Prostate Cancer Screening

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ABSTRACT

Cancer of the prostate gland, a disease primarily found in men over the age of 50, is the most common cancer in North American males. Given the significance of the disease in the male population, much effort has been placed on developing a test for its early detection at a curable stage. To date, prostate specific antigen (PSA), a protein produced by epithelial cells of the prostate, has been considered the best marker for prostate cancer. However, controversy has surrounded the measurement of PSA as a screening test. No randomized controlled trials have shown any definitive net benefit from the test. Accurate measurement of PSA sensitivity and specificity are difficult to obtain. Issues also surround the economic implications of mass screening, as well as the morbidity and emotional impact associated with unnecessary aggressive procedures performed on the basis of an elevated PSA. In evaluating PSA screening, one must consider several factors including the magnitude of the condition as a health care problem, the accuracy of the test, the effects of screening on outcome, and the possible associated risks and benefits.

INTRODUCTION

When Prostate Specific Antigen (PSA) testing was first introduced in 1987, it resulted in a dramatic increase in the reported incidence of prostate cancer. Since its inception there has been considerable controversy as to whether a mass screening protocol involving the measurement of PSA should be implemented. Screening programs have been shown to be beneficial with other cancers such as those of the breast, colon and cervix. Intuitively, early detection of a disease process at an asymptomatic stage would allow for early initiation of treatment and a resultant decrease in morbidity and mortality. This line of reasoning has been applied to prostate cancer; however, to date there is no overall consensus as to the benefits of existing screening methods. This article will provide an introduction to prostate cancer as well as a discussion of the existing screening strategies for it.

UNDERSTANDING PROSTATE CANCER

Prostate cancer is the most common cancer of men in North America, and is second only to lung cancer in mortality. According to the 2000 Canadian Cancer Statistics, the lifetime probability of developing prostate cancer is 11%. Among Canadian men with prostate cancer, there is a 32% likelihood of death due to the disease. It is known that prostate cancer is an androgen-dependent tumour, however little else is known about its etiology. Possible causative factors include a diet high in saturated fatty acids, genetic influences, exposure to environmental toxins and heavy metals, as well as viral infections. No association has been established between prostate cancer and benign prostatic hyperplasia (BPH). Risk factors for prostate cancer are age, family history and ethnicity, with a higher incidence in African American males. Lower urinary tract symptoms are not believed to be contributory factors.

Prostate cancer is a disease of the elderly and is uncommon in men under 50 years of age. Only 8.5% of the deaths from prostate cancer occur in men younger than 65 years of age, whereas 63.1% of the deaths occur in men who are over 75. To date, there is no clear understanding of the natural history of prostate cancer, nor are there any prognostic markers. It is known that prostate cancer is a slow-growing disease. Most patients diagnosed with clinically localized, well- to moderately-differentiated cancers can survive 10 years without aggressive therapy, irrespective of the pathological spread. Thus the pathology of the cancer does not necessarily indicate clinical significance with respect to the risk of dying from prostate cancer. Therefore, in any given individual, it is not possible to accurately predict whether the cancer will progress from its latent to clinically significant
phase. Autopsy studies have reported that roughly 30% of men over the age of 50 show histologic evidence of prostate cancer, which implies that nine million men in the United States harbour latent prostate cancer. Given that approximately 40,000 men die each year from the disease, it is hypothesized that prostate cancer is often an incidental finding and does not always represent a clinically significant disease. Therefore, many men with latent prostate cancer, especially the elderly, will die from other causes. Hence the often-heard expression “more men die with prostate cancer than from it.”

There are no clear signs or symptoms that are specific to the diagnosis of prostate cancer. Prostate cancer is usually clinically silent until it has become locally invasive or has metastasized. Patients can occasionally present with bone pain due to bony metastases, obstructive urinary symptoms, hematuria, or dysuria. However, because these symptoms are not specific to prostate cancer, diagnosis requires the use of a combination of digital rectal exam (DRE) and serum PSA levels. Prostate cancer may be suspected if the DRE reveals a firm, indurated, and asymmetrical nodular mass. However, an abnormal DRE is not specific and can also be due to BPH, prostatitis, prostatic calculi, focal infarction, prior biopsies, or transurethral prostatectomy.

Prostate Specific Antigen is a glycoprotein produced by prostate epithelial cells and hydrolyzes the coagulum of the ejaculate. Prostatic diseases, including prostate cancer, are associated with high serum PSA values due to enhanced production of PSA as well as structural changes of the prostate gland which facilitate PSA circulation. It is important to note that PSA is prostate specific, but not disease specific. Therefore in addition to prostate cancer, PSA may be elevated in BPH, prostatitis, prostatic ischemia, acute urinary retention, prostate surgery, prostatic massage, urethral catheterization, and ejaculation.

When there is suspicion of prostate cancer with either an

| 1 | Sharply circumscribed aggregate of small, closely packed, uniform glands |
| 2 | Greater variation in glandular size. More stroma between glands. More infiltrative margins |
| 3 | Further variation in glandular size. Glands more widely dispersed in stroma. Distinctly infiltrative margins, with loss of circumscription |
| 4 | “Fused gland” pattern; irregular masses of neoplastic glands coalescing and branching. Infiltration of prostatic stroma |
| 5 | Diffusely infiltrating tumour cells with only occasional gland formation. Prominent nucleoli |

abnormal DRE or an elevated PSA level, a definitive diagnosis can only be made by a biopsy of the prostate gland guided by either digital exam or transrectal ultrasound. Prognosis and subsequent treatment strategies are then based on the pathologic evaluation of the biopsy specimen. The cancer is histologically graded using the Gleason Sum System. The two most common architectural patterns are identified and each is assigned a Gleason grade score out of 5. The two scores are added to give a total out of 10 (Table 1). Low scores represent well-differentiated tumours, which are associated with a better prognosis. Poorly differentiated cancers are more likely to metastasize. The degree of spread of the prostate cancer must also be assessed and is done using the TNM (tumour, nodes, and metastases) classification of the American Joint Cancer Committee (Table 2). Based on the stage and prognosis, a treatment strategy is then developed (Table 3).

**PSA SCREENING**

Screening for disease control can be defined as the examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening. Selective screening strategies have been shown to be beneficial in both colon and breast cancer. Prior to the advent of PSA testing, about 60% of patients with prostate cancer presented with clinically evident disease and up to 40% of patients with clinically organ-confined disease had metastases beyond the prostate; cure was therefore not an option for these patients. PSA screening offers the opportunity to detect prostate cancer at an early, asymptomatic stage during which curative treatment may be possible. However, before PSA testing is widely implemented in population-based screening, it must first be shown to have a proven benefit on morbidity and mortality. To date, a consensus has not been reached as to its use in screening for prostate cancer. As of yet, there are no completed randomized control trials that demonstrate that PSA screening is beneficial in reducing mortality from prostate cancer. A longstanding controversy exists between supporters of screening who claim that it will lead to decreased morbidity and mortality, and its opponents who feel that widespread testing will lead to inefficient use of resources as well as...
diagnostic and treatment procedures with possible health complications. To help resolve this debate, an evaluation of the benefit and harm of the proposed screening program must be explored. Five major points should be considered when evaluating any screening protocol:

1) What is the magnitude of the health problem?
2) How accurate is the test in question?
3) Does early detection improve outcome?
4) Is effective treatment available?
5) Does screening do more good than harm?

1. What is the magnitude of prostate cancer as a health problem?

As already stated, prostate cancer is the most prevalent cancer among men in North America, and is the second leading cause of male cancer deaths.\(^1\)\(^1\) It is the third leading cause of potential loss of life from cancer among Canadian men.\(^1\)\(^1\) There is no doubt that prostate cancer is serious when in its progressive form. However, as mentioned, autopsy results show that there is a high prevalence of undiagnosed prostate cancer in men older than 50 years; this ranges from 30% in the seventh decade to 50% by the ninth decade.\(^1\) This suggests that not all cases of prostate cancer are as clinically significant as originally thought. Moreover, in most cases prostate cancer is frequently of an indolent nature and these men will likely die with histologic evidence of prostate cancer and not necessarily from it.\(^1\)

2. How accurate is the PSA test?

Bunting (2002) evaluated the performance of PSA alone in 11 screening trials. With a cutoff of 4.0 ng/ml, results were as follows: average sensitivity of 71%, average specificity of 75%, positive predictive value of 37%, and a negative predictive value of 91%.\(^1\)\(^0\) Higher cutoffs increase specificity but at the cost of sensitivity. However, it should be noted that the studies done have not been equivalent in their methods. Combined use of PSA levels and DRE as screening tools has a higher sensitivity and specificity than PSA alone.\(^1\)\(^0\) Therefore, DRE and PSA levels are used as diagnostic tools for prostate cancer. However, true sensitivities and specificities of combined DRE and PSA are unknown, and with a standard cutoff of 4.0 ng/ml, a significant number of cancers are still missed. In addition, PSA results may lead to false positive results as benign conditions of the prostate such as benign prostatic hypertrophy and prostatitis also result in PSA elevation.

Researchers have put much effort in determining the most appropriate PSA cutoff value. By convention, PSA values greater than 4.0 ng/ml are considered to be abnormal and require closer observation and further investigation. However, it must be noted that PSA levels are age dependent and normally increase with age as the prostate size increases. This leads to the possibility that some older men will have values greater than 4.0 ng/ml but no detectable pathology on biopsy, and thus will unnecessarily undergo an invasive procedure. For this reason, a higher PSA cutoff has been proposed, however it is not guaranteed to be beneficial as it would reduce the sensitivity of the test and would identify only more advanced cancers that are

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prognosis</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Stage I T1a, N0, M0, low grade or score</td>
<td>90% disease-specific survival rate, regardless of treatment type chosen.</td>
<td>Watchful waiting (for small, slow-growing tumours in older men)</td>
</tr>
<tr>
<td>Stage II T1a, N0, M0, intermediate or high grade or score T1b, N0, M0, any grade or score T1c, N0, M0, any grade or score T1, N0, M0, any grade or score T2, N0, M0, any grade or score</td>
<td>For localized tumours that are extensive or poorly differentiated (Gleason score 8-10), 75% will develop metastases within 10 years without aggressive therapy.</td>
<td>Surgery or radiation therapy (for tumours that are localized, but more extensive or poorly differentiated).</td>
</tr>
<tr>
<td>Stage III T3, N0, M0, any grade or score</td>
<td>50% likelihood of progression within 10 years after diagnosis. The risk of recurrence increases if the tumour spreads to the seminal vesicles.</td>
<td>External beam radiation therapy is often used to treat Stage III cancers because it is less invasive than surgery and better suited for bulky tumours. Surgery and watchful waiting also are options.</td>
</tr>
<tr>
<td>Stage IV T4, N0, M0, any grade or score Any T, N1, M0, any grade or score Any T, any N, M1, any grade or score</td>
<td>Spread to lymph nodes at time of hormone therapy (using a GnRH analogue or estrogen therapy) is associated with a risk of developing additional metastatic cancer in the 10 years following treatment.</td>
<td>Hormonal therapy is generally used to improve symptoms and delay the progress of the cancer for another two to three years. If the cancer has spread to only the lymph nodes, hormonal therapy may be used for a longer amount of time.</td>
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Adapted from http://www.health-alliance.com/cancer/Prostate/staging.html
less responsive to treatment. At the same time, it is known that even with the 4.0 cutoff, several cases of prostate cancer are missed as men can have prostate cancer with PSA values less than 4.0. Lowering the PSA cutoff may aid in the identification of asymptomatic carriers, but at the cost of an increased number of biopsies performed as well as increased morbidity associated with biopsies. Thus, despite the finding that a proportion of cancers are missed with a PSA cutoff of 4.0, studies have shown that this value is appropriate as it allows for identification of the majority of cancers and avoidance of unnecessary biopsies.

A number of strategies have been proposed in order to improve the performance of the PSA test. Assessing the PSA levels in relation to prostate volume or density is one such strategy, however, measurement of prostate volume is difficult and not always accurate. Age specific reference ranges have been proposed in which the threshold for biopsy increases appropriately with age, however, this method is not optimal as sensitivity is reduced for older men. PSA velocity, or the measurement of PSA increase over time, may aid in differentiating prostate cancer from other benign conditions, however this approach requires serial PSA measurements three times at least one year apart. Lastly, PSA exists in the blood in both free and bound forms. A ratio of these measures can be obtained to differentiate prostate cancer from benign prostatic hypertrophy, as prostate cancer is associated with a lower percentage of free PSA compared to that of the latter.

3. Does early detection of prostate cancer improve outcome?

The purpose of a screening test is to identify disease in asymptomatic patients during an early stage in the disease process at which time treatment will be effective in altering the natural history of the condition. Screening can only be justified on the condition that those who are screened have a better health outcome than those who are not. Unfortunately in the case of prostate cancer, the natural history is unknown, and therefore it is difficult to definitively state whether treatment alters its course and outcome. Moreover, the only true way to prove whether PSA screening improves outcome is through a randomized controlled trial (RCT). To date there have been no appropriately designed and analyzed RCTs that have shown that the early detection of prostate cancer has a clear net benefit. RCTs are difficult to undertake because patients have to be followed for a minimum of five to 10 years in order to obtain adequate data to measure outcomes. Studies conducted over an extended time frame require increased funding and ongoing patient participation. With the advent of PSA screening, lifetime incidence of prostate cancer has increased to approximately 11%. whereas the lifetime risk of death is about 3%. While there has been a rise in the overall and age-standardized incidence of prostate cancer, there has been little change in the age-standardized mortality rate in Canada. Therefore, many argue that PSA screening only identifies early stage, indolent prostate cancers, which, in most cases, would not progress to an aggressive, fatal form. The benefit of early detection of prostate cancer by PSA screening has only become apparent though indirect evidence. That is, early stage disease is more likely to be identified in men who are screened for elevated PSA than in those who are not screened, and the former are more likely to be able to receive treatment before the disease progresses.

Survival data suggest that men with localized disease at diagnosis live longer than those with more advanced disease. However, one must take into account several biases that arise out of PSA studies. Two major biases include lead-time bias, and length-time bias. Lead-time bias refers to a situation in which survival appears to be lengthened because the diagnosis was made early, rather than because death was delayed. Length-time bias refers to preferentially detecting slow-growing indolent tumors, as opposed to aggressive tumors that are only briefly present. Moreover, the slow-growing tumours are associated with a better prognosis than the aggressive tumours.

The natural history of prostate cancer is not well known. Like many cancers, prostate cancer likely has a spectrum of aggressiveness. The time from development of the disease to the onset of symptoms is longer in the indolent form than in the aggressive form. Thus the indolent cancer is likely to be detected by screening before the onset of symptoms, whereas the latter form may have an asymptomatic phase insufficient in duration to allow for detection of the cancer prior to the onset of clinical manifestations. Thus screening brings in a detection bias that makes PSA screening appear more favorable than it actually is.

Until well designed RCTs are done to determine whether early detection actually has any effect on survival, the question of whether early detection improves outcome will remain unanswered. Two RCTs are currently underway: the Prostate, Lung, Colorectal and Ovarian (PLCO) trial; and, the European Randomized Study of Screening for prostate cancer. Preliminary results from these studies are scheduled to be released in 2005-2006.

4. Is effective treatment available?

There are essentially four modes of treatment for cases of prostate cancer that are detected at an early, asymptomatic stage: radical prostatectomy, radiation therapy, androgen deprivation by hormonal means (GnRH agonists, estrogen therapy or castration), and no therapy (“watchful waiting”). To date, no RCTs have been done to compare the effectiveness of the different treatment strategies. Arguments supporting the use of radical prostatectomy or radiation therapy have been based on uncontrolled observational studies. However, no treatment modality has been proven to be more effective over another. Until studies are completed exploring the benefits and harms of these treatments, the most effective treatment will remain unknown.
The use of the PSA test is recommended to monitor patients with established cancer. The PSA test should not be repeated more often than once a month.

The use of a PSA test is recommended for men with moderate or severe symptoms of prostatism in whom treatment is contemplated.

A serum PSA determination may be considered for any man over the age of 40 years with a life expectancy of 10 years or more, who has a higher risk of prostate cancer than possible periodic repeat testing (e.g. every two years).


When the PSA is below the laboratory's diagnostic cutoff (e.g. 4.0 µg/L or an age-adjusted value), and the DRE is negative, no further action is usually taken, other than possible periodic repeat testing (e.g. every two years).

A serum PSA determination may be considered for any man over the age of 40 years with a life expectancy of 10 years or more, who has a higher risk of prostate cancer. Within the context of higher risk is included a family history (first degree relative) of prostate cancer or men of African ancestry.

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The use of the PSA test is recommended to monitor patients with established cancer. The PSA test should not be repeated more often than once a month.

Table 4. Ontario Prostate Specific Antigen (PSA) Clinical Guidelines – Summary of the Recommendations

PSA determination should not be used as a population-wide mass screening test for the early detection of prostate cancer in asymptomatic males.

A PSA determination is recommended for any man with a life expectancy of ten years or more found to have: a prostatic nodule on DRE, an abnormal-feeling prostate, focal lesion, discrete change either in texture, fullness or symmetry which provokes increased suspicion of prostate cancer, and when investigating a secondary carcinoma of unknown origin.

The committee recommends the use of the PSA test to monitor patients with established cancer.

When the PSA is below the laboratory’s diagnostic cutoff (e.g. 4.0 µg/L or an age-adjusted value), and the DRE is negative, no further action is usually taken, other than possible periodic repeat testing (e.g. every two years).

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The use of the PSA test is recommended to monitor patients with established cancer. The PSA test should not be repeated more often than once a month.


5. Does screening do more good than harm?

Since the advent of the PSA test, there has been a push for routine PSA screening for men over the age of 50. However, to date there has been no prospective randomized clinical trial that demonstrates that the benefits of widespread screening and subsequent investigations and treatment are greater than the drawbacks.

An argument for screening is that more cancers are detected at an earlier, clinically localized stage. A Hybritech study which involved 17,157 white men and 804 black men who were mostly between the ages of 50 and 69 showed that over 90% of cancers detected in both groups were clinically localized at the time of diagnosis. It is suggested that if prostate cancer were detected in ways other than screening, the figures for finding localized disease would be a lot less than 90%. The majority of cancers detected in the Hybritech study were thought to be potentially curable at time of diagnosis because not only were they clinically localized, but were also of a lower grade. Clinically localized, low-grade cancers are considered to be the most treatable with curative therapy such as radical prostatectomy.

The basis of the argument in favour of screening is twofold. Firstly, screening detects a high proportion of clinically localized cancers. Secondly, there is a high disease-specific survival rate for radical prostatectomy. However, the critics of this argument suggest that screening may detect only indolent, non-aggressive prostate cancers that may never have become symptomatic. As a result of screening, many men would be subjected to invasive investigations such as TRUS and biopsy. Physical effects of these investigations include infection, bleeding, and hemospermia. These side effects are very common and difficult to cure. Persistence of hemospermia causes considerable distress. The psychological effects of the screening process cannot be understated. Many men and their families experience significant anxiety when awaiting the possible diagnosis of cancer. Normal results provide reassurance, but the possibility of a false negative result remains, leading to a constant state of anxiety in many patients.

One must take into account these side effects when weighing the pros and cons of screening. That is, the reduction in morbidity and mortality resulting from prostate cancer must clearly outweigh the morbidity and mortality caused by the detection and treatment of the disease. While the differences in effectiveness between treatment strategies remain unknown, their adverse effects have been clearly identified. Side effects from standard therapies such as radical prostatectomy and external beam radiation therapy include sexual dysfunction and incontinence as well as a significant reduction in quality of life. A study showed a 30-day post-radical prostatectomy mortality of 0.5%, with no effect of age. Furthermore, compared to other malignancies, prostate cancer has a relatively small impact on the average years-of-life-lost. Studies indicate that the benefit gained from aggressive therapy for well- to moderately-differentiated tumours is small, especially for those with less than 10 years of life expectancy. In addition, patients with early stage prostate cancer have good outcomes even without treatment. Therefore, further evidence must be obtained before a mass screening program can be implemented.

CONCLUSION

Prostate cancer is an important and widely prevalent disease in North America. It is the most common cause of cancer in men and the second leading cause of cancer death. PSA screening has been suggested as a strategy to detect early-stage disease. In order to implement a screening protocol, it must satisfy certain requirements. This article has
outlined issues that a screening protocol must address. A protocol must demonstrate clear benefits of not only early stage detection, but also of early stage treatment.

Data suggest that PSA screening could be cost effective for younger men. Therefore, men between the ages of 50 and 75 years of age should be informed about the risks and benefits of the PSA test in order to make an informed decision. Ontario does not advocate a population-wide screening program. Until studies are completed, the controversy of whether to screen patients will be unresolved. In all cases, it is imperative that there be a thorough discussion between the patient and the physician. This discussion should cover the likelihood of diagnosis of prostate cancer, the sensitivity and specificity of the PSA test, the cost of the test (it is not covered by the Ontario Health Insurance Program in asymptomatic individuals), the anxiety associated with a positive test, and the lack of evidence regarding reduction in mortality as a result of screening. After this discussion, the patient can make a calculated decision regarding the PSA test.

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AUTHOR BIOGRAPHIES

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REFERENCES