Screening for Prostate Cancer

By John W. Feightner
There is poor evidence to include or exclude the digital rectal exam (DRE) from the periodic health examination for men over 50 years of age (C Recommendation). While DRE has limitations in its ability to detect early prostate cancer, there is insufficient evidence to recommend that physicians who currently include DRE in their examinations should change that behaviour.

There is insufficient evidence to include prostate specific antigen (PSA) screening in the periodic health examination of men over 50 years of age. Exclusion is recommended on the basis of low positive predictive value and the known risk of adverse affects associated with therapies of unproven effectiveness (D Recommendation).

There is also fair evidence to exclude transrectal ultrasound from the periodic health examination of asymptomatic men over 50 years of age. (D Recommendation)

Burden of Suffering

Prevalence

Prostate cancer and its early detection have received increasing attention during the early part of the 1990s. It is the second most frequent cause of death from cancer among men (an estimated 3,800 deaths in 1993), and ranks third in terms of potential years of life lost from cancer among Canadian men. Excluding congenital anomalies and perinatal causes of potential years of life lost, prostate cancer ranks ninth among all causes for males. The lifetime risk of dying from prostate cancer is 3%. There is a rapid rise in incidence over the age of 60. While there has been an increase both in the overall incidence of prostate cancer and in the age-standardized incidence, there has been little change in the age-standardized mortality rate in Canada. This supports the hypothesis that the increased incidence does not reflect a true increase in the actual disease among Canadian males.
Natural History

One of the major challenges in dealing with the early detection of prostate cancer is the lack of a clear understanding of its natural history. Autopsy studies indicate a prevalence of histologic cancer in the range of 20% of men of average age 50 and 43% of men aged 80. Hence, the often heard expression “more men die with prostate cancer than from prostate cancer”. This is an indication that, particularly in older age groups, prostate cancer is often an incidental finding and can exist without creating major morbidity and mortality. Unfortunately, the natural history of this disease has not been defined. Thus, there is no way of predicting for any individual which cancer, particularly those found at an earlier stage, will progress to be clinically significant in terms of potential morbidity and/or mortality. This issue is critical to the consideration of early detection. Cancers detected at an earlier stage have a better prognosis, even if untreated, than more advanced tumours. However, if an early or small cancer is found as a result of early detection efforts, the physician cannot currently advise the patient whether he is at significant clinical risk (and thus whether therapies of unproven effectiveness are worth the risk – see discussion on Early Detection Plus Therapy).

Maneuver

Virtually all of the studies used to evaluate the test characteristics of the early detection maneuvers for prostate cancer have inherent methodologic study design problems. Most significant is the reality that patients with a negative test do not undergo gold standard assessment. This is clearly not feasible when the gold standard represents prostatectomy or extensive biopsy. In the studies that have been published, however, there is no attempt to systematically monitor individuals with negative tests over time to ensure that prostate cancer does not develop subsequently. Many of the studies suffer from “filtration bias” wherein the subjects are not representative of the general population but reflect only those individuals arriving at urologists’ offices or individuals with genito-urinary symptoms. More recent studies have attempted to identify the positive predictive value of screening in groups that would more closely approximate the general population.

With only a few exceptions, studies suffer from a selection bias in that some of the detection tests are only conducted on patients where there has already been a “positive” finding such as a positive digital rectal examination. This does not provide a true estimate of sensitivity and specificity.

Hence, the approximations of sensitivity and specificity are only rough estimates. While many have confidence in these estimates, slight changes in sensitivity and specificity can have a major impact on the
overall accuracy of any test. This, combined with the low prevalence of clinically detectable prostate cancer leads to the concern regarding a low positive predictive value and a high rate of unnecessary biopsies.

Three strategies have been considered and used in early detection of prostate cancer.

Digital Rectal Exam

This is the oldest detection strategy and represents the simplest technology for early detection. While easy to perform, it has serious limitations as an early detection maneuver because only the posterior and lateral aspects of the prostate can be palpated – leaving 40-50% of cancers beyond reach. The examination does appear to be skill-related and there is some evidence that the accuracy of urologists surpasses that of generalist physicians. In asymptomatic males, the estimates of sensitivity and specificity vary. Representative estimates of sensitivity and specificity range between 33-58% and 96-99%, respectively. In one study, the sensitivity increased to 67% with repeat examinations (average 1.9 per patient) with a slightly decreased specificity of 97%. A representative estimate of the positive predictive value for DRE is 28%.

Transrectal Ultrasound (TRUS)

While this technique was initially promoted as a potential early detection strategy most would currently view it as a diagnostic test only. Its test characteristics have improved as the technology has improved. The diagnostic accuracy of the image depends on the skill of the interpreter and, although it is a safe procedure, it is expensive both in terms of cost and time compared to other maneuvers. Studies have generally indicated a high sensitivity of 97% but a lower specificity at 82%. While the technique can detect lesions as small as 5 mm, it has a high false positive rate which is reflected in the lower specificity.

Prostate Specific Antigen (PSA)

The prostate specific antigen represents a major development in terms of biochemical markers for the early detection of prostate cancer. Compared to DRE, the principal advantage of PSA is its ability to detect prostate cancer at an earlier stage. However, like all early detection tests, its test characteristics and ability to contribute to the net benefit of patients requires careful evaluation. As with the other tests for early detection, sensitivity and specificity can only be approximated. Because sensitivity and specificity can not be accurately estimated, most of the evaluation of PSA as a screening test has focused on its positive predictive value. A “positive” PSA level is established somewhat arbitrarily. The most common threshold is
4 μg/L although, some authors have suggested a cut point as low as 3 μg/L and others as high as 10. Most, although not all patients with an elevated PSA will move to ultrasound guided biopsy to establish whether pathological evidence of cancer can be established. Several studies have reported positive predictive values for PSA. Of concern, is that these numbers range from a low of 8% to a high of 33%.<12,20-25> This means that at best, 67% of patients identified as having a positive PSA will undergo unnecessary biopsy, and evidence indicates that this could be as high as 92%.

Because PSA is produced by the epithelial cells of the prostate rather than cancer-specific cells, its elevation can reflect benign hypertrophy of prostate tissue instead of or as well as prostate cancer. Coupled with the inherent difficulties of sampling prostate tissue using existing biopsy techniques, this creates a significant problem. In response to these concerns, investigators have begun to explore alternate approaches to using PSA. These include the use of serial PSA’s looking for rapid rise, the use of PSA levels in relation to the size of the prostate on ultrasound, and the use of age-standardized levels for PSA. While these efforts may hold promise, they have been insufficiently evaluated and, hence, should not be considered for widespread use at this point in time.

To some degree the accuracy of early detection efforts begs the question of whether early detection makes a difference in terms of net benefit to the patient. For an individual patient, does early detection of prostate cancer do more good than harm?

Effectiveness of Screening and Treatment

“Is cure possible in those for whom it is necessary, and is cure necessary for those in whom it is possible?”

- Willet Whitmore

Early Detection Plus Therapy

As with all early detection efforts, the most rigorous evaluation comes in the form of a randomized controlled trial. Difficult and challenging as this may be, it is the only design which will effectively control for important biases. This situation is particularly true with a cancer whose natural history is unknown. Hence, the strongest evidence would emerge from randomized controlled trials evaluating early detection efforts that were linked to therapy. Evidence of this quality does not exist regarding the effectiveness of the early detection of prostate cancer. One case-control study (level II-2 evidence) has raised doubts about the effectiveness of early detection with the digital rectal exam.<7> In effect, there was no difference in the frequency of screening DRE’s in 139 men with metastatic prostate cancer from the
Kaiser Permanente Medical Care Program compared to matched men from the program with no diagnosis of metastatic prostate cancer.

In the absence of acceptable evidence for early detection efforts, one turns to a search for sound evidence of the effectiveness of therapy for the condition once it is identified. Unfortunately, there is no adequate evidence from comparative studies to evaluate the main therapeutic options for prostate cancer, particularly for early stage lesions.

A randomized controlled trial to evaluate screening is underway and a randomized trial to evaluate therapy is in the planning stages in the U.S. European trials evaluating various aspects of therapy are also underway but no results are as yet available.

Effectiveness of Therapy

There are essentially three approaches to dealing with prostate cancer that is detected at an early stage - no therapy but careful monitoring (sometimes referred to as "watchful waiting"), radiation therapy, and radical prostatectomy. The only data available for all three approaches come from descriptive studies which cannot rule out important biases and which often are not generalizable to the broader health care system and the population it serves.

In a Scandinavian study, Johansson and colleagues studied a population-based cohort of 223 patients with early stage prostate cancer for a mean of 123 months.<sup>26</sup> These individuals were selected on the basis of early stage cancer from 654 new cases of prostate cancer identified over a seven year period. The final entry of patients included some with somewhat more advanced cancers. The population was somewhat older with a mean age of 72 years. During the mean observation period of almost 10 years, only 19 patients (8.5%) died from their prostate cancer. The overall progression-free survival rate was 53.1%.

In a structured literature review focusing on articles addressing the treatment of localized prostate cancer, Wasson and coauthors concluded that they were unable to determine treatment effectiveness for localized prostate cancer as a result of the low methodologic quality of the studies.<sup>27</sup> They further concluded that "until better scientific evidence is available, patients and their physicians cannot make informed choices based on knowledge of the benefits of radical prostatectomy, radiation, or watchful waiting".

In the absence of evidence from properly conducted comparative studies, other approaches to weighing the available data have been attempted. Fleming and co-workers used a decision analysis strategy to evaluate alternate treatment strategies for clinically localized prostate cancer.<sup>28</sup> Specifically, they addressed radical prostatectomy, external beam radiation therapy and watchful waiting
(with delayed hormonal therapy if and when metastatic disease developed). Their results indicated no clear net benefit for any therapy. In a selected group ages 60-65, with higher grade tumours, there was an indication that radical prostatectomy or radiation therapy might provide a small benefit. If the higher estimates of treatment efficacy were used there was a quality-adjusted survival improvement of less than one year. If the lower estimates of treatment efficacy were used, watchful waiting was always equal to or better than radical prostatectomy or radiation therapy. As with all decision analysis, the conclusions are affected by the data on which the analysis is based. Some have criticized the choice of metastatic rates and the discounting used for complications. This debate will no doubt continue until more rigorous evidence is available.

Finally, a pooled analysis of data from six non-randomized studies evaluating observation plus delayed hormone therapy for clinically localized cancer, demonstrated a 10-year disease-specific survival of 87% for men with grade one or grade two tumours.<29>

High-Risk Individuals

Men with a strong family history for prostate cancer and African-North American men carry a higher risk than the general population. However, it is not clear that an identified cancer in such individuals will behave differently biologically than cancers in normal-risk men. Hence, there is no evidence to suggest that early detection efforts will provide more benefit to such individuals than to normal-risk individuals.

Cost and Adverse Effects

While difficult to evaluate, the overall cost and adverse effects associated with a program for the early detection of prostate cancer can be substantial and can be clinically significant. Although the dollar costs of a single DRE or PSA is relatively small, subsequent biopsy costs, especially for false positive screening tests, and the cost associated with subsequent unproven therapy represent a significant cascade of costly actions.

Formal attempts at evaluating even this limited perspective of costs are few. Even more challenging is the documentation of adverse effects. Case series data from the few major centres are not generalizable, and informal patient self-reports can create underestimates. Alternately, data from older populations may over-estimate adverse effect rates in younger men.

The only structured review of the available literature from 1982 to 1991 suggests the following adverse effect rates for radical prostatectomy: a surgical mortality rate of just over 1%; complete incontinence in 7% and any incontinence in 27%; impotence in 32%
with the more recent “nerve sparing” radical prostatectomy (but as high as 85% with other techniques); stricture rates of 12% and bowel injury requiring colostomy or long-term treatment of 1%.<27>

Rates for external beam radiation are lower for procedure-related mortality (0.2%), any incontinence (6.1%), complete incontinence (1.2%), and stricture (4.5%). They are higher for bowel injury (2%). The impotence rates are reported as 42%.

Risks associated with biopsy include prostatitis, epididymitis, and hematuria. It may be that the rate of 4.4% for these events reported in 1984 have improved with newer techniques.

Recommendation of Others

The U.S. Preventive Services Task Force concluded that there was insufficient evidence to recommend for or against the use of DRE in the periodic health exam;<4> PSA and TRUS were not recommended for routine screening. The National Cancer Institute in the United States concluded “there is insufficient evidence to recommend transrectal ultrasound and serum tumour markers for routine screening in asymptomatic men”.

A review by the British Columbia Office of Technology Assessment recommends against the use of PSA as a routine screening test.<3> The Canadian Cancer Society does not recommend routine use of PSA.

The Canadian Urological Association and the American Urological Association recommend annual screening for men between ages 50 and 70 with both DRE and PSA. The Canadian Urological Association in its policy statement did not describe the basis on which the evidence was reviewed nor the strength or weakness of the associated evidence. The American Cancer Society recommends annual PSA for men beginning at age 50.

Conclusions and Recommendations

There are two main philosophical views concerning early detection of cancer. One view holds that the major goal is to search aggressively for asymptomatic cancer and having found it, remove it. While the effectiveness of therapy may not be established, and its associated adverse affects may be recognized, the main mission is to detect cancer early. This view emphasizes the importance of developing tests which can detect cancer early, even if such tests may label many individuals falsely and subject them to subsequent unnecessary, invasive investigations.

The alternate view considers early detection and treatment as a single package and asks whether there is evidence that such combined efforts do more good than harm. This is the question of greatest
importance, both from the individual patient’s perspective as well as that of the population. Hence, while evaluating the performance of early detection tests is part of the picture, one must also evaluate the effectiveness of therapy and whether the use of available early detection tests ultimately provides overall net benefit to the patient. This is the view taken by the Canadian Task Force on the Periodic Health Examination.

Based on the absence of evidence for effectiveness of therapy and the substantial risk of adverse effects associated with such therapy; and the poor predictive value of screening tests, there is at present insufficient evidence to support wide-spread initiatives for the early detection of prostate cancer.

The Task Force does not recommend the routine use of PSA as part of a periodic health examination. While PSA can detect earlier cancer, it is associated with a substantial false positive rate. This, combined with poor evidence to support the effectiveness of subsequent therapy and clear evidence of substantial risk associated with such therapy, means that the widespread implementation of PSA would expose more men to uncertain benefit, but to definite risks. For these reasons the Task Force recommends that PSA be excluded from the periodic health examination (D Recommendation).

The Task Force debated recommending the exclusion of DRE from the periodic health examination because of its limited performance as an early detection test. However, DRE has been routine practice for many physicians for the early detection of prostate abnormalities and the available evidence was not considered sufficiently powerful to advise physicians who currently include DRE as part of a periodic health examination in men aged 50 to 70 to discontinue the practice. At the same time, the evidence is insufficient to advocate the inclusion of DRE for those physicians who do not currently include it as part of the periodic health examination for men aged 50 to 70. Hence, the decision to retain a C Recommendation for DRE – there is insufficient evidence to include DRE or exclude it from the periodic health exam.

Based on the available evidence for TRUS, the Task Force recommends against the routine use of this procedure as part of a periodic health examination (D Recommendation).

These recommendations are made on the basis of the evaluation of the best available evidence using the Canadian Task Force guidelines, and the ethical imperative that early detection efforts must be proven to result in more good than harm before being incorporated into the periodic health examination.
Patient Consent

The ethical imperative for prevention and early detection efforts is to ensure that such efforts, initiated and promoted by the physician, are proven to do more good than harm. If, in the absence of such proof, a physician decides to offer PSA to a patient, it has been argued that the patient should be fully informed of the balance of benefits and risks, and should provide informed consent for such testing. With prostate cancer screening, this should occur before ordering PSA levels, since the nature of the cascade of events which follows a positive test would make discussions occurring later in the sequence more difficult and ill-timed.

Unanswered Questions (Research Agenda)

The most important need is for randomized trials of early detection and randomized trials to evaluate the effectiveness of therapy. Such trials are underway in Europe and North America or are in the planning stages. While it will take some time before the results are available, this does not argue against the vital need for such data.

Because the natural history of prostate cancer is poorly understood, research into predicting which early cancers will become clinically significant and result in important morbidity and mortality remains a high priority.

In the absence of effectiveness of therapy and until such time as a proper trial of early detection is conducted, the importance of continued major initiatives of research into PSA may be questioned. Any efforts which do occur should focus on careful and proper evaluation of the test characteristics whether it be for serial PSA’s, PSA density, or PSA age-related norms.

Evidence

The literature for this review was identified through the MEDLINE data base and from the identification of additional studies from the citations of articles from the original search.

This review was initiated in 1993 and the recommendations finalized by the Task Force in June 1994.
Selected References


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<td>Digital Rectal Examination (DRE)</td>
<td>Routine screening results in increased detection of early cancers but the maneuver can only detect small cancers in the posterior and lateral aspects of the prostate. The effectiveness of therapy is unproven but carries significant risks of important adverse effects.</td>
<td>Overview and decision analysis of cohort analytic (descriptive) studies&lt;27-29&gt; (II-3)</td>
<td>Poor evidence to include or exclude DRE from the periodic health examination (PHE) for men over 50 years of age (C); while DRE has limitations in its ability to detect early prostate cancer, there is insufficient evidence to recommend that physicians who currently include DRE in their examinations should change that behaviour.</td>
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<td>Prostate specific antigen (PSA)</td>
<td>While PSA can identify prostate cancer at an earlier stage, the false-positive rates range from 67% to 93%. The effectiveness of therapy is unproven but carries significant risks of important adverse effects.</td>
<td>Cohort analytic (descriptive) studies&lt;19-25&gt; (II-3)</td>
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<td>Transrectal Ultrasound (TRUS)</td>
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<td>Fair evidence to exclude from the periodic health examination of asymptomatic men over 50 years of age (D)</td>
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* DRE can also be done for other reasons (other than to detect prostate cancer).