XIAOYE ZHU

SCREENING for PROSTATE CANCER

effect on mortality and risk-based screening strategy

Screening for Prostate cancer

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Xiaoye Zhu

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We build too many walls and not enough bridges.

Isaac Newton

Voor mijn ouders

Contents

General introduction

Chapter 1

Prostate cancer

Chapter 2

Screening for prostate cancer: have we resolved the controversy?

Chapter 3

Scope and outline of the thesis

1 Prostate cancer

PROSTATE

The prostate is located between the bladder and the penis (Figure 1). The prostate is just in front of the rectum. The urethra runs through the center of the prostate, from the bladder to the penis, letting urine flow out of the body.

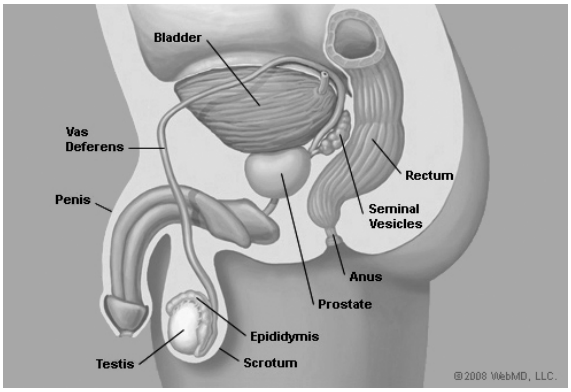

Figure 1: Male reproductive and urinary system. Adapted from http://men.webmd.com/picture-of-the-prostate.

The prostate secretes fluid that nourishes and protects sperm. During ejaculation, the prostate squeezes this fluid into the urethra, and it is expelled with sperm as semen. In younger men the prostate is about the size of a walnut, however, the prostate usually enlarges with age. The mean weight of the "normal" prostate in adult males is about 11 grams, usually ranging between 7 and 16 grams [1].

PROSTATE SPECIFIC ANTIGEN (PSA)

PSA is a glycoprotein produced by prostate epithelial cells. PSA levels may be elevated in men with prostate cancer because PSA production is increased and because tissue barriers between the prostate gland lumen and the capillary are disrupted, releasing more PSA into the serum. Studies have estimated that PSA elevations can precede clinical disease by 5 to 10 years [2-3].

However, PSA is also elevated in a number of benign conditions, particularly benign prostatic hyperplasia and prostatitis. In addition, there are transient causes of PSA elevation, some of which are significant enough to affect the performance of PSA as a screening test. For example, prostate biopsy may elevate PSA levels by a median of 7.9 ng/mL within 4 to 24 hours following the procedure [4]. Baseline levels are expected after two to four weeks. Similarly, a transurethral resection of the prostate (TURP) can elevate PSA levels by a median of 5.9 ng/mL [4]. Levels will remain elevated for a median

time of approximately three weeks. A screening PSA test should not be performed for at least six weeks following either of these procedures. Digital rectal examination (DRE) has minimal effect on PSA levels, leading to a median elevation of only 0.4 ng/mL [5]. Ejaculation can increase PSA levels by up to 0.8 ng/mL, though normalization usually occurs within 48 hours [4,6].

The 5-alpha reductase inhibitors (5-ARIs) finasteride and dutasteride lower PSA levels. Finasteride reduces PSA by approximately 50% within six months of use, though the effects can vary widely, ranging from –81% to +20% [7]; dutasteride has been reported to lower PSA levels 48 to 57% [8]. Some experts recommend doubling the measured PSA value before interpreting the result for men on finasteride [9]. Results from the Prostate Cancer Prevention Trial (PCPT) suggest that PSA values be corrected by a factor of 2 for the first two years of finasteride therapy, and by 2.5 for longer-term use [10].

Test performance

Determining the accuracy of PSA testing has been difficult because most men with "normal" PSA values will not undergo biopsy unless their DRE is abnormal. This work-up bias tends to overestimate sensitivity and underestimate specificity [11].

Another problem in assessing the accuracy of PSA is that the transrectal needle biopsy is not a perfect gold standard. Investigators have suggested that the false-negative rate of sextant prostate biopsy is about 20% [12], though the recent trend towards obtaining 12 samples has increased the detection rate [13].

Additionally, protocols that use large numbers of biopsies to evaluate men with an elevated PSA may be detecting incidental cancers that were not the reason of the PSA elevation. One review assumed that nonpalpable cancers smaller than 1.0 cm^3 would not cause elevated PSA levels, and estimated that approximately 25% of cancers detected by PSA screening were too small to have accounted for the PSA elevation that prompted a biopsy [14].

The diagnostic performance of PSA ideally needs to be calibrated against clinically significant cancers. However, there is no consensus on defining such cancers. Although some experts consider tumors with Gleason scores ≥7 to have a greater risk for progression, there is no certainty that these cancers will lead to early death or reduce quality of life.

PROSTATE CANCER

The oldest known case of prostate cancer was diagnosed in a 2700 year old skeleton of a Scythian king, aged 40 to 50 at the time of death, found in the steppe of Southern Siberia, Russia [15]. Although it is unsure whether the advanced case of prostate cancer

caused the king's death, the skeleton showed that the cancer had metastasized. It may seem odd that so few examples of prostate cancers have been discovered in the historical record. However, prostate cancer rarely strikes men in their 40s, but usually in older men. The fact that life expectancies in the past were so much lower than today may account for the relative rarity in ancient times. It is entirely possible that men simply did not live long enough for symptoms to develop.

In 2008, a total of 903000 new cases of prostate cancer and 258000 prostate cancer deaths are estimated worldwide, making it the second most commonly diagnosed cancer in men and the sixth leading cause of male cancer death [16]. In the United States, the lifetime risk of developing prostate cancer is 16%, but the risk of dying of prostate cancer is only 2.9% [17]. Corresponding numbers in Western Europe are approximately

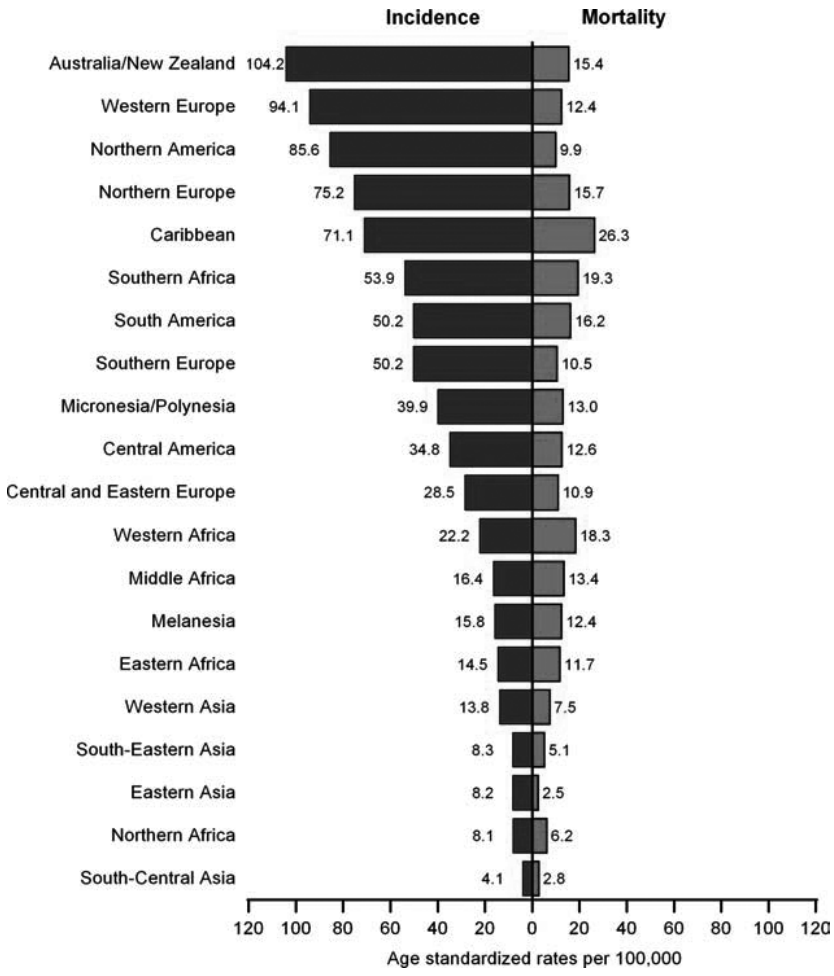

Figure 2: Age-standardized rates of prostate cancer incidence and mortality. Obtained from [16].

9 and 3%, respectively [18,19]. Wide variation exists internationally for the incidence and mortality of prostate cancer (Figure 2). Estimated incidence rates remain most elevated in the highest resource regions worldwide including North America, Oceania, and western and northern Europe. Mortality rates tend to be higher in less developed regions of the world including parts of South America, the Caribbean, and sub-Saharan Africa [18,19].

Clinical presentation

Most men with early stage prostate cancer have no symptoms attributable to the cancer. Urinary frequency, urgency, nocturia, and hesitancy are seen commonly but are usually related to a concomitant benign prostate enlargement. Hematuria and hematospermia are uncommon presentations of prostate cancer but their presence in older men should prompt consideration of prostate cancer in the differential diagnosis. Bone pain may be the presenting symptom in men with metastatic disease but an initial diagnosis because of bone metastases has become unusual [20].

Diagnosis

The digital rectal examination and the PSA assay are two important tests to detect changes in the prostate gland. Most men currently diagnosed with prostate cancer undergo a biopsy because of a suspicious PSA level. However, digital rectal examination retains an important role for detection as some cases have a prostate nodule that prompts the biopsy.

On digital rectal examination, asymmetric areas of induration or frank nodules are suggestive of prostate cancer. In contrast, symmetric enlargement and firmness of the prostate are more frequent in men with benign prostatic hyperplasia. Digital rectal examination can detect tumors in the posterior and lateral aspects of the prostate gland. Tumors not detected by digital rectal examination include the 25 to 35% that occur in other parts of the gland, and small cancers that are not palpable.

PSA testing has revolutionized prostate cancer screening and led to a dramatic increase in the incidence of prostate cancer. Although PSA was originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment, it became widely adopted for cancer screening by the early 1990s. Subsequently, several professional associations issued guidelines supporting prostate cancer screening with PSA [21].

When the digital rectal examination or the PSA test is deemed suspicious, prostate biopsy is indicated. Typically, it is performed with transrectal ultrasound guidance although perineal biopsy and MRI targeted biopsies are sometimes used. Transrectal ultrasound may image prostate cancer as a hypoechoic area but the test is used to direct prostate biopsy rather than as a diagnostic modality.

Staging

The extent of the disease is classified according to the Tumor, Node, Metastasis (TNM) classification (Table 1). The stage of the disease is predictive for the prognosis [17]. Also, it is important in selecting the appropriate treatment. The local stage of the tumor is generally based on digital rectal examination and/or transrectal ultrasound, known as the clinical stage. Multiparametric MRI has emerged as a promising method for staging purposes, although the use of an endorectal coil may be preferable [22]. The pathological stage, i.e. the definitive stage, can only be obtained after a radical prostatectomy.

Grading

Tumor grade describes the degree of the cellular differentiation as assessed by light microscopy. Prostate cancer is graded using the Gleason score. This system gives a grade of differentiation ranging from 1 to 5, where grade 1 is very well differentiated and 5 is poorly differentiated or anaplastic (Figure 3). The Gleason score is the sum of the primary Gleason grade (the most common pattern) and the secondary grade, which is the next most common pattern (but which should comprise of greater than 5% of the total tumor tissue). In cases where only one pattern is identified, the primary grade is doubled, e.g. 3+3 = 6. The Gleason score therefore ranges from 2 to 10.

The system was updated in 2005, under the auspices of the International Society of Urological Pathology. The consensus was that Gleason score 2–4 should rarely if ever be

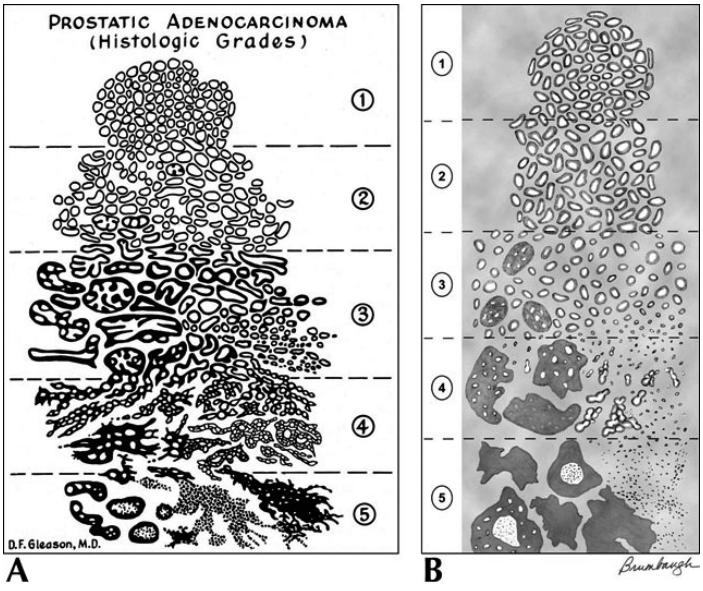

Figure 3: Schematic representations of (A) conventional and (B) modified Gleason grading systems. The most important changes between them are in patterns 3 and 4. In the modified system, most cribriform patterns and also poorly defined glands are included in pattern 4. Adapted from [23].

Table 1. Tumor, Node, Metastasis (TNM) stage definitions for prostate cancer (2009 edition)

Primary tumor (T)	
Clinical (cT)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5 percent or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5 percent of tissue resected
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule•
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic (pT)Δ	
pT2	Organ confined
pT2a	Unilateral, one-half of one side or less
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck◊
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and/or pelvic wall
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Pathologic	
pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)
Distant metastasis (M)§	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. • Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2. Δ There is no pathologic T1 classification. ◊ Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease). § When more than one site of metastasis is present, the most advanced category (pM1c) is used.

diagnosed on needle biopsy. Furthermore, certain patterns originally considered Gleason pattern 3 should be classified as Gleason pattern 4 and all cribriform cancer should be graded pattern 4 [23]. These artificial changes have resulted in disease upgrading. Comparing the original and modified Gleason system on needle biopsy material, Gleason 6 cancers decreased from 48.4% to 22% of the total, whereas Gleason 7 increased from 25.5% to 67.9% [24].

Consequently, it is difficult to compare prostate cancer data from different time periods because survival rates seem to improve due to this upgrading. Cancers with Gleason score 6 from the early 90s might be assigned with Gleason score 7 or higher nowadays. This reclassification towards higher grading resulted in apparent improvement in survival, which has been referred to as the Will Rogers phenomenon [25].

Treatment

Different types of treatment are available for patients with prostate cancer, depending on PSA, tumor characteristics, age, comorbidity, and patient preferences. Standard treatments for clinically localized prostate cancer (<=cT2) include radical prostatectomy, radiation therapy, or active surveillance. Radical prostatectomy involves removal of the prostate and seminal vesicles. It can be performed using either an open or laparoscopic technique. The laparoscopic technique can be performed with robotic assistance. The perceived advantage of radical prostatectomy is that there is no better way to cure a cancer that is completely confined to the prostate than total surgical removal. Patients opting for surgery should be referred to surgeons with considerable experience in order to optimize the likelihood of effective cancer control and to minimize the likelihood of complications [26].

Radiation therapy is another option for the treatment of localized prostate cancer. The goal of radiation therapy is to deliver a therapeutic dose of radiation to the tumor while minimizing radiation to normal tissues. Currently, radiation therapy is most commonly delivered by means of conformal, externally applied techniques. Prospective studies have shown that higher doses of radiation can be delivered safely with the use of conformal techniques, with better cancer control than is achieved with the use of nonconformal techniques. The advantages of radiation therapy are that it is noninvasive or minimally invasive and it is less likely than radical prostatectomy to cause certain complications such as severe urinary incontinence.

There are no data from well-controlled, randomized trials comparing the treatment outcomes of radiation therapy and surgery. Nonetheless, observational data suggest that the long-term disease control achieved with contemporary radiation therapy is similar to that achieved with radical prostatectomy [27].

For locally advanced prostate cancer, radiation therapy along with androgen ablation is generally recommended, although radical prostatectomy may be appropriate as an

alternative to radiation therapy in some cases. Metastasized prostate cancer cannot be cured and will in time always lead to death unless death from other causes comes first. Temporary suppression of the disease is possible using different types of hormonal therapy; chemotherapy is an option in the terminal phase of the disease [28].

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2 Screening for prostate cancer: have we resolved the controversy?

Curr Opin Support Palliat Care 2010

Xiaoye Zhu, Monique J. Roobol, Fritz H. Schröder

ABSTRACT

Prostate cancer (PCa) screening has long been a source of controversy. In this review, we discuss the interim results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Implications of these studies will also be underlined.

RECENT FINDINGS

With systematic prostate-specific antigen-based screening, the ERSPC reported a statistically significant PCa-specific mortality reduction of 20% favoring screening in the intention-to-treat analysis and 31% in the secondary analysis. In contrast, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed no mortality reduction. On the basis of critical appraisal of the study design and methods, it is justified to rely on the results of the ERSPC, as the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial is rather a comparison between a screening group and a less screened group.

SUMMARY

Despite the effects demonstrated by the ERSPC, there is currently insufficient evidence to introduce a population-based screening program. The studies evaluating quality of life and cost-efficiency need to be completed with the highest urgency and their results should be considered together with more mature data from the ERSPC to reach an effective implementation of screening on PCa. Meanwhile, we have to improve the screening test, screening protocol and further develop an accurate individualized risk assessment to decrease the rates of overdiagnosis and overtreatment, while the mortality reduction and the detection of clinically relevant PCa should be maintained.

INTRODUCTION

Screening of prostate cancer (PCa) using prostate-specific antigen (PSA) is one of the most controversial subjects in urology, if not in all of medicine. PCa is the second most common male cancer worldwide and the most frequently occurring in Europe [1]. Current lifetime risk of a PCa diagnosis and dying from PCa is about 16 and 3%, respectively, in the USA [2].

Although PCa is not rare, it has a variable natural history, ranging from indolent to strikingly aggressive with a long preclinical phase. As we are still awaiting a breakthrough in the treatment of advanced disease, earlier diagnosis of clinically significant disease currently seems to afford the best opportunity of 'stemming the tide'. For PCa screening, our aim is to detect early cases of invasive cancer and thus decrease the PCa mortality [3].

Current PCa screening is PSA based. PSA is produced almost exclusively by prostate epithelial cells [4]. However, PSA levels can be raised not only in PCa, but also in non-malignant conditions such as benign prostatic hyperplasia, infection, or chronic inflammation [5,6]. Its value as possible tumor marker is first described in 1979 by Wang et al. [7]. Since the approval of PSA tests in 1986 by the US Food and Drug Administration, it has been widely used for the early detection of PCa [8,9]. In 1984, 5.1% of all newly diagnosed PCa were detected by PSA testing. By 1990, this percentage has already increased to 60.6% of the PCa diagnosed in the USA [10].

With the widespread use of PSA testing, a decline of 30% in the US PCa mortality rate was observed during the 1990s. The correlation between PSA screening and the observed mortality reduction was however unclear. On the basis of mathematical modeling, Etzioni et al. [11] reported that 45- 70% of the observed decline in PCa mortality could be plausibly attributed to the stage shift induced by screening.

Moreover, several ecological studies [12-15] have provided some information about the mortality effect of screening with conflicting results. Opponents of screening point to the fact that there was also a decrease of PCa mortality in countries where screening is not prevalent [16]. The true effect of screening regarding PCa mortality can therefore only be observed in a randomized controlled trial (RCT). Hence, the results of the two large scale RCTs, the European Randomized Study of Screening for Prostate Cancer (ERSPC) [17] and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [18], had been awaited with great anticipation.

Surprisingly, the effects of these two studies are contradictory [19*,20*]. The following key question is: does screening reduce PCa mortality? To answer this question we first have to reconcile the apparent discrepancy between the two RCTs.

PROSTATE, LUNG, COLORECTAL AND OVARIAN CANCER SCREENING TRIAL

The characteristics of both the PLCO trial and the ERSPC study are listed in Table 1. PCa-specific mortality was the primary endpoint in both studies. In the PLCO trial, 76,693 men, age 55-74 years, were randomized to either screening or control group at 10 centers within the US from 1993 to 2001. Men in the screening group were offered annual PSA testing for 6 years and DRE for 4 years. Those who had a PSA ≥ 4.0 ng/mL or suspicious findings on the DRE were considered screen positive and where advised to seek diagnostic evaluation. Men and their primary physicians decided further evaluation.

At a follow-up of 7 years with 98% of the data available, the PLCO trial reported no mortality benefit from combined screening with PSA testing and DRE. The data at 10 years were 67% complete and consistent with the overall findings (Fig. 1).

However, approximately 44% of the men in each study arm had undergone one or more PSA tests before randomization. This high rate of pre-screening can obscure ben-

Table 1. Characteristics and results of the PLCO trial and the ERSPC study [19-22]

	PLCO	ERSPC
Methods		
Participants	55-74 years, n=76,693	Core group 55-69 years, n=162,387
Screening test (cut-off)	PSA (≥4.0 ng/ml), DRE	PSA (≥3.0 ng/ml)
Screening interval (percentage participants)	1 year	4 years (87%), 2 years (13%)
Primary endpoint	PCa-specific mortality	PCa-specific mortality
Mean follow-up (years)	7	9
Results		
Contamination	40-52% for PSA	20-31% for PSA
Compliance	85% for PSA en 86% for DRE, <50% for biopsy	82% for PSA, 86% for biopsy
PCa (cumulative incidence)		
Screening	2820 (7.4%)	5990 (8.2%)
Control	2322 (6.1%)	4307 (4.8%)
PCa-specific death (per 10,000 person-years)		
Screening	92 (2.0)	214 (3.3)
Control	82 (1.7)	326 (4.3)
PCa-specific mortality	No risk reduction	*Intention-to-screen analysis:* 20% relative risk reduction (p=0.04) NNS: 1410; NNT: 48 *Secondary analysis:* 31% relative risk reduction (p=0.01)

PSA=prostate-specific antigen; DRE=digital rectal examination; TRUS=transrectal ultrasound; NNS=number needed to screen; NNT=number needed to treat; PCa=prostate cancer

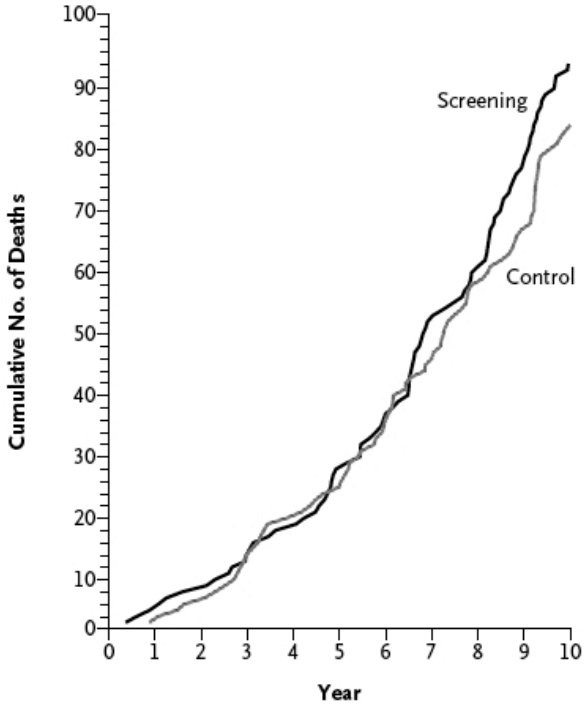


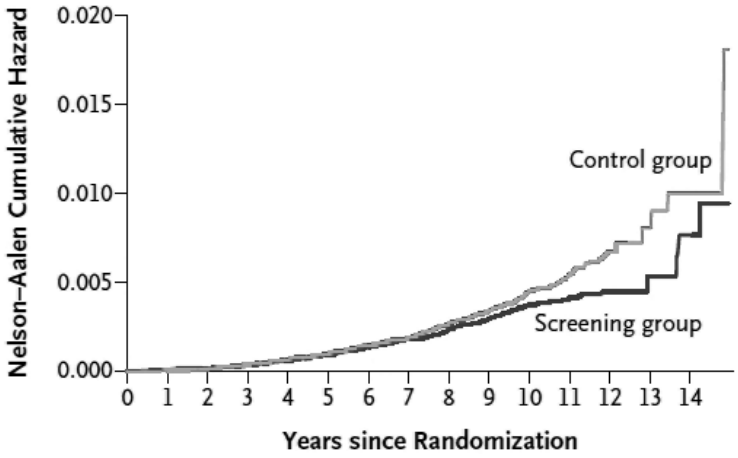
Figure 1: Cumulative number of PCa specific death within the PLCO trial (*previously published by Andriole et al.* [20]. Copyright © 2009 Massachusetts Medical Society. All rights reserved.)

efit from screening. In addition, the rate of PSA testing in the control group was 40% in the first year and increased to 52% in the sixth year. The rate of screening by DRE in the control group ranged from 41 to 46%. Furthermore, despite a high compliance rate in the screening arm for PSA (85%) and DRE (86%), less than 50% of those who had a biopsy indication were actually biopsied [21].

Although no significant PCa mortality reduction was noted, after combining the two arms, the authors observed a 25% lower cumulative PCa death rate at 10 year in those who had undergone previous testing at baseline compared with men who had not been tested [20*]. This suggests beneficial effect on PCa mortality by screening.

EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER

The ERSPC study was conducted in eight European countries and also started in 1993. The ERSPC included 162,243 men aged 55-69 years and used a PSA cutoff of 3.0 ng/mL. A screening interval of 4 years was applied. For the third planned interim analysis, the data of France were not included because of the short duration of follow- up, as their participation initiated only in 2001. This was agreed at time of inclusion of France within ERSPC.



No. at Risk			
Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Figure 2: Cumulative risk of PCa specific death within the ERSPC study (*previously published by Schröder et al.* [19]. Copyright © 2009 Massachusetts Medical Society. All rights reserved.)

The intention-to-screen (ITS) analysis showed significant relative reduction of 20% in PCa mortality in favor of screening at a median follow-up of 9 years [19*]. As an ITS analysis reflects the effect in the screening population and not for the individual, a secondary analysis adjusted for noncompliance and contamination was performed, which revealed a relative risk (RR) reduction 31% in favor of screening [22]. The trend seen in the mortality curves suggests larger effects with longer follow-up (Fig. 2).

Compliance and contamination rates are lower in ERSPC. The compliance rate was 82% for PSA testing, comparable to the PLCO trial. However, the compliance rate in the ERSPC with biopsy recommendation was 86% and thus much higher than in PLCO. This significant difference is very likely to have contributed to the different outcomes of the trials [23]. The level of contamination in the control group was estimated in the order of 20-31% [22,24].

Some point out the possible heterogeneity with the ERSPC, since the study is conducted in 8 different centers. However, stratification per center revealed that all centers showed a reduction in PCa mortality in the screening arm, ranging from 16-26%. Moreover, several committees, such as a cause of death committee and a data and safety monitoring committee were summoned to ensure the quality of the data.

Secondary endpoints studied within the ERSPC include metastatic disease. This is clinically relevant and more powerful in detecting important effects, because events occur earlier than PCa death [25]. Kerkhof et al. [26*] demonstrated very recently, based on data from the Rotterdam section of ERSPC, that screening significantly reduces the occurrence of metastatic PCa. The ITS analysis showed a relative risk reduction of 25%

in favor of screening (p=0.02). In the secondary analysis, the reduction improved to 32% (p=0.02) [26*].

IMPLICATIONS AND IMPROVEMENTS

As we suggested above, the PLCO trial is a comparison between two screening strategies with rather similar intensity and can therefore not answer the question whether active screening as compared to no screening has an effect on PCa mortality. We shall now focus on the implications of the ERSPC results and future perspectives.

The ERSPC provides the first convincing proof that screening can reduce PCa mortality. The reduction in mortality is comparable to that observed in screening programs for other cancer types such as breast cancer and colorectal cancer [27,28], but the risk of overdiagnosis and the number needed to treat is much greater. Inherent to screening is however the detection of slower-growing cancers, because more aggressive tumors have a greater likelihood of becoming clinically apparent between screenings. Therefore, a certain degree of overdiagnosis is inevitable. In the ERSPC, 1410 men had to be screened and 48 additional men had to have curative treatment in order to save one man's life in excess of the control group mortality. Increased PCa incidence by 70% has been reported. This percentage of men diagnosed with PCa in excess to men diagnosed in the absence of screening is likely to decrease after longer follow-up to about 50% [29].

Given the beneficial effect demonstrated by the ERSPC, it is likely that more men will choose to have a PSA test. How can we manage this increasing demand with respect to overdiagnosis and overtreatment?

It is necessary to find ways to detect only those cancers that actually need treatment in order to reduce the *number needed to treat*. A first step toward this goal is avoiding potentially unnecessary biopsies. Another concern is that a considerable percentage of screen-detected cancers is indolent and probably does not need to be detected at all or can still be detected later in a curable stage [29-31].

This situation has led to the development of the Risk Calculator, a stepwise prediction tool available in Dutch, English and Russian on the website of the European Association of Urology (http://www.uroweb.org/) or through http://www.prostate-riskcalculator.com. With the selective approach of the Risk Calculator, the reduction of biopsy and the identification of potentially indolent PCa are combined [32,33]. The use of the Risk Calculator has been recently evaluated. The authors demonstrated that through adding available prebiopsy information (prostate volume, outcomes of DRE and transrectal ultrasound) to the PSA level and also considering previous screening visits, a considerable reduction of unnecessary biopsies can be achieved [34*]. Applying such a risk-based strategy to the Dutch screening population decreases the number of prostate biopsies

with 33%. This reduction coincides with missing 14% of the PCa cases that was detected with the purely PSA-based biopsy indication. The large majority of missed cases were potentially indolent PCa and their proportion increased with repeat screening. In addition, only one man was lost to PCa death. Given the long lead-time [29] of PCa, it seems likely that a missed cancer diagnosis at the initial screening visit still results in a curable PCa at a future screening round.

Escapes

An aspect that we poorly understand at this time is the large proportion of men who, in spite of screening, escape all efforts of treatment and progress or die of PCa. As the ERSPC study showed a relative risk reduction of 20-30%, we still have to deal with 70-80% of all PCa death which occurred despite screening. Although it is unlikely that all PCa deaths can be avoided, it is reasonable to suggest that a part of these deaths is preventable. Further research will include identifying and characterizing these so-called 'escapes', and comparing different screening strategies to achieve improvement on present screening algorithm, resulting in an increase in PCa-specific mortality reduction. Such strategies need to be developed.

One possibility is to change the PSA cut-off value for taking a biopsy. The downside of lowering the threshold is that additional PCa are likely to be detected in the low PSA ranges, where non-aggressive PCa accumulate [35,36]. At this time, PSA cut-off values of 2.5, 3.0 or 4.0 ng/mL provide a reasonable balance between excessive detection rates and the risk of missing relevant PCa [37]. As shown above, unnecessary biopsies and cancer diagnoses can be avoided by applying the Risk Calculator.

Furthermore, another uncertainty concerns how to best biopsy the prostate to diagnose PCa since classical and lateralized sextant biopsies would miss a substantial portion of detectable cancers in the order of 20-25%. Therefore, Schröder et al. [38**] studied the clinical outcomes during an 11-year follow-up period for cancers, potentially missed at the first round of screening but was detected by screening 4 and 8 years later or as interval cancer. On the basis of the data from ERSPC Rotterdam, the authors concluded that the number of potentially missed cancers with a poor outcome in terms of progression-free survival and deaths from PCa is very low. The rate of deaths due to PCa in those men with an initial negative biopsy of 0.23% compares favorably to the 0.35% rate of overall PCa mortality. Hence, lateralized sextant biopsy seems not to be obsolete if repeated screening is applied [38**].

In addition, Van Leeuwen et al. [39] showed that within a screening program, men with a smaller prostate volume and an initially high PSA level were at greater risk of cancer detection and of an aggressive cancer during follow-up [39]. This information supports the need for an adapted biopsy scheme, especially developed for a systematic screening situation.

In summary, a more aggressive screening is likely to detect more PCa but will probably also raise the burden of overdiagnosis and overtreatment. Consequently, a more individualized approach in screening is required in the future to significantly improve the detection of clinically relevant PCa while reduce the rates of overdiagnosis.

Active surveillance

It is clear that not every screen-detected PCa needs treatment. An option to manage early-detected PCa is active surveillance [40]. Active surveillance aims to avoid overtreatment in men with small, localized, well-differentiated PCa, by initially withholding radical treatment. Instead, the tumor is closely monitored with the purpose of switching to active local therapy with curative intent if there is progression. This approach seems feasible and well tolerated, at least in the medium term according to the two largest prospective observational studies [41,42*].

CONCLUSION

With the recently published interim results of the ERSPC and PLCO trial, the controversy surrounding PCa screening remains not only unresolved but it has also been stirred up. Factors contributing to this controversy include contradiction between the effects of the studies, but even more important issues relating to overdiagnosis and overtreatment, and therefore lack of international consensus about routine screening.

However, in the future the controversy might focus less on whether or not to screen, but rather on how to screen, in terms of minimize the harm while retain the benefits of screening. Given that PLCO is more a randomization between a screening group and a less screened group and, therefore, cannot show any benefit of screening, it is justified to rely on the effects demonstrated by the ERSPC. With systematic PSA-based screening, this study demonstrated with a mean follow-up of 9 years a PCa-specific mortality reduction of 20% and 31% after secondary analysis. In the future, the ERSPC will very likely provide even more convincing estimates. Thus, the fact that PCa screening reduces PCa-specific mortality seems to be undisputed.

Nevertheless, the balance between PCa mortality reduction and excess incidence of PCa is subtle, and inherent to the latter increased costs and morbidity. Currently, there is insufficient evidence to introduce a population-based PCa screening program. The results of the ERSPC support the need to complete studies evaluating quality of life and cost-efficiency with the highest urgency. The results of these studies should be considered together with more mature data from the ERSPC to reach an effective implementation of screening on PCa.

Meanwhile, it is our responsibility to improve the screening test, screening protocol and further development of an individualized risk assessment to decrease the rates of overdiagnosis and overtreatment, while maintain the mortality reduction and the detection of clinically relevant PCa.

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3 Scope and outline of the thesis

SCOPE

It is well established that prostate cancer screening by PSA testing reduces disease-specific mortality. However, the effect of screening is influenced by many factors. Some of these factors, such as repeated screening, treatment, and the type of randomization are addressed in the second part of this thesis.

Despite the allocation to the intervention arm of the ERSPC trial, some men still died from prostate cancer. In the third part an effort is made to identify and characterize these men, and to define points of improvement for future screening purposes.

Although PSA testing has high sensitivity, it lacks specificity. Levels of PSA can be elevated in men without prostate cancer. Furthermore, many of the cancers diagnosed in the PSA-era would never have been diagnosed without screening and may not be life-threatening. The majority of these newly-diagnosed cancers are still treated aggressively, e.g. by radical prostatectomy and radiation therapy. These modalities, however, carry the risk of certain complications. The fourth part of this thesis contributes to improvement of the current screening strategies in order to reduce the burden of prostate cancer.

OUTLINE

In the second part of this thesis we describe studies which evaluated the efficacy of screening. **Chapter 4** compares the disease-specific survival of men diagnosed with prostate cancer at the first screening round vs. men diagnosed at the second screening round. The aim is to assess the effect of repeated screening. In **Chapter 5** survival outcomes after radical prostatectomy between screen-detected men and patients from the control arm are compared. **Chapter 6** describes differences in mortality outcomes between the Rotterdam branch and the Göteborg branch of the ERSPC trial.

In the third part of the thesis, men who died from prostate cancer despite their allocation to the intervention arm of the ERSPC are studied. These men are identified and characterized in **Chapter 7**. Men with prostate cancer diagnosed during the screening interval are described in **Chapter 8**. Their disease-specific survival is compared with patients from the control arm. **Chapter 9** outlines the principle differences between the conventional Kaplan-Meier method and the competing-risks analysis. The extent of overestimation by the first method is quantified.

The fourth part underlines the need for a risk-based strategy for prostate cancer screening and provides recommendations for future directions. **Chapter 10** examines the positive predictive value of prostate biopsy triggered by PSA in consecutive screening rounds. In **Chapter 11**, risk factors for prostate cancer and evidence for a risk-based screening strategy are summarized. **Chapter 12** introduces a novel tool, which can predict the risk of prostate cancer in 4 years after an initially negative screen.

II Effect of prostate cancer screening

Chapter 4

Disease-specific survival of men with screen-detected prostate cancer: competing-risks analysis of first round vs. second round cancer in the ERSPC

Chapter 5

Long-term radical prostatectomy outcomes among participants from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam

Chapter 6

Efficacy and effectiveness study design within the European Randomized Study of Screening for Prostate Cancer: consequences for prostate cancer incidence, overall mortality and prostate cancer-specific mortality

4 Disease-specific survival of men with screen-detected prostate cancer in the ERSPC: competing-risks analysis of first round cancer vs. second round cancer

Submitted

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ABSTRACT

Background

It is unknown if repeated PSA testing improves disease-specific survival in men with screen-detected prostate cancer (PCa).

Objective

To compare the disease-specific survival of men with PCa diagnosed at the first round (R1) vs. those at the second round (R2) in the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Design, setting, and participants

Data were derived from men with screen-detected cancer in the ERSPC. Screening was carried out with an interval of 4 yrs in most centers; in men with a PSA >= 3.0 ng/mL prostate biopsy was recommended.

Outcome measurements and statistical analysis

Because of the age difference between R1 and R2 patients, only those aged >=59 yrs at diagnosis were included. Data from both groups were truncated at 7 yrs because of the difference in follow-up length. Fine and Gray competing-risks regression models were used to determine whether R2 (vs. R1) was associated with improved disease-specific survival. Sensitivity analysis was performed in those who were compliant with the screening protocol (i.e. attending the screening round as scheduled).

Results and limitations

1683 and 1499 men were diagnosed with PCa at R1 and R2, respectively. Men diagnosed at R2 had a 2.9-fold lower risk of dying from PCa as compared to those diagnosed in R1 (p=0.001). After controlling for age at diagnosis, PSA, clinical stage, biopsy Gleason score, M status at diagnosis and primary treatment modality, R2 patients had a 2.0 fold lower risk to die from PCa as compared to those from R1 (p=0.028). The risk was 2.3-fold lower in favor of R2 cases after adjustment for compliance (p=0.017). Limitations include the still relatively short follow-up, and possible bias due to lead time and length time.

Conclusions

Men with PCa detected in the ERSPC at R2 have more favorable prognostic factors and only half the risk of dying from the disease within 7 yrs after diagnosis, compared with their counterparts from R1.

INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has demonstrated a 21% prostate cancer (PCa) mortality reduction in favor of population-based PSA screening after a median follow-up of 11 yrs [1].

A shift toward more favorable tumor characteristics with repeated screening was observed in the ERSPC [2,3]. Men diagnosed at the second round (R2) had more favorable prognostic factors, such as clinical stage and Gleason grade than those diagnosed at the first round (R1). It has been shown that men in the screening arm who developed metastatic disease and/or died from PCa were mainly those detected at R1 [1,4-5]. However, these men also had longer follow-up as compared to those diagnosed in the later screens. Therefore, it is unclear whether repeated screening improves survival outcomes.

We compared the disease-specific survival of men with R1 cancer vs. men with R2 cancer after adjustment for the difference in length of follow-up. This knowledge could help understand the data of our screening trial and might be used as reference for health professionals who are asked for advice by previously PSA tested and untested men, and for the determination of future public health policies.

METHODS

Study population

Data used in this study were derived from men with PCa in the screening arm of the ERSPC study. This screening trial was initiated in the early 1990s in European countries, to determine whether a reduction of PCa mortality could be achieved by PSA-screening [6]. The study population and protocol have been described in detail previously [7,8].

In summary, the pre-defined core age group included men between the ages of 55 and 69 yrs at entry of whom 72,891 were randomized to the screening arm. Screening was carried out with an interval of 4 yrs and of 2 yrs in one center. Men with a PSA of 3.0 ng/mL or above were recommended prostate biopsy. Exceptions are described in [8]. Ethical review and approval has been obtained in all centers. The trial is registered in the ISRCTN under number 49127736.

Definitions

R1 cancers (n=1683) were defined as cases diagnosed at the first or an early repeat visit. R2 cancers (n=1499) were cases detected during the second visit; that is either at the planned second visit or at the second visit in a later screening round if a participant had skipped the previous scheduled visit. In total, 1426 of the 1683 (84.7%) R1 patients were

compliant to the screening protocol (i.e. attending the screening round as scheduled), vs. 1375 of the 1499 (91.7%) R2 patients.

Follow-up

Data on mortality were collected by linkage to the national registries and by patient chart review. Each trial center followed the common core protocol and provided key data to the independent data center every 6 months [9]. Follow-up for mortality analyses began at diagnosis.

Causes of death were evaluated in a blinded fashion and according to a standard algorithm or, after validation, on the basis of official causes of death. Only deaths classified as definitely or probably caused by PCa were classified as such [10].

Statistical analysis

To preserve a comparable age distribution between men with R1 PCa and men with R2 PCa, only those aged 59 yrs or older at screening were included in the analyses. Data on clinical stage, biopsy Gleason score, and treatment modality were unknown in 65, 35, and 91 patients, respectively. These missing data were imputed based on correlations between all predictor variables. We used the first imputation dataset of a multiple imputation procedure with inclusion of round of diagnosis, year of diagnosis, age at diagnosis, PSA, clinical stage, biopsy Gleason score, treatment modality, M status at diagnosis and PCa death as variables in the model. A total of 191 values were missing, making up 0.7% of all covariate values required for the prediction model.

Descriptive statistics were used to characterize the study population at diagnosis. The clinical parameters between R1 vs. R2 PCa were compared using chi-square analyses for categorical variables. For the continuous variables age at diagnosis and PSA level at diagnosis, a Wilcoxon rank-sum test was used to compare the medians and the distributions. Cumulative hazards of death from PCa were calculated according to the Nelson-Aalen method [11].

Univariate and multivariable competing-risks regression models according to Fine and Gray [12] were used to determine whether R1 vs. R2 PCa was associated with death from the disease. Death from PCa was the event of interest, while death from other causes was considered competing event. Using death as endpoint in a survival analysis may be misleading, but in this context survival refers to death over time in those subjects diagnosed with PCa. It is therefore not a mortality analysis, as mortality refers to death rate (events over person years) in all study subjects (with or without PCa). The multivariate regression model included R1 vs. R2 round PCa, age at diagnosis, PSA at diagnosis, clinical stage, biopsy Gleason score, M status at diagnosis and treatment. Since the median follow-up of cancers from R2 was only 6.5 yrs compared with 9.7 yrs for those from R1, the competing-risks analysis was carried out by truncating the data at 7 yrs.

In men who were compliant to the screening protocol, i.e. attending the screening rounds as scheduled, sensitivity analysis was performed.

Statistical analysis was performed using SPSS 17 and STATA 12 software. All analyses were two-sided with a significance level set at 0.05.

RESULTS

In R1, 40164 men were screened in whom 1683 cancers (4.2%) were found, compared with 1499 cancers (3.6%) in 41914 men screened in R2, Table 1 compares the characteristics of the two groups of cancers. Patients diagnosed at R1 were younger and had a significantly higher median PSA level at diagnosis. In addition, a significantly greater proportion of men with R1 PCa, as compared to men from R2, had a higher clinical stage, biopsy Gleason score and M+ disease. Primary treatment modalities were different between the two groups; patients from R2 were less often treated by radical surgery and were put under surveillance more often. At the end of follow-up, 419 out of 1683 men (24.9%) diagnosed with PCa at R1 died, of whom 93 men (5.5%) died from

Table 1. Descriptive statistics of men with screen-detected prostate cancer

		1st round		2nd round		
No. patients		N=1683		N=1499		
			IQR		IQR	p
Age at diagnosis (yrs), median		65.3	62.8-67.6	67.0	63.2-70.6	<0.001
PSA at diagnosis (ng/mL), median		6.1	4.2-11.0	4.7	3.7-6.6	<0.001
			%		%	p
Clinical stage, n	T1c	830	49.3	1053	70.3	
	T2	600	35.7	382	25.5	
	T3	238	14.1	53	3.5	
	T4	15	0.89	11	0.73	<0.001
Biopsy Gleason score, n	<=6	1180	70.1	1178	78.6	
	7	389	23.1	248	16.5	
	>=8	114	6.8	73	4.9	<0.001
M status at diagnosis	0	1687	98.5	1489	99.3	
	1	26	1.5	10	0.67	0.019
Treatment, n	Surgery	786	46.7	542	36.2	
	Radiotherapy	539	32.0	516	34.4	
	Hormone therapy	105	6.2	52	3.7	
	Surveillance	253	15.0	386	25.8	<0.001
Overall deaths		419	24.8	171	11.5	
Prostate cancer deaths		93	5.5	15	1.1	<0.001

Table 2. Descriptive statistics of men who died from prostate cancer

		1st round		2nd round		
No. of patients		N=93		N=15		
			IQR		IQR	p
Age at diagnosis (yrs), median		66.3	62.9-67.6	68.5	63.6-71.1	0.017
PSA at diagnosis (ng/mL), median		12.5	6.1-31.8	8.7	4.8-16.1	0.27
			%		%	p
Clinical stage, n	T1c	17	18.3	8	53.3	
	T2	38	40.9	5	33.3	
	T3	32	34.4	1	6.7	
	T4	6	6.5	1	6.7	0.016
Biopsy Gleason score, n	<=6	27	29.0	5	33.3	
	7	39	41.9	4	26.7	
	>=8	27	29.0	6	40.0	0.51
M status at diagnosis	0	82	88.2	13	86.7	
	1	11	11.8	2	13.3	0.87
Treatment, n	Surgery	32	34.4	6	40.0	
	Radiotherapy	33	35.5	3	20.0	
	Hormone therapy	21	22.6	4	26.7	
	Surveillance	7	7.5	4	25.0	0.087
Benign biopsy at previous visit		-		3	20.0	-

the disease. In R2 patients, 171 out of 1499 men (11.4%) died of whom 15 (1.0%) died from PCa.

Table 2 summarizes the characteristics of these lethal cancers; the percentage provided should be interpreted with caution given the small number of events. Men diagnosed at R2 and who eventually died of the disease were older, had lower initial PSA and more often clinically localized disease (<=cT2) when compared to men detected at R1. Furthermore, of the 15 PCa deaths from R2, 3 men had undergone prostate biopsy at the previous visit, which did not show any malignancy at that time.

Table 3 and 4 show the competing-risks regression models with truncated data at 7 yrs. Men diagnosed at R2 had a 2.9-fold (1/0.34) lower risk of dying from PCa as compared to those diagnosed at R1 (Table 3). After adjusting for age at diagnosis, PSA level, clinical stage, biopsy Gleason score, M status at diagnosis and primary treatment modality (Table 4), men with R2 PCa still had a lower risk to die from the disease (HR 0.49, 95% CI 0.26-0.93, p=0.028).

The sensitivity analysis in compliant men is shown in Table 5: men with R2 PCa were significantly less likely to die from PCa compared with men with R1 PCa (HR 0.44, 95% CI 0.22-0.86, p=0.017). The Nelson-Aalen plot shows incremental divergence of the unadjusted cumulative hazards of death from PCa between the two groups (Figure 1). The

Table 3. Competing-risks regression model to predict death from prostate cancer – Univariate analysis with truncated data at 7 yrs

		HR	95% CI	p
Screening round	1st	ref		
	2nd	0.34	0.19-0.65	0.001

HR=hazard ratio; 95% CI=95% confidence interval; ref=reference category.

Table 4. Competing-risks regression model to predict death from prostate cancer - Multivariate analysis with truncated data at 7 yrs

		HR	95% CI	p
Screening round	1st	ref		
	2nd	0.49	0.26-0.93	0.028
Age at diagnosis		1.01	0.92-1.11	0.80
PSA		1.00	1.00-1.00	0.011
Clinical stage	T1c	ref		
	T2	2.18	1.09-4.35	0.028
	T3	2.41	1.09-5.29	0.029
	T4	2.41	0.38-15.4	0.36
Biopsy Gleason score	<=6	ref		
	7	3.33	1.65-6.71	0.001
	>=8	10.4	5.13-21.2	<0.001
M status at diagnosis	0	ref		
	1	5.85	1.88-18.2	0.002
Treatment	Surgery	ref		
	Radiotherapy	1.26	0.66-2.40	0.49
	Hormone therapy	1.47	0.47-4.59	0.50
	Surveillance	1.75	0.68-4.48	0.25

HR=hazard ratio; 95% CI=95% confidence interval; ref=reference category.

number at risk table shows that despite the limited length of follow-up of R2 cancers, still nearly 900 men were at risk at 6 yrs after diagnosis; only 4 of these men died during the following time period (which can be deducted from the graph).

DISCUSSION

In the present study, we have found that men diagnosed with PCa at R2 had more favorable prognostic factors and a 2.9-fold lower risk of dying from the disease as compared to patients from R1 over a 7 yr time period after diagnosis. The risk was 2.0-fold after adjustment for age at diagnosis, PSA level, clinical stage, biopsy Gleason score, M status

Table 5. Sensitivity analysis to predict death from prostate cancer in men who were screened as scheduled

		HR	95% CI	p
Screening round	1st	ref		
	2nd	0.44	0.22-0.86	0.017
Age at diagnosis		1.02	0.93-1.14	0.59
PSA		1.00	1.00-1.00	0.020
Clinical stage	T1c	ref		
	T2	2.00	0.97-4.12	0.061
	T3	2.29	0.96-5.46	0.062
	T4	2.54	0.39-16.4	0.33
Biopsy Gleason score	<=6	ref		
	7	2.48	1.16-5.32	0.020
	>=8	10.0	4.79-21.1	<0.001
M status at diagnosis	0	ref		
	1	5.25	1.44-19.2	0.012
Treatment	Surgery	Ref		
	Radiotherapy	1.26	0.64-2.50	0.49
	Hormone therapy	1.51	0.42-5.39	0.53
	Surveillance	1.83	0.70-4.79	0.22

HR=hazard ratio; 95% CI=95% confidence interval; ref=reference category.

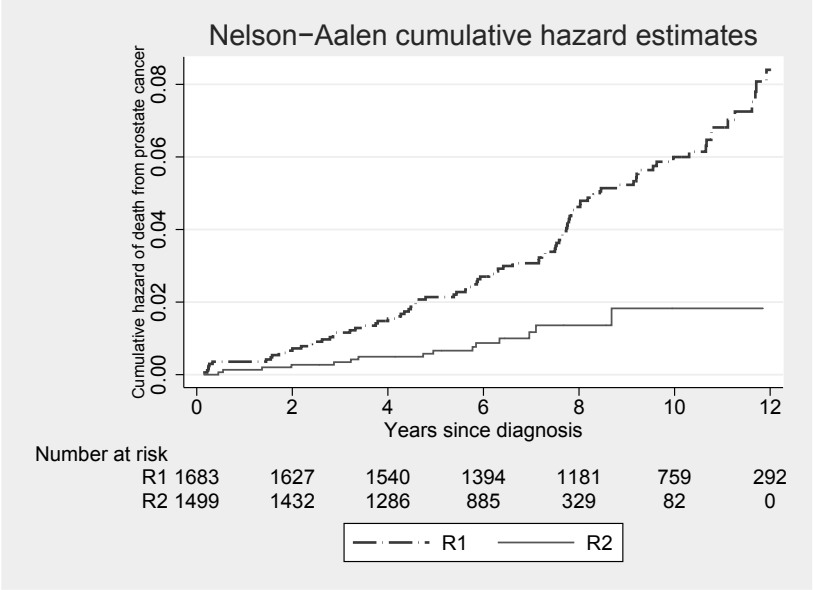

Figure 1: Cumulative hazard of death from prostate cancer of screen-detected men

at diagnosis and primary treatment modality. When controlled for compliance, it was shown that men who attended R2 as scheduled and were subsequently diagnosed with PCa had a 2.3-fold lower risk of PCa death compared to patients who visited R1.

Our results should be accounted for lead-time, length bias and overdiagnosis. Lead-time indicates the amount of time gained by screening, i.e. how much earlier disease is detected through screening compared with absence of screening. A close related concept is the sojourn time, which is the duration of the pre-clinical detectable phase. Length bias refers to the fact that different cancers have different sojourn times, depending on their aggressiveness. Overdiagnosed cases are cancers with a sojourn time equal to infinity, i.e. cases that would not have been diagnosed during lifetime if there had been no screening.

In breast cancer screening, the first screen is usually assumed to capture most of the slowly growing cancers [13,14]. Conversely, a previous report from the ERSPC study group showed that the lead-time in yrs for R2 (5.9, 95% CI 5.4-6.4) was only slightly shorter than that for R1 (6.8, 95% CI 6.4-7.3) [15]. Also, Table 1 in the present study shows that both the absolute number and proportion of T1c cancer, which may be used as surrogate for low-risk disease, are higher in R2. Despite the adjustment for known predictors in our analyses, it remains difficult if not impossible to completely control for lead-time and length time.

Several other factors may have caused the difference in survival between R1 and R2 patients. One of these factors is advances in treatment, which have improved survival outcomes over time. This may have been beneficial to patients from R2, as they were on average diagnosed 4 yrs later than the patients from R1. Another probable factor to explain the survival difference is tumor volume. In a study of men with screen-detected focal PCa, defined as <=3 mm tumor involvement in only 1 biopsy core without Gleason pattern 4 or 5, it was shown that the median tumor volume measured in the prostatectomy specimen decreased from 0.18 mL in R1 cancers to 0.07 mL in R2 cancers [16]. Repeated screening was therefore associated with a lower tumor volume. Although we do not have data on tumor tissue on biopsy for the entire ERSPC, subanalysis with data from the Rotterdam and Göteborg branch showed that the percentage tumor tissue was significantly lower in R2 cancers, and appeared to be a significant predictor for disease-specific survival (data not shown).

Comorbidity might be another explanatory factor, as some studies have shown that men with severe comorbidity are more likely to die from causes other than PCa [17-19]. It is possible that patients from R2 had more comorbidities than those from R1, who were younger at the time of diagnosis. However, in the present study, patients from R2 were on average less than 2 yrs older than their counterparts from R1 (Table 1), making this hypothesis less likely.

The United States Preventive Services Task Force recently reviewed the literature on PCa screening and released an updated recommendation against PSA screening [20].

Although there is evidence that screening reduces the incidence of metastatic PCa and disease-specific mortality from well conducted randomized trials, the panel concluded that the harms outweigh the benefits. Many PCa experts believed that this recommendation was inappropriate [21-23], and it has added fuel to the yet heavily debated question of screening for PCa.

In this perspective, our observation that repeated screening improves disease-specific survival in men with screen-detected PCa is encouraging. Men who were screened for the second time were less likely to die from PCa within the available follow-up. It is possible that the R1 has already eliminated a large proportion of the more advanced cancers. Some men with PCa diagnosed at the first visit already had symptoms and harbored aggressive or metastasized disease without knowing they had PCa. Those with more advanced disease may have been treated initially with curative intent, but eventually succumbed to the disease. A possible implication of our findings is that we may expect that the PCa mortality rates will further decrease in the screening arm once the natural history of the "bad" R1 cancers has reached its endpoint. However, next to screen-detected cases which are described in this paper, PCa in the screening arm also includes interval cancers and cancers in unscreened subjects (non-attendees) [1]. Men with these cancers have a higher risk of dying from the disease than men with screen-detected cancers [4,24]. Therefore, additional data are needed to evaluate the exact effect of R1 cancers on PCa mortality rates in the screening arm.

Our findings, with some limitations, are applicable to the large populations of men worldwide who are seeking PSA testing. The results may be used as a reference for health professionals advising men who consider to be screened, and for public health services in preparing recommendations concerning PSA-screening. If a well-informed man wishes to be rescreened after an initially negative screen, he can be told that he has about half the risk of death from PCa *if* he is diagnosed, as compared to a man diagnosed with PCa at the first screen.

Obviously, our data should not be used primarily to encourage screening, as other variables are needed to decide whether to rescreen or not [25]. Also, there are several aspects with respect to the generalizability of our findings which must be discussed. First, the ERSPC is conducted in Europe, where the background rates of PSA testing were relatively low when compared to rates in the US. If a screening program is initiated in a country where PSA-screening is already widespread, difference in disease-specific survival between R1 and R2 cancers may be smaller, but our data on R2 survival outcomes would still be applicable as these patients have been screened before.

Second, most participants from the ERSPC were Caucasians. Also, the ERSPC is a population-based trial, meaning that each participant followed the same screening protocol, whereas more and more evidence points out that we may need to work toward

an individualized risk-based strategy [26-28], to be able to maximize the benefits of PSA testing and minimize its harms such as overdiagnosis.

Strengths and limitations

To our knowledge, this is the first report offering better understanding of the differences in disease-specific survival between R1 and R2 cancers in a screening setting. Our findings may provide the opportunity to foresee mortality outcomes if a screening program is introduced. The data were derived from the ERSPC study, which is the largest randomized PSA-based screening trial to date. Strengths of our study include the prospective collection of data on cancer characteristics and the determination of cause of death by an independent committee. Also, only 0.7% of the original data required for the regression models were missing; these values were imputed which increases efficiency of analyses and limits any selection bias [29].

However, our data are subject to some caveats. Although the median follow-up of the ERSPC study (counting from the time of randomization) is 11 yrs at this time, it is still relatively short considering the protracted natural history of PCa. Only 18.5% (590/3182) of the study population died during this period of follow-up. Our findings might change with longer follow-up. Indeed, Johansson et al. found a large increase in the PCa mortality in localized cancers during follow-up of 15-20 yrs [30]. Second, screening protocols differed within the branches of ERSPC. Screening was carried out with an interval of 2 yrs in Sweden compared with 4 yrs in other centers. This may have influenced our results. However, after excluding Swedish data we found similar results as in Table 4, showing that patients from R2 had a lower risk to die from PCa than those from R1 (HR 0.46, 95% CI 0.24-0.88, p=0.018). Also, different PSA threshold have been used over time to prompt prostate biopsy. Therefore, we had performed a subanalysis including those who had a PSA level of 4.0 ng/mL or higher at diagnosis, and found similar results as our primary analysis in Table 4 (HR 0.45, 95% CI 0.22-0.89, p=0.023).

CONCLUSION

Men diagnosed with PCa at R2 in the ERSPC have more favorable prognostic factors and an about 2-fold lower chance of dying from the disease within 7 yrs after diagnosis, compared with their counterparts diagnosed at R1. This is encouraging as it implies that repeated screening improves disease-specific survival. Well-informed men who are seeking PSA testing after an initially negative screen can be informed about this benefit, *if* they are diagnosed with PCa at repeated screening.

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5 Long-term radical prostatectomy outcomes among participants from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam

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ABSTRACT

Objective

To examine the long-term outcomes of radical prostatectomy (RP) among men diagnosed with prostate cancer from the screening and control arms of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Patients and methods

Among 42376 men randomized during the period of the first round of the trial (1993 – 1999), 1151 and 210 in the screening and control arms were diagnosed with prostate cancer, respectively. Of these men, 420 (36.5%)screen-detected and 54 (25.7%) controls underwent RP with long-term follow-up data (median follow-up 9.9 years). Progression-free (PFS), metastasis-free (MFS) and cancer-specific survival (CSS) rates were examined, and multivariable Cox proportional hazards models were used to determine whether screen-detected (vs. control) was associated with RP outcomes after adjusting for standard predictors.

Results

RP cases from the screening and control arms had statistically similar clinical stage and biopsy Gleason score, although screen-detected cases had significantly lower prostate-specific antigen (PSA) levels at diagnosis. Men from the screening arm had a significantly higher PFS (p=0.003), MFS (p=0.001) and CSS (p=0.048). In multivariable models adjusting for age, PSA level, clinical stage, and biopsy Gleason score, the screening group had a significantly lower risk of biochemical recurrence (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.23-0.83, p=0.011) and metastasis (HR 0.18, 95% CI 0.06-0.59, p=0.005). Additionally adjusting for tumor volume and other RP pathology features, there was no longer a significant difference in biochemical recurrence between the screening and control arms. Limitations of the present study include lead-time bias and non-randomized treatment selection.

Conclusions

After RP, screen-detected cases had significantly improved PFS, MFS and CSS compared with controls within the available follow-up time. The screening arm remained significantly associated with lower rates of biochemical recurrence and metastasis after adjusting for other preoperative variables. However, considering also RP pathology, the improved outcomes in the screening group appeared to be mediated by a significantly lower tumor volume.

INTRODUCTION

PSA screening is controversial despite evidence that it leads to a significant stage migration with reductions in metastatic disease and prostate cancer-specific mortality [1-2]. In the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, the screening group underwent annual PSA screening for 6 years and the majority of controls received opportunistic screening [3]. The lack of a mortality difference between the groups has generated questions regarding the comparative efficacy of organized and contemporary opportunistic screening in the US.

A related issue is whether organized screening influences treatment outcomes. In 2006, Roehl et al. [4] compared tumor features and radical prostatectomy (RP) outcomes between 464 men diagnosed with prostate cancer as part of a different organized USA screening program versus 2713 cases who were not. The screening group had more favorable prognostic features at diagnosis, including lower PSA levels and less high-grade disease. Additionally, they reported a significantly higher 7-year progression-free survival (PFS) rate after radical prostatectomy in the screening versus the referred population (83% vs. 77%, $p < 0.001$). However, as with the PLCO, there were high rates of screening in the "referred" group, of which 57% had clinical stage T1c disease.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1993 to study whether PSA testing reduces prostate cancer mortality. At the beginning of the trial, opportunistic PSA screening was less common in Europe compared to the USA [5]. Van der Cruijsen-Koeter et al. [6] previously reported that men randomized to the screening arm of the Rotterdam ERSPC from 1993 to 1999 had significantly more favorable prognostic features at prostate cancer diagnosis than men from the control arm. This included a significantly lower PSA and Gleason grade at diagnosis, as well as lower rates of locally-advanced disease (T3/T4), and distant metastases. However, the outcomes of treatment were not reported in that study. The objective of the current study was therefore to compare pathological tumor features and long-term radical prostatectomy outcomes between men from the screening and control arms diagnosed during the same time interval. Due to concern regarding lead-time bias affecting the overall results, we also examined outcomes in relation to numerous clinical and pathological prognostic factors.

PATIENTS AND METHODS

The Rotterdam section of the ERSPC was initiated in 1993, as previously described [1,7]. Lateralized sextant biopsy was recommended for abnormal DRE/TRUS or a PSA level ≥4 ng/mL (until May 1997), and thereafter for a PSA ≥3 ng/mL [7]. During the period from

1993 to October 1996, men with a negative biopsy were rescreened 1 year later. The study protocol received approval from the local Ethics Committee and the Minister of Health of the Netherlands. The ERSPC trial is registered under the ISRCTN number 49127736.

From 1993 to 1999, 42376 men were randomized. In the Netherlands, randomization was performed after informed consent. During this period, prostate cancer was detected in 1151 men in the screening arm (either at initial screening or repeat screening 1 year later); during the same time period, 210 men in the control arm were diagnosed with prostate cancer (by routine regional health care providers). Cancer incidence in the control arm was assured by linkage with the regional cancer registry. Of the men with prostate cancer, 420 (36.5%) screen-detected and 54 (25.7%) controls underwent RP with long-term follow-up data. The study population therefore consisted of all men (n=474) diagnosed with prostate cancer from 1993 to 1999 from the screening and control arms who subsequently underwent RP; whereas the remaining 887 men diagnosed with prostate cancer who did not undergo RP were excluded. Treatment decisions were based upon patient and physician preference (not part of the study protocol). There was no minimum follow-up period required for inclusion in the study. The median follow-up was 9.9 years (9.3 years in screening arm and 10.0 years in control arm) and follow-up was complete up to December 31, 2008.

Demographics and tumor features were prospectively recorded. RP specimens were reviewed by pathologists at the treating hospital. Organ-confined disease was defined as pathological stage T2 with negative lymph nodes. The follow-up protocol after RP consisted of PSA measurements every 3 months for 1 year, every 6 months for the second year, and then annually. The criteria for biochemical recurrence was a postoperative PSA level >0.2 ng/mL. Chart review was performed every 6 months for all men with prostate cancer by a team of data managers to assess possible progression of the disease. Causes of death in cancers were evaluated by an independent causes of death committee according to an algorithm that is used in all ERSPC centers [8].

Comparisons between RP cases from the screening and control arms were made using the t-test, Wilcoxon rank-sum, chi-square, and Fisher's exact tests. The Kaplan-Meier method was used to examine the three main endpoints in the study: progression-free survival, metastasis-free survival (MFS) and cancer-specific survival (CSS). Comparisons between the screening and control arms were made using the log-rank test.

In addition, multivariable Cox proportional hazards models were used to determine whether screen-detected (vs. control) prostate cancer was associated with each of the three endpoints after adjusting for standard predictors. The "preoperative" model included screening arm (vs. control), PSA, clinical stage, biopsy Gleason score and age. Due to the small sample size with clinical stage T3, we categorized clinical stage as impalpable (T1) vs. palpable (≥T2) for this analysis. "Postoperative" models were applied incorporating screening arm (vs. control), pathologic stage and prostatectomy Gleason

grade. Separate models additionally adjusted for tumor volume were also applied in the subset (n=369) with tumor volume data.

RESULTS

Table 1 compares the clinical and pathological features between cases diagnosed in the screening and control arms. Patients from the control arm were slightly older and had a significantly higher median PSA level at diagnosis. Although clinical stage and biopsy Gleason scores were not significantly different between the groups, a significantly greater proportion of controls were classified in the D'Amico intermediate- and high-risk categories. At RP, men from the control arm were significantly more likely to have positive surgical margins and seminal vesicle invasion. Additionally, tumor volume was significantly higher in RP specimens in men from the control arm.

Table 1. Comparison of clinical and pathologic tumor features between men from the screening and control arms of the Rotterdam ERSPC treated by radical prostatectomy.

	Screening arm	Control arm	p-value
Number of patients	420	54	
Mean age at diagnosis, years	63.5	64.8	0.047
Median (mean, range) PSA level at diagnosis ng/mL	5.4 (6.5, 0.6-43)	9.1 (12.1, 1.2-94)	<0.001
Clinical stage			
T1	187 (44.5%)	21 (38.9%)	0.524
T2	192 (45.7%)	28 (51.8%)	
T3	41 (9.8%)	5 (9.3%)	
Biopsy Gleason			
≤6	306 (73.7%)	33 (64.7%)	0.205
7	90 (21.7%)	16 (31.4%)	
8-10	19 (4.6%)	2 (3.9%)	
D'Amico risk group			
Low	221 (53.3%)	18 (34%)	0.03
Intermediate	95 (22.9%)	20 (37.7%)	
High	99 (23.9%)	15 (28.3%)	
Organ-confined	316 (75.8%)	37 (69.8%)	0.344
Extracapsular extension	76 (20.3%)	14 (31.8%)	0.078
Positive surgical margins	103 (25.1%)	20 (37.7%)	0.049
Seminal vesicle invasion	16 (3.9%)	8 (16%)	0.003
Lymph node metastases	2 (0.5%)	1 (2%)	0.304
Prostatectomy Gleason score			
≤6	248 (62.3%)	26 (53.1%)	0.214
7	137 (34.4%)	21 (42.9%)	
8-10	13 (3.3%)	2 (4.1%)	
Median tumor volume (Mean, range), cc (n=369)	0.68 (1.1, 0.001-13.5)	2.9 (3.4, 0.03-16.8)	<0.001

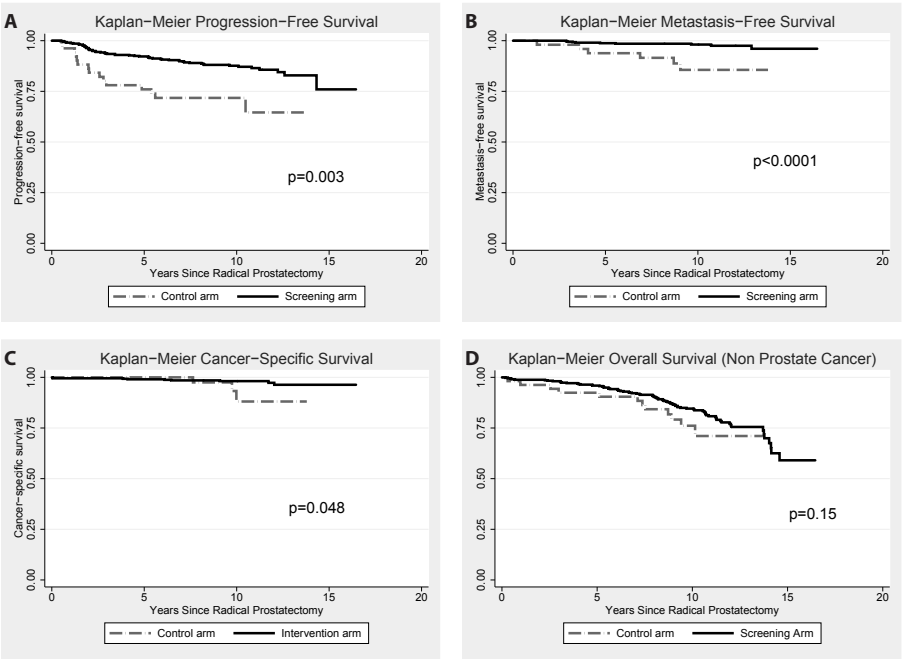

Figure 1: Biochemical PFS, MFS, CSS and overall survival in screen-detected men and controls

With a median follow-up of 9.9 years, biochemical recurrence occurred in 69 (14.6%) and 15 (3.2%) developed metastatic disease. In all, 105 men (22.2%) died during follow-up, including 12 (2.5%) from prostate cancer. Kaplan-Meier survival curves are shown in Figure 1, stratified by screening and control arms. After RP, men from the screening arm had a significantly higher 10-year PFS (88% vs. 72%, p=0.003), MFS (98% vs. 86%, p<0.001), and CSS (98% vs. 88%, p=0.048), compared to men from the control arm. Overall survival was also significantly better in the screening vs. control group (p=0.04 log-rank); however, this appears to be accounted for by the higher rates of prostate cancer death in the control group. Excluding the prostate cancer deaths, however, there was no difference (p=0.15) between the screening and control groups in overall mortality (Figure 1d).

Table 2. Multivariable models to predict time to biochemical recurrence, metastasis, and cancer-specific mortality based upon preoperative features.

	HR (95% CI); p		
	Biochemical progression	Metastasis	Prostate cancer mortality
Screening group (vs. control)	0.43 (0.23-0.83), p=0.011	0.18 (0.06-0.59), p=0.005	0.59 (0.11-3.06), p=0.531
PSA (continuous)	1.04 (1.02-1.06), p<0.001	1.00 (0.95-1.06), p=0.953	1.01 (0.96-1.06), p=0.662
Clinical stage (T1 vs. ≥T2)	2.20 (1.34-3.61), p=0.002	1.38 (0.45-4.22), p=0.577	0.46 (0.10-2.16), p=0.325
Biopsy Gleason score	2.31 (1.61-3.32), p<0.001	1.96 (0.89-4.33), p=0.097	1.99 (0.84-4.70), p=0.116
Age (continuous)	1.04 (0.98-1.10), p=0.196	1.03 (0.92-1.16), p=0.607	1.09 (0.95-1.27), p=0.227

Table 3. Multivariable models to predict time to biochemical recurrence, metastasis, and cancer-specific mortality based upon postoperative features incorporating stage and grade at prostatectomy (a), and additionally considering tumor volume (b).

(a)

	HR (95% CI), p-value		
	Biochemical Progression	Metastasis	Prostate Cancer Mortality
Screening group (vs. control)	0.43 (0.23-0.81), p=0.009	0.24 (0.07-0.81), p=0.021	0.44 (0.09-2.09), p=0.302
Organ-confined	0.50 (0.30-0.85), p=0.01	0.48 (0.15-1.53), p=0.213	0.43 (0.12-1.56), p=0.199
RP Gleason	3.1 (2.08-4.72), p<0.001	5.41 (2.17-13.48), p<0.001	4.30 (1.60-11.58), p=0.004
(b)			
Screening group (vs. control)	0.65 (0.27-1.56), p=0.338	0.71 (0.08-6.52), p=0.763	0.47 (0.05-4.41), p=0.509
Organ-confined	0.74 (0.38-1.43), p=0.365	0.44 (0.10-2.02), p=0.293	0.42 (0.07-2.52), p=0.342
RP Gleason	2.56 (1.59-4.12), p<0.001	4.98 (1.70-14.64), p=0.003	5.33 (1.55-18.31), p=0.008
Tumor volume (continuous)	1.31 (1.16-1.49), p<0.001	1.12 (0.90-1.39), p=0.297	1.15 (0.90-1.46), p=0.262

Table 2 shows the Cox proportional hazards models for each endpoint including preoperative features. After adjusting for PSA, clinical stage, biopsy Gleason score, and age, men from the screening arm had significantly better PFS (HR 0.43, 95% CI 0.23-0.83, p=0.011) and metastasis-free survival (HR 0.18, 95% CI 0.06-0.59, p=0.005). The difference in PFS among screened men did not reach statistical significance in the multivariable model (HR 0.59, 95% CI 0.11-3.06, p=0.531), although this analysis was limited by the small number of events.

In multivariable models adjusting for the stage and grade at RP (Table 3a), men from the screening group again had significantly better PFS (HR 0.43, 95% CI 0.23-0.81, p=0.009) and MFS (HR 0.24, 95% CI 0.07-0.81, p=0.021) than men from the control arm. Table 3b shows separate postoperative multivariable models in the subset with tumor volume measurements. After additional adjustment for tumor volume along with stage and grade, there was no longer a statistically significant association between screening arm with PFS and MFS.

DISCUSSION

In the current study, we demonstrated that men from the screening arm of the Rotterdam ERSPC had significantly improved outcomes after RP, as compared to men from the control arm.

Previously, the Swedish Prostate Cancer Group reported a significant reduction in metastasis and cancer-specific mortality in men randomized to RP compared with watchful waiting [9]. The survival advantage persisted in all pathological subgroups, including low-risk disease. Nevertheless, the majority of patients in this study were diagnosed with prostate cancer clinically.

There is less data on the long-term outcomes of RP in screen-detected cases. The PIVOT trial performed at Veterans Affairs hospitals in the USA (~50% T1c) suggested that the benefits of RP were confined to higher risk cases [10].

The present study only included men who had a RP from the screening and control arms of the Rotterdam ERSPC. Although this analysis therefore does not provide data on what the outcomes would have been without treatment, the results do suggest that screening was useful to diagnose higher risk patients within the window of curability. By contrast, controls were diagnosed with higher risk disease and larger tumor volumes, resulting in a reduced likelihood of surgical cure during follow-up.

Further stratification by Gleason score showed that there was a PFS advantage with RP for men in the screening arm compared with controls with Gleason 7-10 disease; whereas, Gleason 6 cases in both arms had better oncological outcomes with no statistically significant difference (data not shown).

One of the most intriguing findings in the present study was that tumor volume appears to be a critical determinant of treatment outcome. This was surprising considering previous findings from our group suggesting that tumor volume was associated with RP outcomes on univariate analysis, but was no longer significant after adjusting for other clinicopathological variables among men with screen-detected prostate cancer [11]. However, the present study included a larger sample size from both the screening and control arms, including a wider range of tumor volumes and longer follow-up for survival endpoints.

Indeed, the current results suggest that one of the ways that screening improves survival outcomes is through a reduction in the volume and therefore burden of disease at diagnosis. It is noteworthy that many of the published criteria for "insignificant" disease incorporate measurements of tumor volume, which are frequently utilized in management decisions [12,13]. The robust relationship between this variable with long-term outcomes suggests that its inclusion in risk stratification tools is appropriate. In the future, it is possible that advances in MRI or other markers may further aid in the assessment of tumor volume prior to definitive therapy [14]. As in prior studies [15], Gleason score was also a robust predictor of RP outcomes.

Several limitations of the study warrant discussion. First, RP specimens were examined at the treating hospital and central pathologic review was not performed. In addition, of the men who were randomized during 1993 to 1999, fewer men in the control arm underwent RP. However, this might be explained, at least in part, by the significantly worse stage distribution in the control arm. For example, in the overall ERSPC trial from which this population was drawn, at 9 years the screening arm had a 41% relative reduction in metastases at diagnosis [1]. Since RP is only indicated for clinically localized disease, fewer men are candidates for this type of curative therapy in the absence of screening. Nevertheless, treatment was not randomly assigned and some of the dif-

ferences between groups may have already been dampened in the process of surgical selection. For example, it is also possible that some patients with higher risk localized disease underwent radiation therapy rather than RP. Although the final sample size was limited with a relatively small number of events, it was sufficient to obtain statistically significant results for survival endpoints.

Lead-time bias can be considered to have affected the results, since screening at 4 year intervals has been shown to advance the diagnosis of prostate cancer by about 11 years with respect to the control arm [16]. Methodology to adjust for lead time bias in the present situation is not available, and it is unclear to what extent this bias can be decreased or even eliminated by reporting outcomes in relation to clinical and pathological prognostic factors. Accordingly, the overall Kaplan-Meier plots must considered as less reliable. Because men in this study were followed for a median of 9.9 years after RP, additional follow-up will be essential for the evaluation of long-term survival endpoints. Finally, we do not have data on the type of RP or surgeon case load, which has been shown to influence outcomes after radical prostatectomy [17].

In conclusion, among men treated by RP from the Rotterdam section of the ERSPC, screen-detected cases had significantly improved PFS, MFS, CSS than controls within the available follow-up time (median 9.9 years). The reduction in biochemical progression and metastases in cases from the screening arm persisted after adjusting for other preoperative features (PSA, clinical stage, Gleason score and age) or RP features (pathological stage and grade). However, subgroup analysis showed that the improved outcomes in the screening group appeared to be mediated by a significantly lower tumor volume. This suggests that a reduction in tumor burden at diagnosis is a mechanism through which PSA screening improves treatment outcomes.

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6 Efficacy and effectiveness study design within the European Randomized Study of Screening for Prostate Cancer: consequences for prostate cancer incidence, overall mortality and prostate cancer-specific mortality

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ABSTRACT

Objective

To assess the impact of different study design on outcome data within the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Methods

Observed data of the Gothenburg center (effectiveness trial with upfront randomization before informed consent) and the Rotterdam center (efficacy trial with randomization after informed consent) were compared to expected data, which were retrieved from national cancer registries and life tables. Endpoints were 11-year cumulative prostate cancer (PC) incidence, overall mortality, and PC-specific mortality.

Results

In Gothenburg, the 11-year PC incidence was in both the intervention (12.4%) and control arm (7.3%) higher than predicted (5.8%). The observed overall mortality in both the intervention (17.8%) and control arm (18.5%) was higher than predicted (15.9%). The observed PC-specific mortality in the intervention arm was 0.56% vs. 0.83% in the control arm, while the expected mortality was 0.83%. In Rotterdam, the observed PC incidence in the intervention arm (10.4%) was higher than expected (4.4%). The incidence in the control arm was 4.6%. The observed overall mortality was lower than expected: 13.6% in the intervention arm and 14.0% in the control arm vs. an expected mortality of 16.1%. The observed PC-specific mortality was in both the intervention arm (0.27%) and control arm (0.41%) lower than expected (0.65%).

Conclusions

Our results suggest that an efficacy trial with informed consent prior to randomization may have introduced a "healthy screenee bias". Therefore, an effectiveness trial with consent after randomization may more accurately estimate the PC-specific mortality reduction if population-based screening is introduced.

INTRODUCTION

Randomized controlled trials (RCT) are the most reliable method of determining the effects of medical interventions [1,2]. Depending on the study design and the aspects of the interventions that the trial aims to evaluate, RCTs can either be classified as efficacy or effectiveness trials [3-5].

Efficacy trials are designed to determine whether an intervention produces the expected results under ideal circumstances [3-5]. Efficacy trials have a few common features. First, participants of efficacy trials are often selected (poorly adherent participants and those with conditions which might dilute the effect are often excluded). Second, the outcomes are indirectly generalizable to the clinical setting in routine practice, meaning that it has to be evaluated whether the effect in the general population will be similar to that in the selected population.

Effectiveness trials on the other hand measure the degree of beneficial effect when the intervention is used in routine practice [3-5]. Participants of effectiveness trial are in principle representative for the general population and the interventions are applied as it would be in common practice. Hence, the outcomes are directly generalizable to routine practice.

The European Randomized Study of Screening for Prostate Cancer (ERSPC, ISRCTN49127736) was initiated to evaluate the effect of screening with prostate-specific antigen (PSA) testing on prostate cancer (PC)-specific mortality [6]. The ERSPC study is conducted in eight countries and each center adhere to a common core study protocol. Due to different legal requirements for running randomized studies, randomization of men into the trial differed among the participating countries. In three centers, men underwent upfront randomization; no written informed consent was necessary before invitation (effectiveness trial). In the other centers, only those who provided written informed upon invitation underwent randomization (efficacy trial) [7,8].

Because of this difference in randomization the estimated benefit of screening might differ between an efficacy and effectiveness trial. Therefore, the present study evaluates potential differences between the Rotterdam and the Gothenburg branch of the ERSPC (efficacy and effectiveness study design respectively), by comparing the observed and expected PC incidence, overall mortality and PC-specific mortality in each center. The findings may contribute to the interpretation of the outcome data of the ERSPC study.

MATERIAL AND METHODS

In both Gothenburg (effectiveness trial) and Rotterdam (efficacy trial), observed data were compared to expected data. The median follow-up was 14.0 years in Gothenburg

(IQR 10.2-14.0) and 11.1 years (IQR 9.4-12.4) in Rotterdam. In order to present robust data and on the basis of the shortest median follow-up, the endpoints were 11-year cumulative PC incidence, overall mortality, and PC-specific mortality.

Observed data

Observed data were retrieved from men participating in the Gothenburg center and the Rotterdam center of the ERSPC. The screening algorithm used in Gothenburg has been described previously [9]. In brief, the study population comprised men from Gothenburg aged 50-64 years at December 31, 1994. Directly from the population registry a total of 10,000 were randomized to the intervention and 10,000 to the control arm. After randomization, men in the intervention arm were invited (with written information of the study) to biennial PSA-screening. Men with a prior diagnosis of PC at randomization (identified through registry linkage with the regional cancer registry) were not invited, nor were those who died or emigrated before the randomization date. Men allocated to the intervention arm were re-invited every second year until they had reached the upper age limit (67-71 years), died, emigrated or were diagnosed with PC. Men in the control arm were not contacted because no informed consent was needed, but the PC incidence and mortality were assured by linkage with the cancer registry.

The screening algorithm used in Rotterdam has been described previously [10]. In summary, men living in Rotterdam and surrounding area aged 55-74 years between December 1, 1993 and December 31, 1999, were identified form population registries and invited to the study. Men with a prior diagnosis of PC were excluded. First, men received an invitation letter together with an information leaflet, providing information about the design and purpose of the study, as well as the screening procedures. After written informed consent was obtained, randomization was carried out. A total of 21,210 were randomized to intervention and 21,166 to the control arm. Men in the intervention arm were invited for PSA-screening with a 4-year interval until the age of 74 years. Men who refused participation at the first screening round were not re-invited at second or following screening rounds. Mortality data of all participants who died in the period up to December 31, 2008 were obtained by linking the trial database with Statistics Netherlands.

In both centers, the PC incidence was routinely checked by means of linkage to the national or regional cancer registry. The cause of death among those men with PC was determined by an independent national causes-of-death committee using predefined flow charts or by an international committee if no consensus was reached [11].

To achieve a similar age distribution between the Gothenburg and Rotterdam study population, only men aged 55-64 years at randomization were included in this study.

Expected data

The expected data were based on men who were similar to the study population with respect to gender, calendar age, calendar year, and country of participation. The expected Swedish data on PC incidence and PC-specific mortality were obtained from the Swedish Cancer Registry at the National Board of Health and Welfare in Sweden. This registry has a coverage close to 100% [12]. Expected overall mortality was calculated both from National and Gothenburg city statistics, also available from the National Board of Health and Welfare in Sweden.

The expected Dutch data with respect to PC incidence and PC-specific mortality were retrieved from the Dutch Cancer Registry, which has a completeness of 98% [13]. The expected overall mortality was obtained from nationwide life-tables from the Human Mortality Database [14]. This database contains original calculations of death rates and life tables for national populations, as well as the input data used in constructing those tables. A detailed description of the methodology is described here (http://www.mortality.org/Public/Docs/MethodsProtocol.pdf).

Statistical analysis

The *observed* cumulative incidence of the three endpoints was calculated as 1 minus the observed survival, which was estimated according to the life table method [15]. The distribution of survival times is divided into a number of intervals. For each interval, the number of subjects that entered the respective interval alive, and the number of events occurred in that interval were computed.

The *expected* mortality of all endpoints was calculated as 1 minus the expected survival. The expected survival rates were calculated according to the established Ederer II method [16,17]. This method is widely used for estimating expected survival, for the purpose of estimating relative survival. The Ederer II approach controls for heterogeneous observed follow-up times by accounting for when the matched individuals are at risk. Confidence intervals were calculated on the log cumulative hazard scale.

All analyses were performed from the time of randomization until the event (diagnosis of PC, death from PC or overall death), emigration or last follow-up, which occurred first. Statistical analyses were carried out with STATA Statistical Software, release 11 (StataCorp LP, College Station, TX, USA), subroutine "strs" (http://www.pauldickman.com/rsmodel/stata_colon/).

RESULTS

After age selection, 5,896 men in the intervention arm and 5,950 men in the control arm were included in Gothenburg. In Rotterdam, 12,422 men were included in the interven-

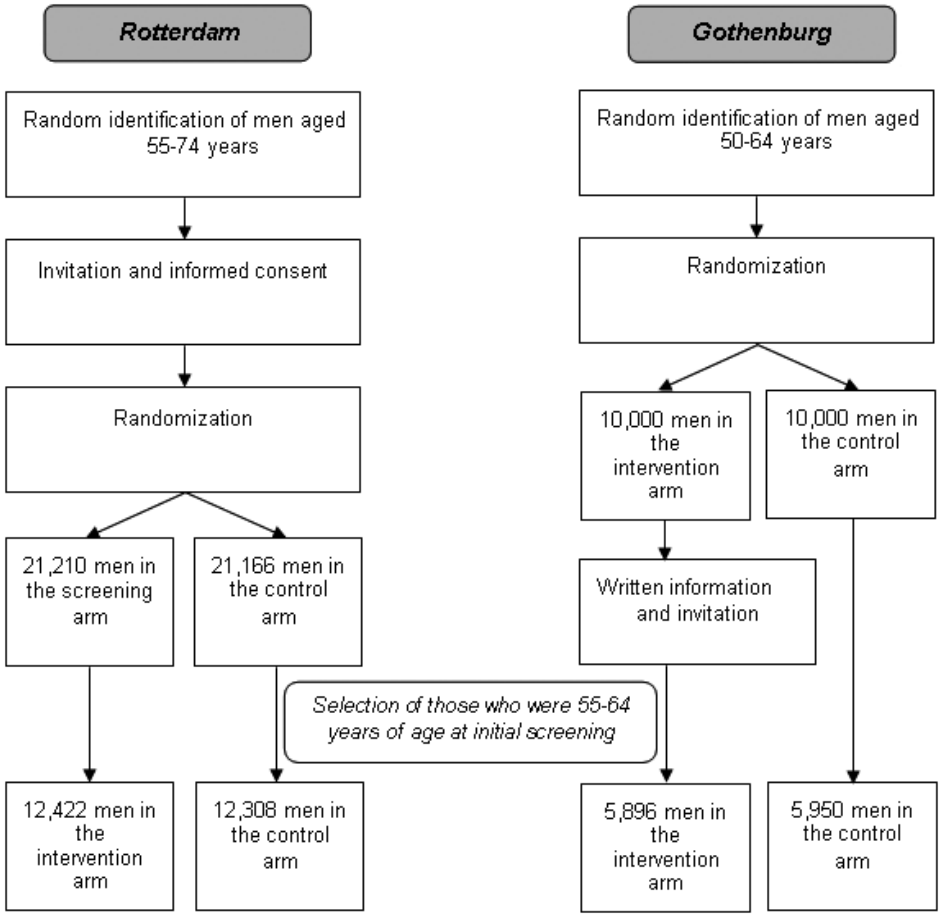

Figure 1: Flowchart of the observed data

tion arm and 12,308 men were included in the control arm (Figure 1). Overall, 76.0% of the men allocated to the intervention arm participated in at least one screening round in Gothenburg. In Rotterdam, where consent was obtained before random assignment, the response rate for participation and thus randomization was 48.1%. Of all men randomized to the intervention arm in Rotterdam, 94.2% participated in the first screening round resulting in a net participation rate of 45.3%. Figures 2-4 illustrate the observed and expected cumulative incidences. Again, it should be noted that the median follow-up is 11 years in Rotterdam vs. 14 years in Gothenburg.

PC incidence

PC incidence in both intervention and control arm are presented in Figure 2A (Gothenburg) and 2B (Rotterdam). In the Gothenburg study, the observed 11-year cumulative PC incidence was 12.4% (95% CI 11.5-13.3%) in the intervention arm and 7.3% (95% CI

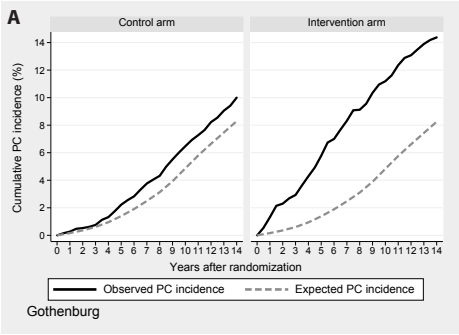

Figure 2A: Observed and expected prostate cancer incidence Gothenburg

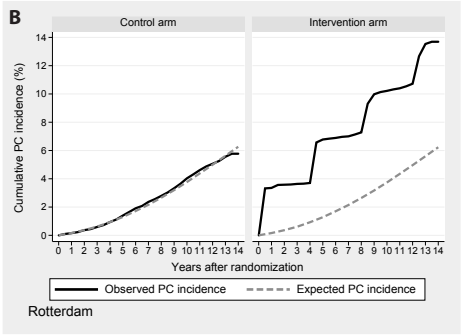

Figure 2B: Observed and expected prostate cancer incidence Rotterdam

6.6-8.0%) in the control arm; both of them higher than the expected cumulative PC incidence of 5.8%. In the Rotterdam study, the observed 11-year cumulative PC incidence in the intervention arm (10.4%, 95% CI 9.9-11.0%) was also higher than the expected cumulative incidence (4.4%). The incidence in the control arm was 4.6% (95% CI 4.2-5.0%).

6

Overall mortality

Figure 3A (Gothenburg) and 3B (Rotterdam) show the observed and expected overall mortality in both centers. In the Gothenburg study, the observed 11-year cumulative overall mortality after randomization was 17.8% (95% CI 16.6-18.8%) in the intervention arm and 18.5% (95% CI 17.6-19.5%) in the control arm. Both rates were higher than the expected cumulative incidence based on the Swedish general population (15.9%), but similar to the cumulative incidence based on the Gothenburg city statistics (17.9%). In the Rotterdam study, the observed 11-year cumulative overall mortality was lower than the expected cumulative overall mortality (13.6% [95% CI 13.0-14.2%] in the intervention arm and 14.0% [95% CI 13.4-14.7%] in the control arm vs. expected incidence of 16.1%).

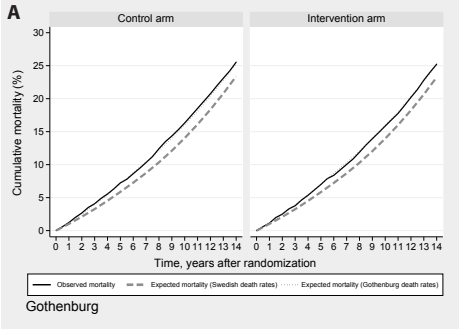

Figure 3A: Observed and expected overall mortality Gothenburg

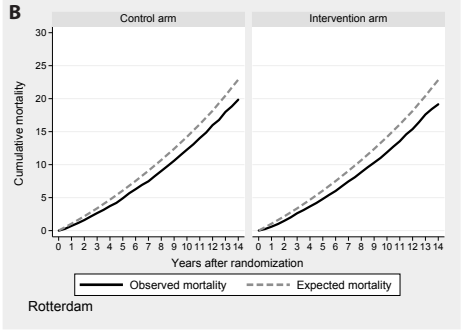

Figure 3B: Observed and expected overall mortality Rotterdam

PC-specific mortality

Figure 4A (Gothenburg) and 4B (Rotterdam) present the observed and expected PC-specific mortality in both centers. In the Gothenburg study, the observed 11-year cumulative PC-specific mortality was 0.56% (95% CI 0.39-0.81%) in the intervention arm, and 0.83% (95% CI 0.61-1.12%) in the control arm compared to the expected cumulative incidence of 0.83%. In the Rotterdam study, the observed 11-year cumulative PC-specific mortality was 0.27% (95% CI 0.19-0.39%) in the intervention arm and 0.41% (95% CI 0.30-0.55%) in the control arm, whereas the expected cumulative incidence was 0.65%.

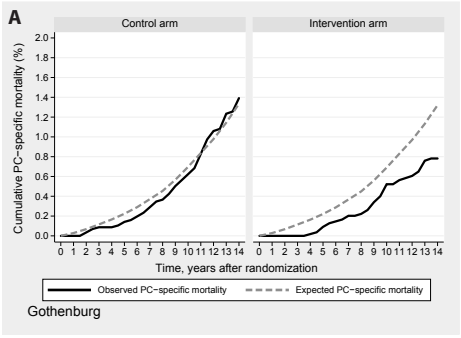

Figure 4A: Observed and expected prostate cancer-specific mortality Gothenburg

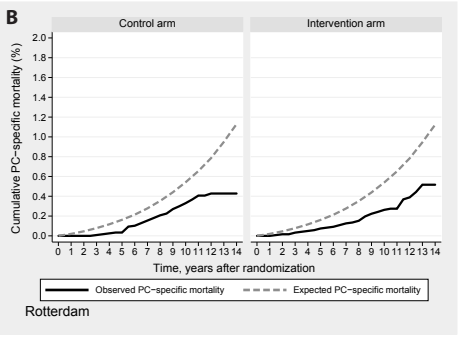

Figure 4B: Observed and expected prostate cancer-specific mortality Rotterdam

DISCUSSION

The United States Preventive Services Task Force recently reviewed the literature on PC screening and released an updated draft recommendation against PSA screening [18]. There is insufficient evidence that the benefits outweigh the harms. One of the reasons is that some screening trials did not show benefit in terms of mortality reduction. Therefore, it is critical to understand the mechanisms behind the different outcomes within the trials.

In this study, we provide a unique opportunity to interpret the outcome data of the ERSPC study by investigating the impact of a different study design within the multicenter screening trial.

Gothenburg

In Gothenburg, the observed overall mortality in both the intervention and in the control arm were higher than the expected Swedish data, but similar to the expected Gothenburg city data (Figure 3A). This "city effect" is in line with observations from previous studies, reporting that men living in urban areas have a worse health status and shorter life expectancy than those in rural areas [19,20].

A second important finding is that the observed PC incidence in the control arm is higher than expected. This may be due to the higher rate of contamination (i.e. use of PSA testing in the control arm) in the study cohort than anticipated in the general population, although this would be somewhat unexpected since men in the control arm were not contacted about the study. Recent studies however showed that approximately one-third of all Swedish men aged 50-75 years had a PSA test between the years 2000 and 2007 but with large geographical differences and rather high rate of contamination in the Gothenburg area [21,22].

The observed and predicted PC-specific mortality in the control arm were similar in Gothenburg despite the higher observed PC incidence than expected. This indicates that the un-organized PSA testing that has taken place in the control arm has not influenced PC-specific mortality so far. Also at a national level there have been no signs of decreased PC-specific mortality in Sweden despite a steadily increasing PC incidence [21]. However, in the present study the excess incidence was rather low the first three years (Figure 2A). Therefore, the effect of contamination on PC-specific mortality may show up with longer follow-up.

Rotterdam

In Rotterdam, the overall mortality for men in both intervention and control arm were lower than expected. This can be explained by the so-called "healthy screenee bias" which has been introduced in the Rotterdam cohort [23]. Previous studies have shown that men who chose to participate were healthier than men in the general population [24-26].

Another finding in Rotterdam is that the observed and the expected PC incidence in the control arm were almost identical. This seems to be unexpected because of a peak in contamination in the control arm within the first months of randomization and an estimated overall contamination rate between 25-40% [27,28]. It is possible that a similar trend in PSA-testing and contamination has taken place in the general Dutch population and has resulted in the similar observed and expected PC incidence.

Interestingly, men in the control arm of Rotterdam were at a lower risk of dying from PC than expected despite similar observed and expected PC incidence. An important explanation for this outcome is the healthy screenee bias which occurred as a result of the applied efficacy study design. Approximately 11% of men who signed the informed consent and thus participated in the Rotterdam center underwent PSA-testing within four years before study entry [29]. This may have led to "pre-selection" of the study population at baseline, which has been suggested as one of the possible explanations why no screening benefit was demonstrated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [30]. Furthermore, the PC-specific mortality may have been lower in the control arm because they were in better health than men in the general population: although debatable, there is some evidence that comorbidity

(e.g. obesity and metabolic syndrome) is associated with increased risk of dying from PC [31,32]. In addition, early contamination in the control arm [27] is likely to have resulted in detection of cancers with more favorable prognostic factors [33,34] and also contributes to the lower observed PC-specific mortality than expected. However, it is unlikely to be able to determine the precise effect of each of these explanations on the lower observed PC-specific mortality. An alternative explanation could be a still undetermined environmental factor; therefore the exact mechanism behind the difference in observed and expected incidence has yet to be elucidated. To our knowledge this difference in observed versus expected cancer-specific mortality has not been described in randomized studies for other cancers.

Notably, the observed PC mortality in Rotterdam appears to have reached a plateau after 11 years, especially in the control arm. However, it is difficult to determine at this point whether this is an effect of the study design or due to the incomplete follow-up. Nevertheless, these few events late in the study will not change the overall results.

Implications

As a consequence of the efficacy design, the study cohort in Rotterdam appears to be a selected, "healthier" group when compared to the general population. This has been reflected in lower overall mortality and more importantly, lower PC-specific mortality in the control arm than expected. In turn, this may lead to underestimation of the PC-specific mortality reduction and the "true" screening effect. The same is probably true for studies with similar design as for example the PLCO trial. Despite its nearly 4-fold size of study population and higher average age at randomization, the number of men dying from PC in the PLCO trial (n=158) [35] was about twice as high as in the Gothenburg trial (n=78) [36]. Also, the PLCO trial took place in the United States, where PSA testing was already widespread; the ERSPC was conducted in Europe, where background rates of PSA testing were very low. Moreover, 40% of men in the control arm in the PLCO trial underwent PSA testing in the first year, with contamination reaching 52% by year six. Contamination in the ERPSC in the early years was no more than 15% [30].

Because of the effectiveness design, the trial in Gothenburg was carried out in a population-based cohort. Men from the control arm were not aware of their participation in the trial, and the PC-specific mortality in the control arm is similar to that in the general population. Therefore, although in both Rotterdam and Gothenburg a lower PC-specific mortality was observed in the intervention arm compared to the control arm, the achieved reduction of PC-specific mortality in Gothenburg may be more representative for the "true" effect of PSA-testing when a population-based screening program is introduced. The difference in randomization may also partly explain the observations made in the main reports of the ERPSC [7, 8] showing that Gothenburg strongly contributes to the achieved mortality reduction.

Limitations

Some limitations of the present study should be discussed. First, we did not compare the observed outcomes between Gothenburg and Rotterdam. Clearly, this would be interesting, but the purpose of this study was to relate the observed data with the predicted in each center and not to make a head-to-head comparison between the two branches of the ERSPC study. Such comparison would necessarily need an analysis of all other existing differences, such as background risk [37], screening algorithms [38], contamination rate and treatment. Second, unlike the expected data, the observed data do not include men with prevalent PC. This may have led to an underestimation of the PC-specific mortality in the observed data. Third, in Gothenburg we compared the observed data on overall mortality with both Swedish and Gothenburg-specific expected data; it would be interesting to make the same comparisons in Rotterdam as well. The Rotterdam-specific expected data were however not available. Should the mortality in Rotterdam be lower than in the general Dutch population, the interpretation of the results might differ. Last, the results are based on a screening trial with a single PSA threshold for all participants; therefore, the conclusions are probably not applicable when an individualized risk-based screening strategy is implemented.

In conclusion, the difference in study design is likely to have contributed to discrepancies in the observed data and the expected data, in terms of PC incidence, overall mortality and more importantly PC-specific mortality. The observed PC-specific mortality in the control arm in a screening trial with randomization after informed consent (efficacy trial) appears to be lower than expected when compared to a trial with randomization prior to informed consent (effectiveness trial). This may result in underestimation of the PC mortality reduction. Our results suggest that an effectiveness trial may more accurately estimate PC-specific mortality reduction if population-based screening is introduced. Obviously, other factors such as false-negative screening tests and unnecessary biopsies, overdiagnosis, quality of life and costs must be considered before a screening program can be launched.

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III Prostate cancer mortality in the screening arm

Chapter 7

Identifying and characterizing "escapes" – men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam)

Chapter 8

Disease-specific survival of men with prostate cancer detected during the screening interval: results of the European Randomized Study of Screening for Prostate Cancer-Rotterdam after 11 years of follow-up

Chapter 9

Overestimation of prostate cancer mortality and other-cause mortality by the Kaplan-Meier method

7 Identifying and characterizing "escapes" – men who develop metastases or die from prostate cancer despite screening (ERSPC, section Rotterdam)

Int J Cancer 2011

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ABSTRACT

We aim to identify and characterize "escapes", men who developed metastasis and/or died from PCa in spite of screening, in the framework of the novel international ESCAPE-project. With this knowledge, the ultimate goal is improve screening strategy. In this paper, we focus on the study cohort of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam. In all, 21210 men were randomized to the screening arm of whom 19950 were actually screened. The screening interval was 4 years. Men with PSA ≥3.0 ng/mL were recommended to undergo lateralized sextant prostate biopsy. The follow-up was complete until January 1, 2009. Of the 19950 screened men, 2317 were diagnosed with PCa. Of these cancers 1946 were detected in a screening round and 371 during an interval. The median follow-up was 11.1 years for the whole cohort and 7.3 years for men diagnosed with PCa. In total we identified 168 escapes among 2317 cancers (7.3%) within our screening cohort of 19950 men (0.8%). More than half of these escapes were found in the initial screening round (94 out of 168). Possible mechanisms behind escaping are non-attending, inadequate screening tests, the relative long screening interval, the age cut-off at 75 years and undertreatment. International co-operation is crucial to compare the escapes of our cohort with other study groups participating in the ESCAPE-project which have different, more aggressive screening strategies. Subsequently, we can achieve improvements of the current screening algorithm, which hopefully will further decrease PCa-specific mortality without increasing overdiagnosis and overtreatment.

INTRODUCTION

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has recently published the results of the third interim analysis. A significant difference in prostate cancer (PCa) mortality has been shown in favor of screening of 20% in the intention-to-screen analysis [1]. In a secondary analysis adjusted for non-compliance and the use of PSA driven testing in the control arm, the benefit of screening in terms of PCa mortality increases to about 30% [2]. Screening also significantly reduces the occurrence of metastatic PCa. The intention-to-screen analysis showed a relative risk reduction of 25% in favor of screening, whereas the secondary analysis demonstrated a reduction of 32% [3]. Downsides of the results of ERSPC are the large number of men needed to be screened and the large number of cancers needed to be treated in order to save one life.

An aspect that is poorly understood at this time is the substantial proportion of men who escape all efforts of treatment and develop metastasis or die from PCa in spite of screening. In this paper, we define "escapes" as men who had metastatic PCa at diagnosis, or developed metastases and/or died from PCa. The 20-30% relative risk reduction of PCa death seen in ERSPC shows that 70-80% of all PCa deaths in the screened population occurred despite screening. Although it is unlikely that all PCa deaths can be avoided, it is reasonable to suggest that a part of these deaths are *preventable* with better screening regimens and treatment. Such avoidable cases may be identified by comparing ERSPC-detected cancers to those detected by different, more stringent screening regimens, hopefully resulting in a further decrease in PCa-specific mortality. In order to have sufficient number of events and be able to compare different screening strategies, international co-operation is crucial.

Further research will also include identifying the proportion of *unpreventable* escapes. One study shows that with the most aggressive screening method and radical treatment, some men still have cancers that develop and progress so fast that they die from PCa [4].

Recently a novel international consortium, the so-called ESCAPE-project group has been established. Participating centers in the ESCAPE-project include study groups of the Washington University [5-7], Johns Hopkins University [8,9] and ERSPC, section Rotterdam (Erasmus MC, University Medical Center) [10,11]. In this report, we present the first step of this ambitious project by identifying and characterizing "escapes" within the screening arm of ERSPC Rotterdam. With this knowledge the ultimate goal is to improve current screening strategies.

MATERIAL AND METHODS

Characterization of the study population

The ERSPC is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening on PCa-specific mortality. Presence of PCa was excluded prior to randomization. In section Rotterdam upfront written informed consent was used (efficacy trial). Men were screened at 4-year intervals. A prostate biopsy was indicated for men with a PSA level ≥ 4.0 ng/mL and/or abnormal digital rectal examination (DRE) and/or transrectal ultrasound examination (TRUS). Since May 1997, a PSA threshold of ≥ 3.0 ng/mL has been used as the sole screen-test. In screen-positive men, sextant biopsies were indicated; they were lateralized from June 1996, as described by Eskew [12]. An additional biopsy was taken from any suspicious area on TRUS. After PCa had been diagnosed, the treatment decisions were left to the regional health care providers. The total Rotterdam study cohort (n=42376 men; screening arm 21210 men and control arm 21166 men) and the screening algorithm have been described previously [13].

Of the 21210 men randomized to the screening arm, 19970 were actually screened in the first round. In this initial round, 20 men were found to have PCa diagnosed previously and were excluded from further analysis as this was the exclusion criterion for participation in the ERSPC. The remaining cohort of 19950 men was eligible for our analysis. At 4 and 8 years after the initial screening round, these men were invited to undergo repeat screening unless they had passed the age of 75 years. Men who did not attend a screening round were not re-invited for further screening. The follow-up with respect to clinical evaluations, deaths and cause of death was complete up to January 1, 2009.

Definition of escapes

For this study, we selected men who had been diagnosed with metastatic PCa at diagnosis or during follow-up, and/or who had died from PCa within ERSPC Rotterdam. These cases are defined as "escapes". Metastatic disease was defined as distant metastases identified by imaging or, when data on bone scans were missing, by a PSA level > 100 ng/mL. Deaths from PCa were determined by an independent cause-of-death committee, according to a standard algorithm [14]. The categories of "definitely PCa death", "probably PCa death", and "intervention-related deaths" were used as primary outcome measures for disease-specific mortality.

We defined screen-detected cancer as cancer diagnosed in a formal protocol screening round. Interval cancer was defined as cancer detected outside the study protocol (due to clinical symptoms, opportunistic screening, TURP for benign disease or cystoprostatectomy specimens).

To characterize the escapes, data were collected regarding age, PSA level, clinical stage, and Gleason score. As we were interested in the clinical features of the escapes

at diagnosis, a clinically relevant classification of high-risk cancer was made. This was defined as PCa with ≥ cT3, or PSA > 20 ng/mL, or Gleason score ≥ 8 according to the 2002 American Joint Commission on Cancer [15]. The tumor classification T2c was not included in the high-risk classification for this analysis, because studies suggest that men with such cancers have outcomes similar to those of men with intermediate-risk PCa [16].

Stage and grade classification

All cancers were classified according to the TNM 1992 classification and graded using the Gleason grading system [17,18].

RESULTS

The study population is shown in the flow diagram in figure 1. From December 1993 up to January 2009, 2317 men were diagnosed with PCa, see table 1. Of these cancers, 1946 were detected in a screening round and 371 were detected during an interval. The exact numbers of cases per screening round and interval are given in table 1.

Up to January 2009, 2317 men were diagnosed with PCa in a screening round or during an interval: 40 men had metastatic disease at diagnosis of whom 20 died from PCa; 115 men developed metastases during follow-up of whom 72 died from PCa; and 13 men died from PCa without records of clinically observed metastases (8 men were attributed

Table 1. No. of screened men, prostate cancers (PCa) and escapes^ with follow-up time

	No. (%) of cases		No. (% of PCa) of escapes				Median time, years	
	No. at risk	PCa	Metastasis at diagnosis	Metastasis during follow-up	PCa death	Total	Follow-up*	Diagnosis to escape`
Round 1	19950	1078 (5.4)	9 (0.8)	80 (7.4)	61 (5.7)	94 (8.7)	10.3	6.1
Interval 1	18872	75 (0.4)	4 (5.3)	7 (9.3)	9 (12.0)	12 (16.0)	6.6	1.6
Round 2	12529	550 (4.4)	3 (0.5)	7 (1.3)	6 (1.1)	12 (2.2)	7.1	1.9
Interval 2	11979	151 (1.3)	10 (6.6)	9 (6.0)	14 (9.3)	21 (13.9)	4.1	0.2
Round 3	7739	318 (4.1)	0	2 (0.6)	3 (0.9)	3 (0.9)	2.7	1.0
Interval 3	7421	145 (2.0)	14 (9.7)	10 (6.9)	12 (8.3)	26 (17.9)	1.7	0.0
Screen-detected		1946	12 (0.6)	89 (4.6)	70 (3.6)	109 (5.6)	8.2	5.7
Interval detected		371	28 (7.5)	26 (7.0)	35 (9.4)	59 (16.0)	3.3	0.2
Totals		2317	40 (1.0)	115 (5.0)	105 (4.5)	168 (7.3)	7.3	3.3

^ defined as men with metastatic PCa at diagnosis or during follow-up and/or men who died from PCa
* from diagnosis until escape or death or censoring date January 1, 2009; relates to all men with PCa
` relates only to escapes

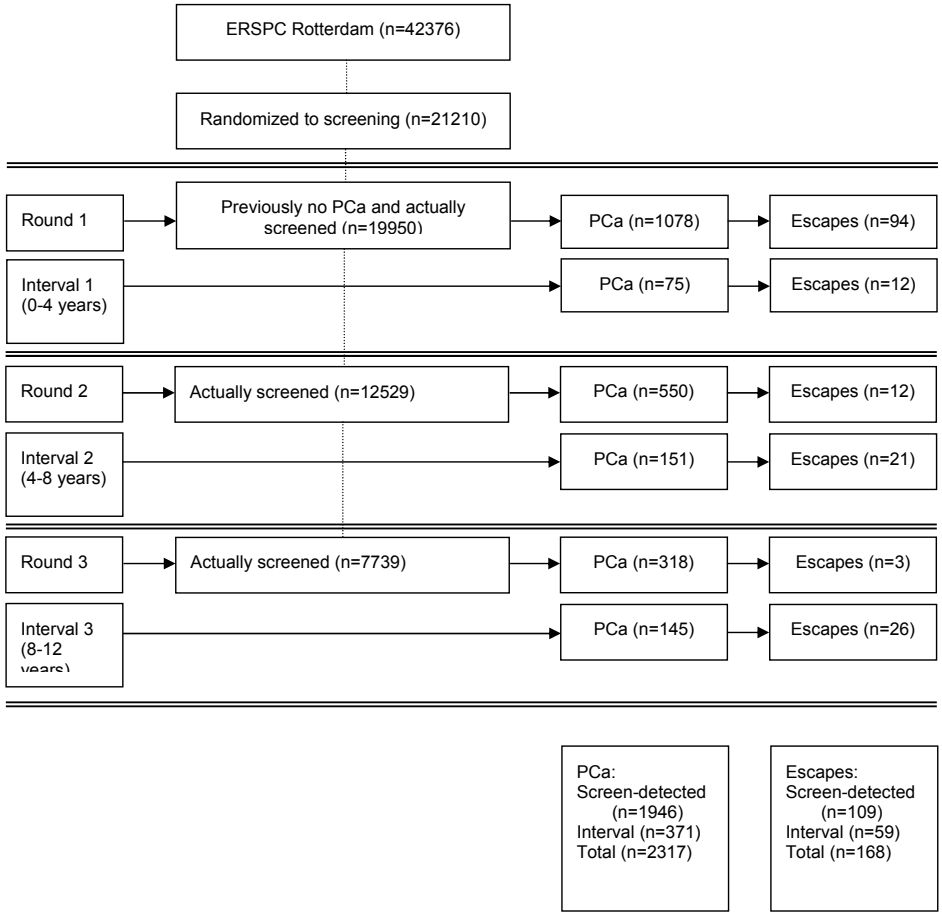

Figure 1. Flow diagram of the study population.

as "intervention-related deaths"; in 5 cases the information on dissemination was very limited). Thus, in total we identified 168 escapes (109 in a screening round and 59 during an interval). The proportion of escapes in the initial screening round was 56% (94 out of 168).

The median follow-up for the screening cohort of 19950 men was 11.1 years. For men diagnosed with PCa the median follow-up was 7.3 years, starting at time of diagnosis. The median time from diagnosis to escape was 3.3 years. For screen-detected escapes this was 5.7 years, in contrast to only 0.2 year for interval escapes.

The characteristics of all escapes are outlined in table 2. The median age at diagnosis was 68 years for screen-detected escapes, and 74 years for interval escapes. Of all escapes, 80 (47.6%) were clinically localized (≤ cT2) at diagnosis. Among the screen-detected escapes, 75 (68.8%) men had a Gleason score of ≤7. In the interval escapes, 15 (25.4%) men had a Gleason score ≤7. The proportion of high-risk PCa detected in a screening

Table 2. Characteristics of escapes^

		No. (%) of cases								
		Round 1 (n=94)	Interval 1 (n=12)	Round 2 (n=12)	Interval 2 (n=21)	Round 3 (n=3)	Interval 3 (n=26)	Screen-detected (n=109)	Interval-detected (n=59)	Total (n=168)
Age at baseline	years, median	68	71	63	68	62	69	67	70	68
Age at diagnosis	years, median	68	72	67	74	70	77	68	74	69
PSA at baseline	ng/ml, median	16.3	9.3	2.5	2.6	1.7	1.7	12.7	2.6	7.6
PSA at diagnosis	ng/ml, median	16.3	42	5.4	54	82	102	13.6	56.6	20.3
Clinical T stage	T1	15 (16.0)	3 (25)	5 (41.7)	6 (28.3)	1 (33.3)	6 (23.1)	21 (19.3)	15 (25.4)	36 (21.4)
	T2	23 (24.5)	3 (25)	7 (58.3)	3 (14.3)	1 (33.3)	7 (26.9)	31 (28.4)	13 (22)	44 (26.2)
	≤T2	38 (40.4)	6 (50)	12 (100)	9 (42.9)	2 (66.7)	13 (50)	52 (47.7)	28 (47.5)	80 (47.6)
	T3	50 (53.2)	4 (33.3)	0	7 (33.3)	1 (33.3)	5 (19.2)	51 (46.8)	16 (27.1)	67 (39.9)
	T4	6 (6.4)	2 (16.7)	0	5 (23.8)	0	6 (23.1)	6 (5.5)	13 (22)	19 (11.3)
	Unknown	0	0	0	0	0	2 (7.7)	0	2 (3.4)	2 (1.2)
Gleason score	≤6	21 (22.3)	2 (16.7)	5 (41.7)	1 (4.8)	1 (33.3)	4 (15.4)	27 (24.8)	7 (11.9)	34 (20.2)
	7	43 (45.7)	0	4 (33.3)	3 (14.3)	1 (33.3)	5 (19.2)	48 (44.0)	8 (13.6)	56 (33.3)
	≤7	64 (68.1)	2 (16.7)	9 (75)	4 (19.0)	2 (66.7)	9 (34.6)	75 (68.8)	15 (25.4)	90 (53.6)
	≥8	30 (31.9)	2 (16.7)	3 (25)	8 (38.1)	1 (33.3)	15 (57.7)	34 (31.2)	25 (42.4)	59 (35.1)
	Unknown	0	8 (66.7)	0	9 (50)	0	2 (7.7)	0	19 (32.2)	19 (11.3)
High-risk PCa at diagnosis*		74 (78.7)	9 (75)	3 (25)	17 (81.0)	2 (66.7)	24 (92.3)	79 (72.5)	50 (84.7)	129 (76.8)

^ defined as men with metastatic PCa at diagnosis or during follow-up and/or men who died from PCa

* defined as 2002 American Joint Commission on Cancer clinical stage ≥ T_3, or PSA > 20 ng/ml, or Gleason score ≥ 8

round varied from 25% to 78.7%. For those escapes detected during an interval, 75% to 92.3% were high-risk at diagnosis.

Table 3 gives details of the characteristics of the interval escapes. Some of these were lost as they decided not to continue after PSA testing, others did not attend the last scheduled round, and still others passed the age cutoff and were therefore not re-invited for screening. Of the 59 interval escapes, 13 actually attended the last scheduled screening round. Twenty-five men were over the age cutoff of 75 years: the median age of these men at diagnosis was 81 years.

The initial treatment modalities of the escapes are listed in table 4. Radical prostatectomy was the initial therapy in 14.7% of the screen-detected escapes but in only 1.7%

Table 3. Specification of interval escapes^

	No. (% of total escapes) of cases				
	High-risk PCa at diagnosis*	Metastasis at diagnosis	Metastasis during follow-up	PCa death	Total escapes
Interval 1, lost after PSA test	6 (85.7)	1 (14.3)	5 (71.4)	5 (71.4)	7
Interval 1, attended	3 (60)	3 (60)	2 (40)	4 (80)	5
Interval 2, attended	4 (66.7)	2 (33.3)	3 (50)	3 (50)	6
Interval 2, not attended	6 (100)	3 (50)	2 (33.3)	5 (83.3)	6
Interval 2, too old	7 (77.8)	5 (55.6)	4 (44.4)	6 (66.7)	9
Interval 3, attended	2 (100)	2 (100)	0	1 (50)	2
Interval 3, not attended	7 (87.5)	5 (62.5)	3 (37.5)	1 (12.5)	8
Interval 3, too old	15 (93.8)	7 (43.8)	7 (43.8)	10 (62.5)	16
Totals	50 (84.7)	28 (47.5)	26 (44.1)	35 (59.3)	59

^ defined as men with metastatic PCa at diagnosis or during follow-up and/or men who died from PCa
* defined as 2002 American Joint Commission on Cancer clinical stage ≥ T3, or PSA > 20 ng/ml, or Gleason score ≥ 8

Table 4. Modality of initial treatment among escapes^

	Escapes	Initial treatment, No. (%) of cases				
		Radical prostatectomy	Radiotherapy	Androgen deprivation	Active surveillance	Watchful waiting
Round 1	94	12 (12.8)	67 (71.3)	11 (11.7)	0	4 (4.3)
Interval 1	12	0	6 (50)	6 (50)	0	0
Round 2	12	3 (25)	3 (25)	2 (16.7)	3 (25)	1 (8.3)
Interval 2	21	1 (4.8)	2 (9.5)	16 (76.2)	0	2 (9.5)
Round 3	3	1 (33.3)	0	2 (66.7)	0	0
Interval 3	26	0	2 (7.7)	21 (80.7)	0	3 (11.5)
Screen-detected	109	16 (14.7)	70 (64.2)	15 (13.8)	3 (2.8)	5 (4.6)
Interval-detected	59	1 (1.7)	10 (16.9)	43 (72.9)	0	5 (8.5)
Totals	168	17 (10.1)	80 (47.6)	58 (34.5)	3 (1.8)	10 (6.0)

^ defined as men with metastatic PCa at diagnosis or during follow-up and/or men who died from PCa

of the interval escapes. The proportions of radiotherapy as initial treatment were 64.2% for the screen-detected escapes and 16.9% for the interval escapes. 13.8% of the screen-detected escapes received androgen deprivation as initial treatment, vs. 72.9% of the interval escapes.

DISCUSSION

In this paper we present the first step of a novel international co-operation, the so-called ESCAPE-project. We identified and characterized men who had metastatic PCa at diagnosis or during follow-up, and/or who died from PCa within the screening arm of ERSPC, section Rotterdam. The rationale behind this approach is that a substantial proportion of men still develop metastases or die from PCa despite screening. Some of these events might be avoidable. To our knowledge this the first paper describing in detail the characteristics of the cancers which escape systematic screening. Comparing the characteristics of escapes between different study cohorts in the future will provide information to improve the screening algorithm. Furthermore, a certain quantity of cancers may become identifable upfront as unavoidable 'escapes' (e.g. non-attenders). We then could estimate which proportion of detectable cancers may be missed because they cannot be cured anyway. Such knowledge will provide the baseline for the future development of strategies which decrease the numbers of "unnecessary" biopsies [19]. Obviously, the emphasis is on *what proportion*, as it is yet not possible to predict *which cancers* will escape with present screening tests.

We identified 168 escapes, that is 7.3% of all cancers (screen-detected and interval) and 0.8% of all men in the screening arm of ERSPC, section Rotterdam. The percentage escapes of men diagnosed with PCa at screening was 8.7% in the initial round (prevalence screen). This percentage dropped to 2.2% in the second and 0.9% in the third round (incidence screens) indicating a certain degree of effectiveness of the applied screening algorithm used. The higher proportion (94 of 168) escapes at the prevalence screen is not unexpected. It can be explained by more unfavorable characteristics of the cancers detected at that time as more aggressive PCa were diagnosed compared to cancers at the incidence screens [20]. The prevalence screen from our study in fact represents a cross-section of an unscreened population. Some studies have regarded patients presenting with disease at the first screening (prevalent cases) as unscreened [21]. Applying this rule will exclude 94 escapes and decrease the number of escapes by more than 50%. As we agree that the prevalent cases should be looked at differently, we don't believe that they should be excluded. The reason is that in the control arm the prevalent cases are present in the same quantity. Therefore, excluding the prevalent cases in the screening arm will lead to an imbalance, which will confound the efficacy

of the screening trial. In addition, we should keep in mind that the follow-up of men detected with PCa at the prevalence screen is longer. Therefore it seems inevitable that more events (i.e. metastasis and PCa death) could occur.

Stage redistribution among screen-detected escapes has been observed in consecutive rounds. All escapes found in the second round were clinically localized (≤cT2), compared to the 40.4% in the first round. The contrast was less obvious between the third and the first round, possibly due to the small numbers of escapes in the third round. Overall, nearly half (47.6%) of the escapes were localized PCa at diagnosis in our study. This finding supports the hypothesis that the usefulness of clinical stage in predicting outcomes is questionnable by use of presently available tools [22].

It is important to determine the cause of escape. We should ask ourselves whether the mechanism behind escaping is inappropiate screening strategy or insufficient therapy or perhaps a combination of those two. First, we will adress the possible limitations in our present screening strategy.

One reason for escape is the number of biopsies taken during screening. Perhaps more extended biopsies may have improved the quality of screening and provided ability to decrease the number of escapes. It has been shown that adding four lateral biopsies to the sextant protocol will increase the detection rate by 25.5% [23]. On the other hand, Schröder et al. recently studied potentially missed cancers in men with initial negative sextant biopsies [11]. Based on the data from ERSPC Rotterdam and 11-year follow-up, the authors concluded that the number of potentially missed cancers with a poor outcome in terms of progression-free survival and deaths from PCa is very low. Hence, sextant biopsy doesn't seem to be obsolete if repeated screening is applied.

A noticeable finding among the 59 interval escapes is that 25 (42.4%) were no longer screened as they passed the age of 75 years at the time of the scheduled screening round. The median age of these men in the last attended screening round was 73 years, with a median PSA of 3.0 ng/mL at that time. At diagnosis, the median age was 81 years with a median PSA of 83.5 ng/mL. Although it is beyond the scope of this study to arbitrate the age cutoff for screening, we should consider that a part of the older men still develop high-risk PCa and/or die from PCa. This observation is in concordance with evidence that older men are more likely to develop tumors of a higher grade than are younger patients [24,25]. Individualized decisions about the optimal age of cessation regarding screening should therefore be based on patient health status but not on chronological age [26]. Another finding from table 3 is that only 13 of the 59 interval escapes actually attended the last scheduled screening round. The other 46 men passed the age cutoff, simply did not attend the last round or were lost after PSA test. It is justified to state that the first mentioned 13 men truly escaped. Translating this observation to population-based screening we must assume that some cancers will always escape due to non-attending. This finding is in line with the observations by Bergdahl et al.[27]. The authors reported

a higher cumulative PCa mortality among non-attendees. At 13 years the cumulative PCa mortality was 0.8% among non-attendees compared with 0.3% among attendees ($p<0.005$).

A potential limitation of the current screening algorithm may be the duration of the chosen screening interval. The very high PSA level at diagnosis (56.6 ng/mL) among interval escapes might suggest that the current interval of 4 years is too long. However, in this study the group of interval cancers is heterogeneous and also includes men who were no longer screened because they had passed the age cutoff. For future purposes of determining the optimal screening interval, only "true" interval cancers (i.e. excluding men who were not compliant to biopsy recommendation and men who were diagnosed *after* a time period equal to the screening interval) should be taken into account. Nevertheless, preliminary observations using the incidence of advanced disease as the endpoint do not suggest a difference between two and four yearly screening [28]. Obviously, more evidence on this issue is warranted.

Another possible mechanisme behind escaping is undertreatment. In ERSPC Rotterdam, 57.7% of the escapes initially received either radical prostatectomy (RP) or radiotherapy, compared to approximately 61% of the screening arm for the whole ERSPC [1]. Although these treatment rates are similar, it is still possible that a part of these escapes were undertreated. It has been demonstrated that immediate postoperative radiotherapy after surgery significantly improves 5-year clinical or biological survival by approximately 20% [29]. Therefore, we analyzed in detail the treatment modalities of the 52 screen-detected escapes which were clinically localized (≤cT2) at diagnosis. These men were classified initially as "curable". Of them, 13 were treated with RP (25%) with, however, two intervention-related deaths. Pathologic findings at prostatectomy revealed that 3 specimens were ≤pT2 and 10 were ≥pT3. Of the eight men suitable for adjuvant radiotherapy, three men received it. This may suggest that the other five men were undertreated. Nevertheless, these numbers are too small to draw any definite conclusions. Furthermore, evidence is still lacking that immediate adjuvant radiotherapy improves metastasis-free survival and disease-specific survival in PCa patients [30].

Besides men who underwent radical prostatectomy, 29 of the 52 escapes who were "curable" at diagnosis received radiotherapy (55.8%) as first treatment modality. None of them were treated with immediate adjuvant androgen deprivation. Several authors reported that immediate androgen deprivation with an LHRH agonist given after radiotherapy improves both overall and disease-specific survival [31,32]. Therefore, a part of these men may have benefited from immediate adjuvant therapy. However, due to the discrepancy in patient characteristics between these trials and our limited group of 29 men, a clear interpretation is challenging. Of the remaining 10 clinically localized escapes, androgen deprivation was the initial treatment for five (9.6%) men whereas active surveillance/watchfull waiting was carried out in five (9.6%) men.

Another observation is that among the 52 screen-detected escapes who initially had clinically localized PCa, more men underwent radiotherapy than RP (29 vs. 13). This large difference may be explained by the fact that of these 52 men, 22 were diagnosed with high-risk PCa and among these men the ratio of radiotherapy vs. RP was 15 to 3. In contrast, in the remaining 30 men with low or intermediate-risk PCa, the ratio was 14 to 10, respectively. In other words, radiotherapy was more frequently offered to men with high-risk PCa among the clinically localized escapes. This finding is in line to the results reported by Wolters et al.[33]. The authors showed that men with a higher PSA level and Gleason score, were more likely to be treated with radiotherapy than RP. It is possible that if men, who were theoretically suitable for RP, chose RP instead of radiotherapy, they would have had a different disease-specific survival. However, currently there is no consensus regarding the optimal treatment of men with high-risk PCa.

Additionally, we observed that only 18.6% of the interval escapes underwent curative therapy (RP, radiotherapy or active surveillance) compared to 81.7% of the screen-detected escapes. This discrepancy could be explained by the higher risk category at diagnosis for those cancers detected during an interval.

A limitation of this study is the relatively shorter follow-up for cancers detected at the incidence screens and during intervals. This underlines again the importance of international co-operation so more events could be analysed and compared including differences in screening procedures such as shorter screen intervals and longer follow-up.

Another limitation is we defined only men with metastasis and/or died from PCa as escapes. It has been well documented that biochemical failure after surgery or radiotherapy is an independent predictor for PCa death [34,35]. However, different definions of biochemical recurrence have been applied after both surgery and radiotherapy [36-39]. Therefore, we prefered solid endpoints such as metastasis and PCa death.

Based on our present findings, it is too soon to make adjustments on the Rotterdam screening algorithm. This descriptive study identified those men who escaped all efforts of screening and treatment. Possible mechanisms behind escaping are non-attending, inadequate screening algorithm (screening test, interval and age cut-off) and/or undertreatment. Our hope is that the ESCAPE-project will provide information to improve future screening regimens in order to decrease the proportion men who suffer clinical progression and death from PCa despite screening. Any future improvements of the current screening algorithm should further decrease PCa-specific mortality. In addition, accurate individualized risk assessment should be implemented in future screening algorithms in order to decrease the rates of overdiagnosis and overtreatment. Further objective of the ESCAPE-project should be the identification of the proportion of 'unpreventable' escapes, i.e. men who will not benefit from screening. Such knowledge will provide the baseline for the future development of strategies which decrease the numbers of "unnecessary" biopsies.

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8 Disease-specific survival of men with prostate cancer detected during the screening interval: results of the European Randomized Study of Screening for Prostate Cancer-Rotterdam after 11 years of follow-up

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ABSTRACT

Background

In a screening program, interval cancers are cancers which are diagnosed between two screening visits.

Objective

To assess the disease-specific survival (DSS) of men with prostate cancer (PCa) detected during the screening interval.

Design, Setting and Participants

Within the European Randomized Study of Screening for Prostate Cancer (ERSPC) section Rotterdam, a total of 42376 men identified from population registries (55–74 year of age) were randomized to a screening or control arm. The median follow-up was 11 years.

Intervention

Men with prostate-specific antigen ≥3.0 ng/mL were recommended to undergo lateralized sextant biopsy. The screening interval was 4 years.

Measurements

The disease-specific survival of men with interval cancers was compared to that of men with prostate cancer in the control arm; the secondary endpoint was overall survival. Causes of death were determined by an independent committee.

Results and Limitations

In the screening arm, 139 men were diagnosed with interval cancer of whom 8 died of the disease. In the control arm, the corresponding numbers were 1149 and 128, respectively. When comparing men with interval cancer to men with PCa in the control arm, no statistically significant difference in disease-specific mortality (HR=1.12; 95% CI 0.53-2.36; p=0.77) and overall mortality (HR=0.98; 95% CI 0.68-1.38; p=0.90) was found, adjusted for age, prognostic factors and treatment modality. The follow-up is too limited to address the difference in DSS stratified for screening interval.

Conclusions

In the setting of population-based PCa screening at 4-year intervals, the DSS of men with interval cancer seems to be similar to that of men with PCa in the control arm. Given that interval cancers contribute significantly to death from PCa, further benefit in DSS in the screening arm may be achieved by decreasing the occurrence of interval cancer. However, the balance between mortality reduction and overdiagnosis should be preserved.

INTRODUCTION

In a screening program, interval cancers (ICs) are cancers which are diagnosed between two screening visits. Therefore, ICs are either cancers that have developed after the previous screen, or cancers that were "missed" at the last screen.

In cancer screening literature, the disease-specific survival (DSS) of participants with ICs has been compared to that of cancer in the control arm (CCs) which are by definition clinically detected [1-6]. This is important because the comparison could have implications for the screening algorithm. For instance, if the DSS of men with ICs is superior to CCs or similar to that of screen-detected cancers, it may indicate certain degree of effectiveness of the applied screening algorithm. Adapting the screening algorithm towards a more aggressive strategy would probably not improve the screening effect. Instead, relatively more indolent cancers will be detected, especially in the setting of screening for cancers with a long preclinical detectable phase such as prostate cancer (PCa).

In contrast, if the DSS is similar or worse among ICs as compared to CCs, the detection of ICs could be interpreted as a failure of screening. Furthermore, if ICs significantly contribute to disease-specific mortality, a high rate of ICs will diminish the observed reduction of the disease-specific mortality in the screening arm.

In PCa screening literature, ICs are rarely mentioned. One reason may be that the incidence of ICs is very low because of the short interval (1-year) that is in general use and is recommended in the United States [7]. No previous study has compared ICs to CCs with respect to survival outcomes. Therefore, within the European Randomized Study of Screening for Prostate Cancer (ERSPC)-section Rotterdam, we investigated whether the DSS is similar between men with PCa diagnosed during an interval and men diagnosed with PCa in the control arm. The results could have impact on the interpretation of outcome data of the ongoing screening trials and development of future screening strategies.

METHODS

Study population

The ERSPC is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening on PCa-specific mortality. The screening algorithms used have been extensively described previously [8].

In the Rotterdam section, a total of 42376 men aged 55-74 years were identified from population registries. After written informed consent was obtained, randomization was carried out. Between November 1993 and December 1999, 21210 men were randomized into the screening arm and 21166 into the control arm.

In the screening arm, a prostate biopsy was indicated for men with a prostate-specific antigen (PSA) ≥4.0 ng/mL and/or abnormal digital rectal exam (DRE) and/or transrectal ultrasound examination (TRUS). Since May 1997, a PSA threshold of ≥3.0 ng/mL has been used as the sole screen-test. In screen-positive men, sextant biopsies were indicated; they were lateralized from June 1996, as described by Eskew [9]. An additional biopsy was taken from any suspicious area on TRUS. The screening interval was 4 years. Men were invited to undergo repeat screening unless they had passed the age of 75 years. After PCa had been diagnosed, the treatment decisions were left to the regional health care providers.

In the control arm, all men received standard medical care, which meant that the evaluation of symptoms, the diagnosis of PCa, and subsequent treatment was provided by general practitioners and local urologists in line with clinical practice guidelines.

Follow-up

PCa cases were identified through linkage with the regional cancer registry. The mechanism of detection was also recorded based on chart review. Deaths were identified by linking the ERSPC database to the database of the Central Bureau of Statistics in the Netherlands. The follow-up was complete until December 31, 2008. The median follow-up measured from randomization was 11.1 years.

Definitions

ICs were defined as cancers diagnosed in men who had a PSA test at the last screening round, either: 1) before the next scheduled screening round, or 2) within a time period equal to the screening interval of 4 years for men who have reached the upper age limit for screening [10]. Any cancers detected in the control arm were defined as CCs. Cancers were classified according to the TNM 1992 classification and graded using the Gleason grading system [11,12]. Causes of death were determined by an independent cause-of-death committee [13]. The primary endpoint was disease-specific mortality, with overall mortality being the secondary endpoint.

Statistical analysis

The clinical parameters between the groups were compared using Mann-Whitney U test for the continuous variable, and Chi-square analyses for categorical variables. Cox regression analysis was used to determine hazard ratios (HR) and 95% CI. The analysis for disease-specific mortality was adjusted for age, prognostic factors at diagnosis (i.e. PSA, T-stage and biopsy Gleason score), and primary treatment modality (i.e. surgery, radiotherapy, androgen deprivation therapy, watchful waiting or active surveillance). The analysis for overall mortality was controlled for age. Follow-up time was measured from the date of diagnosis until date of death or date of censoring (January 1, 2009), whichever occurred

first. Proportional hazard assumption was tested and found to be applicable, using log-log survival curves. All statistical tests were two-sided. A p-value <0.05 was considered significant. The SPSS v.17.0 statistical package was used (SPSS Inc., Chicago, IL, USA).

RESULTS

The median age of the whole study population was 63 years at randomization. Of the 21210 men who were randomized to the screening arm, 19950 men without prior PCa actually underwent screening at the first round. The control arm was comprised of 21166 men including 27 men with a prior diagnosis of PCa. Details are presented in the trial flow-diagram (Figure 1).

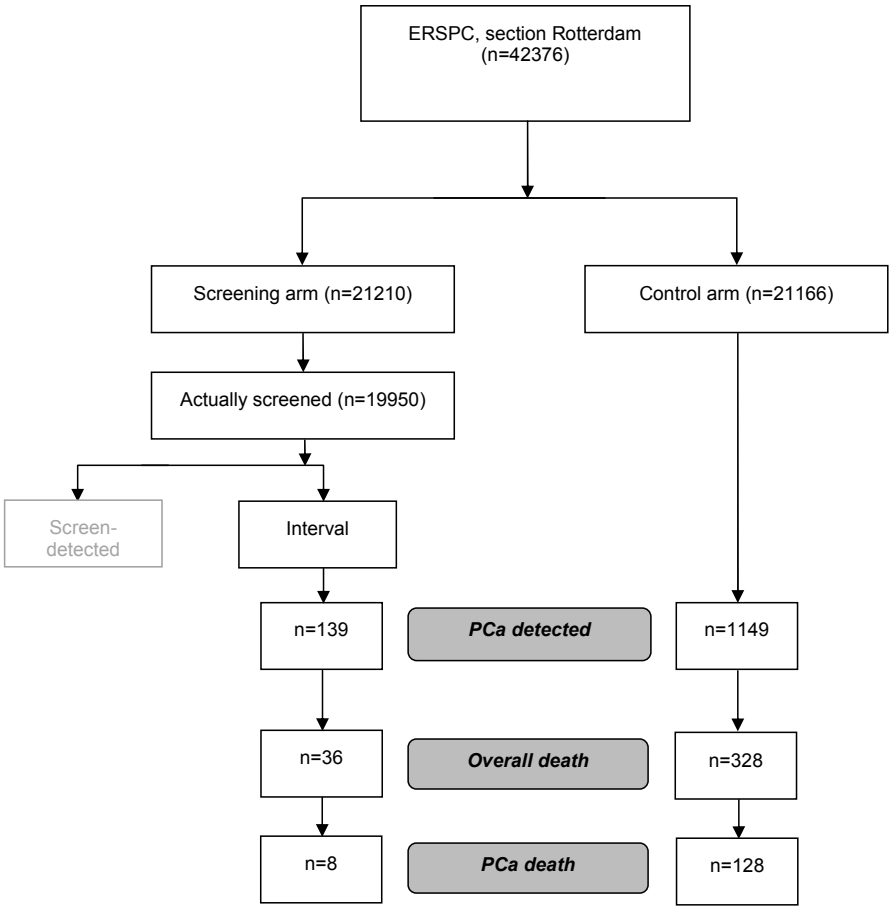


Figure 1: CONSORT trial flow-diagram.
ERSPC = European Randomized Study of Screening for Prostate Cancer; PCa = prostate cancer.

Cancer detection and tumor characteristics

In the screening arm, interval PCa was identified among 139 men at a median age of 70 years (cancer detection rate: 0.7%). The median time from last screening visit to diagnosis was 2.5 years (interquartile range [IQR]: 1.7-3.3 years). In the control arm, 1149 men were diagnosed with PCa at a median age of 72 years (cancer detection rate: 5.4%). The characteristics of these cancers are outlined in table 1. Of all ICs, 90.6% were clinically localized at diagnosis (≤T2), compared to nearly three-quarter of all CCs. The biopsy Gleason score was ≤6 in 50.4% of the ICs and 43.6% of the CCs.

Mechanism of detection

Table 2 shows the distribution of the detections mechanisms in ICs and CCs. In both groups the diagnosis was mainly based on 1) clinical symptoms; 2) opportunistic screen-

Table 1. Prognostic factors and treatment modalities of men with interval cancer and men with prostate cancer in the control arm

		Interval (n=139)	Control arm (1149)	p-value*
Age (yr), median (IQR)		70 (67-73)	72 (67-75)	0.08
PSA (ng/ml), n (%)	<3.0	21 (15.8)	44 (3.8)	<0.001
	3.0-10.0	70 (52.6)	434 (37.8)	
	10.0-20.0	23 (16.5)	301 (26.2)	
	20.0-100.0	21 (15.1)	273 (23.8)	
	>100.0	4 (2.9)	97 (8.4)	
T-stage, n (%)	T1a/b	34 (24.5)	102 (8.9)	<0.001
	T1c	56 (40.3)	432 (37.6)	
	T2	36 (25.9)	315 (27.4)	
	T3	8 (5.8)	235 (20.5)	
	T4	4 (2.9)	49 (4.3)	
	Unknown	1 (0.7)	16 (1.4)	
Biopsy Gleason score, n (%)	=<6	70 (50.4)	501 (43.6)	<0.001
	7	17 (12.2)	306 (26.6)	
	>=8	10 (7.2)	184 (16.0)	
	Unknown	42 (30.2)	158 (13.8)	
Primary treatment modality, n (%)	Surgery	28 (20.1)	182 (15.8)	<0.001
	Radiotherapy	33 (23.7)	332 (28.9)	
	Androgen deprivation therapy	23 (16.5)	372 (32.4)	
	Surveillance^	54 (38.8)	251 (21.8)	
	Unknown	1 (0.7)	12 (1.0)	

* Mann-Whitney U test for the continuous variable and Chi-square analyses for categorical variables

^ comprised of both active surveillance and watchful waiting

NOTE: Percentages may not sum to 100 due to rounding

ing or contamination; or 3) incidental findings (i.e. found during cystoprostatectomy or transurethral resection of the prostate).

In men with ICs, significantly fewer cancers were detected due to clinical symptoms and more cases were identified as incidental findings, compared to men in the control arm. The proportion of diagnosis due to opportunistic screening is similar in both groups.

Table 2. Mechanisms of detection in men with interval cancer and men with prostate cancer in the control arm

	Interval (n=139)	Control arm (1149)	p-value*
Clinical symptoms^	46 (33.1)	575 (50.0)	<0.001
Opportunistic screening	54 (38.8)	433 (37.7)	
Incidental findings	38 (27.3)	121 (10.5)	
Unknown	1 (0.7)	20 (1.7)	

* Chi-square analysis
^ including lower urinary tract symptoms, erectile dysfunction, hematuria or hematospermia, and symptoms of metastatic disease
NOTE: Percentages may not sum to 100 due to rounding

Primary treatment modalities

Table 1 summarizes the primary treatment modalities of the two groups. Almost half of both men with ICs (43.8%) and men with CCs (44.7%) received treatment with curative intent (radical prostatectomy or radiotherapy). The proportion of men who underwent surveillance was greater in the interval cases. Androgen deprivation therapy was more often applied as initial treatment among CCs than in ICs: 32.4% vs. 16.5% respectively.

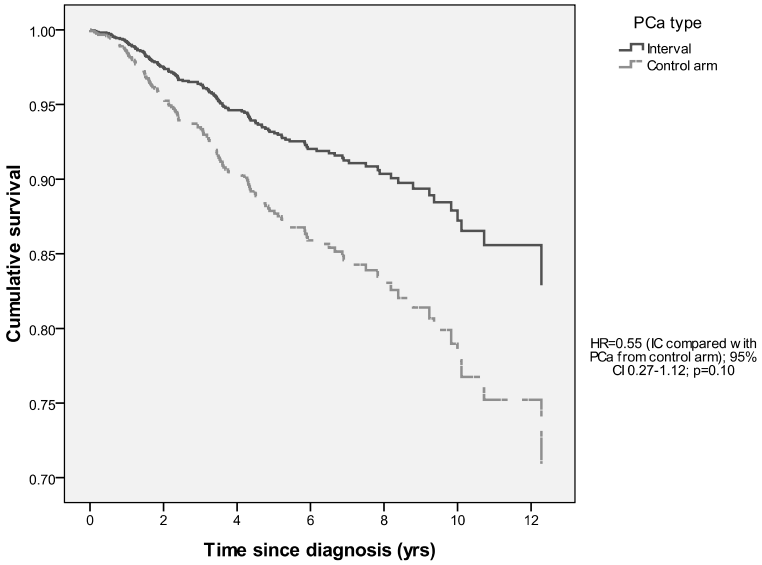
Disease-specific survival

Figure 2 depicts the unadjusted DSS in both groups. Of the 139 men with ICs, 8 died from PCa (5.8%). The median time from diagnosis to PCa death was 2.4 years (IQR: 0.6-3.5 years). Of the 1149 men with CCs, 128 died from PCa (11.1%) with a median survival of 3.0 years (IQR: 1.6-4.7 years). Although statistically not significant, there seems to be a trend of lower disease-specific mortality in men with ICs, compared to men with CCs (HR=0.55; 95% CI 0.27-1.12; p=0.10).

Figure 3 shows the adjusted DSS in both groups. After controlling for age, prognostic factors and treatment modality, the risk of dying from PCa was not statistically different between the two groups (HR=1.12 for ICs compared to CCs; 95% CI 0.53-2.36; p=0.77).

Overall survival

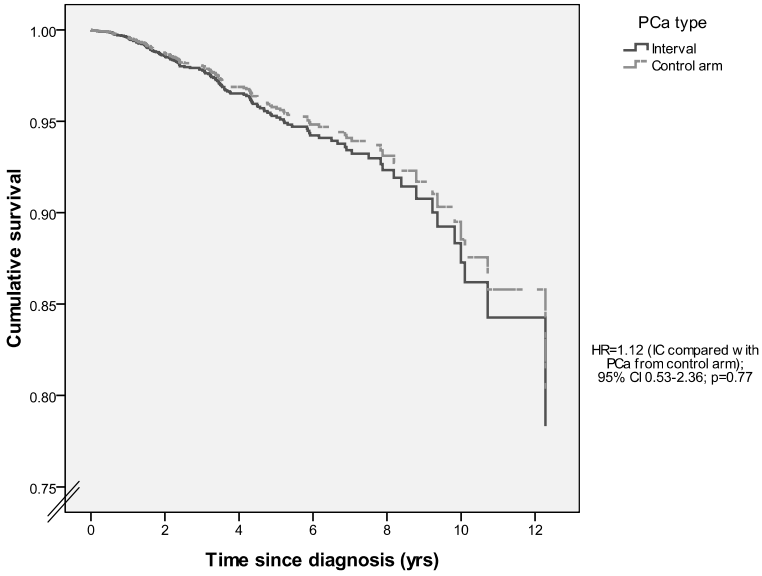
Figure 4 presents the overall survival in both groups. In men with ICs, 36 died (25.9%); in the control arm, 328 men with PCa died (28.5%). After adjusting for age, no statistically



No. at risk

Interval PCa	106	74	39	17	5	1
Control arm PCa	864	597	355	173	68	20

Figure 2: Disease-specific survival of men with interval cancer and men with prostate cancer in the control arm: unadjusted



No. at risk

Interval PCa	106	74	39	17	5	1
Control arm PCa	864	597	355	173	68	20

Figure 3: Disease-specific survival of men with interval cancer and men with prostate cancer in the control arm: adjusted for age, prognostic factors and treatment modality

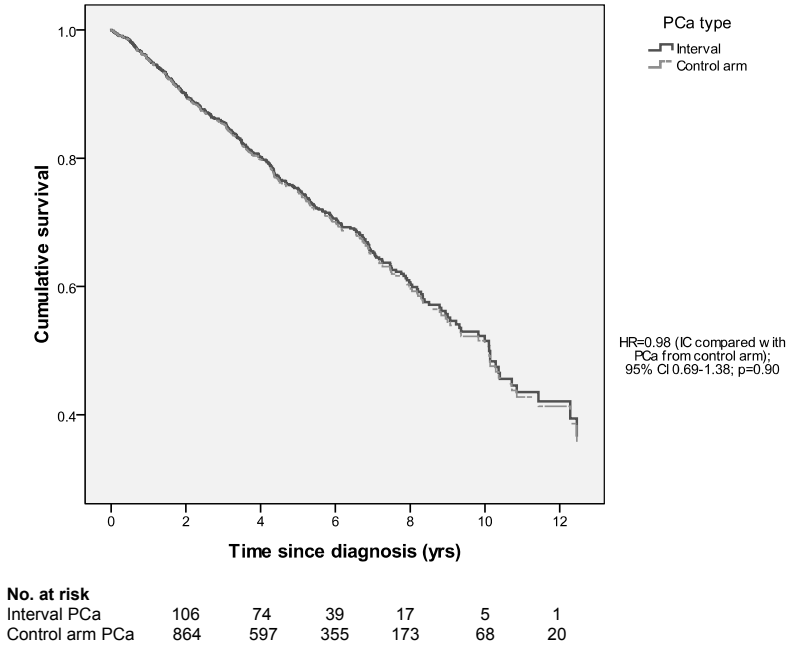


Figure 4: Overall survival of men with interval cancer and men with prostate cancer in the control arm

significant difference in overall mortality was found between the two groups (HR=0.98 for ICs compared to CCs; 95% CI 0.68-1.38; p=0.90).

DISCUSSION

This study on men within the ERSPC section Rotterdam assessed the survival outcomes of ICs and CCs, 11 years after randomization. On the basis of our findings, it seems that ICs had more favorable prognostic factors than CCs; although statistically not significant, the DSS was superior among men with ICs in the univariate analysis. However, after controlling for age, prognostic factors, and treatment modality, the DSS and overall survival were similar in both groups. These findings have some relevant implications.

First, the detection of the ICs in ERSPC Rotterdam could be regarded as a failure of the current screening algorithm, at least for those ICs with potentially aggressive characteristics. Although the numbers are small and the difference was statistically not significant, our data showed for men who have died from PCa, the median survival of CCs is longer than ICs (3.0 years vs. 2.4 years, respectively). In addition, cancer screening aims to avoid deaths from the targeted cancer by preventing the development of advanced disease. In this study, the multivariate analysis shows that men with ICs and CCs have a similar

DSS, which could imply that ICs are at the same stage of their natural development as CCs at time of diagnosis.

Recently is has been shown that a third of the total PCa deaths within the screening arm of ERSPC Rotterdam were men with ICs [14]. Therefore, more benefit in DSS in the screening arm may be obtained by reducing the number of ICs. This is important because the effect of screening for PCa is modest; the relative reduction in PCa mortality is 20-30% after a median follow-up of 9 years [15,16]. Although it is unlikely that all PCa deaths can be avoided, a part of these deaths are preventable with better screening regimens and treatment. By reducing the number of ICs and especially those with unfavorable prognostic factors, one may further lower PCa mortality. Obviously, two of the most important negative side effects of a screening program for PCa should be taken into account: unnecessary invasive testing (prostate biopsy) and overdiagnosis with the related overtreatment. Therefore, algorithms incorporating other variables next to PSA (e.g. family history, PSA-subforms, PCA3, outcomes of DRE and TRUS, ultrasound prostate volume, multiparametric MRI) to predict the chance of having PCa with the possibility to differentiate between indolent and potentially aggressive disease are warranted. Such algorithms have already been developed and validated [17-20]. Nevertheless, future studies must further develop an accurate individualized screening algorithm to provide a reasonable balance between mortality reduction and excess incidence of PCa.

Besides an optimal screening algorithm, the use of 5α-reductase inhibitors (5-ARIs) might also contribute to the reduction of ICs. In two large randomized controlled trials, both 5-ARIs (finasteride and dutasteride) were associated with an approximately 25% relative reduction in PCa diagnoses compared with placebo [21,22]. However, the relation between 5-ARIs and high-grade disease is still unclear, and a screening algorithm based on PSA and incorporating 5-ARIs has yet to be developed. Therefore, we should be cautious in recommending 5-ARIs as chemoprevention.

Length of screening interval

To our knowledge, this is the first report comparing the DSS of men with ICs and CCs within a 4-year interval screening program. The 4-year screening interval was chosen for the ERSPC because when the ERSPC protocol was being developed there was limited evidence available on lead time in PCa [23]. If the interval had been 1 or 2 years, the outcomes we reported for the DSS of men with ICs and CCs might have been different. Therefore, other screening trials which have used a shorter interval length and have compared prognostic factors of ICs with CCs should be addressed.

In the Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO), men were screened annually with PSA (abnormal >4.0 ng/mL) and DRE [24]. Grubb 3rd et al. reported 204 ICs among a total of 1902 cancers after 4 consecutive screening rounds [25]. In that study, the characteristics of ICs, such as biopsy Gleason score and stage distribution,

were similar to those of screen-detected PCa from the incidence screenings. A possible explanation is that those ICs were detected not because they became symptomatic, but mainly due to opportunistic screening during an interval. Although the DSS of men from the PLCO with ICs was not reported, it will likely be more similar to that of men with screen-detected cancer than to that of CCs, in contrast to our findings.

In ERSPC section Gothenburg, men were screened biennially, with a PSA of 3.0 ng/mL or greater as threshold [26]. After a 8-year follow-up, Hugosson et al. reported that regarding prognostic factors, ICs were more favorable than CCs, which is in line with our results [27]. Nevertheless, the similarity of DSS in men with ICs and men with CCs remains unclear within a 2-year interval screening program.

Limitations

Some possible limitations of the present study should be mentioned. First, a comparison between ICs, CCs, and screen-detected cases may provide a better sense of the differences in DSS. However, these cases were not included because their number is too small for a useful analysis. Nevertheless, these are subject to another pending publication in a multicenter setting. Second, the prognosis and outcome of ICs are likely to be strongly dependent on the sequential screening interval. Cancers developing as ICs missed at the prevalence screen may have different DSS than those missed after subsequent screens. Follow-up is still too short to visualize the effect of repeat screening in the setting of ERSPC Rotterdam. This also limits the usefulness of the present data if one wanted to determine the sensitivity of the screening procedure in use. Future research is needed to address the difference in DSS stratified for screening interval.

CONCLUSIONS

With 11 years follow-up, our results indicate that ICs have more favorable prognostic factors when compared to CCs in the setting of a population-based screening at 4-year intervals. However, the DSS of men ICs is similar to that of men with CCs after adjusting for age, prognostic factors and primary treatment modality. In order to further improve the DSS in the screening arm of the ERSPC, one could reduce the occurrence of potentially aggressive ICs, provided that ICs significantly contribute to death from PCa. Obviously, the balance between overdiagnosis and further mortality reduction should be preserved.

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9 Overestimation of prostate cancer mortality and other-cause mortality by the Kaplan-Meier method

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ABSTRACT

Objective

To assess the extent of overestimation of the cumulative probability of death by the Kaplan-Meier method with the competing-risks regression analysis as reference approach.

Methods

Data were derived from the screening arm of the Rotterdam branch of the European Randomized Study of Screening for Prostate Cancer. The screening arm consisted of 21210 men between the ages of 55 and 74 yrs at study entry. Follow-up concerning mortality was complete through 2008. Endpoints were 5- and 10 yr cumulative probabilities of prostate cancer (PCa) death and death from other causes. Relative bias was defined as the ratio of the cumulative probability of death as determined by the Kaplan-Meier method, relative to the cumulative probability obtained by the competing-risks analysis.

Results

According to the Kaplan-Meier method, the 5 yr cumulative probability of death from PCa was 0.0101, compared with 0.0099 according to the competing-risk analysis [1.8% overestimation]. At 10 yr, these numbers were 0.0347 and 0.0321, respectively [8.0% overestimation]. For death from other causes, the cumulative probabilities at 5 yr were 0.0399 and 0.0397 according to the Kaplan-Meier and the competing-risks method [0.6% overestimation], respectively. At 10 yr, the probabilities were 0.141 and 0.139 [1.7% overestimation], respectively.

Conclusions

When competing events are present, the competing-risks regression analysis is to be preferred over the Kaplan-Meier method in the estimation of the cumulative probability of the event of interest.

INTRODUCTION

The most widely used method to generate time-to-event and survival curves is the Kaplan-Meier method [1]. The complement of the disease-specific survival probability (i.e. 1 - disease-specific survival probability) is often used to estimate the probability of death from an event of interest. However, if a patient experiences events other than the one of interest, i.e. dies from other causes (competing events), problems may arise: if the Kaplan-Meier method is used to estimate the disease-specific survival, competing events are censored in a noninformative way. These events are considered to provide the same information as regularly censored observations (i.e. those observations that are lost to follow-up). This is clearly incorrect: men who die from another cause cannot die of the cause of interest. In the Kaplan-Meier approach, these censored observations are removed from the "at-risk" set and it is then assumed that the individuals removed would have had the same risk as those who were not censored. In general, this results in an overestimation of the probability of the event of interest [2].

The competing-risks analysis is the appropriate approach to estimate the cumulative probability of an event of interest in the presence of competing events [2-4]. In prostate cancer (PCa) research, competing-risks analysis is being used more and more and several papers with this approach have been published.

Nevertheless, disease-specific mortality in the presence of competing events is still frequently estimated by the Kaplan-Meier method. Considering that elderly men with PCa often die from other causes[5-7], a study of the extent of the bias in the Kaplan-Meier estimate is informative and may help clinicians understand the need for competing-risks analysis in the estimation of disease-specific mortality.

METHODS

Study population

Data used in this study were derived from men with PCa in the screening arm of the Rotterdam branch of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The ERSPC was initiated in the early 1990s, to determine whether a reduction of PCa mortality could be achieved by PSA-screening [8,9]. The study population and protocol in Rotterdam have previously been described in detail [10]. The trial is registered in the ISRCTN under number 49127736.

In summary, 42376 men, 55 to 74 yr of age, identified from the population registry were randomized from 1993 to 1999 to a screening (n=21210) or a control arm (n=21166). Screening in the intervention arm was carried out with an interval of 4 yrs. A prostate biopsy was indicated for men with a PSA level >= 4.0 ng/mL and/or abnormal digital

rectal examination and/or transrectal ultrasound examination. Since May 1997, a PSA threshold of >= 3.0 ng/mL was used as the sole screen-test. In screen-positive men, sextant biopsies were indicated which were lateralized from June 1996 as described by Eskew [11]. An additional biopsy was taken from any suspicious area on TRUS. After diagnosis of PCa, the treatment decisions were left to the regional health care providers.

Data on mortality were collected by linkage to the national registry. Follow-up for mortality analyses began at diagnosis and ended at death, or at a uniform censoring date (December 31, 2008). Causes of death were evaluated in a blinded fashion and according to a standard algorithm. Only deaths classified as definitely or probably caused by PCa were classified as death from PCa [12].

Endpoints

Endpoints were 5- and 10 yr probabilities of death from PCa, and probabilities of death from other causes. Based on the probability estimated by the Kaplan-Meier method relative to that of the competing-risks analysis, we determined the extent of overestimation by the Kaplan-Meier method.

Statistical analysis

In the Kaplan-Meier method, men who were alive at the end of the study as well as patients experiencing competing events (death from causes other than the event of interest) were all considered censored in the same way. The Kaplan-Meier approach provides a nonparametric estimate of the overall survival probability in relation to the event of interest. Mortality, either death from PCa or other causes, is calculated as the complement of the survival probability (i.e. 1 - survival probability).

In the competing-risks analysis, death from causes other than PCa is considered a competing event and vice versa. The estimation of the probability is a two-step process and has been described previously [3,13]. In summary, the probability of the event of interest for a given time interval is estimated as the product of the probability of experiencing the event of interest in that time interval given that the individual has survived both the event of interest and the competing events in prior time intervals. Next, cumulative probability is obtained by summing the above calculated probability and the probabilities from all previous time intervals.

All statistical analyses were performed with Stata, version 12 (Stata Corp, College Station, TX, USA). Competing-risks analysis was carried out with the *stcompet* package [14].

RESULTS

After excluding those men previously diagnosed with PCa, 2419 out of 21210 men in the screening arm were diagnosed with PCa through 2008. The median follow-up was 11.1 yr from randomization and 7.2 yr from diagnosis. Of these men with cancer, 106 men (4.4%) died from the disease and 444 men (18.4%) died from other causes.

Table 1 provides the cumulative probabilities of PCa death. At 5 yr, the cumulative probability obtained from the Kaplan-Meier method was 0.0101, compared to 0.0099 according to the competing-risks analysis [ratio: 1.018]. This can be translated into an overestimation of 1.8%. At 10 yr, the cumulative probabilities were 0.0347 and 0.0321, respectively [overestimation: 8.0%].

Table 1. Cumulative probability of prostate cancer death

	No. of men with cancer	No. of events	KM	CR	Overestimation
5 yr	2419	24	0.0101	0.0099	1.8%
10 yr	2419	96	0.0347	0.0321	8.0%

CR=competing-risks analysis; KM=Kaplan-Meier method

Table 2 summarizes the cumulative probabilities of death from other causes. The cumulative probabilities at 5 yr were 0.0399 and 0.0397 according to the Kaplan-Meier and the competing-risks method [overestimation: 0.6%], respectively. At 10 yr, the probabilities were 0.141 and 0.139 [overestimation: 1.7%], respectively.

Table 2. Cumulative probability of death from other causes than prostate cancer

	No. of men with cancer	No. of events	KM	CR	Overestimation
5 yr	2419	76	0.0399	0.0397	0.6%
10 yr	2419	332	0.141	0.139	1.7%

CR=competing-risks analysis; KM=Kaplan-Meier method

Figure 1 shows the cumulative probability of death from PCa, whereas the risk of death from other causes is depicted in Figure 2. The probabilities calculated by both methods are nearly identical at the beginning, the Kaplan-Meier approach will lead to incremental overestimation of both risks, over time.

DISCUSSION

In the Kaplan-Meier method, the estimate of the probability of an event at a certain time is the product of 1) the probability that an individual has survived just prior to that time, and 2) the conditional probability of experiencing the event beyond that time. The cumulative probability is then the sum of these conditional probabilities over time. In

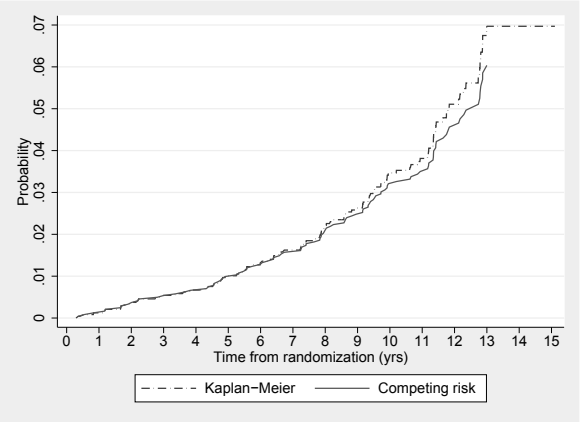

Figure 1: Cumulative probability of prostate cancer death

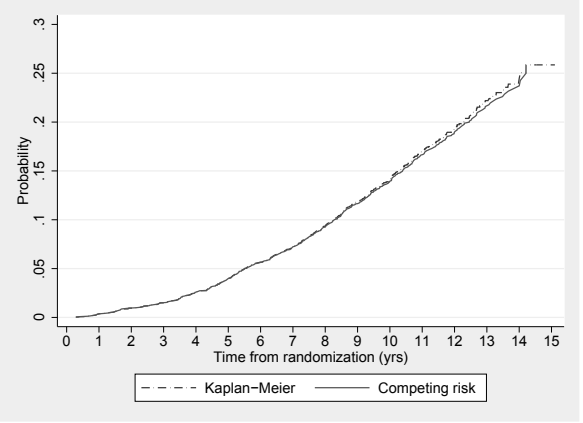

Figure 2: Cumulative probability of death due to other causes than prostate cancer

the competing-risks approach, the cumulative probability can be calculated similarly. The difference lies in the calculation of the probability of an event-free survival just prior to a certain time (step 1). In the Kaplan-Meier method, when an individual experiences an event other than the one of interest (e.g. dies from another cause), he is considered censored in a noninformative way and is eliminated from the risk set, and therefore not included in the calculation of the survival probability. Hence, the Kaplan-Meier method results in overestimation of the disease-specific mortality in the presence of competing events. In the competing-risks analysis, we account for other events and calculate the probability of survival from *any* event, i.e. both the event of interest as well as the other competing events.

As a result of the difference in the methods, the competing-risks analysis provides a projection of the actual rate in the study cohort by taking into account the presence

of competing events, whereas the Kaplan-Meier method is aimed to provide estimates relative to a population not subject to censoring [3,4,13,15]. However, it should be noted that individuals who are lost to follow-up are censored in both approaches. Therefore, if a substantial part of the study cohort has an incomplete follow-up, caution is needed in interpreting both the Kaplan-Meier and competing-risks estimate.

In the present study, we assessed the extent of the overestimation by the Kaplan-Meier method in calculating PCa mortality and other-cause mortality in a screening setting. Our results show that the Kaplan-Meier method performs very well for mortality from other causes, but leads to increasing overestimation with respect to disease-specific mortality. This is to be expected since PCa mortality is relatively uncommon when compared to other causes of death. After 5 yr of follow-up, the cumulative probability of the Kaplan-Meier method was almost identical to that of the competing-risks approach; the overestimation was small: 1.8% for PCa death and 0.6% for death from other causes. This finding can be explained by the fact that merely 5% of the study cohort (120 out of 2419 men with cancer) experienced an event at 5 yr (either PCa death or death from other causes).

However, with longer follow-up and therefore more events (i.e. 16.9% at 10 yr; 408 out of 2419 men), the Kaplan-Meier method leads to incremental bias of the cumulative probabilities. At 10 yr, the overestimation of disease-specific mortality is 8.0%. It is to be expected that this percentage will increase in the future.

Although not unexpected, we observed that men with PCa have a much larger risk of dying from causes other than the disease. At 5 and 10 yrs after diagnosis, the risks were 4.0- and 4.3 fold according to our data. Cronin et al. has previously demonstrated the impact of competing events in men with localized PCa over the age of 70: 90% die within 15 yrs of diagnosis of which 18% from the disease and 72% from other causes [16]. The impact of age and Gleason grade on the probability to die from PCa in relation to other causes has also been shown by the well-known Albertsen tables [7]. For example, a man diagnosed at age 60 with Gleason score 8-10 tumor and managed conservatively has a chance of 81% of dying from PCa vs. 16% from other causes after 15 yrs. In contrast, a patient diagnosed at age 70 with a Gleason 6 tumor has a 30% chance of death from PCa and a 59% chance of death from other causes.

As comorbidity is likely to affect the prognosis of men with PCa, it should be accounted for when choosing the optimal management strategy [6,17,18]. Daskivich et al. found in a retrospective series of 1482 men with nonmetastatic PCa that each point increase in Charlson score was associated with a 2-fold increase in mortality from other causes. Conversely, PCa mortality was rare, especially in men with low and intermediate risk PCa (0.4% and 3% respectively vs. 8% in high-risk patients) [17].

When comparing the extent of overestimation between death from PCa vs. death from other causes, we observed a larger bias for the first (e.g. 8.0% at 10 yr vs. 1.7% for

death due to other causes). This is a logical finding as more deaths from other causes emerged during follow-up than deaths from PCa. Indeed, the extent of the resulting bias of the Kaplan-Meier estimate is positively correlated with the frequency of the competing event.

Our data indicate that the Kaplan-Meier method may provide reasonable estimates when the number of competing events and follow-up is limited. In certain situations, the cumulative probability of an event of interest estimated using the Kaplan-Meier method and the competing-risks analysis can even be similar. For instance, when there are no competing events, that is, when there is only one type of failure, the estimate of the cumulative probability of the event derived from the Kaplan-Meier method and the competing-risks analysis will be identical [2]. However, in case of multiple nonindependent events, competing-risks analysis is needed. This approach does not rely on independence assumptions and hence is more widely applicable to survival scenarios than Kaplan-Meier estimates.

Data used in the present study were derived from the screening arm of the Rotterdam branch of the ERSPC study. Data were prospectively collected and the endpoint (i.e. cause of death) was determined by an independent committee. However, it must be kept in mind that the risks calculated here are only for the purpose to demonstrate the extent of bias of the Kaplan-Meier method. The probabilities cannot be used as reference for urologists or consultation of patients as PCa diagnosis in the screening arm is strongly associated with lead time and overdiagnosis [19].

In conclusion, when competing events are present, the competing-risks analysis is to be preferred over the Kaplan-Meier method in the estimation of the cumulative probability of the event of interest. Failure to account for such competing events results in an overestimation of the risk. Although the overestimation may seem small on the short term, competing-risks analysis should be applied because it is the correct method.

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IV Improving screening strategies

Chapter 10

Positive predictive value of prostate biopsy indicated by PSA-based prostate cancer screening: trends over time in a European randomized trial

Chapter 11

Risk-based prostate cancer screening

Chapter 12

A risk calculator for prostate cancer risk 4 years after an initially negative screen: findings from ERSPC Rotterdam

10 Positive predictive value of prostate biopsy indicated by PSA-based prostate cancer screening: trends over time in a European randomized trial

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ABSTRACT

Objective

To assess the Positive Predictive Value (PPV) of prostate biopsy, indicated by a prostate-specific antigen (PSA) cut-off of >=3.0 ng/mL, over time, in the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC).

Patient and methods

In the Rotterdam section of the ERSPC, a total of 42376 participants identified from population registries (age 55-74 yr) were randomly assigned to a screening or control arm. In the ERSPC men are screened with PSA at a four year interval. A total of three screening rounds were evaluated. Therefore, only men aged 55-69 yr at the first screen were eligible for this study.

Results

PPVs for men without previous biopsy remained equal throughout the three subsequent screens (25.5%, 22.3% and 24.8% respectively). Conversely, PPVs for men with previous negative biopsy dropped significantly (12.0% and 15.2% at the second and third screen respectively). Additionally, in men with and without previous biopsy the percentage aggressive prostate cancers (PCa) (clinical stage >T2b, Gleason score >=7) decreased after the first round of screening from 44.4% to 23.8% in the second ($p<0.001$) and 18.6% in the third round ($p<0.001$). Repeat biopsies accounted for 24.6% of all biopsies, but yielded only 8.6% of all aggressive cancers.

Conclusions

In consecutive screening rounds the PPV of PSA-based screening remains equal in previous unbiopsied men. In men with a previous negative biopsy the PPV drops considerably, however 20% of cancers detected still show aggressive characteristics. Individualized screening algorithms should incorporate previous biopsy status in the decision to perform a repeat biopsy with the goal to further reduce unnecessary biopsies.

Trial registration

ISRCTN49127736.

INTRODUCTION

Prostate-specific antigen (PSA) can be used as a biomarker for the early detection of prostate cancer (PCa) [1]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC) men are screened for PCa with PSA. Results of the ERSPC have shown that PSA-based screening can reduce PCa mortality by up to 29% at eleven years of follow-up after adjustment for noncompliance [2].

Although screening with PSA can reduce the PCa mortality, its use has limitations as a result of the lack of specificity, especially in low PSA ranges [3]. Consequently, if a large group of men is biopsied based on a PSA cut-off, only a modest proportion of men will have PCa. In the ERSPC the PPV of a lateralized sextant prostate biopsy indicated by PSA is approximately 25% at initial screening [4,5]. Already, multivariable risk calculators have been developed to improve the risk stratification and select men at high risk of PCa for conducting biopsies [6-8]. Data on cancer detection and PPV per screening round could further improve risk stratification.

In the ERSPC men are re-screened at a four year interval. In this paper we aim to assess the PPV of lateralized sextant prostate biopsy, indicated by an identical PSA cut-off value in subsequent screening rounds in the Rotterdam section of the ERSPC, stratified by age group and status of previous biopsy. We also evaluate the tumor characteristics of the diagnosed cancers. This knowledge may have implications for future screening strategies.

PATIENTS AND METHODS

The study population and protocol have been described in detail previously [9]. In summary, men aged 55-74 yr, identified from population registries of Rotterdam, were invited for screening. Men previously diagnosed with PCa were excluded [9]. In total, 42376 men who responded by returning the intake questionnaire and who provided informed consent were randomized to a screening (n=21210) or control arm (21166) from November 1993 until December 1999.

Three consecutive screening rounds were evaluated. Men aged 55-69 yr at the first screening round were eligible (16600 men). Age selection was made to provide a cohort of men eligible for at least two consecutive screening visits. Men were rescreened every four year until they reached the age of 75. A prostate biopsy was indicated for those with a PSA >=4.0 ng/mL and/or abnormal digital rectal examination (DRE) and/or transrectal ultrasound (TRUS). From May 1997, a PSA threshold of >=3.0 ng/mL was used as the sole screening test. In screen-positive men, sextant biopsies were indicated; they were

lateralized from June 1996, as described by Eskew et al [10]. An additional biopsy was taken from any suspicious area on TRUS.

Statistical analysis

Data was stratified for age groups 55-59, 60-64 and 65-69 yr at baseline and status of previous biopsy (yes or no). Aggressive PCa was defined as clinical stage >T2b and/or Gleason score >=7 as described by Roobol et al. [7].

The PPV (percentage PCa detected among all men biopsied) was calculated for each screening round and subgroup. The PPV and categorical clinical variables between groups were compared using chi-square test; for continuous variables the Mann-Whitney U test was used. All statistical tests were two sided. A p-value < 0.05 was considered significant. SPSS v.17.0 was used for statistical analysis (SPSS Inc, Chicago, IL, USA).

RESULTS

In total 16600 men, aged 55-69 yr at baseline, were screened in the first screening round, 12120 in the second round and 7740 in the third round. The median age for the whole study population at first screen was 61.1 yr. An overview of the screening rounds is shown in the flow diagram (fig. 1).

Positive predictive value

In total 7553 biopsies were performed: 3104 men were biopsied in the first round, 2789 in the second round and 1660 in the third round (96.3%, 92.1% and 93.5% of men with a biopsy indication). In addition, 288, 266 and 195 men refused a biopsy despite recom-

Table 1. Positive predictive values of prostate biopsies per screening round of the ERSPC Rotterdam

	First round	Second round			Third round		
	Total	Total	No Biopsy round 1	Biopsy round 1	Total	No Biopsy round 1 or 2	Biopsy round 1 and/or 2
Men screened	16600	12120	10552	1568	7740	6085	1655
Men biopsied (%screened)	3104 (18.7)	2789 (23)	1850 (17.5)	939 (59.9)	1660 (21.4)	743 (12.2)	917 (55.4)
PCa, No	790	525	412	113	323	184	139
% aggressive[a]	44.4%	23.8%	24.5% [b]	21.2% [c]	18.6%	20.7% [b]	15.8% [c]
PPV	25.5%	18.8%	22.3%	12.0% [d]	19.5%	24.8%	15.2% [d]

PCa = prostate cancer; PPV = positive predictive value; ERSPC = European Randomized Study of Screening for Prostate Cancer [a] Defined as clinical stage >T2b and/or Gleason score >=7; [b] p<0.001 (as to first round); [c] >0.05 (as to no biopsy); [d] p<0.001 (as to no biopsy)

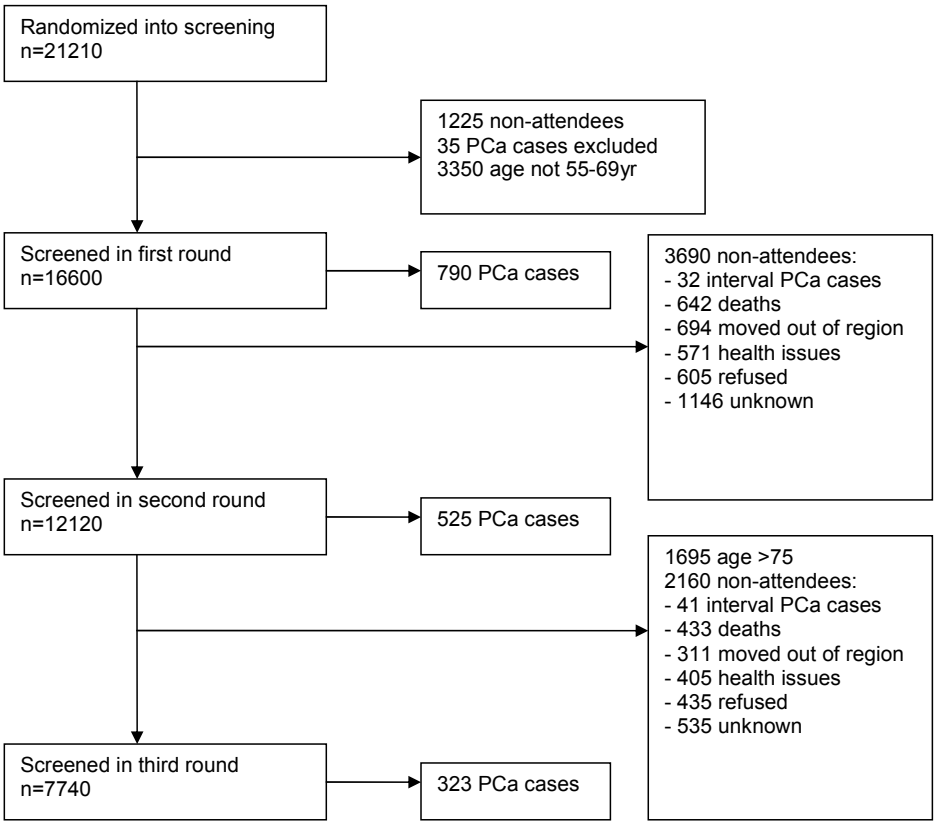

Figure 1: Consort trial flow diagram, screening rounds with a four year interval. PCa= prostate cancer

mendation respectively. The numbers of cancers detected per round were 790, 525 and 323 respectively (table 1). Subsequently, the PPV of prostate biopsy in the first round was 25.5%. In the second round the PPVs for men with and without a biopsy in the first round were 22.3% and 12.0% respectively (p<0.001). In the third round the PPVs for men with and without previous biopsy were 24.8% and 15.2% respectively (p<0.001).

In the first round the PPV of prostate biopsy was higher in the oldest age group (28.8% in 65-69 yr) compared to the younger age groups (23.1% in 55-59 yr, p<0.01; 23.2% in 60-64 yr, p<0.01). In the second and third round the differences between age groups did not reach statistical significance (table 2).

Tumor characteristics

Tumor characteristics per screening round are shown in table 3. The median PSA level and prostate volume, measured by TRUS, were significantly different in the second and third round of screening for men with or without previous biopsy (all p<0.001). The percentage of aggressive PCa (defined as clinical stage >T2b and/or Gleason >=7) was

Table 2. Positive predictive value per age group at baseline and round of screening

	First round	Second round			Third round		
	Total	Total	No Biopsy round 1	Biopsy round 1	Total	No Biopsy round 1 or 2	Biopsy round 1 and/or 2
55 – 59 yr							
Men screened	6498	5061	4630	431	4004	3280	724
Men biopsied	792	937	703	234	747	360	387
PCa, No	183	168	142	26	154	91	63
% aggressive[a]	37.2%	23.2%	23.9%	19.2%	17.5%	13.2%	23.8%
PPV	23.1%	17.9%	20.2%	11.1%	20.6%	25.3%	16.3%
60 – 64 yr							
Men screened	5336	3946	3373	573	2873	2184	689
Men biopsied	1032	958	612	346	667	289	378
PCa, No	239	186	145	41	135	76	59
% aggressive[a]	39.3%	24.7%	24.1%	26.8%	20.0%	27.6%	10.2%
PPV	23.2%	19.4%	23.7%	11.8%	20.2%	26.3%	15.6%
65 – 69 yr							
Men screened	4766	3113	2549	564	863	621	242
Men biopsied	1280	894	535	359	246	94	152
PCa, No	368	171	125	46	34	17	17
% aggressive[a]	51.4% [b]	23.4%	25.6%[c]	17.4%	17.6%	29.4%[c]	5.9%
PPV	28.8% [b]	19.1%	23.4%[c]	12.8%	13.8%	18.1%[c]	11.2%

PCa = prostate cancer; PPV = positive predictive value; [a] Defined as clinical stage >T2b and/or Gleason score >=7; [b] p<0,01 (as to 55-59 yr); [c] p>0,05 (as to 55-59 yr)

significantly higher in the first round compared to the second and third round (44.4%, 23.8% and 18.6% respectively; both p<0.001). No significant difference in percentage aggressive PCa was seen between men with or without previous biopsy in both the second and third screening round (21.2% vs. 24.5% in second round respectively, p=0.549; 15.8% vs. 20.7% in the third round respectively, p=0.337). In total 536 aggressive cancers were found, of which 65.5% were found in the first screen, 25.9% in subsequent screens in men without previous biopsy and 8.6% in men with a previous biopsy. In the first round the percentage aggressive PCa was significantly higher in the oldest age group (65-69 yr) compared to the youngest age group (55-59 yr; 51.4% vs. 37.2% respectively, p=0.002). In all age groups the percentage aggressive PCa decreased after the first screening round as shown in table 2. In the first round 79.6% of PCa were clinically organ-confined (<=cT2). In the second and third round this number increased to 96.2% and 98.4% respectively. No statistically significant difference was seen between men with or without previous biopsy.

Table 3. Tumor characteristics per round of screening

	First round	Second round			Third round		
	Total	Total	No Biopsy round 1	Biopsy round 1	Total	No Biopsy round 1 or 2	Biopsy round 1 and/or 2
PCa, No	790	525	412	113	323	184	139
Age, median	64.6	66.7	66.4	68.2	68.6	68.4	69.3
PSA (ng/ml), median	5.6	3.9	3.6	5.7[d]	4.2	3.7	5.3[d]
Prostate volume (cc), median	35.9	38	36	50.5[d]	42.5	37.2	50.9[d]
Aggressive[a] (%)	351 (44.4)	125 (23.8)	101 (24.5) [b]	24 (21.2) [c]	60 (18.6)	38 (20.7) [b]	22 (15.8) [c]
Clinical stage							
T1 (%)	325 (41.1)	356 (67.8)	290 (70.4)	66 (58.4)	229 (70.9)	127 (69)	102 (73.4)
T2 (%)	304 (38.5)	149 (28.4)	107 (26)	42 (37.2)	88 (27.2)	54 (29.3)	34 (24.5)
T3 (%)	155 (19.6)	20 (3.8)	15 (3.6)	5 (4.4)	6 (1.9)	3 (1.6)	3 (2.2)
T4 (%)	6 (0.8)	-	-	-	-	-	-
Gleason							
<=6 (%)	531 (67.2)	417 (79.4)	324 (78.6)	93 (82.3)	268 (83)	148 (80.4)	120 (86.3)
7 (%)	202 (25.6)	93 (17.7)	78 (18.9)	15 (13.3)	39 (12.1)	26 (14.1)	13 (9.4)
>=8 (%)	50 (6.3)	15 (2.9)	10 (2.4)	5 (4.4)	14 (4.3)	9 (4.9)	5 (3.6)

PSA = prostate-specific antigen; PCa = prostate cancer; [a] Defined as clinical stage >T2b and/or Gleason score >=7; [b] p<0.001 (as to first round); [c] p>0.05 (as to no biopsy); [d] p<0.001 (as to no biopsy)

Table 4 outlines the characteristics at the time of the preceding round of men without previous biopsy, who were diagnosed in later screens. In the second round 46.6% of these men had a PSA of 2.0-2.9 ng/mL in the first round. In the third round a similar amount (48.4%) had a PSA of 2.0-2.9 ng/mL in the second round.

DISCUSSION

Although results of the ERSPC have shown to reduce PCa mortality [2], the US preventive Services Task Force recently released an updated recommendation against PSA screening, as the authors concluded that the harms outweigh the benefits [11,12]. Moreover, a meta-analysis by Djulbegovic et al. [13] concluded that the existing evidence does not support the routine use of screening for prostate cancer. In addition to overdiagnosis, unnecessary biopsies triggered by false-positive screening results could be considered as one of the most important harms, leading to infections and hospital admissions [14].

In the present study, we assessed the PPV of a PSA indicated prostate biopsy throughout subsequent screening rounds of the ERSPC, section Rotterdam. This gives insight in

Table 4. Characteristics of men at the time of the preceding round and of prostate cancers which were eventually diagnosed

	Biopsy	PCa, No (%)	% PCa / Biopsies	Aggressive[a], No (%)	% Aggressive[a] / PCa
Second round, no biopsy first round					
Total	1850	412 (100)	22.3	101 (100)	24.5
Age at baseline					
55-59 yr	703	142 (34.5)	20.2	34 (33.7)	23.9
60-64 yr	612	145 (35.2)	23.7	35 (34.7)	24.1
65-69 yr	535	125 (30.3)	23.4	32 (31.7)	25.6
PSA first round (ng/ml)					
<1.0 ng/ml.	212	29 (7)	13.7	11 (10.9)	37.9
1.0-1.9 ng/ml.	660	133 (32.3)	20.2	27 (26.7)	20.3
2.0-2.9 ng/ml.	755	192 (46.6)	25.4	42 (41.6)	21.9
>=3.0 ng/ml	223	58 (14)	26.0	21 (20.8)	36.2
Reason no biopsy first round					
Medication	9	2 (0.5)	-	-	-
Refused biopsy	11	5 (1.2)	-	3 (3)	-
DRE and TRUS normal	203	51 (12.4)	25.1	18 (17.8)	35.3
Third round, no previous biopsy					
Total	743	184 (100)	24.8	38 (100)	20.7
Age at baseline					
55-59 yr	360	91 (49.5)	25.3	12 (31.6)	13.2
60-64 yr	289	76 (41.3)	26.3	21 (55.3)	27.6
65-69 yr	94	17 (9.2)	18.1	5 (13.2)	29.4
PSA second round (ng/ml)					
<1.0 ng/ml.	153	22 (12)	14.4	4 (10.5)	18.2
1.0-1.9 ng/ml.	269	67 (36.4)	24.9	10 (26.3)	14.9
2.0-2.9 ng/ml.	300	89 (48.4)	29.7	24 (63.2)	27.0
>=3.0ng/ml	21	6 (3.3)	28.6	-	-
Reason no previous biopsy					
Medication	4	1 (0.5)	-	-	-
Refused biopsy	17	5 (2.7)	-	-	-

PSA = prostate-specific antigen; PCa = prostate cancer; DRE = digital rectal examination; TRUS = transrectal ultrasound; [a] Defined as clinical stage >T2b and/or Gleason score >=7;

the screening efficacy of the current algorithm and may be valuable in the development of future screening strategies. Our results demonstrate that during screening rounds the PPV of men without a previous biopsy remained equal (25.5%, 22.3% and 24.8% in first, second and third round respectively). The PPV of prostate biopsy indicated by a PSA cut-off dropped considerably to 12.0%-15.2% in men with a previous biopsy; 20% of cancers detected however still show aggressive characteristics.

Because the PPV depends on the underlying prevalence and the first screening round was performed in a relatively unscreened population, one would expect a decline in PPV after the first round considering the slow natural course of PCa [15,16]. However, data from the PCPT trial has shown that 23.9% of men with a PSA 2.1-3.0 ng/mL harbor PCa [17]. In the current analysis, almost half of the cancers detected in men without previous biopsy originated from the 2.0-2.9 ng/mL PSA group as shown in table 4. The PSA in these men increased and subsequently surpassed the biopsy threshold during the four year screening interval, resulting in equal PPVs of approximately 25%. If we would assume that these cancers were already detectable at the previous screening round, these men may have been diagnosed when the biopsy threshold was set at a PSA of 2.0 ng/mL. However, a lower cut-off would also increase the number of overdiagnosed cancers and unnecessary biopsies [17,18]. Lowering the biopsy threshold to a PSA of 2.0 ng/mL would have increased the number of biopsies with 64%-72% in the current study (data not shown). Applying a shorter screening interval in men with a PSA of 2.0-2.9 ng/mL may be another option. Future research should further address this problem and study the origin of cancers detected in previously screened but unbiopsied men, with the goal to reduce unnecessary biopsies, overdiagnosis and mortality.

Even more important than the actual number of PCa detected, are the characteristics of the cancers. In the first round of screening, we found almost half of the cancers to be aggressive (Gleason score >=7 and/or clinical stage >T2b). Even though the PPV in the second and third round remained equal in men without previous biopsy, the proportion of aggressive PCa decreased to 20.7%-24.5%. Almost all cancers in the second and third round were clinically organ-confined (96.4%-98.4%). If these cancers were detectable in the first screening round, they did not progress to a stage where they became incurable. The low number of cancers detected in the interval period, as described previously [19,20], supports this assumption.

Nevertheless, overdiagnosis is one of the major drawbacks of PCa screening. A simple solution to reduce the number of low risk PCa, which could be considered overdiagnosed, is to raise the PSA cut-off for a biopsy indication [21]. Indeed, if only men with a PSA >=4.0 ng/mL were biopsied, the described PPVs in men without a previous biopsy in the first, second and third round would increase to 26.5%, 28.6% and 34.1% respectively (data not shown). Additionally 32.3%, 66.9% and 64.4% off the non-aggressive PCa would not have been detected, possibly sparing these men the burden of PCa and its treatments. However, and this is undesirable, with this strategy 19.1%, 38.6% and 47.4% of all aggressive cancers would also have been missed in the first, second and third round respectively. The drawbacks of a single PSA cut-off emphasize the need for better risk stratification tools. Already different multivariable risk calculators have been developed to improve risk stratification [22]. An external evaluation of the ERSPC risk calculator step 3 (www. prostatecancer-riskcalculator.com) showed both an improvement

of PPV to 64% and an improved selection of aggressive PCa (personal communication with H.A. van Vugt, Erasmus University Medical Center, manuscript in preparation). Risk calculators will play an important role until better biomarkers and imaging techniques are validated. Several studies have already demonstrated the additional value of MRI in the diagnosis of PCa [23,24].

In men with a previous biopsy a drop in PPV was seen at repeat screening. However, there are still cancers detected. Two explanations can be given. First, it is known that a sextant prostate biopsy does not detect all cancers. In a literature review by Schröder et al. [25], the average proportion of cancers missed with a lateralized prostate biopsy was 19%. Possibly a group of PCa was missed in the first screening round and emerged at repeat biopsy. Although some might suggest a more extended biopsy scheme, only a limited reduction in disease-specific mortality can be expected [25]. Second, some of the cancers that were detected at repeat screening may have developed during the screening interval. This would lower the number of cancers that potentially could have been detected earlier on.

Furthermore, we found that the prostate volume of men with a previous biopsy was significantly higher than men without a previous biopsy. Because a larger prostate is associated with a higher PSA value, these men were more likely to be biopsied. Previous studies have shown a negative association between prostate volume and the risk of PCa [26,27]. This could attribute to the relatively lower PPV in men with a previous biopsy. On the other hand, there are still cancers detected and although the PPV is lower, the percentage aggressive PCa is comparable to men without a previous biopsy. The number of aggressive PCa detected in men with a previous biopsy only accounted for 8.6% of the total number of aggressive PCa found, whereas the number of biopsies in previously biopsied men accounted for 24.6% of the total biopsies. This emphasizes the need for a more individualized screening approach, in which a previous negative biopsy should be taken into account. Already, previous biopsy status is incorporated in step 4 of the ERSPC risk calculator (www. prostatecancer-riskcalculator.com). External validation of this risk calculator in a Canadian and European cohort showed previous biopsy status to be a significant predictor of PCa in multivariable analysis [28,29].

In the first round of screening, tumors detected in the oldest age group were of a higher grade than in the younger age groups. This poorer differentiation in older men was reported before [30, 31]. After the first round this difference is less obvious. Because in the first round the tumors in older men had a longer time to develop, this could be expected. This concurs with a previous study by Boevee et al. [32] and could be seen as an effect of screening.

Some limitations should be mentioned. First, the PPVs provided in this study are calculated for only those who actually underwent biopsy; men with a positive screening test who did not have a biopsy were not included in the analysis. However, in our cohort

the compliance to a biopsy indication was > 90%, and there is no reason to assume the PPV in men who had an indication but did not undergo biopsy would be significantly different from those who actually had a biopsy. Second, sextant prostate biopsy, either classical or lateralized, will miss 23% or 19% of biopsy-detectable PCa [25]. Therefore, the PPV in this study may be underestimated. However, because the number of biopsies remained equal throughout screening rounds a comparison between screens was possible and was not affected by a change in protocol. Last, the biopsy indication has been modified over time: in the first screening round men were initially biopsied based on the results of a PSA test, DRE and TRUS; half way the first round the use of DRE and TRUS as a biopsy indication was omitted, because of limited additional value [33,34]; in the second and third round some men were screened in side studies with different biopsy indications. Even so, a sub analysis in men who were biopsied with PSA >=3 ng/mL as the sole biopsy indication showed only a negligible change in PPVs. Therefore all side studies were included in the current analysis.

In conclusion, the results of this study show that the PPV of PSA-based PCa screening remains equal in previous unbiopsied men. In men with a previous biopsy the PPV drops considerably, however 20% of cancers detected still show aggressive characteristics. In both groups a decline in aggressive PCa is seen after the first screening round. This study indicates that previous biopsy status should definitively be considered in the decision to perform a repeat biopsy. Also, in men without an initial biopsy and a PSA value of 2.0-2.9 ng/mL earlier repeat screening could be considered. Furthermore, future research should study the origin of PCa in men without a previous biopsy. Knowing the origin of these cancers could change the way men are screened, further reducing the PCa mortality and overdiagnosis.

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11 Risk-based prostate cancer screening

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ABSTRACT

Context

Wide-spread mass screening of prostate cancer (PCa) is not recommended as the balance between benefits and harms is still not well established. The achieved mortality reduction comes with considerable harms such as unnecessary biopsies, overdiagnosis, and overtreatment. Therefore, patient stratification with regard to PCa risk and aggressiveness is necessary to identify those men who are at risk and may actually benefit from early detection.

Objective

The aim of this review is to critically examine the current evidence regarding risk-based PCa screening.

Evidence acquisition

A search of the literature was performed using the Medline database. Further studies were selected based on manual searches of reference lists and review articles.

Evidence synthesis

PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of developing PCa. Especially in men with no additional risk factors PSA alone provides an appropriate marker up to 30 years into the future. After assessment of an early PSA test, the screening frequency may be determined based on individualized risk. A limited list of additional factors such as age, co-morbidity, prostate volume, family history, ethnicity and previous biopsy status have been identified to modify risk and are important for consideration in routine practice.

Conclusions

PSA testing may serve as the foundation for a more risk-based assessment. However, the decision to undergo early PSA testing should be a shared decision between an individual and his physician based on information balancing its advantages and disadvantages. In men with a known PSA, risk calculators may hold the promise to identify those who are at increased risk of having PCa and are therefore candidates for biopsy.

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 [1].

PCa has a variable natural history, ranging from indolent to strikingly aggressive with a long preclinical phase. As we are still awaiting a breakthrough in the treatment of advanced disease, earlier detection of clinically significant disease currently seems to afford the best opportunity of 'stemming the tide'. In general, there are two approaches to early detection: screen everyone within a certain age range (e.g. breast cancer and cervical cancer) or screen selectively based on risk-factors (e.g. lung cancer).

For PCa screening, evidence of mortality reduction was shown by prostate-specific antigen (PSA)-based screening in the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the overlapping Göteborg Trial [2-4]. Although several associations in Europe and US have updated their guidelines regarding PCa screening (Table 1), wide-spread mass screening is not recommended because the achieved mortality reduction comes with considerable harms such as unnecessary biopsies, overdiagnosis, and overtreatment [3,5,6]. Therefore, stratification with regard to PCa risk and aggressiveness is necessary to identify those men who are at risk and may actually benefit from early detection [7,8]. In other words, a risk-based strategy is necessary to prevent unnecessary PSA testing and widespread overdiagnosis.

With the current screening algorithm applied in the ERSPC, the relative mortality reduction after a median follow-up of 9 years is modest at 20-30% [2,3]. Recent studies from the ERSPC group have shown that non-compliance to the screening protocol and aggressive interval cancers attribute to a significant proportion of the PCa deaths in the intervention arm [9,10]. With a risk-based strategy, we may improve the screening effect. First, those with intermediate and high risk may be screened with a shorter interval, which may lead to fewer aggressive interval cancers. Second, the compliance might increase among those at high risk if they were informed of their risk status, resulting in fewer non-attendees after being screened once.

The aim of this review is to critically examine the current evidence regarding risk-based PCa screening.

EVIDENCE ACQUISITION

To apply a risk-based screening strategy, one must first know what the risk factors are. Therefore, in this review, we considered articles that have evaluated factors predicting the presence of PCa. It is important to realize that some markers predict the risk of either

Table 1. Summary of recommendations for prostate cancer screening

Organization	Year	Recommendation	Notes
European Association of Urology (EAU) [114]	2011	• Widespread screening is not appropriate. • Offer early detection to well-informed men. • Baseline PSA determination at age 40 yrs has been suggested upon which subsequent screening interval may then be based. • Screening interval of 8 yrs might be enough in men with initial PSA <= 1 ng/ml. • Further PSA testing is not necessary in men older than 75 yrs and a baseline PSA <= 3 ng/ml because of their very low risk of dying from PCa.	Updates previous recommendation of 2008, which predates the ERSPC and PLCO publication
American Urological Association (AUA) [115]	2009	• Offer early detection to asymptomatic men 40 yrs of age or older who wish to be screened and who have an estimated life expectancy of more than 10 yrs. • Future screening intervals should be based upon this baseline PSA level. • A physician should assess the individual patient's health status to determine the appropriateness of PSA testing at any given age.	Updates previous recommendation by lowering age to screening from 50 to 40 (to obtain baseline).
American Cancer Society (ACS) [116]	2010	• Asymptomatic men who have at least a 10-yr life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened. • Men at average risk should receive this information beginning at age 50 yrs. • African American men and men who have a first-degree relative diagnosed with PCa before age 65 yrs should receive this information beginning at age 45 yrs. • Men with multiple family members diagnosed with PCa before age 65 yrs should receive this information beginning at age 40 yrs.	Updates previous recommendation emphasizing informed and shared decision making.
National Comprehensive Cancer Network (NCCN) [117]	2010	• Offer baseline digital rectal exam and PSA testing at age 40 after providing counselling on the pros and cons of early detection. • If African American, if there is a family history of PCa, or if the PSA level is more than 1.0 ng/ml, repeat annually. • Otherwise, repeat at age 45 and annually starting at 50. Screening in men over 75 yrs should be considered individually.	Updates previous recommendation by lowering age to screening from 50 to 40 (to obtain baseline).

ERSPC=European Randomized Study of Screening for Prostate Cancer; PLCO= Prostate, Lung, Colorectal, and Ovary Trial, PCa=prostate cancer

current *or* future PCa, and others have predictive value in both cases. Next to this, we highlighted some most frequently used prediction tools which assess the chance of having PCa.

A search of the literature was performed using the Medline database, by combining the following terms: "prostate cancer", "diagnosis", "screening", "risk factors", "predictive

tools", and "nomograms". A total of 367 records, including original articles, review articles, and editorials, were retrieved. Subsequently, the search results were restricted to the English language, with preference given to article published within the last 10 yr. In total, 152 articles evaluating risk factors and 42 studies reporting on prediction tools were selected based on title and abstract. Further studies were retrieved based on manual searches of reference lists and review articles. The list of references was reviewed the authors of this review to ensure completeness. The articles with the highest evidence were included, reviewed and summarized, with the consensus of all authors of this paper.

EVIDENCE SYNTHESIS

Demographics and medical history

Age

The association between increasing age and PCa risk is very strong [11-14]. However, across the relatively narrow age range typically encountered in many screening programs, age may not be an independent predictor of risk [15]. Furthermore, we do not have clear evidence of when to start and when to cease screening yet.

Ethnicity

Race-related differences in PCa risk may reflect multiple factors, including exposure differences, particularly dietary differences; differences in access to care and detection; and genetic differences. The highest incidence rates for PCa in the world are among African American men. For the period 1988–1992, race-specific US incidence rates ranged from 24.2 per 100,000 for Koreans, 89.0 per 100,000 for Hispanics, 134.7 per 100,000 for whites, and 180.6 per 100,000 for African Americans [16]. African American and Hispanic men commonly are diagnosed at a significantly younger average age (mean, 63.7 yrs and 65.2 yrs, respectively) compared with white men (mean, 68.1 yrs) [17].

Because of their increased risk of PCa [16], and high-grade disease [18] as well as PCa-specific death [11,19], more intensive screening of African Americans is likely warranted.

Family history

A family history of PCa is an important risk factor for developing the disease. The foremost evidence has been demonstrated in two meta-analyses, reporting a relative risk (RR) of approximately 2-3.5 [20,21]. The risk depends on the degree of relatedness and number of affected degrees. Furthermore, among first-degree relatives, risk was significantly higher for men with an affected brother compared to those with an affected father [20,21].

More recently, Brandt et al. used the nationwide Swedish Family-Cancer Database to estimate age-specific risks of PCa according to the number and type (father or brother) of affected first-degree relatives and according to the relative's age at diagnosis [22]. The study included 26651 PCa patients of whom 5623 were familial, and therefore is the largest of familial PCa published to date. The authors found that the hazard ratios (HRs) of PCa diagnosis increased with the number of affected relatives and decreased with increasing age. The highest HRs were observed for men <65 year of age with three affected brothers (HR: approximately 23) and the lowest for men between 65 and 74 year of age with an affected father (HR: approximately 1.8). The pattern of the risk of death from familial PCa was similar to the incidence data, with the highest risk of dying in men with an affected father and two affected brothers (HR: 9.7).

These findings imply that among men with a strong family history (two or more first-degree relatives with PCa diagnosed < 65 year), a heightened surveillance and a lower biopsy threshold are warranted because of a HR > 6.5 [22]. Conversely, one must be reminded that most of the above mentioned studies were performed before or at the beginning of the PSA era; therefore, family history may become less predictive since most cancers are screen-detected nowadays.

Co-morbidity

Co-morbidity has been associated with incident and fatal PCa, but the exact role of obesity [23], diabetes [24-26], metabolic syndrome [27-29] in the development and progression of PCa and PCa-specific mortality has not been elucidated.

Interestingly, a recent analysis of the Prostate, Lung, Colorectal, and Ovary Trial (PLCO) demonstrated benefit from screening in only men in good health [30]. Furthermore, in a study of 1482 men diagnosed with non-metastatic PCa, a 2-fold increase in other cause mortality was shown with each point increase in Charlson score [31]. Another competing risk analysis among 19639 men diagnosed with localized PCa reported that in general, a higher co-morbidity score is associated with higher overall mortality and lower PCa-specific mortality [32]. Altogether, these findings may suggest that PSA screening is less effective among men with high co-morbidity scores.

Previous negative biopsy

A previous negative biopsy is associated with a lower risk of a subsequent positive result for men with the same PSA level, with a greater number of negative biopsies decreasing the risk [33]. It is important to recognize that men who undergo biopsy are typically at increased risk of PCa by definition, as the trigger for biopsy is usually increased PSA and/or an abnormal digital rectal examination (DRE). Thus, while a previous negative biopsy lowers risk compared with no previous biopsy, these men may still have a risk

greater than those without an indication for biopsy and, therefore, can be considered as a population of men at increased risk for PCa [34,35].

PSA and clinical risk factors

PSA

The clinical usefulness of PSA as a marker for PCa was described in the early nineties [36,37]. Catalona et al. showed that serum PSA with a cutoff value of 4.0 ng/mL was useful for screening of PCa [36]. Six years later, the same group suggested a PSA cut-off of 2.5 ng/mL, which was widely accepted after demonstrating a detection rate of PCa in the PSA range 2.5–4.0 ng/mL of 22% [38]. Data from the Prostate Cancer Prevention Trial (PCPT) have shown that there is no cut-off of PSA in which sensitivities and specificities are reasonably matched, but rather a continuum of PC risk at all values of PSA. If one considers a biopsy Gleason score of more than 7 as a parameter of aggressiveness, cut-off values of 4 and 2 ng/mL would miss 59.6 and 24.4% of such lesions [39].

Over the years, PSA has evolved as a useful marker for assessing the risk of future PCa. Studies linking PSA and subsequent risk of developing PCa have been summarized in Table 2. The initial observation was made by Stenman et al. Based on 44 men with PCa selected among 21172 Finnish men, the authors reported associations between baseline PSA and the risk of clinically detected cancer within 6 to 10 years [40].

Gann et al. measured PSA levels in entry blood samples from the Physicians' Health Study and analyzed 366 men who eventually were diagnosed with PCa and 1098 controls. Concentrations were also found to be raised five to six years before diagnosis among the 366 men with palpable PCa [41].

More recently, data from the Baltimore Longitudinal Study of Aging showed that a PSA greater than the age adjusted median in men aged 40-60 was associated with a RR of 3.6 of being diagnosed with PCa at a median follow-up of 13 years [42].

Studies from the Washington University showed similar results. Antenor et al. reported that a baseline PSA greater than the age adjusted mean was associated with a RR of 22 for PCa during a 10-year period in men 40 to 49 years old, and a RR of 12 in those 50 to 59 years old [43]. Loeb et al. found that among men in their 40s who were at-risk and being screened for PCa, those with a PSA of 0.7 to 2.5 ng/mL were at a 14.6-fold higher risk of being diagnosed with PCa within 10 years compared to those with a baseline PSA of less than 0.7 ng/mL (the median). This risk was 7.6-fold higher in men in their 50s with a PSA of 0.9 to 2.5 ng/mL compared to those with a PSA of 0.9 ng/mL (the median) [44].

Several studies from the Malmö Preventive Project (MPP) also demonstrated the use of PSA to stratify risk. A single PSA at or before age 50 predicts clinically significant PCa up to 30 years later [45-47]. Lilja et al. examined 21277 men from the MPP, aged 33-50 years at time of participation, and reported a strong association of baseline PSA with

Table 2. PSA and subsequent risk of developing prostate cancer

Study	Study design	No. of men	Age (yr) at baseline PSA	No. of cases	Results
Stenman et al. [40]	Nested case-control	21172	45-84	44	At a specificity of 92% with a PSA cutoff of 2.5 µg/l, 95% of the cancers developing within the first 5 years, and 52% developing in 6-10 years tested positive.
Gann et al. [41]	Nested case-control (Physicians' Health Study)	22071	40-84	366	With a cutoff for PSA of 4.0 ng/ml, sensitivity for the entire 10-year follow-up was 46%. Sensitivities for detection of total, aggressive, and nonaggressive cancers occurring in the first 4 years were 73%, 87%, and 53%. Overall, specificity was 91%.
Fang et al. [42]	Prospective study (Baltimore Longitudinal Study of Aging)	796	40-60	88	The 25-year disease-free probability for men aged 40 to 49.9 was 89.6% and 71.6% when the PSA level was less than and greater than the median, respectively. The 25-year disease-free probability for men aged 50 to 59.9 was 83.6% and 58.9% when the PSA level was less than and greater than the median, respectively.
Antenor et al. [43]	Prospective study (Washington PSA study)	26111	40-60	2122	Men 40 to 49 years old with initial PSA above the median (0.7 ng/ml) were at a 22-fold higher relative risk for PCa than men with initial PSA below the median. In 50 to 59-year-old men with initial PSA above the median (0.9 ng/ml) the relative risk of cancer detection was 12-fold higher.
Loeb et al. [44]	Prospective study (Washington PSA study)	13943	40-60	661	A baseline PSA level between the median and 2.5 ng/ml was associated with a 14.6-fold and 7.6-fold increased risk of PCa in men aged 40 to 49 and 50 to 59 years, respectively. A greater baseline PSA value was also associated with a significantly greater PSA velocity, more aggressive tumor features, a greater biochemical progression rate, and a trend toward a greater cancer-specific mortality rate.
Lilja et al. [45]	Nested case-control (Malmö Prevention project)	21277	33-50	1312	At a median follow-up of 23 years, baseline PSA measured before or at age 50 was strongly associated with subsequent PCa (AUC: 0.72; AUC for advanced cancer: 0.75).
Vickers et al. [48]	Nested case-control (Malmö Prevention project)	1167	60	126	PSA at age 60 was associated with PCa metastasis (AUC: 0.86) and death from PCa (AUC: 0.90). Ninety percent of deaths from PCa occurred in men with concentrations in the top quarter (>2 ng/ml). Conversely, men aged 60 with concentrations at the median or lower (≤1 ng/ml) had 0.5% risk of metastasis by age 85 and 0.2% risk of death from PCa.
Roobol et al. [51]	Prospective study (ERSPC)	1327	55-65	3	In men with an initial PSA of 1.0 ng/ml or less, 8 cancers were detected based on 2344 subsequent PSA determinations and a PSA of 3.0 ng/ml or greater as biopsy threshold in an 8-year period after the initial screening.
van Leeuwen et al. [52]	Observational study	86484	55-74	5861	Using men with a PSA below 2.0 ng/ml as reference, men in the intervention arm of the ERSPC with a PSA of 2.0-4.0 ng/ml had a 6.8-fold risk of being diagnosed, vs. the 3.7-fold risk in the clinical population in Northern Ireland. For PSA groups 4.0-10.0, and 10.0-20.0 ng/ml, the rate ratios were 12.6 vs. 8.6, and 21.7 vs. 21.5 respectively.

AUC=area under the curve; ERSPC=European Randomized study of Screening for Prostate Cancer; PCa=prostate cancer

subsequent PCa and advanced cancer (area under the curve [AUC] 0.72 and 0.75 respectively). Based on their findings, the authors suggest that men with PSA levels below the median (~0.6 ng/mL) might be expected to benefit little from subsequent annual or even biennial PSA checkups. However, as mentioned in the article, there is insufficient data to suggest that these men need no further screening [45].

Vickers et al. observed that PSA level at age 60 predicts lifetime risk of clinically detected PCa, metastasis, and death from the disease [48]. The authors reported that although only a minority of the men with a PSA of >2 ng/mL develop fatal PCa, 90% (78% to 100%) of deaths from PCa occurred in these men. Conversely, men aged 60 with PSA at the median or lower (≤1 ng/mL) were unlikely to have clinically relevant PCa (0.5% risk of metastasis by age 85 and 0.2% risk of death from PCa).

Data from the ERSPC showed similar association between baseline PSA and risk of having (clinically significant) PCa during follow-up [15,49-52]. Based on 1327 men with an initial PSA of 1.0 ng/mL or less and 2344 subsequent PSA determinations, Roobol et al. found that a 8-year screening interval instead of 4-year would lead to a considerable decrease in the number of screening visits, with a minimal risk of missing aggressive cancer at curable stage [51].

In a recent study comparing the intervention arm of the ERSPC with the population in Northern Ireland, where screening is not routinely performed, van Leeuwen et al. reported a number needed to treat of 724 for men who had a PSA level of 0.0-1.9 ng/mL; the number needed to treat was 60 for men with a PSA level of 10-19.9 ng/mL. Moreover, in men with a baseline PSA of 0.0-1.9 ng/mL, the authors showed only minor profit in PCa-specific mortality of only 0.05 per 10,000 person years in favor of the screened men [52].

There are some arguments against an early PSA test (before age 50). First, it is unknown how the recommendations from the MPP will be implemented in routine practice in terms of compliance. For example, men with a PSA below the median at ages 44-50 and who are asked to return for screening around ages 55-60, may experience the screening interval of 10 years as too long. It is quite possible for these men to have unnecessary tests during that interval due to the need for self-reassurance [53]. On the other hand, men may have a false sense of security if they decide not to return for a repeat screen because they are told to be at low-risk initially, although 19% of men with advanced PCa in the MPP had an initial PSA below the median at ages 44-45 [45]. Considering what we know about the natural history of early PCa it must at present be considered uncertain if and at what time the potentially lethal cancers can be detected in a curable stage. Second, information on PSA values at certain ages and their prediction of aggressive PCa later can be used to decide on whom screening should be focused, but other, preferably prospective, data are required to design a screening program. We need to determine how to deal with these findings in terms of applying further diagnostic

steps and follow-up schemes. Nevertheless, PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of PCa to date [7,15,54].

Digital rectal examination

Catalona et al. reported that DRE in conjunction with PSA enhanced early detection of PCa [55]. Moreover, men with a positive DRE driven biopsy may more often present with poorly differentiated PCa [56]. A possible explanation may be ascertainment bias since men with an abnormal/suspicious DRE are more likely to be biopsied.

However, it is important to note that in routine clinical practice, men with a suspicious DRE are typically candidates for prostate biopsy. Therefore, DRE has limited value as a predictor of future risk as it typically triggers a biopsy.

Prostate volume

Several studies have suggested a correlation between high-grade cancers and men with smaller prostates [57-59]. A prostate volume less than approximately 40 cc has been proposed to identify an increased risk of developing future PCa [57,60]. However, in clinical practice, prostate volume might be a difficult variable to measure and, therefore, seems to have a limited role in screening purposes.

Interestingly, in a very recent study Roobol et al. assessed a new risk calculator incorporating prostate volume based on DRE instead of ultrasound, and found little difference between the new and the original model. The AUCs for predicting significant PCa was 0.85 in the DRE-based risk calculator and 0.86 in the original, ultrasound-based risk calculator [61]. Replacing ultrasound measurements by DRE estimates may therefore enhance implementation of prostate volume into risk stratification in routine practice.

PSA velocity

PSA velocity has been suggested to be useful in distinguishing men with and without PCa [62, 63], and in identifying men with clinically significant disease [64,65] and men at-risk of having life-threatening PCa [66,67]. Several studies from the D'Amico group reported that men with a PSA velocity of more than 2.0 ng/mL during the year before the diagnosis had a significantly higher risk of dying from PCa [68,69].

However, the apparent predictive value of PSA velocity might simply reflect that PSA and PSA velocity are highly collinear [70]. Analyses in prospective studies showed that PSA velocity does not appear to add diagnostic value for PCa detection beyond that of a single PSA in the setting of screening [18,71-75].

PSA-related markers

A number of potential PSA subforms have been identified that might provide additional predictive value in determining the risk of PCa, such as free PSA, BPSA (benign PSA), and

p2PSA ([-2]proPSA) [76]. However, it is most unlikely that a single biomarker will be able to identify men at-risk. Therefore, several authors have examined the predictive value of combinations of PSA molecular subforms. In a prospective multicenter study including 892 men with PSA 2-10 ng/mL, Catalona et al. investigated the relationship of serum PSA, free-to-total PSA and PHI (Prostate Health Index=[p2PSA/free PSA] x √ PSA) with biopsy results. The authors reported that at 80% to 95% sensitivity the specificity (16% and 45% respectively) and AUC (0.70) of PHI exceeded those of PSA and free-to-total PSA. Furthermore, an increasing PHI was associated with a 4.7-fold increased risk of PCa and a 1.61-fold increased risk of aggressive PCa (greater than or equal to Gleason 4+3) [77]. Similar results have been shown by other authors [78-80].

Next to PSA subforms, reports suggest that human kallikrein related peptidase 2 (hk2), a secreted serine protease from the same gene family as PSA [81], could be more strongly associated with PCa than PSA [82-84]. Moreover, a number of studies from the group of Vickers and Lilja showed that combining a kallikrein panel including hk2 could substantially reduce the number of unnecessary prostate biopsies [48,85-89].

Although some of these (combinations of) PSA-related markers are promising, further research is needed to determine whether these are valuable in assessing the long-term risk of PCa. In a recent study, combining multiple kallikrein markers into a multivariate model did not improve the long-term predictive accuracy of PSA for all men, although enhancements were observed when focusing on men with increased PSA [45].

Other risk factors

Since the identification, molecular characterization [90] and commercialization [91] of the prostate cancer gene 3 (PCA3), numerous studies have been published to investigate the performance of the PCA3 test as a prebiopsy diagnostic test and to compare its performance with the serum PSA test [92]. To date, the PCA3 test is not capable of replacing the PSA test in clinical practice; it may however improve the diagnostic accuracy in addition to standard risk factors. Nevertheless, an appropriate cut-off level with acceptable performance characteristics is hard to define [92,93]. Furthermore, there is no evidence of the long-term predictive value of PCA3 in assessing future PCa.

Some genetic markers showed promising results, and may become important in risk prediction in the future [94,95]. However, the influence of SNPs, such as the KLK3, on cancer risk has been disputed [96,97].

Studies of protein-based, and DNA-based urinary markers on their potential use for assessing PCa risk have produced conflicting results [98]. Furthermore, these markers are not routinely examined. Prospective studies in a multivariate setting, including larger sample sizes and avoiding attribution bias caused by preselection on the basis of serum PSA are required.

Prediction tools

Studies of multivariate prediction tools for assessing *future* risk of PCa are lacking, and therefore we will discuss some of the most frequently used tools predicting the presence of *current* PCa (Table 3). These tools require PSA and therefore usually aim at reducing unnecessary biopsies and overdiagnosis. Their strength is that they can provide predictions that are evidence-based and at the same time individualized. With multivariate risk calculators, it is possible to identify men at increased risk of having PCa and therefore candidates for biopsy [99]. Obviously, screening is inseparable from biopsy because there is no point in screening if there are no consequences for screen-positive participants.

PCPT risk calculator

The PCPT risk calculator (http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp) depends on PSA, family history, outcome of DRE, and prior biopsy [18]. The original study reported an AUC of 0.70 for the calculator, slightly higher than the 0.68 reported for PSA alone [18]. One of the reasons for this small size of benefit may be the impact on the predictive value of PSA level on systematically biopsied men, as opposed to the use of a cut-off level. Furthermore, the omission of prostate volume may explain the modest increase in AUC observed over PSA alone.

The PCPT risk calculator has been validated in external populations, with accuracies between 0.57 and 0.74 [100-105]. Because the PCPT was based on an unreferred population, caution should be used when applying the risk calculator to counsel men referred for suspicion of PCa since it underestimates the risk of high grade disease [102]. In addition, lower accuracy in contemporary screened men with extensive biopsy schemes has been reported by Nguyen [103].

ERSPC risk calculator

The ERSPC risk calculator comprises 6 steps (based on 6 different logistic regression models) and is internet-based (www.prostatecancer-riskcalculator.com) [106,107]. Step 3 estimates the chance of positive biopsy in previously unscreened, step 4 previously screened but not biopsied, and step 5 previously screened and biopsied men, according to PSA, ultrasound-assessed prostate volume, outcome of DRE, outcome of transrectal ultrasound, and prior biopsy status [106,107]. Applying threshold for prediction PCa may result in a considerable reduction of unnecessary biopsies at both initial and repeat screening [107].

Studies of external validation of the ERSPC risk calculator reported AUCs between 0.71 and 0.80 [108-111]. Based on Swedish and Finnish cohort of ERSPC, van Vugt et al. reported that the calculator discriminated well between those with and without PCa among initially screened men, but overestimated the risk of a positive biopsy [111]. In

Table 3. Overview most frequently used risk calculators

Risk calculator	Site	No. of patients	Characteristics of patients	Mean no. of cores	Cancer detection (%)	Variables used in model	Accuracy in model	No. external validations	Accuracy in external populations
PCPT	Multicenter United States	2219	PSA ≤3.0 ng/ml; age ≥55 yr; many men likely to have been previously screened	6	21.9	PSA, family history, outcome of DRE, and prior biopsy	0.70	7[100-105]	0.57-0.74
ERSPC	Rotterdam, the Netherlands								
Step 3		3616	Age 55-75 yr; unscreened men	6	24.5	PSA, outcome of DRE, TRUS volume and outcome, and prior biopsy	0.79	2[110, 111]	0.71-0.78
Step 4 and step 5		2896	Previously screened (step 4) and biopsied (step 5)	6	18.9		0.68	3[108-110]	0.71-0.80
Sunnybrook	Canada	3108	Referred population, PSA ≤50	8	42.0	Age, ethnicity, family history, AUA symptom score, PSA, %fPSA, DRE	0.74	1[105]	0.67

PCPT=Prostate Cancer Prevention Trial; ERSPC=European Randomized Study of Screening for Prostate Cancer
DRE=digital rectal examination; TRUS=transrectal ultrasound; %fPSA=percent free PSA

head-to-head comparisons, the ERSPC risk calculator outperformed the PCPT model [108-110]. Although based on the European population, validation in referred men from a North-American cohort showed that the ERSPC risk calculator (AUC=0.71) was superior to the PCPT model (AUC=0.63) and PSA (AUC=0.55) [110].

Sunnybrook risk calculator

The Sunnybrook risk calculator (http://sunnybrook.ca/content/?page=OCC_prostate-Calc), combining age, family history of PCa, ethnicity, urinary voiding symptom score, DRE, PSA, and %fPSA reached an AUC of 0.74 for any PCa and 0.77 for high-grade cancer, significantly greater than conventional screening method of PSA and DRE only (0.62 for any cancer and 0.69 for high-grade cancer) [112].

In a prospective head-to-head comparison in 2130 men who underwent a prostate biopsy, Nam et al. demonstrated that the Sunnybrook calculator performed better than the PCPT model (AUC 0.67 vs. 0.61 for any cancer, and 0.72 vs. 0.67 for predicting aggressive disease [105]. However, the decision curve analysis [113] carried out in the study demonstrated that neither calculators were of clinical benefit because of it does not help decide which probability threshold should be considered acceptable [105].

CONCLUSIONS

To date, PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of developing PCa. Especially in men with no additional risk factors PSA alone provides an appropriate marker up to 30 years into the future. After assessment of an early PSA test, the screening frequency may be determined based on individualized risk. Although retrospective data strongly point towards the potential of risk stratifying men, outcomes such as unnecessary testing, overdiagnosis and mortality reduction remain unknown, and an individualized follow-up scheme after a single PSA needs to be determined. Furthermore, the decision to undergo early PSA testing should be a shared decision between a man and his physician based on information balancing its advantages and disadvantages. A limited list of additional factors such as age, comorbidity, prostate volume, family history, ethnicity and previous biopsy status have been identified to modify risk and are important for consideration in routine practice.

In men with a known PSA, risk calculators may hold the promise to identify those who are at increased risk of having PCa and are therefore candidates for biopsy.

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12 A calculator for prostate cancer risk 4 years after an initially negative screen: findings from ERSPC Rotterdam

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ABSTRACT

Background

Inconclusive test results often occur after PSA-based screening for prostate cancer (PCa), leading to uncertainty on whether, how and when to repeat testing.

Objective

To develop and validate a prediction tool for the risk of PCa 4 years after an initially negative screen.

Design, setting, and participants

We analyzed data from 15,791 screen-negative men aged 55-70 years at the initial screening round of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Outcome measurements and statistical analysis

Follow-up and repeat screening at 4 years showed either no PCa, low risk PCa, or potentially high risk PCa (defined as clinical stage > T2B and/or biopsy Gleason score >= 7 and/or PSA >= 10.0 ng/mL). A multinomial logistic regression analysis included initial screening data on age, PSA, digital rectal examination, family history, prostate volume and having had a previous negative biopsy. The 4-year risk predictions were validated with additional follow-up data up to 8 years after initial screening.

Results and limitations

Positive family history and especially PSA level predicted PCa, whereas a previous negative biopsy or a large prostate volume reduced the likelihood of future PCa. The overall risk of having PCa 4 years after an initially negative screen was 3.6% (IQR: 1.0-4.7%). Additional 8 year follow-up data confirmed these predictions. Although data were based on sextant biopsies and a strict protocol-based biopsy indication, we suggest that men with a low predicted 4-year risk (e.g. <=1.0%) could be rescreened at longer intervals or not at all depending on competing risks, while men with elevated 4-year risk (e.g. >= 5%) might benefit from immediate retesting. These findings need to be validated externally.

Conclusion

This 4-year future risk calculator, based on age, PSA, DRE, family history, prostate volume, and previous biopsy status, may be a promising tool in reducing uncertainty, unnecessary testing, and overdiagnosis of PCa.

INTRODUCTION

The path from (early) diagnosis to treatment of prostate cancer (PCa) knows numerous decision points. This has led to the development of evidence-based prediction models, often presented as nomograms [1,2] or web-based risk calculators [3-5]. A recent review of 36 of these types of prediction tools showed in all studies improvements in predictive ability as compared to taking the decision to biopsy based on a serum PSA level alone [6].

These prediction tools however assess the current risk of having PCa; it is not well known how current risk relates to future risk of PCa. Furthermore, men with a negative prostate biopsy may have clinical characteristics suggestive for the presence of PCa. Guidance in the decision on how and when to retest (i.e. PSA determination and/or prostate biopsy) is hence urgently needed.

Baseline PSA is a powerful predictor for developing PCa [7], but in itself is insufficient to predict future risk reliably. Additional information, such as family history, prostate volume and the outcome of previous biopsies, if taken, needs to be considered as well [8,9].

We aimed to develop a multivariable risk calculator to predict the 4-year risk of having PCa after an initially negative screen. Such a calculator should support decision making on future screening or diagnostic procedures.

MATERIAL AND METHODS

Study population

Data were derived from 21,210 men randomized to the intervention arm of the Dutch section of the European Randomized study of Screening for Prostate Cancer (ERSPC, Rotterdam, 1993-1999). A total of 19,970 men (94.2%) aged 55 to 74 years underwent a first time screening by serum PSA, digital rectal examination (DRE) and transrectal ultrasound (TRUS). If the DRE and/or TRUS was considered suspicious, and/or the PSA was 4.0 ng/mL or higher, a man was eligible for lateralized sextant transrectal prostate biopsy. After May 1997, a PSA >= 3.0 ng/mL was used as the sole biopsy indication [10]. The solely PSA-based screening algorithm was also applied at repeat screening 4 years later (1997-2003) with the exception of two side studies with biopsies performed in the PSA range 1.1 - 2.9 ng/mL [11,12].

We included 15,791 men who underwent screening without being detected with PCa at the initial screen and were eligible for a second screen 4 years later, i.e. who were between 55 to 70 years at the time of the 1st screening round (Figure 1).

Endpoints

The detection of PCa was based on repeat screening 4 years after initial screening (2nd screening round) and from linkage with the national cancer registry which included cancers diagnosed during the screening interval.

A priori, we defined a three-category outcome variable as no PCa, PCa with a low risk of progression (LR PCa), and PCa with potentially high risk to progress. The latter was defined as clinical stage > T2B and/or Gleason score >= 7 and/or PSA > 10 ng/mL. The rationale behind this somewhat conservative definition is to avoid misclassification of aggressive PCa die to undersampling on the biopsy as our results are based on sextant biopsies. Furthermore, data from our group showed that in men with a screen-detected clinically staged T2a/2b PCa and a biopsy Gleason score <7, the percentage of extra-capsular extension (ie. >=pT3) was approximately 15%, whereas in men with a clinically staged T2c PCa and a biopsy Gleason score <7, this percentage was 26% [13].

Future risk prediction

Based on individual clinical information obtained at the time of initial screening, we used multivariable multinominal logistic regression modeling to estimate the 4-year risks of no PCa, LR PCa, and HR PCa. Candidate predictors were age (years), total serum PSA level (in ng/mL), DRE outcome (abnormal / normal coded as 1/0 respectively), self-reported PCa family history (father and/or brother(s) with PCa or no reported first degree relatives with PCa coded as 1/0 respectively), TRUS-assessed prostate volume, and having had a previous negative prostate biopsy (i.e. no PCa found). Since volume estimation by TRUS is not a standard procedure and may be considered as invasive, data on prostate volume were reclassified into three categories that can be estimated by DRE: TRUS-assessed volume < 30 cm^3 was coded as 25 cm^3, >= 30 cm^3 but < 50 cm^3 was coded as 40 cm^3, and >= 50 cm^3 was coded as 60 cm^3. Although DRE estimates may be less accurate than TRUS estimates [14], a DRE-based prediction tool still contains valuable information on prostate volume and is therefore more accurate in risk prediction [13]. The predictors PSA, age, and prostate volume classes were 2-log transformed and centered for a better model fit [3].

Data on DRE and prostate volume were missing (n=8,859 and 9,005, respectively) in men with PSA < 3.0 ng/mL screened after May 1997 due to the change towards a purely PSA-based screening algorithm [10]. These missing data were imputed based on correlations between all predictor variables. We used the first imputation of a multiple imputation procedure with inclusion of age, PSA, DRE outcome, prostate volume, previous negative biopsy status, TRUS outcome, and PCa at 4 years as variables in the model. A total of 17,864 values were missing, comprising 16.9% of all covariate values required for the prediction model. Predictive accuracy was quantified using the area under the

curve (AUC) of the receiver operator characteristic (ROC) analysis [15]. We used SPSS (v 17.0, SPSS Inc, Chicago IL) for the analyses.

Validation of future risk predictions

The 4-year future risk predictions of PCa were categorized into low, intermediate and elevated risk based on the 25% and 75% percentiles of the total calculated probabilities (i.e. the probability of having a LR PCa plus the probability of having HR PCa). For these categories, long term follow-up data were considered as validation. Data were used from repeat screening at 8 years (3rd screening round), complemented by data from linkage with the national cancer registry,

RESULTS

A total of 15,791 men screened at the initial screening round of ERSPC Rotterdam form the study cohort (Figure 1). At the 4 year repeat screening, 12,103 men were actually screened. Of these, 2,120 underwent biopsy while PSA was >= 3.0 ng/mL, and 668 while PSA was between 1.1-2.9 ng/mL. At biopsy, 524 PCa cases were detected, while 40 cancers surfaced clinically during the 4-year screening interval. Hence, a total of 564 PCa cases were detected (cancer detection rate 564/15,791= 3.6%), with 144 PCa cases (144/564=26%) defined as HR PCa. Several differences are noted between the no PCa, LR PCa and HR PCa groups (Table 1). A positive family history and an increased PSA level were significant predictors for both LR and HR PCa at 4 years upon multivariable analysis (Table 2). A previous negative biopsy and a large prostate volume significantly reduced

Table 1 - Baseline characteristics of study cohort (n=15791) at the time of initial screening stratified by screening result 4 years later

Predictor	A: No PCa	B: Low risk PCa	C: High risk PCa
	n=15227	n=420	n=144
Age in years (mean/median; IQR)	61.8/61.4; 57.9-65.4	62.7/62.5; 59.0-66.5	63.0/63.2; 59.7-66.7
PSA in ng/ml (mean/median; IQR)	1.7/1.1; 0.7-2.0	3.3/3.0; 1.8-3.2	3.5/3.1; 1.9-4.2
	% of A	% of B	% of C
Abnormal DRE	10.2	8.1	13.2
Positive family history	6.4	9.0	11.8
Prostate volume class 25 cm^3	40.6	29.0	33.3
Prostate volume class 40 cm^3	46.9	54.0	44.4
Prostate volume class 60 cm^3	12.5	16.9	22.2
Previous negative biopsy	14.3	20.7	27.8

DRE=digital rectal examination; PCa=prostate cancer

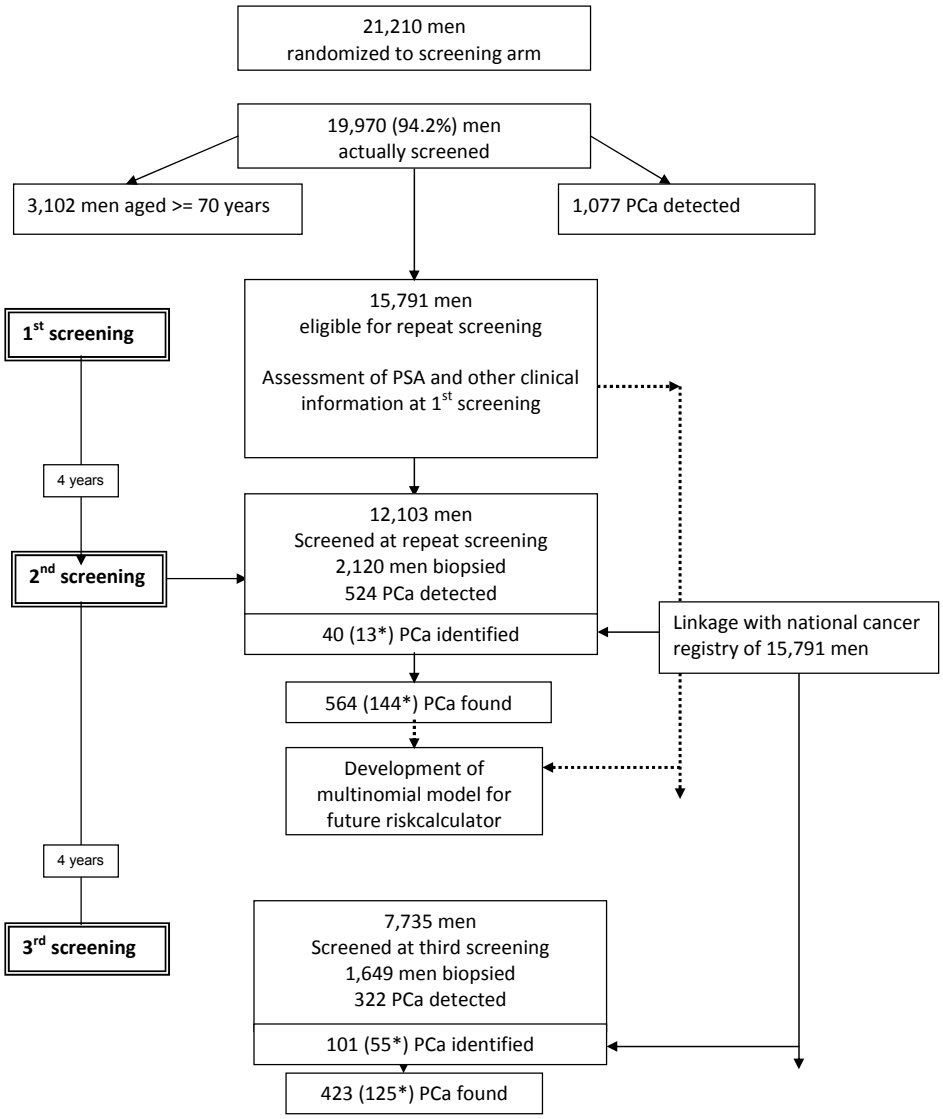


Figure 1: Flow diagram of study cohort and applied analyses. Asterisk denotes high-risk prostate cancer (PCa). PSA = prostate-specific antigen.

the risk of having PCa 4 years later (Table 2). Those men with no PCa could well be distinguished from those with LR PCa and those with HR PCa (AUC 0.79, 95%CI: 0.77-0.81, and AUC 0.81, 95%CI: 0.78-0.85, respectively).

Future risk calculator

We developed a web-based risk calculator (Figure 2, available at www.prostatecancer-riskcalculator.com) based on age, PSA, DRE, family history, prostate volume and informa-

Table 2 - Results of the multivariable multinomial logistic regression analysis

Predictor	Low risk PCa		High risk PCa	
	Odds ratio	95% CI	Odds ratio	95% CI
Age (2-log centered)	1.59	0.57-4.44	2.02	0.35-11.6
PSA (2-log centered)	2.78	2.47-3.12	3.57	2.95-4.33
Abnormal DRE (1/0)*	0.82	0.57-1.19	1.29	0.78-2.16
Positive family history (1/0)	1.46	1.03-2.06	2.01	1.20-3.39
Prostate volume classes (2-log centered)	0.74	0.58-0.95	0.52	0.34-0.79
Previous negative biopsy (1/0)	0.29	0.21-0.40	0.30	0.18-0.48

CI=confidence interval; DRE=digital rectal examination; PCa=prostate cancer
* 1 = yes; 0 = no

tion on previous biopsies, as identified with regression analyses shown in Table 2. For illustration, Figure 2A depicts the predictions for a man of 65 years with a PSA of 2.5 ng/mL and a prostate volume class of 40 cc. If all the other predictors are set on zero, the 4-year risks of LR PCa and HR PCa are 5.5% and 1.7% respectively. An abnormal DRE outcome and having a positive family history (Figure 2B) would increase his risk for HR PCa to 4.2%. In case this man already had a prostate biopsy with a benign result at initial screening (i.e. initially no PCa detected) his future risk of having PCa would decrease to 3.3% (2.0% for LR PCa and 1.3% for HR PCa, Figure 2C).

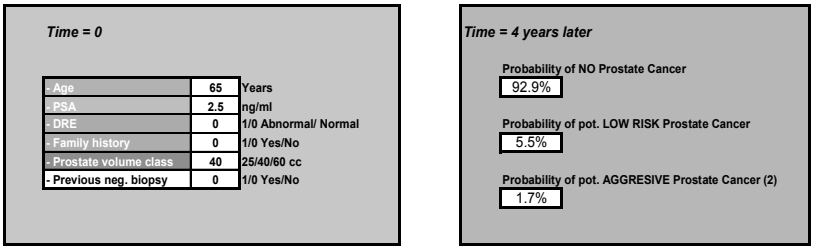
Risk stratification

The mean and median future risks of having PCa 4 years after an initially negative screen were 3.6 and 2.3% (IQR: 1.0-4.7%), respectively. A stratification of future risk into low (<= 1.0%), moderate (1.0 – 5.0%) and elevated risk (>= 5.0%) is proposed in Table 3. Of the 3,858 men with a low 4-year risk, 12 were diagnosed with PCa after 4 years (0.31%). Long-term follow-up data up to 8 years confirm this LR categorization, with only 19 additional cases (0.49%) emerging. Hence the proportion of future PCa in this subgroup over the total period of 8 years remained low ((12+19)/3858 = 0.80%). The overall risk of a future diagnosis of a HR PCa was 0.29% ((6+5)/3858) at 8 year of follow-up.

In men with a 4-year future risk between 1.0 – 5% (n=8332), 194 men were actually diagnosed with PCa (2.3%). Eight year follow-up data showed an additional 216 PCa cases (2.6%). The overall 8-year future risk was 4.9% ((194+216)/8332) for biopsy detectable PCa and 1.1% ((37+53)/8332) for HR PCa.

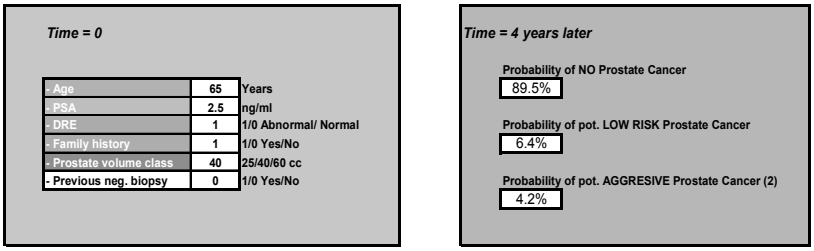
In the elevated risk group (>= 5% future risk; n=3,601), 28.2% (101/358) of all cases detected within 4 years were considered HR PCa. Long-term follow-up data showed an additional 188 PCa cases, resulting in an 8 year future risk of 15.2% ((358 + 188)/3601); 30.8% of all cases detected within 8 years from initial screening were HR.

A



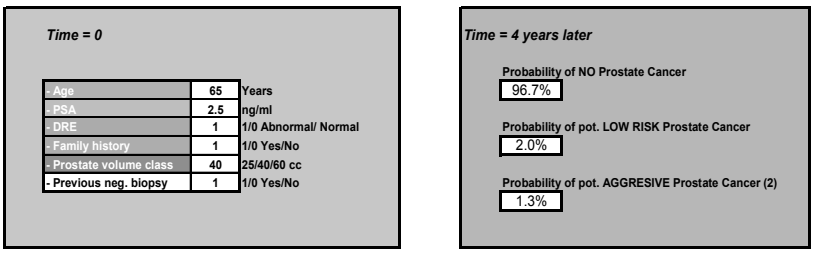
(1) Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off
(2) A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

B



(1) Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off
(2) A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

C



(1) Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off
(2) A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

Figure 2: The future risk calculator: (A) 4-yr future risk of a 65-yr-old man, prostate-specific antigen (PSA) 2.5 ng/ml, normal digital rectal examination (DRE), no family history, prostate volume class of 40 cm^3, and no previous biopsy; (B) 4-yr future risk of a 65-yr-old man, PSA 2.5 ng/ml, abnormal DRE, positive family history, prostate volume class of 40 cm^3, and no previous biopsy; and (C) 4-yr future risk of a 65-yr-old man, PSA 2.5 ng/ml, abnormal DRE, positive family history, prostate volume class of 40 cm^3, and having had a previous negative (neg.) biopsy. Reproduced with permission from SWOP – The Prostate Cancer Research Foundation, Rotterdam. pot. = potential.

Table 3 - Number and characteristics of prostate cancer detected after 4 and 8 years after initial screening, stratified by risk group using information at initial screening

4-year future risk	**A**: n (% of total)	**B**: n of total (low + high risk) PCa detected within 4 years after initial screening; % of **A**	**C**: n of total (low + high risk) PCa detected 4 – 8 years after initial screening; % of **A**
<= 1.0%	3858 (24%)	12 (6+6) (0.3%)	19 (14+5) (0.5%)
> 1.0 - < 5.0%	8332 (53%)	194 (157+37) (2.3%)	216 (163+53) (2.6%)
>= 5%	3601 (23%)	358 (257+101) (9.9%)	188 (121+67) (5.2%)
Total	15791 (100%)	564 (420+144) (3.6%)	423 (298+125) (2.7%)

PCa=prostate cancer

DISCUSSION

By using PSA and other relevant information available at the time of initial screening, it is possible to accurately predict future risk of having LR and HR PCa. The risk calculator is based on readily available information without the necessity of further invasive procedures. The web-based presentation might make it an easily applicable tool to support shared decision making on an individualized future screening strategy.

General practitioners and urologists are increasingly confronted with requests for PSA testing. Several risk assessment tools have been developed to support decision making on having a PSA test or to have a prostate biopsy [3,5,16,17]. We recently studied the implementation of the ERSPC risk calculator into clinical practice and found high compliance with respect to performing a biopsy (83%) [18]. After detecting low PSA values or having a negative prostate biopsy, physicians do however struggle with the question if and how to continue testing.

Furthermore, although PSA-based screening can reduce PCa-specific mortality [19,20], population-based PCa screening programs are not yet acceptable to many due to the high numbers of unnecessary tests and the detection of PCa that would never cause any harm (overdiagnosis) [21]. Therefore, the standard interval of 4 years as applied in the ERSPC may not be appropriate for all men in the age range 55-70 years.

The proposed 4-year risk calculator is expected to be of major assistance in this situation and allows for a more personalized approach. On the basis of available relevant clinical data, the future risk calculator predicts the 4-year risk of having PCa (in general applying a PSA cut-off >= 3.0 ng/mL as biopsy indication). At the same time the future risk calculator displays the probability of being diagnosed with a potentially LR or HR PCa. These predictions may well guide future strategies on retesting and/or repeated biopsy. Men with an overall 4-year future risk <= 1.0% have a very low chance of being diagnosed with a HR PCa (0.2%, Table 3); confirmed by the 8 year data which showed only 5 additional cases between year 4 and year 8 (Table 3). This questions the need for

Table 4 - A possible future risk-based screening algorithm

4-year future risk	Action:
Low (< 1.0%)	No retesting or retesting after 8 years
Intermediate (1.0 – 5%)	Retesting at 4 years
High (>= 5%)	Immediate retesting

rescreening within this time period. Taking into account the age at baseline (55-70 years), further testing in men in the highest age groups will most likely result in the detection of potentially LR PCa leading to overdiagnosis.

In the intermediate risk group the overall PCa detection rate after 4 years is still relatively low (2.3%). The percentage of HR PCa was however 19.1% (37/194). Men with an increased chance of harboring potentially aggressive disease 4 years later can be identified with the future risk calculator (e.g. Figure 2B). These men might benefit from a retesting interval shorter than the currently applied 4-year period. Men in the highest risk group are potential candidates for immediate retesting and re-biopsy since a significant proportion had HR PCa 4 and 8 years later (28% and 36% respectively); earlier detection might have resulted in more favorable prognostic factors at diagnosis. A possible future screening strategy based on this multivariable 4-year future risk assessment is shown in Table 4. This approach will circumvent testing in men with a low chance of being diagnosed with HR PCa and increase testing in men that might benefit from an earlier detection, reducing the two major drawbacks that coincide with the current "one-size-fits-all" screening protocol.

Several strengths and weaknesses need mentioning. Our study is performed in a large population-based cohort of men prepared to consider PSA testing. Data on PCa detection are of high quality and linkage with cancer registry provides complete data of long-term follow-up. The large sample size made that any statistical optimism in our models was limited (high internal validity [22]). External validation is however warranted to confirm our results and to evaluate the applicability of the future risk calculator in other cohorts. The calculator may underestimate or overestimate risks based upon the characteristics of the population, such as age, ethnicity, number of previous PSA tests and number of previous negative biopsies. One should be reminded that only men aged 55-70 yrs were eligible for the present study; nearly all participants were Caucasians and the cohort was relatively unscreened at the time of study entry. In addition, our risk calculations were based on the outcome of lateralized sextant biopsy scheme, which could miss 19% of the cancers [23]. Previous studies have also shown a lower risk of upgrading and upstaging with a greater number of cores [24,25]. Nevertheless, a recent validation of step 3 and 5 of the ERSPC risk calculator ("current risk" calculators) in a North American cohort showed an AUC of 0.71 for PCa prediction, which outperformed the PCPT risk calculator (AUC=0.63) [26].

A final limitation was that data on DRE and prostate volume were missing in more than 50% of the study cohort. We imputed these values to be able to use the information that was always available, such as age and PSA value. Such imputation is increasingly accepted for efficient statistical analysis, and agreed on to be preferable to a complete case analysis [27,28]. However, it required us to make some assumptions on the missing value mechanism ("Missing At Random") [27]. These assumptions may be reasonable since the data collection was prospective and systematic. Results were verified for men with complete values on all predictors and were similar to the results presented after imputation of missing values (data not shown).

The currently applied screening algorithm in ERSPC with PSA >= 3.0 ng/mL as threshold implies that PCa might have been missed, since PCa and potentially aggressive PCa are present at low PSA ranges [29]. Our risk estimates may hence be too low. The validation with 8 year follow-up data showed however that this potential bias was limited. We further note that whether a HR PCa (purely based on clinical tumor characteristics) might indeed develop towards a life threatening disease is also dependent on the clinical status, including presence of comorbidity [30,31]. Because of competing risks, men may die from other causes than PCa. This has elegantly been shown before [30], where it is clear that the chance of actually dying from PCa decreased with increasing comorbidity. On the other hand, men with favorable PCa at detection might eventually suffer from or succumb to the disease if they live long enough.

CONCLUSION

The proposed 4-year risk calculator is a promising tool in reducing uncertainty, unnecessary testing, and overdiagnosis of PCa; all strongly associated with screening solely based on PSA. Further validation is however required. In addition, physicians should always balance the calculated future risks of PCa against potential competing risks of dying from other causes.

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V | General discussion

13 General discussion

GENERAL DISCUSSION

Prostate cancer survival is related to many factors, especially the extent and aggressiveness of tumor at the time of diagnosis. The five-year survival among men with cancer confined to the prostate (localized) or with just regional spread is 100% compared with 31.9% among those diagnosed with distant metastases [5]. While men with advanced stage disease may benefit from palliative treatment, their tumors are generally not curable. Thus, a screening program that could identify asymptomatic men with aggressive localized tumors might be expected to substantially reduce prostate cancer morbidity, painful metastases, and mortality.

However, current evidence suggests that PSA-based screening for prostate cancer is a double-edged sword. After the publication of the two largest screening studies for prostate cancer in 2009 [1,2], the Prostate Lung Colorectal Ovarian Cancer (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC), intense interest in medical and lay press was generated, not only because of their impressive size, but also their opposing outcomes and differing methodologies, making interpretation controversial [6]. In **Chapter 2**, these reports have been discussed in detail, including their differences and the consequences for how to interpret the data.

In the general discussion, the key findings presented in this thesis will be addressed. Both effectiveness and harms of prostate cancer screening will be summarized, as well as recommendations and future directions.

SCREENING EFFICACY

Evidence for screening effects on prostate cancer mortality

In 2010, data from the screening trial in Göteborg, which is one of the ERSPC sites, were published. A 44% relative reduction in prostate cancer mortality was shown in favor of the screening arm. The screening protocol in the Göteborg site differs from that in other ERSPC sites, as it offered screening every two years (vs. every four years) [7]. Also, the results were based on a cohort of men ages 50-64, vs. the predefined core aged group of men between 55-69 in the main ERSPC report. Additionally, the median follow-up of the study cohort was 14 years.

The PLCO results published in 2012 showed a 12% increase in prostate cancer incidence in the screening arm (relative risk: 1.12; 95% CI 1.07-1.17), and a 9% increase in prostate cancer mortality in the screening which was statistically not significant (relative risk: 1.09; 95% CI 0.87-1.36). There was no effect depending on age, pretrial screening, or comorbidity [8]. However, because of several flaws as discussed in **Chapter 2**, these findings should not be interpreted as evidence against screening.

In 2012, the main report from the ERSPC study updated its report with a median follow-up of 11 years, and demonstrated a 21% relative reduction of prostate cancer mortality in an intention-to-treat analysis. It also showed that 1,055 men needed to be invited for screening and 37 cancers needed to be diagnosed and treated in order to prevent one death from prostate cancer, if the follow-up is restricted to 11 years [9]. In a non-truncated analysis, i.e. with all available follow-up, the number needed to invite and to diagnose is 936 and 33, respectively [9]. These figures show a marked improvement compared to the number needed to screening of 1,410 and the number needed to treat of 48 in the 2009 publication [2]. Furthermore, during the added years of follow-up (years 10 and 11), there was a relative reduction in risk of 38%.

It cannot be denied that prostate cancer mortality has declined considerably since the advent of PSA. However, it is important to estimate the effect of screening on the reduction of prostate cancer mortality. Two mathematical modeling teams of the US National Cancer Institute cancer modeling network suggested that between 45 and 70% of the mortality benefit was due to PSA screening [8], whereas changes in primary treatment can explain 33% [9].

However, next to screening efficacy and improvement in treatment, reporting bias might also explain a part of the decline in prostate cancer mortality in the last 20 years. The high mortality rates starting in the late 1980s may be due to incorrect attribution of causes of death associated with the growing number of men diagnosed with prostate cancer who actually died of other causes. Some of these men could have mistakenly been coded on death certificates as dying of prostate cancer, primarily because they were labeled as having the disease. Over time, the attribution of causes of death has improved and this may have led to lower mortality rates.

Some evidence exists that such misattribution of underlying cause of death does occur in prostate cancer [10], and the assignment of the underlying cause of death may differ depending on initial treatment [11].

Screening effects on M+ disease

Reduction of M+ disease has been shown by the ERSPC study group, which reported a 30% reduction in the intention-to-treat analysis after a median follow-up of 12 years [12]. It also demonstrated that the impact of screening on the risk of M+ disease is primarily seen at or shortly after diagnosis but attenuates during follow-up. The relative risk reduction at diagnosis was 50% but fell to 30% after accounting for the M+ cases emerged during follow-up.

The risk reduction of 30% is lower than the risk reduction of 41% noted in the previous report from 2009 [2] and demonstrates that M+ disease still occurs despite early detection efforts. Most cases of M+ detected during follow-up were identified among those with intermediate-risk disease at diagnosis. In addition, most cases that progressed to

M+ disease were diagnosed at the first screening round, suggesting that more intensive screening would not have likely altered the outcomes noted. It is likely that this increase is related to the natural history of cancers that were present in a fairly advanced stage at the first screen. If this assumption is correct, we may expect that the rates of M+ disease during follow-up will decrease further in the screening arm once the treated natural history of these cancers has reached its endpoint.

Other effects of screening

Screening efficacy has also been demonstrated by findings from **Chapters 4** and **5**. Data from men with screen-detected cancers in the ERSPC show that those diagnosed at the second visit had a 2.9-fold lower risk of dying from the disease than those detected at the first visit. After adjustment for known prognostic factors, including age, PSA, clinical stage and Gleason score, and primary treatment modality, the risk of prostate cancer death was still 2.0-fold lower in favor of men diagnosed at the second round. This suggests that the first round has already eliminated a large proportion of the more advanced cancers. Although men with a prior diagnosis of prostate cancer were excluded from the ERSPC trial, some men may already harbored disease without knowing about that. Those with advanced disease diagnosed at the first round may have been treated initially with curative intent, but eventually succumbed from the disease. These findings concur with those from the above mentioned study of M+ disease, as it was demonstrated that the development of metastasis among screen-detected men still emerges after several years of follow-up [12].

In **Chapter 5**, radical prostatectomy outcomes were compared among men diagnosed with prostate cancer from the screening arm and those from the control arm. Data were derived from the Rotterdam branch of the ERSPC. We found that after radical prostatectomy, screen-detected cancer had significantly improved progression-free survival, metastasis-free survival and cancer-specific survival compared with controls. These findings indicate that screening has advanced the moment of diagnosis, and has increased the probability of detecting the cancer in a curable phase [13]. Interestingly, it appeared that tumor volume was an essential determinant of treatment outcome, and therefore implies that one of the ways that screening improves survival outcomes is through a reduction in tumor volume. One of the limitations of the study is that we do not have data on surgical experience, to which surgical outcomes are related [14,15]. Also, as radical prostatectomy is only indicated for clinically localized disease, fewer men are candidates for this type of curative therapy in the absence of screening. Therefore, some of the differences between groups may have already been dampened in the process of surgical selection.

Lead time, length bias and overdiagnosis

Results from **Chapters 4 and 5** should be interpreted with caution. Although we have taken into account known predictors in the multivariate analyses, it remains difficult if not impossible to completely adjust for overdiagnosis, lead time and length biases, which are important issues in the evaluation of prostate cancer screening [16]. They arise from the sojourn time, which is the duration of the pre-clinical detectable phase, assuming that the natural history of the disease follows a three-step process in which an individual's disease status is normal prior to the development of the disease, then passes through a pre-clinical detectable phase and finally to the clinical phase when the disease becomes symptomatic [17].

Lead time is the amount of time by which the detection of a cancer is advanced by screening (Figure 1A). Length bias is inherent to the fact that tumors have different sojourn times, depending on their aggressiveness, and leads to the phenomenon that screen-detected cancers tend to have longer sojourn times than interval cancers (can-

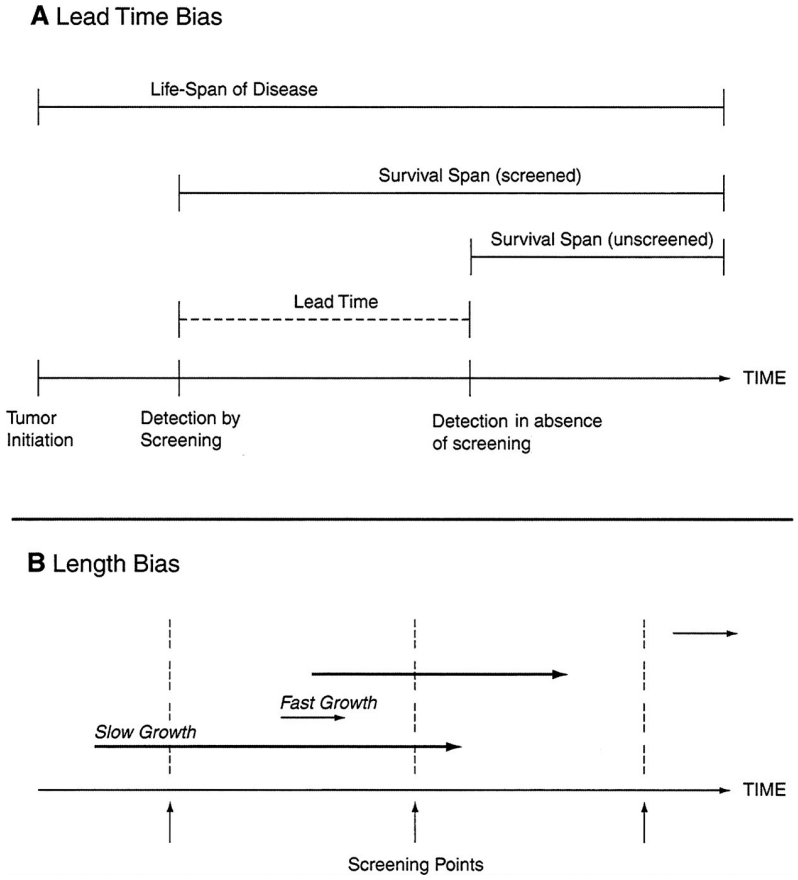

Figure 1: Lead time bias and length bias

cers diagnosed symptomatically between screens), see Figure 1B. Overdiagnosed cases are defined as cancers with a sojourn time equal to infinity i.e., cases that would not have been diagnosed if there had been no screening. Ideally, screening should increase the potential for cure so that death is postponed and survival time further increases beyond the lead time. It is this improvement in survival that is of real interest. However, this component cannot be easily separated from others such as lead time.

A model has been proposed by Wu et al. to correct for these biases [18]. The authors estimated the hazard ratio of prostate cancer death for screen-detected cases against clinically detected cases, which was 0.24 without correction for these biases; 0.76 after correction for lead time and length biases; and 1.03 after further adjustment for overdiagnosis. These findings point out the need to consider possible biases when evaluating survival in prostate cancer patients, especially when comparison is made between screen-detected and clinically detected cases.

Factors that may affect the screening efficacy

The 21% relative reduction in prostate cancer mortality in favor of screening reported by the ERSPC study group in 2012 is based on the intention-to-treat analysis. After adjustment for non-compliance, the relative reduction was 30% [7].

Other factors which may affect the extent of screening efficacy include the type of randomization, which is described in **Chapter 6**. In the Rotterdam branch of the ERSPC, informed consent is needed from all participants because of legal requirements; only those who provided consent were randomized. In the Göteborg branch, randomization took place first and consent was needed from men in the screening arm only. As a consequence, participants in Rotterdam, who had had a higher perceived health status and more knowledge about prostate cancer, appeared to be healthier and sought more often PSA-screening than men from the general population; this "healthy screenee" bias resulted in a lower overall mortality, and more importantly, lower prostate cancer mortality in men from the control arm when compared with the general population. The study in Gothenburg, on the other hand, is more population-based and has resulted in a similar disease-specific mortality of men in the control arm and those from the general population, and may therefore be more appropriate to reflect the "true" screening effect in the context of screening vs. no screening [19].

Other than differences in randomization procedures, background incidence of prostate cancer may also influence outcomes in terms of screening efficacy. It is an established assumption in clinical epidemiology that the absolute risk reduction would be greater among men with a higher baseline risk of death from the event of interest [20]. Also, differences in screening algorithm, such as the length of the screening interval [21,22], threshold of PSA level [2] and the extent of prostate biopsy may affect prostate cancer detection and mortality, and therefore screening efficacy.

Additionally, differences in the management of prostate cancer may alter survival outcomes of patients. Some criticasters have suggested that the mortality reduction achieved in the ERSPC is partly due to an imbalance of treatment modalities between the two arms, i.e. men in the screening arm would have been treated more aggressively [23]. However, such arguments ignore the stage shift associated with screening: after adjusting for stage, there are few differences in treatment between groups [24]. Only a small systematic difference in treatment of men with high risk prostate cancer between the trial arms was previously shown: men in the screening arm were more likely to be treated with surgery compared with men in the control arm, which were more likely to receive radiotherapy or hormone therapy [24]. Whether this could result in a mortality difference is uncertain, but if a difference would occur it is likely to be small. It should be acknowledged that in a randomized screening study, it is general policy to leave treatment decisions to regional health care providers to avoid treatment bias. This is also part of the ERSPC study protocol.

A more recent study has compared the applied treatments between the study arm over time, broken down by tumor stage [25]. For localized disease, the authors confirmed the previous finding as described above, i.e. surgery was more often applied in the screening arm at the beginning of the ERSPC study (1994-1998). However, in later years (1999-2006), the proportion of men underwent surgery was more or less the same in the study arm: 28.8-35.1% in the control arm vs. 31.1-36.1% in the screening arm.

Future perspective concerning screening efficacy

Will the prostate cancer mortality reduction increase with further follow-up? There is no clear answer to this question. Based on the publication of the 9 year data in 2009 [2], some authors have predicted a relative mortality reduction of 30-50% in favor of screening [26,27]. The observed reduction of 21% with 11 year data [7] was clearly lower than most have expected. The reasons why the effect of screening did not increase more during the extended follow-up remain unclear at this time.

The majority of prostate cancer deaths in the intervention arm after 11 years follow-up were screen-detected cancers (45.5%), especially cancers diagnosed at the first screen. Data from **Chapter 4** have shown that men diagnosed with prostate cancer have improved survival outcomes compared with those diagnosed at the first round. A possible implication of this finding is that we may expect that the prostate cancer mortality rates will further decrease in the screening arm once the natural history of the "bad" first round cancers has come to an end. However, next to screen-detected cases, cancers in the screening arm also include cases diagnosed during the screening interval (i.e. interval cancers) and cancers in unscreened subjects (non-attendees) [7]. Men with these cancers have a higher risk of dying from the disease than men with screen-detected cases [28,29].

The proportion of prostate cancer deaths in non-attendees remained stable during the follow-up of the ERSPC study (approximately 30%). Conversely, the proportion in interval cancers increased from about 20% in the early follow-up to 30% in the later years, mainly due to men who had been screened, but did not attend the next scheduled round (non-compliance). Therefore, both non-attendance and non-compliance have a high impact on the prostate cancer mortality in the screening arm. Previously published data from the Göteborg branch of the ERSPC reported similar findings, showing that non-attendees constitute a high-risk group for death from prostate cancer [28]. Although non-attendance is considered inevitable within a population-based screening program, an individualized risk-based strategy may lead to greater compliance if those at high risk were informed on their risk status, resulting in fewer no-shows after being screened once [30]. Prospective evidence is however lacking.

A modeling study from the ERSPC study group, using the Microsimulation Screening Analysis (MISCAN) prostate model, has estimated that per 1000 men followed for their entire life span, annual screening of men between the ages of 55 and 69 years would result in nine fewer deaths from prostate cancer (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), and a total of 73 life-years gained (average, 8.4 years per prostate-cancer death avoided). It is predicted that per 1000 men, 98 men would need to be screened and 5 cancers would need to be detected to prevent one prostate-cancer death [31].

Other cancer screening programs

The benefits of screening for cancer of the colon and breast have been tested in large clinical trials. A recent Cochrane review by Gotzsche et al. identified eight eligible breast cancer screening trials with a total of 600.000 women in the analyses. Three trials with adequate randomization did not show a significant reduction in breast cancer mortality at 13 years (RR 0.90, 95% CI 0.79 to 1.02); four trials with suboptimal randomization showed a significant reduction in breast cancer mortality with an RR of 0.75 (95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI 0.74 to 0.87). The absolute risk reduction was 0.05%. The NNT is estimated to be 10 at 10 yrs.

Breast cancer screening led to 30% overdiagnosis and overtreatment, or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Also, breast cancer screening appears to be cost-effective [32]. The United States Preventive Services Task Force (USPSTF) recommends biennial screening mammography for women between the ages of 50-74 years, and against routine screening for women before the age of 50 [33].

The 23% predicted reduction in life-years gained due to quality-of-life effects in prostate cancer screening is higher than the 8% estimated for breast-cancer screening [34]. In addition to cancer deaths avoided, screening for breast cancer allows the use of less radical treatment (e.g. lumpectomy vs. mastectomy) in early detected cancers, whereas screening for prostate cancer often leads to a substantial increase in active therapy, despite the upcoming strategy of active surveillance [35,36]. Also, among women undergoing breast-cancer screening, an average of 15 life-years are gained per breast cancer death that is prevented, whereas among men undergoing prostate-cancer screening, only 8.4 life-years are gained per prostate-cancer death avoided because of an older age at diagnosis and shorter life expectancy among men [31].

The benefits and harms of screening for colorectal cancer were summarized by Hewitson et al.[37,38]. The authors found that the fecal occult blood test reduces disease-specific mortality by 16%. After adjustment for non-compliance, a reduction of 25% in favor of screening was shown. There was no difference in overall mortality. Colorectal cancer screening also appears to be cost-effective [39].

Prostate cancer screening provides a similar relative reduction in disease-specific mortality as compared with breast cancer and colorectal cancer screening. However, the absolute mortality reduction of prostate cancer screening is very modest, and a relatively high number of men need to be screened to prevent one man from death from the disease. Furthermore, the number of additional men diagnosed with cancer with PSA screening is higher than in other cancer screening programs. Additionally, cost-effectiveness has yet to be determined for prostate cancer screening. These different aspects need to be addressed before a population-based screening program can be launched.

HARMS FROM SCREENING

Related to screening and diagnostic procedures

PSA testing often produces false-positive results: after four screening rounds in the PLCO trial, men in the screening arm had a 12.9% cumulative risk for at least 1 false-positive result and a 5.5% risk for at least 1 biopsy due to false-positive result [40]. In the ERSPC study, approximately 75% of men who underwent biopsy for an elevated PSA level, had a false-positive result [7]. It has been reported that men with false-positive PSA tests are more likely than control subjects to worry about prostate cancer, have a higher perceived risk for prostate cancer, and report problems with sexual function for up to 1 year after testing [41]. Furthermore, men with false-positive PSA results were more likely to have repeated PSA testing and additional biopsies during the 12 months after the initial negative biopsy [42].

False-negative results also occur, as there is no PSA level that rules out prostate cancer. Data from the (Prostate Cancer Prevention Trial) PCPT have demonstrated that the prevalence of prostate cancer was 8.8% among men with PSA level up to 1.0 ng/mL, 17.0% among those with values of 1.1-2.0 ng/mL, 23.9% among those with values of 2.1-3.0 ng/mL, and 26.9% among those with values of 3.1-4.0 ng/mL [43].

In the Swedish branch of the ERSPC, levels of anxiety were assessed through questionnaires among 1781 screen-positive (PSA > or = 3 ng/mL) men [44]. A multinomial logistics model for repeated measurements, adjusted for age, PSA level, heredity, biopsy finding and urinary symptoms, revealed that anxiety awaiting the PSA was only influenced (increased) by the existence of previously elevated PSA tests ($p<0.001$). No anxiety associated with biopsy was reported by 45% of the study participants, while 6% experienced high levels of anxiety. Levels of anxiety decreased significantly with subsequent rounds of examinations ($p<0.001$) and with increasing age ($p=0.002$).

In the PLCO trial, harms associated with diagnostic evaluations, including biopsy, were reported to be infection, bleeding, clot formations and urinary difficulties (68 events per 10,000 evaluations) [3]. In the Rotterdam branch of the ERSPC trial, among 5,802 biopsies performed, reported harms were fever (3.5%), urinary retention (0.4%), hospitalization for signs of prostatitis or urosepsis (0.5%), and hematuria (22.6%) and hematospermia (50.4%) more than three days after biopsy [45].

It is unclear whether prostate biopsy is associated with increased short-term mortality. Data from the ERSPC study did not show an increased mortality after biopsy: no statistically significant difference in cumulative 120-day mortality between screening-positive men (i.e. with biopsy indication) and screening-negative men (0.24% and 0.24%, respectively) was found [46]. Conversely, Gallina et al. extracted data from the Quebec Health Plan and compared the mortality rate between men who underwent biopsy and a control sample. They reported a 1.3% risk of death within 120 days after prostate biopsy vs. 0.3% ($p < 0.001$) in the control group [47]. Of men aged <= 60 years, 0.2% died within 120 days versus 2.5% aged 76-80. The risk of death after biopsy decreased with the number of procedures: 1.4% with 1 session, 0.8% with 2 sessions, and 0.6% with 3 or more sessions. In the multivariable model, first ever biopsy, increasing age and comorbidity predicted higher mortality. One of the main limitations of this study is that the control population was not matched for comorbidity.

Related to diagnosis and treatment of screen-detected prostate cancer

The PCPT trial revealed that there is an enormous pool of biopsy detectable cancer in men with normal PSA values, defined as 4.0 ng/mL or less. At the end of the study period, participants without a diagnosis of prostate cancer were scheduled to undergo a biopsy in which a minimum of six cores were obtained: 449 of the 2950 men (15.2%) were diagnosed with prostate cancer; 361 of the 428 cancers with a known Gleason pattern

were scored 6 or less (84.3%) [43]. With screening, we tap into this pool and increase the incidence of prostate cancer [6,7]. Overdiagnosis as result of screening has been estimated to be approximately 50% [48]. This is of particular concern, as these men are not likely to benefit from any associated treatment; but they are subject to harms of the given treatment.

In the US, 90% of men with PSA-detected prostate cancer undergo early treatment [33,34]. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry show that among 11,892 men analyzed, 6.8% elected surveillance, 49.9% prostatectomy, 11.6% external-beam radiation, 13.3% brachytherapy, 4.0% cryoablation, and 14.4% androgen deprivation monotherapy. Notably, next to overtreatment of low-risk disease, data from this study also suggest undertreatment of high-risk disease [35].

Radical prostatectomy

The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), which allocated men with prostate cancer to either radical prostatectomy or watchful waiting, is a landmark study in prostate cancer treatment. According to data from the SPCG-4 trial, symptoms such as erectile dysfunction and urinary incontinence were seen early and remained stable with longer follow-up in the radical prostatectomy group, whereas in the watchful waiting group the symptoms increased over time. After a median follow-up of more than 12 years, the prevalence of erectile dysfunction (defined as an inability to have erection spontaneously or elicited) was 84% (146 of 173) in men allocated radical prostatectomy, 80% (122 of 153) in those allocated watchful waiting, and 46% (95 of 208) in the control group, which was population-based and matched for region and age. The prevalence of urinary leakage after radical prostatectomy in the SPCG-4 trial was 41% (71 of 173), 11% (18 of 164), and 3% (six of 209), respectively [49]. However, the finding that men assigned to watchful waiting had similar risk for erectile dysfunction as did those receiving surgery should be interpreted with caution, especially since almost a third of patients in the watchful-waiting group received androgen-deprivation therapy, which will have affected their quality of life and sexual function, compared with less than a fifth of men receiving surgery.

Other studies have reported a 20-70% decrease of sexual function, and 15 to 50% of men having urinary problems after surgery [50,51].

In addition, radical prostatectomy is associated with a 30-day mortality rate of 0.50% [52-54]. Advanced age and increased number of serious comorbidities are associated with higher perioperative mortality, although absolute rates are less than 1%, even in men at higher risk.

Radiotherapy

Radiotherapy is associated with a 25-45% risk for erectile dysfunction in men with previously normal erectile function, a 2-16% risk of urinary incontinence in previously continent men, and a 6-25% risk for bowel dysfunction in men with previously normal bowel function [50,55]. The effect on bowel dysfunction is most pronounced in the first months after treatment [56].

However, further improvement in radiotherapy planning and delivery in the future may decrease side-effects and permit administration of higher doses. Related to the anatomy of the prostate, these higher doses may favor rectal sparing while not readily sparing the urethra and bladder neck. As a result, we may see a future shift from dose-limiting long-term rectal morbidity towards long-term urinary morbidity. In the absence of prospective randomized trials comparing different types of surgical and radiotherapy-based treatments in prostate cancer, the introduction of validated tools for reporting functional and clinical outcomes is crucial for evaluating and identifying each individual's best treatment choice [57].

Quality of life

In the SPCG-4 study, Johansson et al. reported that men's symptoms deteriorated over time when reporting their quality of life in both arms of the trial. Also, the incidence of anxiety increased in the SPCG-4 cohort compared with matched men in the non-cancer observational group. These findings are helpful and indicate that prostate cancer reduces quality of life in general, irrespective of treatment received [49].

Heijnsdijk et al. reported that the benefit of PSA screening was diminished by loss of QALYs due to long-term effects after the diagnosis [31]. In their study, Microsimulation Screening Analysis (MISCAN) was used to predict the number of quality-adjusted life-years (QALYs) gained with PSA screening. The use of QALYs should be commended, as we now can quantify harms and benefits with the same measure. The number of QALYs was predicted using utility estimates for various health states. The utility estimates were obtained from the Cost-Effectiveness Analysis Registry and additional studies and ranged from 0 (death or worst imaginable health) to 1 (full health). Per 1000 men of all ages who were followed for their entire life span, the authors predicted that annual screening of men between the ages of 55 and 69 years would result in a total of 73 life-years gained (average, 8.4 years per prostate-cancer death avoided). The number of QALYs that were gained was 56 (range, −21 to 97), a reduction of 23% from unadjusted life-years gained.

These results suggest that men will gain from PSA screening. However, the predicted QALYs are sensitive for the utilities used and their accuracy is debatable: the most favorable utility estimates resulted in 97 QALYs gained, and the least favorable in 21 QALYs lost. The utility estimate for the post-recovery period had a considerable effect. If no loss

in utility in this period was assumed, screening resulted in 72 QALYs gained, whereas a utility estimate of 0.93 instead of 0.95 for the remaining lifetime resulted in 6 QALYs gained. Another limitation includes the lack of data corrections for the detection mode (screen or clinically), advances in treatment, the short term of follow-up of the ERSPC data used, and lack of data on long-term morbidity from treatment. This tells us that the net effect of prostate cancer screening can be a loss or a gain, depending on utilities.

Studies which may be able to provide more definitive results about how much treatment affect the quality of life of an individual include the ERSPC and the Prostate Testing for Cancer and Treatment (ProtecT) trial, although definitive findings from the latter are not expected to be reported before 2016 [58]. Until more definitive results about QALYs become available, shared decision making should be recommended. In the future, an individualized decision-support model with QALYs gained or lost as endpoint may provide men with assistance in the decision regarding PSA screening. However, it is yet to be determined how to translate the term QALY into an easily understandable concept for lay person. Also, a more precise model to estimate QALYs need to be provided.

Prostate cancer deaths despite screening

One of the most obvious and therefore studied downsides of screening is overdiagnosis. However, not many are aware of the fact that despite screening, a significant proportion of men still die from prostate cancer. A relative reduction of 20-30% means that of all prostate cancer deaths in the screening arm, 70-80% died from the disease despite being offered systematic screening. Data from **Chapter 7** show us that most of those who eventually developed metastases and/or died from prostate cancer were men diagnosed at the initial screening round [29]. In addition, we found that 25 out of 168 "escapes" were men who were no longer screened as they passed the upper age-cut-off. Other possible mechanisms to this "escape" phenomenon may be: non-attending, inadequate screening test, the relative long screening interval of 4 years, and undertreatment.

Besides screen-detected cancers, some cases are found during the screening interval. These cancers were either missed at the previous screen, or they have evolved since the last visit. **Chapter 8** describes the disease-specific survival of men with these interval cancers, by comparing them with men with cancer in the control arm. This is critical in the assessment of the screening protocol, because worse survival outcomes in men with interval cancer may indicate that improvement of the applied protocol is needed. Our results indicate that interval cancers had more favorable prognostic factors than cancers in the control arm. The univariate analysis shows that men with interval cancer were less likely to die from the disease than patients in the control arm. However, after adjustment for age, prognostic factors, and treatment modality, the disease-specific survival was similar between the two groups. This does not necessarily mean that the detection of interval cancers is a failure of the applied screening algorithm: 38.8% of men were diag-

nosed during the screening interval because they actively sought screening between two scheduled screening visits; 27.3% of the cases were incidental findings, i.e. found during cystoprostatectomy or transurethral resection of the prostate. The remaining 33.1% were diagnosed because of clinical symptoms; these men may have benefit from earlier detection [59].

This last subgroup should also be targeted in attempts to further reduce the prostate cancer mortality. Although it is questionable whether these men could be identified upfront and would be ready to follow a different screening procedure, a recent study by Van Leeuwen et al. showed that a 2-year screening interval significantly reduced the incidence of advanced prostate cancer. However, the 2-year interval increased the overall risk of being diagnosed with (low-risk) prostate cancer [22]. Therefore, instead of applying a shorter screening interval, we should focus on a more individualized screening algorithm, in order to avoid increasing unnecessary testing and overdiagnosis.

We should be aware that no screening strategy is able to eliminate death from prostate cancer. There will always be cancers that escape detection despite screening. Obviously, we should not pursue the most aggressive screening algorithm, but the most effective one while balancing the benefits and harms of screening.

Estimation of the probability of death from prostate cancer

In cancer research, survival curves are frequently generated with the Kaplan-Meier method [60-62]. The complement of the survival probability (i.e. 1 - survival probability) is often used to estimate the probability of death from an event. This approach may, however, overestimate the disease-specific mortality in the presence of competing risks. With the Kaplan-Meier method, men who die from causes other than the event of interest are censored non-informatively; it does not take into account the fact that men who have died from other causes cannot die from the event of interest. An alternative to the Kaplan-Meier is the competing-risks analysis, which accounts for death from other causes [63,64].

Chapter 9 illustrates the overestimation by the Kaplan-Meier method in estimating the cumulative probability of death from prostate cancer in men with the disease. In this study, the Kaplan-Meier estimates were compared with estimates provided by the competing-risks method. With 5 years follow-up, there was an overestimation of 1.8% by the Kaplan-Meier approach; this increased to 8.0% at 10 years. It is to be expected that with longer follow-up, the overestimation by the Kaplan-Meier will further increase. Therefore, in the presence of competing events, the competing-risks analysis is to be preferred in the estimation of disease-specific mortality.

RECOMMENDATION OF THE UNITED STATES PREVENTIVE SERVICES TASK FORCE (USPSTF)

The USPSTF recently reviewed the literature on prostate cancer screening and released an updated recommendation against it [56]. Although there is evidence from well conducted randomized trials that screening reduces the incidence of metastatic prostate cancer and disease-specific mortality, the panel concluded that the harms outweigh the benefits. Many prostate cancer experts believed that this recommendation was inappropriate [65-67], and it has added fuel to the yet heavily debated question of screening for prostate cancer.

Although using the balance of harms and benefits in this way is commendable, it has an important shortcoming. It involves an "apples and oranges" comparison because the units of measure for benefits (prostate cancer deaths averted) and harms (overdiagnosis and overtreatment) differ. Therefore, the decision about where the balance lies is necessarily subjective. As mentioned earlier, reporting screening efficacy after adjustment for quality of life (QALYs) might be a better measurement to assess the balance of benefit and harm [31].

Also, there are several shortcoming from the USPSTF report, which are elegantly addressed by Carlsson et al. [65]. In summary, the USPSTF draw definitive conclusions based on incomplete data; for example, current results from the ERSPC are based on a median follow-up of 11 years, but the follow-up for those who have prostate cancer is only 6 years, which is still relatively short considering the long natural course of prostate cancer. More than 80% of the participants of the trial are still alive, whereas in general, data are considered mature if at least 50% of the study population is dead. Second, the USPSTF addressed the lack of reduction in overall mortality as one of the key findings. However, both the ERSPC and the PLCO trial have not been designed for this purpose. In the power calculation, which is cited in all reports, the endpoint (prostate cancer mortality) and the resulting power are clearly determined upfront. Third, data from incomparable screening trials were combined by the USPSTF panel, which resulted in the statement that most trials did not show significant effect of PSA screening. For example, the PLCO trial was considered as low risk of bias, while contamination was as high as 50% in the control arm, up to 70% of men in the screening arm with positive PSA test were not compliant with the biopsy recommendation, and 40% of the participants have been prescreened [3,68]. Therefore, the PLCO trial results should not be interpreted as evidence against benefit from PSA screening.

Additionally, several other important issues have not been taken into account: 1) a significant proportion of deaths in the ERSPC trial were men with advanced cancer diagnosed at the first screen; men with cancer diagnosed at the second screen have an improved survival (**Chapters 4** and **7**); 2) PSA screening reduces the risk of metastatic

disease [12]; 3) there are several mechanisms currently available with the aim to reduce overdiagnosis and overtreatment [69]; 4) overdiagnosis is not applicable to an individual, and does not always lead to overtreatment.

In conclusion, this recommendation won praise from some and strong denunciation by others but left most men wondering what to do. The USPSTF focused criticism on short-term studies that showed limited efficacy of uniform PSA cut-offs without any consideration of relevant risk factors such as family history and race. A growing body of evidence suggests that individualized strategies for cancer screening may overcome shortcomings of one-size-fits-all recommendations such as those of the USPSTF. Despite these points of criticism on the report of the USPSTF, they deserve credit for making us more aware of the harms of PSA screening.

IMPROVE SCREENING STRATEGIES

Considering that there are some substantial shortcomings to the one-size-fits-all screening strategy as applied in screening trials, we are obliged to optimize current screening algorithms, in order to offer men who are seeking screening the best available strategy in clinical practice.

Improve detection of (potentially aggressive) cancers

Positive predictive value

The performance of PSA as a screening test can be assessed by the positive predictive value, which is the proportion of men with a positive test who have biopsy-detectable prostate cancer. Overall, the positive predictive value for a PSA level >4.0 ng/mL is approximately 30%, meaning that slightly less than one in three men with an elevated PSA will have prostate cancer detected on biopsy [70,71]. For PSA levels between 4.0-10.0 ng/mL, the positive predictive value is about 25% [70]; this increases to 42 to 64% for PSA levels >10 ng/mL [70,72]. Obviously, the positive predictive value is very likely to be higher in a clinical cohort.

However, nearly 75% of cancers detected within the "grey zone" of PSA values between 4.0-10.0 ng/mL are organ-confined and potentially curable. The proportion of organ-confined cancers drops to less than 50% for PSA levels > 10.0 ng/mL [70]. Thus, detecting the curable cancers in men with PSA levels less than 10.0 ng/mL presents a diagnostic challenge because the high false-positive rate leads to many unnecessary biopsies.

The positive predictive value of PSA was examined for the Rotterdam branch of the ERSPC study (**Chapter 10**): it remained equal throughout consecutive screening rounds

in men who have not been biopsied before. Because the positive predictive value depends on the underlying prevalence and the first screening round was performed in a relatively unscreened population, one would expect a decline in positive predictive value after the first round considering the slow natural course of prostate cancer [73,74]. However, data from the PCPT trial has shown that 23.9% of men with a PSA 2.1-3.0 ng/mL harbor prostate cancer [43]. In our study, almost half of the cancers detected in men without previous biopsy originated from the 2.0-2.9 ng/mL PSA group. Apparently, the PSA levels in these men increased during the four year screening interval and subsequently surpassed the biopsy threshold, resulting in equal positive predictive values of approximately 25% [75].

In men who had been biopsied before and who had a benign result, the positive predictive value dropped considerably in subsequent screening rounds (12.0 and 15.2% at the second and third screening, respectively); but a significant proportion of the cancers diagnosed still show aggressive characteristics (21.2 and 15.8% of the cases at the second and third screening, respectively) [75]. These findings imply that the current screening protocol is suboptimal, and underline the need for a different, more individualized approach for screening.

Risk-based screening

Population-based data show decline in mortality and metastatic disease through screening but at a high cost, as discussed throughout this thesis. Also, some men die from the disease despite screening, as shown in **Chapter 7** [29]. To minimize the harms and maximize the benefits of screening, we need a risk-based approach.

Chapter 11 reviews current evidence regarding risk-based prostate cancer screening. Despite its limitations, PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of developing prostate cancer and die from the disease. Especially in men with no additional risk factors, PSA alone provides an appropriate marker up to 30 years into the future [30, 76]. After assessment of an early PSA test, the screening frequency may be determined based on individualized risk. A limited list of additional factors such as age, comorbidity, prostate volume, family history, ethnicity, and previous biopsy status have been identified to modify risk and are important for consideration in routine practice.

In men with a known PSA, risk calculators may hold the promise of identifying those who are at increased risk of having prostate cancer and are therefore candidates for biopsy. Risk calculators are increasingly used in the clinical setting. There are several benefits to these tools. They can provide predictions that are evidence-based and at the same time individualized. With multivariate risk calculators, it is possible to identify men at increased risk of having prostate cancer and who are therefore candidates for biopsy.

The decision to undergo early PSA testing should be a shared one between a man and his physician based on information balancing its advantages and disadvantages. A challenge with risk assessment tools is that the "product" is not a yes/no recommendation, but a level of risk. Both clinicians and men may find it difficult to interpret the meaning of the provided risk. One way to determine whether it is worthwhile to undergo prostate biopsy is to compare the probability of having significant cancer with the risk of serious complications as a result of prostate biopsy. In Europe, the rate of hospital admission after prostate biopsy is estimated to be less than 1% according to data from the ERSPC trial [45]. Participants in the ERSPC are, however, healthier when compared with men in the general population [19,77]. In the US, Loeb et al. showed that in the Medicare population the rate of hospitalization within 30 days of prostate biopsy (6.9%) was more than double that in a control population (2.7%) [78].

Another way to interpret predictions provided by risk calculators is to compare the risk of detection of low-grade cancer with the risk of detection of high-grade cancer. This is already available with the ERSPC risk calculators. As there is growing consensus that there may be a net negative impact of a detection of a Gleason 3 + 3 tumor in most men, if the risk of low-grade cancer is 20% and the risk of high-grade cancer is <2%, a man could be told that he has a 10-fold greater risk of potential detection of an indolent tumor than of one of consequence. Other possibilities are not to communicate the probability of having cancer, but the probability of not having cancer, or to communicate relative risk instead of absolute risk [79].

Finally, it should be noted that there is no single level of risk that prompts biopsy in all men; their interpretation of a risk of cancer will be different, as will their life expectancy, their aversion to risk of overdiagnosis, and other consequences of detection.

Future risk calculator

Chapter 12 describes the recently developed risk calculator based on data from ERSPC Rotterdam, which can predict the risk of having prostate cancer within 4 years in men with an initially negative screen [80]. The rationale behind this calculator is the uncertainty surrounding the follow-up of men screened negatively for prostate cancer, and in particular those men who have adverse characteristics such as persistent PSA elevation and digital rectal examination abnormality.

Based on variables including age, family history, digital rectal examination, prostate volume, PSA and previous biopsy results, the future risk calculator can predict the risk of prostate cancer in 4 years. In addition, we have proposed a stratification of future risk into low (<=1.0%), moderate (1.0–5.0%), and elevated risk (>=5.0%), based on the mean and median future risks of having prostate cancer. This information enables discriminating an individual with high risk of having cancer from someone with low risk. For example, a 65-year-old man with a PSA of 2.5 ng/mL, a prostate volume class of 40 cm^3, a normal

digital rectal examination and no family history, would have a 4-year risk of 5.5% for low-risk cancer and 1.7% for high-risk cancer. An abnormal digital rectal examination and a positive family history would increase this man's risk for high-risk cancer to 4.2%. If this man had already had a prostate biopsy with a benign result at the previous screening, his future risk of having cancer would decrease to 3.3%. Such predictive information is of considerable value and will potentially provide benefits for men and physicians by reducing uncertainty, unnecessary testing, and overdiagnosis of prostate cancer. Furthermore, the web-based presentation might make it an easily applicable tool to support shared-decision making on an individualized future screening strategy. This calculator is readily available on our websites: http://www.prostatecancer-riskcalculator.com, and http://www.prostaatwijzer.nl.

Although this novel calculator is accurate in estimating the risk of future prostate cancer, validation in external cohorts may further help confirm its results. The predictive value of nomograms outside of the model populations may not be the same, because of differences such as age, ethnicity, number of previous PSA tests, template of the biopsy performed, and number of previous negative biopsies. External validation of the future risk calculator may, however, not be that easy, as it requires up to 4 year of follow-up data to verify the outcomes. However, we might rely on the previous promising results of the calculators based on the ERSPC; several studies have shown adequate discrimination and calibration of these prediction models in contemporary, independent cohorts [81,82].

FUTURE APPROACH TO SCREENING

Prostate cancer is an important healthcare problem and it has been established through several studies that PSA screening is effective in reducing the relative risk of metastatic disease and prostate cancer death. The main concern is whether the benefits of screening outweigh the potential harms: the substantial risks for overdiagnosis and overtreatment, and men dying from the disease despite screening. Therefore, we need to screen smarter, with less intensive assessment for those at low risk, and more careful assessment of those at high risk.

Ideally, in the future, a biomarker will be discovered that will say "normal" in some men and "cancer" in others who have prostate cancer. Given the heterogeneity of disease and the experience in the science of biomarkers, this is unlikely in the near term.

Until that ideal future, instead of using PSA as the sole screening tool, we should take advantage of validated risk-stratifying tools that already allow avoidance of unnecessary biopsies and selective diagnosis of aggressive cancers. General practitioners and urologists should be informed about the possible advantages of risk stratifying tools,

and they should be encouraged to use them when screening is indicated. Furthermore, we need to continuously improve and validate current nomograms. It should be kept in mind that a useful nomogram is dependent not only upon its predictive accuracy but also on the usability, so that it can be routinely employed.

Age and screening interval

Current evidence suggest that screening may be discussed with men at age 50, though not with men who have a comorbidity that limits their life expectancy to less than 10 years [83]. African-American men, and men with risk factors such as strong family history may be offered the possibility to discuss about screening at age 40-45 [69,83].

The optimal screening interval remains uncertain. The ERSPC study group has compared two sites with a different screening interval [22]. It was found that a 2-year screening interval significantly reduced the incidence of advanced prostate cancer; however, the 2-year interval increased the overall risk of being diagnosed with (low-risk) prostate cancer compared with a 4-year interval.

Modeling studies with regard to the optimal screening interval have produced inconsistent findings. Ross et al. concluded that the most efficient strategy would be to screen men at age 40 and 45 years and then biannually from age 50 to 75, while still using the 4.0 ng/mL cut-off as a threshold for prostate biopsy [84]. Conversely, Heijnsdijk et al. found that annual screening in men at age 55-69 would provide more QALYs than quadrennial screening (56 vs. 41 QALYs per 1000 men, respectively) [31].

Another area of uncertainty is the age where screening should be stopped. A study from the Malmö Prevention Project has shown that men aged 60 with PSA at the median or lower (<=1 ng/mL) were very unlikely to have clinically relevant prostate cancer; the risk of metastasis by age 85 was 0.5% and the risk of death from prostate cancer was 0.2% [30]. Similar results were found by the Baltimore Longitudinal Aging Study, showing that 94% of the cancer would still be detected if screening was discontinued for men with a PSA level of <= 1.0 ng/mL at age 65 [85]. However, as shown in **Chapter 7**, a significant proportion of men who developed metastasis or died from prostate cancer in the screening arm of the Rotterdam branch of the ERSPC were diagnosed at age 75 and older. Therefore, in deciding when to cease screening, we should also consider a man's comorbidity. Elderly men may still benefit from screening if they are otherwise healthy. An analysis using SEER-Medicare data showed that a higher comorbidity score is associated with higher overall mortality and lower prostate cancer mortality [86].

Informed decision

Because preferences of an individual are a deciding factor in determining whether to screen or not, structured, well-designed, and validated counseling of men who wish to be tested should be standard procedure. Contrary to the USPSTF recommendations, and

considering the present knowledge of risks and benefits, health professionals should be allowed the option of offering screening for prostate cancer to men at risk.

Useful summaries of discussion points have been provided by the American College of Physicians and the American Cancer Society [83,87]. In short, men should be informed about the benefit of screening, in terms of reducing the risk of dying from prostate cancer; the substantial risk of being overdiagnosed, meaning that the cancer never would have caused problems during a man's lifetime; the diagnostic procedures and their limitations; and the uncertainty regarding the optimal treatment modality once cancer is detected.

It may be challenging to provide comprehensive and balanced information about prostate cancer screening during clinic visits [88]. Consequently, efforts have focused on using decision aids to help men understand screening issues and make informed decisions for screening. These interventions include videotapes [89,90], written information leaflets [91-93], and online tools, such as the PSA screening decision aid provided by the SIU with the assistance of men's health movement Movember (http://www.siu-urology.org). The various strategies were shown to be consistently effective in increasing a man's knowledge about prostate cancer and screening [89-93]. Furthermore, most men receiving such information were less interested in undergoing PSA testing or receiving aggressive treatment [89,90,93].

Active surveillance

Overdiagnosis, when recognized, is amenable to solutions. These include restricting screening attempts to higher-risk individuals and reducing the burden of therapy by avoiding unnecessary treatment. Therefore, several researchers have proposed the concept of active surveillance as a strategy intended to minimize the harms of overdiagnosis [94,95]. It is an approach wherein patients are monitored carefully with serial PSA measurements, and repeat biopsies to identify early signs of progression. The aim of active surveillance is to postpone or even avoid active treatment from men who are deemed to have disease that is unlikely to progress.

Results of the phase 2 observational studies demonstrated that it is feasible and safe in the intermediate time frame. One of challenges of active surveillance is how to define its inclusion criteria, as these are slightly different in each large surveillance cohort. Most of them reflect variation of low-grade, low-volume disease with a low PSA at diagnosis. Ideally, only men who have disease that will not progress and cause symptoms during their life time should be managed expectantly. However, preliminary results show that the proportion of men moving from surveillance to active treatment ranges from 14% to 41% [94,96], although some of these men underwent treatment because of anxiety [97].

Another limitation of active surveillance is that we cannot be certain when the patient needs treatment, since we still do not fully understand the natural history of screen-de-

tected cancers. Ideally, we want to identify those men with clinically significant disease at an early stage and within the window of curability. In the PRIAS study, it was shown that in men under surveillance how eventually had undergone radical prostatectomy, 29% had unfavorable pathologic outcomes defined as pT3-4 and or Gleason >=4+3 [97]. Although this rate may seem high, it should be kept in mind that other studies, which have evaluated pathologic outcomes after radical prostatectomy in men with low-risk cancer, reported rates of upgrading between 21% and 36% [97]. These data show that a considerable amount of men who are deemed to have low-risk cancer according to characteristics at diagnosis harbor more aggressive disease on radical prostatectomy. Therefore, unfavorable outcomes in men initially under active surveillance may merely reflect the limitations in the initial staging and grading, rather than true disease progression during the follow-up. However, these percentages of upgrading after radical prostatectomy also question the reliability of risk calculators, which are usually based on biopsy Gleason scores.

It is important to stress that even the cohort with the longest follow-up time has been observed for too short a time to draw definitive conclusions regarding mortality risks in men under active surveillance. Also, the exact benefit and harm of immediate treatment vs. active surveillance remain to be quantified. Results from the ProtecT trial may shed light on this issue, although it will take several years for the data to mature [58].

Nevertheless, we can conclude that active surveillance for favorable risk prostate cancer is feasible and appears to be well tolerated. This strategy provides the benefit of an individualized approach based on PSA kinetics and biopsy outcomes. Uncertainty remains regarding the inclusion and follow-up criteria, quality of life issues on the long-term, and the impact of delayed treatment in men reclassified as higher risk.

EPILOGUE

Prostate cancer is the second leading cause of cancer death in American men, behind only lung cancer. About one man in 36 will die from prostate cancer. Almost 90000 deaths from prostate cancer were estimated to have occurred in 2008 in Europe, ranking it the third most common cause of cancer death amongst men, after lung and colorectal cancers [98]. Prostate cancer is also the most common cancer in American men [99].

With this perspective, a screening program to reduce prostate cancer mortality seems like a logical next step. With the introduction of the PSA test, unorganized screening has become widespread worldwide. A 2001 population-based telephone survey of US adults showed that 75% of men more than the age of 50 years had had a PSA test and 54% had a PSA test within the previous year [100]. A 2005 National Health Interview Survey reported that 49% of 50- to 79-year-old men had a PSA test in the past 2 years [101].

However, an organized screening program has yet to be launched. The main reason is that there is truth on both sides of the debate for and against PSA testing. Prostate cancer mortality has declined considerably—by 40%—since the advent and widespread uptake of PSA testing in the late 1980s in North America. Large, highly powered, contemporary clinical trials have confirmed the impact of PSA testing in reducing metastasis and cancer-specific mortality [5,7], and projection models have attributed as much as one-half of the observed decline in mortality to PSA screening [8]. However, some overinterpret the absolute impact of this decline for an individual man and fail to acknowledge the considerable, well-documented problems of prostate cancer overdetection and overtreatment. On the other hand, screening effect may be underestimated for those who have actually underwent screening [102]. Despite extensive research there are still some unresolved issues regarding the long-term effect of screening, the magnitude of the screening benefit in different populations, the extent of overdiagnosis and overtreatment of low risk disease, the optimal treatment for localized disease and the costs of these policies.

Follow-up data from the ERSPC study and ongoing trials such as the ProtecT trial [58] may help address these screening and treatment dilemmas.

The USPSTF recently recommended against PSA screening. Although there are several shortcomings to their report, it should further encourage us to reduce the burden of overdetection of indolent disease as well as to improve our ability to identify lethal tumors early, when treatment would be most successful.

It is uncertain whether the USPSTF recommendation against PSA testing would have much effect of the existing pattern of PSA testing. Screening does reduce prostate cancer mortality but not by very much and at a high cost. Therefore, we need to focus on how to make screening more effective and less harmful. We need to screen and treat only those most likely to benefit.

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VI Appendices

SUMMARY

The first part of this thesis provides background information on the prostate, the PSA test, prostate cancer (**Chapter 1**), and prostate cancer screening (**Chapter 2**). The scope of this thesis, outlined in **Chapter 3**, was to demonstrate the efficacy of screening which is affected by several factors, to address points of improvement, and to provide recommendations concerning future directions of prostate cancer screening.

In the second part, we studied the effect of screening. In **Chapter 4** we compared the disease-specific survival of men diagnosed with prostate cancer at the first screening round vs. men diagnosed at the second screening round. After adjustment for known predictors and primary treatment modality, patients diagnosed at the second round had a 2-fold lower risk of dying from the disease as compared with those from the first round within a similar follow-up time. This finding implies that repeated screening improves disease-specific survival.

In **Chapter 5** we found that radical prostatectomy is associated with improved outcomes in men with screen-detected prostate cancer, in terms of lower rates of biochemical recurrence and metastasis after adjustment for preoperative variables, when compared with men with cancer in the control arm. The improved outcomes in the screening group appeared to be mediated by a significantly lower tumor volume.

The extent of screening efficacy in a randomized trial is affected by many factors. One of these is the type of randomization. **Chapter 6** summarizes the differences in outcomes between two sites of the ERSPC trial: Rotterdam, where only men were included and randomized if they had provided informed consent, and Göteborg, where men were first randomized and consent was only needed from those in the screening arm. Our findings indicate that the study design in Rotterdam has introduced a "healthy screenee bias", resulting in a lower overall mortality and more importantly, lower disease-specific mortality in the control arm when compared with the general population. As a result, the prostate cancer mortality reduction achieved in Rotterdam may underestimate the "true" effect of screening vs. no screening.

The third part of this thesis focuses on men in the screening arm who died from prostate cancer despite their allocation to the intervention arm of the ERSPC trial. In **Chapter 7** we identified and characterized men from the screening arm who developed metastasis or died from prostate cancer in the Rotterdam branch of the ERSPC study. The majority of these "escapes" were diagnosed at the first screening round. These men had worse prognostic factors at diagnosis when compared to men diagnosed at later screening rounds. Several possible mechanisms may have accounted for this "escape" phenomenon: non-attending, inadequate screening test, the relative long screening interval of 4 years, the age cut-off at 75 years, and undertreatment.

Chapter 8 describes the disease-specific survival of men diagnosed with prostate cancer during the screening interval, i.e. between two scheduled screening visits. When compared with men with prostate cancer in the control arm, men with interval cancer had an improved survival. However, after adjustment for known prognostic factors, and treatment modality, the disease-specific survival was similar between the two groups. We also found that some men were detected during the screening interval because they actively sought screening between the scheduled screening visits, while other tumors emerged rapidly and were diagnosed because they caused clinical symptoms.

The Kaplan-Meier method has been widely used to generate survival curves. The complement of the survival probability (i.e. 1 - survival probability) is often used to estimate the probability of death from an event. However, in the presence of competing risk events, the Kaplan-Meier method may overestimate the disease-specific mortality. Competing-risks analysis is being used increasingly in cancer research, as it accounts for events other than the event of interest (e.g. death from other causes). **Chapter 9** outlines the principle differences between the two methods and demonstrates that the competing-risks analysis is to be preferred in the estimation of disease-specific mortality.

The fourth part underlines the need for a risk-based screening strategy and provides recommendations for future screening strategies. The positive predictive value of prostate biopsy prompted by a PSA-threshold in consecutive screening rounds was examined in **Chapter 10**. In men who have not been biopsied before, the positive predictive value remained equal over time. Conversely, in those who have had a benign biopsy in the previous screening round, the positive predictive value dropped considerably, although still a considerable proportion of the cancers diagnosed showed aggressive characteristics.

As a growing body of evidence suggest that we need an individualized and tailored approach in the future to retain the benefits of screening and reduce the harms of screening, current evidence regarding risk-based screening was reviewed in **Chapter 11**. We showed that to date, PSA is the single most significant predictive factor for identifying men at increased risk of developing prostate cancer and die from the disease. Especially in men with no additional risk factors (e.g. first-degree relatives with prostate cancer diagnosed before age 65, black men), PSA alone provides an appropriate marker up to 30 year into the future. In men with a known PSA, risk calculators may hold the promise of identifying those who are at increased risk of having prostate cancer and are therefore candidates for biopsy.

In men who have been screened negatively for prostate cancer, the future risk calculator may be a helpful tool in deciding whether when of how to rescreen. **Chapter 12** describes this novel tool, which can accurately predict the risk of (aggressive) prostate cancer in 4 years. Such predictive information is of considerable value and will potentially

provide benefits for men and physicians by reducing uncertainty, unnecessary testing, and overdiagnosis of prostate cancer.

In the fifth part of this thesis, the key findings of the studies addressed are discussed in relation to the literature, and recommendations for future direction are proposed.

SAMENVATTING

Het eerste deel van dit proefschrift geeft achtergrondinformatie over de prostaat, de PSA test, prostaatkanker (**hoofdstuk 1**) en prostaatkankerscreening (**hoofdstuk 2**). Het doel van dit proefschrift, dat wordt beschreven in **hoofdstuk 3**, omvat het aantonen van het effect van screening, het bespreken van mogelijke verbeteringen van het huidige screening programma en het geven van aanbevelingen omtrent screening in de toekomst.

Een drietal studies worden gepresenteerd in het tweede deel, dat het effect van screening onderzocht. In **hoofdstuk 4** vergeleken we de ziektespecifieke overleving van mannen gediagnosticeerd met prostaatkanker in de eerste screening ronde met mannen uit de tweede screening ronde. Na correctie voor bekende voorspellers en de primaire behandelingsmodaliteit hadden de patiënten uit de tweede ronde een twee keer zo laag risico op het overlijden aan de ziekte in vergelijking met mannen uit de eerste ronde. Deze bevinding impliceert dat herhaalde screening de ziektespecifieke overleving verbetert.

In **hoofdstuk 5** vonden we dat na radicale prostatectomie, mannen met door screening gedetecteerd prostaatkanker betere overlevingsresultaten hadden dan mannen met prostaatkanker uit de controle arm van de ERSPC studie. Deze verschillen drukten zich uit in lagere incidentie van biochemisch recidief en metastase, na correctie voor preoperatieve variabelen. De betere resultaten in de screening arm leken vooral bewerkstelligd te zijn door een aanzienlijk lager tumor volume.

De omvang van het effect door screenen in een gerandomiseerde studie wordt beinvloed door vele factoren. Een van deze is de manier waarop gerandomiseerd wordt. **Hoofdstuk 6** presenteert een overzicht van de verschillen in de resultaten tussen de Rotterdamse en Göteborgse tak van de ERSPC studie. In Rotterdam waren alleen mannen opgenomen en gerandomiseerd als ze toestemming hadden verleend na schriftelijke informatie, terwijl in Göteborg mannen eerst gerandomiseerd waren en toestemming van alleen mannen uit de screening arm nodig was. Onze bevindingen wijzen erop dat het studie ontwerp in Rotterdam een "healthy screenee bias" heeft geïntroduceerd, wat resulteerde in een lagere totale sterfte en belangrijker nog, lagere ziektespecifieke sterfte in de controle arm in vergelijking met de algemene bevolking. Als gevolg hiervan wordt het "echte" effect van screening ten opzichte van geen screening mogelijk onderschat in Rotterdam.

Het derde deel van dit proefschrift richt zich op mannen in de screening arm die aan prostaatkanker sterven ondanks hun toewijzing aan de interventie arm van de ERSPC studie. In **hoofdstuk 7** zijn mannen geïdentificeerd en gekarakteriseerd die uitzaaiingen ontwikkeld hadden of overleden waren aan prostaatkanker in de screening arm van de Rotterdamse tak van de ERSPC studie. Het merendeel van deze "escapes" waren

gediagnosticeerd in de eerste screening ronde. Deze mannen hadden minder gunstige prognostische factoren bij diagnose in vergelijking met mannen die gedetecteerd werden tijdens latere screening rondes. Het "escape" fenomeen kan toegeschreven worden aan verschillende mechanismen: het niet bijwonen van een screening ronde, de beperkingen van de screening test, de relatief lange screening interval van 4 jaar, de leeftijdsgrens van 75 jaar en onderbehandeling.

Hoofdstuk 8 beschrijft de ziektespecifieke overleving van mannen gediagnosticeerd met prostaatkanker tijdens het screening interval, dat wil zeggen tussen twee geplande screening bezoeken. Deze mannen hadden een betere overleving dan mannen met prostaatkanker uit de controle arm. Echter, na correctie voor bekende prognostische factoren en de primaire behandelingsmodaliteit, was de ziektespecifieke overleving vergelijkbaar tussen de twee groepen. Sommige mannen werden tijdens het screening interval gediagnosticeerd omdat ze actief op zoek waren naar screening tussen de geplande bezoeken door, terwijl bij andere mannen tumoren zich snel hadden ontwikkeld en hebben geleid tot klinische symptomen.

De Kaplan-Meier methode wordt veelvuldig gebruikt om overlevingscurven te genereren. Het complement van de overlevingskans (1 - overlevingskans) wordt vaak gebruikt om de kans op overlijden te bepalen. Echter, in de aanwezigheid van concurrerende risicogebeurtenissen kan de Kaplan-Meier methode de ziektespecifieke mortaliteit overschatten. Competing-risks analyse wordt meer en meer gebruikt in het onderzoek naar kanker omdat er rekening mee wordt gehouden met andere gebeurtenissen (bijvoorbeeld dood door andere oorzaken). **Hoofdstuk 9** beschrijft de voornaamste verschillen tussen de twee methoden en wijst uit dat de competing-risks analyse de voorkeur heeft in de schatting van ziektespecifieke mortaliteit.

Het vierde deel benadrukt de noodzaak van een op risico's gebaseerde screening strategie en geeft aanbevelingen voor de toekomst. De positief voorspellende waarde van een prostaatbiopsie op basis van een PSA-drempel werd onderzocht in **hoofdstuk 10**. Bij mannen die niet eerder gebiopteerd waren, bleef de positief voorspellende waarde gelijk over tijd. Omgekeerd, bij diegenen die een biopsie hadden ondergaan in de vorige screening ronde en destijds geen prostaatkanker hadden, nam de positieve voorspellende waarde aanzienlijk af in latere rondes. Echter, een aanzienlijk deel van de later gediagnosticeerde kankers blijkt gekenmerkt te zijn door agressieve eigenschappen.

Steeds meer studies wijzen erop dat risicoprofilering de potentie heeft om de voordelen van screening te behouden en de nadelen van screening te verminderen. **Hoofdstuk 11** geeft inzicht in de huidige literatuur met betrekking tot het screenen op basis van individuele risico's. Tot op heden blijft PSA de meest belangrijke voorspeller voor het identificeren van mannen met een verhoogd risico op prostaatkanker en sterfte aan de ziekte. Vooral bij mannen zonder andere risicofactoren (bijv. eerstegraadse familieleden

met prostaatkanker gediagnosticeerd voor de leeftijd van 65 jaar, zwarte mannen), is PSA alleen een geschikte marker tot 30 jaar in de toekomst. Bij mannen waarvan de PSA waarde bekend is, zijn risico calculators in staat om degenen die een verhoogd risico op prostaatkanker hebben en dus geschikte kandidaten zouden zijn voor biopsie, te identificeren.

Bij mannen die eerder negatief zijn getest voor prostaatkanker, is de toekomst risico calculator mogelijk een geschikt hulpmiddel om te bepalen of en wanneer herhaalde screening moet plaatsvinden. **Hoofdstuk 12** beschrijft dit nieuw hulpmiddel, waarmee op basis van een individueel risicoprofiel de kans op (agressieve) prostaatkanker binnen 4 jaar te voorspellen is. Dergelijke voorspellende informatie is van grote waarde en biedt voordelen voor patiënten en artsen door het verminderen van onzekerheid, onnodige testen en overdiagnose van prostaatkanker.

In het vijfde deel van dit proefschrift worden de belangrijkste bevindingen van de beschreven studies besproken in relatie tot de literatuur. Ook worden er aanbevelingen voor de toekomst gegeven.

CURRICULUM VITAE

Xiaoye Zhu is geboren op 29 april 1985 in Shanghai. Op bijna 10-jarige leeftijd verhuisde hij naar Nederland. Zijn eerste woordjes Nederlands heeft hij in groep drie op een multiculturele basisschool in Zeist geleerd. In 2003 heeft hij het gymnasium op het Christelijk Lyceum afgerond en begon hij met zijn studie geneeskunde in Utrecht. Gedurende deze studie groeide zijn belangstelling voor de urologie, waar hij ook zijn oudste co-schap en wetenschappelijke stage liep.

Na het behalen van zijn artsenbul in 2009 heeft Xiaoye vier maanden gewerkt als arts-assistent op de afdeling urologie in het UMC Utrecht. In januari 2010 begon hij met zijn promotietraject op het screeningbureau Urologie in het Erasmus MC in Rotterdam, onder leiding van prof. dr. C.H. Bangma, dr. M.J. Roobol en prof. dr. F.H. Schröder, waar deze dissertatie het resultaat van is.

Op 1 januari 2013 is Xiaoye begonnen met zijn vooropleiding heelkunde in het St. Antonius Ziekenhuis in Nieuwegein (opleider: dr. P.M.N.Y.H. Go). Aldaar zal hij de opleiding tot uroloog vervolgen in 2015 (opleider: dr. P.L.M. Vijverberg) en voortzetten vanaf 2017 in het UMC Utrecht (opleider: prof. dr. J.L.H.R. Bosch).

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- Erasmus summer program, NIHES	2010	5.5
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• Introduction to data-analysis		
• Regression analysis		
• Survival analysis		
- Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2010	0.5
Seminars and workshops		
- Multi-disciplinair behandeling prostaatkanker	2010	0.5
- ISPO, Florence	2011	0.5
- IARC, Lyon	2012	1
Presentations		
- NVU najaarsvergadering, Nieuwegein	2010	0.5
- ERSPC, Peschiera and Rotterdam	2011	1.5
- ERSPC, Yllasjarvi	2012	1
- ASCO Genitourinary Cancers symposium, Orlando	2011-12	1
- EAU, Vienna	2011	1
- EAU, Paris	2012	1
- AUA, Washington	2011	1
- AUA, Atlanta	2012	1
- DONAMO NKI-AVL, Amsterdam	2012	0.5
(Inter)national conferences		
- PRIAS study user meeting, Amsterdam	2010	0.5
- ERSPC meetings 2010, 2011 and 2012	2010-12	1.5
- NVU 2010, 2011 and 2012	2010-12	1.5
- SEOHS, Rotterdam	2010	0.5
- ASCO Genitourinary Cancers symposium, Orlando	2011	0.5
- EAU annual meetings 2011 and 2012	2011-12	1
- AUA annual meetings 2010, 2011 and 2012	2010-12	1.5
- Prostate Action Forum, Rotterdam	2012	0.5
- Active Surveillance Symposium, Rotterdam	2012	0.5
- Global Congress on Prostate Cancer, Brussels	2012	0.5
Other		
- Department Journal Club	2010-12	1
- Department internal course	2010-12	1
- PhD researcher meeting	2010-12	1
Total		32

ASCO	American Society of Clinical Oncology
AUA	American Urological Association
EAU	European Association of Urology
ERSPC	European Randomized Study of Screening for Prostate Cancer
IARC	International Agency for Research on Cancer
ISPO	Institute for Cancer Research and Prevention
NVU	Nederlandse Vereniging voor Urologie
PRIAS	Prostate cancer Research International: Active Surveillance
SEOHS	Symposium Experimenteel Onderzoek Heelkundige Specialismen