Prostate cancer has been the focus of several recent reports in the US news media. Additional attention has been focused on this issue due to the disclosure by several prominent US individuals that they have or have had prostate cancer. These include US presidential candidate, Senator Robert Dole, Gulf War hero, retired General Norman Schwarzkopf and the billionaire financier Michael Milken. Such specific cases highlight the fact that prostate cancer—"the man's cancer"—has risen sharply both in incidence and prevalence over the last few years.

In men, prostate cancer is the most common type of cancer in the US and the second leading cause of cancer mortality. In 1996, it is estimated that there will be 317,100 new cases and 41,400 deaths as a result of prostate cancer in the US. The lifetime probability of a man developing prostate cancer is one in five. Currently the adjusted death rate from this disease among men living in industrialized countries of the world is greater than 15 per 100,000 population.

What has caused this epidemic? A partial answer is the use of prostate specific antigen (PSA) as a screening test which has led to the diagnosis of many cancers that would have otherwise have remained undiagnosed, and never become clinically significant. This then leads to the question now being debated in the literature, fuelled by contradictory guidelines from several highly respected agencies: to screen or not to screen with PSA?

The American Cancer Society (ACS) and the American Urological Association (AUA) currently recommend annual PSA testing for all men aged 50 years and older. The American Academy of Family Physicians (AAFP), Canadian Task Force on the Periodic Health Examination (CTF) and National Cancer Institute (NCI) all recommend against routine PSA screening in asymptomatic men. Furthermore, the recently published guidelines by the United States Preventive Services Task Force (USPSTF) also recommend against routine PSA screening.

The criteria for disease screening were established in 1968 by Wilson and Junger. They are that: (i) the disease entity must be an important health problem; (ii) there should be a suitable test; (iii) the test should be acceptable to the population at risk; (iv) facilities for diagnosis and treatment should be available; (v) there should be a recognizable latent or early symptomatic stage; (vi) the natural history of the disease should be understood; (vii) there should be an acceptable treatment for patients with recognizable disease; (viii) there should be an agreed on policy concerning whom to treat as patients; (ix) case-finding and treatment should be economically balanced in relation to all medical expenditures; and (x) case-finding should be a continuous process.

In this 'Selections', five recent articles on the use of PSA as a screening test will be reviewed.


This study was conducted to evaluate PSA as a screening test for prostate cancer. While PSA had been used to monitor prostate cancer following therapy, its use as a screening tool was unknown.

The study group consisted of 1653 men who responded to calls to participate in a study of PSA measurement as a screening test for prostate cancer. The comparison group was comprised of 300 men who were being evaluated with an ultrasound-guided biopsy of the prostate for prostate problems. PSA levels were obtained in the entire study group and in 235 men in the comparison group. Those in both groups with PSA values of 4 or higher were evaluated with a digital rectal exam (DRE), transrectal ultrasound (TRUS) and a biopsy. They were staged both clinically and pathologically.

The results were then analysed to compare the overall accuracy of these tests and their accuracy in combination with each other. PSA was shown to have the highest positive predictive value. The combination of a DRE plus PSA was shown to be the most accurate test pair.
It is noted by the authors that 21% of the men in the comparison group with prostate cancer had PSA levels below 4. Additionally, they point out that PSA levels greater than 10 occurred in men with benign prostatic hyperplasia. This insufficient sensitivity and specificity makes PSA measurements alone an inappropriate screening test for prostate cancer.

Concern was also expressed by the authors about increasing morbidity and mortality as a result of treating latent prostate cancers that would not have become clinically significant. Additionally, they comment on the problem of missing lead-time bias and incorrectly concluding that screening with PSA improves survival from prostate cancer. Finally, they conclude that PSA measurement would be a useful adjunct to DRE and TRUS in the detection of prostate cancer.

Comment
This was a well conducted study where the authors did not make unsupported claims about the utility of PSA as a screening test for prostate cancer. They clearly demonstrate that PSA alone should not be used to screen for prostate cancer. Unfortunately, the cruc of their study is currently being ignored by many enthusiasts of PSA screening.


The investigators conducted an extensive search through the computerized databases and bibliographies in order to identify all related publications. Using the Markov model, they predicted that PSA alone, or in combination with DRE or TRUS, will prolong unadjusted life expectancy by 0.6–2.2 days for men between 50 and 70 years of age. However, when QALE was considered, a net loss of 3–13 days would be observed, with cost-effective ratios ranging from $113 000 to $729 000. DRE alone does not show any positive gain in the reduction of mortality at any age. The results from separate analysis among black men and high risk men did not vary noticeably. The sensitivity analysis indicates, however, that the results were affected by the efficacy of the treatment.

Finally, the authors concluded that, with current screening techniques and available treatment, screening for prostate cancer among asymptomatic men shows no gain in QALE and dramatically increases costs. Thus, screening should not be recommended.

Comment
This study was the first to use a Markov model in an attempt to resolve the controversy over using PSA as a screening test. The Markov model has been increasingly used in current medical research to assess health related outcomes and for decision making. With the current lack of information from randomized clinical trials on screening for prostate cancer, a complicated model such as the Markov can provide some useful information for policy makers and clinicians. Nevertheless, the limitations of these types of studies must be recognized.

First, the majority of the data used in the analysis were obtained from published articles. These data could be outdated or biased to some degree. For instance, the complication rates and mortality figures in published articles may not represent the state of current medical practice. Therefore, by using those data in the model, the results could be negatively affected.

Second, death rates due to prostate cancer are significantly affected by tumour grade. It is established that poorly-differentiated prostate tumours result in higher mortality rates than well- or moderately-differentiated tumours. The authors failed to distinguish between these types when they performed the analysis, thus their results could be misleading.

Finally, utilities play an important role in the screening analysis. The authors recruited a group of physicians for the assessment of outcome utilities, however, the reliability of this assessment has never been checked. Due to their profession and knowledge of the disease, the opinions of medical experts should not be assumed to represent the general consensus of patients undergoing treatment.

In summary, this study provides useful information. However, the debate will continue since there is still
no definitive answer to the question on whether or not asymptomatic patients should be screened for prostate cancer.


This study was conducted to evaluate PSA testing as a screening tool for prostate cancer. Using a nested case-control methodology, the authors selected cases and controls from the ongoing Physicians' Health Study. The sensitivity and specificity of PSA for all of the prostate cancers diagnosed were calculated. Additionally, these calculations were performed independently for aggressive and non-aggressive cancer subgroups. The optimal cut-off for an abnormal PSA level, lead-time for PSA tumours and the relative risk of prostate cancer were also evaluated.

The sensitivity, while initially high at 72%, decreased significantly to 30% at 10 years of follow-up. The overall sensitivity was 46%. The specificity was 91% for the entire study period. Baseline PSA levels were more sensitive for aggressive versus non-aggressive cancers. The optimal cut-off for an abnormal PSA level was calculated to be 3.3. Using the baseline PSA, the average lead-time for detected prostate cancers was 5.5 years. The relative risk of developing prostate cancer increased with an increasing baseline PSA level. It ranged from 5.5 (95% CI 3.3-9.2) for PSA levels between 2 and 3, to 22.2 (95% CI 12.9-38.2) for PSA levels between 4 and 10.

The authors conclude that a single PSA measurement is highly sensitive and specific for aggressive prostate cancers diagnosed within 5 years. They also state that it provides a lead-time which falls between the mean lead-times for mammography (1.7 years) and cervical cytology (10-20 years). However, they caution against its use as a screening tool until the cost implications are more fully examined; there is evidence demonstrating reductions in mortality following treatment of diagnosed prostate cancers; and there is a clear policy on whom to treat.

**Comment**

This is an elegant study nested within a larger randomized trial. Not only is it very cost-effective, it also provides useful estimates of the sensitivity and specificity of a solitary PSA measurement. Additionally, lead-time estimates for a diagnosis of prostate cancer and relative risks for a variety of cut-off levels are given.

The authors do not recommend using PSA as a screening test for prostate cancer. Instead they provide information which should be used, along with cost and treatment considerations, to evaluate the utility of PSA as a screening test. They state that while PSA has the highest validity of any cancer screening marker, there is still a need to develop cost effective screening strategies which incorporate its use.

The accompanying editorial, however, while hailing the article as historically significant and stating that the cost effectiveness of screening is unknown, proceeds to recommend an aggressive approach to prostate cancer management.


The authors performed a decision analysis using a Markov mathematical model to evaluate the outcomes of annual screening of asymptomatic men for prostate cancer starting at 50 years of age.

The investigators approached their study goals in several steps. First, they defined four basic stages of disease progression including no cancer, cancer, post treatment, and death. Four major adverse outcomes of the post treatment were considered for each stage of the cancer. A total of 23 specific health states were created and used in the Markov model. The probability of each state was estimated from published articles.

Second, they generated a screening algorithm which included DRE, PSA and TRUS. Initially, DRE or PSA would be performed. If a nodule was found or PSA came up positive, then biopsy would be performed. TRUS would be considered if the DRE was negative, but the PSA was positive. If either of those tests was normal, further testing would be postponed until the following year. The sensitivity and specificity of the tests were calculated based on previous studies.

Finally, the authors calculated life expectancy using the reports from the National Cancer Institute. Ten married couples from the University of Texas were recruited in the study to obtain the utility assessment using time trade-off method. In short, this is a method to determine the amount of life expectancy in a specified suboptimal state of health a patient would be willing to trade for a shorter life expectancy in a perfect state of health.

The authors found that if quality of life was considered, screening would cause a net loss of 8 quality-adjusted life months over non-screening. However, if quality-of-life considerations were ignored, screening would prolong life expectancy by nearly 7 months. The decision to screen is sensitive to changes in the patients' preference regarding adverse effects of treatment.

In conclusion, the authors stated that annual screening for prostate cancer among asymptomatic men is not recommended when quality-of-life preferences are taken into account.
Olmsted County, Minnesota, was selected for the study due to the unique Rochester Epidemiology Project, where a unified medical record database for this geographically self-contained medical care system exists. Serum PSA screening began in 1987 in this community. Prostate cancer incidence was studied for the population of Olmsted County for 1983–1992. Prostate cancer cases were identified by review of indexes for the Rochester Epidemiology Project for diagnosis of prostate cancer or history of radical prostatectomy. Community medical records were then reviewed to ascertain Olmsted County residency, stage of disease, symptoms of obstructive voiding, haematuria, bone pain, and perineal pain. Two electronic data files were sorted to identify the first PSA test for each year of the study by individual Olmsted County resident.

From 1983 to 1992 there were 511 biopsy confirmed cases of prostate adenocarcinoma in Olmsted County. Thirty-eight cases were excluded, 28 for having only a clinical diagnosis and 10 for autopsy diagnosis. During the study period, there was a 3.4-fold rise in the age-adjusted incidence of prostate cancer. The greatest increase in annual incidence occurred in 1988 when it doubled. The greatest rise in age-adjusted incidence of organ-confined cancers also occurred in 1988, a 2.6-fold increase from the previous year.

Age-specific incidence rates were 25, 119 and 137 cases/100 000 person-years in 1983, 1986 and 1988, respectively, for the 50–59 year olds. For 60–69 year olds, rates were 187, 388, 645 and 1275 cases/100 000 person-years in 1983, 1986, 1988 and 1991, respectively. However, age-specific incidence began to decline significantly after 1990 and 1991 for the older cohorts (60–69, 70–79 and 80 + year olds) using a hierarchical model with interaction terms for both age and calendar year.

There were significant differences between cases identified before and after 1987 in terms of demographic factors and clinical presentation. The male population of Olmsted County was older in post-PSA years and pre-PSA incident cases were more often identified at Stage C. The pre-PSA versus post-PSA cases were also significantly different with respect to symptoms of haematuria and bone pain. During the post-PSA years, the proportion of incident cases with any of the above recorded signs or symptoms decreased from 77% (1987) to 64% (1992). This paper reports that 31% of incident cases were asymptomatic and had a screening PSA.

Age-specific utilization of PSA screening increased every year from 1987 to 1992 for all age groups. Also, age-specific utilization of PSA screening was generally greater for each older age group in each calendar year of the study, except for the oldest men (85 years old), whose PSA utilization increased less rapidly than younger age groups between 1989 and 1992. The percentage of Olmsted County men who had at least one PSA in their lifetime increased with age: 6,
23, 43 and 64% for men 40-49, 50-59, 60-69 and 70-79 years old, respectively.

Comment
The authors attribute the cause of increased prostate cancer incidence in Olmsted County to PSA testing and increased public knowledge regarding prostate cancer. They believe that the recent decline in incidence rate for the oldest age groups is due to the identification of previously undiagnosed cases with consequent exhaustion of the prevalence pool, and a stage/age shifting towards younger men with clinically localized disease. Early depletion of detectable disease pool in older age groups compared with younger age groups is attributed to greater age-specific utilization of PSA tests in older age groups. Presumably, increased utilization of PSA testing in 50-59 year olds will result in similar patterns in the future.

The study also identified increases in prostate cancer incidence for most age groups during the pre-PSA years, albeit at a lesser rate of increase than the immediate post-PSA years. The authors do not explain this finding. It is possible that increased public and physician awareness of prostate cancer led to an increased use of digital examinations and consequent prostate cancer diagnosis in the absence of PSA testing. Alternatively, there could be an underlying increase in actual disease frequency. The role of lay and professional awareness of disease in the secular trend of prostate cancer was acknowledged, but not quantitatively assessed in this study.

Fundamental to any successful screening programme is the assumption that treatment in the detectable, asymptomatic phase improves prognosis. In this study, it is noteworthy that disease stage shifted towards organ-confined cancers in the post-PSA testing years. This suggests that PSA screening at least has the potential to reduce morbidity and mortality from prostate cancer if future studies show that organ-confined disease can be modified by therapeutic interventions.

This study supports the hypothesis that recent increases in prostate cancer incidence are due, at least in part, to the increase in PSA screening rather than underlying changes in actual disease frequency due to environmental or other factors. However, analytic studies are needed to fully test this hypothesis by adjusting for confounding bias due to changes over time in public and professional attitudes and practices regarding prostate cancer.

Summary
The use of PSA has clearly led to an increase in the diagnosis of prostate cancer. However, diagnosis of a disease is insufficient by itself to qualify a test as an effective screening tool. Where PSA fails as a screening test, and perhaps why it is not recommended for use as one by the AAFP, CTF, NCI and the USPSTF, is that earlier diagnosis resulting from its use has not been shown clearly to decrease mortality from the disease. Once diagnosed it is unclear which cancers will be aggressive and which will remain quiescent for the duration of a person’s natural life. Controversies also exist about whom to treat and what that treatment should be. In some instances of prostate cancer, it is clear that the treatment is worse than the disease. Furthermore, the costs of screening for prostate cancer in the US has been estimated to be between $12 and 28 billion in the first year alone. This is prohibitively expensive, especially given that screening for prostate cancer has not been shown to be effective in reducing mortality from the disease.

Further research to develop a more sensitive and specific screening test than PSA should continue. Optimally, this new screening test should be able to differentiate between aggressive and slow-growing tumours. There also needs to be some standardization of treatment for the various grades of prostate cancer. This can only be done after conducting definitive large scale randomized controlled trials. Three such trials by the NCI and the ACS are ongoing and should provide valuable information in the dealing with this problem. Trials also aimed at discerning the aetiology of this cancer would be most helpful in planning to combat this disease through a variety of primary prevention programmes.

Finally, for the practising family physician who has to deal with this dilemma on a patient by patient basis, rather than on a global epidemiological level, the decision-making can be even more complex. Since there is not a clear-cut choice on this issue, and until clearer answers emerge from ongoing trials, it would seem most prudent for the practising physician to give the patient the available information about the potential risks and benefits of PSA testing to make an informed decision, and then proceed accordingly.

References
Selections from current literature


