Screening for prostate cancer

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Introduction

Prostate cancer is currently the most common human internal malignancy and the second most common cause of cancer death in men. The disease has increased dramatically in incidence since 1989 when PSA (Prostate Specific Antigen) first became available in Canada, and began to be used for early detection and screening for prostate cancer. The incidence of prostate cancer increased by about 300% over the next decade, an unprecedented rise. This was largely due to an increase in case findings resulting from the PSA test. Since about 2000, incidence rates have fallen again as the prevalent cases have been treated and the incidence rates again reflect new ('incident') cases of the disease. Mortality rates initially continued to rise, but over the last 5 years have fallen about 25%.

PSA, the marker that is used for screening, is an enzyme that is secreted into the seminal fluid in high quantities. Its sole function is to liquefy the seminal coagulum after ejaculation, thereby allowing sperm to be freely mobile. It is not in fact prostate specific; PSA is present in peri-urethral glands and breast tissue and is secreted in milk. In normal prostate glands, the PSA back-diffuses into the interstitial fluid from the lumen of the prostatic ducts. Thus the serum PSA increases in men with benign prostatic hypertrophy (BPH). In prostate cancer, the cells lose their polarity and the PSA leaks directly into the serum. This means that prostate cancer results, gram for gram, in a much more substantial increase in the PSA compared to BPH. It also means that there are some differences between the PSA molecule associated with prostate cancer and the PSA associated with benign prostatic enlargement, related to enzymatic processing of the PSA molecule which occurs in the lumen of the prostatic ducts. This results in a lower ratio of free to total serum PSA in prostate cancer than BPH. (FREE of prostate cancer = more FREE PSA).

The differential increase of serum PSA in prostate cancer compared to benign disease creates the opportunity to use the serum PSA level as a screening test for prostate cancer. It has been so used for more than 15 years. The age adjusted cut-offs for PSA are listed in Table 1. It has become absolutely clear that patients whose cancers are detected by PSA screening are at a much earlier, more curable stage. However there are trade offs.

Prostate cancer incidence increases with age. It is unheard of in men under 40; rare in men between 40 and 50, although less rare in those with a strong family history or who are black; and extremely common in men over 60. It is usually

slow growing, requiring about 10 years from diagnosis of localized disease to death, even in those with aggressive disease. Thus, there are few benefits to early detection in men who have a life expectancy of 10 years or less (i.e. age 75 or greater); and these benefits are likely to be outweighed by the risks. The traditional approach to prostate cancer screening is an annual PSA and digital rectal exam beginning at age 50 and stopping in the early 70s. Men with the risk factors mentioned above should begin at age 40. The approach can be fine tuned in a number of ways. If the initial PSA is quite low, repeat testing can be delayed for 2-5 years. A low free-to-total PSA ratio can also play a role in identifying patients at risk.

The controversy over screening is based on the following issues:

Prevalence of occult prostate cancer
Prostate cancer is unique amongst human cancers, in that microfoci of the disease occur normally with aging. Even men in their 20s and 30s often harbour microscopic areas of cancer (1). In men over 50, about 50% harbour microscopic areas of cancer. In most men, these don't cause any problems. Men from all races and regions in the world develop these foci of cancer, although the rate of diagnosis and mortality varies 100 fold between Asia (where it is low), and North America and Scandinavia, where it is high. A central research question currently is finding the explanation for this dramatic difference between races in regions, in spite of the fact that all men develop the microfoci with age.

The stage migration effect
Prostate cancer tends to be a slow growing disease, which can take 20 to 40 years from inception to lethality. When PSA screening was first introduced, many patients who harboured the disease for a prolonged period were diagnosed after an initial PSA test. Many of these patients had substantial volumes of prostate cancer, which was often locally advanced. However, as the many prevalent patients with slow growing prostate cancer were diagnosed and treated, the average extent of cancer, including the volume, the stage, and PSA at diagnosis, has fallen steadily. Indeed, a recent study by Stamey, one of the fathers of PSA, comparing the correlation between PSA and the volume of prostate cancer, showed that this fell from 0.68 in the early 90s to 0.12 in 2003 (2). In other words, once the initial cases with substantial volume of disease were diagnosed and treated, subsequent serially-screened, newly diagnosed patients tend to have smaller volume cancer. The relationship between PSA and prostate cancer volume dropped off dramatically.

The over-diagnosis problem
The Prostate Cancer Prevention Trial is a landmark study recently published (3). This study randomized 18,000 healthy men with normal PSAs and DREs (digital rectal exam) to Proscar®, (a drug which reduces the level of DHT, the active intracellular androgen) vs. placebo. The goal was to determine if Proscar®

prevented prostate cancer. All patients were biopsied at the end of the trial (after 7 years of treatment). This was the first time that a large group of normal men, with normal PSAs, had had systematic prostate biopsies.

The study made an extraordinary observation: that 1 in 4 normal men on the placebo arm subjected to systematic prostate biopsies were found to have prostate cancer. In other words, many of the latent, sub-clinical, autopsy cancers were being detected by the biopsy needle. One in 4 is about 10 times the mortality rate for the disease and suggests that prostate cancer diagnosed by needle biopsy in many men is not clinically significant. (The study also found that Proscar® reduced the rate of a positive biopsy by 25%; but that is the subject of a different article). Importantly, the PSA did correlate with the likelihood of a positive diagnosis; but even with a low PSA, some men had a positive biopsy. The likelihood of prostate cancer at each PSA level is shown in Table 2.

The natural history of prostate cancer

Additional recent data supports the view that many men with low grade prostate cancer have clinically insignificant disease, but that higher grade cancer is life threatening. Peter C. Albertsen studied about 800 men in Connecticut whose prostate cancer was managed with observation alone, and has 20 year follow-up on these patients (4). Patients with low grade cancer had about a 20% risk of dying of prostate cancer, untreated, by 20 years. Patients with intermediate cancer had a 65% chance of prostate cancer death; and patients with high grade cancer rarely survived 20 years without dying of the disease. Thus prostate cancer is clearly a spectrum of diseases, rarely life-threatening at the favourable end, but highly lethal at the unfavourable end.

The Benefit of Treatment

A key component of a successful screening program is proof that early detection and treatment improves the disease outcome. Large scale screening studies addressing the impact of screening are currently ongoing. A definitive study, carried out in Scandinavia and reported recently, has demonstrated unequivocally that radical prostatectomy reduces prostate cancer mortality and improves overall survival compared to no treatment (5). This study, remarkably, randomized 600 men between surgery and watchful waiting. At 10 years, the deaths from prostate cancer were reduced by 50%. The patients in this study were not, primarily, diagnosed on the basis of PSA screening. Most either had voiding symptoms resulting in prostate surgery at which time cancer was found, or a nodule. They tended to have intermediate or high grade cancer. The study has demonstrated that patients with intermediate to high grade cancer benefit from surgical removal of the prostate.

However, the study does not address the benefit of local therapy for small volume, low grade disease referred to above.

The fall in mortality with screening

Since 1990, shortly after PSA testing became available, prostate cancer mortality began to fall in many constituencies. In Canada and the US, it has fallen by 25%. This is a major achievement. The degree to which this has been due to PSA screening is controversial. (Other causes could include improved treatment, greater use of hormonal therapy, and the influence of ascertainment bias of cause of death, a well recognized correlation between falling incidence and falling mortality). Several population-based studies have addressed this. In the Austrian province of Tyrrol, an aggressive program has resulted in 95% of men between 50 and 70 being screened for PSA. In the last 15 years, the mortality in Tyrrol has dropped by 45% compared to the rest of Austria, where screening for PSA is uncommon. This dramatic difference suggests that PSA screening has played at least some role in the steady fall in prostate cancer mortality seen in the last decade.

Active surveillance: a solution to the over-treatment problem

At Sunnybrook Health Sciences Centre in Toronto, we have attempted to resolve the over-treatment conundrum by offering patients with favourable risk cancer (Gleason score 6 or less, 3 or fewer cores positive and 50% or less of each core involved, and PSA 10 or less), an approach of close surveillance. (6) This involves monitoring PSA rate of change and periodic repeat biopsy with selective delayed intervention for patients who show signs of rapid rise in PSA or grade progression. We now have approximately 500 patients on this program. Two thirds have avoided the necessity for local therapy. One third has been treated, with radiation or surgery, for progression. Most of these have been cured. Only 2 patients have died, for a prostate cancer 10 year survival rate of 99.5%. In retrospect, both of these patients were likely incurable at the time of diagnosis. Thus, to date, not a single patient who appeared curable at the time of diagnosis, and received delayed therapy, has suffered a preventable prostate cancer death. This approach, pioneered in Toronto, is now the subject of an international randomized trial comparing it to standard therapy (surgery or radiation).

Who to biopsy

At this point in time, there is no clear consensus as to what the PSA threshold for a biopsy should be. In the near future, risk nomograms will be used, rather than a specific cut-off. For now, it is appropriate to continue to use age adjusted norms, which have the benefit of greater sensitivity in younger men, and more specificity in older men. A rapid increase in PSA has been shown to be associated with more aggressive prostate cancer. Thus in the ‘grey zone’ between 2.5 and 6.5, men who have a rapid rise in PSA (greater than 2.0 ng/ml/year) should also be considered for a biopsy.

Currently, the Free to Total PSA ratio is used primarily to determine if a patient with a negative initial biopsy should have a second set of biopsies.

The future

A number of new markers are under investigation which may prove to be superior to PSA. The most promising one is uPM-3, urinary PCR based marker. In addition, current research efforts are leading to a 'risk grouping' approach. This means that all relevant risk factors, including age, race, family history, PSA, prostate volume, and perhaps individual genetic polymorphisms, are incorporated into an algorithm which then accurately estimates the risk of prostate cancer in an individual.

Summary

PSA screening detects prostate cancer at a point in time when it is more likely to be curable. Patients with intermediate and high risk prostate cancer clearly benefit from early detection and treatment. The risk of over-treatment of clinically insignificant disease is real, but can likely be addressed effectively by adopting a policy of surveillance with selective delayed intervention for those patients with favourable risk disease. Such patients would also be appropriate for secondary prevention strategies. This approach will result in the patients with life-threatening disease receiving appropriate therapy, while those with clinically insignificant disease will be spared the morbidity of treatment.

References

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Table 1
Age adjusted norms for PSA (ng/ml)

Age 40-50	2.5
50-60	3.5
60-70	4.5
70-75	6.5

Table 2
Likelihood of prostate cancer at each PSA level in the Prostate Cancer Prevention Trial

PSA < 0.5	6.6%
.6-1	10%
1-2	17%
2-3	24%
3-4	27%