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Screening for Adenocarcinoma of the Prostate

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Adenocarcinoma of the prostate is the second leading cause of cancer and the third leading cause of death from cancer in American men. For American black men it is the number one cause of cancer and death from cancer. The clinical incidence of carcinoma of the prostate is approximately 69 per 100,000 men, but the prevalence is between 5% to 40% of men over age 50 (1). Certainly this makes cancer of the prostate the most prevalent cancer in males. Unfortunately, over half of the patients presenting with this disease have either significant locally advanced or metastatic disease.

The need for a screening method for cancer of the prostate has been recognized for some time and was advocated as early as 1905 by Young (2). However, great care must be exercised when evaluating the value of any potential screening test. It is far too easy to become optimistic based on seemingly high sensitivity and specificity values for a given test. The true usefulness of any testing modality lies in its "predictive value" (3). Given that a particular test is positive, the probability that the patient actually has prostate cancer is its predictive value:

$$\text{Sensitivity} = \frac{\#TP}{\#TP + FN}$$

$$\text{Specificity} = \frac{\#TN}{\#TN + FP}$$

$$\text{Predictive Value Positive} = \frac{S \times P}{(S \times P) + ([1 - SP] \times [1 - P])}$$

where TP = true positives, FN = false negatives, TN = true negatives, FP = false positives, S = sensitivity, P = prevalence, and SP = specificity.

Unfortunately, predictive value is seldom referred to whenever the subject of screening is broached. In prostate cancer, if predictive values were used they would be questionable because of the large discrepancy between the prevalence of the disease and its clinical incidence. Since only one third of the patients with prostate cancer will ever manifest the disease clinically, the question is raised as to whether or not we will be screening patients, at considerable expense, who do not need treatment. This issue is beyond the scope of this brief review but has been reviewed elsewhere (4).

If we accept "prevalence" as being in the 5% to 40% range, the predictive value of most modalities discussed herein is still not high enough to warrant their consideration as screening tools. In fact, the American Urologic Association (AUA) recently published a directive strongly discouraging the use of prostate specific antigen (PSA) and prostate ultrasound as screening modalities (5). However, these modalities as well as others are available for the evaluation of adenocarcinoma of the prostate.

Creatine Kinases/Alkaline Phosphatase

Since Gutman and Gutman (6) discovered the association between acid phosphatase and adenocarcinoma of the prostate, investigators have been looking for a prostate serum marker. Potential serum markers that have been evaluated in the past years include creatine kinase, alkaline phosphatase, ribonuclease, lactate dehydrogenase isoenzymes, hydroxyproline, polyamines, alfa-fetoprotein, and beta human chorionic gonadotropin, among others. The best, according to Fair et al (7), is creatine kinase. This is an enzyme that catalyzes the transfer of a phosphate group from phosphocreatine to adenosine diphosphate. There are three bands of creatine kinase. The BB band is found exclusively in the genitourinary system, especially in the cytoplasm of normal and cancerous prostate tissue. Unfortunately, the sensitivity is less than 15% and the specificity is approximately 45% in large clinical trials. Therefore, creatine kinase has limited value for following patients with known carcinoma of the prostate and is of no value as a screening tool. The alkaline phosphatase test has similar problems with sensitivity and specificity and is of value only for following response to therapy in patients with known disease.

Acid Phosphatase

The acid phosphatases have been the mainstay of serum markers for evaluation of prostate carcinoma since the 1930s when they were discovered by Gutman and Gutman (6). Acid phosphatase is an enzyme that hydrolyzes phosphate esters at a PH of < 7.0. They are ubiquitous, being found in serum, red and white blood cells, the spleen, kidney, bone, and numerous other organs such as the prostate. In the prostate acid phosphatase is found in the lysosomal fraction of epithelial cells. Its concentra-

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tion in the prostate is 1,000 times greater than that of any other organ or cell. Of the nine isoenzymes of acid phosphatase, isoenzyme 2 has the greatest activity in the prostatic acid phosphatase test. Semen is the only tissue fluid with isoenzyme 2 activity.

When the prostate becomes cancerous it retains its ability to produce acid phosphatase, although the overall tissue concentrations are reduced, as measured by qualitative histochemical studies. There is a circadian rhythm found in the serum levels of acid phosphatase in patients with cancer of the prostate but not in normal patients, necessitating repeated measurements in following patients with known prostate carcinoma.

Prostatic acid phosphatase (PAP) is assayed by numerous methods including enzymatic studies, radioimmunoassays (RIAs), counterimmunoelectrophoresis, enzyme-linked immunosorbent assay, and fluorescent immune antibodies. Much controversy existed in the 1970s regarding RIA versus enzymatic studies. However, numerous investigators found significant problems with the specificity and sensitivity of both methods (8-12). The enzymatic method of detecting acid phosphatase is very specific but not very sensitive, and the RIA is very sensitive but much less specific (13). Bruce et al (9) and Cooper and Finkle (14) confirmed that acid phosphatase levels as determined by either enzymatic or RIA methods are not effective in distinguishing between benign prostatic hypertrophy (BPH) and localized adenocarcinoma of the prostate. Therefore, the acid phosphatases have no value as screening tests. Acid phosphatase has much more value for following patients with known disease to evaluate their response to therapy or to predict disease progression.

Prostate Specific Antigen

Discovered by Wang et al (15) in 1979, PSA is a relatively new marker for evaluating patients with adenocarcinoma of the prostate. Its concentration is similar in normal, benign, and malignant tissue. This secretory-like protein is found in the seminal fluid and is a small molecule but highly immunogenic. It is entirely different from PAP, and with it either polyclonal or monoclonal antisera are easily generated. PSA is not prostate cancer specific; it is prostate tissue specific.

PSA is an excellent marker for evaluating patients with known adenocarcinoma of the prostate, but, as with acid phosphatase, false elevations occur in patients with BPH and "falsely" normal levels may be obtained in patients with known prostate carcinoma. Ban et al (16) found elevated PSA levels in only 25% of patients with known carcinoma. Stamey et al (17) recently reported that BPH contributed an average serum level of 0.3 ng/mL per gram of prostate tissue resected. While this value may be high, others have found that approximately 20% of patients with BPH have elevated PSA levels (18-20). As with PAP, the value of PSA is in following patients with known carcinoma. PSA should not be utilized as a screening tool. The AUA recently made the following statement on PSA (5):

> Serum PSA is not effective as a screening test for prostate cancer. At present, serum PSA appears to be most useful for determining the presence of residual cancer after ablative surgical procedures and determining early recurrence following radiation therapy, radical surgery, or hormonal therapy. Further study will be required to define other roles of PSA in prostate cancer patients.

Other Modalities

There are no radiographic studies suitable to use as screening modalities for carcinoma of the prostate. However, the recent development of prostatic ultrasound has raised the hope that it may be useful in this way. Perhaps prostatic ultrasound may become as valuable as the mammogram in females. However, the high cost of this test and the low clinical incidence of prostate carcinoma make its usefulness questionable. According to the AUA (5):

> Transrectal prostatic ultrasonography, because of its relative lack of specificity and sensitivity, cannot be recommended for mass screening for carcinoma of the prostate in asymptomatic male patients.
>
> Transrectal ultrasonography is not recommended for routine use in the patient who has no symptoms to suggest prostatic carcinoma, no physical findings of prostatic carcinoma, and/or no laboratory or radiographic evidence of prostatic carcinoma.

Aspiration cytology and random core needle biopsies of the prostate could be effective screening tools. However, because of the invasive nature and possible complications of these tests, they cannot be used for large-scale unselected population screening (21).

The digital rectal examination is currently the most effective screening tool for adenocarcinoma of the prostate. In evaluating the rectal examination as a screening test for adenocarcinoma of the prostate, Thompson et al (22) found that screened patients were discovered at an earlier clinical stage (stage B) than unscreened patients (70% versus 40%, although pathologic downstaging lowered this to 43% versus 28%). As determined by McNeal et al (23), we can miss as many as 25% of the patients with adenocarcinoma of the prostate due to the anterior origin of this disease. Thus a high index of suspicion and thorough rectal examination are extremely important. The rectal examination is easy to perform, can be done by all physicians, and therefore remains the gold standard in screening for prostate carcinoma (24).

Guinan et al (25) compared five tests for the diagnosis of adenocarcinoma of the prostate: aspiration cytology, prostatic ultrasound, acid phosphatase, PSA, and rectal examination. Not the most rigorous of studies, their results are probably unfairly biased against prostatic ultrasound since the transducer used was only 3½ to 4 MHz, well below the capacity of transducers currently in use. The study included 280 men, mean age 68.1 years, who underwent a transrectal biopsy. Of these patients, 28 had histologic diagnosis of adenocarcinoma of the prostate. The results of the study permitted calculation of relative sensitivity and specificity values for each modality. The authors developed an "efficiency coefficient," defined as the percentage of patients correctly determined to have prostate cancer. The formula utilizes prevalence, sensitivity, and specificity:

$$(pa + [1 - p]b) \times 100$$

where a = sensitivity, b = specificity, and p = prevalence (percentage of patients with carcinoma of the prostate in the population studied).

The efficiency coefficients were 63% for aspiration cytology, 71% for prostatic ultrasound, 74% for PSA, 66% for acid phosphatase, and 75% for rectal examination. As evident from these data, the digital rectal examination was superior to all other modalities and is the least expensive of these tests. As more work is completed, prostatic ultrasound may surpass the digital rectal examination as a screening tool. However, primary care physicians and urologists should continue to trust a well-performed rectal examination as an effective screening procedure for adenocarcinoma of the prostate (26). Patients should not be routinely subjected to PSA, PAP, aspiration biopsy, or ultrasonic testing until the predictive values of these tests become much higher.

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