8. PROSTATE CANCER SCREENING

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The core references for this chapter include recent review articles about prostate cancer screening as well as the recommendations published by the American Cancer Society, the American Urological Association (AUA), the U.S. Preventive Services Task Force (USPSTF), the Canadian Task Force on the Periodic Health Examination, the American College of Physicians (ACP) and the American Academy of Family Physicians (Garnick, 1993; Garnick, 1996, Kramer et al., 1993, Scardino, 1989, Gohagan et al., 1994; Woolf, 1995; Mattlin et al., 1993; USPSTF, 1996; Canadian Task Force, 1994, ACP, 1997; Coley, 1997). Recent review articles were selected from a MEDLINE search identifying all English language review articles published on prostate cancer screening since 1992. Where the core references cited studies to support individual indicators, these have been included in the references. Whenever possible, these have been supplemented with the results of randomized controlled trials.

Screening for prostate cancer remains extremely controversial and no consensus currently exists among the various physician and health policy organizations on whether screening should be routinely offered (Table 8.1). The American Cancer Society recommends that all men age 50 and older receive prostate cancer screening annually with digital rectal examination and prostatic specific antigen (Mettlin, 1993). At the other extreme, the American College of Physicians recommends against screening with the following strongly worded statement: “Routine PSA measurement without a frank discussion of the issues involved is inappropriate. Patients who elect to be screened either by digital rectal examination or PSA measurement, should provide verbal informed consent.” (ACP, 1997) In spite of this lack of consensus, screening for prostate cancer with PSA is rapidly spreading and is expected to dramatically increase the numbers of asymptomatic localized cancers diagnosed in the next few years.

Since screening places a burden upon patients (time, expense, potential complications, and anxiety) as well as upon providers and the health care system, five general conditions should be met for any screening intervention to be worthwhile (Hulka, 1988):

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1. The disease should represent a substantial public health burden;
2. The asymptomatic, non-metastatic phase should be recognizable;
3. Good screening test or tests should be available (i.e., reasonable sensitivity, specificity, and predictive value; low cost; low risk; and acceptable to the person being screened);
4. The curative potential should be substantially better in early stages compared with advanced stages of disease;
5. Treatment of screen-detected cases should decrease cause-specific mortality rates.

We will examine how screening for prostate cancer performs against these criteria.

**IMPORTANCE**

Prostate cancer (adenocarcinoma) is now the most common cancer in men. In men 75 and older, prostate cancer and benign prostatic hypertrophy together account for about ten percent of office visits each year (Top 30 Diagnoses, 1996). In 1993, the annual incidence of prostate cancer was estimated to be 165,000. Since the FDA approved the use of PSA testing in association with digital rectal examination for early detection of prostate cancer in August 1994, increasing numbers of tumors are being diagnosed and treated before they are palpable. It is estimated that 317,000 new cases will be diagnosed in 1996 and 41,400 deaths in the United States will occur in that same year (Parker et al., 1996). The lifetime risk of dying of prostate cancer is 3.4 percent for American men (Ries et al., 1994). Thus, prostate cancer does represent a substantial health burden.

**SCREENING**

**Recognizable Asymptomatic Phase**

The goal of screening or early detection programs for cancer is to identify the disease early enough in the natural history that treatment can significantly change the outcome. In the case of prostate cancer, early detection is defined as before the disease has spread beyond the confines of the gland itself, as treatment for metastatic disease is merely palliative. This is sometimes referred to as “stage shift.” That is, screening results in more cases being identified at an earlier stage of the disease. Without
screening, approximately 60 percent of newly diagnosed cases of prostate cancer are Stage III or IV and 40 percent are Stage I or II. However, only about half of the cancers clinically determined to be Stage I or II will be found at surgery to be truly organ-confined (Garnick, 1993). The only screening test that has been demonstrated to possibly be associated with "stage shift" is prostate specific antigen (PSA), with up to twice as many cancers being diagnosed while still localized as compared to no screening. However, the increase in the number of localized cancers detected may simply be a reflection of "lead time bias," when a disease is diagnosed earlier in its natural history given the false impression that survival has been prolonged, or "length time bias," which occurs when screening selectively identifies less aggressive tumors because those are the ones that remain clinically "silent" and are therefore preferentially detected in the asymptomatic state (Kramer, 1993). This is especially important because prostate cancer appears to be largely made up of clinically insignificant tumors with only a few becoming clinically important over the patients' lifetimes. Autopsy studies suggest that 40 percent of men age 50 to 70 and 65 percent of men 70 to 80 have clinically undetected prostate cancer, and, in men over 80, it approaches 100 percent (Baron et al., 1995). It is therefore imperative to have survival data from randomized controlled trials of prostate cancer screening to ensure that screening results in "stage shift" and not just "lead time" or "length time" biases.

Accuracy of Screening Tests

The principal screening tests for prostate cancer are digital rectal examination (DRE), the serum tumor marker prostate specific antigen (PSA) and transrectal ultrasound (TRUS). The gold standard against which these tests are compared is pathologic confirmation using biopsy specimens from the prostate (although biopsy may not be a true gold standard because one study has shown that 25 percent of men with one previously negative biopsy were found on a subsequent biopsy to have cancer) (Keetch et al., 1993). Unfortunately, since biopsies are generally not performed in men who have a normal test, the false negative rate of screening tests for prostate cancer are not known. Therefore, the true sensitivity and specificity of DRE, PSA, and TRUS cannot be determined. More importantly, unlike other cancer
screening tests currently in use, such as mammography for breast cancer or Pap smears for cervical cancer, no randomized controlled studies have tested the efficacy of screening for prostate cancer in reducing mortality or morbidity.

**Digital Rectal Exam**

Until recently, DRE was the only screening test for prostate cancer available. Because it requires little time and no significant additional cost, it has generally been integrated into many physicians’ routine periodic physical examinations of middle-aged and older men. However, the sensitivity of DRE is limited with studies reporting sensitivities ranging from 18 to 90 percent in detecting prostate cancer in asymptomatic men, when compared against PSA or TRUS (Kramer et al., 1993; Catalona et al., 1991; Catalona et al., 1994; Chodak et al., 1989; Varenhorst et al., 1993; Babaian et al., 1992). It is important to note that these numbers do not represent the true sensitivity of DRE, as neither PSA or TRUS is a “gold standard” test for the detection of prostate cancer. The positive predictive value of DRE is quite low, reported in the range of four to 30 percent. Seventy to 85 percent of men with an abnormal rectal exam have a prostate biopsy without evidence of malignancy (Vihko et al., 1985; Pedersen et al., 1990; Chodak et al., 1989; Pedersen et al., 1990; Richie et al., 1993; Gustafsson et al., 1992).

Interrater reliability is only slightly better than chance, even among urologists (Smith et al., 1995; Varenhorst et al., 1993). In addition, two case-controlled studies have failed to show a mortality benefit from screening for prostate cancer with digital rectal exam (Friedman, 1991; Gerber et al., 1993). Hence, even though it is often a traditional part of the periodic physical examination of older men, there is little evidence to recommend periodic DRE alone as a quality indicator of screening for prostate cancer.

**Prostate Specific Antigen**

PSA is a serine protease which is produced almost exclusively by prostatic epithelial cells (Oesterling, 1991). PSA levels in the serum are increased in prostate cancer (Stamey, 1987; Labrie, 1996). Case control studies have shown that screening with PSA increases the number of men who are found with localized prostate cancer rather than metastatic disease (Auvinen et al., 1996; Catalona et al., 1993; Mettlin, 1994; Labrie et al., 1996; Epstein et al., 1994).
Using a cut-off of 4 ng/dl, PSA has been reported to have a sensitivity of up to 80 percent when compared with prostate biopsy performed to evaluate an abnormal DRE or TRUS. However, it lacks specificity because false positive results are common in patients with benign prostatic hypertrophy (BPH) and prostatitis (Labrie, 1996; Mettlin, 1994; Catalona, 1994). Among men with BPH, 25 to 46 percent will have elevated PSA values (Oesterling, 1991; Sershon, 1994). PSA values in normal men appear to vary by race and age, though this may simply be a reflection of variations in the size or volume of the normal prostate (Oesterling, 1993; Oesterling et al., 1995; Dalkin et al., 1993; Morgan 1996). New techniques currently under investigation which may improve the accuracy of PSA screening include: using age-adjusted and race-adjusted reference ranges (Moul et al., 1995; El-Galley et al., 1995); measuring the PSA density (the PSA concentration divided by the volume of the gland) (Benson et al., 1992; Epstein et al., 1994); the rate of change in PSA levels over time (Carter et al., 1992); and measuring the ratio of free PSA to that complexed to alphal-chymotrypsin (since the latter accounts for a larger proportion of the PSA in men with prostate cancer than men with BPH) (Oesterling et al., 1995; Stenman et al., 1991; Auvinen et al., 1996). Currently, there are insufficient data to recommend any of these newer techniques, and they are not yet widely available.

Even the reported positive predictive value of 20 to 35 percent may overestimate the percentage of men with an elevated PSA found to have prostate cancer on biopsy. These estimates are derived from studies that included either patients seen at urology clinics or community volunteers, many of whom had obstructive symptoms and therefore were not truly asymptomatic (Cooner et al., 1990; Catalona et al., 1994; Catalona et al., 1993; Richie et al., 1993; Brawer et al., 1992; Bretton, 1994; Muschenheim et al., 1991; El-Galley et al., 1995). Many men undergo biopsies of their prostate for the evaluation of an elevated serum PSA when they do not have prostate cancer. While the PSA test itself is only a blood test of low risk and acceptable to most patients, a prostate biopsy is much more invasive and associated with more discomfort. Two to 40 percent of men who have biopsies are reported to experience minor, self-limited complications; mostly bleeding and urinary tract infections (Desmond, 1993; Webb, 1993). Therefore, any consideration of widespread
screening with PSA must take into account the number of prostate biopsies that will result as well.

Combined PSA and DRE

One way to decrease the number of false positive results in screening for prostate cancer is to use both PSA and DRE and only consider the test abnormal if both tests are abnormal. When the results of both PSA and DRE are abnormal, the positive predictive value increases from 27 to 32 percent, to 44 to 49 percent. However, combining the two tests significantly reduces the sensitivity of screening (Catalona, 1994; El-Galley, 1994). In one study, when PSA and DRE were combined the sensitivity dropped from 68 percent with PSA and 41 percent for DRE to only ten percent if both were required to be abnormal. When screening for prostate cancer is recommended, current practice usually includes both DRE and PSA, with a positive result on either being sufficient to proceed with further evaluation. The Office of Technology Assessment has estimated that this strategy would result in prostate biopsies for 15 percent of men screened between the ages 50 to 59, 28 percent for ages 60 to 69, and 40 percent at ages 70 to 79 (OTA, 1995).

Transrectal Ultrasound

TRUS has a reported sensitivity of 30 to 68 percent for detecting prostate cancer in asymptomatic men; this is lower than PSA because TRUS cannot distinguish between benign and malignant nodules (Simak et al., 1993; Carter et al., 1989; Catalona et al., 1991; Catalona et al., 1994). When other screening tests are normal the positive predictive value drops to five to nine percent (Babaian, 1992). In addition to these unfavorable test characteristics, TRUS is uncomfortable and costly.

Effectiveness of Screening

"Is cure possible in those for whom it is necessary, and is cure necessary for those in whom it is possible?" - Willet Whitmore

This quote summarizes the dilemma of treating prostate cancer; approximately two-thirds of patients who present with metastatic cancer will die of their disease within five years, with the other one-third succumbing to some other cause of death first (VACURG, 1967). The only hope is to identify cases of prostate cancer before the disease has become widespread so that patients can be cured. However, while most American experts recommend
treating localized prostate cancer with either radical prostatectomy or radiation therapy, evidence that such treatment benefits patients is lacking. The only randomized controlled trial of radical prostatectomy with no treatment failed to demonstrate a survival advantage with radical prostatectomy; however, the reliability of this result is often questioned because of small sample size (Graversen et al., 1990). Several non-randomized studies of expectant management (treatment deferred until disease progression) of patients with localized prostate cancer have demonstrated ten year disease-specific survival rates of approximately 85 percent and ten year overall survival rates of approximately 60 percent. These results were comparable to those obtained with radical prostatectomy and radiation therapy (Woolf, 1995; Mettlin, 1993; ACP, 1997; Hulka, 1988). The only randomized controlled trial comparing radical prostatectomy with radiation therapy used time to first treatment failure as its primary endpoint and showed an advantage for radical prostatectomy, though the study is limited both by its choice of endpoint and a different staging between the study arms (Paulson, et al., 1982; Hanks et al., 1988). At the 1987 NIH Consensus Conference on Prostate Cancer, no consensus regarding treatment was reached and none has been reached since.

Both radical prostatectomy and radiation therapy cause substantial complications which negatively impact patient quality of life. Up to 30 percent of men who undergo radical prostatectomy report the need for pads or clamps for incontinence, and about 60 percent report having no erections after surgery, with up to 90 percent reporting no erections sufficient for intercourse during the past month (Garnick et al., 1993; Catalona et al., 1993; Fowler et al., 1993). In addition, surgery is associated with a 0.5 percent to one percent risk of perioperative death (Garnick, 1993). Radiation therapy is associated with a much lower incidence of incontinence and impotence but does carry about a ten percent risk of bowel dysfunction (Garnick, 1993).

Finally, there is controversy as to whether screening identifies those cancers which will have a negative impact on patients’ survival or merely insignificant cancers that would not have manifested themselves during the patients’ lifetimes. This possibility is significant in prostate cancer because while one-third of men older than 50 will have prostate cancer discovered incidentally at autopsy, clinically apparent prostate cancer
develops in only ten percent of men during their lifetime, and only three percent of men die of prostate cancer (Epstein et al., 1986). There is concern that screening programs may identify the two-thirds of prostate cancers, so-called “indolent cancers”, that would have never manifest themselves during the individuals’ lifetimes, resulting in substantial impact on quality of life (Kramer et al., 1993).

SUMMARY

With respect to the five criteria proposed for a worthwhile cancer screening test, the data on current prostate cancer screening are as follows:

1. Prostate cancer does represent a substantial public health burden.
2. The asymptomatic, non-metastatic phase of prostate cancer is recognizable (though studies must be controlled so that “indolent cancers” are not identified and treated).
3. There is incomplete evidence on the test characteristics of DRE and PSA, though it does appear that their sensitivity, specificity, and positive predictive value are not adequate to consider them “good” screening tests. TRUS is not acceptable as a screening test due to its low positive predictive value and also because of patient discomfort, technical difficulty, and cost. Its role remains in the evaluation of abnormal DRE and PSA tests.
4. Because of a lack of randomized controlled trials, it remains controversial as to whether patients with localized prostate cancer live longer when treated with radical prostatectomy or radiation therapy than if not treated until symptoms develop.
5. As yet, there is no evidence that treatment of prostate cancer cases detected by screening decreases cause-specific mortality rates.

Because there is insufficient evidence that screening with either DRE or PSA or both reduces mortality from prostate cancer, and no consensus exists on the issue among organizations that make screening recommendations (Table 8.1), we do not recommend any quality indicators for prostate cancer screening.
Table 8.1
Organizational Recommendations Regarding Prostate Cancer Screening

<table>
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<tr>
<th>Organization</th>
<th>Recommendation</th>
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<tr>
<td>American Cancer Society (Mettlin, 1993)</td>
<td>Annual examination for early detection of prostate cancer with DRE and PSA beginning at age 50 (annual DRE to begin at age 40 for rectal cancer screening).</td>
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<tr>
<td>American Urological Association (AUANet, 1992)</td>
<td>Annual DRE and PSA measurement substantially increases the early detection of prostate cancer. These tests are most appropriate for male patients 50 years of age and older and for those 40 or older who are at high risk, including those of African-American descent and those with a family history of prostate cancer. Patients in these age/risk groups should be given information about these tests and should be given the option to participate in screening or early detection programs. PSA testing should continue in a healthy male who has a life expectancy of ten years or more.</td>
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<td>U.S. Preventive Services Task Force (UPSTF, 1996)</td>
<td>Routine screening for prostate cancer with digital rectal examinations, serum tumor markers (e.g., PSA) or transrectal ultrasound is not recommended (D Recommendation).</td>
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<td>Canadian Task Force on the Periodic Health Examination (CTFPHE, 1994)</td>
<td>There is poor evidence to include or exclude the DRE from the periodic health examination for men over 50 years of age (C Recommendation).</td>
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<td>There is insufficient evidence to include PSA screening in the periodic health examination of men over 50 years of age. Exclusion is recommended on the basis of low p sensitivity, specificity, positive predictive value, and the known risk of adverse effects associated with therapies of unproven effectiveness (D Recommendation).</td>
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<td>There is also fair evidence to exclude transrectal ultrasound from the periodic health examination of asymptomatic men over 50 years of age (D recommendation).</td>
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<td>Organization</td>
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<td>American College of Physicians (ACP, 1997)</td>
<td>Rather than screening all men for prostate cancer as a matter of routine, physicians should describe the potential benefits and known harms of screening, diagnosis, and treatment; listen to the patient’s concerns; and then individualize the decision to screen. The College strongly recommends that physicians help enroll eligible men in ongoing clinical studies.</td>
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<tr>
<td>American Academy of Family Physicians (AAFP, 1996)</td>
<td>Counsel about the known risk and uncertain benefits of screening for prostate cancer (applies to men age 50 to 65).</td>
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<tr>
<td>National Cancer Institute (CancerNet PDQ, 1997)</td>
<td>There is insufficient evidence to establish whether a decrease in mortality from prostate cancer occurs with screening by digital rectal examination, transrectal ultrasound, or serum markers including PSA.</td>
</tr>
</tbody>
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REFERENCES


Baron E, and Angrist A. Incidence of occult adenocarcinoma of the prostate after fifty years of age. Archives of Pathology 787-793.


Top 30 Diagnoses (ICD-9-CM Codes) for Men Ages 65-74 and Men Ages 75+


