Prostate Cancer:

When to worry, when to test?

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How prevalent is it?

Prostate cancer is currently the third most common cancer killer in men causing an estimated 4,200 deaths in 2003. One in eight Canadian men will develop prostate cancer in their lifetime. While the incidence has been increasing in recent years, the mortality rate has been declining slightly.

What are the risk factors?

The risk factors are unknown, yet there are associated risk factors (Table 1). Most cases show an adenocarcinoma. The aggressiveness is defined by the Gleason grading system, which is based on a scale of 1 to 5 where the lower number indicates a well differentiated and the higher number indicates poor differentiation. The system grades the two most common patterns. The two numbers are added together to give the Gleason Score. This score is the single most important piece of prognostic information that can be gathered in patients with prostate cancer. It is more informative than the stage (Table 2).

Table 1
Associated risk factors for prostate cancer

- Family history: Including prostate, breast, and ovarian cancer
- Race: Highest incidence in African-American males followed by North American Caucasians; lowest incidence in East Asians
- Diet: A high fat diet is felt to contribute to a higher incidence of prostate cancer

Marshall's worry

Marshall, 48, comes to your office for the first time for a physical exam. His wife is worried about the possibility of prostate cancer.

- In your history, would you inquire about a family history of prostate, breast, colon or ovarian cancer?
- Would you be looking for any particular symptoms?
- In your exam, would you do a digital rectal exam (DRE)?
- If you do, and it is normal, would you do a prostate specific antigen (PSA)?

For a more on Marshall, go to page 101.

Table 2
The stages of prostate cancer

T1	Within the gland, not palpable on DRE.
T1a + T1b	Unsuspected cancers found in tissue removed at the time of a TURP.
T1a	Low Gleason score.
T1b	A higher and more extensive amount of cancer.
T1c	Not palpable on DRE but found as a result of a biopsy carried because of an elevated PSA; this is far the most common stage found today and accounts for more than 70% of new cases in Canada.
T2	Palpable on DRE but that feels to be confined within the gland.
T2a	Indicates involvement in one lobe.
T2b	Indicates involvement in both lobes. Bear in mind that the DRE is, at best, only 50% accurate.
T3	Indicates extra capsular spread.
T3a	Indicates extra capsular spread into the surrounding fat.
T3b	Indicates extra capsular spread into the seminal vesicles.
T4	Indicates invasion of local organs such as the bladder or down the urethra or rarely into the rectum.

Node status is indicated by N0 for no nodes or N+ for nodal involvement and metastases are indicated by M0 for no metastases or M+ in the event of a positive bone scan.

These stages are based on the Tumor, Nodes, Metastases (TNM) system.

DRE: Digital rectal examination
TURP: Transurethral resection

Table 3
Age-related values

Readings should be:

Less Than	Age
2.5 ngms/mL.	< 49
3.5 ngms/mL	50 - 59
4.5 ngms/mL	60 - 69
6.5 ngms/mL	> 70

What are the symptoms?

Early prostate cancer has no symptoms. Obstructive or irritative urinary symptoms are usually due to other problems. If a prostate cancer is causing urinary tract symptoms, it is an indication that the cancer is quite advanced. It is for this reason that it is so important to look for this disease early rather than waiting for symptoms to develop. Symptoms of advanced disease include obstructive or irritative voiding symptoms, hematuria, and renal failure (due to obstruction of the distal ureters), and bone pain. Asthenia, weight loss, and anemia are also findings in advanced disease.

How do you investigate for prostate cancer?

Prostate specific antigen (PSA) is a simple blood test that detects prostate cancer at an earlier stage than any other tool currently available. PSA will aid the diagnosis of prostate cancer five to seven years earlier than the clinical exam. PSA as a population-screening tool is not proven to be of benefit as of yet. PSA testing for a patient who comes to your office for his annual physical examination is a very different situation to population screening. Most practicing urologists

Table 4
Investigations

Prostate biopsy: Elevated PSA above their age related range, or a significant rise in PSA from one test to the next, or an abnormal DRE.

Bone scan: Only if PSA > 20 ngms per mL. CT scan and MRI are at this time of no diagnostic value in men with prostate cancer.

PSA: Prostate specific antigen
DRE: Digital rectal exam
CT: Computed tomography
MRI: Magnetic resonance imaging

More on Marshall

His father had prostate cancer; his mother had colon cancer. His DRE is normal, and PSA is 3.1. Would you want a biopsy?

Biopsy showed a Gleason 7 cancer. As Marshall is 48, a radical prostatectomy was carried out.

There were no complications and he returned to work in 4 weeks. PSA undetectable 4 years after the operation.

strongly advocate the use of PSA testing in such men. Generally speaking, men between 50 and 70 are the classical candidates for PSA testing. For patients at high-risk or with a family history, PSA testing should be seriously considered from the age of 40 onwards. My own practice is to check the PSA at the age of 40, if normal then to check it again at 45. If the test is normal, I would check it again at 50. This recommendation is not universal. It is very important to understand that an elevated PSA in a young man is a far more sinister finding than an elevated PSA in an older man as, in the older age group, an enlarging prostate contributes to a PSA elevation much more than in the young man. This procedure is exactly opposite to screening mammography where the highest positive predictive value is in the older female. PSA should not be measured in men with a life expectancy of less than 10 years. The third way to look for prostate cancer is the digital rectal exam (DRE). The DRE should always be used in combination, as PSA will miss cancer in between 20% to 30% of cases, many of which may be detected by an abnormal DRE. The specificity of PSA is between 60% to 70%. The specificity can be improved by the use of age-related values (Table 3). Age-related values are in standard use in most centres throughout North America.

The specificity of PSA is between 60-70%.

Free/total PSA and PSA velocity are occasionally useful, but not recommended for general use. PSA levels can fluctuate over time in a man without necessarily indicating cancer. There are many factors that can elevate or lower PSA readings. The most common cause of elevated PSA is an enlarged, benign prostate. Prostatitis and urinary tract infection will also cause elevation. It is therefore very important not to measure a PSA in a man who has a lower urinary tract infection until it has been treated and resolved for at least

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four weeks. Prostate cancer also elevates PSA, as does manipulation of the prostate by either cystoscopy or biopsy. Androgen supplements may also elevate the PSA. It is important in such patients to measure PSA before initiating androgen replacement therapy and then to monitor it at regular intervals as recommended by the Canadian Sexual Health Council. PSA level is lowered by hormone treatment for prostate cancer. Levels are also significantly reduced by five alpha reductase inhibitors, such as finesteride and dutasteride. These medications will drop the PSA by approximately 50% and will tend to keep it at this level. Finesteride, 1 mg, which is used for the treatment of baldness, will also reduce PSA levels by about 48%. DRE will have no impact on PSA levels, so it is quite safe to measure a PSA after you have done a physical exam (Table 4).

What is the treatment?

The management of prostate cancer is quite controversial. Options include watchful waiting, radical prostatectomy, external beam radiation, interstitial radiation (brachytherapy), and cryosurgery. There is minimal level one evidence available in the literature to indicate that one treatment option is superior to any of the others. Watchful waiting is generally recommended for an older man with lower grade disease, particularly if his life expectancy is less than 10 years.

Radical prostatectomy is surgery to remove the entire prostate and is the most common surgical management for prostate cancer in North America. It is an invasive procedure but the mortality is approximately

0.2%. Because radical prostatectomy is so common today, the complications are significantly lower than they were 10 years ago. Nonetheless, there is a risk of impotence, urinary incontinence, and bladder neck contracture or stricture formation. The risk of impotence varies depending upon the patient's age, the location of the disease, the extent of the disease, and whether or not a nerve sparing procedure is feasible or performed. It goes without saying that if a man is having erectile dysfunction prior to surgery or any other form of treatment for prostate cancer, then this problem will be exacerbated. Half of men over 50 have some erectile dysfunction.

External beam radiation continues to be refined and today most centres offer three-dimensional conformal radiation. This procedure targets the prostate more accurately, reducing damage to surrounding structures and therefore reducing complications and side-effects. This also allows the use of increasing doses of radiotherapy to treat the cancer. Brachytherapy is a surgical procedure during which radioactive seeds (iodine or palladium) are inserted into the prostate and left insitu permanently. The seeds emit radiation in a very small radius thereby giving a high concentration of radiotherapy to a localized area. Cryosurgery is the use of extreme cold to destroy the target tissue. The technique is a minor surgical procedure and is very similar to that of brachytherapy. It is in use in a limited number of centres in North America and 10- and 15-year results

remain to be reported. However, five-year results are comparable to other treatment modalities. It is a treatment that is very well-tolerated in the elderly man. Impotence is the main side-effect. A prospective, randomized Phase III trial comparing watchful waiting and radical prostatectomy was reported last year from Sweden. The six-year results show a clear benefit in favour of treatment compared to watchful waiting when measured using disease specific mortality and the development of metastases. Further reports from this series are awaited with interest. A prospective randomized phase III trial comparing external beam radiation and cryosurgery has been completed in Calgary, and will be reported in a further two years. The American College of Surgeons is conducting a prospective randomized Phase III trial comparing brachytherapy and radical prostatectomy in low grade disease and patients are currently being accrued to this trial. These trials will help to elucidate which treatments offer the best results for men with localized prostate cancer.

Treatment options for advanced disease are limited to the use of hormone withdrawal therapy. The gold standard is a bilateral orchidectomy but it has been shown that the use of luteinizing hormone-releasing hormone (LHRH) agonists yield similar results. This form of treatment however is palliative with a duration of approximately two years before the cancer becomes hormone independent. Upon treatment, men may experience side-effects, such as loss of energy, loss of libido, hot flashes, anemia and, with long-term treatment, osteoporosis. Because of these side-effects, and also because of cost, intermittent treatment is currently being investigated and explored and is in use in many centres. Transurethral resection of the prostate can be used in men who develop lower tract obstructive symptoms due to their advancing cancer. Ureteric stenting or nephrostomy tube placement can be used for obstructive uropathy and focal external beam radiation can be used successfully for the symptomatic relief of localized bone pain. New forms of chemotherapy are being extensively investigated in the men with advanced disease. CME

Take-home message

1. Prostate cancer is currently the third most common cancer killer in men.
2. PSA is a simple blood test that detects prostate cancer at an earlier stage better than any other tool currently available.
3. The management of prostate cancer is quite controversial. Options include watchful waiting, radical prostatectomy, external beam radiation, interstitial radiation (brachytherapy), and cryosurgery.