PROSTATE CANCER: TO SCREEN OR NOT TO SCREEN

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DISEASE BURDEN, TRENDS, AND RISK FACTORS

Prostate cancer is the most commonly diagnosed form of cancer, other than skin, among men in the United States, and is second (to lung) as the leading cause of cancer death in US men. The American Cancer Society estimates that in 2003, among US men, 220,900 new cases and 28,900 deaths will occur, accounting for about 33% and 10% of cases and deaths, respectively. Incidence rates rose by 84% between 1987–1992, declined by about 24% between 1992–1994, and then leveled off between 1994–1999. The incidence rates peaked in 1992 for Whites and in 1993 for Blacks. Incidence rates in the United States are at 169/100,000 (1995–1999). US death rates peaked in 1991 at 27/100,000, decreased to 23.7/100,000 during 1994–1998 but increased to 33.9/100,000 during 1995–1999. The life time probability of ever developing and dying from prostate cancer for 1997–1999 was about 17% and 3.3%, respectively.[1]

Several published papers have reviewed the epidemiology of prostate cancer and have identified a number of factors that increase the risk of developing the disease. The risk factors include age (more than 70% of cases are diagnosed in men over the age of 65); race (Blacks have the highest rates in the world); family history of prostate cancer (5%–10% of cases are hereditary); diets high in total fat intake, and a history of previous prostate disease. Total and age-specific incidence and mortality rates in US Blacks are substantially higher than in Whites.[2–6] Reports from autopsy series summarized by Coley et al[7] show a 30% prevalence rate in men over the age of 50 years. The rates increase from 12% in the 40–49 age group to 43% in

age group of 80 and older. Given these rates and the estimated 25.5 million men age 50–70 in the United States,[8] it is estimated that there are more than 7.6 million "autopsy" cancers in men ages 50–70. However, the great majority of these cases are "occult" or biologically inactive.

PROSTATE CANCER DETECTION

A number of screening tests have been used to detect and monitor prostate cancer. They include the Digital Rectal Examination (DRE), the earliest test used, the Prostate Specific Antigen (PSA), which is most commonly used, and the Transrectal Ultrasonography (TRUS), used primarily as a diagnostic test with DRE and PSA.[7]

The Digital Rectal Examination (DRE) is a manual probing of the prostate through the rectum; it can detect tumors located in the peripheral zone of the prostate gland. Until the late 1980s, it was the test of choice for prostate screening. Although the DRE has been used for sometime now, careful evaluation of its efficacy/effectiveness in reducing mortality from prostate cancer has not taken place. The DRE has limited ability to detect prostate cancer since small tumors often form in the part of the prostate that cannot be reached by DRE. Clinicians have difficulty distinguishing between benign abnormalities and cancer. The experience and skill of the examiner influences interpretation and accuracy. The reported sensitivity, specificity, and predictive value positive ranges associated with DRE are 55%–69%, 89%–97%, and 11%–29%, respectively. Three observational case-control studies have examined its accuracy in detecting advanced prostate cancer or mortality from prostate cancer

using chart reviews to document exposure to DRE. Two studies found no relationship[10,11] while a third study found a reduction in mortality, or a protective effect, among men screened with the DRE (OR and 95% CI: 0.51[0.31–0.84]).[12]

The PSA is widely used for detection and followup. However, it cannot distinguish between benign abnormalities and cancer and it fails to detect some prostate cancers. About 20% of patients with biopsy-proven prostate cancer have PSA levels within normal range. Values greater than 4.0 ng/mL are associated with sensitivity, specificity, and predictive value positive of 71% (range of 43%–81%), 75% (range of 59%–93%), and 37% (range of 28%–49%), respectively.

There are at least 6 different assays for PSA determination in the United States and variations do exist among assays for men with known prostate cancer. Normal PSA ranges increase with age and are significantly higher in African Americans than in Whites.[9]

Brawer[9] summarized a number of studies reporting on prostate cancer detection yield from PSA-based screening studies and noted that the predictive value positive range from 17.1 to 41.9. The estimated detection rates (3.8–6.7) were generally higher than the observed detection rates (1.8–3.3).

DILEMMAS OF PROSTATE CANCER

The principal question facing the scientific community relative to prostate cancer is whether prostate cancer screening reduces mortality from prostate cancer or not. Two additional questions related to prostate cancer screening that must also be addressed are: 1) Which cancers will progress to become clinically significant and which will not? 2) Is treatment of early stage prostate cancer more effective than no treatment in prolonging a man's life? Answers to these 2 questions are beyond the scope of this presentation.

SCREENING RECOMMENDATIONS BY PROFESSIONAL AND GOVERNMENTAL GROUPS

There is no consensus among professional organizations to screen or not to screen for prostate cancer at this time. The American Cancer Society (ACS),[13] the American Urologic Association (AUA),[14] the American Academy of Family Physicians (AAFP),[15] The American College of Physicians (ACP),[16] and the American Medical Association (AMA)[17] recommend that providers discuss with patients the potential benefits and harms of screening with PSA, give consideration to patient preferences, and individualize the decision to screen. They all agree that the most appropriate men for screening are those over the age of 50 years with a life expectancy of at least 10 years and younger men at increased risk for prostate cancer. Some groups recommend annual screening after age 50 and earlier for men at high risk. Other interested professional groups or governmental agencies such as the Agency for Health Care Policy and Research (AHCPR),[18] the United States Preventive Services Task Force (USPSTF),[19] the National Cancer Institute (NCI),[20] and the Canadian Task Force on the Periodic Health Examination (CTFPHE),[21] either make no recommendations (AHCPR) or are against screening for prostate cancer at this time (USPSTF, NCI, CTFPHE). The Centers for Disease Control and Prevention makes no recommendations of its own, but follows the recommendations of the USPSTF.

MANAGING UNCERTAINTY AND CONFUSION IN CLINICAL PRACTICE

Primary care providers are expected to balance uncertainty related to prostate cancer. The duty is to provide quality health care to their patients and at the same time be aware and concerned about possible malpractice litigation. The clinical practice is influenced by physicians' knowledge, attitudes, and beliefs about specific disease entities, the populations affected, as well as the cost and other related issues. Practice guidelines, which are based on accurate and current science-based medical information, increase physician knowledge and practice patterns.

The question, then, is why does prostate cancer create so much confusion among healthcare professionals? The fundamental source of confusion stems from failure to distinguish between the criteria required for mass screening used to establish public health policy and the criteria used for early detection and case findings at the provider/patient level.

DISEASE AND TEST CRITERIA FOR MASS SCREENING AND EARLY DETECTION

There are a number of established criteria to justify mass screening for a disease in the general population. These criteria have been outlined and discussed by Miller[22] and are described and expanded herein:

1) The disease or condition should be a serious health problem, which means it has to be associated with high morbidity and mortality.

2) There should be a defined target population with a reasonable disease prevalence in the screened population. Screening for rare diseases is associated with high false positive rate.

3) There should be a recognizable preclinical detectable disease state with known natural history.

4) There should be a reliable test with known and acceptable sensitivity and specificity values associated with the test. The test should be associated with

minimal risk and discomfort and should be acceptable by both the patient and the practitioners.

5) Treatment for cases detected by screening during the preclinical state should be associated with reduced mortality and morbidity more than treatment after symptoms appear. This means that early detection and intervention must improve outcome.

6) There should be facilities available for diagnosis and therapy so as not to overload an already burdened system.

7) Screening should be cost-effective. The benefits of the screening program should outweigh the cost.

The criteria for early detection is primarily based on the standard of medical care required for early detection and case findings. Although the same tests and objectives are used for detecting prostate cancer, mainly PSA and DRE, the criteria are different. Central to the difference in the criteria is that population-based benefit must be proven for mass screening.

WHY LACK OF CONSENSUS ON PROSTATE CANCER SCREENING?

There are 2 important scientific issues related to prostate cancer screening that have precipitated much discussion in the medical and public health community, some confusion among the public, and a lack of consensus by experts, professional organizations, and governmental groups. First, evidence from randomized, controlled clinical trials are required to satisfy public health policy for mass screening. Second, experts differ in their interpretation of critical data elements pertaining to prostate cancer screening and patient management.

Currently there are 2 major prostate cancer randomized screening trials underway to determine if screening tests reduce mortality from prostate cancer. The PLCO Cancer Screening Trial,

which is sponsored by the NCI,[23,24] and the European Randomized Trial of Prostate Cancer.[25] The goal of the PLCO trial, which has been underway since 1994, is to enroll about 75,000 men ages 55–74 randomized equally to screening and control groups. The screened group will receive DRE and PSA initially and annually for 3 years. The control group will receive "usual care." Both groups will be followed for 10–14 years with the primary end point being mortality. The European Randomized Trial of Prostate Cancer screening includes 5 participating centers in 5 countries. A total of 180,000 men ages 50–74 will be randomized after consent in 4 of 5 centers and screened every 4 years. The screening group will receive PSA, DRE, and TRUS while the control group receives normal health care. The end points include mortality, quality of life and cost effectiveness. Unfortunately results from both trials will not be available before 2007–2008.

The Quebec Prospective Randomized Controlled Trial[26] was the first trial to publish data on 46,000 men who were randomized to be screened or not to be screened and followed for 8 years. Results showed no difference in mortality rates between men placed in either an invited group (4.5 deaths/1000) or the uninvited group (4.8 deaths per 1000).

Meanwhile, the main source of difference related to prostate cancer screening stems from the difficulty in the interpretation of data from ecological studies estimating cancer screening benefits. Overestimation of cancer screening benefits can result from 2 basic phenomenon: 1) lead time bias, and 2) length bias sampling. For example, if survival time is measured from date of diagnosis to death and is increased by screening, the date of diagnosis is advanced without an increase in total years lived. The length bias sampling assumptions regarding prostate cancer stem from the fact that PSA-detected prostate cancers progress at rates that are slower

than cancers detected clinically and that PSA preferentially detects clinically insignificant tumors as defined by volume, grade, stage, and progression potential.[22,27–29]

MEASURES OF IMPROVED OUTCOME IN CANCER SCREENING AND LEVELS OF SCIENTIFIC EVIDENCE

Screening may detect small cancers that otherwise may not be found clinically. Prostate cancer is a good example. Autopsy series have uncovered many cancers that are not biologically active (occult). The discovery of such cancers through screening will increase the incidence of cancer, increase survival, and give the appearance of stage shift without a reduction in mortality. Therefore, measures of improved outcome in order from the strongest to the weakest are: 1) a decrease in cause-specific mortality, 2) reduction in incidence of advanced stage cancers, 3) an increase in survival, and 4) a shift in stage.[27–29]

The scientific community has identified 5 levels of scientific evidence in support of the measures of improved outcome in cancer screening. The evidence from the strongest to the weakest: 1) evidence from at least one well-designed and well-conducted randomized controlled trial, 2) evidence from nonrandomized controlled trials, 3) evidence from cohort and case-control studies, preferably from more than one center or group, 4) evidence from multiple time series with or without intervention, and 5) evidence from ecological studies and the opinion of expert groups. Evidence from all of these sources is considered in making a determination about the value of screening in the early detection of cancer in asymptomatic individuals.[27–30]

Under each level, the evidence should be obtained from a number of endpoints. These endpoints relate to cancer mortality, cancer incidence and a

generally accepted intermediate end point, if appropriate. This is applicable to the first 4 levels. Opinions of respected authorities, which are based upon clinical experience or reports of expert committees, use any of the designs using non-validated surrogate endpoints.

Experimental studies, such as RCT, provide the highest level of evidence because randomization eliminates known and unknown biases such as selection, lead time bias, length bias sampling, healthy volunteer and other biases, and also other potential confounders when testing a detection procedure to determine its effect on outcome. It also makes the experimental and control groups comparable with respect to both known, but more importantly, unknown factors that may influence the outcome. Observational studies, such as cohort and case-control studies, do provide indirect evidence for the effectiveness of screening. They do not prove a mortality reduction effect, but they can suggest a mortality reduction. The potential for bias in observational studies, especially the case-control design, is high if the methodology employed in the design and analysis lacks scientific rigor. The absence of controls in descriptive studies renders them useful only for describing trends and formulating hypotheses. The potential for bias and confounding is much greater than in either experimental or analytical studies. The performance of screening tests such as sensitivity, specificity, and predictive values are first reported in descriptive studies. Likewise, shifts in stage, increase in survival rates, and even reduction in deaths are first noted in descriptive studies.

TRENDS IN PROSTATE INCIDENCE, MORTALITY, AND SURVIVAL BY RACE, GRADE AND STAGE

The most recent trends on prostate cancer incidence and mortality by race,

grade, and stage for the time period 1973–1996 and 1999 as well as five-year relative survival for 3 time periods have been obtained from the Surveillance Epidemiology and End Results (SEER) National Cancer Institute Registry.[31] Estimated annual percent change of prostate cancer incidence and mortality between 1973 and 1999 shows some remarkable trends. Although the incidence rates remain significantly higher in Blacks compared to Whites, throughout the 27-year time period, the trends by race are similar. The 2% annual rise in incidence between 1973–1986 was followed by a dramatic rise between 1986 and 1992, subsequently declined, and has leveled off during the 1994–1999 period. Trends in mortality rates by race, which are generally twice as high in Blacks as Whites, are also similar; they increased by an average of 2%–3% annually between 1973–1992, peaked in 1992 and 1993 in Whites and Blacks respectively, then began to decline by about 2.3% to 3.5% annually. Increases in incidence up to 1989 are probably due to increase in tumor detection caused by increased incidental detection following prostatectomy for putative benign prostatic hyperplasia. The rise in incidence rates between 1986 and 1992 and more specifically after 1989 can be easily attributed to early diagnosis with PSA in asymptomatic men. However, the rate of decline in incidence in both Blacks and Whites after 1992/1993 is more difficult to interpret. The declines in mortality between 1991 and 1999 in White men and between 1993 and 1999 in Black men are about 21.6% and 16%, respectively. Declines during the same time period occurred in all ages. The trends in mortality in both Blacks and Whites parallel the trends in incidence and are also difficult to interpret.

Most of the increase in incidence was seen in localized and regional disease. Incidence of distant-stage disease at time of diagnosis showed little increase initially then began to show sub-

stantial decreases beginning in 1991 in both Black and White men. Similar trends are reported by grade of disease at time of diagnosis. As expected, the shift in stage (ie, the increase in early stage, which was followed with a decline in distant stage) are consistent with screening; however, the short interval between the increase in screening, which was followed with a decline in mortality, are not consistent with screening, given our understanding of the natural history of prostate cancer.[32] During the last 10 years, improvement in prostate cancer treatment, which included an increase in the rates of radical prostatectomy, new development in hormone therapy, and refinements in radiation therapy all have contributed to the declines in prostate cancer death rates.[33,34] Feuer et al[35] explained the decreases in mortality to misclassification bias in assigning the cause of death for prostate cancer over time known as "attributable bias" as well as to improved treatment. They argued that if the percentage of death so attributed is stable then the prostate cancer mortality rate would be expected to increase and decrease in close approximation to the incidence of prostate cancer in the population. While data from SEER indicate a substantial improvement in survival for both Blacks and Whites, the survival experiences of Blacks lags behind that of Whites by about 5–10 percentage points.

ARGUMENTS FOR AND AGAINST SCREENING WITH THE PSA PLUS THE DRE

Given the current state of the scientific evidence, it is not surprising to have arguments for and against screening. Small summarized these arguments.[36] The arguments for screening with the PSA plus the DRE include: 1) prostate cancers can be detected. The DRE plus PSA have a fair predictive value positive if PSA is >10 ng/mL or PSA rate of change is useful if PSA is be-

tween 4.0–10 ng/mL. 2) PSA is inexpensive, easy and somewhat reproducible; and 3) increased early detection of prostate cancer may result in increased cure rates. The arguments against screening with the PSA plus the DRE include: 1) screening tests, available now, lack sensitivity and specificity; 2) screening will primarily identify clinically insignificant prostate cancer; 3) the likelihood of detecting non-organ confined disease (incurable) already being present is high (PSA>10 ng/mL) to make such testing unnecessary; 4) high costs, discomforts, and morbidity associated with biopsies and TRUS must be considered; and 5) a false sense of security from a "negative" screen and unnecessary worry when a clinically insignificant cancer, which otherwise remain occult is discovered. Two other items, not noted by Small, should be added to the arguments presented against screening: 1) the natural history of prostate cancer is poorly understood; and 2) the impact on mortality and morbidity of surgery compared with watchful waiting in patients with operable cancer is uncertain.

POTENTIAL ADVANTAGES AND DISADVANTAGES OF PROSTATE CANCER SCREENING

It is also argued that the potential benefits or advantage of prostate cancer screening may result in: 1) improved prognosis for some cases detected by screening; 2) less radical treatment to cure some early cases; 3) reassurance for those with negative tests results; and 4) resource saving. It can also be equally argued that the potential disadvantages of prostate cancer screening include: 1) longer prognosis for cases whose prognosis is unaltered; 2) over treatment of borderline abnormalities; 3) false assurance of false negative results; 4) anxiety as well as the morbidity associated with

a false positive result; and 5) hazard of the screening tests and resource cost.

PUBLIC HEALTH POLICY AND CONTROL MEASURES REGARDING PROSTATE CANCER

There are 2 basic arguments for prostate screening, each championed by prominent public health screening experts and clinicians. The first argument states that we should marshall all available resources, including early detection, to reduce prostate cancer mortality until results from randomized controlled trials prove that such efforts are ineffective or cause net harm. The second counter argument states that we should avoid the risks of early detection unless a net benefit of screening can be definitely shown in clinical trials.

Three of the most important risk factors in prostate cancer identified from epidemiologic studies (age, race, and family history) are not modifiable. Therefore, the absence of modifiable risk factors precludes any effective primary prevention approaches at this time. Secondary prevention through screening remains controversial even for high-risk groups. Widespread prostate cancer screening should be approached with caution until results of clinical trials and observational studies provide evidence that screening does more good than harm.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures 2003*. Atlanta, Ga: American Cancer Society; 2003.
2. Dijkman GA, Debruyne FMJ. Epidemiology of prostate cancer. *Eur Urol*. 1996;30:281–295.
3. Haas GP, Sakr WA. Epidemiology of prostate cancer. *CA Cancer J Clin*. 1997;47:273–287.
4. Nomura AMY, Kolonel LN. Prostate cancer: a current perspective. *Epidemiologic Reviews*. 1991;13:200–227.
5. Ross RK, Schottenfeld D. Prostate cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York, NY: Oxford University Press; 1996: 1180–1206.
6. Pienta KJ, Esper PS. Risk factors for prostate cancer. *Ann Intern Med*. 1993;118:793–803.
7. Coley CM, Barry MJ, Fleming G, et al. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. *Ann Intern Med*. 1997;126(5):394–406.
8. US Bureau of the Census. *US 2000 Census of the Population*. Washington, DC: Bureau of the Census; 2000.
9. Brawer MK. How to use prostate specific antigen in the early detection or screening for prostate carcinoma. *CA Cancer J Clin*. 1995; 45(3):148–164.
10. Friedman GD, Hiatt RA, Quesenberry CP Jr, et al. Case-control study of screening for prostate cancer by digital rectal examination. *Lancet*. 1991;337:1526–1529.
11. Richert-Boe KE, Humphrey LL, Glass AG, et al. Screening digital rectal examination and prostate cancer mortality: a case-control study. *J Med Screen*. 1998;5:99–103.
12. Jacobsen SJ, Bergstralh EJ, Katusik SK, et al. Screening digital rectal examination and prostate cancer mortality: a population-based case-control study. *Urology*. 1998;52:173–179.
13. American Cancer Society Guidelines for the early detection of cancer: update of the early detection guidelines for prostate, colorectal, and endometrial cancers. Update 2001—testing for early lung cancer detection. *CA Cancer J Clin* [serial online]. 2001;51:38–75. Available at: www.cancer.org. Accessed February 14, 2003.
14. Prostate-specific antigen (PSA) best practice policy. American Urologic Association (AUA). *Oncology (Huntingt)*. 2002;14:267–272.
15. American Academy of Family Physicians. Periodic health examinations. Revision 5.3, August 2002. Available at: www.aafp.org/.exam.xml. Accessed February 15, 2003.
16. American College of Physicians. Screening for prostate cancer. *Ann Intern Med*. 1997;126:480–484.
17. American Medical Association. Report of the Council on Scientific Affairs (A-00). Screening and early detection of prostate cancer. June 2001. Available at: www.ama.assn.org/ama/pub/article/2036-2928.html. Accessed February 15, 2003.
18. Harris RP, Lohr KN, Beck R, et al. Screening for prostate cancer. Systematic Evidence Review No. 16 (prepared by the Research Triangle Institute, University of North Carolina Evidence-Based Practice Center under contract no. 290-97-0011). Rockville, Md: Agency for Healthcare Research and Quality; December 2001. Available at: www.ahrq.gov/clinic/serfile.htm.
19. *Guide to Clinical Prevention Services Report of the US Preventive Services Task Force*. 3rd ed. Baltimore, Md: Williams and Wilkins; 2003.
20. National Cancer Institute. Prostate cancer (PDQ): screening. Available at: http://

www.cancer.gov/cancerinfo/pdq/screening/prostate/healthprofessional/html. Accessed February 17, 2003.

21. Screening for prostate cancer. Canadian Task Force on Preventive Health Care. Ottawa: Health Canada; 1994. Available at: www.ctfphe.org/index.html. Accessed February 14, 2003.

22. Miller AB. Fundamental issues in screening for cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* 2nd ed. New York, NY: Oxford University Press; 1996:1433–1452.

23. Prorok P. The National Cancer Institute Multi-Screening Trial. *Can J Oncol.* 1994;4(suppl 1):102–105.

24. Gohagan JK, Prorok PC, Kramer BS, Cornett JE. Prostate cancer screening in the prostate, lung, colorectal, and ovarian cancer screening trial of the National Cancer Institute. *J Urol.* 1994;152:1905–1909.

25. Schroder FH. The European Screening Study for Prostate Cancer. *Can J Oncol.* 1994; 4(suppl 1):102–105.

26. Labrie F, Candas B, Dupont A, et al. Screening decreases prostate cancer deaths: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate.* 1999;38:83–91.

27. Morrison AS. *Screening in Chronic Disease.* Oxford: Oxford University Press; 1985:48–63.

28. Screening of Cancer, PDQ Support Care/Screening/Prevention Information. National Cancer Institute Med News (208/03092). Available at: http://imsdd.meb.uni-bonn.de/cancernet/303092.html. Accessed February 15, 2003.

29. Prorok PC, Connor RJ. Screening in the early detection of cancer. *Cancer Invest.* 1986;4(3): 225–238.

30. Cook DJ, Guyatt GH, Laupacis A, et al. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* October 1992;102(suppl):305s–311s.

31. Ries I, Eisner M, Kosary C, et al. SEER cancer statistics review, 1973–1999, National Cancer Institute, 2002. Available at: http://seer.cancer.gov/csr/1973–1999. Accessed February 15, 2003.

32. Etzioni R, Legler JM, Feuer EJ, et al. Cancer surveillance series: interpreting trends in prostate cancer. Part III: Quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. *J Natl Cancer Inst.* 1999;91:1033–1039.

33. Harris R, Lohr KN. Screening for prostate cancer: an update of the evidence for the US Preventive Services Task Force. *Ann Intern Med.* 2002;137:917–929.

34. Feuer EJ, Merrill RM, Hankey B, et al. Cancer surveillance series: interpreting trends in prostate cancer. Part II: Cause of death misclassification and the recent rise and fall in prostate cancer mortality. *J Natl Cancer Inst.* 1999;91:1025–1032.

35. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer. Part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. *J Natl Cancer Inst.* 1999;91:1017–1024.

36. Small EJ. Prostate cancer: who to screen, and what the results mean. *Geriatrics.* 1993; 48(12):28–38.