the current study we compared the characteristics of cancers detected either by a suspicious DRE or by PSA-based screening in the PSA range 2.0-3.9 ng/ml. In this way, the value of DRE at low PSA levels (the range of interest) can be evaluated. Are potentially aggressive PCs more efficiently detected at a curable stage by DRE-based screening or screening based on a PSA cut-off? The answer to this question may help to elucidate the controversy about the value of DRE at low PSA levels.

## METHODS

### Study population

In the Rotterdam area all men in the age group 55-75 years were identified by the population registry and asked to participate in a randomised screening study for PC. Men who responded by returning the intake questionnaire and a signed informed consent form were randomised (N=42,376). The total screening cohort of ERSPC (section Rotterdam) consisted of 21,210 men (aged 55-74 years), of whom 19,970 men were actually screened. These men were screened by means of a serum PSA determination and, depending on the screening protocol, a DRE and transrectal ultrasound (TRUS). Sextant biopsy was proposed if indicated. A more detailed description of study characteristics has been published elsewhere[120].

In the current study we investigated two different study populations of the screening cohort, both in men that presented with PSA levels between 2.0-3.9 ng/ml. The first group was biopsied in case of a suspicious DRE (group-1, N=1,877). In the 2nd group all men were offered biopsy, regardless of the DRE result (group-2, N=801). The result of TRUS as a screening test was not considered in this study. For group-1 we used data of the first screening round with a screening protocol based on both the PSA value and DRE result (biopsy indication if PSA≥4.0 ng/ml and/or DRE abnormal, December 1993-April 1997) (figure 1). For group-2 we used data of a side-study performed in the second screening round. During this side-study, biopsy was recommended in all men with a PSA value of 2.0 ng/ml or higher (April 2001-August 2002). At the first screen, 4 years earlier, these men had had a biopsy indication if their PSA was ≥3.0 ng/ml. Participants in group-2 who had formerly been biopsied in the first screening round (N=85) were excluded from our study population.

We compared cancer detection rate (CDR, the proportion PCs in screened men), positive predictive value (PPV, the proportion PCs/number of biopsied men) and tumour characteristics between the two groups.

### Techniques

PSA values were assessed (Beckman Coulter-Hybritech; San Diego, California) before the other tests were performed. DRE was performed by a trained physician. Nodularity and induration were considered abnormal. TRUS-guided lateral sextant transrectal prostate biopsy was performed, in line with the findings of Eskew *et al.*[121], using a Bard (C.R. Bard, Convington, GA) spring-loaded biopsy gun and an 18-G biopsy needle. According to the biopsy protocol, no additional, lesion-directed biopsy core was taken in case of an abnormal DRE. TRUS was also used to assess the prostatic volume. The TNM 1992 system was used for clinical staging of the detected carcinomas. Clinical stage, based on DRE, was defined by the screening physician.

### Pathological examination

Biopsy specimens were histopathologically analysed by a single pathologist (TvdK). PCs were graded according to the GS system.

The ERSPC was approved by the institutional board of the Erasmus MC, University Medical Center and by a national board (required by Dutch law for population screening studies).

## RESULTS

### Group-1: screening on the basis of an abnormal DRE

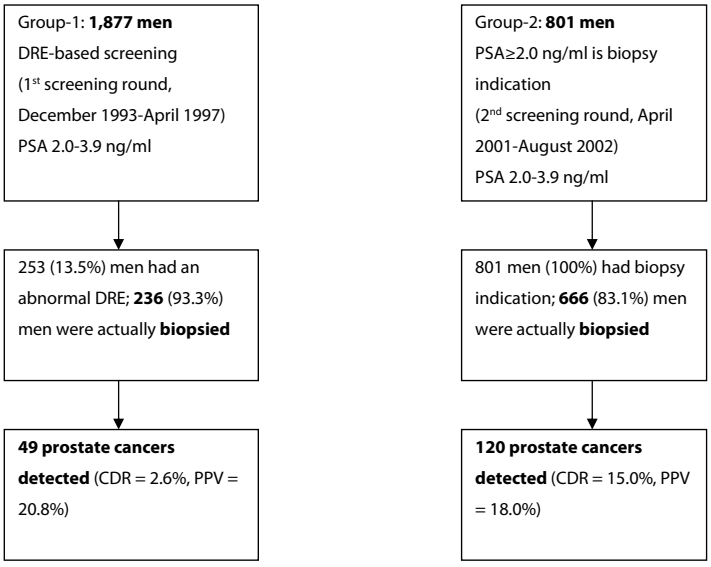
Of the 1,900 men with a PSA value between 2.0 and 3.9 ng/ml, a DRE result was available in 1,877 men (98.8%). Consequently, group-1 consisted of 1,877 men. These participants had a

mean age of 64.9 years (median 65.0). Their mean PSA value was 2.8 ng/ml (median 2.7). Of 1,837 (97.9%) participants the prostatic volume was assessed. Mean prostatic volume was 39.8 ml (median 37.3). Two hundred and fifty-three (13.5%) men had an abnormal DRE of whom 236 (236/253=93.3%) were actually biopsied. The reason for cancelling biopsy was refusal after PSA determination (N=10) and due to medication (N=7). Forty-nine PCs were detected (figure 1). The PPV was 20.8% (49/236) and the CDR was 2.6% (49/1,877). To detect 1 PC, it was necessary to biopsy 5 men (table 1); 10 biopsies were needed to detect 1 PC with GS≥7. Organ confinement (clinical stage T2, based on DRE) was found in 38 PCs (77.5%), 10 PCs (20.4%) had clinical stage T3 and one (2.0%) had T4. Moderately to poorly differentiated tumours (GS≥7) were found by DRE in 46.9% (23/49) (table 2). Initial treatment in this group was radical prostatectomy (RP) in 38.8% (N=19; organ confinement in 89.5%, GS≥7 in 52.9%), radiotherapy (RT) in 46.9% and watchful waiting (WaWa) in 14.3%.

### Group-2: screening on the basis of PSA cut-off (≥2.0 ng/ml)

In the second screening round, in a side-study during the limited period of 16 months, 886 men presented with a PSA between 2.0-3.9 ng/ml. Eighty-five men (9.6%) were excluded from this study because they had undergone a prior biopsy in the first screening round (all had had a benign biopsy result). Group-2 consisted therefore of 801 men with a PSA value

**Figure 1.** Two groups of screened men, biopsied either if they had an abnormal DRE or if they had a PSA value ≥2.0 ng/ml. All included men presented with a PSA value between 2.0 and 3.9 ng/ml.




CDR (cancer detection rate) = number of detected cancers divided by number of men screened
PPV (positive predictive value) = number of detected cancers divided by the number of men biopsied
DRE, digital rectal examination; PSA, prostate-specific antigen

**Table 1:** Comparison of two groups of men with a PSA value of 2.0-3.9 ng/ml, screened by lateralised sextant biopsy with either an abnormal DRE or a PSA≥2.0 ng/ml as a biopsy indication.

| Comparison of men screened by means of DRE or PSA in the PSA range 2.0-3.9 ng/ml | | |
|---|---|---|
| | DRE is biopsy indication (group-1) | PSA≥2.0 is biopsy indication (group-2) |
| N men screened | 1,877 | 801 |
| N men with biopsy indication | 253 (253/1,877 = 13.5%) | 801 (801/801 = 100%) |
| N men biopsied | 236 (236/253 = 93.3%) | 666 (666/801 = 83.1%) |
| N PCs | 49 | 120 |
| PPV | 20.8% (49/236) | 18.0% (120/666) |
| CDR | 2.6% (49/1,877) | 15.0% (120/801) |
| No. of Bx needed to find 1 PC | 4.8 | 5.6 |

PPV, positive predictive value, the proportion PCs/number of biopsied men; CDR, cancer detection rate, the proportion PCs/number of screened men; DRE, digital rectal examination; PSA, prostate-specific antigen

between 2.0 and 3.9 ng/ml, who did have a PSA<3.0 ng/ml 4 years before in 98%. The mean age of these men was 66.6 years (median 66.5). Their mean PSA value was 2.7 ng/ml (median 2.6). Mean prostatic volume was 40.9 ml (median 39.8; prostatic volume was assessed in 664 (99.7%) men). Six hundred sixty-six of the 801 men (83.1%) were actually biopsied. The reasons for not complying with biopsy recommendations were refusal after PSA determination



**Table 2:** Tumour characteristics of prostate cancers at PSA values 2.0-3.9 ng/ml. Biopsy indication was based on DRE (group-1) or PSA threshold value ≥2.0 ng/ml (group-2). The last column is hypothetical; the number of screened men in group-2 is multiplied by factor 2.343 for better comparison with group-1.

| Biopsy indication | Abnormal DRE (group-1) | PSA≥2.0 ng/ml (group-2) | **Group-2 multiplied by 2.343** |
|---|---|---|---|
| N men screened | 1,877 | 801 | **1,877** |
| Mean age in years (median) | 64.9 (65.0) | 66.6 (66.5) | |
| Mean TRUS volume in ml (median) | 39.8 (37.3) | 40.9 (39.8) | |
| N PCs (%) | 49 (100) | 120 (100) | **281** |
| Clinical stage (%)* | | | |
| T1c | - | 99 (82.5) | **232** |
| T2 | 38 (77.6) | 17 (14.2) | **40** |
| T3 | 10 (20.4) | 4 (3.3) | **19** |
| T4 | 1 (2.0) | - | **-** |
| Organ confined tumours (%) | 38 (77.6) | 116 (96.6) | **272** |
| Gleason score (%) | | | |
| <7 | 26 (53.1) | 102 (85.0) | **239** |
| 7 | 15 (30.6) | 15 (12.5) | **35** |
| >7 | 8 (16.3) | 3 (2.5) | **7** |

DRE, digital rectal examination; PSA, prostate-specific antigen; PC, prostate cancer; TRUS, transrectal ultrasound

*The clinical stage was based on DRE

(N=124), or medication which could not be discontinued (N=11). In the biopsied group 120 cancers were detected (PPV=18.0% (120/666), CDR 15.0% (120/801)). To detect 1 PC, it was necessary to biopsy 6 men (table 1); 37 biopsies were needed to detect 1 PC with GS≥7. Organ confinement was found in 116 PCs (96.6%), of which 99 (82.5%) were T1c cancers. PSA-based screening detected 18 (15.0%) moderately to poorly differentiated tumours (GS≥7). Of the 99 detected T1c cancers, 15 (15.2%) were classified as GS≥7 (13 GS=7, 1 GS=8, 1 GS=10) (table 2). RP was the initial treatment in 39 (32.5%, N=39; organ confinement in 86.1%, GS≥7 in 38.9%) cases, RT in 38 (31.7%) and WaWa in 41 (34.1%). Information on initial treatment was missing in two (1.7%) cases.

Considering the detection of organ confined PC for the two screened populations, DRE-based screening had a detection rate of 2.0% (38/1,877, group-1) and PSA-based screening 14.5% (116/801, group-2). Detection of moderately to poorly differentiated PCs, cancers with a GS of ≥7, amounted to 1.2% (23/1,877, group-1) versus 2.3% (18/801, group-2). Results have been summarised in table 2.

In order to evaluate the detection frequency of potentially aggressive PCs, that is PCs with GS≥7, per PSA level, the studied PSA range was split into 2.0-2.9 and 3.0-3.9 ng/ml for both group-1 and 2 (table 3). To selectively find GS≥7 cancers in these two PSA ranges, it was necessary to biopsy 16 men in group-1 and 31 men in group-2 to find one PC at PSA 2.0-2.9 ng/

**Table 3:** Tumour characteristics of prostate cancers at PSA values 2.0-2.9 ng/ml compared to values of 3.0-3.9 ng/ml. Biopsy indication was based on DRE (group-1) or PSA threshold value ≥2.0 ng/ml (group-2). The last column represents the entire PSA range (2.0-3.9 ng/ml).

| **GROUP-1** | PSA 2.0-2.9 ng/ml | PSA 3.0-3.9 ng/ml | **PSA 2.0-3.9 ng/ml** |
|---|---|---|---|
| N men (%) | 1,184 (63.1) | 693 (36.9) | **1,877 (100)** |
| N men biopsied (%) | 129 (54.7) | 107 (45.3) | **236 (100)** |
| N PCs (%) | 15 (30.6) | 34 (69.4) | **49 (100)** |
| Gleason score (%) | | | |
| <7 | 7 (26.9) | 19 (73.1) | **26 (100)** |
| ≥7 | 8 (34.8) | 15 (65.2) | **23 (100)** |
| PPV % GS≥7 PCs | 6.2 (8/129) | 14.0 (15/107) | 9.8 (23/236) |
| CDR % GS≥7 PCs | 0.7 (8/1,184) | 2.2 (15/693) | 1.2 (23/1,877) |
| **GROUP-2** | | | |
| N men (%) | 547 (68.3) | 254 (31.7) | **801 (100)** |
| N men biopsied (%) | 455 (68.3) | 211 (31.7) | **666 (100)** |
| N PCs (%) | 73 (60.8) | 47 (39.2) | **120 (100)** |
| Gleason score (%) | | | |
| <7 | 67 (65.7) | 35 (34.3) | **102 (100)** |
| ≥7 | 6 (33.3) | 12 (66.7) | **18 (100)** |
| PPV % GS≥7 PCs | 1.3 (6/455) | 5.7 (12/211) | 2.7 (18/666) |
| CDR % GS≥7 PCs | 1.1 (6/547) | 4.7 (12/254) | 2.3 (18/801) |

PSA, prostate-specific antigen; PC, prostate cancer; DRE, digital rectal examination; PPV, positive predictive value, the proportion PCs/number of biopsied men; CDR, cancer detection rate, the proportion PCs/number of screened men

ml. Seven men in group-1 and 18 men in group-2 had to be biopsied to find one PC in range 3.0-3.9 ng/ml. The PPV and CDR for both groups and PSA ranges are depicted in table 3.

## DISCUSSION

Due to its poor performance, especially at low PSA levels, DRE has been omitted from the ERSPC[9, 14, 16, 55]. The subsequent screening protocol, based on a PSA cut-off value slightly increased the PPV[14]. However, a certain fraction of clinically diagnosable tumours may be missed with using a PSA cut-off value. It is uncertain if PSA-based screening will detect these cancers at a still curable stage at the moment that the PSA has risen above the threshold value. In the current study, we compared DRE-based screening versus screening with a PSA cut-off value as the sole biopsy indication. The value of TRUS was not studied because it had been previously shown that this is not a valuable test for the early detection of PC in a screening program[9-11].

The proportion of men with a biopsy indication that was actually biopsied, was higher in group-1 than in group-2 (93.3% versus 83.1%). One reason to keep using DRE as a screening test is a higher compliance rate for biopsy than men who were screened by PSA cut-off. Of all men who did not undergo the recommended biopsy, men with an abnormal DRE (N=253) refused in 4.0% (group-1). This is in contrast to the men in which only PSA cut-off 2.0 ng/ml was used (group-2, N=801), in which 15.5% refused biopsy. The number of detected PCs in biopsied men (PPV) was comparable in both groups, (20.8% for group-1 and 18.0% for group-2). The number of PCs detected per screened group (CDR) was higher in group-2 which was expected, because in the PSA-based protocol all men had a biopsy indication (in spite of the lower percentage men actually biopsied in this group). If the studied PSA range was split into PSA 2.0-2.9 and 3.0-3.9 ng/ml, it appeared that, although low numbers, more potentially aggressive tumours were detected in the latter PSA range in both groups. Furthermore, CDR of GS≥7 tumours in that range in group-2 was twice the CDR of group-1 (table 3). More men were treated by watchful waiting in group-2 (34.1% versus 14.3%). Ninety percent of these men had a T1c PC.

To make a better comparison between group-1 and 2, we multiplied the number of participants in group-2 by 2.343. In that hypothetical case, group-1 and group-2 consisted both of 1,877 men (table 2). This results in a comparable number of T2 and T3 cases (T2, 38 in group-1 versus 40 in group-2; T3,11 versus 19) but an additional 232 T1c cancers when using the PSA-based screening algorithm. The detection rate of highly differentiated PC (GS<7) was much higher in group-2 (239 compared to 26), therefore one can conclude that PSA-based screening led to overdiagnosis (large number of possibly indolent PCs, that is T1c cancers with favourable GS). At the same time, however, PSA-based screening detected twice the number of GS=7 cancers, which cannot not be ignored. The question is if the detection of

more of these potentially aggressive cases outweighs the diagnosis of a considerable number possibly indolent PCs. The answer to this question cannot result from our data. Lowering the PSA cut-off to 2.0 ng/ml may have identified the aggressive cancers in group-2 at the expense of detecting a large proportion of cancers to be classified as indolent and a considerable amount of additional biopsy sessions with the coinciding stress and costs. On the other hand, DRE-based screening (group-1) missed a considerable amount clinical significant, potentially aggressive tumours. Although a guideline in how to handle screening at low PSA levels in daily practice is obviously needed, it is not possible to draw one straight-forward conclusion in using DRE or a low PSA cut-off value. This study demonstrated the need of a more selective screening test to selectively detect those cancers in low PSA ranges with aggressive tumour characteristics.

Due to the used selection criteria, only few radical prostatectomy specimens were available for evaluation (N=19 in group-1 and N=39 in group-2). With such low numbers conclusions are not allowed to be drawn without the interference of the component chance. Therefore we used the biopsy GS data. A problem of a GS based on prostate biopsy is the possible discordance with the GS after examination of the radical prostatectomy specimen. Upgrading as well as undergrading of biopsy GS after radical prostatectomy occurs in considerable cases[109, 110]. Our contemporary data and the following studies must be compared in this context.

Compared to our biopsy results, Kravchick *et al.* reported higher numbers of moderately to poorly differentiated disease on biopsy (GS≥7) in the PSA 2.0-4.0 ng/ml range. A total of 171 men underwent biopsy (recommended if PSA was 2.0-4.0 ng/ml). Mean age was lower (63.3 years) and prostatic volume was higher (50.5 $cm^3$) than in our study group. The mean number of biopsy cores was 10 in contrast to our sextant biopsies[130]. In this group 39 PCs were detected, which represented a CDR of 22.8%, compared to 15.0% in our group-2. Of these tumours, 69.2% had biopsy GS<7 (compared to 85.0% in our study). Consequently, 30.8% of the PCs had by biopsy a GS≥7, which is double the percentage we found (15%). An explanation for finding more PCs with a higher GS are likely to be the differences in the study population (unscreened versus prescreened men) and the larger number of biopsy cores taken (a mean of 10 cores in comparison to 6 cores in our study) through which undergrading could be less.

In 555 men (PSA 2-4 ng/ml) Catalona *et al.* detected 235 men with PC, in which in 224 men a biopsy GS was known (6 and 10 core biopsies). Ninety percent had a GS<7, 7% had GS=7 and 4% had GS>7. These findings are similar with ours (85% biopsy GS<7, 12.5% GS=7 and 2.5% GS>7) although it is not clear if men in Catalona's study had a normal or abnormal DRE. Of these men, 137 underwent RP, of which 79% had GS<7, 18% had GS=7 and 3% had GS>7. The percent of pathological GS≥7 was higher than that identified by biopsy. Thus, as would be expected, some cancers were upgraded based on the prostatectomy specimen[109]. In contrast, Catalona *et al.* concluded in another study that more than 80% of cancers, detected

in a population of men with normal DRE and PSA between 2.6-4.0 ng/ml, were considered significant tumours and thus were worth finding[117]. However, they defined significant PC as any cancer involving more than 1% of the total prostatic volume or having a GS=7 or higher in the prostatectomy specimen. The mean prostatic volume of their participants with PC was 33.7 $cm^3$; their cut-off volume can than be estimated at approximately 0.3 $cm^3$, which is lower than the commonly applied[90] 0.5 $cm^3$ and would explain in part the higher rate of significant PC in their study. In a third study[128], this group found supportive evidence for a lower PSA cut-off (2.6-4.0 ng/ml) to detect a significantly higher percentage of organ-confined tumours (88% versus 63% at PSA 4.1-10.0 ng/ml) without detecting more clinically insignificant (11.9% versus 11.5%; organ confined, tumour volume <0.2 $cm^3$, GS<7[20]) or clinically unimportant cancers (23.8% versus 26.9%; organ confined, tumour volume <0.5 $cm^3$, GS<7[105]), based on radical prostatectomy specimens)[128]. This paper does however not mention if the selected population is screened before in the biennial screening program of the study.

In our current study we compared men screened in the first screening round (group-1) to men screened in the second round (group-2). This comparison is biased by the different characteristics of an unscreened and prescreened group of men. Formerly biopsied men (N=85; all had had a benign biopsy result) were excluded. Ninety-eight percent of the men in our study group-2 had a PSA value <3.0 ng/ml in the first screening round. While the biopsy indication in the first round was PSA≥3.0 ng/ml, it is unlikely that a large proportion of cancers were detected that could bias the results in group-2.

Apart from a possible selection bias, the participants in group-2 were 1 year and a half older than men in group-1. As PC incidence rises with rising age[97-99], it is possible that a small part of the higher cancer detection can be attributed to the higher age in group-2. Prostatic volume was comparable in our group-1 and 2 (mean volume 39.8 and 40.9 ml), so prostatic volume did not play an important role as a negative predictor for finding prostate cancer[30]. In group-1 13.5% (253/1,877) had an abnormal DRE result. Of all men in group-2 who already agreed to undergo a biopsy, 12.0% (80/666) had an abnormal DRE result. Thus, the rate of abnormal DREs is comparable in both groups (assuming that the men who refused to undergo a biopsy in group-2 are normally distributed in having a normal or abnormal DRE result). Although only 21 men with an abnormal DRE had PC in group-2, and comparison with group-1 is difficult, the distribution of GS shows the same trend (the number of men with GS<7 is the largest).

To our knowledge, it is unfortunately not possible to relate our data to those of the Prostate Cancer Prevention Trial on the basis of the information in available publications at this moment[24, 33, 91].

## CONCLUSIONS

Considering the populations and the need to detect aggressive but confined cancers, PSA as a biopsy indication outperformed DRE in the PSA range 2.0-3.9 ng/ml at the price of more biopsies (13.5% versus 100% if all would comply) and subsequently the diagnosis of a large number of T1c cancers with a Gleason score of 6, generally regarded as clinically insignificant. However, PSA-based screening also revealed a considerable amount (15.2%) of potentially aggressive tumours that were present as T1c cancers. A new screening test that selectively and preferably objectively detects potentially aggressive prostate cancers is needed, especially at low PSA ranges, which represent the majority of men in this age range.

# Part IV

## The value of the digital rectal examination in men biopsied for an elevated PSA

**Chapter 7**
The role of the digital rectal examination in subsequent screening visits in the European Randomized study of Screening for Prostate Cancer (ERSPC), Rotterdam.
*European Urology, 2008 Sep;54(3):581-8*

**Chapter 8**
Digital rectal examination and the diagnosis of prostate cancer – a study based on eight years and three screenings within the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam.
*European Urology, 2008*

**Chapter 9**
The interobserver variability of digital rectal examination in a large randomised trial for the screening of prostate cancer.
*The Prostate, 2008 Jun 15;68(9):985-93*

# Chapter 7

## The role of the digital rectal examination in subsequent screening visits in the European Randomized study of Screening for Prostate Cancer (ERSPC), Rotterdam.

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*European Urology, 2008 Sep;54(3):581-8*

## ABSTRACT

### Background

The value of digital rectal examination (DRE) as screening test for prostate cancer is controversial in the current prostate-specific antigen (PSA) era.

### Objectives

To determine 1) the additional value of a suspicious DRE for the detection of prostate cancer in men with an elevated PSA level in subsequent screenings and 2) the tumour characteristics of prostate cancers detected in men with a suspicious DRE.

### Design, setting and participants

Within the screening study, from 1997-2006 men aged 55-75 years were invited for an every 4-year PSA determination. A PSA level ≥3.0 ng/ml prompted a DRE and a transrectal ultrasound (TRUS)-guided, lateralised sextant biopsy. Throughout the three screenings of the ERSPC, Rotterdam, 5,040 biopsy sessions were evaluated.

### Measurements

We determined the positive predictive values (PPVs) of a suspicious DRE and normal DRE, which entailed, respectively, the proportion of prostate cancers detected in men with a suspicious DRE or normal DRE divided by, respectively, all biopsied men with a suspicious DRE or normal DRE.

### Results and limitations

At initial screening, the PPV of a suspicious DRE, in conjunction with an elevated PSA level, to detect prostate cancer was 48.6% compared to 22.4% for men with a normal DRE. Both PPVs decreased in consecutive screens: respectively, 29.9% versus 17.1% (screen 2) and 21.2% versus 18.2% (screen 3). Respectively, 71.0% ($p<0.001$), 68.8% (<0.001) and 85.7% ($p=0.002$) of all prostate cancers with a Gleason score >7 were detected in men with a suspicious DRE at screens 1, 2 and 3. A limitation is that only biopsied men were evaluated.

### Conclusions

At initial and subsequent screenings, the chance of having cancer at biopsy was higher in men with a suspicious DRE compared to men with normal DRE (to a lesser extent in subsequent screenings), and the combination of a PSA≥3.0 ng/ml with a suspicious DRE resulted in detecting significantly more PCs with Gleason score >7. DRE may be useful in more selective screening procedures to decrease unnecessary biopsies and overdiagnosis.

## INTRODUCTION

Prostate cancer (PC) screening is performed widely throughout the United States, and the incidence of PC is increasing[131]. Early detection has, however, not yet been shown to reduce prostate-specific mortality and, therefore, PC screening is being tested in two large randomised trials[21, 129]. Before the prostate-specific antigen (PSA) era, the only tool for early detection of PC was the digital rectal examination (DRE). DRE is subjective[132], and many men who are destined to die of PC never develop a palpable abnormality[133]. After implementation of PSA as a screening test, disease detection subsequently increased dramatically[134, 135]. At present, serum PSA testing is used primarily to screen for PC, although it is known not to be a specific test. There is a considerable overlap among PSA levels in men with normal prostates, benign prostate hyperplasia, and localised PC. PSA-based PC screening has resulted in more frequent detection of small volume, low-grade, and organ-confined cancers (stage shift)[136, 137]. Many of these cancers have the histological characteristics of autopsy tumours, that is, tumours that have not become symptomatic during life[138]. Concerns have been risen about the possibility of overdiagnosis and overtreatment of PCs, of which the detection and subsequent treatment is unlikely to benefit patients[64, 136, 139]. In an attempt to avoid unnecessary biopsies and overdiagnosis, nomograms were developed[140-143]. In addition, the prediction of a screen-detected, possible indolent PC is conceivable using a new nomogram[54].

The number of men who undergo prostate biopsy increases, because screening for PC becomes more common and because of the trend to lower the PSA cut-off value for biopsy[144]. A question that arises is if it is still useful to perform DRE in prescreened men in whom these small and possibly insignificant tumours are detected more frequently. The objectives of this study were to determine the positive predictive value (PPV) of an abnormal DRE for the detection of PC in men biopsied because of a PSA level ≥3.0 ng/ml within the European Randomized study of Screening for Prostate Cancer (ERSPC), Rotterdam. We aimed to answer the following questions: 1) what is the additional value of an abnormal DRE next to a PSA level ≥3.0 ng/ml as an indication for biopsy, and 2) does DRE have an additional effect in the selective identification of more hazardous prostate cancers, that is, tumours with a Gleason score >7?

## MATERIALS AND METHODS

### Study population

In the screening arm of the ERSPC, Rotterdam, men aged 55-75 years were invited for every 4-year PSA determination, and a PSA level ≥3.0 ng/ml prompted a transrectal ultrasound (TRUS)-guided lateralised sextant biopsy (May 1997 to October 2006). All men underwent a DRE prior to biopsy. When biopsy results were benign, participants were re-invited 4 years

later. A detailed description of the study design has been published previously[21]. In the current study 5,040 biopsy sessions throughout three screens were evaluated for the presence of PC in relation to the DRE result. Because a previous negative biopsy is a negative predictor for detecting PC[30, 55], men with and without a previous biopsy were evaluated separately for PPVs of PSA and DRE and tumour characteristics in screens 2 and 3 (figure 1).

### Predictive value: definitions

The study cohort consisted of men who were biopsied. The PPV to find PC in men with a normal DRE and an elevated PSA level (≥3.0) was defined as the proportion PCs found in men with a normal DRE divided by the total number of men biopsied with an elevated PSA and a normal DRE ($PPV_{nDRE}$). The additional predictive value of a suspicious DRE (i.e., in men with a PSA level ≥3.0 and a suspicious DRE) for finding PC entailed the proportion of PCs found in men with a suspicious DRE divided by the total number of men with a suspicious DRE ($PPV_{sDRE}$). The overall PPV of this screening procedure was the combination of $PPV_{nDRE}$ and $PPV_{sDRE}$: $PPV_{overall}$ = proportion PCs detected divided by the total number of biopsied men.

### Techniques

Screening entailed determination of serum PSA concentration (Beckman-Coulter Hybritech Tandem-E Assay, CA, USA). TRUS was performed using a Bruel-Kjaer model 1,846 mainframe and a 7-MHz biplanar endorectal transducer, with the subject in the left lateral decubitus position. Nodularity and induration were considered abnormal on DRE, and a hypoechoic lesion was considered suspicious on TRUS. Lateral sextant transrectal prostate biopsy[121, 145] was performed, using a Bard spring-loaded biopsy gun (Convington, GA, USA) and an 18-gauge biopsy needle. An additional biopsy was taken in case of a suspicious area on TRUS. Clinical stage was based on DRE.



### Pathologic examination

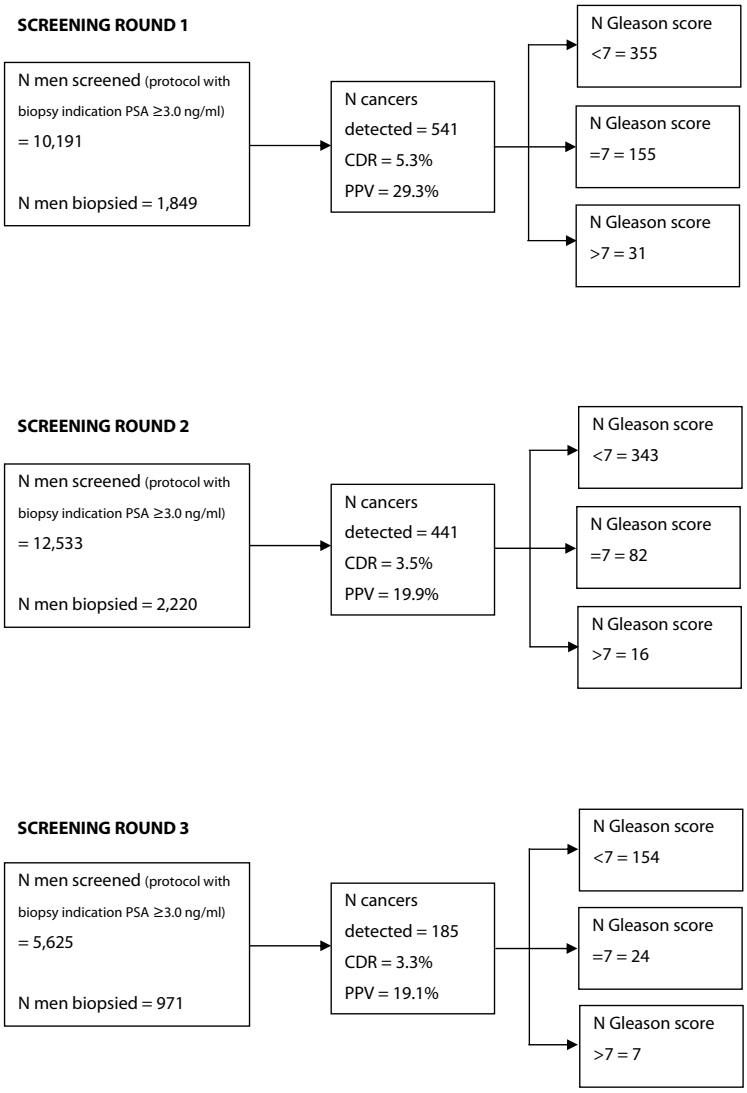
Biopsy specimens were analysed histopathologically by a uropathologist, and PC was graded according to the Gleason score (GS) system[107, 108]. A potentially aggressive PC was defined as having a GS>7.

### Statistical analyses

Chi-square tests were used to test the relationship of the outcome of DRE and the GS of PCs that were detected.

The ERSPC was approved by the institutional board of the Erasmus MC, University Medical Center in Rotterdam and by the Minister of Health.

**Figure 1:** Flow charts. Number of men screened and biopsied and number of cancers detected and their Gleason scores are displayed for screens 1, 2 and 3.




## RESULTS

### Predictive values

Throughout three screens, 5,040 biopsy sessions were evaluated for the presence of PC in relation to the DRE result. The number of men that were biopsied because of a PSA value ≥3.0 ng/ml was 1,849 (18.0% of all men who underwent a PSA test), 2,220 (17.7%), and 971 (17.3%) for screens 1, 2 and 3, respectively. As a result of these biopsy sessions, respectively, 541

(5.3% of all men who underwent a PSA test), 441 (3.5%), and 185 (3.3%) PCs were detected at subsequent screenings. Of the participants biopsied at screen 2, 43.2% (958 of 2,220) had undergone an earlier biopsy (with benign result). For participants biopsied at screen 3, this proportion was 67.1% (652 of 971). At the initial screening, 26.3% of the participants who were biopsied had an abnormal DRE; this proportion was 21.6% and 28.2%, for screens 2 and 3, respectively. The predictive value of an abnormal DRE ($PPV_{sDRE}$) was 48.6% compared to the PPV to find PC in men with a normal DRE ($PPV_{nDRE}$) of 22.4% at initial screening. Throughout the consecutive screens the $PPV_{sDRE}$ remained higher than the $PPV_{nDRE}$, although both PPVs decreased in screens 2 and 3 (table 1).

**Table 1:** Overall positive predictive value in men with an abnormal or normal DRE, biopsied as indicated by a PSA value of ≥3.0 ng/ml in three subsequent screening visits.

| | | Screening visit 1 | Screening visit 2 | Screening visit 3 |
|---|---|---|---|---|
| N biopsied | | 1,849 | 2,220 | 971 |
| N PCs | | 541 | 441 | 185 |
| N abnormal DRE (%) | | 486 (26.3) | 479 (21.6) | 274 (28.2) |
| | PCs found | 236 | 143 | 58 |
| | $PPV_{sDRE}$ | 236/486=48.6% | 143/479=29.9% | 58/274=21.2% |
| N normal DRE (%) | | 1,363 (73.7) | 1,741 (78.4) | 697 (71.8) |
| | PCs found | 305 | 298 | 127 |
| | $PPV_{nDRE}$ | 305/1,363=22.4% | 298/1,741=17.1% | 127/697=18.2% |

$PPV_{overall}$ was 541/1,849=29.3% for the first, 19.9% for the second and 19.1% for the third screening round; DRE, digital rectal examination; PC, prostate cancer; PPV, positive predictive value.

$PPV_{nDRE}$ = proportion PCs in men with normal DRE/ total number of biopsied men with normal DRE

$PPV_{sDRE}$ = proportion PCs in men with abnormal DRE/ total number of biopsied men with abnormal DRE

$PPV_{overall}$ = proportion PCs detected/ total number of biopsied men

### No previous biopsy

In men biopsied for the first time at screen 2 or screen 3, the proportion of participants with an abnormal DRE was 20.8% (screen 2) and 27.0% (screen 3). The PPV of an abnormal DRE ($PPV_{sDRE}$) was 39.5% at screen 2 and 38.4% at screen 3, lower but in the range of the $PPV_{sDRE}$ of 48.6% at initial screening. The PPV for men with a normal DRE ($PPV_{nDRE}$) amounted to 22.1% for screen 2 and 24.9% for screen 3, values comparable to the $PPV_{nDRE}$ of 22.4% at initial screening (table 2).

### Previous biopsy

In this group, 22.5% and 28.8% respectively, had a suspicious DRE in screen 2 and screen 3. $PPV_{sDRE}$ as well as the $PPV_{nDRE}$ decreased at the second and third screening (table 2).

**Table 2:** The positive predictive value in men screened in screening rounds 2 and 3; men previously biopsied at an earlier screening visit (with benign result) were compared to men not previously biopsied.

| | | Screening visit 2 | | Screening visit 3 | |
|---|---|---|---|---|---|
| | | Previous Bx | No previous Bx | Previous Bx | No previous Bx |
| N biopsied | | 958 | 1,262 | 652 | 319 |
| N PCs | | 116 | 325 | 94 | 91 |
| N abnormal DRE (%) | | 216 (22.5) | 263 (20.8) | 188 (28.8) | 86 (27.0) |
| | PCs found | 39 | 104 | 25 | 33 |
| | $PPV_{sDRE}$ | 39/216=18.1% | 104/263=39.5% | 25/188=13.3% | 33/86=38.4% |
| N normal DRE (%) | | 742 (77.5) | 999 (79.2) | 464 (71.2) | 233 (73.0) |
| | PCs found | 77 | 221 | 69 | 58 |
| | $PPV_{nDRE}$ | 77/742=10.4% | 221/999=22.1% | 69/464=14.9% | 58/233=24.9% |

Bx, biopsy; PC, prostate cancer; DRE, digital rectal examination

$PPV_{nDRE}$ = proportion PCs in men with normal DRE/ total number of biopsied men with normal DRE

$PPV_{sDRE}$ = proportion PCs in men with abnormal DRE/ total number of biopsied men with abnormal DRE

### Tumour characteristics

Men with or without a previous biopsy were taken together for the evaluation of tumour characteristics, as there was no obvious difference (data not shown). Of the cancers that were palpable on DRE, 71% were organ-confined at initial screening. At the second and third screenings, this proportion was 92% and 93%, respectively. Potentially aggressive PCs (GS>7) were statistically significantly more often detected in men who had an abnormal DRE. This was seen throughout all three consecutive screens (table 3). Of all potentially aggressive PCs, 71.0%, 68.8% and 85.7% respectively, were detected in men with an abnormal DRE in the consecutive screens.

## DISCUSSION

The proportion of men undergoing a prostate biopsy (for PSA level ≥3.0 ng/ml) that had an abnormal DRE was comparable in the three screenings (table 1). Having a suspicious DRE led to a greater chance of having PC at initial screening: the PPV of an abnormal DRE was twice that of a normal DRE. Although both predictive values decreased in subsequent screenings, the chance for finding PC remained higher in men with an abnormal DRE in screen 2 and screen 3. A factor possibly influencing the chance of finding PC is prostatic volume[55]. Because we used lateralised sextant biopsies instead of volume-adjusted biopsy schemes[146], some cancers might have been missed, specifically in larger prostates. The mean prostate volume became larger in the later screens (49.6, 52.6 and 55.8 ml, respectively). A larger prostate results in a higher PSA level and, therefore, in indication for a biopsy if the PSA threshold of 3.0 is exceeded. Because these PSA elevations are mostly associated with benign prostate hyperplasia, the indication for a biopsy remains in each consecutive screening, which results

**Tables 3A, B and C:** Biopsy Gleason score of detected prostate cancers in men with an abnormal or normal DRE in screens 1, 2 and 3, respectively. Participants who were biopsied previously and participants who were not were taken together in tables 3B and 3C.

**Table 3A**

| **SCREENING VISIT 1** | | | | |
|---|---|---|---|---|
| DRE | Biopsy Gleason score <7 (%) | Biopsy Gleason score =7 (%) | Biopsy Gleason score >7 (%) | Total |
| Normal | 233 (65.6) | 63 (40.6) | 9 (29.0) | 305 |
| Abnormal | 122 (34.4) | 92 (59.4) | 22 (71.0) | 236 |
| Total | 355 (100) | 155 (100) | 31 (100) | 541 |

Chi-square test p<0.001

**Table 3B**

| **SCREENING VISIT 2** | | | | |
|---|---|---|---|---|
| DRE | Biopsy Gleason score <7 (%) | Biopsy Gleason score =7 (%) | Biopsy Gleason score >7 (%) | Total |
| Normal | 249 (72.6) | 44 (53.7) | 5 (31.2)) | 298 |
| Abnormal | 94 (27.4) | 38 (46.3) | 11 (68.8) | 143 |
| Total | 343 (100) | 82 (100) | 16 (100) | 441 |

Chi-square test p<0.001

**Table 3C**

| **SCREENING VISIT 3** | | | | |
|---|---|---|---|---|
| DRE | Biopsy Gleason score <7 (%) | Biopsy Gleason score =7 (%) | Biopsy Gleason score >7 (%) | Total |
| Normal | 112 (72.7) | 14 (58.3) | 1 (14.3) | 127 |
| Abnormal | 42 (27.3) | 10 (41.7) | 6 (85.7) | 58 |
| Total | 154 (100) | 24 (100) | 7 (100) | 185 |

Chi-square test p=0.002



in a lower PPV. At screen 2 and screen 3, some participants were biopsied for the second or third time. This is likely to be a major reason for the lower PPVs, as we know that having had a previous negative biopsy is associated with a lower chance of detecting cancer in consecutive screens[30]. To analyse this further, we evaluated men with and without a previous biopsy separately in screens 2 and 3.

In men without a previous biopsy, an abnormal DRE still predicted a greater chance to have PC than a normal DRE in screens 2 and 3 (table 2). Although the $PPV_{sDRE}$ at screens 2 and 3 was somewhat lower than at initial screening, DRE was valuable in predicting the presence or absence of cancer in addition to the chance based on an elevated PSA level.

In men previously biopsied, both the $PPV_{nDRE}$ and the $PPV_{sDRE}$ decreased dramatically, especially at screen 3. The proportion of men with an abnormal DRE was comparable in men with and without a previous biopsy. As the PPV in men with an abnormal DRE decreased in men previously biopsied, apparently the nodus or induration that was palpated became less specific for the presence of PC. As mentioned previously, one explanation for this observation is related to the prostate volume. In men with a previous negative biopsy, the prostate

volume was greater than in men not previously biopsied (61.8 versus 45.5 ml in screen 2 and 60.3 versus 46.7 ml in screen 3). Another possible explanation is the fact that men screened at repeat visits represent a selective cohort. After all, a considerable number of PCs have already been detected at initial screening. It is known from previous ERSPC studies that PCs found at repeat screening are in general smaller tumours, which might be missed by DRE more frequently[35, 147]. Consistent with our finding, Lopez-Corona *et al.*[148] concluded in a cohort of 343 men with a previous negative biopsy, DRE was not a statistically significant predictor in their nomogram for a positive repeat prostate biopsy. In contrast, Eggener *et al.*[149], using a multivariate analysis to identify predictors of subsequent PC in men with an initially negative biopsy, concluded that men with an initial PSA value of 2.6-4.0 ng/ml, an abnormal DRE and a negative previous biopsy had almost twice the risk for subsequent diagnosis of PC compared to the men with a normal DRE. However, the PPV of an abnormal DRE in this group was 18%, comparable with our $PPV_{sDRE}$ in previously biopsied men (table 2).

A limitation of the current study is that the value of DRE is not addressed in the total screened population, since we evaluated only biopsied men. The value of DRE could only be verified in men who underwent biopsy (i.e., men with a PSA level ≥3.0), which is the gold standard for defining if PC is present. Furthermore, we did not correct for the influence of a lesion-directed biopsy core in case of a hypoechoic lesion on TRUS. The proportion of men with an additional biopsy core was larger in men with a suspicious DRE in all screening rounds (respectively, 51% versus 15%, screen 1; 39% versus 11%, screen 2; 16% versus 7%, screen 3). Intuitively, biopsy of a suspect area on TRUS would lead to detecting more PCs. However, a recent study showed that the value of an additional biopsy core is poor, since only 3.5% of the visible cancers were detected solely by the 7$^{th}$ biopsy core[150]. Another limitation is that, compared to more extensive biopsy schemes, the lateralised sextant biopsy technique misses PCs. However, a stage shift to more favourable tumour characteristics at subsequent screens[35, 151] and a low interval cancer rate[125, 152] was shown, which suggest, with the follow-up time available, that lateralised sextant technique does not miss a considerable number of potentially aggressive cancers.

Throughout three consecutive screens, there was a statistically significantly more frequent detection of potentially aggressive PCs (GS>7) in men who had an abnormal DRE. This is in line with the findings of other large PC screening studies, indicating that an abnormal DRE is associated with having high-grade (GS≥7) disease[47, 61, 63]. When looking separately at participants who were previously biopsied and those who were not, an abnormal DRE was still associated with a greater chance of finding a potentially aggressive PC. In men with one previous benign biopsy result versus men with two previous biopsies (data not shown), the same trend was seen. However, DRE as a screening tool is not reconsidered within the ERSPC, Rotterdam. An evaluation four years after the omission of DRE showed that this did not result in an increased interval cancer rate or PC detection at subsequent screening[153]. Preliminary third-round data indicate similar findings. Furthermore, most men undergoing population-

based screening for prostate cancer will have serum PSA levels <3.0 ng/ml, leading to an eminent financial and logistic burden. In addition, the very low PPV of <10% in the PSA range <3.0 ng/ml[16] and the resulting rate of 90% biopsies (unnecessary) seems unacceptable both clinically and in terms of future health care policy.

An increasing number of men are screened for the presence of PC, and the population of men with a previous negative biopsy is growing. We know already that having a previous cancer-negative biopsy[30] lowers the risk of detecting PC at later screens. This study showed that in men with a previous biopsy, a PSA level ≥3.0, and a normal DRE, the chance to find PC was relatively low (10.4% and 14.9% in screen 2 and screen 3 respectively). These non-palpable PCs had a GS<7 (potentially indolent) in 91% (round 2) and 88% (round 3) of the cases. The potentially aggressive PCs found in this group amounted to 0.3% of all PCs detected in screens 2 and 3. In this setting, DRE can be used for a more selective biopsy strategy. It may be justified to postpone biopsy to a later screening in men with a previous negative biopsy, an elevated PSA level, and a normal DRE in order to lower the risk of overdiagnosis (the detection of potentially indolent PCs) and to reduce the number of unnecessary biopsies. The application of DRE could have prevented approximately 70% (table 2) of the men in this cohort with a previous biopsy from having another biopsy after 4 years. At the same time, using this strategy will result in missing T1c PCs with a GS<7. At later rescreenings these cancers could, however, most probably be detected because of the consistently elevated PSA levels in these men, conversion to a suspicious DRE, or on the basis of new markers. Recently published data on an active surveillance policy of cancers with clinical stage ≤T2 and a biopsy GS< 7 suggest that this delay in detection is not causing harm[78]. However, for a definitive answer we need to wait for the conclusive outcomes of the ERSPC and PLCO[21, 129]. Another point is that a small number (0.3% of all cancers detected in screens 2 and 3 in this study) of potentially aggressive PCs might be missed at a still curable stage. In a population-based screening setting, the risk of missing a few potentially aggressive cancers should be weighed carefully against preventing unnecessary biopsies in numerous men.

In general, the added value of DRE in conjunction with the PSA cut-off of 3.0 is limited, since a suspicious DRE does not modify the biopsy indication. However, in men with a suspicious DRE, the risk of harbouring high-grade disease is greater than in men with a normal DRE, a finding that can be implemented in future risk calculators for high-grade PC. Secondly, in the selective group of men with a previous negative biopsy, a normal DRE can possibly prevent unnecessary biopsies.

## CONCLUSIONS

In men who underwent their first biopsy (indication, PSA level ≥3.0 ng/ml), an abnormal DRE contributed to the predictive value (in addition to the chance based on an elevated PSA) in

detecting prostate cancer and in the selective detection of potentially aggressive cancers. Overall, in men with and without an abnormal DRE, the predictive value decreased in subsequent screening rounds because of increasing proportions of previously biopsied men. In participants with a previous cancer-negative biopsy, there was no additional value of an abnormal DRE to detect cancer; however, relatively more prostate cancers with a Gleason score >7 were detected. A suggestion for the use of DRE in subsequent screens in previously biopsied men may be that in case of a normal DRE, biopsy can be postponed to a subsequent visit, without missing a substantial number of potentially aggressive prostate cancers, in order to reduce the number of unnecessary biopsies and overdiagnosis.

# Chapter 8

## Digital rectal examination and the diagnosis of prostate cancer – a study based on eight years and three screenings within the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam.

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*European Urology, 2008*

## ABSTRACT

### Background

Evidence indicates that an abnormal digital rectal examination (DRE) is a risk factor for high-grade prostate cancer.

### Objective

To determine whether men with an initially suspicious DRE, a prostate-specific antigen (PSA) level ≥3.0 ng/ml, and a benign prostate biopsy are at higher risk for detecting (significant) prostate cancer at rescreening than men with an initially normal DRE, and whether an adaptation of the rescreening interval is warranted for this group.

### Design, setting and participants

Within the ERSPC Rotterdam 2,218 men underwent biopsy of the prostate (from 1993-2000) with a benign result at initial screening. The serum PSA was determined every 4 years. A PSA level of ≥3.0 prompted a DRE and lateralised sextant biopsy.

### Measurements

Number and characteristics of prostate cancers found at repeat screenings and as interval cancers were compared between men with or without a suspicious DRE result at initial screening. Multivariate logistic regression analyses were performed to evaluate if an initially suspicious DRE was a significant predictor for detecting cancer at consecutive screenings.

### Results and limitations

After 4 years, the total number prostate cancers detected in men with and without an initially suspicious DRE was, respectively, 27 (6%) versus 103 (6%) (p=0.99). After 8 years these numbers increased, respectively, to 45 (10%) versus 167 (10%) (p=0.88). The proportion of clinically significant prostate cancers was 2% and 3%, respectively, for the group with initially normal and abnormal DRE after 8 years. Having a suspicious DRE result at initial screening was not a significant predictor for detecting prostate cancer after 4 years (odds ratio (OR)=1.15, p=0.59) or 8 years (OR=1.41, p=0.43). A limitation of this study is the relatively short follow-up of 8 years.

### Conclusions

During a follow-up of 8 years after initial cancer-negative biopsy, an initially suspicious DRE did not influence the chance for detection of cancer or significant cancer at later screens. An adaptation of the rescreening interval on the basis of the initial DRE outcome is not warranted in future population-based screening for prostate cancer.

## INTRODUCTION

In December 1993 the European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated to evaluate the influence of screening on prostate cancer (PC) mortality. The ERSPC Rotterdam started with a screening protocol using a serum prostate-specific antigen (PSA) cut-off of 4.0 ng/ml and/or an abnormal digital rectal examination (DRE) or transrectal ultrasound (TRUS) as indication for a lateralised sextant prostate biopsy. Halfway through the first screening it was decided to discontinue the use of DRE and TRUS as screening tests for the detection of PC[12, 13, 16, 34, 56]. Instead, from May 1997, the PSA cut-off for recommending biopsy was lowered to 3.0 ng/ml. This decision was made because at PSA levels <4.0 ng/ml the positive predictive value (PPV) and sensitivity of DRE were low[16], and obtaining a biopsy in all participants with PSA levels from 3.0-3.9 ng/ml increased the overall PPV and improved false-positive biopsy rates significantly at equal detection rates[14]. Repeat screening was offered after 4 years in all men with PSA levels <3.0 ng/ml and in men with PSA levels ≥3.0 ng/ml with a benign biopsy result.

Nowadays the use of DRE as screening tool is controversial. However, there is evidence that an abnormal DRE is a risk factor for high-grade disease[47, 61]. Men who have had a cancer-negative biopsy and continue to have an elevated PSA level are candidates for repeat biopsies in later screens. The objective of this study was to analyse whether in men with an initially negative biopsy result and an elevated PSA level (≥3.0 ng/ml), the initial DRE result is a risk indicator for detecting (significant) PC at subsequent screenings and whether an adaptation of the rescreening interval is warranted in men with an initially abnormal DRE in population-based screening programs.

## PATIENTS AND METHODS

### Study population

Our study cohort consisted of men participating in the first screening round of the ERSPC Rotterdam. Men with a PSA level ≥3.0 ng/ml, a benign biopsy result, and a normal or suspicious DRE result at initial screening were included in the study population (N=2,218).

We assessed the number and characteristics of PCs detected in these participants at repeat screenings after 4 years (screen 2) and 8 years (screen 3), and of interval cancers (ICs; i.e., clinically detected PCs between screening rounds or in men who refused further screening after the initial biopsy). Men with a suspicious DRE result were compared to men with a normal DRE at first screening. To assess the number of ICs, the total cohort of 2,218 men was linked to the Cancer Registry. In this way we noticed the cancers detected outside the study centre. Unfortunately the exact reason for undergoing another prostate biopsy and the biopsy method used outside the study were not known. A more detailed description of the study design has been published previously[154].

### Techniques

Screening entailed a determination of serum PSA concentration (Beckman-Coulter Hybritech Tandem-E Assay, CA, USA). In case of nodularity or induration DRE was considered suspicious. After rectal examination TRUS was performed using a Bruel-Kjaer model 1,846 mainframe and a 7-MHz biplanar endorectal transducer, with the patient in a left lateral decubitus position. Lateralised sextant prostate biopsy[121, 145] was performed using a Bard spring-loaded biopsy gun (C.R. Bard, Convington, GA, USA) and an 18-gauge biopsy needle. If present, a hypoechoic lesion on TRUS was an indication for an additional biopsy core; a palpable nodule on DRE was not. Clinical stage was defined as the most advanced stage based on DRE and TRUS.

### Pathological examination

Biopsy specimens were analysed histopathologically, and PC was graded according to the Gleason score (GS) system. Significant PC was arbitrarily defined as clinical stage >T2a (according to the TNM classification 1992) or GS≥7, or both. The threshold of clinical stage >T2a for significance was based on former evidence that prognosis of cT2b tumours and higher is worse than for cT2a and cT1c[155-158].

### Statistical analyses

The chi-square test was used to assess differences for binary variables. For continuous variables, the Student's t-test and Mann-Whitney U test were used. All tests were two-sided. A p-value of <0.05 was considered statistically significant. Two separate logistic multivariate regression models were created. These evaluated the relationship between the DRE result at screen 1 and the likelihood of detecting cancer at screen 2 and screen 3 correcting for other initial round predictors. This analysis determined whether an abnormal DRE at initial screening (in men with a PSA≥3.0 ng/ml and a negative biopsy) led to a higher risk of detecting PC in subsequent screenings. In addition to the initial DRE result, other participant-related characteristics at initial screening were used in this model to correct for their influence on the detection of PC: log-transformed PSA level (in ng/ml), age (in years), logtransformed prostate volume (in ml), a hypoechoic lesion on TRUS, and previous biopsy (in addition to the negative biopsy at initial screening). For the OR, a p-value <0.05 was considered statistically significant.

The ERSPC was approved by the institutional board of the Erasmus MC, University Medical Center in Rotterdam, and by the Minister of Health of the Dutch government.

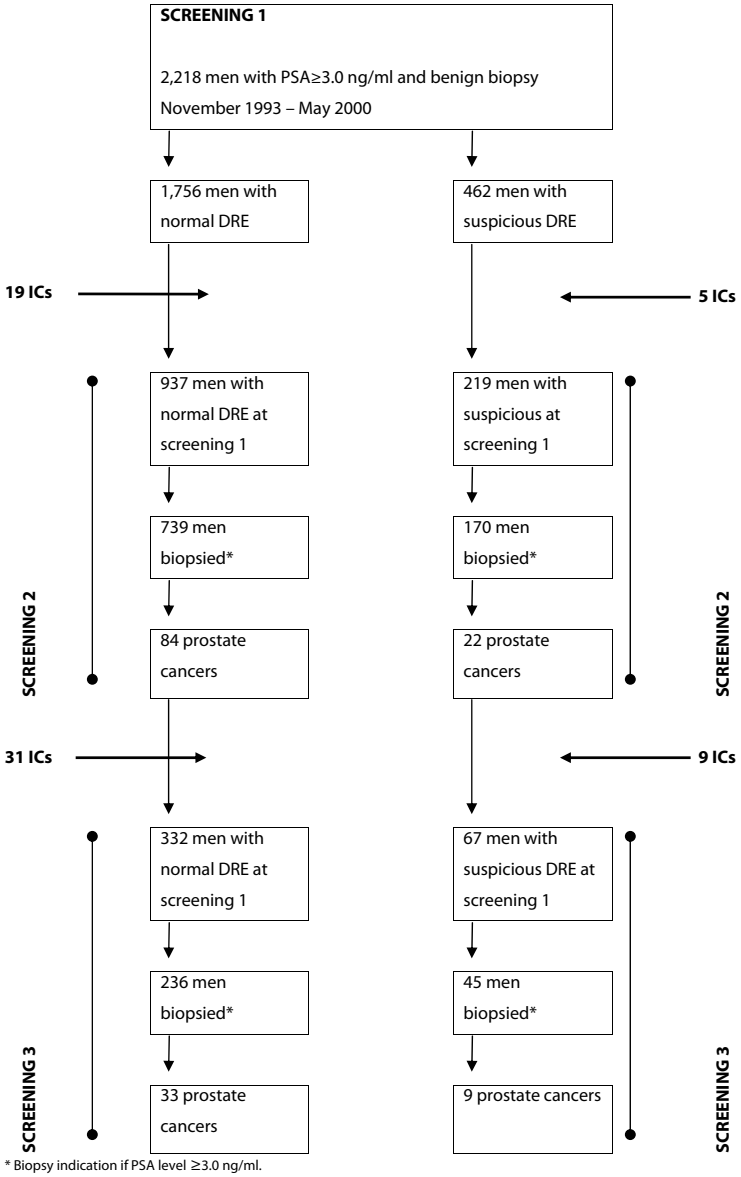
## RESULTS

### Number of cancers detected

At initial screening 2,218 men had a PSA≥3.0 ng/ml and a negative biopsy result. Of these men, 462 (21%) had a suspicious DRE and 1,756 (79%) had a normal result (figure 1). On the

basis of this initial DRE result the included subjects were evaluated in subsequent screenings. The descriptive variables at first screening are displayed in table 1. Some men discontinued screening after each round owing to crossing the age limit of 75 years, comorbidity, death, moving or refusal. Consequently, 1,156 participants were eligible for screening after 4 years

**Figure 1:** Consort diagram. The results of three screening rounds have been summarised, and the number of interval cancers (ICs) is shown. Screening 2 was performed between January 1998 and June 2004 and screening 3 was performed between March 2002 and August 2007.




* Biopsy indication if PSA level ≥3.0 ng/ml.

(screen 2), of whom 937 (81%) had a normal DRE at initial screening and 219 (19%) initially had suspicious DRE findings. In 70% (739 of 937) of the men with an initial normal DRE and in 78% (170 of 219) of the men with an abnormal DRE, a biopsy was performed at the second screening. The total number of PCs detected in men with and without an initially abnormal DRE was 27 (6%, among which were 5 ICs) and 103 (6%, among which 19 ICs), respectively (p=0.9935). After 8 years, 332 (83%) of the 399 men screened at screen 3 had an abnormal DRE and 67 (17%) men had a normal DRE at initial screen. The numbers of cancers detected amounted to 45 (10%, among which 14 ICs) in men with an initially abnormal DRE and 167 (10%, among which 50 ICs) in men with an initially normal DRE (p=0.8841). The proportion ICs (number of ICs divided by total number of men with benign biopsy at first screening) was 1.1% after 4 years in both groups. After 8 years this proportion amounted to 2.8% for men with an initially normal DRE and 3.0% for men with a suspicious DRE. During an 8-year follow-up, in total 167 PCs were detected in men with an initially normal DRE and 45 PCs in men with an abnormal DRE.

**Table 1:** Descriptive variables at time of the initial biopsy, given as the mean (median, interquartile range) age, PSA value and prostate volume and TRUS outcome, given as number (proportion) with a hypoechoic lesion.

| Variable (at initial screen) | DRE normal | DRE suspicious for PC | P-value (two-sided) |
|---|---|---|---|
| N (%) | 1,756 (79.2) | 462 (20.8) | |
| Age, years | 65.4 (65.7, 61.2-69.8) | 67.0 (67.9, 63.1-71.3) | <0.001* |
| PSA level, ng/ml | 5.9 (4.8, 3.9-6.6) | 5.5 (3.6-6.1) | <0.001** |
| Prostate volume, ml | 54.0 (48.2, 38.2-62.7) | 50.5 (45.4, 36.3-60.1) | 0.009** |
| Hypoechoic lesion on TRUS, N (%) | 275 (15.7) | 133 (28.8) | <0.001*** |

*Student's t-test; ** Mann-Whitney U-test; ***Chi-square test

Participants were included in the study if they had a PSA level ≥3.0 ng/ml and a benign biopsy result at initial screening



### Tumour characteristics

The tumour characteristics of all cancers detected at screen 2 and 3, depicted by initial DRE result, are displayed in table 2. Tumour characteristics of ICs, assessed by linking the whole study population of 2,218 men to the Cancer Registry, are shown in table 3. The GS was unknown in about 50% of the ICs because pathological analysis was undertaken outside the study centre.

Ten (2%) significant PCs (all screen-detected) were detected in men with an initially abnormal DRE after 4 years. In men with an initially normal DRE, 23 (1%) significant cases were detected, of which 2 were detected as ICs. Eight years after initial screening (screen 3) these numbers amounted to 13 (3%) significant cancers detected in men with an initially abnormal DRE, of which 2 ICs. Thirty-seven (2%) significant cases, of which 11 were ICs, were diagnosed in participants with a normal initial DRE.

**Table 2:** Tumour characteristics of screen-detected prostate cancers (based on biopsy specimen) in screening round 2 and 3 (respectively, 4 and 8 years after the initial screening).

| | | **Screen 2** | | **Screen 3** | |
|---|---|---|---|---|---|
| DRE result at first screening | | normal | abnormal | normal | abnormal |
| Clinical stage (%) | T1c | 53 (63.1) | 8 (36.4) | 22 (66.7) | 6 (66.7) |
| | T2a | 17 (20.2) | 5 (22.7) | 8 (24.2) | 2 (22.2) |
| | T2b and c | 14 (16.7) | 6 (27.3) | 3 (9.1) | 1 (11.1) |
| | T3 | - | 3 (13.6) | - | - |
| | Total | 84 | 22 | 33 | 9 |
| Gleason score (%) | <7 | 72 (85.7) | 18 (81.8) | 30 (90.9) | 9 (100) |
| | 7 | 9 (10.7) | 3 (13.6) | 3 (9.1) | - |
| | >7 | 3 (3.6) | 1 (4.5) | - | - |
| | Total | 84 | 22 | 33 | 9 |

**Table 3:** Tumour characteristics of interval cancers.

| | | **Interval 1** | | **Interval 2** | |
|---|---|---|---|---|---|
| DRE at first screening | | normal | abnormal | normal | abnormal |
| Clinical stage (%) | T1a, b and c | 13 (68.4) | 2 (40) | 19 (61.3) | 4 (44.4) |
| | T2a | 4 (21.1) | 3 (60) | 4 (12.9) | 4 (44.4) |
| | T2 b and c | - | - | 4 (12.9) | 1 (11.1) |
| | T3 | 1 (5.3) | - | 1 (3.2) | - |
| | T4 | 1 (5.3) | - | 2 (6.5) | - |
| | missing | - | - | 1 (3.2) | - |
| | Total | 19 (100) | 5 (100) | 31 (100) | 9 (100) |
| Gleason score (%) | <7 | 8 (42.1) | 1 (20) | 10 (29.0) | 5 (55.6) |
| | 7 | - | - | 2 (6.5) | 1 (11.1) |
| | >7 | 2 (10.5) | - | 2 (6.5) | 1 (11.1) |
| | missing | 9 (47.4) | 4 (80) | 17 (54.8) | 2 (22.2) |
| | Total | 19 (100) | 5 (100) | 31 (100) | 9 (100) |

The first interval comprised the 4 years between screens 1 and 2, and the second interval the 4 years between screens 2 and 3
For interval 1, 54% (13/24) of GSs were unknown for interval 2, 47.5% (19/40) of GSs were unknown

### Logistic regression analysis

At second screening (screen 2), 909 men underwent biopsy and were included in the regression analysis with the presence of PC as the dependent variable (table 4). When correcting for all other variables that could have influenced the detection of PC, there was no indication that an abnormal DRE at initial screening influenced the odds of detecting PC at second screening (p-value was non-significant). A larger prostate volume was associated with a lower risk of cancer detection (OR=0.085, p=0.001). All remaining predictors had no significant influence. At screen 3, 281 men were biopsied and included in the analysis. Again, a suspicious DRE at first screening did not significantly influence the detection of PC at screen 3, and initially

**Table 4:** Odds ratios for predictor variables assessed at round 1 for detecting prostate cancer at screen 2 and screen 3 studied by multivariate logistic regression analysis.

| Predictor | **Prostate cancer at screen 2** | | **Prostate cancer at screen 3** | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | p | Odds ratio (95% CI) | p |
| Digital rectal examination* | 1.151 (0.687-1.928) | 0.594 | 1.411 (0.597-3.331) | 0.433 |
| Log-PSA level* | 0.904 (0.229-3.567) | 0.885 | 0.702 (0.055-9.026) | 0.786 |
| Age* | 1.044 (0.993-1.098) | 0.093 | 0.997 (0.899-1.106) | 0.959 |
| Log-prostate volume* | 0.085 (0.020-0.368) | 0.001 | 0.016 (0.001-0.291) | 0.005 |
| Transrectal ultrasound* | 0.793 (0.439-1.434) | 0.443 | 0.658 (0.267-1.622) | 0.363 |
| Previous biopsy (in addition to first round biopsy) | - | - | 0.905 (0.326-2.508) | 0.847 |

* at time of initial screening; CI, confidence interval

In these analyses all men biopsied were included (respectively N=909 for screen 2 and N=281 for screen 3). A p-value <0.05 was considered statistically significant

having a larger prostate volume decreased significantly the risk of detecting PC at screen 3 (OR=0.016, p=0.005). The influence of other variables was not significant (table 4).

## DISCUSSION



Within ERSPC Rotterdam, all men with a benign biopsy result were invited for repeat screening 4 years later. The current study analysed whether men with a benign prostate biopsy and an initially abnormal DRE were at higher risk for the detection of significant of PC in the following years and whether an adaptation of the rescreening interval is warranted in this group. Therefore, participants with a PSA level ≥3.0 ng/ml, a benign biopsy, and either an initially normal (group-1) or abnormal DRE (group-2) were followed for 8 years, during which they were screened for the second time (after 4 years) and third time (after 8 years). The two groups were evaluated for the number of cancers detected (found at screening or clinically detected as ICs), and tumour characteristics were compared. During the follow-up period no significant difference was found in the total number of cancers detected in both groups. Moreover, the proportion of ICs, which gives an indication of the effectiveness of the screening program and the appropriateness of the length of the screening interval[152], was similar as well.

Table 1, however, shows significant differences in parameters that influence the risk for detection of PC. The prostate volume was significantly larger in men with a normal DRE at initial screening. A larger prostate volume lowers the chance of detecting PC[55], and, furthermore, can lead to understaging as well, as in a large-volume prostate a nodus is more difficult to palpate. However, during the 8-year follow-up in the current study these missed and understaged cancers would most probably have been detected (as ICs or as higher stage). In addition, the older age of patients and the more frequently found hypoechoic lesions on TRUS in the group with abnormal DREs, increased the risk for detection of PC in this group, although we know TRUS

is a poor predictor[9, 11, 55-57]. Likely a clinical bias of the investigator who tends to see suspicious lesions on TRUS when palpating an abnormality may explain this observation. On the other hand, the higher PSA levels in the group with normal DRE increased the risk of finding PC in men with a normal DRE. To correct for all these predictor variables and to analyse the effect of DRE on the risk of finding PC, multivariate logistic regression analyses were performed. The results showed that DRE was not a significant predictor for diagnosing PC on repeat screenings.

Considering the tumour characteristics, one must realise that in general the detection rate of significant PC, defined as a cancer with clinical stage >T2a or biopsy GS≥7, is low in men with a previous cancer-negative biopsy result. Using this definition of significant PC means that a cancer with biopsy GS<7 but clinical stage >T2a was considered significant. This arbitrary classification seems, however, justified, as undergrading of biopsy specimens is frequently reported[35, 109, 110]. The comparison of tumour characteristics showed no distinct differences in the detection of significant disease in men with an initially abnormal or normal DRE result, although we had to base our conclusions on a small sample with a substantial part of the ICs with unknown Gleason scores.

In a previous study on screening results of ERSPC Rotterdam it was concluded that DRE as screening test for PC might be replaced by screening using the PSA cut-off of 3.0 ng/ml only[62]. Simultaneously, it was shown that DRE might pick up aggressive cancers more selectively than screening by serum-PSA alone, especially in the PSA range 3.0-4.0 ng/ml. However, the absolute number of moderately and poorly differentiated cancers was similar in the PSA-based protocol (biopsy indication, PSA≥3.0 ng/ml) and in the old protocol (biopsy indication, PSA≥4.0 and/or DRE/TRUS abnormal). Furthermore, only a small proportion of men with a suspicious finding on DRE were eventually diagnosed with a PC with GS 7-10. In addition, coincidence should not be denied as an important factor: a substantial proportion of cancers detected by abnormal DRE/TRUS showed tumour volumes <0.5 ml and were not likely to be palpated. Those should be considered as false-positives[62]. On the contrary, Borden *et al.*[61] found, using a multivariate logistic regression analysis, that an abnormal DRE was an independent predictor for PC and for high-grade PC on initial biopsy in a referral population. Likewise, other studies that retrospectively examined radical prostatectomy specimens showed that palpable tumours (cT2) were significantly more likely than nonpalpable (cT1c) tumours to have a higher GS in referral populations[157-159], and in a screening cohort[47].

Apparently, in the selective cohort for our study, an initially abnormal DRE was not predictive of a higher risk for detection of significant PC at repeat screenings. It was already known that a previous negative biopsy lowers the risk of detecting PC at later screenings[30]. The current findings are useful for the management of patients with a negative biopsy result who continue to have an indication for biopsy. It is not necessary to rescreen men with an initial suspicious DRE earlier or more frequently than men without palpable abnormalities.

However, this study concerns a screening setting and does not consider the undeniable value of DRE in individual patients in urological daily practice.

Although we believe that our study results are of value for determining a screening interval that is of sufficient duration to protect men from unnecessary biopsies and short enough to prevent the occurrence of advanced disease at subsequent screenings or large numbers of ICs, there are some shortcomings to our study. First, the study population is a selective screening cohort of men with an initially negative biopsy and a PSA level ≥3.0 ng/ml. The conclusions drawn apply for this setting only. Second, we have followed these men for 8 years; we have to await, however, the final conclusions of ERSPC to relate our findings to PC mortality. Third, the results were possibly biased because of using two previously mentioned two different protocols at first screening. Some participants were biopsied for an abnormal DRE/TRUS and others were biopsied for an elevated PSA level only. However, to minimise the possible bias, all included subjects were selected for an initial PSA of ≥3.0 ng/ml and only 5.7% (127 of 2,218) of men were biopsied for an abnormal DRE/TRUS. Another limitation is that the lateralised sextant biopsy technique misses PCs compared to more extensive biopsy schemes. However, data from the ERSPC Rotterdam show a stage shift to more favourable tumour characteristics at subsequent screens[35, 151] and a low IC rate[152], which suggest, with the follow-up time available, that the lateralised sextant technique does not miss a substantial number of potentially aggressive cancers. Finally, the number of biopsied men in the two groups influences the chance to detect PC: the more men biopsied, the more cancers could be detected. The overall proportion of biopsied men in the two groups analysed is 56% (975 of 1,756) versus 47% (215 of 462) for normal and abnormal initial DRE, respectively. However, the identical proportion ICs diagnosed in both groups (3%), which is a measure of the sensitivity of screening and thus for biopsy rate, is suggestive of a minor influence of the difference in proportion of men biopsied. Furthermore, if the proportion of men biopsied in the group with initially abnormal DRE was extrapolated to 56% (equal to the proportion in men with initially normal DRE), a total of 259 men would have been biopsied and 37 PCs instead of 31 PCs would have been detected (according to the PPV of 14.4% (31 of 215) in this group). Analysis of the extrapolated total number of cancers diagnosed in both groups did not show a statistically significantly difference between men with an initially normal or abnormal DRE (Pearson chi-square 0.92, p=0.35; data not shown).



## CONCLUSIONS

During an 8-year follow-up, the current study found no evidence that men with an initial PSA level ≥3.0 ng/ml, a cancer-negative prostate biopsy, and an abnormal DRE are at higher risk for the detection of prostate cancer or clinically significant prostate cancer as compared to men with an initial PSA level ≥3.0, a negative biopsy and an initially normal DRE. An adaptation of the rescreening interval on the basis of DRE outcome is not warranted in this particular group of men in future population-based screening for prostate cancer.

# Chapter 9

## The interobserver variability of digital rectal examination in a large randomised trial for the screening of prostate cancer.

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## ABSTRACT

### Background

To analyse to what extent the percentage of suspicious digital rectal examination (DRE) findings vary between examiners and to what extent the percentage of prostate cancers detected in men with these suspicious findings varies between examiners.

### Methods

In the first screening round of the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam, 7,280 men underwent a PSA determination and DRE of whom 2,102 underwent prostate biopsy (biopsy indication PSA≥4.0 ng/ml and/or suspicious DRE and/or TRUS). Descriptive statistics of DRE outcome per PSA range were used to determine the observer variability of six examiners. Because this analysis did not correct properly for other predictors of a suspicious DRE (PSA level, biopsy indication, TRUS outcome, prostate volume and age), a logistic regression analysis controlling for these explanatory variables was performed as well.

### Results

In 2,102 men biopsied, 443 prostate cancers were detected (PPV=21%). For all PSA levels the percentage suspicious DRE varied between examiners from 4% to 28% and percentage prostate cancer detected in men with a suspicious DRE varied from 18% to 36%. Logistic regression analysis showed that three of six examiners considered DRE significantly more often abnormal than others (ORs 3.48, 2.80, 2.47, $p<0.001$)). For all examiners the odds to have prostate cancer was statistically significantly higher in case of a suspicious DRE (ORs 2.21-5.96, $p<0.05$). This increased chance to find prostate cancer was not significantly observer-dependent.

### Conclusions

Three of six examiners considered DRE significantly more often suspicious than the others. However, under equal circumstances a suspicious DRE executed by each examiner increased the chance of the presence of prostate cancer similarly.

## INTRODUCTION

In the setting of early detection of prostate cancer (PC) the digital rectal examination (DRE) is used as a test to indicate prostate biopsy. The result of the DRE is usually expressed as abnormal, that is, nodularity or induration is felt which is suspicious for PC, or as normal. The DRE is in this setting generally believed to be a highly subjective test. However, very few studies are known which analyse the subjectivity of DRE in more detail. Smith *et al.*[132] concluded that the findings within the same prostate on the same day by two different examiners were often divergent. On the other hand, there is also a study that found a good correlation between different observations of examiners when the prostate was assessed in a systematic way[160]. At present, serum PSA testing is mostly used as screening test for prostate cancer. PSA is, however, not a specific test for cancer of the prostate as a considerable overlap between PSA levels exists in men with normal prostates, benign prostate hyperplasia and localised prostate cancer. Some researchers suggested the use of DRE to screen more selectively in order to lower the risk of unnecessary biopsies and overdiagnosis by showing evidence that the rectal examination can be used to detect aggressive prostate cancers more selectively[47, 61, 157-159].

In the current study we examined within the European Randomized Study of Screening for Prostate Cancer (ERSPC, section Rotterdam) the interobserver variability of DRE. The best way to evaluate interobserver variability is to digitally examine participants more times at the same day by different examiners. This type of analysis would however have meant an undesirable burden to the participant and would have interfered with the logistics of the screening procedure. We describe an alternative method to compare the digital findings of different examiners that is not hampered by these drawbacks. The aim of this study focused on the following issues. Firstly, to what extent does the percentage of suspicious DRE findings vary between examiners in a prostate cancer screening setting and, secondly, to what extent does the cancer detection rate in men with these suspicious findings vary between examiners.

## MATERIALS AND METHODS

### Study population

In the Rotterdam area men aged 55-75 years between December 1993 and May 1997 were identified by the population registry and asked to participate in the ERSPC. Men who responded by returning the signed informed consent form were randomised either to the screening or to the control arm. Men in the former arm were screened by serum PSA assay, a DRE, and a transrectal ultrasound (TRUS). Initially in the first screening round, lateralised sextant biopsy was proposed in participants with a PSA level ≥4.0 ng/ml and/or a suspicious DRE/TRUS finding at a low PSA value (0.0-3.9 ng/ml). Later, the biopsy protocol changed, but

this was not relevant for the data of the current study. The study population is displayed in figure 1. A more detailed description of the study design has been published previously[120].

### Techniques

Screening entailed a determination of serum PSA concentration (Beckman-Coulter Hybritech Tandem-E Assay; CA, USA). Examiners who examined more than 400 participants at initial screening were included in this study (N=6). These examiners, who performed the DRE and TRUS after comprehensive training, were resident urologists (four out of six; examiners numbered 1, 2, 4 and 5) or ultrasound technicians (two out of six; examiners numbered 3 and 6).

Nodularity and induration were considered abnormal (suspicious for PC) on DRE. TRUS was performed using a Bruel & Kjaer® model 1,846 mainframe and a 7-MHz biplanar endorectal transducer, with the subject in the left lateral decubitus position. Hypoechoic lesions were considered suspicious (abnormal). Lateral sextant transrectal prostate biopsy was performed, in line with the findings of Stamey *et al.*[145] and Eskew *et al.*[121], using a Bard spring-loaded biopsy gun (Convington, GA, USA) and an 18-gauge biopsy needle. An additional biopsy core was taken from a suspicious area on TRUS, if present. At the time of performing DRE/TRUS, the members of the screening team were not aware of the PSA value.



### Pathological examination

Biopsy specimens were histopathologically analysed by a single uropathologist.

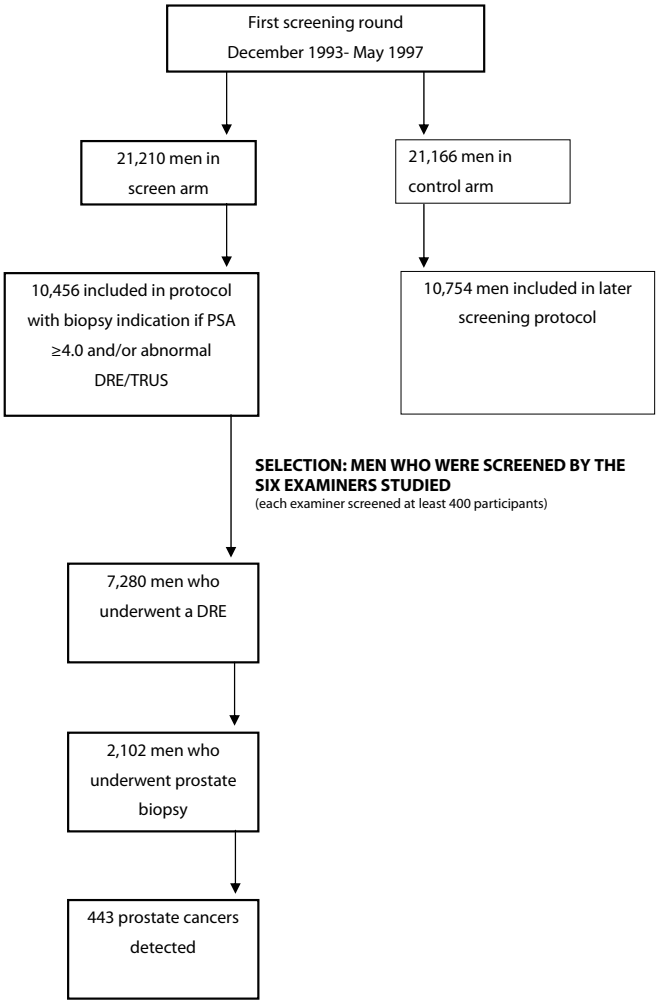
### Statistical analyses

The study focused on two issues: 1) To what extent does the percentage of suspicious DRE findings vary between examiners and 2) to what extent does the percentage of cancers detected in men with these suspicious findings vary between examiners.

Both issues were studied on the basis of descriptive statistics. This approach, however, did not control properly for possible differences in the patient mix. Therefore, multivariate logistic regression was used in addition (amongst others in order to correct for the PSA ranges in which PCs were found). In the first setting, the outcome of the DRE (suspicious or not) served as the dichotomous dependent variable. The predictors used in this model were 2log transformed PSA and 2log transformed prostate volume, TRUS outcome (coded as 1 for suspicious and zero otherwise), an indicator variable for biopsy indication used (PSA threshold; 1 for PSA≥4 ng/ml, 0 otherwise), age and indicator variables for the individuals carrying out the digital rectal exam. Arbitrarily, examiner 2 was chosen as reference. A likelihood ratio test was carried out to test whether a model including indicator variables for the examiners yielded a better fit to the data than an otherwise identical model without these indicators. In the second setting, the outcome of the biopsy (cancer or no cancer) served as the dependent variable. The same predictors were used as in the initial setting augmented with DRE (coded as 1 if suspicious, 0 otherwise). In this setting, all indicator variables for the examiners

were entered into the regression, thus making a not-suspicious rectal exam the reference for the odds-ratios estimated for the different examiners in this setting. Again, a likelihood ratio test was used to check whether including the examiner into the model (by means of indicator variables for each examiner) led to a model that significantly better described the observations. For the Odds-ratios, a p-value <0.05 was considered statistically significant. The goodness-of-fit Hosmer-Lemeshow statistics of the logistic models for DRE and PC were calculated, and the model was considered acceptable if this test had a p-value >0.05.

**Figure 1:** Consort diagram of the studied population of the ERSPC Rotterdam.




PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound

The ERSPC was approved by the institutional board of the Erasmus MC, University Medical Center and by the Minister of Health (required by Dutch law for population screening studies).

## RESULTS

### Descriptive statistics

At initial screening 7,280 men underwent a PSA test and a DRE (figure 1). Of these men, 2,102 underwent prostate biopsy (biopsy indication: abnormal DRE/TRUS and/or PSA≥4.0 ng/ml) and 443 PCs were detected (positive predictive value 21%), of which 246 (56%) were diagnosed in men with an abnormal DRE. Baseline characteristics are displayed in table 1. The variation between the six examiners in the proportion of abnormal DRE results for all PSA levels as well as for PSA ranges <4.0, 4.0-9.0, and ≥10.0 ng/ml is summarised in table 2. The higher the PSA range, the more abnormalities were felt. The differences in proportion abnormal DRE between examiners were comparable throughout the PSA ranges. Higher PSA levels correlated with higher PC detection rates (given an abnormal DRE; table 3). At PSA levels <4.0 ng/ml on average 13% of men with an abnormal DRE had PC (averaged between six examiners). The cancers found with normal DRE and PSA<4.0 ng/ml were detected by TRUS. The proportion PC in men with a suspicious DRE were on average 46% for PSA 4.0-9.9 and 81% for PSA>10.0 ng/ml. The differences in this proportion between the six examiners became larger with rising PSA (18% difference at PSA<4.0 ng/ml, 22% at PSA 4.0-9.9 and 28% at PSA≥10.0). Having an abnormal DRE led more often to the detection of PC compared to men with a normal DRE (table 3). This finding was more obvious in the higher PSA ranges (proportion PC in men with abnormal DRE versus proportion PC in men with normal DRE was 13% versus 10% for PSA<4.0, 46% versus 17% for PSA 4.0-9.9 and 81% versus 38% for PSA≥10.0 ng/ml).



**Table 1:** Baseline characteristics of participants included in this study.

| | Men who underwent DRE N=7,280 |
|---|---|
| Age (years)* | 64.0 |
| PSA value (ng/ml)* | 2.7 |
| Prostate volume (ml)* | 36.3 |
| % abnormal DRE (N/men who underwent DRE) | 14 (1,006/7,280) |
| % abnormal TRUS (N/men who underwent DRE) | 13 (937/7,280; 0.4% unknown) |
| % men with Bx indication (N/men who underwent DRE) | 29 (2,102/7,280) |
| % men with PC (N/men who underwent DRE) | (443/7,280) |

*mean values are displayed

DRE, digital rectal examination; TRUS, transrectal ultrasound; Bx, biopsy

**Table 2:** Number of abnormal DRE results per examiner per PSA range.

| PSA range (ng/ml) | Examiner | Abnormal DRE (%) | Total participants |
|---|---|---|---|
| All PSAs | 1 | 162 (28) | 570 |
| | 2 | 44 (6) | 696 |
| | 3 | 53 (5) | 1,004 |
| | 4 | 447 (18) | 2,449 |
| | 5 | 20 (4) | 465 |
| | 6 | 280 (13) | 2,096 |
| | Total | 1,006 (14) | 7,280 |
| <4.0 | 1 | 77 (22) | 345 |
| | 2 | 31 (5) | 602 |
| | 3 | 37 (4) | 869 |
| | 4 | 257 (14) | 1,864 |
| | 5 | 12 (3) | 407 |
| | 6 | 273 (13) | 2,037 |
| | Total | 687 (11) | 6,124 |
| 4.0-9.9 | 1 | 67 (36) | 186 |
| | 2 | 8 (10) | 78 |
| | 3 | 10 (9) | 117 |
| | 4 | 152 (31) | 493 |
| | 5 | 5 (11) | 46 |
| | 6 | 4 (8) | 50 |
| | Total | 246 (25) | 970 |
| ≥10.0 | 1 | 18 (46) | 39 |
| | 2 | 5 (31) | 16 |
| | 3 | 6 (33) | 18 |
| | 4 | 38 (41) | 92 |
| | 5 | 3 (25) | 12 |
| | 6 | 3 (33) | 9 |
| | Total | 73 (39) | 186 |

Total number of participants included in analysis was 7,280

DRE, digital rectal examination; PSA, prostate-specific antigen

A shortcoming of analysing the data by descriptive statistics was that the distribution of patients with PSA levels in the ranges <4.0, 4.0-9.9, and ≥10.0 ng/ml was significantly different between the six examiners ($p<0.001$, Kruskal-Wallis test). Tables 2 and 3 illustrate that if more men had a higher PSA in the patient mix, the chance was greater that men had an abnormal DRE and were diagnosed with PC. For this reason logistic regression analyses were used in order to correct for possible differences in patient mix.

**Table 3:** Proportion of prostate cancers in men with a suspicious DRE result and in men with a normal DRE result per PSA range and per examiner.

| PSA range | Examiner | Proportion PC in men with sDRE | Proportion PC in men with nDRE |
|---|---|---|---|
| **Bx indication: PSA≥4.0 ng/ml and/or DRE and/or TRUS abnormal** | | | |
| All PSAs | 1 | 35.5 (54/152) | 21.5 (40/186) |
| | 2 | 26.8 (11/41) | 18.6 (16/86) |
| | 3 | 22.4 (11/49) | 14.5 (25/172) |
| | 4 | 29.3 (120/410) | 15.3 (80/522) |
| | 5 | 35.0 (7/20) | 18.3 (11/60) |
| | 6 | 18.4 (43/234) | 14.7 (25/170) |
| | Total | 27.2 (246/906) | 16.5 (197/1,196) |
| **Bx indication: DRE and/or TRUS abnormal** | | | |
| <4.0 ng/ml | 1 | 20.6 (14/68) | 13.5 (7/52)* |
| | 2 | 10.3 (3/29) | 22.2 (2/9)* |
| | 3 | 2.9 (1/34) | 1.6 (1/61)* |
| | 4 | 9.4 (21/223) | 10.7 (15/140)* |
| | 5 | 8.3 (1/12) | 0* |
| | 6 | 16.7 (38/227) | 10.8 (14/130)* |
| | Total | 13.2 (78/593) | 9.6 (39/406)* |
| **Bx indication: PSA≥4.0 ng/ml** | | | |
| 4.0-9.9 ng/ml | 1 | 40.9 (27/66) | 20.4 (23/113) |
| | 2 | 62.5 (5/8) | 16.2 (11/68) |
| | 3 | 44.4 (4/9) | 18.2 (18/99) |
| | 4 | 46.3 (69/149) | 15.2 (50/330) |
| | 5 | 60.0 (3/5) | 16.2 (6/37) |
| | 6 | 50.0 (2/4) | 25.7 (9/35) |
| | Total | 45.6 (110/241) | 17.2 (117/682) |
| **Bx indication: PSA≥4.0 ng/ml** | | | |
| ≥10.0 ng/ml | 1 | 72.2 (13/18) | 47.6 (10/21) |
| | 2 | 75.0 (3/4) | 33.3 (3/9) |
| | 3 | 100.0 (6/6) | 50.0 (6/12) |
| | 4 | 78.9 (30/38) | 28.8 (15/52) |
| | 5 | 100.0 (3/3) | 55.6 (5/9) |
| | 6 | 100.0 (3/3) | 40.0 (2/5) |
| | Total | 80.6 (58/72) | 38.0 (41/108) |

Total number of participants who underwent a biopsy was 2,102 (906 with suspicious DRE and 1,196 with normal DRE)

Bx, biopsy; sDRE, suspicious digital rectal examination; nDRE, normal digital rectal examination; PSA, prostate-specific antigen; PC, prostate cancer

* According to the study protocol, the biopsy indication of these men was based on an abnormal TRUS result

### Logistic regression on DRE result

The DRE result was known in 7,280 participants, of which 7,105 men were included in the analysis (of 175 men predictor information was incomplete). Table 4 shows odds ratios for five examiners and the other explanatory variables (arbitrarily, examiner 2 was used as reference examiner). Examiners 3 and 5 considered DRE abnormal approximately as often as the reference examiner (odds ratio (OR) approximately 1, p-value not significant). The others (examiners 1, 4 and 6) judged the DRE suspicious for cancer significantly more often under equal circumstances than the reference examiner (OR>1, p-value significant). Including the examiners into the logistic regression model with a suspicious DRE as the output variable led to a significantly better fit (LR test, p-value < 0.01). This implies that apparently different examiners have significantly different thresholds for calling a finding suspicious. Furthermore, if the PSA level doubled, the odds of an abnormal DRE increased 1.25 times (OR=1.25). The biopsy indication used (referred to as PSA level ≥4.0 ng/ml), TRUS outcome (normal or abnormal) and age also significantly increased the odds of finding an abnormal DRE, whereas prostate volume decreased these odds significantly (if the prostate volume doubled, the odds of an abnormal DRE changed by 0.67).

**Table 4:** Odds ratios for predictors for an abnormal result of the digital rectal examination (suspicious for prostate cancer) studied by multivariate regression analysis.

| Parameter | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| Examiner 1 | 3.48 (2.38-5.08) | <0.001 |
| Examiner 3 | 0.84 (0.55-1.29) | 0.424 |
| Examiner 4 | 2.80 (2.00-3.93) | <0.001 |
| Examiner 5 | 0.716 (0.39-1.28) | 0.265 |
| Examiner 6 | 2.47 (1.74-3.50) | <0.001 |
| 2log PSA level | 1.25 (1.14-1.37) | <0.001 |
| PSA≥4.0 ng/ml* | 1.42 (1.09-1.85) | 0.009 |
| TRUS | 4.08 (3.45-4.82) | <0.001 |
| 2log prostate volume | 0.67 (0.57-0.78) | <0.001 |
| Age | 1.06 (1.04-1.07) | <0.001 |

Examiner 2 was used as reference-examiner. Odds ratios for all other examiners must be interpreted in relation to examiner 2. In this analysis 7,105 of the 7,280 participants with known DRE result were included. A p-value <0.05 was considered statistically significant. Hosmer-Lemeshow test p-value 0.0851

* used as an indicator variable for biopsy indication

### Logistic regression on the presence of PC

Of 2,102 participants who underwent a prostate biopsy the DRE result was known. Of these men 2,084 were included in the analysis (of 18 predictor information was incomplete). Table 5 shows the odds ratios for having PC in case of an abnormal DRE for all examiners and other explanatory variables. The reference situation was the situation that DRE was normal. It was assumed that a normal DRE was independent of the examiner who performed the DRE. This

**Table 5:** Odds ratios for predictors for the chance to find prostate cancer if participants had an abnormal digital rectal examination, studied by multivariate regression analysis.

| Parameter | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| DRE by examiner 1 | 2.21 (1.42-3.45) | <0.001 |
| DRE by examiner 2 | 2.53 (1.03-6.23) | 0.043 |
| DRE by examiner 3 | 2.61 (1.00-6.77) | 0.049 |
| DRE by examiner 4 | 2.56 (1.85-3.54) | <0.001 |
| DRE by examiner 5 | 5.96 (1.37-25.86) | 0.017 |
| DRE by examiner 6 | 3.13 (1.98-4.97) | <0.001 |
| 2log PSA level | 3.16 (2.59-3.86) | <0.001 |
| PSA≥4.0 ng/ml* | 1.20 (0.77-1.89) | 0.420 |
| TRUS | 2.78 (2.13-3.63) | <0.001 |
| 2log prostate volume | 0.26 (0.20-0.33) | <0.001 |
| Age | 1.02 (1.00-1.04) | 0.051 |

The reference situation is the situation in which the digital rectal examination is normal. Of the 2,102 men who underwent a biopsy, 2,084 were included in this analysis. A p-value <0.05 was considered statistically significant.

Hosmer-Lemeshow test p-value 0.0653

* used as an indicator variable for biopsy indication





presumption was confirmed in a separate logistic regression model (data not shown). For all examiners, the odds for PC were statistically significantly ($p<0.05$; p-value for examiner 5 was 0.049) higher than the reference odds (non-suspicious DRE). Examiner 5 seemed to predict the presence of cancer best (odds ratio 5.96), however the uncertainty in this estimate was considerable. PSA value and TRUS outcome also significantly increased the odds to find cancer, whereas prostate volume significantly decreased these odds. The biopsy indication used (PSA level ≥4.0 ng/ml) and age were non-significant. Including all six examiners into the logistic regression model with cancer detected as the output variable did not lead to a

**Table 6:** Odds ratios for predicting the presence of prostate cancer in case of an abnormal DRE for examiner 5 compared to the other examiners.

| Parameter | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| DRE suspicious | 2.57 (1.97-3.34) | <0.001 |
| DRE suspicious according to examiner 5 | 2.27 (0.53-9.73) | 0.270 |
| 2log PSA level | 3.17 (2.61-3.87) | <0.001 |
| PSA≥4.0 ng/ml* | 1.12 (0.73-1.71) | 0.608 |
| TRUS | 2.72 (2.09-3.53) | <0.001 |
| 2log prostate volume | 0.26 (0.20-0.33) | <0.001 |
| Age | 1.02 (1.00-1.05) | 0.052 |

Odds ratios for the other explanatory variables are mentioned as well. Of the 2,102 men who underwent a biopsy, 2,084 were included in this analysis. A p-value <0.05 was considered statistically significant.

Hosmer-Lemeshow test p-value 0.155

* used as an indicator variable for biopsy indication

significantly better fit (LR test, p-value 0.8). This implies that apparently different examiners have a comparably increased probability to detect cancer given a suspicious finding. A final logistic regression analysis in which the indicator variables for all the examiners except for examiner 5 were pooled showed that examiner 5 did not significantly better predict the presence of cancer in case of an abnormal DRE (table 6).

## DISCUSSION

The best way to analyse interobserver variation in the assessment of the prostate by DRE is to digitally examine participants several times on the same day by different examiners and using kappa statistics (Cohen[161]) in order to quantify the interrater agreement. Two studies on this subject using kappa statistics showed contradictory results[132, 160]. This type of analysis would however have meant an undesirable burden to the participant and would have interfered with the logistics of the screening procedure. Therefore we have used descriptive statistics and multivariate logistic regression analyses as alternative methods.

Although the descriptive statistics analysis gave an indication of the variability of the DRE result between examiners, no straightforward conclusions could be drawn because the PSA level influenced the probability of finding an abnormal DRE and finding PC in case of an abnormal DRE. Other predictors for a suspicious DRE (PSA level, TRUS outcome, biopsy indication, prostate volume and age) varied per examiner as well and therefore the raw DRE performance data per examiner had to be controlled for the examined patient population of each examiner to allow a proper interpretation. This was achieved by using a multivariate logistic regression model.

### Between-examiner variation of the percentage of men with a suspicious DRE

Logistic regression analysis showed that DRE is a subjective test (table 4, likelihood ratio test for the logistic model with DRE as dependent variable, see results section). Some examiners (odds ratio larger than 1 with p-value <0.05) found DRE significantly more often suspicious for cancer than others (odds ratio near to 1 with p-value ≥0.05). None of the examiners diagnosed a statistically significantly disproportionably low percentage of men with a suspicious DRE (i.e. odds ratio <1, p<0.05).

### Between-examiner variation of the detection of PC given a suspicious DRE

Although there apparently existed a considerable variation in the frequency of suspicious findings on DRE between examiners, a suspicious finding on DRE was, however, consistently associated with an increased PC detection probability (see odds ratios in table 5). An examiner that considers DRE more often abnormal than others generates more biopsy indications (at PSA levels <4.0 ng/ml) and detects more cancers. This is compatible with the knowledge

that in men in the age group involved a large reservoir of small PC is present[138, 139]. More biopsies find more PCs. A larger number of insignificant cancers might be detected because of performing more biopsies on the basis of a suspicious DRE. If it is desirable to detect and treat these cancers is a debatable issue. The current article cannot give an answer to the question whether doing more or less DRE-driven biopsies will contribute to lowering PC mortality.

### Interpretation of the multivariate logistic regression model

As indicated above our data showed that the odds to detect PC were approximately 2.5 (table 6) times higher if an examiner felt abnormalities at DRE when compared to the situation of a non-suspicious DRE (assuming all other variables equal). This observation was not examiner-dependent (see likelihood ratio test for the logistic regression model with cancer detected as the dependent variable). Furthermore, the estimated odds-ratio of 2.5 was apparently not strongly dependent on the biopsy indication used (table 6: the odds ratio for indicator PSA≥4 ng/ml is not significantly different from 1). This is a relevant observation as the biopsy indication was different for PSA≥4 ng/ml (all men were biopsied) when compared to PSA<4 ng/ml (only men with a suspicious DRE and/or TRUS were biopsied). In other words, the odds-ratio of 2.5 was not dependent on the frequency of DRE-driven biopsies. A constant multiplying effect of a suspicious DRE (2.5 times) on the odds to detect cancer implies that the increase in the probability induced by a suspicious DRE varies as a function of PSA (and other parameters such as TRUS finding and prostate volume).



As shown in table 3 the positive predictive value of DRE (proportion prostate cancer in men with an abnormal DRE) at PSA<4.0 ng/ml is 20% at most. Correcting for TRUS result and other explanatory variables in a multivariate regression analysis led to an odds ratio of 2.5 for a suspicious DRE to detect PC and means that a suspicious DRE multiplies the odds to detect cancer by 2.5. In the PPV of at most 20% (table 3) this multiplying DRE effect is included. The data currently evaluated for interobserver variability in the present article are based on the first screening round of the ERSPC Rotterdam and are similar to the data analysed by Schröder *et al.*[16] which showed a positive predictive value of a suspicious DRE of 13% in the PSA range below 4.0 ng/ml. Because of this poor performance of DRE the ERSPC Rotterdam decided in May 1997 to omit DRE as a screening tool. Lowering the biopsy indication to a PSA cut-off of 3.0 ng/ml or greater without the use of DRE as a biopsy indication improved the overall PPV from 18.2% (biopsy indicated if DRE/TRUS abnormal or PSA≥4.0) to 24.3% (biopsy indicated if PSA≥3.0). The number of biopsies necessary to detect 1 case of PC accordingly changed from 5.2 to 3.4[14]. Furthermore, the cancer detection rate (proportion of PC in those screened) was similar for both protocols: respectively 4.7 for biopsies based on PSA≥3.0 and 5.0 for the protocol with DRE/TRUS. Screening became more efficient as the costly and time-consuming DRE and TRUS had not to be performed anymore while the CDR remained equal and the PPV improved. In addition, 75% of the cancers that were detected on the basis of a suspicious DRE at PSA<3.0 (and would not be detected with the new protocol) had a prostate cancer with a

tumour volume <0.5 ml in the radical prostatectomy specimen. A malignancy of the prostate with tumour volume <0.5 ml is unlikely to be palpated and these DREs should be considered as false-positives[14]. As suggested by Stamey *et al.*[90] prostate cancers smaller than 0.5 ml are not likely to reach a clinically significant size. The cancers found as a consequence of DRE in this PSA range have a high likelihood of being indolent based on the mentioned 75% that has a tumour volume <0.5 ml. In addition, there is increasing evidence that the proportion of indolent prostate cancer is inversely related to PSA[35, 54]. Cancers in men with low PSA levels (PSA<3.0 ng/ml) that were missed as a result of the omission of DRE would most probably have been detected at subsequent screenings. The protocol change was evaluated in a recent study that showed that omitting DRE and TRUS did not result in an increased detection of prostate cancers or interval cancers after 4 years[153].

In conclusion, although the risk of detecting PC increases roughly 2.5 times in case of a suspicious DRE, the omission of this tool as a sole indicator for prostate biopsy is justified. In an optimal situation the biopsy indication should be based on a chance threshold to detect prostate cancer, or preferably to detect potentially aggressive disease. DRE, TRUS, PSA and other pre-biopsy characteristics should be included in the algorithm that defines the chance to detect cancer in a lateralised sextant biopsy.

After adjustment for case mix, different observers vary when comparing suspicious DRE rates. However, the predictive values to detect PC (PPVs) for the different examiners are comparable given a palpable abnormality on DRE (see likelihood ratio tests in the results section). An explanation for this paradoxical observation is that the proportion of disease is constant in the group of men with palpable abnormalities. An examiner with a low threshold will detect many palpable abnormalities, an examiner with a higher threshold fewer. For both examiners the PPVs will be comparable since for both examiners the ratio of the number of abnormalities related to a malignancy and abnormalities related to a non-malignancy is roughly equal.

Finally, it must be noted that although variables such as DRE outcome, TRUS findings and (to a lesser extent) prostate volume are all subject to interobserver variability, they can play a role in the prediction of the chance to detect prostate cancer. Several investigators found that the incorporation of these so-called subjective variables next to the PSA value in predictive models improved the prediction of having prostate cancer[142, 162, 163]. Moreover, evidence exists that the DRE can be used to detect aggressive prostate cancers more selectively[47, 61, 157-159]. This issue will be evaluated within ERSPC Rotterdam in a future article.

## CONCLUSIONS

The digital rectal examination for diagnosing prostate cancer is a subjective test. Some examiners considered the DRE significantly more often abnormal than others. However, a suspi-

cious DRE executed by each examiner statistically significantly increased the chance on the presence of prostate cancer under equal circumstances (the regression model corrected for the other explanatory variables). It was found that DRE increases the odds to detect prostate cancer roughly 2.5 times independent of biopsy indication used. This increased chance to find prostate cancer was not significantly observer-dependent and corroborates the fact that a suspicious DRE is an independent predictor for the presence of prostate cancer.

# Part V

## General Discussion

# Chapter 10

## Discussion

Prostate cancer screening is currently being evaluated for the effect on prostate cancer mortality in two ongoing randomised controlled trials[8]. In the meanwhile, these trials offer an opportunity to evaluate the available and new screening tests. Although using the digital rectal examination for the diagnosis of PC is still advised by the EAU guidelines[164], applying DRE as a screening test is controversial. With the common use of PSA cut-offs lower than the arbitrarily-chosen original value of 4.0 ng/ml[165] as an indication for prostate biopsy, the domain of the digital rectal examination is generally limited to the range below these cut-offs.

## PROSTATE CANCER SCREENING AT LOW PSA LEVELS: WHAT KIND OF PROSTATE CANCERS DO WE FIND?

In 2004, Thompson *et al.* reported a 15.2% prevalence of prostate cancer in 2,950 men with a PSA level below 4.0 ng/ml in the placebo arm of the Prostate Cancer Prevention Trial (PCPT)[91]. The selected participants never had a PSA value of ≥4.0 ng/ml or an abnormal DRE (measured and examined annually) during a 7-year period. At the end of these 7 years all participants were offered a sextant prostate biopsy. In addition to the high prostate cancer prevalence of 15.2%, 14.9% of these cancers had a Gleason score of ≥7. The prevalence of high-grade disease also increased with the PSA level, from 12.5% (PSA≤0.5 ng/ml) to 25% (PSA 3.1-4.0 ng/ml). Therefore, Thompson and colleagues concluded that biopsy-detectable prostate cancer, including high-grade cancers, is not rare among men with PSA levels ≤4.0 ng/ml and even in men with PSA<2.0 ng/ml.

With this new insight, the previously used PSA cut-off points and the omission of DRE became questionable because of the fear of missing a considerable number of cancers and even potentially aggressive disease at low PSA levels. However, several comments suggested that many of the PCs found in the PCPT resemble autopsy cancers with no clinical relevance[92, 166]. To analyse this suggestion in more depth, the prevalence and tumour characteristics of PCs found at low PSA in the PCPT were compared to those found in the ERSPC Rotterdam, in autopsy studies and in cystoprostatectomy series as described in **chapter 4** of this thesis.

The prevalence of prostate cancer in autopsy studies, cystoprostatectomy series and two more recent series[139, 167] was similar or higher than the prevalence in the control group of the PCPT. An explanation for this difference is the examination of the whole prostate specimen in the former series versus the biopsy specimens in the PCPT. In the most recent study, Haas *et al.*[139] performed 18-core needle biopsies on autopsy prostates from 164 men who had no history of prostate cancer. Prostate cancer was present in 47 (29%) prostates. Of the 47 prostates 20 (43%) were judged to be clinically significant. Comparison of the PCPT with the ERSPC Rotterdam was only possible to a certain extent. The prevalence of PC was lower in the ERSPC. Partially, this can be explained by the higher age of the participants included in the PCPT.

At the moment a side study within the ERSPC Rotterdam is being performed by using the promising molecular marker PCA3[82, 83] as a biopsy indication. Preliminary results show that almost 85% of all participants undergoing a PSA and PCA3 test have a biopsy indication based on these two tests. Consequently, many men with PSA levels below 3.0 ng/ml are being biopsied. With the completion of the PCA3 analysis an improved comparison between ERSPC and PCPT can be made for the prevalence of prostate cancer at low PSA levels and their tumour characteristics.

The reviewed studies for which comparison of tumour characteristics was possible, generally contradict the findings of the PCPT. The favourable characteristics (tumour volumes <0.2 or 0.5 ml, confinement to the prostate and Gleason score <7) of tumours detectable at low PSA levels[68, 103, 105, 106] seem to justify the conclusion that an unknown but sizeable proportion of the cancers found at biopsy in apparently normal men are clinically unimportant but compatible with autopsy cancers. Although the proportion of GS≥7 cancers in the PCPT control arm is larger than in the ERSPC Rotterdam and several other studies, PCPT cancers may still largely resemble indolent tumours. As the cancers in the PCPT were biopsy-detected, tumour volume and confinement to the prostate (or not) are unknown, but may be similar as in the reviewed series because these cancers were also unsuspected in men with no complaints or an abnormal DRE or PSA findings. The higher prevalence of indolent cases, as compared to the significant and possibly life-threatening cases, put the value of screening in men with these low PSA levels (<3.0 ng/ml) in question.



In a very recent paper, Schröder *et al.*[168] evaluated if all PCs in men with serum PSA levels <3.0 ng/ml should be detected. This analysis was done by comparing 12-year follow-up data of the ERSPC with the results of the control arm of the PCPT, in which all men with PSA<3.0 ng/ml were biopsied[91]. Within the ERSPC a total of 15,852 men presented with an initial PSA value <3.0 and 700 cancers were detected in this population. Applying the positive predictive value (PPV) of the PCPT, 3,472 cancers would have been detected in the first seven years of the ERSPC by using the PCPT screening protocol. This means that 2,772 cancers were missed due to the ERSPC screening protocol (biopsy indicated if PSA≥3.0 ng/ml). Only 80 of those 2,772 cancers which remain undetected with the use of a PSA cut-off of 3.0 ng/ml as a biopsy indication (in men aged 55-74 years screened every 4 years) were diagnosed after those initial 7 years at a rescreen or as interval cancers and only 6 of these 2,772 (0.22%) died during a 12-year observation period. Their detection within the ERSPC cohort would have required 12,315 additional biopsies.

A 12-year follow-up period is likely to be too short. Still, one might have expected that at least those cases which show patterns of moderately or poorly differentiated cancers, which have been detected in the PCPT trial but were missed in ERSPC, would have surfaced clinically in larger numbers. This is clearly not the case, suggesting that men presenting with PSA values of <3.0 ng/ml should not be biopsied but can be followed.

## THE OMISSION OF DRE AS A SCREENING TOOL

In 1998 Schröder *et al.* showed that the PPV of a suspicious DRE in the PSA range below 4.0 ng/ml was only 13%[16]. Because of this poor performance of DRE, different screening modalities were evaluated[9]. PSA≥3.0 ng/ml as sole biopsy indicator (without DRE and TRUS) showed the most favourable results: the number of biopsies was decreased by 12% while the number of cancers detected decreased by an acceptable 8%[9] (i.e. the cancer detection rate remained similar). Furthermore, other studies[118, 128, 169] concluded that a majority of the cancers detected in the PSA range 3.0-4.0 ng/ml were clearly significant and suitable for curative treatment, therefore providing another argument to implement a screening protocol with PSA≥3.0 ng/ml as threshold for biopsy.

In a study by Hoedemaeker *et al.*[68] three subsets of radical prostatectomy specimens were evaluated: T1c tumours, non-T1c tumours with PSA≤4.0 ng/ml and non-T1c tumours with PSA≥4.0 ng/ml. The group of tumours detected by DRE and/or TRUS in the lowest PSA ranges had the most favourable pathological stages, a considerable fraction (43%) fitting the criteria for 'minimal tumour' and 86% with a tumour volume smaller than 0.5 ml. A minimal tumour was defined as a tumour smaller than 0.5 ml, lacking Gleason pattern 4 or 5, and confined to the prostate (stage pT2). Men with low PSA levels were therefore considered most likely to harbour clinically insignificant tumours. Based on these findings all men in the ERSPC Rotterdam with a PSA≥3.0 ng/ml have received a prostate biopsy from May 1997 onwards.

The protocol change was validated with respect to detection rates and PPVs in different PSA ranges[14]. Lowering the biopsy indication to a PSA cut-off of 3.0 ng/ml without the use of DRE as a biopsy indication improved the overall PPV from 18.2% (biopsy indicated if DRE/TRUS abnormal or PSA≥4.0) to 24.3% (biopsy indicated if PSA≥3.0). The number of biopsies necessary to detect 1 case of PC accordingly changed from 5.2 to 3.4[14]. Furthermore, the cancer detection rate (CDR, proportion of PC in those screened) was similar for both protocols: respectively 4.7% for biopsies based on PSA≥3.0 and 5.0% for the protocol with DRE/TRUS. Screening became more efficient as the costly and time-consuming DRE and TRUS had not to be performed on all participants anymore while the CDR remained equal and the PPV improved. In addition, 75% of the men who were diagnosed with cancer on the basis of a suspicious DRE at PSA<3.0 ng/ml (and would not be detected with the new protocol) had a prostate cancer with a tumour volume <0.5 ml in the radical prostatectomy specimen. In fact, these tumours were too small to palpate. This finding was confirmed by a study of Vis *et al.* that concluded that a relatively high proportion of prostate cancers diagnosed in men with low PSA levels and in which a biopsy was prompted by a suspicious DRE and/or TRUS, are considered to be detected by chance only[123].

Another justification of PSA-based screening is that this procedure detected clinically significant disease more frequently in the PSA range 0-3.9 ng/ml than DRE/TRUS-based screening in a study that compared the tumour characteristics of cancers found by the two proto-

cols[62]. This study showed that in the case that all participants with a PSA 3.0- 3.9 ng/ml were biopsied (biopsy indication PSA≥3.0 ng/ml), more significant cancers were detected than if men were biopsied in case of an abnormal DRE/TRUS in the range 0-3.9 ng/ml. In fact, at PSA levels below 3.0 ng/ml, 289 rectal examinations were required to find one case of significant prostate cancer[62]. The detection of a substantial proportion of these PCs at PSA levels <3.0 ng/ml was based on serendipity only, as 72% of these cancers had a tumour volume <0.5 ml in the radical prostatectomy specimen. With these low tumour volumes DRE and TRUS should be considered false-positive.

However, without rectal examination a certain proportion of clinically diagnosable prostate cancers are missed and the question of their later detection with elevated PSA values (≥3.0 ng/ml) at a still curable stage is unresolved. This thesis evaluated the omission of DRE as an indicator for prostate biopsy and the value of DRE used in addition to a PSA cut-off value as biopsy indication.

## EVALUATION OF THE OMISSION OF DRE AS A BIOPSY INDICATOR



The risk of omitting DRE and TRUS, and therefore the omission of biopsies at PSA<3.0 ng/ml, is that potentially aggressive tumours at these low PSA levels remain undetected at screening. These could surface as interval cancers (i.e. prostate cancers detected between two screening rounds), or as tumours with PSA levels progressed to values above 3.0 ng/ml with possibly unfavourable prognostic characteristics when detected at subsequent screens. The omission of DRE may also lead to more prostate cancer specific deaths.

The number of missed cases with potentially aggressive tumour characteristics depends both on the prevalence below the threshold value for biopsy, and on the effectiveness of the screening tests used to detect these cases. The study described in **chapter 5** compared the prevalence and prognostic factors of tumours found in the second screening round of the ERSPC Rotterdam between two groups of men who had initially (at first screening) been screened either with DRE/TRUS or without these tests.

Screening without DRE at low PSA levels (PSA<3.0 ng/ml) did not lead to the detection of significantly more PCs 4 years later as compared to screening with the use of DRE. No significant difference in the percentage of poorly differentiated tumours at biopsy or at radical prostatectomy was found between the 'old' and 'new' screening regimen. Furthermore, the prevalence and tumour characteristics of interval cancers were similar in both groups. However, the group initially screened without DRE showed more often extraprostatic extension at radical prostatectomy. Although this conclusion is based on a small number of radical prostatectomy specimens (N=75) and the difference was only just significant (p=0.035), this is an observation which is to be kept in mind during further follow-up.

Based on this study it was concluded that screening without DRE and TRUS did not lead to the detection of more aggressive PCs after four years and that the risk of screening without these tools seems acceptable.

Preliminary results of the third screening round, i.e. 8 years of follow-up after the prevalence screen, show similar findings that justify the change to the PSA cut-off of 3.0 ng/ml as sole biopsy indication.

In **chapter 6** the omission of DRE as a screening tool was monitored by comparing the characteristics of cancers detected either by a suspicious DRE or by PSA-based screening in the PSA range 2.0-4.0 ng/ml. In this way, the value of DRE could be evaluated at low PSA levels, which is the domain of DRE since the currently used cut-offs of 2.6[117, 128], 3.0[14, 62] or 4.0[129] ng/ml. For PSA values below 2.0 ng/ml Beemsterboer *et al.* had already shown a very unfavourable balance between the number of biopsies performed and the number of prostate cancers detected, with PPVs between 2% and 5%[9].

PSA-based screening using a cut-off of 2.0 ng/ml detected approximately twice the number of potentially aggressive (GS≥7) tumours per number of screened men than the regimen using DRE (CDRs of respectively 2.3% versus 1.2%). A considerable amount (15%) of T1c-cancers (detected by the PSA-based protocol) were potentially aggressive (GS≥7). At the same time, PSA-based screening detected a substantial number of potentially indolent (T1c, GS<7) cases. On the other side, DRE seemed to detect more selectively high-grade cancers, but also missed many of these. Considering the PSA range 2.0-4.0 ng/ml and the need to detect aggressive but confined disease, PSA as a biopsy indication outperformed DRE at the price of more biopsies and subsequently a larger number of overdiagnosed cases.

The results of this study were reassuring for the decision to omit DRE as a biopsy indication and to use the PSA cut-off of 3.0 ng/ml instead. In the PSA range 3.0-4.0 ng/ml the detection rate of potentially aggressive disease (biopsy GS≥7) was more than twice the detection rate in the group screened with DRE (4.7% versus 2.2%). However, the price paid was that 18 men had to undergo a biopsy to find 1 clinically significant cancer. Nevertheless the overall PPV, i.e. the proportion of cancers of any Gleason score detected all biopsied men, was acceptable with 22.3%.

If the currently used PSA cut-off of 3.0 ng/ml should be lowered to 2.0 ng/ml remains a question. To find 6 additional potentially aggressive cancers in this PSA range, another 455 participants had to be biopsied. In other words, 1 significant cancer was detected in 80 men biopsied. Additionally, numerous potentially indolent cancers were detected. This imbalance makes the indication for prostate biopsy in every man with a PSA≥2.0 ng/ml very questionable. As already mentioned by Schröder *et al.*, the evaluation of men with PSA 2.0 to 2.9 ng/ml would only be useful if screening could be more selective[15]. Unfortunately, until now a selective screening tool is not available.

The fact that performing biopsies at PSA levels below 3.0 ng/ml is not medically acceptable is also illustrated by the already mentioned study that compared the outcome of the PCPT to 12 years of follow-up of the ERSPC Rotterdam[168]. A very much unfavourable balance between the number of participants needed to be biopsied to detect one missed cancer (by using a PSA cut-off of 3.0) was shown.

## EVALUATION OF THE DRE IN MEN WITH ELEVATED PSA LEVELS

If DRE seems not valuable as a screen test to indicate prostate biopsy, is it still useful to perform a DRE in addition to a PSA cut-off of 3.0 ng/ml? In other words, is DRE of additional value in men with an elevated PSA to detect cancers or even to identify the more hazardous prostate cancers?

In **chapter 7** was shown that the chance to detect prostate cancer at initial screening in men biopsied for an elevated PSA (≥3.0 ng/ml) with a suspicious DRE was approximately twice the chance of men with a normal DRE. This additional value of a suspicious DRE was however limited since the biopsy indication was not altered and all men with a PSA≥3.0 ng/ml would nonetheless have undergone biopsy. Nevertheless, the risk of harbouring high-grade disease (in this study defined as biopsy Gleason score >7) was consistently higher in men with a suspicious DRE result, a finding that is in line with other large prostate cancer screening trials indicating that an abnormal DRE is associated with having high-grade disease[47, 61, 63].



This finding can be valuable for individual risk determinations of the chance to harbour significant disease by incorporating the DRE result in future algorithms.

Currently, prostate cancer screening becomes more common in Western countries. An increasing number of men want their PSA level to be determined and for this reason a considerable rise in numbers of men undergoing a prostate biopsy is evident. Obviously, many prostate cancers are detected. However, a substantial fraction (70-80 %) of the screened men have a benign biopsy result. Having had a previous biopsy lowers the risk of being diagnosed with PC at later screens[30]. The additional predictive value of an abnormal DRE was marginal in men with a previous biopsy, but a suspicious DRE was still associated with a higher chance of detecting high-grade disease in these men.

Taking these two facts together, leads to a recommendation for possible use of the rectal examination for more selective screening in order to find a balance between the numbers of detected, clinically significant cancers, and the burden to the screened individual. In men with a previous biopsy, an elevated PSA level and a normal DRE, the chance to find prostate cancer is quite low (1 out of 7-10 men biopsied was diagnosed with cancer, **chapter 7**). Ninety percent of these relatively few cancers had the characteristics of potentially indolent disease (T1c and GS<7) and only very few had potentially aggressive features (0.3% of all cancers detected at second and third screening). Therefore, it may be considered justified to

postpone biopsy in men with a previous biopsy, an elevated PSA and a normal DRE in order to lower the risk of overdiagnosis and to reduce the number of unnecessary biopsies. The potentially indolent cancers that are missed in this way and that will possibly become harmful in the future will most probably be detected in time for curative treatment at subsequent screenings because of their elevated PSA level, a conversion of the DRE result or by new markers. However, the risk of missing the few cancers with potentially aggressive features by postponing biopsy in the selected men should be weighed carefully against preventing numerous men from an unnecessary biopsy.

Evidence exists that an abnormal DRE is a risk factor for detecting high-grade disease[47, 61], which is also illustrated by the studies that form **chapter 6 and 7** of this thesis. In order to detect these potentially life-threatening cancers in time, we evaluated if the DRE is useful in the risk assessment for diagnosing these cancers at a later moment.

In **chapter 8** we analysed if men with a suspicious initial DRE, an elevated PSA level (≥3.0 ng/ml) and a benign biopsy result were at higher risk of being diagnosed with prostate cancer or in particular significant (in this study defined as clinical stage >T2a or GS≥7) prostate cancer at later screens. The second aim of the study was to evaluate if men with an initially abnormal DRE should be recommended to undergo rescreening earlier than after the standard four years.

A cohort of 2,218 men with a PSA≥3.0 ng/ml and a benign biopsy result, of which 1,756 had a normal DRE and 462 had a suspicious DRE, were followed for 8 years. During the follow-up these two groups were evaluated for the number of cancers detected and the tumour characteristics of these cancers.

After three consecutive screenings (8 years) identical proportions of men with prostate cancer (10%) were detected in both groups. No distinct difference was detected in the number of high-grade prostate cancers (2% for the participants with an initial normal DRE and 3% for an abnormal DRE). Additionally, multivariate logistic regression analyses showed that initially having a suspicious DRE was not a significant predictor for detecting prostate cancer during the follow-up. In conclusion, rescreening earlier than the established four years seemed not necessary for men with an initially suspicious DRE, an elevated PSA and a benign biopsy result.

As already mentioned, the proportion of men with a previous cancer-negative biopsy result is increasing. At this moment the management of men with a previous negative biopsy is unclear. This thesis gave two suggestions for an eventual adaptation of the screening protocol in these men. In **chapter 7** it was concluded that it was justified to postpone biopsy to a later screening in men with a previous cancer-negative biopsy, an elevated PSA level and a normal DRE. To the contrary, in **chapter 8** it was pointed out that men with an initially normal DRE,

an elevated PSA and a previous benign biopsy did not have a decreased risk for diagnosing prostate cancer or potentially aggressive disease at subsequent screens.

At first sight, these two conclusions seem to contradict each other. However, when looking at both study populations carefully, the apparently contradictory conclusions become comprehensible because of differences in the populations and study methods. The most important difference is that in **chapter 7** three consecutive screening rounds were separately evaluated. Some participants included in screenings 2 and 3 in **chapter 7** had undergone a previous biopsy, others had not. The population for which the postponement of a subsequent biopsy was suggested, was a selection of men with a previous biopsy and a present PSA level ≥3.0 ng/ml. Furthermore, in these selected men, the PSA at earlier screens was not necessarily elevated to levels above 3.0 ng/ml, as in earlier screens biopsy could be indicated by an abnormal DRE or TRUS while the PSA level was below 4.0 ng/ml. In addition, some men had rapidly increasing PSA levels influencing the chance to detect PC.

Contrary to the three separately analysed screening rounds in **chapter 7**, the population analysed in **chapter 8** was followed from initial screening for 8 years and three screenings. All included participants had at first screen a PSA≥3.0 ng/ml and were subsequently biopsied at later screens if the PSA had remained above 3.0. However, as in this study the initial DRE result was evaluated, participants could have a conversion from for example a normal DRE at initial screening to an abnormal at second or third screening. In the second screening round 23% (210 of 909 biopsied) had a conversion of the DRE result and in the third round this proportion was 31%. Conversion of the outcome of DRE can explain the fact that the initial DRE is not of value for the risk assessment of detecting cancer later screens. Unfortunately, virtually no information is available on the phenomenon DRE conversion over time and further research on this subject is needed.

Considering the conclusions of both studies, the initial DRE result seemed not predictive for the diagnosis of cancer at later screenings (in men with an initial PSA≥3.0 ng/ml and a benign biopsy), whereas an abnormal DRE result at the time of biopsy in men with a previous negative biopsy and an elevated PSA (thus neglecting the initial DRE result) did lead to a higher risk of the diagnosis prostate cancer compared to men with a normal DRE. The latter conclusion suggests the use of a longer screening interval in the selected population of participants with a normal DRE, a previous biopsy and an elevated PSA.



## THE DIGITAL RECTAL EXAMINATION IS SUBJECTIVE, BUT PREDICTIVE FOR CANCER

One of the major criticisms on the digital rectal examination used as a screening test for prostate cancer is its subjectivity. Only two studies that analyse the subjectivity of DRE are known[132, 160], and show contradictory results. In **chapter 9** the interobserver variability of DRE

within the first screening round of the ERSPC Rotterdam was investigated. At that time DRE was still used as a screening test for prostate cancer in Rotterdam.

Six examiners were evaluated for their variability in DRE outcome (normal or abnormal) and for the variability in the proportion prostate cancers detected in case of an abnormal DRE result in a study population of 7,280 men. As expected, DRE was shown to be a subjective test: some examiners considered the DRE significantly more often abnormal than others. However, a suspicious DRE executed by each examiner statistically significantly increased the chance on the presence of prostate cancer under equal circumstances. A suspicious DRE was shown to be an independent predictor for the presence of prostate cancer, as a suspicious DRE increased the odds to detect prostate cancer approximately 2.5 times independent of the biopsy indication used. Clearly, the different examiners had different thresholds for calling a DRE suspicious. But in case of a suspicious DRE, each examiner consistently showed increased odds for diagnosing prostate cancer as it was actually not possible to discriminate between cancer and no cancer and the proportion of disease is constant in the group of men with palpable abnormalities.

The increased risk of diagnosing prostate cancer for men with a suspicious DRE is in accordance with the conclusions of **chapter 7**, which showed a higher chance to detect prostate cancer at initial screening in men with a suspicious DRE biopsied for an elevated PSA (≥3.0 ng/ml). However, these results concern data from the first screening round of the ERSPC Rotterdam and the additional predictive value of an abnormal DRE became less at later screenings, especially in men with a previous biopsy (**chapter 7**).

Furthermore, the data evaluated for the interobserver variability of DRE (finding a 2.5 times increased risk of detecting PC if the DRE was suspicious) are similar to the data analysed by the study that concluded that the predictive value of DRE was poor at PSA levels below 4.0 ng/ml[16]. Although the risk of detecting PC increases roughly 2.5 times in case of a suspicious DRE in the current study, the omission of DRE as a sole indicator for prostate biopsy is still justified because of its poor positive predictive value at low PSA levels. Moreover, Bozeman *et al*. showed that DRE is an inferior screening tool for prostate cancer. However, they concluded also that an abnormality on DRE in patients diagnosed with prostate cancer was most likely to represent cancer and thus, in most patients, cancer was not diagnosed serendipitously[170]. Although not useful as a biopsy indicator on its own, DRE can play a role in the prediction of the chance to detect prostate cancer by incorporation in predictive models next to other variable such as serum PSA[142, 162, 163, 171, 172].

## IS DRE SELECTIVE FOR HIGH-GRADE DISEASE?

Several researchers suggested the use of DRE to screen more selectively in order to lower the risk of unnecessary biopsies and overdiagnosis by showing evidence that the rectal examina-

tion detects aggressive prostate cancers more selectively than PSA-based screening. Borden *et al.* concluded that an abnormal DRE was an independent predictor for high-grade prostate cancer on initial biopsy in a referral population[61]. Others showed that palpable tumours (cT2b) were significantly more likely to have a higher Gleason score than non-palpable tumours by retrospectively examining radical prostatectomy specimens in referral populations[157-159] and in a screening cohort[47].

Recently, the study group of Catalona has published a paper that stated that a substantial proportion of prostate cancers detected by DRE at PSA levels less than 4.0 ng/ml have features associated with clinically aggressive tumours[63]. They suggested that the omission of DRE from screening protocols might compromise treatment outcomes as omitting DRE at PSA levels less than 3.0 ng/ml would have detected 14% fewer prostate cancers overall and 7% fewer prostate cancers with a Gleason score of 7 or higher.

Unfortunately, bias in this report does not allow proper comparison with our data. The study is based on the data of participants who underwent radical prostatectomy. How did this selection influence the outcome? A number of 1,335 screen-detected cancers were not radically operated. Within this group, a considerable number could probably have had palpable abnormalities. Moreover, the investigators did not mention how many participants had to undergo a biopsy to find the cancers. Next to the bias mentioned above and the fact that this study concerns non-randomised volunteers instead of a randomised controlled population, another important problem of this report is that the study groups (i.e. prostate cancer detected by DRE alone, PSA alone, or by DRE and PSA) included several statistically relevant parameters that influenced the chance of detecting prostate cancer or high-grade disease. For example, the PSA level was significantly higher in the group with elevated PSA and abnormal DRE compared to the group with elevated PSA alone. This likely increased the risk of detecting (high-grade) prostate cancer in the first group. Another unexplained issue is the reported PPV of an abnormal DRE of 18% in men with PSA levels below 4.0 ng/ml that is in sharp contrast to the findings of an earlier report of the same study group[13], in which a PPV of 10% was reported for an abnormal DRE and a PSA level below 4.0 ng/ml.

In line with the findings of the Catalona group, **chapter 6 and 7** of this thesis showed that DRE seemed to detect high-grade prostate cancers more selectively than screening with a PSA cut-off alone. However, the protocol using DRE missed also numerable significant cancers.

DRE as screening tool is not being reconsidered within the ERSPC Rotterdam. An evaluation four years after the omission of DRE showed that this did not result in an increased interval cancer rate or PC detection at subsequent screening (**chapter 5**). As mentioned previously, this finding was confirmed by the recent paper of Schröder *et al.*[168]. Is was shown that, using the PSA cut-off 3.0 ng/ml, a very unfavourable number of participants would be needed to be biopsied to detect one cancer in the PSA range below 3.0. Together with the low PPV of DRE at low PSA levels[16], it does not seem necessary to reconsider the renewed use of DRE as a biopsy indicator at PSA<3.0.

## THE TRANSRECTAL ULTRASOUND AS A SCREENING TOOL

This thesis deals with digital rectal examination. However, within the ERSPC Rotterdam transrectal ultrasound (TRUS) was evaluated and omitted at the same time. The performance of DRE and TRUS was similar as illustrated by a study of Rietbergen *et al.*[173]. In a study that evaluated 3,963 men undergoing a PSA test, a DRE and a TRUS, 173 prostate cancers were detected. DRE alone would have diagnosed 47.1% of all cancers and TRUS alone would have detected 45.3% of the cancers.

In general, the value of TRUS is considered limited as a screening test for prostate cancer[9, 11, 55, 56]. Defining a lesion suspicious on TRUS is highly investigator-dependent and hypoechoic lesions, which are considered suspicious for prostate cancer, are not very specific[57]. Next to hypoechoic lesions, prostate cancers can have iso-echoic or hyperechoic characteristics[58-60].

Nevertheless, TRUS is very useful in performing systematic prostate biopsies. For this reason the TRUS-guided systematic prostate biopsy is the gold standard in obtaining prostatic tissue in men indicated for prostate biopsy.

Still, an additional biopsy core is taken if a hypoechoic lesion is visible. If active screening for prostate cancer will prove to be beneficial in terms of prostate cancer mortality reduction, the first question that arises will be what the appropriate screening algorithm should be.

For this reason we have recently investigated the value of taking an additional hypoechoic lesion directed biopsy in addition to a systematic, lateralised, sextant biopsy for the detection of prostate cancer[150].

The performance of TRUS as a screening tool was poor. The value of the additional biopsy core was limited since only 3.5% of the visible cancers were detected solely by the 7$^{th}$ biopsy core at first screening. However, a substantial part of these cancers were clinically relevant and would have been missed without the additional biopsy. This finding was less clear in subsequent screenings (round 2 and 3), even in men who were not previously biopsied. Therefore, only in men screened for prostate cancer for the first time, an extra lesion-directed biopsy core in addition to the lateralised sextant biopsy is advisable.

## FURTHER RESEARCH

Whether screening for prostate cancer has a beneficial effect on prostate cancer mortality will become clear after the completion of the ERSPC and PLCO. At that time the effect of having a suspicious DRE on prostate cancer-specific mortality will become clear as well. And the question if it was indeed beneficial to omit DRE as a screening test for prostate cancer will be answered definitively.

The genuine performance of DRE at low PSA levels can only be evaluated if all men in this PSA range are biopsied as was done in the control arm of the Prostate Cancer Prevention Trial[91]. With the current use of low PSA cut-offs there is a considerable amount of overdiagnosis and many unnecessary biopsies are performed. As there are indications that DRE can detect significant cancers selectively, the potential usefulness of DRE should be further established. Currently, the PCA3 urine test is being evaluated within the ERSPC Rotterdam screening arm as an indicator for prostate biopsy, independent of the PSA value. Until now, 85% of the entire study group that underwent the PSA and PCA3 test had a biopsy indication, including a large number of men with a PSA<3.0 ng/ml. In the near future enough data will be available to investigate the selectivity of DRE for significant disease at very low PSA levels in the ERSPC Rotterdam.

Another interesting question can be answered with the completion of the PCA3 analysis. As explained in **chapter 4**, prostate cancer prevalence at PSA levels beneath 4.0 ng/ml is lower in the ERSPC compared to the PCPT[14, 16, 55, 91, 138]. However, within our study cohort not every participant was biopsied and the results were partially extrapolated. With the completion of the PCA3 analysis an improved comparison between ERSPC and PCPT will become possible for the prevalence of prostate cancer at low PSA levels and their tumour characteristics.



The development of more selective screening procedures in order to lower the number of unnecessary biopsies and overdiagnosis has high priority. Targets of future research are promising molecular markers that selectively detect high-grade disease. But also the development of risk calculators[65, 66], in which DRE can be incorporated, to predict the chance on significant prostate cancer is being investigated. By using a risk calculator, the biopsy indication will be defined by a certain chance threshold for having prostate cancer.

If population-based screening for prostate cancer will proof to decrease the number of men that die from prostate cancer, the optimal screening algorithm has to be formulated. Next to the decision to omit DRE as a screening test, optimal values for the lower and upper age limit, the PSA threshold and the screening interval[152, 174] have to be defined. Alternatively, a risk calculator[65, 66] to determine the risk of prostate cancer in an individual can be used. Passing a certain risk threshold indicates a prostate biopsy (see www.uroweb.org for the developing risk calculator based on ERSPC data).

## CONCLUSIONS

From the results combined in this thesis, the following conclusions can be drawn and practical implications can be given:

- Omitting DRE as a screening test in men with low PSA levels did not lead to missing a relevant number of cancers. PSA-based screening with a 3.0 ng/ml cut-off remains adequate.
- Choosing a cut-off for PSA-based screening is arbitrary. However, the balance between numbers of participants needed to be biopsied to detect one cancer is very unfavourable at PSA levels between 2.0 and 3.0 ng/ml. Therefore, a PSA threshold of 2.0 ng/ml is not advisable without additional modifications.
- At first screening, men with a suspicious DRE are at higher risk of being diagnosed with prostate cancer compared to men with a normal DRE.
- The additional predictive value of a suspicious DRE for the detection of prostate cancer in men with an elevated PSA is lost in previously biopsied men.
- At PSA levels above the cut-off value for prostate biopsy, an abnormal DRE increases the chance to detect high-grade disease in men undergoing their first or repeat biopsy.
- Used as a screening test at low PSA levels DRE however missed a considerable number of significant cases, which is unacceptable in a screening situation. Therefore, the use of DRE will be predominantly in the setting of risk-calculators, algorithms that calculate individual risks of prostate cancer or particularly high-grade disease.
- The number of men actively asking for prostate cancer screening increases. Consequently, the proportion of men with a benign biopsy result and a continuous biopsy indication is growing. Biopsy can generally be postponed to a later screening without an important chance of missing a significant prostate cancer in men with a previous benign biopsy, an elevated PSA and a normal DRE.
- In contrast, the initial DRE result in men with a negative biopsy and an elevated PSA at first screening is not predictive for diagnosing prostate cancer at subsequent screens.
- In case of an initially suspicious DRE result there is no need to shorten the screening interval of 4 years.
- DRE is a subjective test.
- This thesis evaluated the DRE as a screening test, and it was shown that an abnormal DRE at low PSA levels led in only 10% to the diagnosis of prostate cancer in a screening setting. However, the unquestionable value of DRE in individual patients in urological daily practice is not considered. Every urologist has to keep in mind the exceptional patient who presents with a very low PSA value and locally advanced cancer.

Finally, the question that is posed in the title of this thesis should be answered: is DRE outdated or still a valuable test? The answer to this question is two-sided.

As a screening test to indicate a prostate biopsy the DRE is outdated. It has been proven that DRE has a low PPV at low PSA levels. The trend has been to lower the cut-offs in PSA-based screening which reduced the domain of DRE to lower PSA ranges and consequently

resulted in even lower PPVs. Furthermore, the number of previously biopsied men is increasing, in whom the value of DRE is less clear.

However, DRE is still valuable on a more individual basis when incorporated into algorithms that function as calculators for the risk of finding prostate cancer at biopsy or the risk of harbouring significant disease. Instead of performing a biopsy for an elevated PSA level or suspicious DRE outcome alone, a risk threshold would form the indication, calculated by using several clinical and laboratory variables. For this reason DRE should still be carried out in population-based screening programs, but not as a sole indicator of prostate biopsy.

Importantly, we need to await the final conclusions of the ERSPC to evaluate the value of DRE in the light of prostate cancer specific mortality.

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# Summary

The *first part* of this thesis includes in short the history of the European Randomized Study of Screening for Prostate Cancer (ERSPC, **chapter 1**) and an introduction (**chapter 2**) in prostate cancer screening in general. The prostate-specific antigen (PSA), corner stone in prostate cancer screening, is addressed and its limitations are evaluated. Several suggestions for improving screening procedures are mentioned and the potential role of the digital rectal examination (DRE) for this purpose is suggested. The scope of this thesis (**chapter 3**) entails the role of DRE in screening for prostate cancer. It aims to evaluate whether the omission of the DRE in 1997 in the ERSPC Rotterdam is still justified considering the available data from several screenings. Another focus of this thesis is to investigate if DRE is valuable in predicting prostate cancer and, in particular, significant prostate cancer in men who are biopsied for an elevated PSA level.

The *second part* of this thesis deals with prostate cancer screening at low PSA levels and the types of cancers that are found in this range. It has been suggested that many prostate cancers found at PSA levels ≤4.0 ng/ml resemble autopsy cancers and are potentially indolent or insignificant cancers. In **chapter 4** the prevalence and tumour characteristics of prostate cancers detected in this low PSA range are evaluated by comparing screening studies, cystoprostatectomy series and autopsy data. The favourable characteristics of tumours detectable at very low PSA levels seem to justify the conclusion that an unknown but sizeable proportion of the cancers found at biopsy are clinically insignificant.

Until May 1997 participants were offered prostate biopsy in case of a PSA value above 4.0 ng/ml and/or an abnormal result on DRE and/or transrectal ultrasound (TRUS). Later, the screening protocol was changed and a PSA level of 3.0 ng/ml or higher became the only indication for biopsy (PSA-based screening).

The omission of the DRE as a screening tool is evaluated in the *third part* of this thesis. The risk of omitting DRE and TRUS, and therefore the omission of biopsies at PSA<3.0 ng/ml, is that potentially aggressive tumours at these low PSA levels remain undetected at screening. These can surface as interval cancers, i.e. prostate cancers detected between two screening rounds, or as tumours with PSA levels progressed to values above 3.0 ng/ml with possibly unfavourable prognostic factors at a subsequent screening.

**Chapter 5** compares the prevalence and prognostic factors of tumours found in the second screening round of the ERSPC Rotterdam between two groups of men who had initially been screened either with DRE and TRUS (group-1) or without these tests (group-2).

Group-1 consisted of 5,957 men and in group-2 8,044 men were included, all participants had an initial PSA value ≤3.0 ng/ml. There was no significant difference in second round can-

cer detection rates, positive predictive values, number of poorly differentiated tumours, and number of interval cancers detected.

It can be concluded that omitting DRE and TRUS did not result in an increased interval cancer rate or prostate cancer detection and seems therefore justified based on these 4 years of follow-up.

**Chapter 6:** comparison of the cancer detection rates (CDRs) and tumour characteristics of screen-detected prostate cancers either by DRE or by PSA as biopsy indication at low PSA levels suggests that PSA-based screening should be preferred.

Two populations of men with PSA values between 2.0 and 3.9 ng/ml were studied. Group-1 (N=1,877) was biopsied if DRE was suspicious. In group-2 (N=801) all men were offered biopsy, regardless of DRE result.

In conclusion, PSA-based screening in the PSA range 2.0-3.0 ng/ml detected 15.2% of potentially aggressive (Gleason score (GS) ≥7) tumours as T1cs, but in addition large numbers of possibly insignificant cancers (T1c, GS=6) were diagnosed. DRE seemed to detect more selectively high-grade cancers (46.7% in contrast to 15.0% with PSA-based screening), but also missed many of these. Furthermore, PSA-based screening detected more organ-confined disease (96.6% versus 77.5% for DRE-based screening).

Considering both populations and the need to detect aggressive but confined disease, PSA as biopsy indication outperformed DRE at the price of more biopsies.



The *fourth part* of the thesis investigates the additional value of DRE in predicting prostate cancer and in particular potentially aggressive disease in men who are biopsied for an elevated PSA level. DRE is known to be a subjective test. When using DRE as a part of prostate cancer screening, it is essential to be informed about the interobserver variability of the test.

**Chapter 7** shows that men with an elevated PSA value and an abnormal DRE are at higher risk to harbour prostate cancer compared to men with similar PSA levels and a normal DRE. The additional value of a suspicious DRE for the detection of PC in men with an elevated PSA level in subsequent screenings and the tumour characteristics of PCs detected in men with a suspicious DRE were determined. A PSA value ≥3.0 ng/ml prompted a DRE and a TRUS-guided, lateralised sextant biopsy. In three screens, a total of 5,040 biopsy-sessions were evaluated and the positive predictive values (PPVs) of a suspicious DRE and normal DRE were compared.

The conclusion was drawn that at initial and subsequent screening, the chance of having cancer at biopsy was higher in men with a suspicious DRE compared to men with normal DRE (in subsequent screenings to a lesser extent) and the combination of a PSA≥3.0 ng/ml with a suspicious DRE resulted in detecting significantly more PCs with a Gleason score of 8 or higher. A suggestion for the use of DRE in previously biopsied men in subsequent screens may be that in case of a normal DRE, biopsy can be postponed to a subsequent visit, without

missing a substantial number of potentially aggressive PCs in order to reduce the number of unnecessary biopsies and overdiagnosis.

**Chapter 8** provides insight in the value of the initial DRE result for the prediction of (significant) prostate cancer at later screens. The goal was to investigate whether men with an initially suspicious DRE, a PSA≥3.0 ng/ml and a benign prostate biopsy are at higher risk of detecting (significant) PC at rescreening than men with an initially normal DRE (and elevated PSA and previous biopsy), and whether an adaptation of the rescreening interval is warranted for this group. Within the ERSPC Rotterdam 2,218 men were biopsied with benign result at initial screening. The serum PSA was 4-yearly determined and a PSA≥3.0 ng/ml prompted a DRE and lateralised sextant biopsy. The number and characteristics of PCs found at repeat screenings after 4 and 8 years, and as interval cancers were compared between men with or without a suspicious DRE result at initial screening. Multivariate-logistic-regression analyses were performed to evaluate if an initially suspicious DRE was a significant predictor for detecting cancer at consecutive screens. During the follow-up of 8 years after initial cancer-negative biopsy, an initially suspicious DRE did not influence the chance to detect cancer or significant cancer at later screens. An adaptation of the rescreening interval on the basis of the initial DRE outcome is not warranted in future population-based screening for prostate cancer.

Since DRE is a subjective test, the interobserver variability must be considered in determining its value as a screening test. In **chapter 9** is analysed to what extent the percentage of suspicious DRE findings varies between examiners and to what extent the percentage of prostate cancers detected in men with these suspicious findings varies between examiners. The variability in DRE outcome and in the risk of prostate cancer in case of an abnormal DRE was compared between 6 examiners during the initial screening of the ERSPC by descriptive statistics and multivariate logistic regression analyses. It was confirmed that DRE is a subjective test. Three of six examiners considered DRE significantly more often suspicious than the others. However, a suspicious DRE executed by each examiner increased the chance of the presence of PC similarly, when correcting for the other explanatory variables. It was found that DRE increases the odds to detect PC roughly 2.5 times independent of the biopsy indication used. This increased chance to find PC was not significantly observer-dependent and corroborates the fact that a suspicious DRE is an independent predictor for the presence of PC.

The *fifth part* of this thesis summarises and discusses the previous chapters. These studies are put into perspective and related to each other. Practical implications based on the conclusions of this thesis are given (**chapter 10**).

The DRE has been shown not to be useful as a screening test. It has been proven that DRE has a low positive predictive value (PPV) at low PSA levels. The trend has been to lower the cut-offs in PSA-based screening, which reduced the domain of DRE to lower PSA ranges and

consequently resulted in even lower PPVs. Furthermore, the number of previously biopsied men is increasing. In these men the value of DRE is even less clear.

However, DRE is still valuable on a more individual basis when incorporated into algorithms that function as calculators for the risk on prostate cancer or the risk of harbouring significant disease. Instead of performing a biopsy for an elevated PSA level or suspicious DRE outcome alone, a risk threshold would form the indication, calculated by using several clinical and laboratory variables. For this reason DRE should still be carried out in population-based screening programs, but not as a sole indicator of prostate biopsy.

Importantly, we need to await the final conclusions of the ERSPC to evaluate the value of DRE in the light of prostate cancer specific mortality.

# Samenvatting

In het *eerste deel* van dit proefschrift wordt kort de geschiedenis van de European Randomized Study of Screening for Prostate Cancer (ERSPC) besproken (**hoofdstuk 1**) en een introductie gegeven in de vroegopsporing van prostaatkanker in het algemeen (**hoofdstuk 2**). Het prostaatspecifiek antigeen (PSA) vormt de hoeksteen voor de vroegopsporing van prostaatkanker. De voor- en nadelen van het PSA worden belicht en suggesties gegeven voor verbetering van vroegopsporingsprogramma's, waarbij de potentiële rol van het rectaal toucher (DRE) aan de orde komt.

Doelstelling van dit proefschrift (**hoofdstuk 3**) is het onderzoek naar de rol van het DRE bij de vroegopsporing van prostaatkanker. In het bijzonder evalueert dit proefschrift het weglaten van het DRE als screeningstest, zoals dat sinds 1997 in de ERSPC Rotterdam gebeurt, aan de hand van de beschikbare data van een aantal opeenvolgende screeningsrondes. Verder richt dit proefschrift zich op het onderzoek naar de waarde van het DRE bij het voorspellen van de diagnose prostaatkanker en in het bijzonder het voorspellen van significante, potentieel levensbedreigende prostaatkanker bij mannen die gebiopteerd worden vanwege een verhoogde PSA-waarde.

Het *tweede deel* van dit proefschrift gaat over de vroegopsporing van prostaatkanker bij lage PSA-waarden en het type kankers dat daarbij ontdekt wordt. In de literatuur is gesuggereerd dat vele prostaatkankers bij mannen met lage PSA-waarden (≤4,0 ng/ml) overeenkomsten vertonen met de carcinomen in obductiestudies, die beschouwd kunnen worden als potentieel indolente of insignificante tumoren. In **hoofdstuk 4** worden de prevalentie en de tumorkarakteristieken onderzocht van prostaatkankers bij mannen met deze lage PSA-waarden. Hiertoe worden vroegopsporingsstudies, cystoprostatectomiestudies en obductiestudies vergeleken. De gunstige karakteristieken van de kankers bij zeer lage PSA-waarden lijken de conclusie te rechtvaardigen dat een aanzienlijk deel van de kankers die gedetecteerd worden door middel van prostaatbiopten klinisch insignificant zijn.

Tot mei 1997 werd de deelnemers van de ERSPC Rotterdam geadviseerd om prostaatbiopten te ondergaan, wanneer zij een PSA-waarde van 4,0 ng/ml of hoger hadden en/of wanneer er een afwijking werd gevonden bij DRE of bij transrectale echografie (TRUS) van de prostaat. Na die tijd werd het screeningsprotocol aangepast. DRE en TRUS werden weggelaten en een PSA-waarde van 3,0 ng/ml of hoger werd de enige reden om prostaatbiopten te ondergaan.

Het weglaten van het DRE als screeningstest wordt geëvalueerd in het *derde deel* van dit proefschrift. Het risico van het weglaten van DRE en TRUS uit het screeningsprotocol is dat onder een PSA van 3,0 ng/ml geen prostaatbiopten meer worden genomen en dat kan tot gevolg hebben dat potentieel agressieve tumoren bij deze lage PSA-waarden onopgemerkt

blijven. Deze maligniteiten kunnen op twee manieren toch nog aan het licht komen. De eerste mogelijkheid is dat deze tumoren worden ontdekt als intervalkankers, kankers die tussen twee screeningsbezoeken in aan het licht komen, meestal vanwege klinische verschijnselen. Ze kunnen daarnaast gediagnosticeerd worden bij een volgend screeningsbezoek vanwege een gestegen PSA-waarde (tot boven de afkapwaarde van 3,0 ng/ml) met inmiddels mogelijk ongunstige tumorkarakteristieken.

**Hoofdstuk 5** vergelijkt de prevalentie en de prognostische factoren van tumoren die zijn ontdekt tijdens de tweede screeningsronde van de ERSPC Rotterdam bij twee verschillende groepen mannen (allen met een eerste PSA-waarde <3.0 ng/ml). Groep 1 werd bij het eerste screeningsbezoek volgens het oude protocol door middel van het DRE onderzocht. Groep 2 werd zonder DRE gescreend. Groep 1 bestond uit 5.957 mannen en groep 2 uit 8.044 mannen. Er was geen significant verschil in de proportie gedetecteerde kankers, de positief voorspellende waarden (PPV), het aantal slecht gedifferentieerde tumoren en de proportie intervalkankers.

Het weglaten van het DRE en de TRUS resulteerde niet in een groter aantal intervalkankers of prostaatkankers ontdekt bij een later screeningsbezoek. Op basis van de resultaten van vier jaar na het eerste screeningsbezoek kan geconcludeerd worden dat het weglaten van het DRE gerechtvaardigd is.

**Hoofdstuk 6:** de vergelijking van kankerdetectie en tumorkarakteristieken van kankers opgespoord bij lage PSA-waarden suggereert dat vroegopsporing van prostaatkanker op basis van de PSA-test de voorkeur heeft boven het DRE als screeningstest.

Twee populaties met PSA-waarden van 2,0-3,9 ng/ml werden bestudeerd, van wie in groep 1 (N=1.877) mannen een biopt ondergingen in geval van een abnormaal DRE en groep 2 (N=801) waarin iedereen een biopt onderging (PSA-afkapwaarde 2,0 ng/ml). Screening met behulp van de PSA-waarde detecteerde in het PSA-gebied van 2,0-3,9 15,2% potentieel agressieve tumoren (Gleason score ≥7) in het T1c-stadium, maar daarbij werd ook een groot aantal mogelijk insignificante kankers ontdekt (T1c, Gleason score = 6). Het rectaal toucher leek selectiever de hooggradige kankers op te sporen (46,7% vergeleken met 15,0% in het geval van de PSA-afkapwaarde van 2,0), maar veel van dit soort tumoren bleef ook onopgemerkt. Bovendien werden door middel van de PSA-test meer tumoren gevonden die beperkt waren tot de prostaat (96.6% versus 77,5% bij de DRE-test).

Met het doel van vroegopsporing van agressieve nog te genezen kankers voor ogen, voldeed de PSA-afkapwaarde van 2,0 ng/ml als biopsie-indicatie beter dan het DRE. De prijs hiervoor was het nemen van meer biopten.

Het *vierde deel* van dit proefschrift onderzoekt de toegevoegde waarde van het DRE bij het voorspellen van het risico van prostaatkanker - in het bijzonder dat van potentieel agressieve tumoren bij mannen die worden gebiopteerd vanwege een verhoogde PSA-waarde. Het DRE staat bekend als subjectieve test. Wanneer DRE als onderdeel van de vroegopsporing van

prostaatkanker wordt gebruikt, is het van belang om informatie te geven over de verschillen tussen onderzoekers die de test uitvoeren.

**Hoofdstuk 7** laat zien dat mannen met een verhoogde PSA-waarde en een verdacht DRE een hoger risico hebben op het krijgen van prostaatkanker dan mannen met een vergelijkbaar PSA en een normaal DRE. De toegevoegde waarde van een verdacht DRE bij de betreffende groep mannen voor het opsporen van prostaatkanker in volgende screeningsrondes werd duidelijk, evenals de tumorkarakteristieken van de kankers die gevonden werden bij mannen met een verdacht DRE. Een PSA-waarde ≥3,0 ng/ml vormde de indicatie om een rectaal toucher en prostaatbiopten te ondergaan. Gedurende drie screeningsrondes werden 5.040 biopsieprocedures geëvolueerd en werden de PPV's van een verdacht en een normaal DRE bepaald. De conclusie was dat de kans op het hebben van prostaatkanker hoger is bij mannen met een verdacht DRE dan bij mannen met een normaal DRE in de eerste screeningsronde en, in mindere mate, in de rondes daarna. De combinatie van een verhoogd PSA (≥3,0 ng/ml) en een verdacht DRE resulteerde in de opsporing van significant meer prostaatkankers met een Gleason score van 8 of hoger. Op basis van deze resultaten is het mogelijk om met behulp van het DRE de screeningsprocedure aan te passen voor mannen met een verhoogd PSA en een eerdere goedaardige biopsie-uitslag. De reden om de screeningsprocedure aan te passen is het verminderen van het aantal onnodige biopsieprocedures en zogeheten overdiagnose. In het geval van een normaal DRE bij deze groep mannen kan een biopsie worden uitgesteld tot een volgende screeningsronde zonder het risico om een substantieel aantal potentieel agressieve kankers te missen.

**Hoofdstuk 8** geeft inzicht in de waarde van het DRE-resultaat tijdens het eerste screeningsbezoek voor het voorspellen van de diagnose (significante) prostaatkanker in latere screeningsrondes. Het doel was om te onderzoeken of mannen met een initieel verdacht DRE, een PSA≥3,0 ng/ml en een benigne biopsie-uitslag een hoger risico hebben op het vinden van een (significante) kanker in een volgende ronde en of om die reden de tijd tussen twee screeningsrondes aanpassing behoeft voor hen. Binnen de ERSPC Rotterdam werden 2.218 mannen gebiopteerd met een goedaardige uitslag in de eerste screeningsronde. De PSA-waarde werd elke vier jaar bepaald en een waarde ≥3,0 ng/ml vormde een biopsie-indicatie. Het aantal kankers, met hun karakteristieken, gevonden in volgende rondes (na vier en acht jaar) werd vergeleken tussen mannen met een verdacht en een normaal eerste DRE. Ook het aantal intervalkankers werd vergeleken. Met behulp van multivariate logistische regressieanalyses vond een evaluatie plaats over de vraag of een initieel verdacht DRE een significante voorspeller is voor het ontdekken van kanker bij latere screeningsronden.

Een initieel verdacht DRE bleek de kans op het detecteren van prostaatkanker of significante prostaatkanker bij latere rondes niet te beïnvloeden gedurende een follow-up van acht jaar na de eerste, goedaardige biopsieuitslag. De tijd tussen twee screeningsrondes behoeft om deze reden dan ook geen aanpassing vanwege een initieel verdachte uitslag van het DRE.

DRE is een subjectieve test. De variabiliteit tussen onderzoekers die een rectaal toucher uitvoeren, moet overwogen worden bij het bepalen van de waarde van het DRE als screeningstest. **Hoofdstuk 9** onderzoekt in welke mate de proportie verdacht afgegeven prostaten varieert tussen onderzoekers en hoeveel verschil er zit in de proportie prostaatkankers die ontdekt wordt, indien een onderzoeker het DRE als afwijkend beschouwt. De variabiliteit in DRE-resultaat en in het risico van prostaatkanker bij een verdacht resultaat werd bepaald voor zes onderzoekers tijdens de eerste ronde van de ERSPC Rotterdam met behulp van beschrijvende data en multivariate logistische regressie. Bevestigd werd dat DRE een subjectieve test is. Drie van de zes onderzoekers beschouwden het DRE significant vaker afwijkend. Een verdacht DRE verhoogde de kans op kanker echter op eenzelfde manier bij iedere onderzoeker, wanneer werd gecorrigeerd op overige factoren die van invloed zijn op de detectiekans van prostaatkanker. Het DRE verhoogde de odds om kanker op te sporen 2,5 keer, onafhankelijk van de gebruikte biopsie-indicatie. Deze verhoogde kans om prostaatkanker te vinden was niet significant afhankelijk van de onderzoeker die het DRE uitvoerde. Hiermee wordt het feit bevestigd dat een verdacht DRE een onafhankelijke voorspeller is voor de aanwezigheid van prostaatkanker.

Het *vijfde deel* van dit proefschrift vat voorgaande hoofdstukken samen. Deze onderzoeken worden in een breder perspectief bediscussieerd en aan elkaar gerelateerd. Praktische implicaties gebaseerd op de conclusies van het proefschrift komen aan de orde.



Het is aangetoond dat het gebruik van DRE als screeningstest niet nuttig is. Uit literatuur blijkt dat het DRE een lage PPV heeft bij lage PSA. De trend om de PSA-afkapwaarden te verlagen beperkt het domein van DRE tot nog lagere PSA-waarden met lagere PPV's. Bovendien groeit het aantal mannen die eerder gebiopteerd zijn. Bij hen is de waarde van het DRE zelfs nog onduidelijker.

DRE is echter wel waardevol op een meer individuele manier. Het DRE kan samen met andere klinische en laboratoriumvariabelen worden ingebouwd in algoritmes die de kans op prostaatkanker of significante prostaatkanker kunnen berekenen. In plaats van het uitvoeren van prostaatbiopten op indicatie van een PSA-afkapwaarde of een abnormaal DRE-resultaat vormt een bepaalde kans op kanker de reden om biopten te ondergaan. Hierom zou het DRE op deze manier moeten worden uitgevoerd in een bevolkingsonderzoek voor prostaatkanker.

Het is belangrijk om de uiteindelijke resultaten van de ERSPC af te wachten om definitief de waarde van het DRE te kunnen bepalen in het licht van prostaatkankerspecifieke mortaliteit.

# Curriculum vitae

Claartje Gosselaar wordt op 15 februari 1977 geboren te Delft. In 1996 behaalt zij cum laude haar Gymnasiumdiploma aan het Sint Stanislas College te Delft. Aansluitend start zij de studie Biomedische Wetenschappen aan de Universiteit Leiden en rondt deze in 2002 af bij het Centre for Human Drug Research (CHDR) te Leiden. In 1998 loot zij in voor de studie Geneeskunde aan de Universiteit Leiden. In 2004 behaalt zij cum laude haar artsdiploma.

Tijdens haar studententijd werkt Claartje bij Stichting Bio Implant Services (BIS) in het explantatieteam voor postmortale hoornvlies- en hartklepdonaties. Haar eerste 'echte' baan begint met haar promotieonderzoek bij het screeningsbureau voor prostaatkanker van de afdeling Urologie van het Erasmus MC, waar dit proefschrift het resultaat van is.

In 2005 krijgt zij samen met Jorrit Jansen hun dochter Wies en in 2007 volgt zoon Pelle.

Vanaf 1 maart 2008 is Claartje in opleiding tot huisarts bij het LUMC te Leiden. Op dit moment werkt zij in huisartspraktijk Vroom te Waddinxveen in het kader van haar eerste opleidingsjaar.

# Dankwoord

Een promotie is iets onwerkelijks totdat het boekje daadwerkelijk voor je ligt. En dan nog voelt het surreëel. Op de weg ernaartoe heb ik met plezier onderzoek gedaan, maar ben ik ook de nodige hobbels tegengekomen. Gelukkig heb ik het doel bereikt en rest mij alleen nog iedereen te bedanken die mij heeft geholpen dit proefschrift tot stand te brengen.

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Stijn, jij bent het langst mijn kamermaatje geweest. We hebben samen heel wat 'hoge toppen en diepe dalen' (citaat dr. Roemeling) van het wetenschappelijk onderzoek beleefd. Gelukkig was het in ieder geval gezellig en waren we meestal vol goede moed. Dank!

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Plien, we begonnen onze studie en carrière samen in Leiden, waar jij me wegwijs maakte bij Biomedische Wetenschappen (welke microscoop heb je eigenlijk nodig?). Naast een hele lieve vriendin ben je mijn sportmaatje en volgen we nu beiden de opleiding waar we erg gelukkig van worden: de opleiding tot huisarts! Dankjewel dat je me bij wilt staan bij de verdediging van mijn proefschrift.

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er erg trots op dat ik dit boekje geschreven heb in deze drukke periode van ons leven. Het valt echter compleet in het niet bij de komst van Wies en Pelle die geboren zijn in dezelfde periode. Ze zijn onze liefste schatten en bronnetjes van intens geluk. Ik ben erg gelukkig met, en door jullie.

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Claartje Gosselaar, 2008

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