Review Article

The routine use of prostate-specific antigen for early detection of cancer prostate in India: Is it justified?

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ABSTRACT

Background: The use of prostate-specific antigen (PSA) for early detection of prostate cancer is a widely debated issue. The average Indian urologist is faced with the dilemma of whether PSA testing should be routinely offered to men over 50 years of age. The Urological Society of India is yet to issue any guidelines on PSA testing. This article attempts to explore scientific evidence dealing with this controversial subject.

Materials and Methods: A MEDLINE search was performed using the words 'PSA screening', 'prostate cancer statistics', and 'PSA screening guidelines'. The relevant articles were then analysed for evidence regarding the utility of PSA screening.

Results: Prostate cancer does not qualify to be categorized as a major health problem in India. The natural history of screen-detected cancer is not known. Prostate-specific antigen testing for early detection of prostate cancer has questionable benefits and has a potential to cause harm to asymptomatic individuals. There is no consensus amongst learned medical societies as to what should be the best approach for PSA testing. Most organizations caution against widespread PSA screening and emphasize on informed consent and patient counseling with regard to PSA testing. Randomized prospective trials are ongoing to assess to the true impact of screening on prostate cancer mortality.

Conclusions: There is no scientific rationale to advocate routine use of PSA for early detection of prostate cancer in Indian males. Results of randomized screening trials are awaited to clarify on this issue.

Key words: Prostate cancer, prostate-specific antigen, screening

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INTRODUCTION

The last couple of decades have been witness to a revolution in the methods used for the diagnosis and management of prostate cancer. One of the most hotly debated issues has been the use of prostate-specific antigen (PSA) for early detection of prostate cancer. Literature regarding early detection of prostate cancer emanates predominantly from American and Western European centers, regions where the incidence of prostatic carcinoma is amongst the highest in the World. Use of PSA for screening of prostate cancer has largely been a North American endeavor.[1,2] However, even in the USA, which has the highest incidence of prostate cancer, there is no consensus regarding PSA screening. The American Cancer Society[1] and the American Urological Association[2] recommend an annual PSA test for asymptomatic men above the age of 50 years. The American College of Preventive Medicine[3] and the US Preventive services task force[4] conclude that there is an insufficient evidence to recommend routine population screening with DRE or PSA. The National Health Service of the United Kingdom does not recommend screening,[5] even though the burden of prostate cancer is significant in that country. It is therefore evident that the medical community is deeply split on the benefits of PSA screening even in countries where prostate cancer is a major health problem.

Given this background, most Indian urologists are unsure about the real implications of ordering a PSA test to an asymptomatic Indian male aged above 50 years. This article attempts to explore the issue of use of PSA for early detection of prostate cancer, which should hopefully provide the Indian urologist with a correct perspective on this highly controversial topic.

PRINCIPLES OF SCREENING

Early detection attempts to identify preclinical and asymptomatic cases of a disease in a population at risk using a suitable test, rather than making a diagnosis based on a patient's presentation at a later stage with symptoms and signs. This

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objective can be achieved by employing screening methods, which can be broadly categorized into two types:[6]

1. **Organized screening:** A large number of populations at risk are invited for screening and the process is monitored by an independent authority.

2. **Opportunistic screening:** Patient asks doctor or doctor orders a test on the patient. This process is unmonitored.

In India and other parts of the world, most urologists and general physicians resort to 'Opportunistic screening' whilst ordering for a PSA test. This article debates the use of both organized and opportunistic screening for prostate cancer in India. The question to be answered is: Does routine testing for PSA in asymptomatic men make any sense from a public health perspective?

To answer this question there are seven key questions that need to be addressed:

Is the disease a substantial health problem in Indian males?

Prostate cancer is the most commonly diagnosed male malignancy and the second leading cause of male cancer death in the USA.[7] However, the incidence of prostate cancer varies from country to country, with the highest incidence being found in the Western world and the lowest in the Asian countries. Data obtained from the International Agency for Cancer Research (IARC) suggests very low incidence of prostate cancer in East Asian countries[8] [Figure 1]. In India, prostate cancer is also identified as only the 10th common malignancy affecting men.[8] Numerous factors like contrasting genetic, environmental, and dietary influences may be responsible for the low incidence of prostate cancer amongst Asian populations. Recent studies have demonstrated a significant impact of diet on prostate cancer.[9,10] East Asian diets have been traditionally vegetarian and low in fat content. A diet rich in phytoestrogens, which is found in vegetarian diets, and soy products has been associated with a protective mechanism against prostate cancer.[11] There is a growing evidence that curcumin (turmeric) and a diet rich in vegetables has a significant protective effect on prostate cancer growth.[12-14] These dietary factors could be responsible for the low incidence of prostate cancer in India.

The Indian cancer registry

There is no comprehensive information available on the actual incidence of prostate cancer in India. Efforts have been made by the Indian Council of Medical Research (ICMR) to collect data through the National Cancer Registry. The boost for cancer registration in India began in 1982, through initiation of the National Cancer Registry Program (NCRP) by the Indian Council of Medical Research. The NCRP began with three population-based registries (existing Bombay registry and new registries at Bangalore and Madras) and three hospital-based registries (at Chandigarh, Dibrugarh, and Trivandrum). The data from cancer registries helped in highlighting the magnitude and common sites of cancer in India, and was useful in planning the National Cancer Control Program. The network of population-based cancer registries under NCRP is proposed to be expanded.

There are limited data on cancer incidence available from population-based cancer registries in India which have been published by the ICMR. The most established cancer registry for rural areas in India is at the Nargis Dutt Memorial Hospital at Barshi, Sholapur, Maharashtra. The 'Population-Based Rural Cancer Registry' was commenced under the auspices of ICMR under the NCRP in 1987. At this hospital, the top five male cancers that were identified were hypopharynx, oesophagus, rectum, lung and liver.[15] Similarly, a population-based cancer registry in rural Tamil Nadu showed extremely low incidence of prostate cancer with more than 50% cancers in males involving the head and

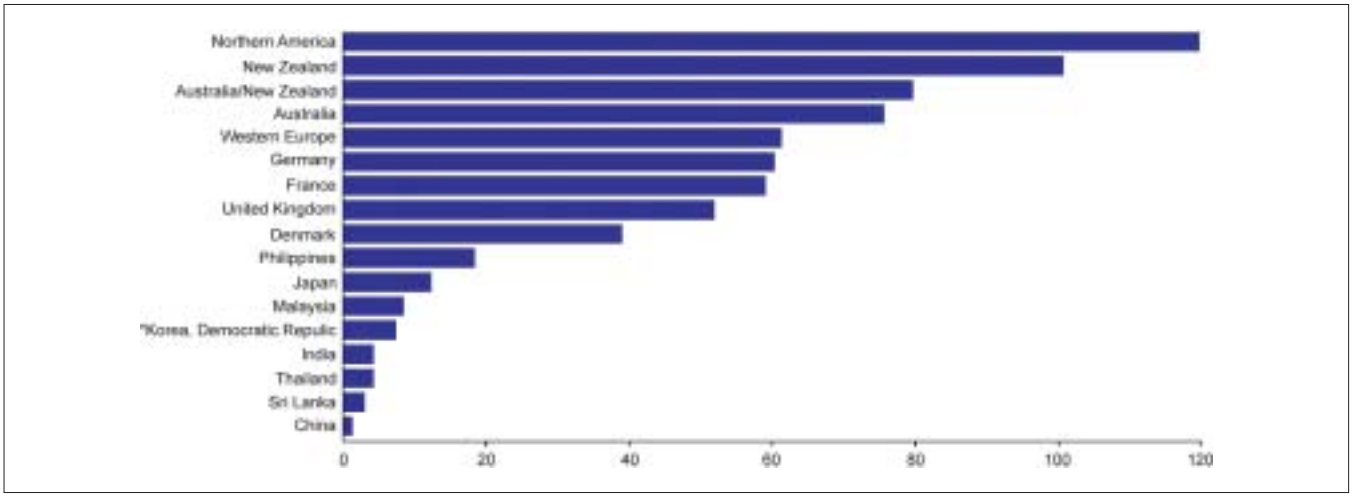

Figure 1: Worldwide statistics of prostate cancer incidence. (adapted from Vol. VIII. Lyon: International Agency for Research on Cancer; International Association of Cancer Registries, 2002)

neck region.[16] The Kolkata population-based cancer registry recorded prostate cancer as the sixth most common cause of cancer in males with the highest incidence of lung cancer followed by cancers of the oral cavity.[17] In cancer registries of Mumbai, Ahmedabad, Chennai, and Bangalore, prostate cancer was the fourth, ninth, ninth, and fifth most common cancer, respectively, amongst males, clearly highlighting the fact that prostate cancer is not a major health problem in India.[15] This data, though skewed, provides some insight into the burden of prostate cancer in India. It is therefore reasonable to conclude that there is no evidence to suggest that prostate cancer is public health problem in India which is in stark contrast to the situation in Western countries.

Is the natural history of the disease well understood?

Many men have a greater chance of dying with, rather than because of, prostate cancer. Whilst the lifetime risk of having a microscopic focus of prostate cancer at the age of 50 years is 42%, the risk of dying from prostate cancer is 3%.[18] Thus, a large number of prostate cancers follow an indolent course, without presenting clinically. Two longitudinal studies with more than 15-year follow-up have demonstrated that, in the large majority of cases detected (by palpation) in the pre-PSA era, prostate cancer progressed very slowly, with death due to other causes most commonly intervening before the cancer becomes life-threatening.[19,20] Short-term monitoring studies of highly selected older men with PSA-detected, nonpalpable, localized prostate cancer do not suggest that delayed or no treatment leads to poor health outcomes.[21,22] Prostate-specific antigen screening results in over-detection (of cases which would otherwise not have been detected) and introduces a lead-time (the time difference between screen detection and clinical detection) in the absence of screening, which may be of the order of 10 years or more.[23] It is therefore logical to assume that the natural history of screen-detected cancer would follow a more prolonged course than that of clinically detected cancer from the pre-PSA era. This is important for men faced with the choice between conservative and curative treatment. In comparison with clinically detected disease, men with screen-detected cancers will have longer to endure any adverse effects of curative treatment and longer to wait for any beneficial effect on survival to emerge.

Whilst there is currently no standard definition for 'clinically significant' prostate cancer, this term may include prostate cancers at risk of progression and which, without screening, would be lethal.[24] Cancers are considered insignificant if their volume is <0.5 cc and there is absence of Gleason 4 or 5. It is likely that a large proportion of screen-detected prostate cancers may never become clinically significant, as shown in a recent analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC).[25] Prostate cancer screening programs should ideally detect a low proportion of 'insignificant' cancers;[26] however, it is estimated that between 18 and 85% of screen-detected prostate cancers may never become clinically significant,[23,27] representing a considerable burden of 'overdiagnosis' and potential overtreatment. Not more than approximately 1 in 8 screen-detected prostate cancers is likely to cause mortality if left untreated.[28]

The knowledge of the natural history of prostate cancer is, however, currently limited to clinically diagnosed cases, whilst little is known of the natural history of screen-detected prostate cancer. It is hoped that greater insight regarding the natural history of screen-detected cancer will soon be obtained from analysis of ongoing randomized trials in Europe and the United States.[29,30]

Does performing the test improve patient outcomes?

Once prostate cancer is detected on biopsy, it remains unclear as to what is the best treatment option. The traditional approach includes radical prostatectomy, radical radiotherapy, brachytherapy or watchful waiting. Bill-Axelson *et al.*,[31] conducted a randomized prospective trial comparing watchful waiting with radical prostatectomy (RP) for the management of localized prostate cancer. This trial demonstrated that prostate cancer mortality was significantly lower in the RP group (30 of 347, 8.6%) vs watchful waiting (50 of 358, 14.4%). The absolute risk in reduction of death from prostate cancer was small (approx. 5%); however, reductions in risk of progression and metastasis was substantial. In a recent update of the trial, there was no extended benefit in survival and metastasis, even after a 10-year follow-up.[32] The 5% absolute improvement in 10-year survival was achieved at the expense of a 35% absolute increase in the risk of erectile dysfunction and a 28% absolute increase in the risk of urinary leakage.[33] Only 12% of patients in the Scandinavian trial had stage T1c disease, and as many as 19% of patients had a PSA level of >20 ng/mL. How can the outcome data, based largely on clinically detected prostate cancer, be applied to men with screen-detected disease? At present, insufficient time has elapsed to observe the natural history of screen-detected prostate cancer; however, it is interesting to compare the 10-year prostate cancer-specific mortality rate of 14.9% for watchful waiting reported by Bill-Axelson *et al.*,[31,34] with the 15-year rate of 7.4-11.6% for screen-detected disease predicted by Nicholson and Harland.[34]

Given the more favorable natural history of screen-detected disease, it seems likely that the absolute survival benefit of treatment will be less compared to treatment of clinically detected prostate cancer. There are two ongoing randomized trials that will address this issue.[29,30] The results of these trials will be important in helping to define the magnitude of the survival benefit for the radical treatment of screen-detected, rather than clinically detected, prostate cancer.

In terms of 10-year freedom from distant metastasis, the absolute benefit of surgery vs watchful waiting was 10% (84.8 vs 74.6%, $P = 0.004$).[31] Hence it could be argued

that 90% of patients did not benefit significantly from RP. Is it possible to identify these patients before surgery? One approach to this problem is active surveillance, in which radical treatment is targeted to those patients with biochemical or histological progression during a close-observation period.[35] This is by contrast to traditional watchful waiting, as specified in the Scandinavian trial, according to which palliative treatment is given to those with symptomatic progression.

Is the test accurate (high sensitivity and specificity)?

Although PSA is the most commonly performed screening test for the early detection of prostate cancer, its performance is very poor. There is no specific cut-off level for PSA to reliably detect prostate cancer. The normal accepted cut-off of 4.0 ng/ml is being seriously challenged because at this level PSA has a sensitivity of only 67.5-80%.[36] In other words, approximately 20-30% of tumors will be missed if PSA alone is used. Also the specificity of PSA testing is 60-70%[37] when the PSA level is 4.0 ng/ml. Prostate cancer may be present in significant proportion of men with a serum PSA <4.0 ng/ml. In a recent prostate biopsy series, positive biopsy rates for prostate cancer in men with serum PSA 2-4 ng/ml are nearly the same as a serum PSA of 2-20 ng/ml.[38] In fact, positive prostate biopsy rates consistently increase with age at PSA levels between 4 and 10 ng/ml with normal digital rectal examinations.[39] Stamey *et al.* (2004) concluded that PSA in the range of 4-10 ng/ml correlates more strongly with benign prostatic hyperplasia (BPH) than with prostate cancer.

Between 1995 and 2001, a large American study screened 6691 men for prostate cancer using PSA. The study showed that the diagnostic performance of total PSA using a threshold of 4 ng/ml was poor. The results indicated that if biopsies were performed only when the PSA was higher than 4 ng/ml, then 82 and 65% of cancers in men below 60 years of age and over 60 years of age, respectively, would be missed.[40] It was demonstrated that as PSA threshold is lowered, there is an improvement in sensitivity with a trade-off in specificity.

An analysis of the prostate cancer prevention (PCP) trial[41] also demonstrated low sensitivity with a PSA cut-off of 4.0 ng/ml: with this cut-off only 20.5% of the prostate cancer cases tested positive and nearly 80% cancers would have been missed. Lowering the PSA threshold for screening increases detection of aggressive cancer at an earlier stage; however, it has the unavoidable trade-off of increased detection of biologically irrelevant cancers.[42] Therefore, a positive screening test does not necessarily mean that an individual is certain to have a cancer, nor does a negative screening test result always confirm the absence of a cancer. Hence PSA, when used alone as a screening test has a poor specificity and sensitivity. Given the above limitations, serum PSA alone does not fulfil the criteria to be labeled as a valid screening test for prostate cancer.

There is evidence that prostate cancer screening decreases mortality

If it were to be convincingly demonstrated that screening reduces prostate cancer mortality then, the case could be made to implement screening and early detection protocols. However, this has not been forthcoming as yet. Widespread PSA screening in the USA began in the early1990s and toward the end of the decade, prostate cancer mortality has shown a declining trend.[43,44] Many authors advocate this decline in mortality due to aggressive PSA screening. Such a sudden decline so soon after the introduction of a screening test for a cancer known for its long latency is unexpected, and is unusual when one considers that the test was in use in the context of controlled clinical trials rather than among the general public until the late 1980s. One cannot exclude the potential contribution of the lead-time and length biases, increased awareness of prostate cancer, increased awareness of screening for prostate cancer, and improved surgical, radiation, and hormonal treatment for early and advanced prostate cancer, to the observed decline in mortality.

Other factors like the increased use of cholesterol-lowering agents (statins), which have an inhibitory effect on prostate cancer and dietary and lifestyle changes may partly account for this decline in mortality.[45]

There has been a paucity of properly conducted prospective clinical trials to observe the impact of screening on prostate cancer mortality.

Prostate cancer mortality in the Tyrol region of Austria, where PSA testing was widely available and encouraged, was compared with mortality in the rest of Austria where the test was not introduced.[46] A reduction in prostate cancer mortality was observed in the Tyrol region compared with the rest of Austria, but the reduction occurred far sooner than may be expected from the application of screening alone.[47] Recently, a study of two cohorts of men from regions with different practice patterns in the United States was reported.[48] Men in Seattle-Puget Sound received a higher exposure to screening and aggressive treatment for prostate cancer than men in Connecticut, with a five-fold difference in PSA testing and RP; however, no significant reduction in the adjusted rate ratio of prostate cancer mortality was observed.

Two randomized controlled trials for prostate cancer screening have been performed. The Quebec trial[49] commenced in 1988 and recruited men aged 45-80 years registered on the 1985 electoral rolls of Metropolitan Quebec City, Canada, and traceable on the health registries. A total of 46 193 men were randomized; 2 : 1 in favor of being invited to screening. Prostate cancer mortality was the primary outcome measured at 11-years follow-up. Eleven years after the commencement of the study, the authors of

the Quebec study reported the relative risk of death from prostate cancer to be 0.39 (95% CI: 0.19-0.65) in men who are screened.

The Quebec study was limited by the lack of adherence to screening from participants randomized to the screening group. Although 31 133 men were randomized to receive screening for prostate cancer, only 23% of participants in this group actually complied with the randomization and were screened. Similarly, approximately 7% of men randomized to the control group were screened for prostate cancer. Therefore, crossover between groups was a significant problem in this trial. Data analysis was also compromised; mortality data was not analysed according to the intention-to-screen principle. The authors of the trial reported a reduction in prostate cancer-specific mortality by comparing mortality in men who were screened to that of men who were not screened, regardless of their initial randomization. Conversely, when this data was analysed, according to the intention-to-screen principle, no significant difference in mortality between the two groups was demonstrated.[50,51] Due to these methodological issues, results from this trial do not give a clear indication of any true benefits or harms associated with screening for prostate cancer.

The Norrkoping trial[52] commenced in 1987 and recruited men from Norrkoping, Sweden, aged 50-69 years registered on the 1987 national population register. A total of 9026 men were identified, with every sixth man 'randomized' to screening. This study was also criticized due to its methodological flaws. Furthermore, the quasi-random method of allocation, lack of allocation concealment, and potentially unblinded outcome assessment compromise the quality of the trial. Both the Quebec and Norrkoping studies have on critical appraisal[51] been found to be biased in terms of methodology. There are two ongoing randomized clinical trials to assess the impact of screening on prostate cancer mortality (the ERSPC, Rotterdam and PLCO, USA). Results from these studies would throw some light on this controversial aspect.

Adequate facilities exist to cope with abnormalities detected

Prostate-specific antigen is obtained from different laboratories in India and there is no standardization. Once PSA is abnormal, there is a need to perform ultrasound-guided transrectal prostatic biopsy. However, this facility is limited to very few centers in India. Also, further treatment in the form of radical prostectomy/radical radiotherapy is not standardized in various centers across India. Given this scenario, it is evident that facilities are inadequate to cope with abnormalities detected in PSA screening program. Therefore mass screening and especially the trend amongst general physicians to order for a PSA test should be discouraged.

Will performing the test likely to cause harm to individuals?

A large number of patients with an elevated PSA are unlikely to have prostate cancer. However, once they know that PSA elevation can be associated with prostate cancer, they resort to regular and frequent PSA checks and this becomes a source of anxiety. Moreover, prostate biopsy is also associated with complications. Radical treatment for prostate cancer may also be associated with harmful side-effects. A randomized control trial demonstrated that RP for palpable disease offers a 5% absolute benefit in terms of 10-year survival; but a 35 and 28% absolute increase in the risk of erectile dysfunction and urinary incontinence, respectively. Studies investigating the impact of screening on healthy individuals[53,54] have demonstrated that PSA screening can cause significant psychological harm to individuals who have false-positive PSA tests. A recent review has concluded that PSA screening is associated with psychological harms and its potential benefits remain uncertain.[55]

Given these arguments, it is evident that prostate cancer is not a major health problem in India, the natural history of screen-detected prostate cancer remains unknown, the PSA test is not reliable for the diagnosis of prostate cancer, and there is no convincing evidence that screening for prostate cancer decreases mortality. Also PSA screening has been found to be associated with significant psychological harm amongst those without prostate cancer. There appears to be no justification for mass or opportunistic screening for prostate cancer in India.

THE POSITION ADOPTED BY VARIOUS LEARNED SOCIETIES WORLDWIDE ON THE ISSUE OF PSA SCREENING

In spite of the high incidence of prostate cancer in North America and Europe, there is a significant difference of opinion amongst learned medical societies and government organizations regarding the use of PSA screening [Table 1].

What does this mean for urologists in India, should they order a PSA test for men older than 50 years?

With so much hype regarding PSA screening, many elderly patients are concerned whether they should undergo a routine PSA test. The American Urological Association[1] and the American Cancer Society[2] recommend PSA testing as a part of 'shared decision-making' between the patient and the urologist. This means that the urologist should explain both the advantages and disadvantages of undergoing a PSA test and offer it only as a part of informed consent. However, there seems to be no consensus regarding what should be conveyed to the patient as a part of the informed consent.[65,66] Moreover, the opinion regarding informed consent for PSA testing is divided among urologists with there being no widely accepted guideline.[67,68] The British Association of Urologists[61] suggests the following points to

Table 1: Position of various learned societies worldwide on the issue of prostate-specific antigen screening for asymptomatic men

Recommendation for screening of asymptomatic men with informed consent after education concerning risks and benefits	American Urological Association[1] American Cancer Society[2]
Recommendation against screening of asymptomatic men	Canadian Task Force on Preventive Health[56] US Task Force on Preventive Health[3] National Cancer Institute[57] American Academy of Family Physicians[58]
Recommend against screening of asymptomatic men but test should be provided on patient demand after counseling of risks and benefits.	National Health Service (UK)[5] American College of Physicians[59] American Medical Association[60] British Association of Urologists[61] European Urological Association[62] European Union[63] Canadian Urologic Association[64]

be incorporated while counseling a patient for the PSA test.

1. The test may detect a cancer and a stage where curative treatment can be offered
2. That the test may detect early prostate cancer in around 5% of men aged 50-65 years
3. That the test will fail to detect some early tumors
4. Prostate-specific antigen testing and subsequent treatment of early prostate cancer may incur risk and may not improve life expectancy in all men

The recommendations of the Department of Health, Govt of UK[69,70] are indicated in Table 2.

Studies indicate that very few patients are actually informed about the PSA test. In a survey published in 2001, hardly 17% of physicians reported that they would decide whether to order a PSA test based on patient preferences.[71] Another study reported that only two-thirds of men who are screened even know that they have been tested.[72] These data suggest that minimal shared decision-making is occurring. Whether informed consent should be used for the average Indian patient is debatable as people in this country are less aware about prostate cancer as compared to their Western counterparts.

This issue is especially pertinent when applied to the majority of Indian patients, especially those with lower level of education and those belonging to the lower socioeconomic class. Interestingly, when informed consent was used for PSA testing in members of the lower socioeconomic class, they were found to be significantly less interested in undergoing the PSA test as compared to those who were not offered informed consent.[73]

Dr Steven Wolf, in an editorial in the American Journal of Family Medicine[74] makes a succinct comment regarding this dilemma: 'Just as the patient must decide, based on personal values, whether the benefits outweigh the risks, the physician must decide whether what is gained by circumventing the challenges of shared decision making is offset by its harms to the patient and physician. It is a personal choice that only conscience, not guidelines, can dictate.'

Table 2: Benefits and disadvantages of prostate-specific antigen (PSA) testing to be conveyed to men whilst counseling for PSA screening.[68,69]

Benefits	Disadvantages	Comments
It may provide reassurance if the test result is normal	It can miss cancer and provide false reassurance	Up to 20% of men with clinically significant prostate cancer will have a normal PSA
It may find cancer early	It may lead to unnecessary anxiety and medical tests when no cancer is present	Conditions such as benign prostatic hyperplasia (BPH), prostatitis, and urinary tract infection can also cause an elevated PSA Men with an elevated PSA will require prostate biopsy to obtain tissue on which a diagnosis can be made. About two-thirds of men with an elevated PSA do not have prostate cancer.
It may detect cancer at an early stage when treatments could be beneficial.	It might detect slow-growing cancer that may never cause any symptoms or shortened lifespan.	Men are more likely to die with prostate cancer than of it. By the age of 80 years, about 60-70% of men will have some cancer cells in their prostate. However, only around 1 in 30 of these men will die of their prostate cancer.
If treatment is successful, the consequences of more advanced cancer are avoided.	The main treatments have significant adverse effects, and there is no certainty that treatment will be successful.	There is no strong evidence to show whether or not treatment of localized prostate cancer will lead to a reduction in mortality.

Given this scenario, it behooves upon tertiary medical institutions which have an interest in prostate cancer, to conduct epidemiological studies on prostate cancer in India, to document the true burden of disease rather than pursue a policy which is increasingly being questioned in the West. In the authors institution, well over 2000 patients have had their PSA done for 'opportunistic screening' and the pick-up rate of prostate cancer is merely approximately 12% (unpublished data), which could be attributed to a chance alone. In spite of using opportunistic screening for the vast majority of elderly males visiting the urology department, there have been not more than 25 radical prostatectomies performed in the author's institution in the last 5 years and the majority have been for clinically detected and locally advanced disease (unpublished data). In spite of routine use of PSA for early detection, no center in India has published results of RP series for screen-detected cancer prostate, indicating the relatively low

incidence of disease which corroborates with data from the Indian Cancer Registry, as cited in the article.

CONCLUSIONS

Given the low incidence of cancer prostate in India and the doubtful utility of screening in populations with a high incidence of prostate cancer, it is not appropriate to advocate routine use of PSA for early detection of prostate cancer in the majority of Indian males. In case a patient requests for a PSA test, or the physician initiates the testing, the patient should be counseled about its benefits and limitations. However, before counseling the patients, it is important that urologists in India are themselves well informed about the benefits and limitations of PSA testing so that they can make individual decisions in the best interests of a particular patient.

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