CME CREDIT

TAKE-HOME POINTS FROM EDUCATIONAL PRESENTATIONS BY CLEVELAND CLINIC FACULTY AND VISITING PROFESSORS

The prostate cancer screening controversy in perspective

KENNETH W. VAUGHN, JR, MD
Section of Preventive Medicine, Department of General Internal Medicine, Cleveland Clinic

ABSTRACT

Until long-term ongoing trials show that screening for prostate cancer is beneficial and cost-effective, physicians should focus screening efforts on high-risk patients most likely to benefit from treatment, and inform patients about the pluses and minuses of current screening, diagnostic, and treatment methods.

ANY SCREENING METHOD should be highly sensitive and specific, easy to perform, noninvasive, inexpensive, and cost-effective. Further, if large-scale screening for a disease is undertaken, effective treatments that improve outcome must be available. There is still some question whether current screening methods for prostate cancer meet these criteria.

On one hand, evidence of the potential benefits of screening prostate-specific antigen (PSA) levels can be seen in a lower incidence of metastatic disease at the time of prostate cancer diagnosis since PSA testing began. In addition, PSA testing has a high sensitivity, ie, it is good at finding cancer, which is important, since early treatment is the only chance for cure.

On the other hand, the benefits and cost-effectiveness of prostate cancer screening methods are not yet proven in long-term randomized clinical trials, and data will not be available for another 10 years. Both of the current screening tools—digital rectal examination and PSA determination—produce false-positive and false-negative results.

Early treatment is the only chance for cure in prostate cancer, and early detection is possible with current methods. Yet cure may not be necessary or even beneficial for many, depending on their age at the time of diagnosis.

CHALLENGES TO SCREENING FOR PROSTATE CANCER

Prostate cancer is very common: more than 184,000 new cases are expected to be identified in 1998, and more than 39,000 men will die of prostate cancer this year.[1]

The natural history of prostate cancer is quite variable, which presents a challenge to screening. Tumor grade is the primary determinate of prognosis. A prostatic tumor may long remain microscopic and indolent, or it may be more aggressive and penetrate the capsule before it is palpable. Even low-grade tumors, given enough time, will eventually metastasize. This variability often results in underestimation of tumor stage, even at the time of surgery.

The benefit of prostate cancer screening is not proven

RISK FACTORS FOR PROSTATE CANCER

The most important risk factor for the development of cancer of the prostate is age, but a diet high in animal fat and a positive family history are other important contributing factors.

Family history

Most cancer of the prostate is sporadic, but about 9% is genetically determined, probably as an autosomal dominant trait. Having a first-degree relative (ie, father or brother) with prostate cancer increases a man's risk to 2.4 times normal. If a first-degree and a second-degree relative have prostate cancer, the risk is increased to 9 times normal. The American Cancer Society and the American Urological Association advise anyone with a family history of prostate cancer to begin PSA screening after age 40.

Race and androgen levels

Prostate cancer is androgen-dependent, and African-American men, in whom androgen levels are higher than in Caucasian men, have a 15% higher risk than Caucasians. Japanese men have a lower overall risk. However, if a Japanese man moves to Hawaii and adopts a Western (high-fat) diet, his risk of carcinoma of the prostate will increase.

Other factors

Vasectomy is probably not a risk factor. Benign prostatic hypertrophy, although frequently found in association with cancer, does not increase the risk. Dietary supplements such as vitamin B and vitamin E, beta carotene, and selenium may decrease the risk slightly. DHEA (dehydroepiandrosterone) may increase the risk.

APPROACHES TO MANAGEMENT OF PROSTATE CANCER

Currently, we have four approaches to the management of carcinoma of the prostate.

Expectant management. Observation without treatment is usually reserved for patients age 75 and older. However, it is not a popular option. Although 84% of patients will survive 10 years without treatment, 42% of them will develop advanced cancer with bone metastasis, and few older patients are willing to accept such a high risk of metastatic bone disease. Still, while observation is perhaps an unusual recommendation for someone with cancer, it may be the most appropriate recommendation for many elderly men.

For very old patients, hormonal therapy may be the best option

Radical prostatectomy. Surgery is still the gold standard for curing prostate cancer and has a 10-year survival rate of up to 94%.[2] Cure is possible only if the tumor is confined within the capsule of the prostate. Earlier detection of low-volume tumors via PSA testing is improving the surgical success rate and permitting more frequent use of nerve-sparing and bladder neck-sparing procedures.

Complications of surgery are common. Postoperatively, incontinence is almost inevitable and may persist in as many as 30% of patients 2 to 4 years after surgery. Impotence occurs in about 30% of patients and can occur even with the newer nerve-sparing procedures.

Radiation therapy. Compared with surgery, radiation has had a lower 10-year survival rate (74%); however, because radiation was often reserved for patients with larger tumors and higher PSA levels, patient selection clearly introduces a significant bias.

Both external-beam radiation and interstitial brachytherapy (radiation via tissue implantation of radioactive "seeds") can result in significant complications, including stress incontinence (50% of patients), severe incontinence (7%), sexual dysfunction (30%), and chronic proctitis (10%). Rarely, proctitis may be so severe that colostomy is required. One in 200 to 500 patients may even die as a result of this treatment.[3]

Recently, with PSA screening identifying a higher percentage of low-volume cancers, radiation therapy has produced success rates comparable to those of surgery.

Primary hormonal therapy. For many older patients, observation is not an option: they want some form of treatment. Their choice is either radiation therapy or primary hormonal therapy. If life expectancy is less than 10 years, hormonal treatment consisting of a luteinizing hormone-releasing hormone agonist or an antiandrogen may be the best option. Complications—hot flashes, decreased libido, and breast tenderness—are self-limiting and do not require discontinuation of therapy.

THE CONUNDRUM OF PROSTATE CANCER

TABLE 1 illustrates the difficulty of deciding whether prostate cancer is worth treating.[4] A 55-year-old man without prostate cancer has a life expectancy of 21.4 years. If he has a well-differentiated, microscopic cancer and does not undergo treatment, his life expectancy does not change. If he has cancer of any grade confined within the capsule and undergoes treatment, life expectancy remains unchanged.

However, if he has a moderately differentiated cancer and does not undergo treatment, life expectancy is reduced to 17.5 years. In this patient, as long as the tumor is confined to the capsule, treatment brings a substantial (4-year) benefit in years of life saved.

Moderately differentiated cancer, if

untreated, reduces life expectancy by 2 years for a 65-year-old, and by only 1 or 2 months for a 75-year-old. But for a 55-year-old man, not treating this cancer reduces life expectancy nearly 4 years. Thus, the age of the patient is key in determining the choice of observation vs treatment. Furthermore, while life expectancy does not change dramatically in the older patient with moderately differentiated cancer without treatment, the incidence of metastatic disease and complications is high in these patients. Therefore, some form of treatment is recommended.

CURRENT SCREENING METHODS: AN APPRAISAL

Digital rectal examination

Digital rectal examination is not sensitive enough to find many early, curable prostate cancers. It underestimates stage II tumors and overestimates stage III tumors 40% of the time, and it has not been shown to reduce mortality or improve quality of life. Its positive predictive value is only 20%. From 15% to 17% of men over the age of 50 will have a suspicious finding if the examination is thorough and focuses on identifying induration, asymmetry, and nodularity within the prostate.

Transrectal ultrasound

Transrectal ultrasound is expensive and operator-dependent and is an unreliable diagnostic method. Its sensitivity is relatively high, but specificity is low. It is best used as a diagnostic technique in follow-up to an abnormal digital rectal examination or elevated PSA levels.

Prostate specific antigen determination

The introduction of PSA level determination has resulted in the discovery of many new cases of prostate cancer, 95% of which are clinically localized and 65% to 75% of which are pathologically localized.[5] Sensitivity is relatively high (92%) but specificity is much lower, since benign prostatic hypertrophy may raise PSA levels above normal in as many as 25% of cases. Age-specific values by race have been defined for PSA, which increases sensitivity.[6] The finding of a low percentage of free (unbound) PSA increases the specificity. The average doubling time for PSA is 4 years, and the PSA level should not increase by more than 0.75 ng/mL per year.

Limitations of PSA. As appealing as it may be, PSA has important limitations as a screening test. PSA levels can be elevated by age, prostatitis, prostatic massage, prostatic infarct, acute urinary retention, and urethral catheterization. Finasteride will lower PSA levels by approximately 50%, possibly resulting in a false-negative value. Up to 40% of tumors confined to the prostate may present with a PSA within the normal range.

In spite of all of this, PSA testing, in conjunction with digital rectal examination, remains our best screening strategy.

PSA, combined with digital rectal examination is our best screening strategy

TABLE 1

Effect of prostate cancer on life expectancy

PATIENT CATEGORY	LIFE EXPECTANCY IN YEARS, BY PATIENT AGE		
	AGE 55	AGE 65	AGE 75
No cancer	21.4	14.5	9.0
Well differentiated, < 0.5 mL, no treatment	21.4	14.5	9.0
Well differentiated, > 0.5 mL, no treatment	17.5	12.6	8.3
Moderately differentiated, no treatment	17.5	12.6	8.3

SOURCE: ADAPTED FROM COLEY CM, BARRY MJ, FLEMING C, FAHS MC, MULLEY AG. EARLY DETECTION OF PROSTATE CANCER. PART 2: ESTIMATING THE RISKS, BENEFITS, AND COSTS. AMERICAN COLLEGE OF PHYSICIANS. ANN INTERN MED 1997; 126:468-479

IS SCREENING FOR PROSTATE CANCER WORTHWHILE?

Arguments against

Some hold that screening for prostate cancer is not worthwhile because it will increase health care costs and is not of proven benefit. There are data to suggest that overall benefit to a population of men is minimal in additional lives saved. Furthermore, those who find disease by screening may want to treat it; however, treatment is not predictably effective and may be given unnecessarily with significant complications.

Arguments in favor

On the other hand, some experts argue that screening is desirable because only early disease is curable, and more early disease is found with screening. This year, 39,000 men will die because their advanced disease cannot be cured, and the magnitude of the problem calls for action. Furthermore, early treatment appears to markedly reduce the risk of metastatic disease.

Proponents of prostate cancer screening believe that screening is effective because before PSA screening was available the incidence of positive lymph nodes at prostatectomy ranged from 25% to 75%, whereas now the incidence is approximately 2% to 3%. Furthermore, before PSA screening, 35% of patients who underwent radical prostatectomy had disease pathologically confined to the prostate. Now, with PSA screening, that number has risen to 72%.

Official positions on screening for prostate cancer

Official recommendations vary widely, but those of the American College of Physicians seem very reasonable.[7] They advise that not all men be routinely screened with PSA. Men ages 50 to 70, African-American men, and those with a positive family history have the most to gain from screening, while men over age 70 have the least to gain.

The magnitude of the problem prohibits inaction

WHAT SHOULD PHYSICIANS DO?

We should continue to encourage patients to enroll in ongoing major clinical trials. The National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian Cancer Trial seeks to determine if PSA is accurate enough and whether it uncovers too many insignificant cancers. The Prostate Cancer Intervention vs Observation Trial (PIVOT) is comparing expectant management with radical prostatectomy.

We cannot be sure of the rate of progression of prostate cancer in an individual, and we may not be certain of the optimal treatment in a specific case. Nevertheless, when it comes to screening for prostate cancer, we should help the patient understand that its value is as yet uncertain, and that it has limitations and implications, and we should come to some agreement as to what is best in his individual case.

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