Update on Screening in Prostate Cancer Based on Recent Clinical Trials

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Abstract: Introduction and Aim: Prostate cancer (Pc) is a major public health problem, affecting 679,000 men and causing 221,000 deaths every year. Over the past decade, there has been a marked decline in Pc mortality corresponding to the introduction of prostate specific antigen (PSA) test as a screening tool (1986). Despite this clear result, the screening recommendations of various organizations differ. Recently, a large number of studies have highlighted the benefits and risks of PSA based screening. The aim of this article is to review the current screening guidelines and summarise the benefits and harms of PSA testing, analysing two large long awaited randomized multicenter clinical trials of PSA screening reported this year.

Methods for the Review: We reviewed the recent literature using PUBMED research, using as words for research: Prostate-Specific Antigen, mass screening, Prostatic neoplasm mortality, follow-up studies, overdiagnosis and overtreatment. In particular, we analysed two clinical trials reported on “The New England Journal of Medicine” this year: the European Randomized Study of Screening for Prostate Cancer (ERSPC) by Schroeder et al. and the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial by Andriole et al.

Results and Conclusions: The goal of a screening is to detect a cancer at an early stage, when it is still curable. In Pc case there are different treatments with curative intent, that are associated with significant morbidity. Some man have an aggressive form for which screening might be helpful but many have a slow growing cancer that would never progress and their detection could cause anxiety and bring unnecessary medical treatment. With this review we tried to understand where we should stop the management: Overdiagnosis or Overtreatment?

Keywords: Prostate neoplasm, screening, prostate specific antigen.

INTRODUCTION

Prostate cancer (Pc) is a major public health problem, affecting 679,000 men and causing 221,000 deaths every year [1]. It constitutes about 11% of all male cancers and accounts for 9% of all cancer deaths among men [2]. Given that the risk of Pc continues to increase with age, the burden of the disease is likely to increase in line with the population life-expectancy. Over the past decade, there has been a marked decline in Pc mortality corresponding to the introduction of Prostate Specific Antigen (PSA) test as a screening tool (1986) [3]. Despite this clear result, the screening recommendations of various organizations differ. The goal of a screening is to detect a cancer at an early stage, when it is still curable and primarily to improve cancer specific survival. Some men have an aggressive form of Pc for which screening might be helpful but other men have a slow growing cancer that would never progress and their detection could bring unnecessary medical treatment.

The aim of this article is to review the current screening guidelines and to summarise the benefits and harms of a screening program, analysing two large long awaited randomized multicenter clinical trials of PSA screening reported in 2009: the European Randomized Study of Screening for Prostate Cancer (ERSPC) by Schroeder et al. and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial by Andriole et al. [4, 5]. We finally analysed two important aspects related to Pc early detection: Overdiagnosis and Overtreatment, trying to understand how these two negative aspects could be better managed.

MATERIAL AND METHODS

We reviewed the recent literature (2008-2010) on PUBMED, using the following words for the research: Prostate-Specific Antigen, screening, Prostatic neoplasm mortality, follow-up studies, overdiagnosis and overtreatment. In particular, we analysed two clinical trials reported on “The New England Journal of Medicine” in 2009: the European Randomized Study of Screening for Prostate Cancer (ERSPC) by Schroeder et al. and the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial by Andriole et al. [4, 5].

CURRENT GUIDELINES ON SCREENING IN PC

At the moment, the main international guidelines are in conflict because of the absence of convincing evidences that Pc screening produces more benefits, in terms of mortality or morbidity reduction, than harms, meaning that finding and treating cancers that will remain quiescent.

The European Association of Urology (EAU) states that “There is no evidence for introducing widespread, population-based screening programme for early Pc detection in all men in a given population” [6]. A less controversial programme, which is also recommended by EAU is using PSA with digital rectal examination (DRE) as an aid to early diagnosis. The decision to undergo early PSA testing should be a shared decision between the patient and his physician: PSA testing and DRE should be offered from the age of 45 years to men with a life expectancy of at least 10 years.
The American Urological Association (AUA) supports the use of a PSA-based screening, which includes PSA testing and DRE, beginning at the age of 50 years to men with a normal risk of Pc and beginning at about 40 years to men at high risk [7]. It is now considered that a man with a positive family history or African-American race is a man with high risk of Pc [6]. The American Cancer Society (ACS) supports screening for Pc with PSA and DRE in men starting at the age of 50 or earlier in African American men or in men with a positive family history [8].

The National Comprehensive Cancer Network (NCCN) revised its Pc screening guidelines several months ago to emphasize the fact that NCCN does not recommend PSA screening for everyone. They recommend a risk-based screening algorithm, including factors such as family history, race and age [9]. NCCN considers that the greatest benefits of Pc screening are for men at high risk for Pc, either because of family history or African-American descent and age < 70 years. In contrast, the US Preventive Services Task Force concludes that there are insufficient evidences in men under the age of 75 years to assess the balance between benefits and side effects associated with screening, and the panel also recommended against screening in men over the age of 75 years [10]. Even without consensus on routine screening, more than half of US men aged 50 and older report having had a PSA test within the past year [11]. Even in the UK, where PSA screening is less common, two-thirds of the men referred to urologist with an elevated PSA were unaware that they had even had their PSA done. The UK Executive National Health System refers that informations about the limitations of PSA testing and the consequence of a positive result are deficient in clinical practice. Informed counselling for the PSA test should form part of the consultation of any physician intending to undertake this test whether for lower urinary tract symptoms (LUTS) or for Pc screening [12].

### WHY SCREENING

The possible advantages related to a Pc screening program are summarized in Table 1.

The clinical characteristics of Pc and its long natural history make it suitable for a screening approach. Different studies showed genetic and epigenetic changes intermediate between normal prostatic epithelium and Pc. These changes are described in several histological lesions, such as atypical small acinar proliferation (ASAP), proliferation inflammatory atrophy (PIA) and prostatic intraepithelial neoplasia (PIN) [13]. A progression from PIN to high grade PIN (HGPIN) and early latent cancer can take more than 10 years and in this case screening might be helpful either to identify patients who need more routine controls or to select patients for a prevention program.

In the US there has been a gradual decline in Pc mortality of approximately 30% since PSA testing has been introduced in the clinical practice [14]. There have been some evidences, supported by statistical analyses, that PSA screening has played a role in this decline [15]. PSA screening represents an important tool for the diagnosis of Pc at an early stage and mortality rates varies considerably depending on tumor stage and Gleason score. Men with a low grade Pc (Gleason score 2-4) have a minimal risk of dying from Pc during 20 years of follow-up (six deaths per 1000 person-year; 95% CI, 0-1) while men with high-grade prostate cancers (Gleason score 8-10) have a high probability of dying from Pc within 10 years of following (121 deaths per 1000 person-year; 95% CI, 90-156) [16]. In the absence of an organised screening programme, by the time of diagnosis, only 55% of tumors are clinically localized [17]. The 5-year survival rate for localized Pc is 100% compared with only 34% for a metastatic disease [18]. At this point, for localized Pc there are three treatment options recommended by American and European guidelines: Active surveillance, radical

### Table 1. Possible Advantages Related to Pc Screening

<table>
<thead>
<tr>
<th>ADVANTAGE</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Control on the long natural history of the disease</td>
<td>Possibility to identify histological lesions that precede and are related to Pc, so to select men for different follow-up or for prevention programs</td>
</tr>
<tr>
<td>Increase in the detection rate</td>
<td>Possibility to detect Pc that could not be detected without a screening program</td>
</tr>
<tr>
<td>Detection at an early stage</td>
<td>Mortality rates varies considerably depending on Pc stage</td>
</tr>
<tr>
<td>Higher efficacy of primary treatments</td>
<td>The efficacy of primary treatment such as active surveillance, radical prostatectomy and radiotherapy is related to an early diagnosis of Pc</td>
</tr>
<tr>
<td>Improvement in cancer specific mortality rate</td>
<td>This is the main advantage that the screening program must demonstrate as final endpoint</td>
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### Table 2. Possible Disadvantages Related to Pc Screening

<table>
<thead>
<tr>
<th>DISADVANTAGE</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Limits of PSA testing</td>
<td>Low sensitivity and specificity rates of PSA in Pc early diagnosis</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>Risk to diagnose an indolent Pc</td>
</tr>
<tr>
<td>Overtreatment</td>
<td>Risk to treat an indolent Pc</td>
</tr>
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</table>
WHY NOT SCREENING

The possible disadvantages related to a Pc screening program are summarized in Table 2.

Limits Related to PSA Testing

The screening program is mainly based on PSA testing. In a study population that has not been previously screened, the PSA test, using a threshold of 4 ng/ml, has a sensitivity of 56% to detect a Pc clinically diagnosed within two years [19]. Actually, there is no universally accepted cut-off or upper limit for PSA level. The finding that many men may harbour Pc despite low levels of serum PSA, has been underscored by recent results from a US prevention study [20]. One way to improve PSA sensitivity is to decrease the “threshold” PSA level, taking into account multiple factors including patient age, family history and comorbidities [21]. The specificity of PSA testing is approximately 60%; this is very low considering that serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. One way to improve PSA specificity is to include several modifications of serum PSA level in the early detection of Pc as PSA density, PSA density of the transition zone, age-specific reference ranges and PSA molecular forms [6].

Overdiagnosis and Overtreatment

Overdiagnosis and overtreatment are probably the most important adverse effects of a Pc screening and are vastly more common than in screening for breast, colorectal or cervical cancer [22].

About 20-40% of Pc diagnosed today are “indolent”, meaning that it is unlikely to progress and lead to complications for the patient. “Overdiagnosis” consists in diagnosing this type of tumors that would otherwise remain clinically unrecognized until the individual died from other causes. “Overtreatment” means invasive treatments of tumors that would unlikely to be harmful.

PSA screening could not differentiate between indolent and lethal Pc. Some men have an aggressive form of Pc for which screening might be helpful, but many have a slow growing cancer that would never progress to cause serious illness during a man’s lifetime and their detection could bring unnecessary treatments and cause significant anxiety [15, 23, 24]. In fact the detection of a slow growing cancer leads the patient to submit to aggressive treatments with all its potential risks, that affect quality of life. With the aim of reducing the risk of overtreatment in this group of patients, two conservative management strategies have been recently proposed: Watchful waiting and Active surveillance. The first refers to the conservative management of Pc until the development of local or systemic progression, at which point the patient would be treated palliatively. Active surveillance, also known as “active monitoring” includes an active decision not to treat the patient immediately but to follow him with close surveillance and treat him at pre-defined thresholds that classify progression. In these cases, the treatment options are intended to be curative. To counsel between immediate treatment and active surveillance with the possibility for deferred curative treatments, it is important to risk-stratify patients at the time of diagnosis. Recent progress has been made in this area with the development of nomograms predicting indolent Pc among screen-detected population [25].

Clinical Trials 2009

Two randomized, controlled trials of Pc screening are being conducted in 2009 and published on “the New England Journal of Medicine” [4,5]. These trials were mainly directed to determine the effect of screening on Pc mortality; the European Randomized Study of Screening for Prostate Cancer (ERSPC) by Schroeder et al. [4] and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening by Andriole et al. [5].

ERSPC Trial

The ERSPC is a randomized, multicenter controlled trial of screening for Pc and the primary outcome was the rate of death from Pc. The European countries that were included in this study are: Finland, Sweden, Italy, The Netherland, Belgium, Switzerland and Spain. Recruitment and randomization procedures differed among countries and were developed in accordance with national regulations. 162,387 men between the age of 50 and 69 year were included in this study. Men in whom a Pc had been diagnosed (according to data from questionnaires or registries) were excluded. At moment the publication does not clearly describe PSA cut-off values or other clinical parameters used for exclusion. At centres, in all countries except Finland, men were randomly assigned in a 1:1 ratio to a screening group that was offered PSA screening at an average of once every 4 years (n = 72 890), or to a control group that did not receive such screening (n = 89 353). Most centres used a PSA cut-off value of 3.0 ng /ml as an indication for biopsy; in other centres men with a PSA value of 4 ng/ml underwent to biopsy and men with PSA between 2.5 and 3.9 ng/ml underwent complementary tests (digital rectal examination and transrectal ultrasonography (TRUS). Most centres used sextant biopsies guided by TRUS. The screening interval at six of the seven centers was 4 years; Sweden used a 2-year interval. Evaluation of specimens from biopsies and radical prostatectomy was performed by local pathologists and standardization of procedures was coordinated and achieved by an international committee. Treatment of Pc was performed according to local policies and guidelines and distribution of treatments applied in the two groups were the same (Fig. 1).

Results from ERSPC

During a median follow-up of 9 years, the incidence of Pc was higher in the screening group than in the control group: 5,990/72,890 (8.2%) Pc detected in screening group and 4,307/89,353 (4.8%) in the control group. The positive predictive value of a biopsy (the number of cancers detected on screening divided by the number of biopsies expressed as a percentage) was on average 24.1% (range, 18.6 to 29.6).
Moreover, there were 261/72,890 Pc deaths in the screening group (0.35 per 1000 person-year) and 363/89,353 (0.41 per 1000 person-year) in the control group. To prevent one prostate cancer death, 1410 men (or 1068 men who actually underwent screening) would have to be screened and an additional 48 men would have to be treated. PSA screening was associated with a 0.71 absolute reduction of Pc deaths per 1000 men after an average follow-up of 8.8 years (median, 9.0). This finding corresponds to a relative reduction of 20% in the rate of deaths from Pc due to a PSA based screening. The rate ratio for death from Pc in the screening group, as compared with the control group was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted P =0.04). The rate ratio for deaths from any cause was 0.99 (95% confidence interval [CI], 0.97 to 1.02; adjusted P =0.50) in the screening group compared with the rate in the control group. The rates of death from Pc in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time. Schroder et al. considered also the percentage of Pc diagnosis in the two groups on the basis of tumor stage and Gleason score. The number of men with positive results on a bone scan was 0.23 per 1000 person-year in the screening group and 0.39 per 1000 person-year in the control group, with a 41% reduction in the screening group (P<0.001). The proportion of men who had a Gleason score ≤ 6 was 72.2% in the screening group and 54.8% in the control group whereas the proportion with Gleason score of ≥ 7 was 27.8% in the screening group and 45.2% in the control group. At this point, no other data on stage and Gleason score stratification in the two groups are provided in the publication [4]. Moreover no data related to a familiar history of Pc have been shown. Results are until preliminary and a future follow-up will provide further information. Authors also considered that overdiagnosis and overtreatment are probably the most important adverse effects from Pc screening. The rate of overdiagnosis has been estimated to be as high as 50% in the screening group. Consistent estimates of overdiagnosis have also been obtained by identifying potentially indolent Pc on the basis of clinical and pathology characteristics. They concluded their study asserting that further analyses and data are needed to introduce a population PSA based screening.

**PLCO Trial**

The Prostate component of the PLCO trial was designed to determine the effect of annual screening based on annual PSA testing and digital rectal examination (DRE) on mortality from Pc. 76,693 men between the age of 55 and 74 year were included in this study. At study entry, subjects completed a baseline questionnaire that inquired about demographic characteristics and medical and screening histories. Actually, the publication does not define PSA cut-off values on other clinical parameters used for exclusion. Men were randomly assigned to a screening group that provided annual PSA testing for 6 years and DRE for 4 years (n = 38,343) or to a control group that is represented by an usual care that might include screening (n = 38,350). All subjects provided written informed consent and exclusion criteria were: a history of a PLCO cancer, current cancer treatment and, starting in 1995, having had more than one PSA blood test in the previous 3 years. In the control group, there was a proportion of men who reported having had a PSA test as part of a routine physical examination in the previous year and it was defined by the authors “PSA contamination”. A serum PSA level of more than 4.0 ng/ml was considered to be suspected for prostate cancer. Men with positive results of the PSA test or suspicious findings on the DRE (nodularity or induration) were advised to seek diagnostic evaluation. In accordance with standard U.S.practice, diagnostic evaluation was decided by the patients and their primary physicians but specific data about it still missed (Fig. 2). No specific data on criteria for biopsy are provided in the publication.

**Results from PLCO**

Cause-specific mortality for each of the PLCO cancers was the primary end-point of the study. After 7 years of follow-up, 2820/38,343 (7.3%) Pc had been diagnosed in the screening group and 2322/38,350 (6.0%) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). At 10 years, with a complete follow-up for 67% of subjects, the excess in the screening group persisted, with 3452/38,343 subjects versus 2974/38,350 subjects. The incidence of Pc was 116 per 10,000 person-year in the screening
The data at 10 years showed a continuing lack of a significant difference in the death rate from Pc between the two study groups. Screening was associated with no reduction in Pc mortality during the first 7 years of the trial, with similar results through 10 years. At 7 years, the total number of deaths (excluded those from prostate, lung, or colorectal cancer) were 2544/38,343 in the screening group and 2596/38,350 in the control group (rate ratio, 0.98; 95% CI, 0.92 to 1.03); at 10 years, the numbers of such deaths were 3953 and 4058 respectively (rate ratio, 0.97; 95% CI, 0.93 to 1.01). The distribution of the causes of death was similar in the two groups. There was little difference between the two groups in terms of the proportion of deaths according to tumor stage and Gleason score. In the screening group, 60% of the subjects had stage I or II tumors (TNM classification), 2% had stage III tumors, and 36% had stage IV tumors; in the control group, 52% of the subjects had stage I or II tumors, 4% had stage III tumors, and 39% had stage IV tumors. The numbers of subjects with advanced (stage III or IV) tumors were 122/2820 (4.3%) in the screening group and 135/2322 in the control group. The number of subjects with Gleason score of 8 to 10 was higher in the control group than in the screening group. No other data on stage and Gleason score stratification and no data on familial history, are provided on the publication [5]. Finally, they concluded that Pc screening provided no reduction in deaths rates at 7 years and that no indication of a benefit appeared with 67% of the subjects having completed 10 years of follow-up. Data about overdiagnosis and overtreatment missed but a final report will be presented by Andriole et al. [5] once the planned duration of follow-up will be completed.

**COMPARATIVE ANALYSES OF THE TWO TRIALS: WHY DIFFERENCES IN PC RESULTS?**

In Table 3 the results of the two studies are summarized and compared.

In Fig. (3) the cumulative risk of death from Pc on the two trials are compared.

Conclusions obtained from these two randomised trials are significantly different: the European study [4] demonstrated a 20% decrease in Pc mortality due to PSA screening, while the PLCO trial [5] did not find any Pc-specific mortality reduction, related to the screening. This conclusive difference must be also analysed on the basis of differences in terms of population and study design between the two studies.

**Psa Contamination**

In the PLCO study, 52% of men in the control group had a PSA test within the past year as part of a routine physical examination, defined by Andriole et al. “PSA contamination” [5]. Andriole referred that PSA testing, that occurred outside the screening measurements, could still have an effect on Pc incidence and mortality in the control group. But he also supported that this “contamination” was not enough to eliminate the distinctly higher number of Pc diagnosed in the control group. Van Leeuwen et al., in their recent analysis, [26] sustained that the outcomes of both the studies will have been weakened by the considerable level of Pc screening in the control population, which may have resulted in an underestimation of the true benefits of Pc screening. Infact he highlighted that opportunistic PSA testing occurred in 8-29% of men in the control population of the ERSPC study and in 20% of men in the control group of the PLCO study.
Table 3. Comparison of Results from the ERSPC and PLCO Studies

<table>
<thead>
<tr>
<th></th>
<th>ERSPC</th>
<th>PLCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>162,387</td>
<td>76,693</td>
</tr>
<tr>
<td>Screening group (number of cases)</td>
<td>72,890</td>
<td>38,343</td>
</tr>
<tr>
<td>Control group (number of cases)</td>
<td>89,353</td>
<td>38,350</td>
</tr>
<tr>
<td>Age (years) at inclusion mean (median) (range)</td>
<td>60.8 (60.1) (55-69)</td>
<td>(55-74)</td>
</tr>
<tr>
<td>Type of screening</td>
<td>PSA test</td>
<td>PSA test + DRE</td>
</tr>
<tr>
<td>DRE at inclusion</td>
<td>-</td>
<td>No suspicious in all cases</td>
</tr>
<tr>
<td>Indication for prostate biopsy</td>
<td>PSA &gt; 3 ng/ml (&gt; 4 ng/ml in some countries)</td>
<td>PSA &gt; 4 ng/ml or suspicious DRE</td>
</tr>
<tr>
<td>Screening interval (years)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Pc detected in the screening group (%)</td>
<td>5990/72890 (8.2%)</td>
<td>3452/38343 (9.0%)</td>
</tr>
<tr>
<td>Pc detected in the control group (%)</td>
<td>4307/89353 (4.8%)</td>
<td>2974/38350 (7.7%)</td>
</tr>
<tr>
<td>Number of deaths from Pc in the screening group (death rate per 1000 or 10000 person-year)</td>
<td>262/72890 (0.35 per 1000 person-year)</td>
<td>50/38343 (2.0 per 10000 person-year)</td>
</tr>
<tr>
<td>Number of deaths from Pc in the control group (death rate per 1000 or 10000 person-year)</td>
<td>363/89353 (0.41 per 1000 person-year)</td>
<td>44/38350 (1.7 per 10000 person-year)</td>
</tr>
<tr>
<td>Rate ratio for death from Pc (95%, [CI]; P value)</td>
<td>0.80 (95% [CI], 0.65-0.98; P = 0.50)</td>
<td>1.11 (95% [CI], 0.83-1.50)</td>
</tr>
<tr>
<td>Estimated overdiagnosis rate in the screening group</td>
<td>50%</td>
<td>No data</td>
</tr>
<tr>
<td>Localized Pc in the screening group</td>
<td>No data</td>
<td>60%</td>
</tr>
<tr>
<td>Localized Pc in the control group</td>
<td>No data</td>
<td>52%</td>
</tr>
<tr>
<td>Advanced Pc in the screening group</td>
<td>0.23 per 1000 person-year (positive bone scan)</td>
<td>40%</td>
</tr>
<tr>
<td>Advanced Pc in the control group</td>
<td>0.39% per 1000 person-year (positive bone scan)</td>
<td>48%</td>
</tr>
</tbody>
</table>
| Gleason score in the screening group | ≤6 = 72.2%  
≥7 = 27.8% | No data |
| Gleason score in the control group | ≤6 = 54.8%  
≥7 = 45.2% | No data |

[27, 28]. Canfield S. [29] sustained that the distribution of Pc did not differ between the screened and control group of the PLCO study mainly because of the rate of pre-screening of 44% in both groups and the rate of contamination of 52% in the control group. In his opinion, this level of contamination might have cut the real estimate benefit of the screening effect. A recent study by van Leeuwen [26] compared two populations, both included in the ERSPC study, the Rotterdam section as the intervention group and a control cohort in Northern Ireland (Table 4). The first group was considered the intervention arm where screening has been done and the second one the control group where PSA screening was not recommended. The end point of this study was to estimate the true benefits of PSA screening with a low level of “PSA contamination” in the control population. In the intervention cohort 11,970 men, aged 55-74 year (median age of 63 years), were screened with an interval of 4 years by PSA measurement, DRE and transrectal ultrasound examination (TRUS). A sextant biopsy was offered to men with PSA ≥ 4 ng/ml and/or suspicious finding on DRE and/or TRUS. After November 1997 a biopsy was prompted by a PSA ≥ 3 ng/ml only. During a median follow-up of 8.5 years, 1153 (9.6%) of these men of the screening group were diagnosed with Pc. In the control group 133,287 men, aged 55-74 year (median age of 63 years) were included and 3962 (3.0%) of these were diagnosed with Pc during the same follow-up. Age and median PSA at diagnosis resulted higher in the control group: median age 70 (control) versus 67 (screening) years, (p < 0.001) and median PSA 18.0 (control) versus 5.1 (screening) ng/ml, (p < 0.001). In the intervention cohort 11 men (0.1% of total) and in the control cohort 862 men (0.6% of total) had a metastasis Pc at diagnosis. It means that there was a significant reduction of 53% in metastasis Pc in the intervention group when compared to the control group. In
the intervention cohort 35 (0.29%) men and in the control cohort 627 (0.47%) men died due to Pc or to Pc intervention-related procedure. This equated to a reduction in Pc mortality of 37% in the intervention population when compared to the control population. After considering the absolute risk difference of deaths per population, the result of this study is that 555 men needed to be screened and 37 cases had to be treated to save one Pc death [30]. The authors also underlined the importance of the follow-up: the cumulative Pc metastases and Pc mortality hazard ratio start to differ after 5 years of observation and this difference is likely to increase with longer follow-up. Hence, screening will only be beneficial in men with a life expectancy of at least 6 to 8 years. Despite their hopeful results, van Leeuwen et al. considered that the impact of overdagnosis, quality of life benefits and cost-effectiveness need to be better assessed before a population-based PSA screening can be recommended. They sustained that a longer follow-up is needed to demonstrate a mortality benefit in favour of PSA screening so that more clinical data must be waited by the ERSPC and PLCO authors.

Also Barry MJ [31] critically analysed the ERSPC and PLCO clinical trials, sustaining that in the PLCO study there was a high level of prescreening in the control group. It can represent the likely explanation for the negative findings reported by Andriole et al. He also referred to a PSA contamination in the control group of the ERSPC trial [4] that was not described by the authors.

In a recent study, Roobol et al. [32] tried to demonstrate whether the Pc specific mortality reduction of 20% reported in the ERSPC trial was influenced by two types of noncompliance: nonattending (ie, nonattending the initial screening round in ERSPC) in men who were randomised to the intervention arm and contamination (ie, the use of PSA testing in men randomised to the control arm). They analysed the occurrence of Pc deaths during a follow-up of 9 years in 162,243 men aged 55–69 year, randomized in 7 centres participating in the ERSPC study. They compared the relative risks (RRs) with 95% confidence intervals between an intention-to-screen (ITS) analysis adjusted for nonattendance and contamination, using a statistical method developed for this purpose. In the ITS analysis, the RR of Pc death in men allocated to the intervention arm and relative to the control arm was 0.80 (95% CI, 0.68-0.96). Adjustment for nonattendance resulted in a RR of 0.73 (95% CI, 0.55-0.93), and additional adjustment for contamination using two different evaluations, led to estimated reductions of 0.69 (95% CI, 0.51-0.92) and 0.71 (95% CI, 0.55-0.93), respectively. Using the method of Cuzick et al. [33], after adjusting for the double effect of nonattendance and contamination, the reduction in Pc mortality increased by 50%, giving a Pc mortality reduction of 31-33% attributable to attending screening.

McNaughton et al. [34] considered the ERSPC study a no uniform study because it pulled together trials from different countries, that used different protocols. He also sustained that the number of men needed to be screened (1400) and treated (48) to prevent one Pc death are too high and he finally maintained a scepticism about a PSA based screening program.

Barry et al. [31] criticized the different kind of diagnosis and treatment of Pc in the screening and in the control group of the ERSPC study. Almost 73,000 men in the screening group underwent biopsy, many more than did men in the control group, though the latter is not reported. It is also unclear, in their opinion, whether the clinicians treated the patients with Pc diagnosis. So it becomes difficult to discriminate the benefit attributable to screening versus that to an improved and unknown specific treatment once a Pc was suspected or diagnosed. He finally highlighted that in the PLCO the screening based on PSA and DRE helped more than in the ERSPC, to ensure that any difference in outcomes was attributable only to screening. Men with a suspicious DRE or a PSA level of more than 4.0 ng/ml were submitted to further diagnostic evaluation.

On the contrary, Canfield S. [29] considered the ERSPC trial a larger and more heterogeneous study that provided a higher power of detection for the true estimation of Pc screening. Canfield criticizes the lower PSA threshold, 3 ng/ml respect the cut point of 4 ng/ml of the PLCO study, which allowed more cases of cancer to be detected. Also Kantoff, in the commentary on Screening for Prostate Cancer [34], sustained this point. Andriole et al. [5], using a higher PSA level to recommend biopsy, could have missed some potential cancers and potentially some lethal cancers.
Many authors criticized both decisions to publish now the results of these two trials. It may represents a premature decision that leaves clinicians and patients ambiguous without any certain answer about the effectiveness of Pc screening.

OVERDIAGNOSIS AND OVERTREATMENT IN THE TWO CLINICAL TRIALS

At now, overdiagnosis and overtreatment are the most important adverse effects of Pc screening. Unfortunately, the publications [4,5] from the two trials did not specifically and fully considered the impact of these events in their studies.

In the ERSPC, men in the screening group were 71% more likely to have Pc diagnosed after 9 years than men in the control group [4]. The rate of overdiagnosis of Pc has been estimated to be as high as 50% in the screening group [35]. Newly diagnosed patients can endure significant anxiety and uncertainty relating to diagnosis. It is possible for a young men to be diagnosed with cancer to have a diagnostic evaluation to endure the adverse effects of a therapy without ever having had a disease related symptoms [36-38]. In the PLCO study, the rate of overdiagnosis of Pc was not reported; authors only reported the complications that occurred during the diagnostic evaluation. Medical complications related with the diagnostic process occurred in 68 of 10,000 diagnostic evaluations after positive results from screening. Such complications, like bleeding, hematoma or pain, are particularly pertinent in cases of overdiagnosis. Barry et al. [31] reported that the smaller difference in screening intensity between the two study groups in the PLCO trial, as compared with the ERSPC trial, is reflected in a smaller risk of overdiagnosis (23% vs more than 70%).

Overtreatment means on invasive treatment in tumors that would unlikely to be harmful. Most men identified with Pc through the screening group of the ERSPC study, are not destined to die of their Pc and thus should not obtain any survival benefit from screening and more for treatment. 72% of men in the screening group of ERSPC Pc with a Gleason score between 2 and 6; therefore many indolent cancers that do not require any treatment have been diagnosed [39]. Other men would have died from their cancer despite treatment. Among the 28% of Pc with a Gleason score between 7 and 10, some will have a disease for which treatment is not likely to be effective [39]. Quantification of overtreatment resulting from the two randomized trials is needed; the rate of overtreatment of Pc has not been estimated in the two studies. Recommended treatments for Pc (Radical prostatectomy, radiotherapy, hormone therapy) are associated with significant morbidity; these dysfunctions can affect in large measure the quality of life of Pc patients.

CONCLUSIONS

The 2009 results do not give an univocal answer to clinically define the actual role of Pc screening. However, the positive role of screening in improving an early diagnosis of Pc is evident. The main problem is related to the high risk of overdiagnosis and overtreatment for clinically insignificant or indolent Pc.

We should begin to dissociate the whole process of PSA screening from Pc treatment. Many people who get diagnosed with Pc do not need to be treated. Some recent trials and the international urological guidelines [6-8] well define the role of active surveillance and which Pc can be followed with success without treatments. Men should be fully informed by primary care physicians and specialists about the screening test itself, its interpretation and eventual treatments, to permit them to make their decisions, considering potential benefits and harms. In particular a Pc screening program may be associated, as positive effect, to an improvement in Pc early diagnosis and to an improvement in Pc related mortality and, as negative effect, to an overdiagnosis of indolent tumors. If we are able to select these insignificant Pc so to follow them without treatment, (active surveillance), the risk of overtreatment could be limited. The interpretation of an unnecessary progression of events (screening, overdiagnosis, overtreatment) should be done at the level of treatment (so to exclude the risk of overtreatment) and not at the level of the diagnosis (so to exclude the risk of overdiagnosis).

REFERENCES


