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European Journal of Cancer 41 (2005) 825–833

European Journal of Cancer

www.ejconline.com

Screening for prostate cancer

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Received 23 August 2004; accepted 2 December 2004
Available online 12 February 2005

Abstract

Epidemiologically, prostate cancer is the most common cancer in the Western world after skin cancer. To date, it is still unknown whether screening for prostate cancer is justified, because results of randomised clinical trials are not yet available. The available screening tests (i.e. prostate-specific antigen (PSA) test) do not always detect cancers that otherwise would have resulted in prostate cancer mortality. Favourable results from prostate cancer screening include an increasing number of men with localised disease and an increase in the number of well-differentiated tumours. However, the risk of overdiagnosis and subsequent over-treatment (due to the diagnosis of localised disease), using aggressive therapies fuels arguments against screening. Therefore, until more evidence is available proving otherwise, prostate cancer screening can only be justified in the context of clinical trials.

Keywords: Prostate cancer screening; ERSPC

1. Introduction

Over the last decade, there has been considerable debate about whether screening for prostate cancer should be performed in asymptomatic men. Prostate-specific antigen (PSA) testing is mainly responsible for the changing statistics in prostate cancer. Presently, two large randomised clinical trials for prostate cancer are ongoing in Europe (The European Randomized Study of Screening for Prostate Cancer, ERSPC trial) and in the United States of America (USA) (The Prostate, Lung, Colorectal and Ovary cancer, PLCO trial). Adequate evidence to answer whether screening reduces mortality will not be available from these randomised clinical trials until 2008. Until then, the debate on screening will continue. The goal of the ERSPC is to evaluate whether population-based screening reduces mortality from prostate cancer whilst balancing the effects of treatment on the patient's quality of life (QoL) and the associated costs. Within the ERSPC, approximately 193 000 men from eight European countries have been recruited and randomised [1].

To justify population-based screening for the disease, Wilson and Jungner [2] developed 10 criteria (Table 1). This table provides the backbone of this Review.

1.1. Controversy

Although the benefit of prostate cancer screening has not yet been established in randomised clinical trials, the American Cancer Society recommends yearly PSA testing and digital rectal examination, beginning at age 50 years in all healthy men [3]. The National Comprehensive Cancer Network (NCCN) even recommends PSA testing in men beginning at age 40 years with a PSA cut-off level for further screening of 0.6 ng/ml. Further, when the biopsy result is negative in the PSA range between 2.6 and 4.0 ng/ml re-screening should be done within 6–12 months [4]. Even without screening, men will more often die with their prostate cancer than from

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doi:10.1016/j.ejca.2004.12.029

Table 1
Ten criteria to justify population-based screening for disease

1	The condition sought should be an important health problem
2	There should be an accepted treatment for patients with recognisable disease
3	Facilities for diagnosis and treatment should be available
4	There should be a recognisable latent or early symptomatic stage
5	There should be a suitable test or examination
6	The test should be acceptable to the population
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood
8	There should be an agreed policy on whom to treat as patients
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10	Case-finding should be a continuing process and not a "once and for all" project

it. Screening will increase the risk of overdiagnosis and this has been calculated to be as high as 48% within a screening population with a 4-year screening interval [5]. McGregor and colleagues [6] calculated that only one in eight screen-detected cancers is likely to kill its host if left untreated. Overdiagnosis results in overtreatment. The serious adverse effects of radical prostatectomy and radiotherapy must be taken into account as well as any reduced mortality in a screened population [5].

1.2. The epidemiology of prostate cancer

Prostate cancer is the now the most common non-cutaneous cancer in the Western world. It occurs mainly in men who are older than 50 years; prostate cancer incidence is highest in men aged 75 years and older [7]. It is estimated that prostate cancer will be diagnosed in 230 110 men in the USA in 2004 (lifetime risk one in six men) and that one in eight men will die from the disease [8]. The importance of prostate cancer as a healthcare problem worldwide is further illustrated in Table 2. Prostate cancer incidence varies widely between countries and ethnic populations. These variations are mostly due to the frequencies of screening. When standardised for age in the world population, the incidences in different parts of the world can be compared. Prostate cancer incidence is highest in countries where PSA testing is accepted (i.e. USA and Canada). According to the standardised incidence ratio (SIR), the incidence in the USA and Canada is almost five and four times higher compared with the world standardised incidence ratio, respectively. These SIRs are followed by Western and Northern European regions that show a 2–3-fold higher rate. In Europe, prostate cancer incidence decreases when heading from the North towards the Mediterranean regions. The lowest incidence is found in China and India (data not shown). Black men are at an increased risk for prostate cancer compared with white men. The risk of dying from prostate cancer is higher in Europe compared with Northern America. Worldwide, the chance of dying from prostate cancer is small [9].

1.3. Natural history

Albertsen and colleagues [10] describe the natural history of prostate cancer. They followed patients with localised prostate cancer ($n = 767$) who were not treated curatively for 15 years. They found a prostate cancer-specific mortality of 4–7%, 6–11%, 18–30%, 42–70% and 60–87% with Gleason scores of 2–4, 5, 6, 7 and 8–10, respectively. In this study, prostate cancer was diagnosed by clinical means between 1971 and 1984. In this era, PSA was not yet in use and accurate staging was lacking in many patients. Therefore, patients with occult

Table 2
Incidence and mortality from prostate cancer worldwide

Country/world part	Incidence	ASR (World)	SIR (%)	Mortality incidence	SMR (%)
United States of America	140.8	104.3	472	26.2	227
Canada	121.1	83.9	388	26.1	216
China	1.5	1.7	8	0.9	13
Northern Europe	80.1	45.4	218	36.3	254
Western Europe	94.5	54.9	260	34.3	245
South Africa	18.4	42.8	194	11.1	333
World	17.8	21.2	100	6.7	100

(Mortality) incidence is noted as the rate of prostate cancers or prostate cancer deaths per 100 000 person years of observation.
ASR, age-standardised rate, the prostate cancer incidence per 100 000 person years that a population would have if it had a standard age structure. The world population was taken as a standard.
SIR/SMR, standardised incidence/mortality ratio, observed number of prostate cancer cases/prostate cancer deaths by the expected number, using the age-specific incidence/mortality of the world as a standard. i.e. a 100% SIR means the observed incidence is equal to the expected incidence, standardised by age.

metastasis might have been included in the analysis. In addition, endocrine therapy was given using different protocols (immediate or delayed) and was not given to every patient [10]. The data are also likely to overestimate risks with respect to screen-detected cancers. Reliable data on the natural history of screen-detected prostate cancer are not yet available.

From autopsy studies, it is known that prostate cancer can be found in 55% of men in their 5th decade of life and 64% in their 7th decade [11]. This illustrates the substantial proportion of prostate cancers that are unlikely to kill the host. Within the ERSPC study, increasingly more focal (a focus of 3.0 mm of cancer or smaller, Gleason score $\leqslant$6 in one biopsy core) prostate cancers are being diagnosed. Similarly, the proportion of patients who are managed by 'watchful waiting' is increasing. After a 5-year follow-up, 70% of the patients managed by 'watchful waiting' had a PSA doubling time of 4 years or longer in the focal cancer group. Longer follow-up is needed to conclude if these tumours can be left untreated and if a PSA doubling time of 4 years is an adequate cut-off point to indicate progression [12]. Johansson and colleagues [13] recently studied 223 patients with organ-confined prostate cancer who were not initially treated. If progression to symptomatic disease occurred, orchidectomy or exogenous oestrogens were offered. The authors found that after a median follow-up time of 21 years, 91% of the patients had died, but prostate cancer was the cause of death in only 16% of the entire cohort, 40% had progression of disease, of whom almost half developed distant metastasis. The most significant predictor for mortality was a poorly differentiated tumour (cause-specific survival of less than 30% after a 5-year follow-up). However, when the patient was diagnosed with an organ-confined well-differentiated tumour, the cause-specific survival after a 20-year follow-up was 72%, without initial treatment. Even with this relatively good cause-specific survival in men with favourable and known tumour characteristics managed by 'watchful waiting', it remains difficult to predict tumour progression in the individual patient. Gleason scores in biopsies are frequently under-graded, as is the clinical stage when compared with data on Gleason scores and pT-stage in radical prostatectomy specimens [14]. Gleason grading in biopsies, as well as in radical prostatectomy specimens, have been shown to be predictive for disease-specific survival after radical prostatectomy [15].

1.4. The available screening test must have a high sensitivity, specificity and positive predictive value (PPV)

An elevation in serum PSA levels may be caused by prostatic adenocarcinoma and this has been proposed to be a suitable screening tool. However, prostatitis, benign prostatic hyperplasia (BPH) and other conditions can also increase serum PSA [16]. Therefore, PSA, although prostate-specific, is not a cancer-specific measure. The most favoured cut-off point to use for PSA as a screening tool, is a PSA level of <4.0 ng/ml. Catalona and colleagues [17] initially used this cut-off point as an indicator for biopsy or if patients had a suspicious digital rectal examination (DRE) for cancer. In the ERSPC trial, a cut-off point of 4.0 ng/ml was initially used as an indication for sextant biopsy, as well as abnormal DRE and transrectal ultrasonography (TRUS) in PSA ranges 1.0–3.9 ng/ml. However, it turned out that the relative sensitivity and PPV of DRE and TRUS was only 37% and 9.7% in the PSA range <4.0 ng/ml, based on a "*a priori* prevalence assessment" [18] (Table 3 shows the sensitivity and specificity of the DRE test alone in men who underwent sextant biopsy for two PSA cut-off points). In addition to these unfavourable test characteristics, it was shown that the proportion of cases with favourable prognostic factors increases at lower PSA values [18,19]. At the same time, evidence has accumulated that in the PSA range 2.0–4.0 ng/ml, up to 65% of cancers were missed by DRE and TRUS. With the (unproven) assumption that most cancers present and detectable in the PSA range 1–3 ng/ml, would still be detectable in a curable stage at re-screening and after having shown that the overall detection rate remained unchanged in this PSA range [20], it was decided to omit DRE and TRUS as screening tests and to biopsy all men with PSA values in the 3.0–4.0 ng/ml range. In Table 4, the incidence of prostate cancer at the first screening round is shown for different PSA ranges. After initially using a point cut-off of <4.0 ng/ml in 1994, Catalona and colleagues now recommend a cut-off point of 2.6 ng/ml as an indictor for biopsy. They found a prostate cancer incidence rate of 22% in the 2.6–4.0 ng/ml PSA range (in biopsies). Tumours in this PSA range had favourable characteristics, they were significantly smaller and were more often organ-confined (88% *vs.* 63%) compared with tumours detected in the PSA range of 4.0 ng/ml and greater [21]. Punglia and colleagues [22] recently reported on the effect of verification bias, which occurs when the "relative" sensitivity and specificity is studied in a population where

Table 3
Sensitivity, specificity, positive predictive value (PPV) and negative predicting value (NPV) of the digital rectal examination (DRE) in two prostate-specific antigen (PSA) ranges in the 1st screening round of the The European Randomized Study of Screening for Prostate Cancer (ERSPC)

PSA cut-off point (ng/ml)	Relative sensitivity (%)	Relative specificity (%)	PPV (%)	NPV (%)
PSA < 3.0	62	42	0.9	55
PSA < 4.0	50	54	16	86

Every percentage is relative since only men who underwent sextant biopsy (n = 4117) are included in this table.

Table 4
Positive predictive value (PPV) and detection rate of PSA ranges in the 1st screening round of the ERSPC

PSA range (ng/ml)	No. men screened	No. prostate cancer	No. biopsies	% PPV biopsy	% PPV detection rate, PSA range
0.0–0.9	7139	4	185	2.2	0.06
1.0–1.9	6205	45	510	8.8	0.75
2.0–2.9	2508	30	221	13.6	1.20
3.0–3.9	1426	179	792	22.6	12.55
4.0–10.0	2235	526	2006	26.2	23.53
>10	457	230	403	57.1	50.33
Total/mean	19970	1014	4117	21.7	5.08

only part of the group was exposed to the test (i.e. not everyone with an increased PSA value will undergo prostate biopsy to confirm prostate cancer). Verification bias masks the true sensitivity and specificity of PSA values. Adjusting for verification bias (i.e. lowering the PSA threshold used for biopsy recommendation from 4.1 to 2.6 ng/ml in men younger than 60 years) simply significantly improved the estimated sensitivity and specificity of the PSA test for the screened population. However, even after adjusting for verification bias, the bias still exists, if not all men were tested. In the prostate cancer prevention trial by Thompson and colleagues [23] (see below) every man in the placebo group was offered a prostate biopsy after the 7-year study period. Therefore, this study was not subject to verification bias. For those with PSA values $\leqslant$4.0 ng/ml, the prostate cancer incidence rate was 15% and of these tumours, 15% contained Gleason pattern 4, which indicates that high grade cancer in the low PSA range is not a rare finding. Similarly, a sub-study performed in the screening arm of the ERSPC trial for patients with PSA levels in the range of 2.0–3.9 ng/ml, prostate cancer was observed in 17% of the sextant biopsies, and the detection rate was 14% four years after the initial screen [24].

Detection and radical treatment of the large proportion of organ-confined prostate cancers in this low PSA range does not automatically lead to lower prostate cancer mortality rates: The high incidence of prostate cancer in sextant biopsies in the age range (61–91 years, with a median of 69 years) of men in the study by Thompson and colleagues is not surprising. It includes the possibility that these biopsies identified cancers that would otherwise only have been detected at autopsy [25,26]. Configuring this possibility, Hoedemaeker and colleagues [27] reported organ-confined tumours in 93% (pT2) and 86% were small tumours (<0.5 ml) for prostate cancers detected in the ERSPC trial by DRE and/or TRUS with PSA levels <4.0 ng/ml. Apart from being diagnosed clinically, half of the radical prostatectomy specimens contained Gleason pattern 4, in line with the data reported by Thompson and colleagues.

To improve the utility of the PSA test, various parameters related to PSA change were introduced (i.e. PSA velocity, PSA doubling time, PSA slope). PSA velocity was put forward as a promising screening tool by Carter and colleagues [28]. They found a PSA velocity of 0.75 ng/ml per year was significantly associated with clinical prostate cancer. However, in the screening arm of the ERSPC trial, PSA velocity was 0.62, 0.46, and 0.03 ng/ml per year in prostate cancer patients, men with negative biopsies and men who were not biopsied (PSA $\leqslant$3.0), respectively. When PSA velocity, as well as PSA doubling time, were tested in receiver operating characteristic analyses (ROC curves), the areas under the curve were only moderately greater than 0.5 (equal to chance) and therefore of very limited use in predicting biopsy outcome in the screened population of the ERSPC [29]. Particularly, in the low PSA range, PSA velocity was not a predictive variable in multivariate analysis in sextant biopsies [30].

When a PSA level of <1.0 ng/ml was considered, as in the Spanish section of the ERSPC, it was found that if these men were repeatedly tested for PSA only four prostate cancers were diagnosed after a 4-year screening interval. In concordance with this, within the Dutch part of the ERSPC, 0.9% of men with a PSA of <1.0 ng/ml showed progression to PSA levels $\geqslant$3.0 ng/ml. However, if that occurred a PPV of 19% was noted [31], (Dr. F.H. Schröder, Erasmus medical centre, Rotterdam, data not shown).

In the ERSPC, TRUS-determined prostate volume was a negative predictor for biopsy outcome after multivariate testing; the smaller the prostate, the higher the prostate cancer incidence [32]. Therefore, PSA density might be predictive for prostate cancer. When using a PSA density cut-off point of $\leqslant$0.1 ng/ml/cm^3 in focal cancers on biopsies (see above), 94% of the cancers were <0.5 ml and organ-confined [33].

In addition to PSA dynamics, other molecular forms of PSA have been researched. The ratio of free to total PSA improved the relative specificity in detecting prostate cancer in the PSA range of 4–10 ng/ml [34]. This was confirmed in several studies, including the Swedish part of the ERSPC [35]. The pro-enzyme of PSA (ProPSA) and Benign PSA (BPSA) are formed in the peripheral and transitional zone of the prostate. The amount of pro-PSA is increased in prostate cancer, whereas BPSA is increased in BPH patients [26,36]. However, when samples of the ERSPC were tested for ProPSA as an individual marker to distinguish between BPH and cancer, it did not improve the specificity further than free PSA levels [37].

The definite diagnosis after PSA elevation can only be made by needle biopsy of the prostate. Systemic sextant biopsy used to be the most commonly used biopsy strategy. The use of this systematic sextant biopsy procedure is now controversial because it has been reported that 23% of cancers are missed by this procedure [38,39]. Vashi and colleagues recommended that the number of biopsy cores be increased as the prostate volume increases and prostate cancer volume decreases, i.e. for a prostate of 40 ml or greater at least 12 cores are needed to detect a tumour of 1 ml [40]. Despite criticism of the sextant biopsy, only 6% of prostate cancers in the 2nd round of the Rotterdam section of the ERSPC trial had a Gleason sore of $\geqslant 4 + 3$ or higher in the sextant biopsy after a 4-year screening interval, which indicates that sextant biopsy and a 4-year interval is adequate to detect more than 90% of the cancers with well differentiated Gleason scores [41]. In addition, the incidence of prostate cancer in biopsies in men who had a benign biopsy in the 1st round, and underwent a biopsy in the 2nd screening round was 10.7%, compared with 22.7% in men who never had a biopsy in a previous round ($P < 0.0001$) [42]. The final decision on the appropriate extent of biopsy procedures will depend on a better understanding of the balance between overdiagnosis and the prevention of prostate cancer deaths.

1.5. Primary prevention

Apart from regional differences, which partly depend on hereditary factors (in the USA African–Americans are at increased risk for prostate cancer), there are also external risk factors that influence the transformation to prostate cancer. For example, if a Chinese man living in China moves to the USA, his risk of developing prostate cancer increases by 50% compared with his risk if he had continued living in China [43,44].

The prostate cancer risk is 2–3-fold higher in men who have a history of prostate cancer in first-degree relatives. In monozygotic twins, there is a concordance of 42% in prostate cancer incidence which is higher compared with dizygotic twins [45]. It is estimated that 5–10% of all prostate cancer cases may have a hereditary basis [46]. In the ERSPC trial, those with a family history did have an increased prostate cancer risk compared with men who did not have 1st degree family members with prostate cancer in a multivariate logistic regression analysis (Dr. M.J. Roobol, Erasmus Medical Centre, Rotterdam, data not shown).

Diet is one of the external risk factors associated with prostate cancer. A diet rich in lycopene (tomatoes), vitamin D and E, high consumption of fish and soybean products was associated with a decreased prostate cancer risk. However, a high consumption of diary products, meat and fat, were associated with an increased prostate cancer risk [47]. Despite the promising epidemiological association between prostate cancer and vegetables and fruit, a recently reported prospective study could not find a significant association between their intake and a decreased prostate cancer incidence [48]. Further prospective studies are needed to establish significant associations between diet and prostate cancer incidence. Alcohol intake has neither a positive nor negative effect on prostate cancer development [49].

Epidemiological evidence suggests there is a link between infections (i.e. sexual transmitted disease) and inflammation (prostatitis) and prostate cancer [50]. In addition to this hypothesis, non-steroidal anti-inflammatory drugs (NSAIDs) are protective for prostate cancer [51].

As it became evident that hormones (androgens) were associated with the development of prostate cancer, the prostate cancer prevention trial was set up [52]. In this trial, participants were randomised into a study and placebo group to examine the effects of finasteride (an inhibitor of the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate) on prostate cancer incidence. There was a 24.8% reduction in prostate cancer over a 7-year period in the study group compared with the placebo group. However, it remains unknown whether this finding will translate into a decrease in prostate cancer mortality or if finasteride only causes a delay in prostate cancer diagnosis. Higher Gleason scores compared with men within the placebo group accompanied the substantial reduction in prostate cancer incidence in men with positive biopsies in the study group. This could also be explained as a direct effect on tumour architecture of androgen deprivation, rather than a biological effect. Finasteride also adversely influences sexual function and this needs to be weighed up against any potential benefits if finasteride is considered as a protective agent.

1.6. Secondary prevention: rationale for screening and results of studies

Worldwide epidemiological surveys demonstrate prostate cancer mortality has decreased since 1993 in several countries. This phenomenon has been seen in both screened and non-screened populations around the world [7,8,53]. However, the decreases in mortality rates are more impressive in countries where screening is more common, such as the USA and Canada. The fall in prostate cancer mortality in the USA has been mostly attributed to the reduction in the number of men who were initially diagnosed with distant metastases and therefore eventually died rapidly [54]. Nonetheless, temporal and geographical differences provide inconclusive evidence suggesting potential benefits from PSA screening. Coldman and colleagues [55] studied the incidence and mortality rates in Canada and confirmed that the incidence of prostate cancer increases with more PSA

use. Strikingly, regions with the smallest increases in incidence had the largest declines in mortality. This suggests that mortality reduction may be (in part) due to factors other than PSA screening. Notably, decreases in mortality were only in part related to prostate cancer.

Final outcome data from one randomised screening trial are available. The authors claim a 62% reduction in disease-specific mortality [56]. However, an earlier report of this study was heavily criticised, because of methodological flaws. This large reduction in mortality resulted from a "screening received" analysis, which disregards the randomisation of patients. The "intention-to-screen" analysis resulted in a 16% increased risk of death in the screened arm (RR = 1.16). But, participation in the screened arm was only 23%. In addition, the time from randomisation to screening was 3 years in the screening arm and therefore the time to observe mortality was 3 years shorter compared with the control group, because men diagnosed with prostate cancer before the screening date were excluded [57].

The Tyrol mass-screening study, wherein PSA testing was freely available in the federal state of Tyrol, showed promising results when prostate cancer mortality was compared with other regions of Austria where PSA testing was not freely available and when compared with the expected death rates in the Tyrol. However, this was not a randomised controlled trial [58]. Several case–control studies were conducted in the USA with DRE and PSA screening that also support the benefit of screening, showing an inverse association between the screening test and the prostate cancer mortality (Odds Ratio 0.7). Nevertheless, the 95% Confidence Interval was 0.5–1.1 and the DRE screening effect could not be separated from the PSA screening effect [59].

The ERSPC trial results will not be available until 2008. However, there is confirmatory evidence that screening results in the identification of cancers with more favourable characteristics. Within the Finnish section of the ERSPC, the proportion of clinically organ-confined prostate cancer in the screening arm was 82% compared with 65% in the control arm [60]. In the Rotterdam section of the ERSPC, radical prostatectomy specimens of patients in the unscreened population were compared with patients from a screened cohort. Metastasis was not seen in the screened cohort, whereas 18% of the control population had metastases. Gleason score and pathological stage were also significantly lower in the screened cohort compared with the unscreened group [61].

Screening may miss its original goal and cause more harm than benefits.

In a series of 103 focal cancers which are increasingly found in subsequent screening rounds in the ERSPC, we found 3% of pT0 cancers (cancer that cannot be found in the radical prostatectomy specimen) as a clear manifestation of overdiagnosis of prostate cancer in a screened population [12]. Screening introduces lead-time: this means that through screening, prostate cancer is diagnosed earlier than it would have been based on clinical incidence. The calculated lead-time for prostate cancer ranges between 4.5 and 12 years. Lead-time depends on patient age and the aggressiveness of the cancer. Younger men and more indolent prostate cancers have longer lead times, compared with older men with high-grade disease [5,62]. As yet, the optimal screening interval in trials is unknown. Yearly PSA testing is recommended in the USA [3]. Thornblom and colleagues [62] who screened with PSA levels >10.0 ng/ml and/or abnormal DRE and TRUS, found no overdiagnosis at all after 12 years of follow-up, when screening was only performed once. All centres in the ERSPC, except Sweden and Belgium, have a screening interval of 4 years. The lead-time in the ERSPC patients from Rotterdam was estimated at a median of 10.7 years, which would imply that a screening interval of 4 years is sufficient [5].

Despite discouragement of PSA testing in Europe due to the lack of convincing evidence of its benefit, PSA testing has become very common. The French urological association recently recommended PSA screening [63]. In a population where the National Health Service does not approve screening, PSA testing was calculated to be as high as 36% in men in the UK between 1994 and 1999. Miller and colleagues [64] recently reviewed over 50 000 patients from the American College of Surgeons National Cancer Data Base (NCDB) and found that 69% of cases were diagnosed without symptoms and most of these men (78%) presenting with prostate cancer in the absence of symptoms were 59 years or younger. In men aged 80 years and older, 46% were diagnosed asymptomatically, which probably indicates detection through screening. This "contamination" may also occur in the control arms of randomised clinical trials and might blur the outcome data.

Recently, Otto and colleagues using data from the Dutch part of the ERSPC, showed that the contamination rate in the control arm, which was measured at a 3-year follow-up was 20.2%. Only 7–8% of men with PSA levels $\geqslant$3.0 ng/ml underwent prostate biopsy. This translates into a contamination rate in the control arm of the ERSPC of 3% per year which may be considered as low and is taken into account by the sample size calculation [65].

1.7. Treatment and Quality of life

Due to PSA screening, an increasing proportion of men are detected with early-stage prostate cancer, allowing curative treatment in these men. Roughly, four treatment options for early-stage prostate cancer are available; surgery, radiotherapy, hormone therapy, and observation, also known as 'watchful waiting'. With increasing age and higher incidence of organ-confined

disease in the screening arm of the ERSPC, increasingly more men are managed by 'watchful waiting'. Especially in men diagnosed with focal cancer, the proportion of management by 'watchful waiting' increased from 10% to 24% in the 1st and 2nd screening rounds, respectively, in the Rotterdam patients in the ERSPC trial [33]. Protocols are now being developed to determine when to treat by 'watchful waiting' and when a patient should be curatively treated (Dr. C.H. Bangma Erasmus Medical Centre, Rotterdam, data not shown). Meanwhile, the proportion of patients treated by radical prostatectomy and radiotherapy decreased slightly in the second screening round [66]. The advantages of radiotherapy and radical prostatectomy are obvious; the intention of treatment is usually curative. However, side-effects of both curative treatments are serious. Aside from sexual dysfunction, which becomes ubiquitous, pre- *vs*. post-therapy effect sizes in localised prostate cancer patients treated by radical prostatectomy and radiotherapy were large and medium for urinary function and bother and there were small and large effects on bowel function, respectively. Urinary function was significantly different pre- *vs*. post-treatment in radical prostatectomy-treated patients and bowel function differed in those given radiotherapy [67]. Despite differences in the side-effects, no association between primary therapy and health-related quality of life could be found [68]. In the ERSPC trial, patients treated with radiotherapy reported decreased quality of life compared with patients treated with radical prostatectomy. However, patients treated with radiotherapy were older [69]. Patients in the ERSPC with screen-detected and clinically diagnosed cancer, reported similar health-related quality-of-life after treatment with radical prostatectomy or radiotherapy. By Contrast, Steineck and colleagues [70] reported on the different effects in patients treated with radical prostatectomy or 'watchful waiting', these authors found that erectile dysfunction (80% *vs*. 45%) and urinary leakage (49% *vs*. 21%) were more common after radical prostatectomy compared with watchful waiting. Apparently, the knowledge of being diagnosed with prostate cancer also influences sexual function, even when no treatment is given ('watchful waiting').

The optimal curative therapy, considering disease recurrence, prostate cancer-specific survival and the side-effects, is not yet clear. There have been very few randomised clinical trials examining treatment for prostate cancer, and those available contain a number of biases and different end-points. Excluding bias is also very difficult because of the long follow-up that is needed and also due to screening a proportion of men who might be over-treated, and will not benefit from treatment. A retrospective analysis of surgery, external beam radiotherapy and brachytherapy showed similar results for early-stage prostate cancer [71]. A complete discussion is not part of this Review. A randomised clinical trial considering radical prostatectomy *vs*. 'watchful waiting' in clinically localised prostate cancer favoured radical prostatectomy with an adjusted Hazard Rate of 0.45 for death from prostate cancer. In this study, a limited proportion of patients with poorly differentiated Gleason scores (i.e. Gleason pattern $4 < 25\%$ and $5 < 5\%$) were included in both arms and therefore were at increased risk of dying from prostate cancer without curative treatment [72].

1.8. Conclusions

Since 1993, an annual PSA test has been recommended in the USA. But, 11 years later, in 2004, there is still no conclusive evidence that PSA screening is beneficial. When examining the points made by Wilson and Jungner in Table 1, only requirements 1–4 and 6 can be met. Point 5, ''a suitable screening test'' can only be partly met, because the PSA test has a low sensitivity. Better tests are urgently needed. The ideal situation would be a test that distinguishes between significant and insignificant prostate cancer. The natural history of prostate cancer is partly understood (point 7). However, we do not understand the natural history of screen-detected prostate cancers which are likely different. Point 8, the policy of whom to treat as patients is a point we have discussed thoroughly in this paper because as increasingly more localised prostate cancers are diagnosed, overdiagnosis and therefore overtreatment accompanied with adverse side-effects seriously influences patients' quality of life. The answer to if screening for prostate cancer reduces disease-specific mortality and can be used continuously or as ''a once and for all project'' is still unknown (point 10). At the moment, there is no scientific basis for population-based prostate cancer screening outside of randomised clinical trials that are designed to assess its effectiveness and identify men who might benefit from screening.

Conflict of interest statement

None declared.

Acknowledgements

Supported by Grants EUR-94-869 and EUR-98-1757 (to Erasmus University Rotterdam) from the Dutch Cancer Society and Grants 002-22820 and 2000-2-1016 (to Erasmus University Rotterdam) from The Netherlands Organization for Health Research and Development (ZONMw), by 5th Framework program grant QLRI-2000-01741 (to Erasmus University Rotterdam) from the European Union, and by Europe Against Cancer.

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