Editorial

Screening for Prostate Cancer: Are We Ready?

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Prostate cancer, a common malignancy worldwide, and a dominating one in western countries, remains one of the great challenges in cancer control (1, 2). Prognosis is poor in cases with spread beyond the gland (3), and therapeutic progress has been slow (4). At first glance, screening appears attractive. Indeed, lively interest and enthusiasm for screening have arisen in recent years, notably in the United States (5–7), although there seem to be fewer proponents for screening in Europe.

Consideration of the value of screening for prostate cancer can start with several advantages. In past decades, considerable methodological development has taken place, and huge empirical experience has been gathered during the implementation and assessment of screening for cancer of the cervix and the breast. Many lessons have been learned, and it would be unwise to ignore them. Hence, it is reasonable to discuss screening for prostate cancer in the context of the general guidelines for screening that have been defined, with considerable agreement, in the past decade (8–13).

Burden of Disease

Incidence data tell us that prostate cancer accounts for at least one-fourth of all cancers among men in Western populations. The American Cancer Society estimated that 132,000 men in the United States were diagnosed with prostate cancer in 1992. Mortality data are impressive too: 34,000 deaths from the disease occur annually in the United States, where 13% of all cancer-related deaths in men are due to this malignancy (14). The 5-year relative survival rate is only about 40% (after exclusion of deaths from other causes) (3). The incidence and mortality are particular features of elderly men: no other cancer shows such a late and steep increase in age-specific incidence. In Denmark only 5% of cases occur before the age of 60, and the disease is rare before age 50 (3). The high risks of death from non-prostate causes in this age group dictate that the time horizon for prevention must be short, at least if “typical” prostate cancer is the target. Otherwise the patients may not live long enough to receive the benefits of the early detection that screening might provide.

Natural History

A scientifically well founded screening intervention requires a clear understanding of the natural history of the target tumor and that of the lesions likely to become detected and treated. No benefit is achieved by detecting cancers that never progress to a symptomatic stage during life. Neither is screening likely to be meaningful if the cancer surfaces clinically at an early stage and can be treated with easy curative local therapy. Any possible gain is derived only from patients with potentially fatal or morbid disease who are diagnosed with screening at a curable stage.

A particular feature of prostate cancer is the high prevalence of histologically malignant lesions found at autopsy. With surprisingly little geographic variation between populations, such “latent cancers” are found in up to one-third of men who undergo autopsy; the prevalence increases markedly with age (15). By definition these were harmless, probably asymptomatic, and not a contributory cause of death. Thus, there is almost certainly a reservoir of clinically benign prostate cancer mixed in with the aggressive, potentially lethal variety. In some populations, the prevalence at autopsy of large and infiltrative latent cancer is 1,000 times higher than the annual incidence of clinically diagnosed tumors (15). In such populations, the latent tumors are so common that less than one-third of the men with histological prostate cancer have it diagnosed clinically (16).

At screening it is particularly likely that the patients detected with early stage disease will have clinically benign tumors, with a few aggressive cancers detected during transit into disseminated disease. Unfortunately, we do not have clinically applicable means to separate the two types of tumors, and so after screening it may be necessary to treat large numbers of clinically benign early stage cases in order to reach the few aggressive ones.

It is not surprising that such a mix of cases has a fairly good natural history, even if initially untreated. The excess death rate is very low, provided that the disease is localized clinically to the gland. The advanced age of many prostate cancer cases adds a further consideration: the high death rates from other causes will further reduce the observed prostate-related mortality. During a 10-year follow-up of cases discovered clinically, 10% or less will die from prostate cancer, corresponding to a corrected survival rate of 85–90% (17, 18). As a consequence of this good prognosis, the combination of earlier diagnosis by screening followed by aggressive local treatment can offer at most a modest benefit. The majority of the early cancers that would be found simply appear not to progress before death from other causes anyway, and the possible beneficial impact on aggressive tumors is masked by the lack of benefit possible in the large numbers of tumors with an excellent prognosis.

Screening Tools

In many clinical settings, the main diagnostic challenge is not to overlook disease among patients who seek advice
because they feel sick. Here, high diagnostic sensitivity is of main importance. False positives due to low specificity may be of more limited concern, since they are relatively few in a patient mix with a high prevalence of disease. The situation is dramatically different in screening. Few individuals (less than 1% in breast cancer screening) have the disease, and none actively requested a diagnostic intervention. Hence, a screening test with only a slightly suboptimal specificity will identify large numbers of healthy individuals as possible cancer patients, and the positive predictive value of a test will be low. The psychological, ethical, and practical consequences are enormous. Such problems enter in a profound manner into prostate cancer screening since a false positive cancer diagnosis cannot easily be ruled out; several core biopsies may be needed, and anxiety may persist.

These difficulties are compounded by the clinical characteristics of prostate cancer. The men with clinical cancer, or just histological cancer, may well have prostate symptoms, but this will not help much in distinguishing them from those without cancer. Urinary symptoms are common among men of all ages, especially older men (19, 20), and so it is not possible to accurately differentiate between the symptoms of normal aging, prostatic hypertrophy, and prostate cancer. Unfortunately, the prostate seems to be an organ where local symptoms will not be very useful in defining a group at particularly high risk of cancer; screening must proceed without much clinical suspicion to guide it to high risk groups. This problem is exacerbated by the lack of epidemiological knowledge about the cancer. To date, there are few established risk factors other than black race and older age (21).

Three different screening tools have been considered for prostate cancer: DRE, TRUS, and PSA (a blood test). Most investigators appear to agree that neither DRE nor TRUS (with currently available technology) is acceptable as the sole screening tool (22, 23). Considerations of sensitivity, reproducibility, acceptance, and costs jointly argue against DRE and TRUS, but somewhat greater hope has been given to PSA (4, 6). Problems related to the lack of a "gold standard" and the existence of a large pool of prevalent (latent) cancers enter in a profound manner into any assessment of sensitivity, specificity, and positive predictive value for DRE, TRUS, and PSA. Therefore, accurate calculations are not possible from available data, and estimates of the test's performance may be overly optimistic (6, 12). The situation is complicated further by the difficulties of calculating the most clinically relevant test characteristics: the sensitivity and specificity for asymptomatic early-stage, but clinically aggressive cancers. Study of the performance of the test in detecting clinically benign tumors or advanced cancers has more limited relevance for understanding the performance of the measurement in screening situations.

The provision of a blood sample is acceptable to almost all men and laboratory costs for PSA are modest. However, a lively scientific literature indicates that the use of PSA as a screening tool presents some difficulties (6). Levels are increased in patients with prostatic hypertrophy as well as in those with advanced prostatic cancer. Efforts to find a better trade-off between sensitivity and specificity by taking into account prostate tissue volume or trends in levels (24, 25) are now ongoing but still experimental. In any case, the test appears to identify both clinically insignificant prostate cancer as well as the more aggressive variety. Thus, it is presently unknown whether further development ultimately will make PSA meet the basic requirements for a sensitive, specific, and reproducible screening tool. We may have to look for new approaches.

Treatment
A basic principle of screening is that a therapy which favorably alters the clinical course of the lesions detected must be available before a screening intervention can be justified. The lack of progress in the treatment of advanced, disseminated disease is not an issue here. What matters is the efficacy of radical local treatment by irradiation, mostly external, or surgical prostatectomy, which is used widely in the United States (26). After screening, such therapy will be applied to patients with early, asymptomatic disease. Hence, favorable results after radical prostatectomy in an uncontrolled, often personal, series of selected patients diagnosed clinically tells us almost nothing about the general impact of the treatment among patients identified through screening (27).

This basic requirement has been somewhat overlooked in discussions of screening for prostate cancer. Clinical trials will be required to clarify the size of the survival benefit conferred by radical prostatectomy, if any (28), and to weigh this against the substantial morbidity that accompanies the procedure: a high risk of impotence and incontinence. However, radical prostatectomy has never been assessed properly in any randomized study. Apart from a small inconclusive published investigation (29), only one trial in Sweden and Finland appears to be underway; reliable survival data may first be available 5–10 years from now.

Conclusions
Screening for prostate cancer is a complex and uncertain undertaking. We lack basic knowledge in a number of areas briefly reviewed here. Therefore, it is difficult to find a scientific foundation for the current recommendations for screening the American Urologic Association, the American Cancer Society, and the American College of Radiology (6). Indeed, unless further investigation indicates that screening will have a net beneficial impact, it clearly should not be done.

The request for randomized screening trials may appear more sensible (6, 21, 30). However, with realistic assumptions concerning possible benefit, any such trial would require large numbers of subjects and a follow-up over many years (12). Moreover, it is possible that screening for prostate cancer would actually do more harm than good (6). This, of course, will greatly complicate the practical and ethical issues surrounding the trial.

What is needed at this point is more basic information about prostate cancer to permit identification of the patients who require aggressive treatment and to document treatment efficacy. Without a characterization of the clinically malignant disease, we lack the focus we need for meaningful study of this cancer. Without knowledge of the benefits of treatment, clinical care (including screening) remains on uncertain ground.

References
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