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# Practical aspects of screening for prostate cancer

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*The introduction and increasing use of the PSA test in the late 80's to early 90's has revolutionized the diagnosis and follow-up of the disease, although the benefits and limitations of the test remain incompletely understood. Only a small proportion of cancers become clinically evident: more men die with the disease rather than of the disease. Screening will thus identify some men with cancer who will not benefit from treatment and it is unclear whether screening would be followed by a reduction in morbidity and mortality. When prostate cancer screening is performed, it should consist of both PSA measurement and digital rectal exam, as these tests are complementary in the early detection of prostate cancer. It is not yet known whether prostate cancer screening improves survival, although this question will hopefully be answered by ongoing clinical trials. While a global recommendation in favour of the practice is not currently warranted, there is considerable patient and physician demand for prostate cancer screening. It therefore appears reasonable to provide screening on request to men aged 50 years and older with at least a 10 year life expectancy, provided they are aware of the controversy surrounding the practice and of the possible implications of a positive or a negative result.*

**Badania przesiewowe w kierunku raka prostaty – uwagi praktyczne**

*Wprowadzone na przełomie lat osiemdziesiątych i dziewięćdziesiątych badanie PSA zrewolucjonizowało leczenie raka prostaty – tak w zakresie diagnostyki, jak i rokowania, aczkolwiek zarówno możliwości i ograniczenia tego badania nie są jeszcze zapewne w pełni poznane. Tylko niewielki odsetek przypadków raka prostaty ujawnia się klinicznie – więcej chorych umiera z rakiem prostaty niż na raka prostaty. Wprowadzenie badań przesiewowych umożliwi wykrycie raka prostaty również u tych chorych, którzy potencjalnie nie odniosą żadnej korzyści z leczenia, a zatem nie jest jasne, czy badania przesiewowe spowodują zmniejszenie śmiertelności z powodu tego właśnie nowotworu. Badania przesiewowe w kierunku raka prostaty powinny obejmować badanie poziomu PSA i badanie per rectum, jako typowe dla rozopoznania wczesnego raka prostaty. Nie wiadomo, czy badania przesiewowe poprawią przeżycie w raku prostaty, ale trwające obecnie badania kliniczne powinny dać odpowiedź na to pytanie. Jak dotychczas badania przesiewowe w tym kierunku nie są powszechne, ale istnieje duże zapotrzebowanie na ich wprowadzenie, wyrażane zarówno przez pacjentów, jak i przez lekarzy. Wydaje się być wskazane objęcie badaniami przesiewowymi mężczyzn powyżej 50 roku życia, którzy wyrażą chęć poddania się badaniu i których spodziewane przeżycie przekracza 10 lat pod warunkiem, że zostali poinformowani o kontrowersjach związanych z badaniem i o możliwych implikacjach, zarówno pozytywnych, jak i negatywnych wyników.*

**Key words:** prostate cancer, screening, cost-effectiveness
**Słowa kluczowe:** rak prostaty, badania przesiewowe, koszty leczenia

## Introduction

Prostate cancer is the most common form of cancer in men in Western countries and the second leading cause of cancer related mortality after lung cancer. The disease exhibits a wide spectrum of behaviour: it can be cured if discovered early but it is a slow-growing malignancy that may lead to an agonizing death if left untreated. Alternatively, many people may harbour prostate cancer without any signs or symptoms, with the tumour only to be discovered at autopsy. However, diagnosis often is complicated by co-morbid conditions, such as prostatitis or benign prostatic hypertrophy that are part of the normal aging process. Despite the theoretical benefits of early screening and detection, the impact on survival remains controversial and the dilemma lies in the long natural history of the disease. Many prostate cancers can be so indolent that a strategy of watchful waiting is a treatment option: hence early discovery of prostate cancer may not affect treatment outcome although it gives rise to much anxiety for patients and family. It is also remarked that currently many countries are undertaking opportunistic screening in that family practitioners order

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a prostate specific antigen (PSA) blood test only for the occasional concerned patients.

## Requirements for a screening programme with special reference to prostate cancer

The requirements for a screening programme can be defined under five main categories, Table I, of disease requirement, test requirement, availability and compliance, cost-effectiveness and avoidance of bias.

## Should screening be undertaken?

Proponents of screening emphasize that early detection can lead to discovery of organ confined disease and the potential for cure. Opponents point to the lack of credible evidence that screening is associated with a decrease in mortality. In addition, population based screening, with subsequent diagnosis and treatment in many men, can be associated with considerable treatment morbidity and mortality for a disease that is often not fatal. Therefore the risks of over-diagnosis (knowledge of having a cancer) and of overtreatment (impotence, incontinence, perioperative death) must be emphasised.

Two studies by the European Organization for Research & Treatment of Cancer (EORTC) [1] and by the Radiation Therapy Oncology Group (RTOG) [2], both for stage T3 disease, have shown that long-term androgen blockade prolongs life in patients receiving the androgen blockade in addition to radiotherapy, when compared to radiotherapy alone. For the EORTC study long-term was defined as three years, and for the RTOG study long-term was defined as indefinite.

In the United Kingdom Medical Research Council study, androgen blockade at diagnosis of locally advanced or asymptomatic patients decreased cancer-specific death compared to delayed treatment [3]. A 69% decrease in prostate cancer death was observed in the Quebec randomised prostate cancer screening study [4]. However there is a dispute if the decrease in mortality is related to recent advances in cancer treatment or early diagnosis of the prostate cancer. Population-based studies in Sweden and Denmark have shown that 62% and 63%, respectively, of patients diagnosed with localised prostate cancer will die from the disease if not treated immediately [5]. Decreases in prostate cancer death rate of 6.3-23% have been found between 1991 and 1997 in the USA and Canada, respectively. The treatment of localised disease has been shown in all the available randomised studies to cause a marked decrease in prostate cancer death [5].

As a rough estimate, the risk of a 50-year-old man with a 25-year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer is 9.5%, and of dying of prostate cancer is 2.9% [6]. Only a small proportion of cancers become clinically evident: more men die **with** the disease rather than **of** the disease. Screening will thus identify some men with cancer who

**Table I. Requirements for a screening programme**

| |
|---|
| Disease requirement |
| Detectable at the pre-clinical stage: *Yes* |
| Survival for early stage disease is better than late stage disease: *Yes* |
| Current treatment more efficacious at an earlier stage: *Yes* |
| Treatment agreed upon for all cases, especially those cases that are borderline: *No* |
| Prevalent: *Yes* |
| Major cause of death: *Yes* |
| Negative effect outweighed by the benefit: *Questionable*, because early treatment of detected cancers may give rise to overtreatment and unnecessary morbidity |
| Test requirement |
| Safe: *Yes* |
| Cheap: *Yes* |
| Sensitive: *Yes* |
| Specific: *Yes*, to a certain extent |
| Tolerable: *Yes* |
| Availability and compliance |
| Sufficient diagnostic and treatment facilities of adequate quality to manage the anticipated workload: *Depends* on individual countries |
| Physicians and other providers will comply with the recommended testing, treatment and follow-up protocol: *Yes* |
| Patients will comply with the testing, treatment and follow-up protocol: *Depends* on many factors, e.g. well-informed public, physician enthusiasm |
| Cost-effectiveness |
| How does the cost-effectiveness of the program compare with those of other health-care programs that are currently competing for the existing resources? *More research needed* |
| Avoidance of bias |
| Lead time *bias*: The cancer will be detected much more early before clinical manifestation |
| Length time *bias*: Due to the slow clinical course of the prostate cancer |
| Volunteer *bias*: Those with genito-urinary symptoms or well-informed are more likely to attend screening |
| Overdiagnosis *bias*: Because detected cancers may not be clinically significant |

will not benefit from treatment and it is unclear whether screening would be followed by a reduction in morbidity and mortality.

**Which populations should be screened?**

About 99% of prostate cancers occur in men over 50 years of age. Currently the application of screening to the general male population is still controversial even though some individuals are at high risk for prostate cancer. These high risk populations are: Africans, those with family history of prostate cancer [7, 8], those potentially linked to the hereditary prostate cancer 1 (HPC1) locus on chromosome 1q24-25 [9] and male carriers of BRCA1/2 mutations [10]. There is a 2-fold and 4-5 fold increased risk in men with one, or with 2 or more affected first-degree relatives respectively. There are no established modifiable risk factors [11].

**Which populations are missed in screening programmes?**

Which populations are missed in screening programmes? Compared with those who attend for screening, those who refuse screening tend to be significantly older, less often married and have a lower level of education. They also have less knowledge about prostate cancer and a less positive attitude towards screening; they have worse general health but fewer urological complaints (American Urological Association symptom score, AUA7 median 2 *versus 4*, $P<0.001$), as found from the European randomised study of screening for prostate cancer (ERSPC) in 1995-1996 [12]. Reasons for refusal were absence of urological complaints, 57%, and anticipated pain or discomfort, 18%. The main reported motives for attending screening were personal benefit, 82%, contribution to science, 49%, and presence of urological complaints, 25%.

**What are the best screening tests?**

In the past, digital rectal examination (DRE) and acid phosphatase were used but nowadays there are more useful parameters for screening such as PSA which is a very important test. In men with PSA <1.0 ng/ml, 1.0-1.9 ng/ml, 2.0-2.9 ng/ml and 3.0-3.9 ng/ml, the detection rate of prostate cancer was respectively 4%, 15%, 27% and 29%. Also, there were no significant racial differences in the PSA adjusted cancer detection rate or in the Gleason score of detected disease [13].

Cut-off values, sensitivity & specificity

The ratio of free prostate specific antigen (FPSA) to total prostate specific antigen (TPSA) in men is generally chosen for screening purposes to have a cut-off value of 0.15 in order to avoid unnecessary biopsies in men with serum TPSA concentration of 4-10 ng/ml. The predictive value of TPSA in this range was 21%, but the predictive value of the FPSA/TPSA ratio of 0.15 was better, at 78%, maintaining at least 90% sensitivity [14].

In patients with TPSA values in the range 4-10 ng/ml the cut-off value of the FPSA/TPSA ratio of 0.15 can be used to eliminate unnecessary biopsies with minimal loss of cancer patient detection. Patients with TPSA values of less than 4 ng/ml were biopsied if they had positive DRE and/or a FPSA/TPSA ratio lower than 0.15. Basso's finding also suggests that the FPSA/TPSA ratio is an excellent index [15]. However, on the contrary, a study using stored serum samples concluded that there was no material advantage in adding free to total PSA in prostate cancer screening trials [16].

As well as the measurement of the percentage FPSA, various other methods have been proposed to increase the specificity of PSA measurement as a screening test. These include age-specific PSA reference ranges and PSA density (PSAD) derived from PSA/volume of the prostate gland [17]. Age-specific PSA cut-offs miss 20-60% of cancers in men older than 60 years of age [18].

Percentage FPSA and PSAD performed equally well for detection of prostate cancer, both with a 95% sensitivity, if cut-offs of 25% FPSA or 0.078 PSAD were used. The commonly used PSAD cut-off of 0.15 detected only 59% of cancers. Percentage FPSA and PSAD also produced similar results for prediction of the post-radical prostatectomy pathological stage. Patients with cancer with high percentage FPSA values of >15% or lower PSAD values of ≤0.15, tended to have less aggressive disease. The results demonstrate that the sensitivity of cancer screening detection is significantly higher with percentage FPSA than with age-specific PSA reference ranges. Percentage FPSA and PSAD provide comparable results, suggesting that percentage FPSA may be used in place of PSAD for biopsy decisions and in algorithms for prediction of less aggressive tumours since the determination of percentage FPSA does not require ultrasound [18].

The complex between PSA and alpha1-protease inhibitor in serum can be used to reduce further the number of false-positive PSA screen results independent of the total and free PSA. In a Finnish study of 304 consecutive PSA screen positive subjects, including 78 with and 226 without prostate cancer, and serum PSA of 4-10 ng/ml or >10 ng/ml, the proportion of serum PSA-alpha1-protease inhibitor of total PSA was lower in cancer cases than in controls: (0.9% versus 1.6%, $P<0.001$). Serum PSA-alpha1-protease inhibitor improves the specificity of total and free PSA in a screening population with total PSA 4-10 ng/ml [19].

PSA density of the transition zone (PSATZD), derived from the PSA/volume of the transition zone, has been shown to be the most useful and valid method for the differentiation between prostate carcinoma and benign prostatic enlargement in the overall patient population and in patients with intermediate PSA levels [20]. Between October 1997 and August 1999, systematic sextant biopsies were performed on 281 patients, including 147 with PSA levels between 4.1 ng/ml and

10.0 ng/ml. The clinical values of PSA, the FPSA to TPSA ratio, alpha-1-antichymotrypsin-PSA complex (PSA-ACT), PSAD, and PSATZD for the detection of prostate carcinoma were compared by using receiver operating characteristic (ROC) curves and logistic regression analyses. According to the ROC curve analysis, PSATZD had the greatest area under the curve in the overall patient population and in patients with intermediate PSA levels. In patients with intermediate PSA levels, at a sensitivity of 90%, PSATZD would have prevented unnecessary biopsies in 68/117 patients who were without prostate carcinoma, whereas PSA, FPSA/TPSA ratio, and PSA-ACT would have prevented unnecessary biopsies in 25, 28, and 25 patients, respectively [20]. ROC curve analysis for PSATZD showed that by using a PSATZD >0.22 ng/ml/cc as a biopsy criterion, 24.4% of negative biopsies could be avoided without missing the detection of a single carcinoma [21].

An elevated PSA does not always mean adenocarcinoma of prostate, lymphoma can cause an elevated PSA [22]. On the other hand, the torti-potential nature of the basal or reserve cells normally present in the prostate acini theoretically may develop into mixed tumours. In the same gland, adenocarcinoma may develop in addition to lymphoma.

False-positive elevation of PSA has been reported due to disease processes outside the prostate gland with the use of the polyclonal assay. Such false-positive test results have been exceedingly rare with the use of the monoclonal assay. A case of B-cell lymphoma of the kidney had been reported to have a significant elevation of serum PSA levels by the monoclonal assay in the absence of either inflammatory or malignant prostate disease. PSA returned to normal during lymphoma-specific chemotherapy [23].

## What is the appropriate cut-off value for PSA screening?

It has recently been suggested that the diagnostic threshold for the PSA assay be lowered to enhance prostate cancer detection. A 24.5% (37/51) incidence of prostate cancer has been reported in men with PSA between 2.5 ng/ml and 4.0 ng/ml [24]. The age-adjusted upper PSA reference values for the three age categories studied of 55-59 years, 60-64 years and 65-70 years, were 5.2 ng/ml, 5.8 ng/ml, and 6.7 ng/ml, respectively [25].

In a screening setting the widely accepted 25-30% positive predictive value (PPV) for PSA >4.0 ng/ml may only apply to white males. A higher PPV of 36-60% is more accurate for black males [26]. Due to the observed higher age-specific serum PSA values in African-American males without prostate cancer compared to white males, this has led some to recommend race-specific PSA reference ranges for the early detection of prostate cancer. However Cooney has showed that among 432 African-Americans, the 95th percentile PSA values were estimated to range from 2.36 ng/ml for men in the fifth decade to 5.59 ng/ml for men in the eighth decade [27]. The 95th percentile values for age-specific PSA were comparable to those observed in a similar study of white males in Olmsted County, Minnesota. The median and 5th percentile values for FPSA/TPSA did not vary significantly with age. Cooney concluded that the minor differences in PSA reference ranges between African-American and white males may not be of sufficient magnitude to recommend the use of race-specific PSA reference ranges for screening.

## When should screening be performed?

PSA and DRE examination should be performed between the age of 50 and 70 years when life expectancy exceeds 10 years. In cases of positive family history the screening should start at the age of 40-45 years [9, 28, 29]. Annual screening seems to be reasonable to avoid missing interval cancers. However there are exceptions to this strategy: the combination of PSA levels <3.0 ng/ml and a percentage FPSA >18% defines a population at a very low risk of cancer of the prostate both at the time of screening and during the following five years. Men in this group may be spared DRE, and longer screening intervals may be considered [30].

Unfortunately due to increasing public awareness, physician liability for delay of diagnosis may be difficult to defend in the court. Hence more PSA tests are offered as a routine in the US and Canada.

## Is screening cost-effective?

To address cost-effectiveness, the Quebec prospective randomized controlled trial on 46,193 men aged 45-80 years, which was completed in November 1988, demonstrated for the first time that early diagnosis and treatment permits a dramatic decrease in deaths from prostate cancer [4]. But the result is still being disputed. The other randomized trial, the ERSPC that was performed in five European countries will not have results available until the year 2007 [31]. Similarly the National Cancer Institute prostate, lung, colorectal, ovarian cancer screening (PLCO) trial, which is a 16-year randomised control study that began in November 1993 cannot yet report any results [32].

The cost of screening was estimated to be 501 French Francs (FF) per person screened and 91,000 FF per cancer detected, based on a theoretical screening protocol and the epidemiological data available in France. The mean cost of curative treatment was estimated to be 44,000 FF per cancer. The theoretical global cost of screening and treatment was estimated to be between 4 billion FF and >10 billion FF [33].

Although men 50-70 years old will potentially benefit the most from PSA screening, this benefit will not be realised until they are in their seventh or eight decade of life. Society must therefore decide if the years of life saved in these men warrant the use of its limited health care resources. This decision will be easier to make when

more randomised, controlled trials are available to quantify the costs and benefits of PSA screening.

**What action to take following abnormal initial results?**

Treatment in older patients should be guided by health status and personal preferences. For those likely to die of causes unrelated to the cancer, should a biopsy be done?

What is the best biopsy technique? Although the sextant biopsy technique has been widely used, concern has arisen that this method may not include an adequate sampling of the prostate, especially for large prostates. In patients with a total prostate volume >45 $cm^3$ and transitional zone volume >22.5 $cm^3$, a single set of sextant biopsies may not be sufficient to rule out cancer. In these patients, a repeat biopsy should be considered in the case of a negative first biopsy [34].

Sometimes the biopsy may be reported as high-grade prostatic intraepithelial neoplasia (PIN). What to do about the presence of PIN is just as confusing and controversial as it ever was. PIN is a considerable risk factor for the presence of prostate cancer, with up to 73% of patients having cancer on rebiopsy. The World Health Organisation Collaborative Project and Consensus Conference on Public Health and Clinical Significance of Premalignant Alterations in the Genitourinary Tract [35] recommended the following. (1) Only patients considered for curative treatment of prostate cancer be further investigated for a PIN biopsy finding. (2) A palpable nodule or tumour suspicious transrectal ultrasonography (TRUS) finding, in conjunction with a finding of high grade PIN on prostate biopsy, should prompt rebiopsy. (3) An elevated PSA level or an elevated PSA density should also warrant repeat biopsy, as the most likely cause of PSA elevation is concomitant prostate cancer. (4) The presence of high grade PIN on biopsy without concomitant prostate cancer in patients suitable for curative treatment, notwithstanding normal DRE, TRUS or PSA, should prompt repeat biopsies, as the association with prostate cancer is significant. (5) The presence of PIN alone on biopsy does not warrant treatment, as a substantial number of rebiopsies yield only PIN.

Various approaches have been suggested for the prevention and treatment of high grade PIN. One approach may be to put patients on total androgen blockade since high grade PIN is androgen-dependent. Patients who are pretreated prior to surgery with hormone deprivation have less PIN at time of radical prostatectomy. As well, PIN is radio-sensitive, hence radiotherapy may be an option. The only way to learn about the natural history and treatment of this condition is to conduct trials.

The next step after biopsy proof is to decide if patient should be treated now or have watchful waiting. A Gleason score of 5,6, or 7 predicts slow progression. The doubling time of PSA should be checked on follow-up. Counselling of patient and family is required to alleviate anxiety for watchful waiting.

**Screening in the United States of America**

The prostate-specific antigen test was approved by the U.S. Food and Drug Administration in 1986 to monitor the disease status in patients with prostate cancer and, in 1994, to aid in prostate cancer detection. However, after 1986, the test was performed on many men who had not been previously diagnosed with prostate cancer, apparently resulting in the diagnosis of a substantial number of early tumours. There is indirect evidence from 208,234 prostate carcinoma cases diagnosed between 1973 and 1993 in the population based Surveillance, Epidemiology and End Results (SEER) program registries that prostate carcinoma screening of men age >50 years decreased the incidence of distant disease, which in turn influenced the mortality rate [36]. The most updated revised prostate cancer screening guidelines of the American Cancer Society recommend that men be informed of the risks associated with prostate cancer screening, e.g., impotence from treatment [36].

**Screening in Canada**

Retrospective data from the Saskatchewan Cancer Registry, one of the oldest provincial registries in Canada, showed there is no survival difference of prostate cancer patients before and during the PSA era [37]. However, a prospective randomised controlled trial in Quebec on 46,193 men aged 45 to 80 years showed a survival benefit for screening [4]. At first visit, screening included a DRE and a measurement of serum PSA using 3.0 ng/ml as the upper limit of normal. TRUS was performed only if PSA and/or DRE was abnormal and biopsy was then performed, only if PSA was above the predicted PSA value. At follow-up visits, PSA alone was used as pre-screening. 137 deaths due to prostate cancer occurred during the period 1989-1996 in the 38,056 unscreened men while only five deaths were observed among the 8,137 screened individuals. The prostate cancer death rates during 1989-1996 were 48.7 and 15 per 100,000 man-years in the unscreened and screened groups, respectively, for a 3.25 odds ratio in favour of screening and early treatment, $P<0.01$. It was concluded that if PSA screening is started at the age of 50 years, or at 45 years in the higher risk population; annual or biannual PSA alone is highly efficient to identify the men who are at high risk of having prostate cancer. Coupled with treatment of localised disease, this approach demonstrates, for the first time, that early diagnosis and treatment permits a dramatic decrease in deaths from prostate cancer [4]. However its result has been disputed.

Due to the shortage of radiation technologists, oncologists and diagnostic radiologists in Canada, the impact of routine screening for prostate cancer will be very great. It will drain a lot of resources from the

universal Medicare system. Currently, PSA screening is not done on a population basis.

**Screening in the United Kingdom**

In the United Kingdom, a 1997 national guidance executive letter EL(97)12 stated that population screening should not be provided by the National Health Service, or be offered to the public until there is effective screening technology for prostate cancer. However, it has recently been reported in the press, *The Sunday Times* of 25 March 2001, that the UK Government has changed its position and some limited form of screening will be introduced sometime in the future.

**Screening in the Netherlands**

The evaluation of the screening procedures for prostate cancer was a part of the protocol of the European randomized study of screening for prostate cancer (ERSPC) [38]. In June 1996, 8612 men, aged 55-74 years were randomised and were screened within the ERSPC in Rotterdam by a PSA level of ≥4.0 ng/ml or a positive DRE or TRUS findings as the indication for biopsy: 430 men had prostate cancer. The protocol was changed in February 1997 and another 7943 men were screened according to the new protocol of a PSA level of ≥3.0 ng/ml. The resulting data were used to compare the two protocols.

The detection rate, defined as the proportion of cancer in those screened, was found to be very similar with rates of 5.0 and 4.7 at PSA cut-offs of respectively ≥4.0 ng/ml and ≥3.0 ng/ml. There was a much larger number of cases of prostate cancer per biopsy in the PSA range of 3.0-3.9 ng/ml than were expected. Tumour characteristics were studied on radical prostatectomy specimens from the original protocol. Prostate cancer detected with the new screening regimen had a similar distribution of Gleason scores but a larger proportion of organ-confined disease. Tumour volumes were smaller in patients with PSA levels of less than 2.9 ng/ml; the proportion of *minimal disease* in that group was 50% compared with 28% in the group with a PSA level 3.0-3.9 ng/ml. Changes were noted in the incidence and treatment of prostate cancer over the period in which new diagnostic tools were introduced within the Rotterdam region. In the period 1989-95, 4344 patients were diagnosed with prostate cancer and the age-standardized incidence increased from 62 to 125 per 100,000 men. This increase mainly comprised of tumours localized to the prostate, while the incidence of advanced cancers remained stable. The proportion of poorly differentiated tumours decreased from 33% in 1989 to 24% in 1995. In the same period the number of patients receiving radiotherapy increased from 80 to 258, while the annual number of radical prostatectomies rose from 17 to 159 [39].

**Screening in Germany**

In Germany, men are entitled from aged 45 years to one annual examination for early detection of cancerous diseases and this examination is funded by the insurance system. In the age group around 60 years about 15% of the men participate and among 1,341,833 men participating in 1987 a total of 1,638 new cases of prostate cancer were detected. The survival rate of patients treated by total prostatectomy is comparable to that of the general population, when adjusted for age distribution and it is possible that screening for prostate cancer might reduce the mortality of the disease [40].

**Screening in Austria**

Horninger summarised the Austrian experience of different prostate carcinoma screening projects: a PSA cut-off of 2.5 ng/ml in men aged 45-49 years and of 3.5 ng/ml in men aged 50-59 years resulted in an 8% increase in the detection rate of organ-confined disease [41]. A total of 284/2272 (13%) had elevated PSA levels and prostate carcinoma was detected in 62 of this group (3%). All underwent radical prostatectomy and histological examination revealed organ confined tumour in all but eight. 98/340 (29%) had biopsies positive for carcinoma; 28 of these patients (29%) had carcinoma that originated in the transition zone only. In the second prospective study, 120/465 (26%) with total PSA levels between 1.25 ng/ml and 6.49 ng/ml and a percentage FPSA<18% were further evaluated and 27 (23%) were found to have prostate carcinoma. ROC curve analysis for PSA transition zone density showed that by using a PSA transition zone density of >22 ng/ml/cc as a biopsy criterion, 24.4% of negative biopsies could be avoided without missing a single carcinoma. High total PSA levels, PSA density and PSA transition zone density correlated significantly with high Gleason scores, capsular penetration, a high percentage of cancer in the prostatectomy specimen and a high cancer volume.

**Screening in Sweden**

A Swedish population based screening study was undertaken in 1988-1989 [30]. 1782 men responded and were examined with DRE, TRUS, and PSA testing (Tandem-Hybritech). Of 1748 men a total of 367 underwent TRUS guided biopsies because of abnormal findings on either DRE or TRUS or serum PSA levels of greater than 10 ng/ml. This resulted in the diagnosis of 64 cases of prostate cancer (3.7%). PSA levels of ≥3.0 ng/ml were found in 55 (86%) of 64 cancer cases and in 399 (24%) of the 1684 benign cases. Among the 1294 with PSA <3.0 ng/ml, nine prostate cancers were diagnosed. This accounted for 14% of all prostate cancers. All 9/1294 with cancer and with PSA <3.0 ng/ml had a percentage FPSA of ≤18%. In the group of 1109 with PSA <3.0 ng/ml and a percentage FPSA >18%, 159 biopsies were performed because of abnormal DRE or TRUS.

However, no prostate cancer was diagnosed in this category of patients. Five years after the screening intervention, seven more cases of prostate cancer were clinically diagnosed in the screened population according to the Swedish Cancer Registry [30].

**Screening in Finland**

Approximately 20,000 men aged 55-67 years from two areas in Finland were identified from the Finnish Population Registry and randomised either to the screening arm (1/3rd) or the control arm (2/3rd) of a prostate cancer screening trial [31]. In the first round of the study the participation rate in the screening arm was 69%. Of the 5053 screened participants, 428 (8.5%) had a PSA concentration of ≥4.0 ng/ml and diagnostic examinations were performed on 399. A total of 106 cancers were detected among this group, corresponding to a positive predictive value (PPV) of 27%. The prostate cancer detection rate based on a serum PSA concentration of ≥4.0 ng/ml was 2.1%. Approximately 90% of screening detected prostate cancers were localised, 85% were clinical stage T1-T2, and well or moderately differentiated. A total of 42% were World Health Organization grade I and 50% were grade II, which suggests a higher proportion of curable cancers compared with cases detected by other means [31].

**Screening in Asia**

Reports of prostate cancer screening are mainly from Indonesia and Japan. PSA and PSAD values in Indonesia have been found to be uniquely much higher than the normally accepted values in Western countries [42]. The most sensitive cut-off points to perform prostate biopsy were a serum PSA level >8.0 ng/ml, and a PSAD of >0.19 at an intermediate serum PSA level of 8-30 ng/ml [17]. The ROC curve revealed an optimum cut-off level of 0.19. At this level of PSA density, the sensitivity of the screening test was 100% and the specificity was 79%. The study authors concluded that in their uncatheterized patients (without retention) series, the PSAD cut-off level for prostate biopsy of 0.19 was higher than that in the Western world: 0.12 or 0.15 [42].

Since 1975 mass screening for prostate cancer has been performed in Japan and the Prostate Research Foundation has analysed the data every year that are collected from all institutes performing a mass screening [43]. Up to 1993, a total of 67, 225 subjects have been examined and the detection rate of prostate cancer was 0.69%. Approximately half of the cancers were stage B and those who had metastatic stage were only 20%. The percentage of subjects with PSA levels of 0.05-4.0 ng/ml, 4.1-9.9 ng/ml and ≥10.0 ng/ml were respectively 89.6%, 7.0% and 3.4%. This distribution is approximately as the same as previous reports from the United States and Canada [43].

Ito reported on the mass screening for prostate cancer in 9671 subjects during the period 1986-1998. The initial screening method was measurement of prostatic acid phosphatase during 1986-1991 and measurement of PSA for the period 1992-1998. As a result, 303 cases of prostate cancer were diagnosed. The prostate cancer detection rate was 3.1% among all subjects observed during the 13-year period. 62% of patients demonstrated a PSA abnormality for more than one year, on average 2.8 years, before prostate cancer diagnosis. Prostate cancer that was diagnosed within one year after a PSA value became abnormal was not associated with bone metastasis. Concerning the relationship between PSA velocity (PSAV) and clinical stage, the proportion of stage B cancers was 86% in the subjects whose PSAV level before diagnosis was ≤0.18 ng/ml/year and it was only 29% in those with PSAV levels of ≥4.5 ng/ml/year. Only 3/86 (3.5%) with prostate cancer with PSAV levels of ≤4.4 ng/ml/year had bone metastasis, and two of these three patients had poorly differentiated adenocarcinoma [44].

**Screening in Africa**

Despite the absence of screening programs in Nigeria, the number of prostate cancer cases has increased in the Nigerian cancer registry, 1980-1996. Prostate cancer has become the highest ranked cancer for incidence in Nigerian men and constitutes 11% of all male cancers. The median age of patients was 67.5 years and the mean age was 71.4 years [45].

**Conclusions**

Prostate cancer is the most common cancer in men in the Western world. The increasing prevalence of prostate cancer can be attributed to a number of causes, including relatively new detection modalities, the increasing life span, and increased public awareness of the disease. The increased awareness has resulted from information in the lay press, recognition of prominent public figures who are living with or have died from prostate cancer, and an increasingly informed public. Currently one randomised study from Quebec, Canada, has shown a survival benefit. We eagerly await the results from the European and American randomised studies. In addition, we also need to find out the most effective method of screening in order to minimise costs, unnecessary biopsies and the anxiety of the general public.

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