Screening for Cancer: Is It Cost Effective?

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Screening is defined as the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures that can be applied rapidly and carried out in the general population or in individuals at high risk. When considering immunochemical or biochemical cancer markers, it might be more appropriate to describe these tests as risk-factor monitors and introduce the concept of two interpretations of these tests: in asymptomatic populations as indicators of probability of cancer, and in patients with previously treated cancer as predictors of recurrence despite initial treatment described as "curative." The successes of screening with alpha-fetoprotein for hepatocellular carcinoma and with catechol metabolites in neuroblastoma are discussed. The major emphasis will be the possible use of CA 125 and prostate-specific antigen (PSA) in risk-factor assessment of ovarian cancer and prostate cancer, respectively. It is important to understand in what context a PSA value >10 μg/L indicates a 67% probability of cancer.

Indexing Terms: fetoprotein · catechol metabolites · CA 125 · prostate-specific antigen · liver · neuroblastoma · ovarian cancer · prostate cancer · monitoring therapy

Cancer screening is generally defined as the use of tests or clinical procedures in the detection of unrecognized disease (1). More recently, it has been suggested that screening is the testing of apparently healthy volunteers from the general population to separate them into those with high and low probability of having a disease (2). As new technology is developed, the definition must include the use of tests to assess risk factors for cancer and to predict individuals with "successfully" treated cancer who will have a recurrence.

The past decade has seen great controversy over the cost and clinical effectiveness of screening to detect unrecognized cancer. In some cancers there is convincing data supporting the contention that early detection will decrease mortality. Studies throughout the world have shown that in women of ages >50 years, breast cancer detection programs can greatly reduce mortality. In a large study in the US (62 000 women monitored for >20 years), the mortality in screened women (mammography and clinical examination) was 50% lower at 5 years than in unscreened women (3). It is not yet established whether screening women younger than 50 years results in reduced mortality. Assuming a cost of mammography of US$50 per patient, the total cost of screening all women in the US over age 50 would be US$2 000 000 000 per year (4). This does not include the costs of biopsies and other diagnostic and clinical procedures that would result from the program.

There is no doubt that clinical intervention triggered by a positive Papanicolaou (Pap) test can result in the prevention of the progression of localized cervical cancer to invasive disease. In a multinational study of almost 2 000 000 women between ages 35 and 64 the incidence of invasive cervical cancer was reduced 64.1% when the interval between Pap tests was 10 years, 83.6% at 5-year intervals, 90.8% at 3-year intervals, 92.5% at 2-year intervals, and 93.5% with annual tests (5). The question of how often Pap testing should be done is still under review. To put the economic cost vs the clinical return in perspective, it has been estimated that screening women between ages 20 and 64 years every 3 years reduces the cumulative incidence of cervical cancer by 91%, requires 15 tests per woman, and yields during the 3 years 96 cases/100 000 tests (32 cases/100 000 per year) (5). If the testing is done yearly, the incidence is reduced 93%, requires 45 tests, and yields 33 cases/100 000 tests. Current recommendations are that Pap testing be done on all women who are or have been sexually active, or at age 18 if a sexual history is difficult to obtain. Smears should be obtained every 1–3 years based on presence of risk factors (e.g., family history). Testing may be discontinued at age 65 if previous smears have been consistently negative. In addition to the Pap test, other laboratory tests are needed because of the small but significant number of women whose smears do not indicate the presence of cancer; the labor-intensive nature of Pap staining; and the fact that Pap smears are generally not available for the poor, the uninsured, the elderly, and those living in urban inner cities or in poor rural areas (6).

Despite the widespread use of screening in colorectal cancer, there is no clear evidence that the use of screening (fecal occult blood and sigmoidoscopy) can reduce the morbidity and mortality in colorectal cancer. The direct cost of a national program to screen all asymptomatic individuals older than 50 would be ~US$1 500 000 000 a year (7). Data from several large-scale studies suggest that screening results in a shift to detection of earlier-stage cancers. The effect on mortality is controversial. The American Cancer Society recommends that digital rectal examinations (DREs) be performed yearly in all individuals at age 40 and yearly occult blood testing at age 50. Sigmoidoscopy should be performed every 3–5 years. Routine screening has not

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1 Nonstandard abbreviations: PSA, prostate-specific antigen; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; CEA, carcinoembryonic antigen; DRE, digital rectal examination; TRUS, transrectal ultrasonography; HBsAg, hepatitis B antigen.

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been recommended for prostate cancer, ovarian cancer, testicular cancer, or pancreatic cancer. However, screening for prostate and ovarian cancer is at this time the subject of general confusion and concern. The question must be considered whether any immunochemical or biochemical test can be added to the diagnostic procedures already in use for screening and whether this would improve the detection rate.

**General Considerations**

When screening for a disease is considered, several factors must be taken into account (6). The disease must be important and common and result in substantial mortality and morbidity. There must be an understanding of the natural history of the disease to assure that early detection can play a role in a reversal of the clinical course, and there must be effective treatment. On the basis of these criteria, breast, prostate, ovary, and perhaps colon cancer would be most suitable for screening. There are already examples of successful screening programs for hepatocellular carcinoma and neuroblastoma, but these are relatively rare tumors in the western world. When a decision is made to apply screening techniques, particularly if biochemical or immunochemical markers are used, an understanding of analytical sensitivity (lowest detectable limit), epidemiological sensitivity (false negatives), analytical specificity (extraneous interference), and epidemiological specificity (false positives) is essential. In addition, the precision of the assay (the ability to reproduce the results) must be known and acceptable for use in large population studies.

Before entering a test or procedure into a full-scale screening program, it is useful to calculate the predictive value of the assay, i.e., the theoretical number of detected cases (8). This is related to sensitivity, specificity, and the prevalence of the disease, either in a normal population or a high-risk group. Prevalence may be for an entire population or for smaller groups divided by age, gender, race, or risk factors. The equation for the positive predictive value (PPV+) is

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PPV^+ = \frac{(\text{sensitivity})(\text{prev.})}{(\text{sensitivity})(\text{prev.}) + (1 - \text{specificity})(1 - \text{prev.})}
\]

If a test with 95% sensitivity (5% false negatives) and 95% specificity (5% false positives) is used in a disease with a prevalence (prev.) of 1% (1000 cases/100 000), the positive predictive rate would be 18%. Only 16 of 100 positive results would be true positives, and 50 of the 1000 cancers would be missed. If the prevalence is 10% (10 000/100 000), the positive predictive rate would be 68%, but still 500 cases per 100 000 screened would be missed.

An interesting exercise is to use published test data for prostate-specific antigen (PSA) and prevalence rates of prostate cancer to calculate the predictive value. A review of the literature, which included 319 patients with prostate cancer, yielded a sensitivity of 57% for PSA when the cutoff value was 4 μg/L and 20% when the cutoff was >10 μg/L (9). In 590 men with benign prostatic hypertrophy, the specificity was 76.2% when cutoff values >4 μg/L were used and 97% for cutoff values >10 μg/L (9). The prostate cancer prevalence data established at autopsy for men ages 50–70 years indicates a rate of 38% (38 000 cases/100 000 screened). With this rate, the positive predictive value with the 4 μg/L cutoff would be 60%; when 10 μg/L is used, 80%.

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\frac{(0.57)(0.38)}{(0.57)(0.38) + (1 - 0.762)(1 - 0.38)} = 0.60
\]

The optimist would say that these data indicate that screening would detect 57 cancers per each 100 cases and 60% of the positive values would be true positives. However, the pessimist would point out that 43 of each 100 cases would be missed and 40% of the positive values would be false positives. When the 10 μg/L cutoff is used, only 20 cases per 100 would be detected and 80 would be missed. However, test results for only 3 persons per 100 with benign disease would be positive. This calculation was based on a prevalence rate calculated from autopsy records of men without clinically evident cancer. When one understands that most of these cancers would be latent and that only 1% of men whose autopsy demonstrated prostate cancer ever have clinically documented disease, it is difficult to recommend PSA as a general population-screening tool until methods are available to identify those individuals with potentially malignant disease. In men ages 55–59 years, the clinical incidence of prostate cancer is only 0.094% (94 cases/100 000); in men >65, it is 0.739% (739 cases/100 000).

**Specific Cancers**

**Neuroblastoma**

Neuroblastoma is a rare cancer. In Japan an extensive screening program has been successfully initiated by analyzing for urinary vanillylmandelic acid and catechol metabolites (9). The initial assays are performed when the child is 6 months old. Studies in Nagoya City included 21 000 children who were screened first with a paper-strip assay of vanillylmandelic acid; the positive specimens were further analyzed with successively more complex tests until finally a HPLC catecholamine procedure confirmed five cases of neuroblastoma (10). In further screening of a half million children, 25 have been confirmed positive patients who have been treated and monitored for 20 months or more; 92% of them are completely free of disease. The program has been underway in Japan for 10 years and was made nationwide in 1985. By 1988, 337 cases were detected and treated and 328 were still alive in 1991 (11).

Although the screening program reportedly improved the 5-year survival rate from 17% to 73%, the program has been questioned and the problem emphasizes the
need to understand the natural history of the disease before screening is initiated (12). Neuroblastoma is a heterogeneous disease and most patients who demonstrate biochemical abnormalities at age 6 months experience spontaneous regression. Patients diagnosed at an early age do not demonstrate the poor prognostic factors related to neuroblastoma (chromosome lp deletion or N-myc oncogene amplification) (13). Based on this understanding of the natural history of the disease and the fact the current 6-month screening programs have not reduced the mortality rate of neuroblastoma in Japan in comparison with other parts of the world, a consensus panel convened by the American Cancer Society concluded that “Mass screening of urine for increased catecholamines at 6 months of age has not been shown to reduce mortality and more widespread implementation of this practice cannot be recommended” (12).

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is an important cancer in sub-Saharan Africa and Southeast Asia, where hepatitis B and hepatitis C are endemic. Worldwide, there are >500 000 cases per year. For more than two decades, efforts have been made to use α-fetoprotein (AFP) in screening for this disease. Early studies, in which relatively insensitive immunodiffusion tests for AFP were used, suggested that AFP was useful in screening in China but not in Africa and indicated biological differences in HCC. In Senegal, 9000 males were screened over 3 years; of the three cases of HCC detected, one was resectable. In South Africa 9000 gold miners were screened and no cancers were detected (9, 14).

In China the screening program started 20 years ago and has been very intense. Screening has been performed in 29 provinces and 2392 counties in a total population of >840 000 000 by 250 000 physicians and 600 000 assistants. The testing was first carried out by immunodiffusion followed by counterimmunoelectrophoresis, reverse hemagglutination inhibition, radio rocket immunoelectrophoresis, and finally radioimmunoassay. In the original report of 343 999 persons screened, 147 had above-normal AFP values and of these 88.4% had HCC. Between 1971 and 1976 in Shanghai 1 967 511 persons were screened and 300 cases of HCC were detected (44.7% were asymptomatic). After resection the 3-year survival rate was 57.1%. Between 1974 and 1976 in Qidong County 1 223 912 people were screened and 479 cases of HCC were detected (35.2% were asymptomatic). The 2-year survival rate was 69% (14).

The sensitivity of the assay is important. In early studies, an immunodiffusion method detected 39/56 patients and there were no false positives. When RIA was used, 49 of the 56 patients were detected, but there were so many false positives that screening was not practical (9). In an attempt to eliminate the interferences from other diseases by use of highly specific monoclonal antibodies, an assay was developed involving two antibodies, each directed at a different epitope of AFP (15). The analytical detection limit was <0.5 μg/L. This method found AFP <5 μg/L in each of 450 normal healthy individuals, in 98.2% of 564 hepatitis B antigen-positive (HbsBAg+) individuals, and in 96.4% of 536 patients with nonmalignant diseases and other cancers. Similarly, no increases were seen in patients with acute or chronic hepatitis or cirrhosis. Increased AFP concentrations (>200 μg/L) were seen in 89.3% (23 of 25) of HCC patients from Africa who were HbsBAg+ and in 79% (45 of 57) of HbsBAg+ HCC patients from the Far East but in only 38% of 16 HCC patients who were HbsBAg negative.

The cost-effectiveness of general population screening, even in high-risk areas of the world, is questionable. An interesting study of screening a particular high-risk group is in the Alaskan native population, which has a high incidence of both hepatitis B and HCC (16). Only individuals who were HbsBAg+ were screened. More than 3000 assays were carried out between 1982 and 1984 on 1394 persons. There were 107 (17%) AFP increases in 602 females, but of these 100/107 were attributed to pregnancy and not to HCC. In 792 men 19 had positive AFP values (2.4%), and in 9 (47.4%) HCC was confirmed. Three of these had normal AFP titers 6 to 12 months before the first increases and three others had normal values in samples stored 15 to 19 months before the first increase was detected. In four of the six patients the tumors were successfully resected and AFP returned to normal. When only males are considered, the positive predictive rate for AFP in this study is 47.4%.

The enormity of AFP screening in the HbsBAg+ population is brought into perspective when one realizes that there are 200 000 000 HbsBAg+ individuals worldwide, of whom 900 000 are in the US (17, 18). Individuals with cirrhosis have a high incidence of HCC and may be considered a high-risk group suitable to be screened with AFP. In Japan 22 of 40 (56%) patients with cirrhosis-related HCC (tumors <2 cm) had low concentrations of AFP (<100 μg/L); it was estimated that at a cutoff of 100 μg/L, 65% of the cases would be missed (19). Serum AFP assays and ultrasonography were performed on 447 Italian patients with cirrhosis (62% of whom were HbsBAg+). The estimated HCC risk for this group was 3%/year; however, the program did not detect the predicted group of HCC patients (20).

Colorectal Cancer

DRE, sigmoidoscopy, and fecal occult blood tests have been recommended as screening procedures for colorectal cancer. There are no clear-cut studies outlining the benefits of screening. Tumor markers are not proposed as screening tools. In our experience, carcinoembryonic antigen (CEA) is increased in <5% of patients with Duke's A cancer (9). In a theoretical evaluation of fecal occult blood testing alone or in combination with sigmoidoscopy of all men in the US at age 65, Wagner et al. (7) calculated that the cost per year if both tests were used would be US$2 849 000 000, or US$1 534 000 000 if only fecal occult blood was used. The program would
presumably detect 33 000 new cases if both procedures were performed and 22 000 cases if fecal occult blood was the only screening tool. The respective costs per year of life gained would be US$42 000 and US$35 000. The authors concluded that this cost was reasonable and the program cost-effective, being no more expensive than mammography screening programs or dialysis programs for end-stage renal disease.

There has been debate whether colon cancer screening will have any beneficial effect on mortality (21). A summary of three European screening studies with fecal occult blood reported 98 193 individuals screened and 99 803 controls who were not screened (22). The screened population had 312 invasive cancers (60% Dukes' A and B), compared with 180 (45% Dukes' A and B) in the unscreened group. It was calculated that the program offered an 11% mortality advantage for the screened population and would result in a 10% reduction in mortality (6000 deaths/year) in the US. The conclusion was that screening is highly advantageous. Of course, it is not known whether the cases discovered by screening would ever become lethal cancers.

Perhaps the most exciting prospects in colorectal cancer are the possibility of using genetic markers to isolate individuals at high risk for cancer at some later date, perhaps even 20 years later. The complex genetic deletions involved in the lengthy progression of normal colonic mucosa through the polyp stage to adenocarcinoma have been described, and fecal measurements of one of the oncogenes has been proposed as a possible marker for risk-factor assessment (23, 24).

In a preliminary study, mutations of the ras oncogene were studied in feces from patients with curable colorectal cancer (24). The mutation looked for was K-ras in codons 12 or 13, which is known to occur in colon cancer tissue. Of 24 tissue specimens, 9 (37%) contained the mutation. The oncogene mutation was detected in DNA purified from stool in 6 of 7 patients with colon cancer who expressed the mutation in tissue. Three other patients who did not express the tissue mutation did not exhibit the oncogene in their stool, just as was the case for three healthy individuals. Mutation in the ras gene was found in 2 of 2 patients with benign adenomas who also expressed the gene in their tissue specimens. Although the procedure did not distinguish between carcinoma and adenoma, it provides, as the authors point out, "the conceptual and practical basis for a new approach for detecting the presence of colorectal tumors in a noninvasive fashion."

Ovarian Cancer

Ovarian cancer is the leading cause of death among gynecological cancers. There are 21 000 new cases each year and 13 000 deaths. If diagnosed and treated at an early stage, the 5-year survival rate is 85%; however, survival is only 4% in advanced disease, and two-thirds of women with ovarian cancer have advanced disease (stage III or IV) at the time of diagnosis (25). Risk factors include age, nulliparity, late first pregnancy, late menopause, and a family history of ovarian cancer. Screening procedures of asymptomatic women have not been useful and the American College of Obstetrics and Gynecology has recommended against routine screening. In a study of ultrasonography, 5439 women were screened, of whom 5.9% had abnormalities; five early cancers were detected, and 37% of the abnormalities were benign gynecological disease (26). An ultrasonography screening program would detect 40 cases/100 000 but there would be >5000 false positives and 160 complications from the diagnostic laparoscopy. However, if a screening program had an 80% sensitivity, it could reduce mortality by 50% (27). For each cancer detected, there would be 50 false positives but 5000 additional patients each year would experience a 5-year survival. For each additional survivor, 30 000 tests would be required at age 40 and almost 50 000 tests at age 50.

CA 125 has been evaluated as a screening test for ovarian cancer. Increases are observed in ~50% of patients with mucinous early (stage I or II) cancer and to a much lesser extent in women with nonmucinous disease (28). A retrospective study was carried out with specimens obtained from the Norwegian Janus Serum Bank, specimens from 39 300 women collected in 1974–1986 (29). Of these, 105 women developed ovarian cancer 1–143 months after the specimen was collected. The cancer patients were compared with 323 matched controls randomly selected from the bank. Fifty percent of the 105 women with ovarian cancer had CA 125 increases >35 kAU/L (arbitrary units) as many as 18 months before diagnosis and 33% had increases >65 kAU/L; only 7% of the controls had CA 125 >35 kAU/L. Twenty-five percent of the cancer patients had increased CA 125 60 months before, compared with only 0.9% of the controls. The conclusion of this study was that CA 125 is useful in screening. In a study of 915 Roman Catholic nuns (30), 36 had CA 125 >35 kAU/L; none had ovarian cancer but many had benign gynecological problems. Four who did not have an increased CA 125 died of nonovarian neoplasms (30). Jacobs et al. (31) used a multimodel approach in screening 1010 asymptomatic postmenopausal women who were first screened with CA 125 and with a pelvic examination. Those with abnormal results were examined by ultrasonography. There was one ovarian cancer, but 28 of 31 (90%) women with increased CA 125 had no clinical abnormality. Of the 28 abnormal pelvic examination results, over half were related to fibroids or cysts. Thirteen women had abnormal ultrasound patterns; in the 12 who consented to laparotomy, one cancer was established.

In a study of 1082 asymptomatic women over age 40, CA 125 values >35 kAU/L were found in 36 (3.3%) (32). Additional specimens were collected and repeat assays were performed on those with the increases. A doubling of the value was considered a true positive. One of the 1082 women had a clinically confirmed stage III ovarian cancer, diagnosed 21 months after the last specimen was collected. The incidence of detection in this study (1 in 1082) would be 93 cases/100 000 screened, compared with the reported clinical incidence of ovarian cancer of 42.2 cases/100 000. Evaluation of these screening stud-
ies suggests that if CA 125 is the only criterion, 30 laparotomies would be performed to confirm each ovarian cancer. Screening asymptomatic women in the US by pelvic ultrasonography and CA 125 would cost US$45 000 000 000. Many factors other than cancer can lead to increases of CA 125 (e.g., pregnancy, menstruation, benign gynecological diseases, pleural, peritoneal inflammation) (33). Until tests are available to discriminate between benign and malignant conditions, screening of asymptomatic women with CA 125 cannot be recommended. Recent studies suggest that urinary gonadotropin fragment may provide the necessary additional information (34).

CA 125 can also be used for evaluation of women with symptoms. In a large study of Scandinavian women with operable pelvic masses, the sensitivity of CA 125 was 87% and the specificity 88%. The prevalence of ovarian cancer in these women was 50% (50 000 cases/100 000) and the positive predictive value of CA 125 screening was 88% (35). CA 125 had a prognostic significance when related to clearance and half-life (t 1/2) in the serum after therapy. Overall survival was significantly higher if the t 1/2 was <20 days and if the CA 125 decreased to <30 kAU/L within 65 days (36).

Breast Cancer

The recommended screening procedures for breast cancer include mammography and a clinical breast examination (4). There are no circulating tumor markers available at this time for screening or as adjuncts to mammography (37). CEA is increased in ~20% of patients with stage I or II disease, and similar findings have been reported for the large group of mucin-type glycoproteins that have been evaluated in breast cancer (CA 15-3, BCM, BR27-29, MCA, CA 549, and CAM 26) (38).

Because our definition of screening includes risk-assessment analysis, it is important to point out that a growing number of reports suggest that tissue analysis of markers in the primary surgical specimen can provide useful and practical information concerning prognosis, total survival, disease-free survival, and risk of recurrence. In addition to the well-established estrogen and progesterone receptor assays, the tissue tests include cathepsin D, HER-2/Neu oncogene, epidermal growth factor receptor, and urokinase-type plasminogen activator antigens (39). When the current confusion about their use is sorted out, presumably it will be possible to identify on the day of surgery the subset of women with negative lymph nodes and small tumors who will have an early recurrence of cancer.

Prostate Cancer

Prostate cancer is the most common cancer of men in the US and has the second highest mortality rate (40). In 1992 it was estimated there would be 132 000 new cases and 34 000 deaths. Between 1973 and 1989 the prostate cancer mortality rate increased by ~16%. The incidence is age-related, and in men between 55 and 59 it is 94/100 000; in those over 65, the incidence is 740/100 000; and in men over 85, 1146/100 000 (41). Autopsy reports indicate an incidence of 38 000/100 000 in men between ages 50 and 70 (42). Clearly, this later prevalence includes a large percentage of men whose disease is latent and would remain indolent and not life-threatening. To be successful, a test will differentiate clinically important cancer from clinically insignificant cancer. Clinical screening has included DRE and transrectal ultrasonography (TRUS) (40). Stage A prostate cancer is by definition not palpable, and <35% of asymptomatic men who have an abnormal DRE will have a positive biopsy.

In men with symptoms such as urinary retention, the sensitivity is much greater. The Board of Directors of the American Cancer Society voted in November 1992 that "PSA be done in conjunction with a digital rectal examination annually on men 50 years and older" (43). For men in high-risk groups or those with family histories of the disease, the Board recommended that PSA screening start at a younger age.

Despite this recommendation, it is still controversial whether PSA can be useful in screening. The most extensive screening study included 1653 healthy men over 50 (44). PSA values were measured in serum from these men on two occasions over a 6-month period. All those with values <4.0 µg/L at both measurements (1516 men or 92% of the population) were not studied further. There were 107 (6%) who had values between 4.1 and 9.9 µg/L; of the 85 of these who had ultrasonic-guided biopsies, 14 (22%) were positive. In the 30 (2%) men with values >10.0 µg/L, 27 had biopsies and 18 (67%) were positive.

The control group was 235 men who had urinary symptoms and were attending a urology clinic. Seventy-four (32%) of these had PSA values between 4.1 and 9.9 µg/L, and 19 (26%) of these were biopsy-positive. In 45 men (14%) with values >10 µg/L, 29 (64%) were biopsy-positive. These percentages are essentially identical to those found in the screened group. Thirteen (11%) of 116 men in the control group with PSA values <4.0 µg/L had biopsy-proven cancers, suggesting that in a normal population ~10% of men with PSA values <4.0 µg/L would have biopsy-proven prostate cancer. Studies during Prostate Awareness Week have suggested that DRE complements PSA in detecting cancer. Sixty-nine percent of men with both abnormal DRE and PSA had biopsy-proven cancer, compared with 24% of men with either abnormal DRE and normal PSA or a normal DRE and abnormal PSA (45).

In a study of 472 asymptomatic men cared for in a general medical practice in Bristol, England, all 7 who had an increased PSA were eventually found to have a cancer; only 1 had had an abnormal DRE (46).

The question of whether the addition of TRUS can improve the sensitivity of prostate cancer screening has been considered. In a study in which DRE, TRUS, and PSA were used, DRE was positive in 11 patients but cancer was found in only 1. TRUS was positive in 18 and, again, cancer was found in only 1. The combination of DRE and TRUS improved the detection rate to 8 in 28. When PSA was added and results for all three mark-
ers were abnormal, biopsy-proven cancer was observed in 36 of 48. The positive predictive value of all three was 62.2%, compared with 15.2% when DRE and TRUS were positive but PSA was negative (47). A study of 1802 men, ages 59–89, seen in a clinical urological practice, involved the use of PSA, DRE, and ultrasonography (48). Biopsies were performed in 835 men with suspicious sonograms; 283 (14.6%) had cancer. In another 123 patients who had an abnormal DRE but a normal ultrasound pattern, biopsies were performed and 6 (4.9%) were positive. There were 366 men who were DRE positive; 209 of these (57.1%) had biopsies, of which 34 (20.2%) were positive. In addition, 236 men had a positive DRE and PSA values >10 μg/L; 227 were biopsied, and 137 were positive (58.1%). In the DRE/PSA-negative population (1205), 394 men were biopsied because of an abnormal sonogram; 17 (4.3%) in this group had cancer.

Another large screening study was carried out at the University of Washington (49). Between December 1989 and November 1990, 1249 men with no history of prostate disease were entered into the study. There were 187 who had PSA values >4.0 μg/L. Of these, 105 elected to have further evaluation (DRE, TRUS, biopsy) at the University of Washington; 16 others sought outside urologic consultation and were lost to the study. In 87 of the 105, PSA was 4.1–9.9 μg/L and 23 (26.5%) had cancer. Eighteen men had PSA >10 μg/L; 9 (50%) had cancer. The data suggested that men with PSA >8.0 μg/L the incidence of prostate cancer is threefold that in men with lower PSA values. Forty-nine individuals with normal DRE had an abnormal PSA; of these, 8 had positive biopsies. Six of 11 patients with negative TRUS but increased PSA had cancer. Brawer et al. (49) concluded that "PSA as the initial test in men older than 50 years offers a simple readily accepted objective and economic approach to the detection of prostate carcinoma. It must be considered an adjunct to but not a replacement for digital examination." In another large study, 1002 men in Quebec City were included; the PSA cutoff was 3 μg/L. At this value, the sensitivity was 89.6% and the predictive value of a negative result was 98.6%. Of the 57 cancers detected, 16 were in men with PSA between 3 and 4 μg/L (50).

A 20-year retrospective study of PSA in serum specimens collected from a geriatric population gives increased support to the usefulness of PSA in screening (51). In those men who never developed a malignancy, the PSA increased slightly in a linear fashion over time. The linear increase was somewhat greater in those with benign prostatic hypertrophy. However, in men who developed cancer, the rate of increase became exponential, and values >4.0 μg/L were observed as many as 10 years before a clinical diagnosis of prostate cancer was made.

Opentemberg and Thompson (42) estimated the cost of prostate screening of all men 50–70 years old. They used an incidence of prostate cancer for this age group of 38%, extrapolated from studies of prostate cancer at autopsy. They calculated that >17 million men would be screened at a cost for screening and treatment of US$27 000 000 000 for those with PSA >4 μg/L; costs would be US$11 300 000 000 if only men with values >10 μg/L were included. In comparison, the current annual rate of spending for clinical management of all men in the US with carcinoma of the prostate is US$255 000 000; that is, the allocation of the health budget for prostate cancer would rise from 0.06% to >5%. The program theoretically would detect 1 627 155 individuals with prostate cancer when 4 μg/L was the cutoff, and 756 337 when values >10 μg/L were used. The authors point out that such a program would create 266 271 impotent men, 61 618 who would be incontinent, and 13 000 requiring a colostomy. There also would be 20 563 treatment-related deaths. However, there is no evidence that such a program would decrease the death rate from prostate cancer.

Whatever the final decision on general screening with PSA, it is important to quote from a recent editorial in the Journal of the American Medical Association (52):

Screening studies conclusively show several facts. These are that PSA used initially alone or with DRE results in 2 to 4 times more prostate cancer detection than DRE alone; both DRE and PSA provide unique information for diagnosis; and finally PSA levels do succeed in detecting lower stage disease.

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