



Review – Prostate Cancer

PSA-based Screening for Prostate Cancer: How Does It Compare with Other Cancer Screening Tests?

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Abstract

Context: Despite the substantive societal impact of prostate cancer, the medical community is currently divided on the balance between benefit and harm of screening for prostate cancer using prostate-specific antigen (PSA).

Objective: To examine whether PSA-based screening for prostate cancer meets current guidelines on efficacy and effectiveness for screening, and how it compares with other currently implemented cancer-screening methods.

Evidence acquisition: A literature search was conducted for reviews and individual studies that have examined the performance of screening for colorectal, cervical, breast, and prostate cancer. Each screening method was assessed using the United Kingdom National Screening Committee guidelines. Data on screening test performance (sensitivity, specificity, etc) were extracted from these articles for comparison.

Evidence synthesis: In common with other cancers for which screening is conducted, prostate cancer represents a significant morbidity and mortality burden. The PSA test can be considered “simple” and “safe” within appropriate boundaries. The sensitivity/specificity profile of PSA is not optimal but has clinical validity: Cases missed at screening detected as interval cases do not have a poor outcome. Early prostate cancer intervention can be beneficial for long-term outcomes, although the benefits need to be weighed against the adverse effects of intervention. Early evidence from screening studies also suggests positive stage and grade shifts, although Level 1 mortality data are still awaited. Robust cost-effectiveness data are still lacking, although current evidence suggests that PSA screening may lie within acceptable limits.

Conclusion: Until better markers become available, PSA can be regarded as an appropriate screening tool for prostate cancer at a population level.

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1. Introduction

Prostate cancer is pre-eminent in Western society: It is the most common malignancy in men, with almost twice as many incident cases as lung cancer [1]. It also represents the third leading cause of male cancer deaths in Europe (after lung and colorectal cancer) [1]. Although the annual death rate from prostate cancer accounts for approximately 12% of its incidence rate [1], among those who die with, rather than because of their tumour, disease- and treatment-related morbidity are significant issues [2]. Furthermore, among those with disease progression (especially to metastatic disease) resource consumption is substantial [3].

Despite the substantive societal impact of prostate cancer, screening using total prostate-specific antigen (PSA) has generated considerable debate within the medical community, with opinion divided on the balance between benefit and harm [4,5]. As a result, differing recommendations exist not only on whether PSA-based screening should be implemented, but also on how it should be implemented if recommended [6–10]. This has resulted in inconsistent practice across the Western world, with significant implications for public health.

A number of criticisms have been levelled against PSA-based prostate cancer screening: too many unnecessary biopsies; an increased detection rate of “insignificant” cancer; dilemmas over treatment versus watchful waiting; uncertain effect on morbidity and mortality; unclear cost-effectiveness. However, in order to fully evaluate PSA-based screening, it is necessary to examine two key questions. First, how well does this form of screening meet current guidelines on efficacy and effectiveness for screening, and second, how does it compare with other cancer-screening methods currently implemented? This article aims to examine both of these questions.

2. Evidence acquisition

2.1. Study acquisition

A literature search was conducted for reviews and individual studies that have examined the performance of screening for colorectal, cervical, breast, and prostate cancer. Data on screening test performance were extracted from these articles for comparison.

2.2. Assessment of cancer-screening programs against agreed criteria

Screening can be defined as “a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by, a disease or its complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of disease or its complications” [11]. For any potential screening program, criteria have been established to assess efficacy and effectiveness. For the purposes of this review, each screening program was assessed using the most comprehensive guidelines currently available, those of the United Kingdom National Screening Committee (Table 1) [11].

2.3. Performance of cancer-screening programs

In order to assess the performance of cancer-screening methodologies, data for sensitivity and specificity, the positive predictive value (PPV), the number needed to screen (NNS) to detect one positive case, and the cost per quality-adjusted life-year (QALY) were gathered. Where possible, these parameters were derived by comparison with a recognised “gold standard” of diagnosis, with both the gold-standard test and the test under consideration conducted in all patients. Cost per QALY figures were compared with the UK National Institute of Clinical Excellence upper threshold of around £30 000 [12,13], and the reported US figure of \$50 000 [14].

3. Evidence synthesis

3.1. Health burden of colorectal, cervical, breast and prostate cancer

A comparison of the health burden of different cancers for which screening can be conducted is presented in Table 2. All of these tumour types represent a significant morbidity and mortality burden.

3.2. Characteristics of common screening approaches

3.2.1. Colorectal cancer

Screening programs for colorectal cancer (CRC) are now implemented or being established in many countries, including the United States, France, Germany, Italy, and the UK [15]. In the United States

Table 1 – Alignment of screening approaches with the guidelines from the United Kingdom National Screening Committee [11]

Criterion	Colorectal cancer	Cervical cancer	Breast cancer	Prostate cancer
Condition is an important health problem	Yes	Yes	Yes	Yes
Latent period or asymptomatic stage	Yes	Yes	Yes	Yes
Cost-effective primary prevention implemented	Limited: dietary advice, but absolute role unclear	Advice concerning sexual transmission and barrier contraception. HPV vaccination likely to be implemented	Tamoxifen and raloxifene are licensed for risk reduction in women with a specified 5-year Gail model risk; strategy variably implemented. No other interventions proven to date	Cost-effectiveness of primary preventative agents 5 α -reductase inhibitors, selenium and vitamin E unclear
Simple, safe, acceptable, precise and validated test	FOBT is safe and simple, but has lower sensitivity than colonoscopy; sigmoidoscopy and colonoscopy are invasive procedures. Sigmoidoscopy has similar sensitivity to FOBT; colonoscopy is 'gold standard'. Risk of perforation with sigmoidoscopy and colonoscopy	Pap and liquid-based cytology are simple and safe; sensitivity and specificity of individual test is relatively poor	High specificity and acceptable sensitivity. High false-positive test rate. Risk of X-ray-induced cancer	Safe and simple; PSA threshold for optimal balance between sensitivity and specificity remains under debate
Policy on further diagnostic evaluation	Yes	Yes	Yes	Yes
Effective treatment or intervention	Colonoscopy to facilitate biopsy and polypectomy. Surgery for localised CRC with adjuvant chemotherapy or radiotherapy; chemotherapy for metastatic CRC; radiotherapy for advanced disease	Colposcopy to facilitate biopsy. Cryosurgery, laser ablation or biopsy to remove pre-cancerous lesions; surgery for localised cancer; radiotherapy or chemotherapy for advanced disease	Biopsy to confirm malignancy followed by surgery, radiotherapy, hormone therapy, chemotherapy, biological treatments or combinations thereof	Biopsy to confirm malignancy, followed by expectant management, surgery, cryosurgery, radiotherapy, or brachytherapy for localised disease; hormone therapy, radiotherapy, or chemotherapy for advanced disease
Evidence-based policy on who and how to treat	Yes	Yes	Yes	Controversial
Grade 1 evidence that screening reduces morbidity and mortality	FOBT data are not Grade 1; other methods not examined	No Grade 1 evidence available	Grade 1 evidence available	No Grade 1 evidence available
Evidence that screening and treatment is clinically, socially and ethically acceptable	Yes	Limited evidence	Yes	Yes
Benefit greater than physical and psychological harm	Yes	Limited evidence; considered to be the case in women aged >25 years	Some evidence of harm as false-positive rate is high	Some evidence of harm as false-positive rate is high
Cost-effective	Yes	Yes; CE ratio differs according to approach and frequency. Additional cost of HPV has been questioned	Yes	Unclear

Table 2 – Selected cancer incidence/mortality rates in the United States [1] and the European Union (25 member states) [80,81]

Cancer type	Colorectal	Cervical	Breast	Prostate
Age-standardised incidence rate (per 100 000 population) [*]	US: 64.2 (M); 46.7 (F) EU: 59.0 (M); 35.6 (F)	US: 9.1 EU: 12.1	US: 128.2 EU: 110.3	US: 165.0 EU: 106.2
Percentage of total cancer cases	US: 10.3% (M); 11.0% (F); 10.6% (M+F) EU: 13.0% (M); 12.9% (F); 13.0% (M+F)	US: 1.6% EU: N/A	US: 26.3% EU: 30.9%	US: 28.5% EU: 24.1%
Age-standardised mortality rate (per 100 000 population) [*]	US: 24.3 (M); 17.0 (F) EU: 26.5 (M); 15.6 (F)	US: 2.7 EU: 4.5	US: 26.0 EU: 25.0	US: 29.1 EU: 23.2
Percentage of total cancer deaths	US: 9.0% (M); 9.7% (F); 9.3% (M+F) EU: 11.4% (M); 12.7% (F); 12.0% (M+F)	US: 1.4% EU: N/A	US: 15.0% EU: 16.7%	US: 9.3% EU: 10.4%

F = female; M = male; N/A = not available.
^{*} Age-adjusted incidence and mortality rates for the US are standardised to the 2000 US standard population; those for the European Union are standardised to the European standard population.

and Italy, screening is recommended from the age of 50 yr; in Germany it is from 55 yr, while in the UK, the program is targeted at those aged 60–69 yr.

A number of large-scale studies, conducted in the United States, Denmark, France, Italy, the UK, and Japan, have examined the role of the fecal occult blood test (FOBT) in CRC screening [16–23]. While specificity figures for the test are high (93–95%), the sensitivity and PPV values vary significantly among studies, with a range of 66–89% for sensitivity and 3–17% for PPV (11–47% for adenomas). This range reflects differences in methodology, study length, and the interval between screens (Table 3). Significantly, only one study has directly compared FOBT with colonoscopy, reporting a sensitivity of 66% for invasive cancer and 27% for advanced neoplasia [22]. This finding indicates that FOBT-based screening programs are likely to miss significant numbers of cancers and premalignant lesions due to a lack of sensitivity, although this may be overcome, in part, by repeating the FOBT on an annual or biennial basis. For those with a false positive result, there is concern over the risk of morbidity with colonoscopy, which, although small, is significant.

As with the FOBT, sigmoidoscopy has a high specificity of 94% for CRC or large polyps and 92% for small polyps [24]. Sensitivity is variable, in the range of 35–70% [25–27], which is likely to reflect the incomplete visualisation of the colon. The procedure is relatively safe, with the risk of perforation low. It is generally recommended that the test be carried out every 5 yr, although no empiric data are available that test different intervals.

To date, no randomised, controlled trials have examined the sensitivity and specificity of colonoscopy screening for CRC. Calculation of sensitivity is difficult because colonoscopy is considered the “gold standard” for detecting CRC and adenomas. In one study in which tandem colonoscopies were performed by two expert examiners, the sensitivity

for detecting large (≥ 1 cm) adenomas was 94% while that for small (≤ 0.5 cm) was 73%; sensitivity for cancer is likely to be greater than 90% [28,29]. The specificity of colonoscopy with biopsy is generally reported to be 99–100%, but this assumes that all adenomas that are detected represent true positives [29]. Colonoscopy has a significant risk of procedural complications, particularly when polypectomy is performed. However, although the risk of serious adverse events increases with age, the risk/benefit ratio is positive in all age groups [30].

Data are available to demonstrate that FOBT screening reduces CRC mortality [16–23], but no definitive data from randomised, controlled trials have demonstrated the effectiveness of sigmoidoscopy or colonoscopy in this regard. NNS values to detect one CRC are 406–559 for FOBT [17–20,23], 211–310 for sigmoidoscopy, and 276 for colonoscopy [22]. For adenomas, the values are 73–196 [17,18,23], 8–10, and 42 [22], respectively. In terms of cost-effectiveness, a review published in 2002 found that all methods range from \$6300 to \$92 000 per life-year saved, with most ranging from \$10 000 to \$40 000 per life-year saved [31]. The U.S. Preventive Services Task Force (USPSTF) also published a systematic review of cost-effectiveness of CRC screening in which the cost per life-year saved ranged from \$10 000 to \$25 000, regardless of which screening method was used [32]. This indicates that CRC screening is likely to be cost-effective based on US and UK thresholds.

3.2.2. Cervical cancer

In 2003, the Council of the European Union adopted a recommendation to implement population-based screening for cervical cancer in all member states of the European Union [33], and national programs have now been introduced in many countries worldwide, including the United States [34]. Routine screening for cervical cancer every 3 yr is generally recommended for women from onset of sexual activity or age 21 (whichever comes first) until age

Table 3 – Characteristics of common screening approaches

Disease/test	PSA for prostate cancer [53,70,72]	FOBT for CRC and precursor lesions [16–23,32]	Sigmoidoscopy for CRC and precursor lesions [24–27,32,82]	Colonoscopy for CRC and precursor lesions [22,29,32]	Cytology for cervical cancer and precursor lesions [35–39,41]	Mammography for breast cancer [43,47–49]
Sensitivity	All tumours: At PSA 2.6 ng/ml = 40.5% At PSA 4.1 ng/ml = 20.5% Gleason \geq 8: At PSA 2.6 ng/ml = 78.9% At PSA 4.1 ng/ml = 50.9%	66–89% for CRC	35–70% for CRC	>90% (considered the “gold standard”)	6–99% dependent in part on stage examined. Mean 59%	77–95%, for 1-yr intervals, 56–86% for 2-yr intervals. Interval cancers used as “gold standard”
Specificity	All tumours: At PSA 2.6 ng/ml = 81.1% At PSA 4.1 ng/ml = 93.8% Gleason \geq 8: At PSA 2.6 ng/ml = 75.1% At PSA 4.1 ng/ml = 89.1%	93–95% for CRC	92–94% for CRC or polyps	99–100%	6–100% dependent in part on stage examined. Mean 75%	94–97%
PPV	29.5% for PSA and DRE, based on for-cause data; 12.8% in screening study [83]	3–17% for CRC; 11–47% for adenoma	Unknown	Unknown	7.3–23.5%	2–22%
NNS to detect one positive case	50–77 for men in their 50s; 21–30 for men in their 60s; 11 for men in their 70s for PSA \geq 4.0 ng/ml	73–196 for adenoma; 406–559 for CRC	8–10 for distal adenoma; 211–310 for distal cancer	42 for adenoma; 183 for high-grade dysplasia; 276 for CRC	100 for CIN 2–3; 300 for cancer	100–303
Cost per life-year saved	\$12 500–\$15 000 based on favourable screening assumptions	\$10 000–\$25 000	\$10 000–\$25 000	\$10 000–\$25 000	\$18 000–\$22 000	\$3750–\$5250

65. Despite this, to date no randomised, controlled studies have been conducted to evaluate the effectiveness of cervical cancer screening.

A systematic review of screening for cervical cancer using conventional cytology reported sensitivity in the range of 6–99% and specificity of 6–100% for detecting “cases”, defined as histologic diagnosis of cervical intraepithelial neoplasia (CIN), grades I–III, or carcinoma (Table 3) [35]. The sensitivity and specificity ranges were dependent on the cytologic and histologic thresholds used in the individual studies. Overall, mean sensitivity of 59% and specificity of 75% have been estimated from the published literature [36], while PPVs of 7.3% and 23.5% have been reported in population-based studies [37,38]. There is evidence to suggest that liquid-based cytology improves the sensitivity of cervical cancer screening by 12%, while specificity remains unchanged [39].

Evidence from observational studies has suggested that the introduction of screening programs reduces the incidence of cervical cancer by 60–90% within 3 yr [40]. A randomised study in India included 35 193 women randomised to screening using conventional cytology [41]: Analysis of the results demonstrated a NNS of 100 for CIN grades II–III and 300 for cancer. Conventional cytology screening every 3 yr has a cost per life-year gained of £10 207 (approximately US \$18 000); increasing to £12 679 (approximately US \$22 000) for liquid-based cytology every 3 yr [39]. Cervical cancer screening therefore falls within acceptable limits of cost-effectiveness.

3.2.3. Breast cancer

Breast cancer-screening programs have been implemented in many countries, including those of the European Union, the United States, Japan, and Australia. Country-specific variations exist in the format of these programs: For example, US guidelines recommend yearly screening from age 40 [42], while the UK screening program targets women aged 50–70 for screening every 3 yr.

A systematic review found that the sensitivity of mammography screening at 1-yr intervals was 77–95%, while for 2-yr intervals it was 56–86% (Table 2) [43]. These estimates were based on using interval cancers as the “gold standard”. While this does not represent an ideal comparator, the lack of other assessment methods limits the use of another “gold standard”. The specificity of a single mammographic examination was 94–97%, and the PPV was 2–22% for abnormal results requiring further evaluation and 12–78% for abnormal results requiring biopsy.

Evidence from randomised, controlled trials has demonstrated that mammographic screening

reduces mortality from breast cancer [44]. Radiation exposure is a potential risk associated with mammography, although firm data are lacking. Evidence suggests that for every 1 million mammograms, 8 excess deaths might be expected [45], and it is likely that this potential would be increased if earlier screening were implemented [46].

Data from large-scale, prospective studies have found the NNS to detect one tumour to be in the region of 100–303 [47,48]. In terms of cost-effectiveness, European data suggest a cost per life-year gained of \$3750–\$5250 in the normal screening population [49].

3.2.4. PSA for prostate cancer

Current guidelines for the use of PSA for prostate cancer-screening differ substantially between the United States and Europe. In the United States, the USPSTF concluded that the evidence is insufficient to recommend for or against PSA screening [9]; however both the American Urological Association [6] and the American Cancer Society [42] recommend that screening be offered to men of 50 yr or older. The Advisory Committee on Cancer Prevention in the European Union stated that “screening for prostate cancer is not recommended as health-care policy” [50]; the most recent view of the World Health Organization is that mass screening should not be supported prior to the availability of large-scale, randomised data [51]. The European Association of Urology also concludes that there is a current lack of evidence to support mass screening [7].

While PSA testing is simple, and the test itself is safe, considerable controversy remains over the performance of PSA testing for prostate cancer identification. The most commonly implemented form of PSA screening is the use of a total PSA threshold to determine the need for further evaluation, typically prostate biopsy. Data from the Prostate Cancer Prevention Trial (PCPT) demonstrate that the risk of a positive prostate biopsy, and the risk of high-grade disease (Gleason score of ≥ 7) rise with increasing PSA level, but that there is no clear cut-off up to a PSA of 4.0 ng/ml that delineates a population with versus without prostate cancer [52]. For example, a PSA of 2.6 ng/ml has a sensitivity of 40.5% and specificity of 81.1% for detecting any prostate cancer, while at 4.1 ng/ml, these values are 20.5% and 93.8% [53]. Sensitivity therefore decreases with increasing PSA level, while specificity increases. Overall, the sensitivity and specificity of PSA is improved for high-grade cancer compared with any prostate cancer, demonstrating that PSA is a better marker of high- than low-grade disease [53]. Taken together, whilst these data

suggest that PSA specificity at these clinically implemented threshold levels is high, the key question is whether the disease that is correctly identified is clinically meaningful for the patient. This question has many facets: One key consideration is whether a reduction in mortality is observed with screening.

To date, large-scale, randomised data for the impact of PSA-based screening on prostate cancer mortality are lacking. However, there is a substantive body of other evidence that PSA testing has had a significant impact on the natural history of prostate cancer. Epidemiological and case-control studies have shown that PSA-based screening results in a stage shift, with diagnosis occurring at earlier pathologic stages that are more amenable to curative treatment [54–58]. In 1993, PSA testing was made freely available to men aged 45–75 yr in the Federal State of Tyrol in Austria: A significant migration to lower stages of prostate cancer has been observed since its introduction [54]. Furthermore, analysis of data from the Rotterdam section of the European Randomised Study of Screening for Prostate Cancer (ERSPC) has revealed a statistically significant shift to more favourable clinical stages and histologic grades on biopsy in the screening arm compared with the control arm [57]. Distant metastases were also found five times more frequently in the control arm, and screened men also had lower 5-yr rates for biochemical progression after surgery, radiotherapy, and endocrine therapy compared with the control arm [59]. These findings are supported by those of another recent study in which the 7-yr progression-free survival rates after radical prostatectomy were higher in patients with screen-detected prostate cancer compared with physician-referred patients ($p = 0.002$) [60].

Although data on mortality are limited, the nonrandomised Tyrol study has demonstrated a statistically significant decline in prostate cancer mortality rates from 1993 to 2000 [58], while 11-yr follow-up in a prospective, randomised, controlled trial in Quebec, Canada has also demonstrated a significant 62% reduction in cause-specific mortality [61]. However, the number of deaths from prostate cancer in both the screened and unscreened arms was not substantial, the analysis was not conducted on an intention-to-treat basis, and the study has been criticised on a number of methodologic points. Aus et al have also reported findings from the Göteborg section of the ERSPC, in which biennial PSA screening was found to significantly reduce the risk of being diagnosed with metastatic prostate cancer after 10 yr of follow-up ($p = 0.0084$) [62]. The authors noted that this outcome is the first prerequisite for

achieving decreased cancer mortality in younger men.

Given that many men who develop prostate cancer do not either develop clinically relevant disease, or die as a result of their disease, over-detection may be a substantial issue. Data from the ERSPC have been used to estimate over-detection, where cancers were designated as “irrelevant” if they would have not otherwise been detected clinically if screening had not been implemented. In this model, between 27–56% of cancer was designated as over-detected, with the rate rising with age [63]. However, there have also been calls to lower the PSA threshold, as a result of the PCPT findings, to increase sensitivity. While it is clear that such an approach will result in more prostate biopsies with an increased negative rate [64], cancer detection would also increase. Although it has been argued that many of the newly detected tumours would be clinically insignificant [65,66], it could also be argued that the development of more advanced disease in a proportion of these men warrants their detection and earlier treatment.

While it is generally believed that a prostate cancer-screening program is clinically, socially, and ethically acceptable to health professionals and the public, there has been some anxiety that psychological harm caused by the screening program could outweigh the benefits in many men with a negative finding, or where the identification of clinically insignificant disease, will have provoked anxiety. However, although the need for a prostate biopsy is associated with significant stress, there is no evidence that overall screening significantly increases psychological stress and anxiety [67].

There are conflicting views on the “value for money” that prostate cancer-screening with PSA represents [68,69]. One cost-effectiveness analysis, using favourable screening assumptions, has determined the marginal cost-effectiveness of screening men aged 65 yr using PSA and digital rectal examination, without adjustment for life quality and without discounting benefits, to be between \$12 500 and \$15 000 per life-year saved [70,71]. However, changing assumptions increased the marginal cost-effectiveness ratio to >\$100 000 per life-year saved. A systematic evidence review conducted by the USPSTF was used to estimate the yield of screening with PSA (using a 4.0 ng/ml threshold for biopsy) in 1000 asymptomatic men with no previous screening [72]. For men in their 50s, the NNS to detect one prostate tumour was 50–77, decreasing to 21–30 for men in their 60s, and decreasing still further to 11 for men in their 70s. These NNS values are favourable when compared

with other cancer-screening programs. However, it must be born in mind that not all cancers detected would result in a prostate cancer-related death.

3.3. Comparison of PSA-based screening for prostate cancer with other cancer-screening approaches

There can be little doubt, as evidenced by the data in [Table 2](#), that prostate cancer represents a significant morbidity and mortality burden, with incidence and mortality rates comparable with other malignancies with established screening programs. One of the requirements of the United Kingdom National Screening Committee guidelines is that cost-effective primary prevention strategies should be implemented wherever possible. In prostate cancer, despite the availability of Level 1 evidence for the effectiveness of 5 α -reductase inhibitor-based risk reduction, implementation is sporadic, and questions remain as to the effectiveness, and cost-effectiveness, of this approach. Randomised data are also still lacking for the role of agents such as selenium and vitamin E in the primary prevention of prostate cancer. However, several of the other screening approaches under consideration also fail to fully meet this criterion ([Table 1](#)). For example, in CRC, dietary advice is typically provided but primary prevention is limited for this condition, while in breast cancer, the use of agents such as tamoxifen is limited. In our view, the requirement that this criterion is met should not be considered as absolute.

As with other common cancer-screening methods, the PSA test itself can be considered simple and safe within appropriate boundaries. In comparison with other screening tests, PSA has a lower sensitivity for any cancer at commonly used threshold values. The specificity of PSA is acceptable: At the 4.1 ng/ml threshold both for any cancer and for high-grade cancer, it is comparable with that of the other screening tests considered ([Table 3](#)). Although the lack of sensitivity could be ameliorated by decreasing the threshold value, this would lead to a decrease in specificity and the PPV, resulting in a substantial burden of biopsies arising from false positive tests. However, evidence from the Rotterdam section of the ERSPC suggests that, using common cut-off values and a 4-yr screening interval, the average tumour stage and grade was lower in subsequent rounds of screening. Furthermore, although the study has found, in concordance with the PCPT, evidence of cancers in men below threshold for biopsy, they have concluded that among men whose cancer is not detected in round one of screening, it is unlikely that a substantial

number progress to noncurable stages at the time of diagnosis in round two [73–75]. Thus, overall, it can be stated that the sensitivity/specificity profile of PSA, while not ideal, has clinical validity: Cases missed at screening detected as interval cases do not have a poor outcome.

If a screening program is to be effective, policies on further diagnostic evaluation and patient selection for intervention, as well as Level 1 evidence of effective interventions, should exist. While further diagnostic evaluation in prostate cancer is well defined, controversy still exists on choice of patients for intervention, and selection of the type of intervention. There is, however, an accumulating body of evidence to support the value of early intervention for prostate cancer. In a large-scale, randomised study of radical prostatectomy (RP) versus watchful waiting in early prostate cancer (typically T2), RP was shown to statistically significantly reduce disease-specific mortality and overall mortality after 10 yr, as well as significantly reducing the risk of metastasis and local progression [76]. However, the outcome of this study needs to be balanced against several important observations. First, the absolute reductions in mortality were not substantial. Second, the reduction in prostate cancer-specific mortality was observed in men aged <65 yr old, but not \geq 65 yr old. Third, the men enrolled in this study did not have their tumours detected through a screening program. Despite this, the observed relative risk reductions in mortality (44% cause-specific and 26% all-cause) were relevant, and the reductions in local recurrence and metastatic disease were of significant clinical relevance. Recently, Wong et al reported the results from an observational study using linked data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare to estimate the association between initial treatment and overall and cause-specific mortality in men aged 65–80 yr with localised prostate cancer [77]. They showed that, after 12 yr of follow-up, men who received active treatment (radiation or RP) had statistically significant improvements in overall and prostate-cancer specific mortality versus men who underwent observation. Subgroup analysis revealed that the benefit associated with treatment was seen in all subgroups examined, including older men, black men, and those with low-risk disease.

Overall, therefore, there is increasing evidence that early intervention can be beneficial for long-term outcomes, although this needs to be weighed against relatively high number-needed-to-treat values, the absolute value of intervention particularly in older men, and the adverse consequences of

surgical intervention. It is clear that overdetection is not a trivial issue with PSA-based prostate cancer screening. Prostate biopsy is an invasive procedure, and the detection of cancer can often lead to a push for treatment, even if the balance of benefits and harms is not justified in an individual man. It has, however, been argued that the problem may lie less with over-screening, and more with a desire to over-treat. Although these data on treatment outcome do not unequivocally argue for the implementation of screening, they do demonstrate that men can be provided with active intervention as a treatment option for early prostate cancer: an option they may be denied in the absence of routine screening. Furthermore, early evidence from screening studies suggests positive stage and grade shifts, although Level 1 mortality data are still awaited. As a result of the lack of strong mortality data at this juncture, robust cost-effectiveness data are still lacking, although current evidence suggests that PSA screening may lie within acceptable limits based on the United Kingdom National Institute of Clinical Excellence threshold of below UK £30 000 per QALY.

4. Conclusions

Despite considerable speculation concerning the appropriateness of PSA-based screening, there is evidence that the test has sufficient sensitivity and specificity for widespread implementation. Although sensitivity for all tumours is not ideal, there is evidence that this is increased for high-grade tumours. Specificity is within acceptable limits, and PPV, an important marker of the burden of unnecessary biopsies, also appears favourable. New biomarkers currently in development, such as the prostate cancer gene 3 (PCA-3), also have promise to improve specificity, and work is ongoing to identify molecular markers of tumour aggressiveness that would help physicians screen out indolent cancers [78,79]. A key focus in the next few years will be to understand how PSA can best be used as a marker of prostate cancer risk, in terms of combining it with other risk factors for the disease (such as age, race, and family history) and defining appropriate screening intervals based on our understanding of PSA as a biomarker, and the natural history of the disease.

Critics of PSA-based screening often highlight the forthcoming availability of data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States, and the ERSPC in Europe, as a reason to defer implementation. However, it is interesting to note the lack of Level

1 evidence for some of the other cancer-screening programs, most notably CRC and cervical cancer. While data from the PLCO and ERSPC will be of great significance, and will also provide robust cost-effectiveness data, there is reason to believe that they will help to establish which men should be screened and at what frequency, rather than whether screening should be conducted per se. The accumulation of evidence to date suggests that PSA-based screening does produce a beneficial grade and stage shift, as well as affording the opportunity to reduce disease-specific and overall mortality. While it can be argued that the balance of benefit against harm for early treatment of prostate cancer is not as substantial as it is for other common malignancies, such as breast and colorectal cancer, it is our contention that identification of prostate cancer through PSA-based screening does not have to imply active intervention, but can allow the opportunity for informed discussion on the pros and cons of therapy that may be missed in the absence of routine screening. Until the time when better markers become available, PSA can be regarded as an appropriate screening tool for prostate cancer at a population level.

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