Education

Éducation

From the *Department of Social and Preventive Medicine, the †Centre de recherche en cancérologie, the ‡Groupe de recherche en épidémiologie and the §Department of Surgery, Université Laval, Quebec City, Que.

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The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series. The list of members of the Alliance appears at the end of this article.

Series editors: *Dr. Neill A. Iscoe, Medical Oncologist, Toronto–Sunnybrook Regional Cancer Centre, and Dr. Michael Jewett, Professor and Chairman, Division of Urology, University of Toronto, Toronto, Ont.*

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Clinical basics

Prostate cancer: 4. Screening

François Meyer,*†‡ MD, DSc; Yves Fradet,†§ MD

The case

A health-conscious 62-year-old man with a recent history of angina is in his general practitioner's office for a scheduled follow-up visit. While vacationing in the United States, he heard about a new test for prostate cancer and wonders if he should have one. His search for information at the library and on the World Wide Web has left him perplexed. He stopped smoking recently, feels well and has no urinary symptoms. His wife, who undergoes mammography regularly, is encouraging him to have the test. He is now seeking his physician's advice.

Physicians' opinions differ on the meaning of the word "screening." To clarify our discussion here, we are adopting Morrison's definition,[1] in which the setting and circumstances of testing are irrelevant:

> 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.

Others distinguish screening from case finding.[2] For them, "screening" applies only when people are invited to participate in mass testing programs or to visit their physician's office for an annual checkup or periodic health examination, whereas "case finding" refers to screening tests administered to patients who are consulting the physician for unrelated illnesses or problems. In the context of the Canadian health care system, such a distinction is confusing, because there are very few organized mass screening programs and annual checkups are no longer recommended.[3] Therefore, screening is usually done in the physician's office during a visit for unrelated reasons, and in most instances, the terms "case finding" and "screening" represent the same reality.

In Canada decisions on screening are generally made in the physician's office. Proposing a test for screening carries a greater ethical responsibility for the physician than requesting the same test for the diagnostic investigation of symptoms. In screening, the physician initiates the process and bears the responsibility that benefit will follow. Clinicians should be prepared to discuss this issue with their patients, to share uncertainties with them, to listen to their concerns and preferences and to provide individual counselling.

Evaluation of screening tests

Since the early 1990s, when the prostate-specific antigen (PSA) test became available, screening for prostate cancer has received considerable attention from the medical profession and the public. The PSA test is attractive because of its simplicity, objectivity, reproducibility, lack of invasiveness and relatively low cost. Its cancer detection capability is superior to that of the digital rectal

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examination (DRE),[4] which has commonly been recommended for the early detection of prostate cancer.

In 1994 the US Food and Drug Administration approved the use of the PSA test in conjunction with DRE as an aid in detecting prostate cancer. Although no Canadian medical organization has come out in favour of screening for prostate cancer,[5] such screening is widely advocated in the United States, especially by the American College of Radiology, the American Urological Association and the American Cancer Society. All of these organizations recommend the combined use of PSA and DRE for screening for prostate cancer. Men with a PSA level over 4 ng/mL, a DRE that raises suspicions of prostate cancer (or both) undergo further examination by transrectal ultrasonography (TRUS) and biopsy. This screening strategy has been used in several programs[6,7] and is being evaluated in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial of the US National Cancer Institute.[8]

To estimate the sensitivity and specificity of the combination of PSA testing and DRE, we obtained data from the American Cancer Society's National Prostate Cancer Detection Project[4] and the European Randomized Study of Screening for Prostate Cancer,[9] in which every participant also undergoes TRUS (Table 1). For comparison, we abstracted similar data for 50- to 59-year-old women, who were chosen at random for screening by both mammography and physical examination in the Canadian National Breast Screening Study[10] (Table 2).

The data in Tables 1 and 2 were used to estimate the validity of the screening tests for prostate and breast cancer (Table 3). Sensitivity is the ratio of the number of people with a positive test result to the total number of people with the disease in the screened population. For prostate cancer, for the data in Table 1, this ratio is 197/226. It is difficult to identify with certainty all cases of cancer present at the time of screening, including those missed by the test. Different methods, based on different assumptions, have been proposed to resolve this problem. For prostate cancer, we considered all cancers found by biopsy in men with abnormal PSA, DRE or TRUS results as cancers present at the time of screening. For breast cancer, we considered all cancers identified in women with a positive test result plus interval cancers diagnosed in the following year as cancers present at the time of screening. The estimated sensitivity of screening for prostate cancer with PSA testing and DRE was 87.2%, whereas that for screening for breast cancer with mammography and physical examination was 90.4%.

The specificity of screening is the ratio of the number of people free of the disease who have a negative test result to the total number of people free of the disease in the screened population (in Table 1, 5828/6997). For the data presented in Tables 1 and 2, specificity was the same for prostate cancer (83.3%) and breast cancer (83.5%).

Thus, the estimated sensitivity and specificity of the combined screening tests for prostate cancer are similar to those of the most sensitive screening strategy for breast cancer. For both cancer sites, these measures are based on healthy asymptomatic subjects responding to an invitation to participate in a screening study.

Table 1: Outcome of initial screening for prostate cancer by prostate-specific antigen (PSA) testing and digital rectal examination (DRE) in 7223 men 55–74 years of age[4,9]

	Prostate cancer		
Test result	Present	Absent	Total
Positive*	197	1169	1366
Negative	29†	5828	5857
Total	226	6997	7223

*A positive test result corresponds to a PSA level of more than 4 ng/mL, a suspicious DRE result or both.
†Men with a false-negative screening test result are those in whom prostate cancer was discovered by biopsy after transurethral ultrasonography yielded abnormal findings.

Evaluation of screening programs

The predictive value of a positive test result is an important measure that is usually considered in the evaluation of a screening program. It is defined as the ratio of the number of people with a positive test result who have the disease to the total number of people with a positive

Table 2: Outcome of initial screening for breast cancer by mammography and physical examination in 19 711 women 50–59 years of age[10]

	Breast cancer		
Test result	Present	Absent	Total
Positive*	142	3230	3372
Negative	15†	16324	16339
Total	157	19554	19711

*A positive test result corresponds to a suspicious finding by mammography, physical examination or both.
†Women with a false-negative screening test result are those in whom breast cancer was discovered during the first year of follow-up (interval cancers).

Table 3: Validity measures of screening tests for prostate and breast cancer

	Prostate cancer	Breast cancer
Sensitivity, %	87.2	90.4
Specificity, %	83.3	83.5
Positive test results, %	18.9	17.1
Prevalence of cancer, %	3.1	0.8
Predictive value of a positive test result, %	14.4	4.2

test result (in Table 1, 197/1366). The predictive value of a positive test result is influenced by the sensitivity and the specificity of the screening test and by the prevalence of the disease at the detectable preclinical phase in the screened population. The prevalence of cancer at the detectable preclinical phase is much higher for prostate cancer than for breast cancer (3.1% v. 0.8%), as is the predictive value of a positive test result (14.4% v. 4.2%). The proportion of test results that were positive (18.9%), the prevalence of cancer (3.1%) and the predictive value of a positive test result for prostate cancer (14.4%) in these studies were slightly lower than those observed in 3 other screening programs using PSA and DRE:[11] 18% to 26%, 3.5% to 4.0% and 15% to 21%, respectively. Therefore, on the basis of the validity measures of the screening tests and the characteristics of the screening programs, screening for prostate cancer appears even more promising than screening for breast cancer.

Teaching points

- The prostate-specific antigen (PSA) test is easy to administer, reproducible and inexpensive. Its cancer detection capability is superior to that of digital rectal examination (DRE) alone.
- Although PSA screening is not advocated by medical organizations in Canada, it is routinely used.
- The estimated sensitivity and specificity of PSA testing combined with DRE for prostate cancer screening are similar to those of the most sensitive screening strategy for breast cancer.
- In the absence of solid evidence of the efficacy of screening, patients and their physicians must make decisions on the basis of personal values and preferences such as the patient's fear of cancer, the potential complications of treatment and the effect of those complications on the patient's quality of life.

Is screening beneficial?

Comparison of the survival rate for cases detected by screen-ing with that for clinically diagnosed cases is flawed because of several biases: selection, overdiagnosis, lead time and length bias. The randomized controlled trial is the only study design that overcomes these biases and provides a valid assessment of the efficacy of screening in reducing disease-specific mortality rates. Over the past 30 years, randomized controlled trials of breast cancer screening with mammography and clinical breast examination have provided overwhelming evidence that screening in women 50–69 years of age reduces breast cancer mortality rates. In contrast, there are no published data on the efficacy of screening for prostate cancer.

Two major randomized trials are underway, the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial[8] and the European Randomized Study of Screening for Prostate Cancer (ERSSPC).[9] The PLCO trial is an efficacy trial in which 37 000 men aged 60–74 years are being screened annually for 4 years for prostate, lung and colorectal cancer. An equal number of men are being followed with routine medical care as controls. Both PSA testing and DRE are being used in the screening for prostate cancer. A 10-year follow-up of all trial participants will be carried out to determine the effect of screening on prostate cancer mortality rate. Recruitment for the trial started in 1993. The ERSSPC is another efficacy trial, started in 1994, in which PSA, DRE and TRUS are being used for screening. The age eligibility criteria and the frequency of rescreening vary from centre to centre. A total of 135 000 men will be recruited into the trial and followed for 10 years. An international collaboration has been established to pool the data from all prostate cancer screening trials to increase statistical power and provide results as early as possible.[12]

Waiting for trial results

These trials in the United States and Europe will not provide a first estimate of the efficacy of screening for prostate cancer before the year 2006. Furthermore, the expected statistical power of the trials will be reduced by poor compliance in the screening arm, contamination in the control arm and an overall downward trend in prostate cancer mortality rates.[13] Thus, there is concern that the question of whether screening for prostate cancer reduces death from that disease will not be answered until much later — or never.

While waiting for the results of trials in other countries, all Canadian organizations that have adopted a position on the prostate screening issue recommend that patients who request screening be given objective information about the potential benefits and adverse effects of early detection and treatment of prostate cancer so that they can make an informed decision. Some men may experience adverse effects from screening (e.g., those with a false-positive test, those with a false-negative test and those in whom earlier detection of cancer does not result in postponement of death), whereas other men might benefit from screening (only those whose death is postponed because of screening and treatment). It is assumed that men considering screening for prostate cancer and their physicians have enough information to weigh the expected good and harm. The main difficulty with

this position is the current absence of any data on the only worthwhile benefit from screening: the reduction of deaths from prostate cancer. Therefore, it is likely that a man's decision to undergo screening for prostate cancer will rest on beliefs rather than objective information.

In evaluating screening programs, it is common practice to consider the 10 criteria proposed by the World Health Organization (Table 4).[14] Screening for prostate cancer clearly satisfies 5 of these criteria, but the status of the other 5 remains uncertain. Furthermore, none of these criteria directly addresses the fundamental question of whether screening reduces the mortality rate of the disease in the screened population.

Prostate cancer is unquestionably an important public health problem. It has a long, detectable, preclinical phase, especially when PSA testing is used for screening. In the Physicians' Health Study, a prospective study of 22 000 physicians in the United States, PSA was measured in stored blood samples.[15] PSA testing up to 4 years before diagnosis would have detected in 73% of the cases of prostate cancer that occurred in this group. The average lead time was 5.5 years, which suggests that the average detectable preclinical phase of prostate cancer exceeds 10 years.[1] This would make screening for prostate cancer very attractive, because the testing would not have to be repeated every year, but possibly only every 5 years or more.

We have a good understanding of the natural history of prostate cancer. The fear that PSA screening would detect a great number of latent cancers that would never have progressed to clinically significant tumours[5,16] now appears unfounded; most prostate cancers detected by PSA screening have been considered clinically significant.[15,17] Furthermore, the detection rates for latent cancer appear to be similar for prostate and breast cancer screening.[18] The concern that there is no way of predicting which screening-detected cancer would have progressed to cause significant morbidity and death[5,16] now appears somewhat overstated. Tumour grade, clinical stage and pretreatment PSA level have been shown to predict independently the progression of prostate cancer after radical prostatectomy,[19] whereas age and tumour volume have not.[11]

There is now some evidence that radical prostatectomy is an effective treatment for the disease. A prospective study of about 60 000 patients treated for prostate cancer in the United States between 1983 and 1992 showed that men referred for radical prostatectomy had a better 10-year survival rate than those for whom the initial treatment decision was radiotherapy or expectant management, particularly for patients with poorly differentiated tumours.[20] The frequency and severity of the adverse side effects of radical treatments are well known. However, many men would gladly accept the risk of iatrogenic impotence and incontinence if radical treatment spares them the pain of metastatic prostate cancer and postpones their death.

This is why it is so important to clearly determine the efficacy of screening in reducing prostate cancer mortality rates. For the first time in record-keeping history, mortality rates from prostate cancer are decreasing in the United States,[21] and a similar trend could be occurring in Canada.[22] This reduction is probably a consequence of better patient management and improved treatment not only for localized tumours but also for advanced prostate cancer. Because prostate cancer mortality rates declined relatively early after the initiation of widespread screening with PSA testing, it is unlikely that screening has contributed to the observed decline.

In the case described at the beginning of this article, the physician can explain that screening for PSA is a good test that detects clinically significant prostate cancers. He can reassure the patient that surgery can improve the survival of men with localized tumours. At the same time, the physician will have to warn the patient that if screening yields a positive result, he may have to face cancer, its treatments and their consequences sooner. Thus the decision as to whether to undergo screening for prostate cancer depends on the patient's personal values and preferences: his fear of cancer, the potential complications of treatment and the impact of those complications on quality of life, in the current absence of proof that screening will delay or prevent death from prostate cancer.

Table 4: Assessment of screening for prostate cancer on the basis of World Health Organization criteria[13]

Criterion	For prostate cancer
Is the disease an important health problem?	Yes
Is there an accepted (effective) treatment for patients with the disease?	Probably
Are there facilities for diagnosis and treatment?	Yes
Is there a detectable preclinical phase of the disease?	Yes
Is there a suitable screening test?	Yes
Is the screening test acceptable to the population?	Yes
Is the natural history of the disease adequately understood?	Partially
Is there a generally accepted strategy to determine which patients should be treated?	To some degree
Are the costs generated by the screening program acceptable?	Possibly
Is there a program for continuous screening?	Premature

References

1. Morrison AS. *Screening in chronic disease*. New York: Oxford University Press; 1985. p. 3.
2. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. 2nd ed. Boston: Little, Brown; 1991. p. 153.

3. Introduction. In: Canadian Task Force on the Periodic Health Examination. *The Canadian guide to clinical preventive health care*. Ottawa: Health Canada; 1994. p. x.
4. Mettlin C, Murphy GP, Ray P, Shanberg A, Toi A, Chesley A, et al. American Cancer Society: National Prostate Cancer Detection Project. *Cancer* 1993;71:891-8.
5. Feightner JW. Screening for prostate cancer. In: Canadian Task Force on the Periodic Health Examination. *The Canadian guide to clinical preventive health care*. Ottawa: Health Canada; 1994. p. 812-23.
6. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA* 1993;270:948-54.
7. Labrie F, Dupont A, Suburu R, Cusan L, Gomez JL, Kouytsilieris M, et al. Optimized strategy for detection of early stage, curable prostate cancer: role of prescreening with prostate-specific antigen. *Clin Invest Med* 1994;16:426-41.
8. Gohagan JK, Prorok PC, Kramer BS, Hayes RB, Cornett JE. The prostate, lung, colorectal, and ovarian cancer screening trial of the National Cancer Institute. *Cancer* 1995;75:1869-73.
9. Schröder FH. The European screening study for prostate cancer. *Can J Oncol* 1994; 4(Suppl):102-9.
10. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992;147:1477-88.
11. Coley MC, Barry MJ, Fleming C, Mulley AG. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. *Ann Intern Med* 1997;126:394-406.
12. Auvinen A, Rietbergen JBW, Denis LJ, Schröder FH, Prorok PC. Prospective evaluation plan for randomized trials of prostate cancer screening. *J Med Screening* 1996;3:97-104.
13. National Cancer Institute. Cancer death rate declined for the first time ever in the 1990s [press release]. 1996 Nov 14. Available: rex.nci.nih.gov/massmedia/pressreleases/cancerdecline.htm (accessed 21 sept 1998).
14. Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: World Health Organization; 1969. Public health paper 34.
15. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;273:289-94.
16. Green CJ, Hadom D, Bassett K, Kazanjian A. *Prostate specific antigen in the early detection of prostate cancer*. Vancouver: British Columbia Office of Health Technology Assessment; 1993.
17. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathological and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994;271:368-74.
18. Benoit RM, Naslund MJ. Detection of latent prostate cancer from routine screening: comparison with breast cancer screening. *Urology* 1995;46:533-7.
19. Zagar GK, Pollack A, von Eschenback AC. Prognostic factors for clinically localized prostate carcinoma. *Cancer* 1997;79:1370-80.
20. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet* 1997;349:906-10.
21. Wingo PA, Ries LAG, Rosenberg HM, Miller DS, Edwards BK. Cancer incidence and mortality, 1973–1995: a report card for the U.S. *Cancer* 1998;82:1197-207.
22. Meyer F, Moore L, Bairati I, Fradet Y. Quebec prostate mortality dropped in 1996. *Cancer Prev Control* 1998;2:163-6.

Reprint requests to: *Dr. François Meyer, Laval University Cancer Research Center, Centre hospitalier de l'Université du Québec, Pavillon Hôtel-Dieu, 11, Côte du palais, Québec QC G1R 2J6; fax 418 691-5562; fmeyer@gre.ulaval.ca*

The following organizations are members of the Prostate Cancer Alliance of Canada: Canadian Association for Nurses in Oncology, Canadian Association of Radiation Oncologists, Canadian Cancer Society (National), Canadian Prostate Cancer Network, Canadian Prostate Cancer Research Foundation, Canadian Urology Association, Canadian Uro-Oncology Group and National Cancer Institute of Canada.