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SCREENING FOR CANCER OF THE PROSTATE: AN EVALUATION OF BENEFITS, UNWANTED HEALTH EFFECTS AND COSTS.
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Summary

Introduction

In November 1993 the Minister of Health and Social Services of Quebec requested the Conseil d'évaluation des technologies de la santé du Québec (the Conseil) to undertake an evaluation of the benefits, adverse health effects and costs of screening asymptomatic men for cancer of the prostate.

Expert opinion is divided on this issue. There is no agreement as to whether asymptomatic males should undergo regular screening in order to detect prostate cancer. There has at the same time, however, been a rapid increase in the use of the prostate specific antigen test (PSA) for this purpose and a concomitant increase in the rates of prostate biopsy and radical prostatectomy.

The question at issue is whether this trend is likely to cause worthwhile gains in terms of reduced morbidity and mortality from prostate cancer or whether it is more likely to result in an increased morbidity and waste of resources without significant health benefits.

To answer this question, it is necessary to determine both the extent of under- and over-detection of the screening tests which may be used and the effectiveness of treatment which may be offered to men in whom prostate cancer is detected.

Terminology

Screening
"Screening" refers here to the regular testing of asymptomatic men to detect prostate cancer at an early stage, either in the context of an organised comprehensive programme, or merely the testing of individuals who visit their doctor ("case finding").

The screening strategy under consideration is based on the annual measurement of prostate specific antigen (PSA) in men aged 50 to 69 years, with subsequent use of other tests when necessary.

"Fatal cancers"
Cancers which would cause death if untreated are referred to as "fatal". To avoid excessive extrapolation of post-operative survival data in various reported series, we consider, except when stated, survival to age 85 years. The term "case fatality rate" describes the percentage of individuals diagnosed with prostate cancer who will die there from before age 85 years.

Epidemiology

Mortality
In Quebec 769 men are reported to have died from prostate cancer in 1992 at an average age of 77 years. By contrast, four times that many men died of lung cancer at an average age of 69 years and 1,300 women died of breast cancer at an average age of 67 years.

Age-specific mortality rates have increased slightly each year, increasing on average 1.0 % per year in Canada over the period 1970 to 1990.

Incidence
The age-standardized incidence rates have been rising more steeply, and in Quebec have averaged 1.5 % per year between 1984 and 1990. A reported 3,006 new cases of prostate cancer were diagnosed in 1992 in Quebec. The average age at diagnosis was 72 years.

Most if not all of the increase in new diagnoses up to 1990 appears to be due to the incidental finding of prostate cancer in the course of transurethral prostatectomy. This is an operation to relieve urinary obstruction caused by non-malignant prostatic enlargement. It has been carried out with increasing frequency over this period. However, since 1990 the average annual incidence rate of prostate cancer has been rising even faster and this is almost certainly due to the introduction and increasing use of the PSA test.

The PSA test in Quebec
The PSA test became widely available in the late 1980's and its use in Quebec has more than doubled each year since 1990. The number carried out in private laboratories is unknown, but in hospital laboratories an estimated 300,000 were performed in 1993. It is probable that more than 250,000 of these tests were carried with the object of screening asymptomatic men.

Radical prostatectomy in Quebec
Radical prostatectomy was a rare operation until recently, numbering less than 100 per year until 1986. In the subsequent 7 years it has increased ten-fold, reaching a volume of nearly 1,100 in 1993.

Summary
Since 1990 PSA testing has increased at least ten-fold and the operation of radical prostatectomy nearly three fold. Thus PSA screening followed by further testing, with eventual surgery, is rapidly becoming de facto accepted practice in Quebec.

Under-detection
The number of cancers that may be missed by screening based on PSA is not known precisely. In the light of the reported data, a value of 15 % under-detection is assumed. The possibility that as few as 5 % or as many as 25 % may be missed, is tested in sensitivity analysis.

Over-detection
The object of screening is to detect those cancers which would have caused death if untreated by age 85 (referred to as "fatal" prostate cancers). The detection of the numerous slow growing prostate cancers which never cause death represents over-detection.

The extent of over-detection was estimated as follows. In the absence of "cures" the prostate cancer mortality rate would precisely reflect the incidence of "fatal" prostate cancers in the population. Because in Quebec the number of treatments aimed at cure has until recently been low, the number of new "fatal" cancers each year in the population can still be deduced from the prostate cancer mortality rate. On this basis it is estimated that there may be 1.5 new "fatal" cancers per year for every 1,000 men between the ages of 50 and 69 in Quebec. Assuming that 15 % of these are not detectable by screening, the number of new detectable, "fatal" cancers in any comparable population would be 1.3 per 1,000 each year.

However, we estimate that in a population subjected to annual screening, approximately 8.3 cancers would be discovered for every 1,000 men screened. According to these estimates, the level of over-detection would be 8.3 - 1.3. Thus, 7 out of every 8.3 or 84 % of screen-detected cancers would not prove fatal even if untreated.

Efficacy of surgery for screen-detected cancers

To simplify this analysis it is presumed that radical prostatectomy is the treatment of choice for localised prostate cancer, and this evaluation will consider only the treatment of localised prostate cancer by surgery. Since there is no convincing evidence to the contrary, radiotherapy is assumed to have the same efficacy as radical prostatectomy.

There are no randomized controlled studies of sufficient size to allow us to judge the efficacy of radical prostatectomy as a treatment for prostate cancer. Of necessity, therefore, estimates must be based on the best evidence that is available. In the absence of controlled trials it is necessary to

compare case fatality rates (CFR) of surgically treated individuals with the CFR of patients who are not treated surgically. Two approaches to the latter estimate were used.

Estimated CFR without surgery based on Quebec

First, estimates of CFR were based on the levels of under- and without surgery reported above, based on Quebec prostate cancer mortality rates. According to this approach even in the absence of mortality rates surgery, only 1.3 of every 8.3 (16 %) cancers detected by screening would prove fatal by age 85. Seven other cancers (84 %) would not prove fatal, irrespective of management.

Estimated CFR without surgery based on observed series

Second, to compare with the above estimate, the case fatality rate of men not treated by surgery or radiotherapy was estimated from two follow-up studies. To facilitate comparison between cohorts we estimated what the CFR would be if the mix of ages, grades or stages in each cohort were adjusted to be the same as might be expected in a population screened annually. Examined in this way, the CFR for unoperated screen-detected prostate cancer, up to age 85 years, was 21.3 % and 21.9 % in these two studies.

The approach based on the population mortality rate therefore, suggested a prostate cancer CFR up to age 85 of 16 %, while that based on observed series suggested a rate of 22 %. Thus, according to these estimates, of every 100 men diagnosed with screen-detected prostate cancer, between 84 and 78 would not die from it. It is by its ability to increase survival above such levels that the efficacy of surgery must be judged.

Estimated CFR of men treated surgically

To compare with these estimates, two substantial surgical series are available. Each provides sufficient data to allow the reported mortality to be similarly adjusted to reflect populations of the same mix of age, grade or stage which would be found in a regularly screened population. The adjusted CFR for operated patients in these two reports was 14.4 % and 15.5 % (average 15 %). Thus of every 100 patients with screen-detected cancers which are treated surgically, 85 would not die of prostate cancer by age 85 years.

Surgical efficacy

Thus, in a population subjected to regular screening, we estimate the benefit resulting from surgery to be of the order of one prostate cancer death averted for every 100 operations (16 % CFR without surgery minus 15 % CFR with surgery). The most optimistic estimate of benefit considered (24 % CFR without surgery minus 15 % CFR with surgery) suggests the possibility that 9 of every 100 operations may avert a death. The probability of such an outcome is very unlikely (0.02).

Adverse health effects

To weigh against these estimates of benefit, the chances of morbidity and mortality associated with surgery must be considered. The chance of a complication of radical prostatectomy will vary with the general health of the patient and the quality of the surgery. However, on average it is estimated that for every 100 operations there will be 7.0 severe but transient complications such as a pulmonary embolism or a myocardial infarction and 0.3 deaths. Long-term or permanent complications include: rectal injury, 0.3 %; urethral stricture, 4.0 %; severe urinary incontinence, 2.0 %; and impotence of previously potent men, 57 %.

Costs

It is estimated that the cost of the screening and treatment of a previously unscreened population would be approximately $ 138,000 per thousand men screened. Thereafter, the costs of annual re-screening would fall rapidly and by the third year would be approximately $ 66,000 per thousand men screened. Averaged over the first 10 years, the costs of screening and treatment would be

approximately $ 77,000 per thousand men per year. Thus, a program involving all 671,000 men aged 50 to 69 years would cost approximately $ 52 million per year over the first 10 years.

At least 10 to 15 years of screening would have to take place before the gains were seen. Thus whatever the health benefits might be, an expenditure of approximately $ 500 million to $ 700 million would be necessary before they started to appear.

The uncertainty concerning the effectiveness of surgery is reflected in the wide range of cost-effectiveness ratios which are conceivable. With health benefits discounted at 5 % over 15 years, the estimate based on the most likely combination of variables (scenario 1) is $ 214,000 per year of life gained. The unlikely combination of variables envisaged in scenario 6, which combines the highest estimate of "fatal" cancers in the population with the lowest rate of "non-fatal" cancers detected, results in an estimated $ 25,000 per year of life gained, when similarly discounted.

Conclusions

Under-detection
It is estimated that approximately 15 % of "fatal" cancers would be missed by a screening strategy based on PSA.

Over-detection
It is estimated that for every "fatal" cancer which requires treatment, approximately 5.4 non-fatal cancers will also be detected (i.e., 84 % of cancers detected by screening would <u>not</u> prove fatal even if untreated).

Effectiveness of surgery
The benefit of radical prostatectomy remains unproven. This analysis suggests that benefit, if any, is unlikely to be substantial for a population subjected to regular screening. According to the estimates considered more probable, 1 in every 100 operations would avert a death. According to the most optimistic and unlikely estimate considered, only 9 of every 100 such operations are likely to avert a death.

Complications of surgery
It can be anticipated that 2 operations of every 100 will probably cause severe long term urinary incontinence and half of the men who were previously sexually potent will become permanently impotent and one of every 300 operations will cause a death.

Policy implications
From the perspective of the health care system, we must conclude as have others, that these health gains are too uncertain to justify the adverse health effects and the use of resources which would be associated with screening for prostate cancer based on PSA. Furthermore, the extent of the benefit which might result is relatively small. This is equally true for an organized comprehensive screening programme as it is for such screening as presently takes place in the context of case-finding.

Individuals may be less concerned with the use of resources than with the chances of benefit or harm which may come to them personally as a result of measurement of PSA. Every man, before his PSA is measured, should therefore, be made fully aware of the possible results of undertaking this test. He should be aware that a normal PSA does not mean there is no cancer; that if cancer is found there is as yet no proof that surgery will improve the chances of survival; that it is unlikely to do so greatly; and that it is associated with significant complications. Accordingly the decision to measure PSA requires careful review with the help of a physician. The information necessary for consideration of this decision is summarized in the following pages.

Prospects of better data

There is no immediate prospect that better data, based on randomized trials of screening, will become available. Current trials will take 10 to 15 years to complete and because of possible changes in technology such trials may never be completed.

For the present, therefore, the decision to undertake screening will have to depend on estimates of the type made in this study. It should be incumbent on those who would disregard such estimates to produce more convincing interpretations of the available data.

THE DECISION TO MEASURE PSA
(Prostate specific antigen)
THE INDIVIDUAL PERSPECTIVE

While there is not universal agreement amongst all experts, two important groups, The Canadian Task Force on the Periodic Health Examination and the Canadian Association of Urologists do not recommend measurement of PSA to detect early cancer as a routine test. For men who wish to consider having this test carried out the following information is provided to assist them in this decision. It is based on a report of the *Conseil d'évaluation des technologies de la santé du Québec*, entitled "Screening for Cancer of the Prostate: An evaluation of benefits, unwanted health effects and costs".

Background. PSA is a normal product of the prostate gland. Increased levels of PSA can be found in the blood when prostates are enlarged or inflamed. PSA also rises when the prostate is affected by cancer. Accordingly, PSA is frequently measured when cancer of the prostate is suspected or to evaluate the progress of already diagnosed cancer. Such uses of the test are not under discussion here.

In men who die of other causes and are subjected to autopsy, unsuspected prostate cancer is often found. It occurs more frequently as age increases, and can be found in over 50% of men above age 70. Most of these cancers grow slowly and never cause any problems. However, some grow more rapidly, spread outside the prostate gland and cause illness and eventually death. It is hoped that if such cancers can be detected before they have spread, they may be removed successfully by surgery. One way to detect them earlier is to measure the level of PSA in the blood and this is the use of the PSA test under consideration here. *Before* a PSA measurement is carried out for this reason, every man should consider carefully the chance of benefit or harm that may result.

The probabilities listed below are based on averages for men aged 50 to 70 years. There is, of course, no average man and each individual must consider his personal chances with his doctor. The following information is furnished as background to such discussions.

What is the chance that the PSA test will be positive? **Between 6 % and 8 %** of PSA tests will be positive (PSA 4 or over).

Does a normal PSA mean that there is no cancer? **No.** In this age group perhaps 15 % of prostate cancers cause no elevation of PSA. So with a normal PSA cancer is unlikely, but its presence cannot be excluded.

Does a raised PSA mean that there is cancer? **Sometimes.** If it is very raised, cancer is probable, but lesser elevations of PSA can be caused by simple prostate enlargement or inflammation. So when PSA is raised it is necessary to take further steps to find out whether there is cancer or not. These consist of a digital rectal examination and a prostatic ultrasound examination. When a lump is felt or a possible abnormality is detected by ultrasound, cancer is more likely. However, it still must be confirmed by needle biopsy.

When no lump is felt and the ultrasound examination is negative, can we conclude there is no cancer? **No.** Not all areas of the prostate can be reached with the finger or even by the ultrasound probe. So, when PSA is raised, even if these tests are negative, a biopsy of the prostate will usually be advised. This involves the insertion of a needle into the prostate, through the front wall of the rectum and the withdrawal of samples of prostate tissue for examination under the microscope. The procedure is virtually painless but may be followed by mild fever for one or two days, necessitating an antibiotic.

If no cancer cells are found at prostate biopsy, does this mean there is no cancer? **No**. Biopsy may miss a cancer. When PSA is raised and the biopsy is negative, further biopsies will usually be recommended.

If cancer is found, will surgery be recommended? **Usually**. But first, tests must be carried out to determine how aggressive the cancer is and wether the cancer has spread too far to be operable or not. If these tests are satisfactory surgery will be recommended.

If cancer is present and is considered to be operable, what are the chances that it will be cured by surgery? First, remember that the chance of benefit for any particular individual will vary with the stage and grade of the cancer which has been diagnosed and with the individual's age and health. These cancers usually grow slowly and surgery is not usually recommended for men over 70 years.

For men under 70 it is estimated that of every 100 cases of prostate cancer detected by screening, even in the absence of surgery only 16 will prove fatal (before age 85). Thus if 100 men undergo surgery, 84 will appear to be cured even if surgery has had no effect at all.

There is as yet no good evidence that survival is significantly improved by surgery. It is quite possible that no more than one of every 100 men undergoing radical prostatectomy may benefit from the operation. The most optimistic, and least likely estimate considered is that 9 of every 100 may benefit.

What are the chances of ill-effects of surgery? These vary with a man's age and health and with the surgeon and hospital in question. The reported results in hospitals where this operation is performed frequently are listed below. One should ask the surgeon in question what complication rates can be expected. The chances listed below suggest probable rates in a good hospital:

Short-term complications (i.e., pulmonary embolism, myocardial infarction): ..... 7.0 %

Long-term or permanent complications:

Death	0.3 %
Bowel injury requiring further surgery	0.3 %
Complete loss of bladder control	2.0 %
Urethral narrowing requiring further treatment	4.0 %
Some leakage of urine on coughing or straining	10.0 %
Impotence (of previously potent men)	57.0 %

Each man should therefore consider carefully the probabilities of benefit and harm which may result from surgery ***before*** PSA is measured. Men who consider that the risks and inconveniences associated with surgery outweigh the uncertainty of benefit ***would be wise not to have their PSA measured in the first place***.