American Cancer Society Guideline for the Early Detection of Prostate Cancer

Update 2010

Andrew M. D. Wolf, MD[1]; Richard C. Wender, MD[2]; Ruth B. Etzioni, PhD[3]; Ian M. Thompson, MD[4]; Anthony V. D'Amico, MD, PhD[5]; Robert J. Volk, PhD[6]; Durado D. Brooks, MD, MPH[7]; Chiranjeev Dash, MD[8]; Idris Guessous, MD[9]; Kimberly Andrews[10]; Carol DeSantis, MPH[11]; Robert A. Smith, PhD[12]

Abstract

In 2009, the American Cancer Society (ACS) Prostate Cancer Advisory Committee began the process of a complete update of recommendations for early prostate cancer detection. A series of systematic evidence reviews was conducted focusing on evidence related to the early detection of prostate cancer, test performance, harms of therapy for localized prostate cancer, and shared and informed decision making in prostate cancer screening. The results of the systematic reviews were evaluated by the ACS Prostate Cancer Advisory Committee, and deliberations about the evidence occurred at committee meetings and during conference calls. On the basis of the evidence and a consensus process, the Prostate Cancer Advisory Committee developed the guideline, and a writing committee drafted a guideline document that was circulated to the entire committee for review and revision. The document was then circulated to peer reviewers for feedback, and finally to the ACS Mission Outcomes Committee and the ACS Board of Directors for approval. The ACS recommends that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision with their health care provider about screening for prostate cancer after they receive information about the uncertainties, risks, and potential benefits associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process. Men at average risk should receive this information beginning at age 50 years. Men in higher risk groups should receive this information before age 50 years. Men should either receive this information directly from their health care providers or be referred to reliable and culturally appropriate sources. Patient decision aids are helpful in preparing men to make a decision whether to be tested. **CA Cancer J Clin 2010;60:70–98.**

CME CNE

To earn free CME credit or nursing contact hours for successfully completing the online quiz based on this article, go to **http://CME.AmCancerSoc.org.**

Executive Summary

Although there have been substantive advances in our understanding of prostate cancer screening since the last American Cancer Society (ACS) guideline update in 2001, there remain significant uncertainties regarding the overall value of detecting prostate cancer early. Emerging evidence that periodic testing with prostate-specific antigen (PSA) may reduce the likelihood of dying from prostate cancer must be weighed against the serious risks

[1]Associate Professor of Medicine, University of Virginia School of Medicine, Charlottesville, VA; [2]Chair and Alumni Professor, Department of Family and Community Medicine, Thomas Jefferson University Medical College, Philadelphia, PA; [3]Full Member, Program in Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center, Seattle, WA; [4]Chairman and Professor, Department of Urology, The University of Texas Health Science Center, San Antonio, TX; [5]Chair, Division of Genitourinary Radiation Oncology, Dana-Farber Cancer Institute, and Professor of Radiation Oncology, Harvard Medical School, Boston, MA; [6]Professor, Department of General Internal Medicine, Ambulatory Treatment and Emergency Care, The University of Texas M. D. Anderson Cancer Center, Houston, TX; [7]Director, Prostate and Colorectal Cancers, Cancer Control Science Department, American Cancer Society, Atlanta, GA; [8]Doctoral Candidate, Department of Epidemiology, Emory University, Rollins School of Public Health, Atlanta, GA; [9]Doctoral Candidate, Department of Epidemiology, Emory University, Rollins School of Public Health, Atlanta, GA, and Head of the Unit of Population Epidemiology, Department of Community Medicine and Primary Care, Geneva University Hospitals, Geneva, Switzerland, and Research Fellow at the Community Prevention Unit, Institute of Social and Preventive Medicine, Lausanne University, Lausanne, Switzerland; [10]Research Associate, Cancer Control Science Department, American Cancer Society, Atlanta, GA; [11]Epidemiologist, Surveillance and Health Policy Department, American Cancer Society, Atlanta, GA; [12]Director, Cancer Screening, Cancer Control Science Department, American Cancer Society, Atlanta, GA.

incurred by early detection and subsequent treatment and particularly against the risk of treating many men for screen-detected prostate cancer who would not have experienced ill effects from their disease if it had been left undetected.

Against this backdrop of uncertainties, risks, and potential benefits, we have developed a guideline that accentuates the importance of involving men in the decision whether to initiate and continue testing for prostate cancer. To engage in this decision, men must have a basic understanding of the importance of prostate cancer, the potential benefits of early detection, the strengths and limitations of PSA testing, and the risks of finding and treating screen-detected cancer. In the guideline statement, we have attempted to provide the core elements of information necessary for an informed decision. How men use this knowledge will depend heavily on the value they place on the various elements: Is the opportunity to potentially lower a man's probability of dying from cancer worth the risk of deleterious effects of treatment? Does the realization that some men are treated unnecessarily outweigh the reassurance that comes from finding cancer at an early stage? Health care providers can and should play a critical role in helping men to make this decision by assuring that they have adequate information and by helping them to clarify their values relevant to the decision. Given the complexity of the issues involved and the time constraints faced by health care providers, we encourage providers and patients to use prostate cancer screening decision aids to facilitate the process and better ensure a decision that is truly commensurate with the patient's values. For men who are unable to decide, the screening decision can be left to the discretion of the health care provider, who should factor into the decision his or her knowledge of the patient's general health preferences and values.

In view of the delay between diagnosis through screening and the expected mortality benefit, we continue to recommend that men whose life expectancy is less than 10 years not pursue prostate cancer early detection. The likelihood of benefit in these men is sufficiently low to be outweighed by the risk of harms stemming from treatment, which will be experienced in the near term. Conversely, we continue to recommend that men at higher risk for developing prostate cancer at earlier ages—African American men and

We acknowledge the members of the American Cancer Society (ACS) Prostate Cancer Advisory Committee (listed below) for their vital contributions to the development of this guideline. In addition, Robert J. Volk, PhD (The University of Texas M. D. Anderson Cancer Center, Houston, TX); Louise Walter, MD (University of California-San Francisco, San Francisco, CA); and Chiranjeev Dash, MBBS, MPH and Idris Guessous, MD (Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta GA) made major contributions as external experts. We also thank the reviewers, including members of the ACS Primary Care Advisory Committee, the ACS Mission Outcomes Committee, and the ACS Board of Directors for their helpful comments and recommendations.

American Cancer Society Prostate Cancer Advisory Committee: Andrew M. D. Wolf, MD (Chair), Associate Professor of Medicine, University of Virginia School of Medicine, Charlottesville, VA; Claudia R. Baquet, MD, MPH, Associate Dean for Policy and Planning and Director, Center for Health Disparities, University of Maryland School of Medicine, Baltimore, MD; Gerald Chodak, MD, Chicago, IL; Jennie Cook, American Cancer Society National Assembly Life Member, Larkspur, CA; Anthony V. D'Amico, MD, PhD, Chair, Division of Genitourinary Radiation Oncology, Dana-Farber Cancer Institute and Professor of Radiation Oncology, Harvard Medical School, Boston, MA; Ruth B. Etzioni, PhD, Full Member, Program in Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center, Seattle, WA; Thomas D. Fogel, MD, Cabrillo Radiation Oncology Medical Center and Coastal Radiation Oncology Medical Group, Ventura, CA; Paul A. Godley, MD, PhD, MPP, Professor, Hematology/Oncology, University of North Carolina School of Medicine and Member, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Cynthia M. LeBlanc, EdD, MA, Vice-chair, American Cancer Society National Board of Directors, Richmond, CA; Terry Mason, MD, Chief Medical Officer, Cook County Health and Hospitals System, Chicago, IL; Viraj Master, MD, PhD, Assistant Professor of Urology, Emory University School of Medicine, Atlanta, GA; Andrew L. Salner, MD, Director, Department of Radiation Oncology and Director, Cancer Program, Hartford Hospital, Hartford, CT; Virgil H. Simons, Founder and President, The Prostate Net, Secaucus, NJ; Ian M. Thompson, Jr., MD, Chairman and Professor, Department of Urology, The University of Texas Health Science Center, San Antonio, TX; and Richard C. Wender, MD, Chair and Alumni Professor, Department of Family and Community Medicine, Thomas Jefferson University Medical College, Philadelphia, PA

ACS Staff (Atlanta, GA): Kimberly Andrews, Research Associate, Cancer Control Science Department; Durado D. Brooks, MD, MPH, Director, Prostate and Colorectal Cancers, Cancer Control Science Department; J. Leonard Lichtenfeld, MD, MACP, Deputy Chief Medical Officer; Robert A. Smith, PhD, Director, Cancer Screening, Cancer Control Science Department.

Corresponding author: Durado D. Brooks, MD, MPH, Director, Prostate and Colorectal Cancers, Cancer Control Science Department, American Cancer Society, 250 Williams Street, Atlanta, GA 30303; durado.brooks@cancer.org.

DISCLOSURES: Members of the American Cancer Society Prostate Cancer Advisory Committee were asked to disclose relationships, including potential financial conflicts of interest. The following was disclosed: G. Chodak has served on the advisory board for Watson Pharmaceuticals and Ferring Pharmaceuticals; V. Simons has served as a consultant to the State of New Jersey Office of Cancer Control and Prevention for their Cancer Education and Early Detection program, has served as co-investigator to various university-based research studies on reaching African American men to promote disease risk awareness and/or early detection, and is the recipient of educational grants from AstraZeneca, Sanofi-Aventis, GTx, Genentech, and Abbott Oncology for a Patient/Professional Symposium Educational Program (see Form 990 at http://www.guidestar.org for more information); I. Thompson has served as a consultant to Mission Pharmacal and to Veridex for a new biomarker that is being tested for future application to the FDA for detection of prostate cancer. All revenues from this consultancy are transmitted to the University of Texas Health Science Center. He has also received grant support from the Early Detection Research Network, NCI. No other potential conflicts relevant to this article were reported.

 doi 10.3322/caac.20066.

Available online at http://cajournal.org and http://cacancerjournal.org

men with a family history of prostate cancer in non-elderly relatives—be provided the opportunity for informed decision making at an earlier age than average-risk men.

For providers and their patients who choose to be tested, we offer guidance regarding the frequency of testing, based on the PSA level, and on how to act on the testing result. Lacking definitive answers from randomized trials, we consider the traditional PSA level of 4.0 ng/mL a reasonable threshold for further evaluation. However, acknowledging that there is no true PSA cutoff point distinguishing cancer from noncancer, we suggest that providers consider individualized decision making when PSA levels fall in the indeterminate range of 2.5 ng/mL to 4.0 ng/mL, particularly for men at increased risk for high-grade cancer based on non-PSA risk factors.

We are hopeful that future advances in the early detection of prostate cancer will lead to the ability to distinguish accurately between indolent and aggressive cancers and that the adverse effects of prostate cancer treatment will be reduced sufficiently to tip the balance clearly in favor of screening. Until then, however, it will remain incumbent on health care providers and the health care system as a whole to provide men with the opportunity to decide whether they wish to pursue early detection of prostate cancer.

Introduction

The burden of suffering from prostate cancer in the United States is significant. In 2009, approximately 192,000 men were diagnosed with prostate cancer, and 27,000 men were expected to die from this disease.[1] Approximately 2.2 million living American men have been diagnosed with prostate cancer, and some are living with metastatic disease, a painful and functionally limiting stage of the disease.[2] Prostate cancer is by far the most commonly diagnosed cancer among American men and remains the second leading cause of cancer death in men.[1] The PSA blood test has changed the landscape of prostate cancer, creating a dramatic rise in the incidence since its dissemination 20 years ago and helping to shift the stage of disease at the time of diagnosis to a much earlier and potentially more curable stage.[3-5] However, testing for the early detection of prostate cancer remains a source of uncertainty and controversy.

Screening for PSA was introduced on the basis of inferential evidence that elevated PSA levels were associated with occult prostate cancer. During the 20-year period since significant PSA testing began, there has been a decline in prostate cancer mortality. Although some have attributed this decline in deaths to screening, others question whether the decline in prostate cancer mortality in the United States might be caused by improvements in cancer treatment.[6,7] Observational data and quasi-experimental studies have produced mixed results in terms of the contribution of PSA to this reduction in mortality.[8,9] Non-experimental data generally are regarded as an insufficient basis for health policy, which has been deferred in anticipation of results from two prospective randomized trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the prostate arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States. Yet, as opposed to resolving the controversy, new questions were raised by the publication of the preliminary results of these two trials in 2009.[10,11] The ERSPC demonstrated a 20% reduction in prostate cancer-specific mortality in men randomized to an invitation to screening compared with controls, whereas the PLCO did not demonstrate a reduction in mortality. Although the benefits of prostate cancer screening are uncertain, the burdens associated with the early detection and treatment of prostate cancer are known. It has been estimated that between 23% and 42% of screen-detected cancers would never have been diagnosed in the absence of screening.[12] This degree of potential overdiagnosis and the associated overtreatment of invasive disease appears to be greater than that for any other cancer for which routine screening currently occurs. Moreover, the adverse effects from treatment of prostate cancer are serious and potentially life-altering. There is a significant risk of sexual, urinary, and bowel-related symptoms, depending on the type of treatment selected.[13-15] Thus, the abundance of data now available regarding prostate cancer early detection supports neither a clear mandate to screen nor a proscription against screening.

Against this backdrop of uncertainty and controversy, the ACS charged its Prostate Cancer Advisory Committee with the goal of revising its guideline on the early detection of prostate cancer to reflect current evidence. The specific aims were to address the following areas: 1) recommendations to providers

and patients regarding offering screening to average-risk men; 2) recommendations to providers and patients regarding screening higher risk men, principally African American men and men with one or more first-degree relatives with prostate cancer; 3) recommendations regarding the most appropriate screening test or combination of tests and periodicity if a man chooses to undergo screening; and 4) recommendations regarding the advisability, nature, and content of shared decision-making discussions between men and health care professionals.

Guideline Development and Methods

The process began by commissioning a series of systematic evidence reviews. The three broad content areas included early detection of prostate cancer, harms of therapy for localized prostate cancer, and shared and informed decision making in prostate cancer screening.

Within the domain of early detection of prostate cancer, search strategies addressed the following subdomains: 1) efficacy of screening in reducing mortality from prostate cancer; 2) test characteristics of prostate cancer screening in asymptomatic men, including sensitivity, specificity, and predictive value; and 3) physical and psychological harms associated with screening. Abstracted information included the study setting and design, screening test, participant characteristics (including age, race/ethnicity, educational status, and socioeconomic status), study arms (eg, case and control definitions), proportion of participants screened, follow-up duration, confirmatory tests, outcome measures (eg, mortality), and measure of associations (eg, hazard ratios). For the subdomain of screening harms, information on methods used for measuring harms (eg, anxiety questionnaire, general psychological distress/mental state questionnaire) was abstracted.

Searches related to the harms of treating clinically localized prostate cancer were limited to radical prostatectomy, external-beam radiation therapy, brachytherapy, androgen-deprivation therapy, watchful waiting, and active surveillance. The search strategy related to informed and/or shared decision making (IDM/SDM) for prostate cancer screening identified intervention studies that targeted asymptomatic men without a diagnosis of prostate cancer. The following designs were considered eligible for inclusion as intervention studies: randomized controlled trials, randomized controlled trials with preintervention and postintervention, preintervention and postintervention with control, and preintervention and postintervention without control. Extracted IDM/SDM outcomes were categorized as 1) knowledge, 2) screening rates, 3) screening intention, 4) decisional conflict, 5) decisional confidence, 6) decisional anxiety, 7) decision/role preferences, 8) satisfaction, and 9) other.

Studies were identified by searching Medline for articles that were published between January 1950 and June 2009. The initial searches were not limited to a specific study design. Review articles and congress abstracts also were searched for relevant articles. Two authors (I.G. and C.D.) independently reviewed titles, abstracts, and full texts for eligibility and independently abstracted data from selected publications. When appropriate, data were stratified based on patient characteristics, such as age, race, and positive family history of prostate cancer. Data were entered into a custom database that was developed specifically for this review using Microsoft Access Software 2007 (Microsoft Corporation, Redmond, WA). Any discrepancies in the study selection and data abstraction process were resolved through discussion by the two authors.

The results of the systematic reviews were provided to all members of the ACS Prostate Cancer Advisory Committee for review before meeting and were supplemented with presentations by experts (both committee members and invited outside experts) at a face-to-face meeting of the committee. Deliberations about the evidence occurred at the committee meetings and in a series of conference calls that preceded and followed the meeting. Relevant literature that was not captured by the systematic reviews was disseminated by individual committee members to the entire committee.

The ACS Prostate Cancer Advisory Committee developed the prostate cancer early detection guideline by consensus, and a writing committee drafted a guideline document, which was circulated to the entire committee for review and revision. Then, the guideline with the supporting document was circulated to peer reviewers for feedback and then to the ACS Mission Outcomes Committee for review. The Mission Outcomes Committee approved the guideline, suggested modifications to the supporting doc-

ument, and forwarded the documents to the ACS Board of Directors for final approval.

American Cancer Society Guideline for Early Prostate Cancer Detection

The ACS recommends that asymptomatic men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process. Men at average risk should receive this information beginning at age 50 years. Men at higher risk, including African American men and men who have a first-degree relative (father or brother) diagnosed with prostate cancer before age 65 years, should receive this information beginning at age 45 years. Men at appreciably higher risk (multiple family members diagnosed with prostate cancer before age 65 years) should receive this information beginning at age 40 years. Men should either receive this information directly from their health care providers or be referred to reliable and culturally appropriate sources. Patient decision aids are helpful in preparing men to make a decision whether to be tested.[16] For men who are unable to decide, the screening decision can be left to the discretion of the health care provider, who should factor into the decision his or her knowledge of the patient's general health preferences and values.

Asymptomatic men who have less than a 10-year life expectancy based on age and health status should not be offered prostate cancer screening. At age 75 years, only about half of men have a life expectancy of 10 years or more. Men in this age group with significant comorbidities, as well as younger men with life-limiting comorbid conditions, are not likely to benefit from screening. For example, men with New York Heart Association Class 4 congestive heart failure, moderate-to-severe chronic obstructive pulmonary disease, end-stage renal disease, moderate-to-severe dementia, or life-limiting cancer would not be expected to benefit from screening. Life-limiting comorbid conditions become more common as men age; thus, it is important to consider overall health status—not age alone—when making decisions about screening.

Core elements of the information to be provided to men to assist with their decision include the following (please refer to the ensuing sections of this article for more detailed, quantitative information related to each of these core elements):

- Prostate cancer is an important health concern for men.
- Screening with the PSA blood test alone or with both PSA and digital rectal examination (DRE) detects cancer at an earlier stage than if no screening is performed.
- Prostate cancer screening may be associated with a reduction in the risk of dying from prostate cancer; however, evidence is conflicting and experts disagree about the value of screening.
- For men whose prostate cancer is detected by screening, it is not currently possible to predict which men are likely to benefit from treatment; some men who are treated may avoid death and disability from prostate cancer, whereas others who are treated would have died from unrelated causes before their cancer became serious enough to affect their health or shorten their lives.
- Depending on the treatment selected, treatment for prostate cancer can lead to urinary, bowel, sexual, and other health problems. These problems may be significant or minimal, permanent or temporary.
- The PSA and DRE may produce false-positive or false-negative results, meaning that men without cancer may have abnormal results and get unnecessary additional testing, and clinically significant cancers may be missed. False-positive results can lead to sustained anxiety about prostate cancer risk.
- Abnormal results from screening with the PSA or DRE require prostate biopsies to determine whether or not the abnormal findings are cancer. Biopsies can be painful, may lead to complications like infection or bleeding, and can miss clinically significant cancer.
- Not all men whose prostate cancer is detected through screening require immediate treatment, but they may require periodic blood tests and prostate biopsies to determine the need for future treatment.

In helping men to reach a screening decision based on their personal values, once they understand the uncertainties, risks, and potential benefits, it can be helpful to provide reasons why some men decide for or against undergoing screening. For example:

- A man who chooses to be screened might place a higher value on finding cancer early, might be willing to be treated without definite expectation of benefit, and might be willing to risk injury to urinary, sexual, and/or bowel function.
- A man who chooses not to be screened might place a higher value on avoiding the potential harms of screening and treatment, such as anxiety or the risk of injury to urinary, sexual, or bowel function.

The screening decision is made best in partnership with a trusted source of regular care. Men who have no access to regular care should be tested only if high-quality, informed decision-making can be assured through community-based screening programs. Such programs also must assure that participants with abnormal screening results receive appropriate counseling and follow-up care if needed. Availability of follow-up care must not be an afterthought. Unless these program elements are in place, community-based screening should not be initiated.

Once a screening decision has been made, the decision should be readdressed when new research becomes available that significantly alters the balance between benefits, risks, and uncertainties regarding prostate cancer early detection. In the absence of new information, the decision should be readdressed periodically, because a man's health status, values, and preferences can change over time.

For men who choose to be screened for prostate cancer after considering the possible benefits and risks:

- Screening is recommended with PSA with or without DRE.
- Screening should be conducted yearly for men whose PSA level is 2.5 ng/mL or greater.
- For men whose PSA is less than 2.5 ng/mL, screening intervals can be extended to every 2 years.
- A PSA level of 4.0 ng/mL or greater historically has been used to recommend referral for further evaluation or biopsy, which remains a reasonable approach for men at average risk for prostate cancer.
- For PSA levels between 2.5 ng/mL and 4.0 ng/mL, health care providers should consider an individualized risk assessment that incorporates other risk factors for prostate cancer, particularly for high-grade cancer, that may be used to recommend a biopsy. Factors that increase the risk of prostate cancer include African American race, family history of prostate cancer, increasing age, and abnormal DRE. A previous negative biopsy lowers the risk. Methods are available that merge this information to achieve an estimate of a man's overall risk of prostate cancer and, more specifically, of his risk of high-grade prostate cancer (see "Beyond Prostate-Specific Antigen: Individualized Risk Assessment," below).

Informed and Shared Decision Making

When the evidence is not clear that the benefits of screening outweigh the risks, an individual's values and preferences must be factored into the screening decision. In light of the uncertain balance between the benefits and risks of prostate cancer screening, it is vital to involve men in the decision whether to screen. This ethical mandate to involve men in the decision-making process stems in part from the preventive nature of screening. By definition, screening involves performing a medical intervention on individuals who are otherwise healthy; ie, they exhibit no symptoms or signs of the disease. This scenario confers a greater responsibility on the provider to uphold the doctrine of *primum non nocere*—first, do no harm—than in the case of interventions on symptomatic conditions. Although it is not clear how heavily the balance of benefit and risk must favor a benefit to obviate the need for informed decision making, it is clear that this point has not been reached for prostate cancer screening.

For informed decision making related to prostate cancer screening to occur, the individual should: 1) understand the basic aspects of prostate cancer and the role of screening (core knowledge); 2) understand the uncertainties, risks, and potential benefits associated with testing and the option to not be tested (core knowledge); 3) consider his preferences and values about screening (values); 4) choose a level of participation in the decision with which he is comfortable (role preference); and 5) make (or defer) a decision based on his values and preferences (values-based decision). This definition is adapted from definitions that were developed by the Centers for Disease Con-

trol and Prevention Task Force on Community Preventive Services[17] and by the U.S. Preventive Services Task Force.[18] Shared decision making is the subset of informed decision making that is carried out between the patient and his health care provider in the clinical setting.[17,18] Given the value-dependent nature of prostate screening decisions, health care providers have a particularly important role in the decision for or against testing. First, they can provide men with information on the benefits, limitations, and uncertainties related to screening for prostate cancer. Second, they can help men to explore their values related to prostate cancer screening. Third, they can help men to integrate their knowledge of the benefits and risks of prostate cancer screening with their values to make a decision about screening. Finally, even with adequate information, some men desire a less active role and defer the decision whether to screen to their health care provider. In this situation, although every effort should be made to engage the patient, the provider may use his or her discretion in deciding whether to recommend screening. If possible, the provider should incorporate any knowledge of the patient's health preferences and values into the decision.

Although there are no established criteria for what comprises the key information to impart about prostate cancer screening for informed decision making to occur, core elements were identified from a structured review of the relevant literature and from expert consensus. These core elements of informed decision making are described in the ACS guideline statement for prostate cancer screening in the preceding section and should be included in patient discussions and decision aids.

For most men, the decision to be screened for prostate cancer is not based solely on the facts about screening. A man's values usually play a major role in the decision, and a health professional and decision aids can assist in that decision by helping the patient elucidate his values. One helpful approach can be to provide reasons why some men decide for or against screening, which are outlined in the guidelines statement above.

Offering values-oriented scenarios is one technique to allow men to explore and integrate their values with the information they have received about prostate cancer screening to help them decide whether to be tested. The juxtaposition of the two values scenarios parallels the dichotomous nature of the decision faced by the patient (ie, screen vs no screen). Although there is no evidence to support the superiority of this approach over others,[19] there is randomized trial evidence that a prostate cancer screening decision aid using values-matching scenarios can help to lower men's decisional conflict.[20]

Tools to Facilitate Informed and Shared Decision Making

The challenge of offering every eligible man the opportunity to make an informed decision about prostate cancer screening can be daunting to the health care provider. The key obstacles to IDM/SDM cited by providers are time constraints and the complexity of the issue.[21] These barriers likely contribute to the recent findings from the National Survey of Medical Decisions, which demonstrated that prostate cancer discussions with patients did not meet recommended criteria for shared decision making, because discussions were not balanced (predominately emphasizing benefits) and typically did not engage men to determine personal preferences.[22] Given these barriers, patient decision aids can serve as effective adjunctive tools to facilitate IDM/SDM. The ideal decision aid should provide balanced information regarding prostate cancer screening options, reflect up-to-date information regarding benefits and risks, provide methods for clarifying values, and suggest ways to discuss the decision with health care providers.[16,23] Decision aids for prostate cancer screening are available in print, web-based, and CD format. Low-literacy versions have been developed but are not yet widely available.[20] Criteria are available for selecting a high-quality decision aid from the International Patient Decision Aids Standards (IPDAS) Collaboration.[23] Several patient decision aids have been evaluated against the IPDAS criteria. Those that are accessible online are listed in Table 1. It is important when selecting a decision aid that either it reflects the latest key information related to making a decision about testing (for example, the recent results from the U.S. and European randomized trials) or that the health care provider is able to supplement an otherwise effective tool with the latest data.

TABLE 1. Decision Aids for Prostate Cancer Screening

SUPPORTING ORGANIZATION	TYPE OF DECISION AID	TITLE & ON-LINE ACCESS
American Cancer Society	Downloadable Document (PDF)	"Should I Be Tested for Prostate Cancer" Available at: www.cancer.org/prostatemd
Foundation for Informed Medical Decision Making	Video and On-Line Interactive Resource	"Is a PSA Test Right For You?" Available through Health Dialog at http://www.healthdialog.com
Centers for Disease Control and Prevention	Downloadable Document (PDF)	"Prostate Cancer Screening: A Decision Guide" Available at: http://www.cdc.gov/cancer/prostate/pdf/prosguide.pdf "Prostate Cancer Screening: A Decision Guide for African Americans" Available at: http://www.cdc.gov/cancer/prostate/pdf/aaprosguide.pdf "La Detección del Cáncer de Próstata: Una Guía para Hispanos en los Estados Unidos" Available at: http://www.cdc.gov/cancer/prostate/pdf/prostate_cancer_spanish.pdf
Mayo Clinic.com	On-Line Resource	"Prostate Cancer Screening: Should you get a PSA test?" Available at: http://www.mayoclinic.com/health/prostate-cancer/HQ01273
University of Cardiff, U.K.	On-Line Interactive Resource	"PROSDEX: A PSA Decision Aid" Available at: www.prosdex.com

Evidence for the Impact of Informed and/or Shared Decision Making on Screening Decisions

There is an emerging body of evidence regarding the impact of decision aids on prostate cancer screening.[16,24] There is strong, consistent evidence that patient decision aids improve patients' knowledge of prostate cancer screening, but no consistent evidence has demonstrated the superiority of one media format over others (ie, printed material, video, or internet-based), although this issue has not been explored adequately in low-literacy populations. Most studies have indicated that decisional conflict is reduced among men who use a decision aid, and virtually all studies that have examined role preference indicate that decision aids prompt men to prefer or assume a more active role in making the screening decision.[24]

Informed Decision Making in Community-Based Screening Programs

There are implicit obstacles to IDM/SDM in community-based screening programs. First, men who attend screening programs may be inherently self-selected to desire screening and may not be amenable to efforts at informed decision making. Second, there may not be an opportunity for shared decision making in community-based screening, because there is often no opportunity for interaction with a health care provider who has an adequate understanding of the participants' overall health status. This makes the accurate selection of men who have at least a 10-year life expectancy—the target population for informed decision making for prostate cancer screening—virtually impossible. On the basis of these concerns, the ACS discourages participation in community-based prostate cancer screening programs unless they can provide adequately for an informed decision-making process and appropriate follow-up care. These programs have a special obligation to provide high-quality, objective, informed decision making either through interaction with trained personnel or through the use of validated, high-quality decision aids appropriate to the target population. Moreover, it is incumbent on such programs to assure that participants with abnormal screening results receive appropriate counseling and follow-up care. Because virtually all men age 65 years and older have health insurance through Medicare, they should be discouraged from participating in community-based screening programs and should be referred to a primary care provider.

In summary, because of the uncertainties, risks, and potential benefits of prostate cancer screening, there is an ethical mandate to provide men who are considering screening with the opportunity to engage in an informed decision-making process. Because of the complexity of the decision and the importance of individual values, men should have the opportunity to be assisted by a health professional in reaching this decision. Because there is now an established body of evidence supporting the value and effectiveness of decision aids in facilitating informed decision making, the availability and use of such aids should be promoted.

Evidence Review: Impact of Prostate Cancer Screening

Since the last major ACS prostate cancer early detection guideline update in 2001, there have been numerous studies examining the impact of prostate cancer screening on prostate cancer-specific mortality and morbidity. The ACS Prostate Cancer Advisory Committee conducted this evidence review to determine whether the weight of current evidence supports or refutes a benefit to prostate cancer screening in terms of preventing premature death or advanced disease. This evidence summary organizes the review by types of evidence: randomized controlled trial evidence, case-control evidence, and evidence from surveillance data and ecologic studies.

Randomized Controlled Trial Evidence for Prostate Cancer Screening

Because of the inherent limitations of non-experimental studies to control for known biases in the evaluation of cancer screening,[25,26] evidence from randomized controlled trials conventionally is regarded as necessary to determine the efficacy of a screening test. Before the publication of the PLCO and ERSPC trials in 2009, results from two prospective trials of prostate cancer screening had been published. However, both the Quebec Prostate Cancer Study[27] and the Norrkoping Trial[28] had significant methodologic shortcomings, making it impossible to reach any conclusion regarding the efficacy of screening.[29]

More recently, the long-awaited results of two large prospective randomized controlled trials of prostate cancer screening with PSA testing were published and reported different conclusions: the U.S.-based PLCO study demonstrated no benefit to screening, whereas the European ERSPC demonstrated a 20% reduction in prostate cancer mortality (risk ratio, 0.80; 95% confidence interval [CI], 0.67-0.98; $P = .01$).[10,11] While observing a reduction in prostate cancer deaths in the study group compared with the control group after an average of 8.8 years of follow-up, the ERSPC investigators also noted that one death from prostate cancer was prevented for every 48 men who were treated for screen-detected disease. Because it is early in the follow-up period, this estimate of the number needed to treat may become smaller over time.

The PLCO study[11] enrolled 76,693 men ages 55 years to 74 years who were screened annually with a serum PSA test and a DRE, whereas the ERSPC combined the findings of several trials[10] that enrolled a total of 162,243 men ages 55 years to 69 years. These men generally were screened every 4 years mostly with PSA only. In the PLCO study, prostate biopsy was recommended for men whose PSA exceeded 4 ng/mL or whose DRE revealed a suspicious nodule; whereas, in the ERSPC, a PSA of 3 ng/mL generally was used without DRE to trigger a biopsy. In each study, continued follow-up will be necessary to determine longer term outcomes for key endpoints. In the PLCO study, 44% of men had been screened previously with up to two PSA tests before randomization; undoubtedly, this high level of prescreening reduced the number of prevalent prostate cancers in the study population. There was virtually no prescreening in the ERSPC study population. The anticipated contamination rate (ie, a man in the control arm getting a PSA outside of the study) was 20% in the design of both studies and increased during the PLCO study to 38%. The actual contamination rates were estimated at 52% in the PLCO trial[11] and 6% in the ERSPC.[30] In men who were randomized to PSA screening, 15% in the PLCO study and 18% in the ERSPC did not undergo PSA screening. Thus, combining the problems of noncompliance in the screening arms and contamination in the control arms of these studies, in the PLCO study, screening occurred in 85% of men in the screening arm versus an estimated 52% of men in the control arm compared with 82% versus 6% in the ERSPC. Compared with the PLCO study, the ERSPC was much closer to the ideal but rarely attainable goal of perfect adherence to the randomization assignment, in which 100% of the group invited to screening is screened versus no screening in the group assigned to usual care. Both studies demonstrated an increased incidence of prostate cancer in the screened arm compared with the control arm, although additional follow-up will be necessary before conclusions can be drawn with measurable confidence about the rate of overdiagnosis.

Poor compliance with a recommendation for prostate biopsy among men with positive screening results was a shortcoming of the PLCO study. Only 40% of men with abnormal results in the first round of screening actually underwent a biopsy; and, by the

third round of screening, the biopsy rate had dropped to 30%; overall, less than half of the men who had abnormal screening results underwent a biopsy. In contrast, 85.8% of men who had abnormal screening results in the ERSPC were adherent with the recommendation to undergo biopsy.[31] Failure to follow through with biopsy would make it more difficult to demonstrate an impact of screening.

The other major difference between the two studies that may have contributed to the different outcomes was the choice of a PSA cutoff point. Both studies began with a PSA threshold of 4.0 ng/mL as the value for biopsy referral, and both included DRE in the screening protocol. However, many but not all of the ERSPC countries lowered the PSA threshold to 3.0 ng/mL and dropped the DRE midstudy.

In the PLCO study, the intention-to-screen analysis revealed that there was no reduction in prostate cancer-specific mortality with PSA screening after an average of 7 years with a hazard ratio of 1.13 and a 95% CI of 0.75 to 1.70. In contrast, the ERSPC reported a hazard ratio of 0.80 and a 95% CI of 0.65 to 0.98, reflecting a 20% reduction in prostate cancer mortality after an average follow-up of 9 years. When adjusting for contamination and nonattendance (ie, failure to screen with PSA in the screening arm) in the ERSPC, the hazard ratio improved to 0.69 (95% CI, 0.51-0.92), representing a 31% reduction in the risk of prostate cancer mortality.[32] However, one issue that will be of continuing interest is that men who were diagnosed with prostate cancer in the screening arm of the ERSPC were more likely to receive treatment at a university hospital than at a nonuniversity hospital, which may mean that they tended to receive more intense, modern therapy. Furthermore, full treatment details were not available for all patients in the analysis that compared therapy in the screening arm with that in the control arm, and this was a greater problem in the control arm. Among the explanations was postrandomization consent used in the Scandinavian countries and in Italy, which made it more difficult for the investigators to retrieve clinical information. Postrandomization consent may have created some selection biases favoring the screened arm.[33]

In summary, the two largest prospective randomized studies of prostate cancer screening have come to differing conclusions regarding the efficacy of screening. However, the differences in the two studies with regard to the extent of prescreening, contamination, compliance with biopsy, and the PSA cutoff point and the unknown extent of differential treatment in the two arms of the ERSPC may explain why a significant reduction in prostate cancer mortality was noted in the ERSPC but not in the PLCO study.

Evidence from Case-Control Studies

In case-control studies of cancer screening, screening histories before diagnosis among men who later died of cancer (cases) are compared with screening histories during a comparable time interval among men who did not die of cancer (controls). The controls generally are required to still be alive at the time of the analysis or at the end of study follow-up. The idea behind these studies is that, if screening indeed is protective, then those men who eventually died of prostate cancer should have received less screening than those who did not die of the disease. In this case, the odds ratio (OR) resulting from the analysis is less than one and is interpreted as the odds of being screened among men who subsequently die of prostate cancer divided by the odds of being screened among men who did not die of prostate cancer.

Case-control studies require an accurate ascertainment of screening, which can be complex when the same test is used for screening purposes and for diagnostic workup in response to suspicious symptoms, which often is the case. It can be particularly challenging to ascertain the reason for testing from medical claims records, which are the primary source of information on screening used in most studies. Some studies exclude tests that were conducted at the time of diagnosis because of the difficulty classifying them as bona fide screening tests. However, Weiss has demonstrated that excluding such tests is not acceptable and will lead to a bias in favor of screening.[34] Results from these studies also are sensitive to the time interval during which cases were diagnosed and the length of follow-up after diagnosis.

Several case-control studies of screening for prostate cancer have been conducted with mixed results. Agalliu et al analyzed data on 706 cases and 645 controls in Washington State.[35] The cases were diagnosed between 1993 and 1996 and were followed until 2006. That study produced an OR of 0.38 (95% CI, 0.19-0.77), suggesting a strong protective effect of PSA or DRE screening. Screening behavior was

ascertained through a questionnaire that was conducted within a few years of the date of diagnosis for the cases and over a similar period for the controls. A similar OR (0.32; 95% CI, 0.20-0.52) was reported by Jacobsen et al, who studied the association between prostate cancer death and DRE within 10 years before diagnosis for cases and over a comparable period for controls.[36] Their study included 173 cases and 346 controls but omitted tests that were conducted at the time of diagnosis, based on concern about misclassifying diagnostic tests as screening tests. A later study in the same population included 74 cases and 192 controls and reported an OR of 0.34 (95% CI, 0.17-0.71) associated with tests done 1 to 5 years before diagnosis, but the OR increased to 1.05 (95% CI, 0.45-2.44) when tests that were performed up to the time of diagnosis were included.[37] Weinmann et al studied PSA and DRE testing in 171 cases and 342 controls.[38] In that study, the cases died of prostate cancer between 1992 and 1999, and screening histories were evaluated for up to 10 years before diagnosis. The OR was 0.7 (95% CI, 0.46-1.1), suggesting a trend in favor of screening. In contrast, a case-control study by Concato et al of PSA and DRE screening included 501 cases and 501 controls. Cases were diagnosed with prostate cancer between 1991 and 1995 and died of their disease by 1999. Those investigators reported no protective effect of screening, with an OR of 1.13 (95% CI, 0.63-2.06).[39]

How can we explain these seemingly contradictory results? These studies differed in several important ways. First, all of the studies with the exception of that by Agalliu et al[35] ascertained exposure to screening by retrospectively abstracting information from medical records. In contrast, in the study by Agalliu et al, men were asked explicitly whether they had been screened. Second, the intervals of follow-up (for mortality) and of screening status ascertainment differed across the studies. Finally, the calendar interval over which screening took place differed across studies. For example, the study by Jacobson, et al[36] took place before the PSA era, and the study by Concato et al[39] was conducted early in the PSA era, whereas others, such as the study by Agalliu et al,[35] were conducted after PSA screening became fairly routine in the locations studied. It is likely that the study by Concato et al[39] did not allow enough time to ascertain either mortality among cancer cases or screening exposure among the controls. Conversely, the study of Jacobsen et al[36] likely overstates the protective effect of screening by excluding men whose screening tests were conducted at the time of cancer diagnosis. These methodological limitations—and the resultant conflicting results—preclude any definitive conclusions from the current case-control literature regarding the impact of prostate cancer screening on mortality.

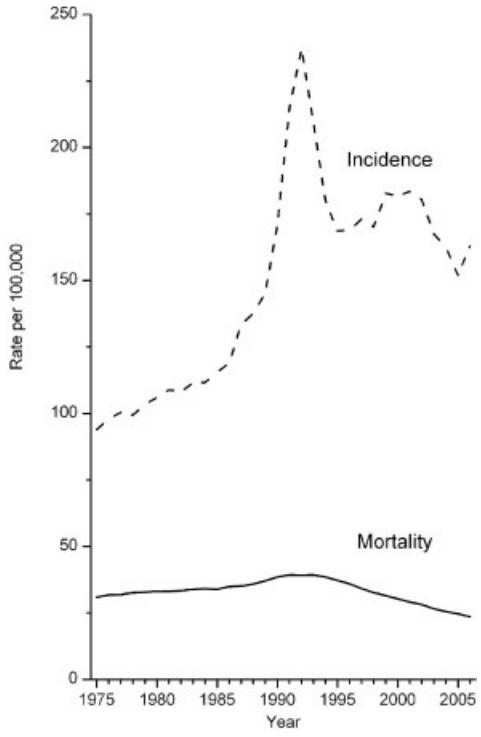

FIGURE 1. Trends in prostate cancer incidence and mortality rates, US, 1975-2006. Data Source: Incidence–Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 registries, 1973-2006, Division of Cancer Control and Population Sciences, National Cancer Institute, 2009. Mortality–National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Evidence from Incidence and Mortality Trends

Widespread screening using the PSA blood test started in 1991 after the publication of a high-profile study demonstrating that elevations in PSA in asymptomatic men were associated with a higher risk of having prostate cancer.[5] Since then, significant shifts in prostate cancer incidence, stage of diagnosis, and age-adjusted mortality have occurred (Figs. 1 and 2). Although similar trends have been observed in other high-resource nations, the greatest changes have occurred in the United States, the nation with the highest uptake of prostate cancer screening.

As shown in Figure 2, the incidence rate of distant stage prostate cancer per 100,000 men has dropped from an annual rate of approximately 21.6 in 1991 to

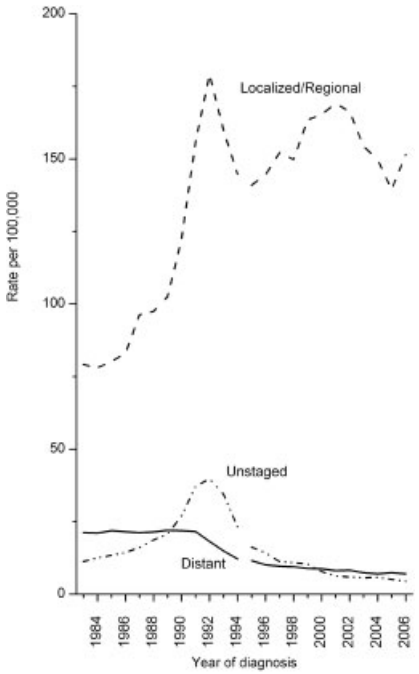

FIGURE 2. Trends in prostate cancer incidence rates by stage at diagnosis, US, 1983-2006. Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 registries, 1973-2006, Division of Cancer Control and Population Sciences, National Cancer Institute. Note that data for years 1995-2006 are based on the November 2008 data submission and data for years 1983-1994 are based on the November 2006 submission, therefore may not be comparable.

7.0 in 2006.[2] Age-adjusted prostate cancer mortality rates rose steadily at an annual rate of 0.9% from 1975 through 1987 and 3% from 1987-1991. Although age-adjusted mortality rates began to fall in 1991 at about 0.6% per year, the rate of decline accelerated significantly in 1994. From 1994 through 2005, U.S. age-adjusted prostate cancer mortality rates have fallen at a rate of 4.1% per year and fell below the 1985 (pre-PSA) mortality rate in 1997.[2] Thus, as of 2006, the most recent year for which mortality data are available, age-adjusted prostate cancer mortality has fallen to levels last observed in the 1940s.[1]

Although improved treatment of prostate cancer and other factors likely contribute to these trends, the decrease in incidence of late-stage disease, the rise in early stage diagnosis, and the fall in mortality rates to levels well below rates reported before the advent of screening all are consistent with a potential screening benefit.[40,41]

International and Regional Comparisons

On the basis of the hypothesis that effective screening will lead to lower disease-specific death rates in a population, regional and international mortality trends have been compared, because some areas have more intense screening than others. Two comparisons have been cited widely: a comparison of prostate cancer mortality trends between the United States, where there is a high prevalence of screening, and the United Kingdom, where prostate cancer screening is less common,[42] and a comparison between the state of Connecticut and the Seattle, Washington, metropolitan area.[43,44]

Initial prostate cancer trends in Connecticut and Seattle were not consistent with a screening benefit.[44] PSA screening was adopted in the Seattle area earlier than in Connecticut. Despite higher incidence and treatment rates in Seattle, prostate cancer mortality rates in the two regions remained virtually identical in the first few years after the emergence of screening.[44] Comparisons of more recent trends in these two areas continue to reveal similar patterns in age-adjusted mortality, although the early differences in screening rates that had been the basis of the comparison essentially had converged by 1997.[43,45] A recent editorial also pointed out that there are important differences in treatment modalities between the two regions as well, making it difficult to determine the impact of screening.[7] In sum, the overall trends observed in Connecticut and Seattle are not inconsistent with a possible beneficial effect of screening.

Studies comparing prostate cancer mortality trends in the United States and the United Kingdom have not always reached the same conclusions. Oliver and colleagues concluded that, despite much higher rates of PSA screening in the United States compared with the United Kingdom, mortality differences between the countries were too small to conclude that PSA screening was contributing to a reduction in deaths.[42] More recently, Collin et al[9] reported a striking decline in prostate cancer mortality in the United States compared with the United Kingdom between 1994 and 2004. However, because both screening and treatment patterns have been so different in the two countries, it is difficult to attribute differences in mortality to screening alone.

An often cited regional comparison is between the Austrian state of Tyrol and the other Austrian states. In 1993, Tyrol embarked on an aggressive screening campaign, including free PSA testing without DRE, for men ages 40 years to 79 years. Nearly all potentially curable men underwent modified radical prostatectomy.[46] A significant decline in prostate cancer mortality was documented in Tyrol beginning 2 years

after initiation of this intervention compared with other states in Austria. A shift toward earlier stage disease also was observed, consistent with a possible screening benefit, although, as noted by the authors, the Tyrol program also emphasized excellence in therapy. Thus, improvements in treatment also may have contributed to the decline in prostate cancer deaths.[46] The most recent follow-up to 2005 indicates that prostate cancer mortality was 54% lower than expected in Tyrol compared with only 29% lower in the rest of Austria ($P < .001$)[47]

Temporal and regional screening and mortality trends cannot prove conclusively that screening reduces the likelihood of dying from prostate cancer. Many factors determine whether or not men participate in screening, whether they pursue definitive diagnosis and therapy, and the type and quality of treatment they receive. Ecologic studies are particularly vulnerable to confounding influences, such as the timing and intensity of screening, differential trends in therapy, and common biases, particularly selection bias, which can heavily influence the outcome of observational studies.

In summary, despite the abundance of data that have accumulated regarding the impact of prostate cancer screening on morbidity and mortality, the evidence remains conflicted regarding whether or not there is a benefit from screening. Case-control studies are notoriously difficult methodologically[48] and, in the case of prostate cancer screening, do not provide a clear answer regarding screening efficacy. Evidence from surveillance data and ecologic studies appears to demonstrate an association between screening and reduced rates of late-stage disease at diagnosis and prostate cancer mortality, but the inherent limitations of this type of evidence preclude definitive conclusions. The two randomized trials of prostate cancer screening, the PLCO and ERSPC studies, come to differing conclusions, with one observing a benefit in reduced prostate cancer mortality and one not observing a benefit. Although the evidence remains conflicted regarding whether prostate cancer screening is associated with a reduction in the risk of dying from prostate cancer, it is clear that any benefit is accompanied by a significant rate of overdiagnosis, overtreatment, and morbidity from treatment, as described in detail below.

Evidence for Harm from Prostate Cancer Early Detection

Harms associated with prostate cancer screening include harms related to DRE and PSA testing, prostate biopsy, and overdiagnosis (collectively referred to as "screening harms") as well as harms related to the treatment of prostate cancer after a positive biopsy (treatment harms).

Screening Harms

Risks of Phlebotomy and Digital Rectal Examination

Harms related to phlebotomy for PSA testing are assumed to be the same as for any other small blood volume phlebotomy and generally are negligible.[49] In the screening arm of the PLCO trial, the PSA test led to complications at a rate of 26.2 per 10,000 screenings (primarily dizziness, bruising, and hematoma) and included three episodes of fainting per 10,000 screenings.[11]

The most frequent complication of DRE in men is discomfort, which can be significant and may explain why it has been demonstrated that DRE poses a barrier to screening.[50] DRE also can lead to rectal bleeding and even syncope, but adverse events are rare.[11] In summary, neither phlebotomy for PSA testing nor DRE poses a significant risk for serious injury.

Risks Associated with Prostate-Specific Antigen

The most frequently reported direct harms associated with prostate cancer screening relate to anxiety. Anxiety has been studied with respect to undergoing PSA screening, receiving a positive PSA result, receiving a positive biopsy, and receiving a false-positive PSA result. Measures of anxiety/distress have been based on general (not prostate cancer-specific) questionnaires/scales, specific questionnaires/scales for prostate cancer (eg, Prostate Cancer Worry scales, Impact of Events scales), and a surrogate marker for anxiety (cortisol level). One study reported a higher level of anxiety/stress (estimated by cortisol level) among prostate cancer screening attendees compared with nonattendees,[51] whereas four others studies produced no evidence of excess anxiety among attendees.[52-55] Studies that assessed anxiety before and after screening reported a decrease in anxiety after a negative test report.[51,56,57]

Anxiety levels in participants who had a positive PSA test were compared with anxiety levels in the general population in two studies. Participants with positive PSA results who were waiting for a biopsy had marginally higher anxiety (based on responses to a generic questionnaire) than the general population and had significantly higher cortisol levels.[52,56] Studies using a cancer-specific questionnaire demonstrated that the prevalence of severe anxiety was low (6%) but that a moderate level of anxiety was frequent (49%) among participants who had positive PSA results who were waiting for a biopsy.[56] Anxiety levels before biopsy and at baseline (ie, before the PSA test) were compared in two studies. One study, using a generic questionnaire, reported a small, nonsignificant decrease in anxiety compared with baseline, whereas serum cortisol levels were not statistically significantly higher among participants who were waiting for a biopsy compared with baseline.[52] Anxiety levels after biopsy (compared with levels before biopsy) decreased significantly after the receipt of negative biopsy results.[52] In the Swedish arm of the ERSPC, anxiety was highest during the first round of PSA screening and decreased in subsequent rounds of screening.[56] The most significant predictor of anxiety in later rounds was high anxiety during the first round of screening.

Two studies compared anxiety among participants who had false-positive results and participants who had true-negative results. Both studies reported a significantly higher impact on prostate cancer-specific psychological state among participants who had false-positive results compared with participants who had true-negative results, including greater worry, false perception of elevated cancer risk, and, ironically, the perception that "life is better" after a false-positive result (the "dodged a bullet" phenomenon).[57,58] Statistically significant differences were observed at 6 weeks and 1 year after PSA testing.[58] It also was reported that participants who had false-positive results underwent more tests and visits (eg, at least one follow-up PSA test, had another biopsy, visited a urologist) in the year after a false-positive test compared with those who had true-negative results.[58]

In summary, there is weak evidence, based largely on a surrogate marker (cortisol level) and general anxiety questionnaires, that there is a low level of anxiety associated with the prostate cancer screening process and that there is slightly greater anxiety when individuals are waiting for a biopsy. There is stronger evidence, based on two well designed surveys, that men with false-positive PSA results have higher short-term and long-term prostate-specific cancer worry than men with true-negative results and that men who have false-positive results have more subsequent tests/visits compared with men who have true-negative results. Given the high prevalence of false-positive screens, these deleterious effects are not inconsequential.

Biopsy Risks

Prostate biopsy generally is performed transrectally, using an ultrasound probe to direct a biopsy needle. The biopsy needle, thus, traverses the rectal wall into the prostate and most easily samples the posterior part of the prostate, the region where the majority of clinically significant prostate cancers develop. The two primary risks are bleeding and infection. Hematuria is observed in about 6% to 13% of patients,[59,60] but the risk of serious bleeding that requires transfusion is low. To reduce the risk of bleeding, anticoagulants generally are discontinued in advance. The risk of infection occurs as the needle traverses from the rectum into the prostate, although infections associated with biopsy are rarely severe enough to require hospitalization.[61,62] To reduce the risk of infection, antibiotic prophylaxis usually is used. The optimal duration of prophylaxis may be as short as 1 day, but infections may develop even with appropriate antibiotic prophylaxis.[63,64] The rate of urinary tract infection ranges from 0.3% to 4%, and serious infections appear to have a rate of less than 2%.[65]

Although it typically is not included in the "risk" category, perhaps one of the greatest potential risks of prostate biopsy is that a prostate cancer may be missed. In a prospective study of over 1000 men with PSA levels >4 ng/mL, 10% of patients who had negative initial biopsy results were diagnosed with prostate cancer on repeat biopsy.[66] The likelihood of a diagnosis of prostate cancer on a repeat biopsy also is associated with patient risk factors, such as high-grade prostatic intraepithelial neoplasia on initial biopsy, advanced age, PSA velocity, or a higher PSA transition zone density, and the detection rates in these risk groups are up to 2 or 3 times higher than those in the groups without risk factors.[67,68] In addition, in some patients who have been identified

with a lower grade cancer, a biopsy may miss concurrent high-grade disease.

Overdiagnosis and Overtreatment

Most men with prostate cancer die from other causes before their disease becomes symptomatic. It has been estimated that, before the advent of PSA screening, only 25% of prostate cancers were detected clinically.[69] Thus, the use of a sensitive screening test for the detection of prostate cancer creates the potential for a significant rate of overdiagnosis and overtreatment, which is the detection and treatment of disease by screening that would never have been diagnosed within the lifetime of the patient. Overdiagnosis and the consequent overtreatment of prostate cancer are significant contributors to the harms and costs associated with PSA screening.

The frequency of overdiagnosis can be quantified by comparing incidence trends in the presence of screening with those in the absence of or before the introduction of screening. Screening induces predictable changes in disease incidence that consist of an initial increase in incidence as screening rates increase and then stabilize, followed by a decline in incidence. The magnitude of the increase, the duration of time before incidence begins to decline, and the eventual level at which incidence stabilizes all are somewhat informative about how much overdiagnosis is occurring.

The measurement of overdiagnosis in a population depends on knowledge of the mean lead time associated with the screening test, which is the measure of the average lead time by which the screening test advances the diagnosis of disease, and the background disease incidence, which also depends on the diagnostic intensity in the absence of screening. For example, in the United States, transurethral resection of the prostate for benign prostatic hyperplasia became popular in the early 1980s and led to an increase in the incidental diagnosis of prostate cancer. Thus, the PSA test was introduced at a time of historically high background incidence of the disease. This was not the case in other countries and must be taken into account when comparing overdiagnosis estimates across countries.

In the United States, several studies have estimated overdiagnosis frequencies using data on prostate cancer incidence rates before and after the introduction of PSA screening. Etzioni et al[70] and Telesca et al[71] analyzed data for blacks and whites separately, assuming that disease incidence would have remained constant at the level observed in 1987, just before the advent of screening. Those investigators consistently observed higher estimates of overdiagnosis among blacks, but their models could not distinguish between two potential reasons for this finding, namely: 1) more latent prevalent disease in blacks, and 2) lower levels of background intervention that had an impact on incidence in the absence of screening. For whites, Etzioni et al estimated that the screening-related overdiagnosis rate was 29% and Telesca et al estimated it at 22.7%; for blacks, the corresponding rates were 44% and 34.4%. Note that the model used by Telesca et al included younger men (ages 50 years and older), whereas the model of Etzioni et al considered only men older than age 65 years, which explains why the estimates of Telesca et al are lower.

Recognizing that different estimation approaches and analytic assumptions could affect overdiagnosis estimates, Draisma et al[12] developed overall U.S. population estimates of overdiagnosis based on three different models. All models used the same input data on disease incidence patterns and also on screening use in the United States, but each model had a different way of conceptualizing and modeling disease progression and diagnosis and produced somewhat different results. The estimates of overdiagnosis produced by the three models ranged from 23% to 42% of screen-detected cancers.

A different estimate of the extent of overdiagnosis and overtreatment associated with prostate cancer screening recently has come from publication of the results from the ERSPC.[10] In that study, after an average of 8.8 years of follow-up, the investigators estimated that 48 men with screen-detected cancer must be treated to prevent one death from prostate cancer. Given the long natural history of prostate cancer, it is possible that this number will decrease with longer follow-up, because screening during the trial could have prevented deaths that, in the absence of screening, would have occurred after the end of the trial. Moreover, the 48 men who were treated included overdiagnosed cases as well as clinically relevant cases that would have been diagnosed later.

We conclude that the possibility of overdiagnosis is an important consideration when counseling individual men regarding the benefits and risks of pros-

tate cancer screening and when developing recommendations for population screening. Although the possibility of overdiagnosis and overtreatment is real for any disease that is diagnosed through screening, it is a particular concern in prostate cancer screening. Any possible benefits of a potential population screening policy must be weighed against the harms in terms of the likely frequencies of overdiagnosis and overtreatment associated with that policy.

Adverse Effects of Radical Prostatectomy

Radical prostatectomy, performed through a range of approaches (laparoscopic, retropubic, robotic, or perineal), generally involves the removal of the entire prostate gland along with the attached seminal vesicles. Depending on preoperative risk assessment, ie, preoperative PSA level, biopsy Gleason sum, clinical stage, etc, removal of the pelvic lymph nodes is performed concurrently.[72] After removal of the prostate, the bladder is rejoined to the urethra, and a catheter is left in place for a period of time, ranging generally from 1 week to 2 weeks.

There are two sets of possible adverse effects of radical prostatectomy: perioperative and longer term. During the operation itself, the primary risk is that of bleeding. Rates of blood transfusion range widely by procedure and by surgeon but can be as high as 20% and are related to a variety of risk factors, including prostate size and body mass index.[73,74] Rectal injury is an unusual complication.[75] A recent review of a national database indicated that 30-day complication rates were approximately 22% (heart, lung, and blood vessel-related complications collectively comprised half of these).[73] Death within 30 days was noted in 0.1% to 0.2% of patients.

The two primary longer term adverse effects of surgery are urinary and sexual. Urinary adverse effects can take two forms. An anastomotic stricture can develop in which the bladder is joined to the urethra (urinary channel). Recent data suggest that this develops in 5% to 14% of men.[73,76] Although some anastomotic strictures have no functional impact, if urinary flow is diminished sufficiently, then surgical incision of the stricture may be required. Such an incision has the potential to result in urinary incontinence.

A more common urinary adverse effect is total or stress urinary incontinence. The precise rate of this complication is understood poorly at a national level, because definitions vary widely. Total urinary incontinence refers to a total lack of control of urination with a continuous passage of urine. This degree of incontinence is unusual after surgery. Stress incontinence is a more common immediate postoperative complication, and most men have a gradual return of urinary control within a few weeks to months. Contemporary data would suggest that long-term incontinence rates after surgery are from 12% to 16%, and there is a need for subsequent procedures to resolve incontinence in about 8% to 9% of patients.[73] The 2007 American Urological Association Localized Prostate Cancer Guideline reported very high rates of variability in the reporting of urinary incontinence among treatment series; these may be because of differences in surgical outcomes, definitions of "incontinence," and diligence of evaluation and reporting.[77] The difficulty in assessing urinary incontinence is based in part on its impact on the individual man. Some men may have a small amount of urinary dribbling when coughing, sneezing, or lifting an object but may not be bothered sufficiently to relate this occurrence as "incontinence." Other men may wear a urinary pad in their underwear for "insurance," just in case they might leak, even if this rarely occurs. For these men, the prospect of such potential leakage may be so bothersome that it is deemed "incontinence."

Sexual dysfunction is the other common adverse event after radical prostatectomy. Like urinary incontinence, it is difficult to quantify for various reasons. First, many men who undergo radical prostatectomy are older with weaker erections and less frequent intercourse at baseline. Many also may use medications or other treatments to aid with sexual function. In addition, with nerve-sparing prostatectomy, the quality of erections after surgery often gradually returns with a return to maximal function delayed in some men by as long as 1 or 2 years.[78] Consequently, erectile dysfunction rates after surgery will vary greatly, depending on the time of assessment. In addition, assessment of quality of erections is at least as difficult as assessment of urinary function, especially with the variable nature of erections, the use of pharmacologic treatments, and the known differences in assessment based on whether the physician or the patient renders the assessment. Despite these caveats, long-term rates of erectile dysfunction after

surgery in contemporary series range from 19% to 27%.[73] Hu et al recently reported that, as with urinary incontinence, there is a higher rate of erectile dysfunction with minimally invasive radical prostatectomy compared with radical retropubic prostatectomy—27 per 100 person-years versus 19 per 100 person-years, respectively.[73]

Adverse Effects of Radiation Therapy

Radiation therapy can be delivered in two forms, external-beam radiation therapy and interstitial brachytherapy ("seed therapy"). With the advent of conformal-based external-beam techniques (intensity-modulated[79] and image-guided radiation therapy[80]) and real-time dosimetry[81] for seed therapy, a more precise and conformal delivery of radiation therapy has resulted in lower, but not absent, acute and late toxicity.[82]

Acute toxicities that can present during treatment in up to 50% of men who receive either form of radiotherapy include, most prominently, lower urinary tract symptoms (urgency, dysuria, and nocturia), loose bowel movements or diarrhea, and hemorrhoidal and anal irritation. These symptoms generally are self-limited and usually respond to symptomatic treatment.

Late toxicities generally are referred to as those that begin 6 months or later after the completion of treatment. As with surgery, the most commonly encountered toxicity is erectile dysfunction, which affects up to 50% of men.[82] The likelihood of erectile dysfunction correlates with age and baseline impairment of sexual function. Less common toxicities include increased bowel frequency (up to 4%), rectal bleeding (up to 4% but more common among men who are receiving anticoagulants), and urethral stricture, which is observed more commonly among men who underwent prior transurethral resection of the prostate (up to 2%).[82] These symptoms, if they are sufficiently severe, may require treatment, which is largely supportive rather than curative.

Adverse Effects of Hormonal Therapy

Adverse effects of hormonal therapy are covered only briefly here, because this treatment is used primarily for patients with advanced disease, which is diagnosed more commonly after symptoms develop. Hormonal therapy includes a wide variety of treatments designed to affect cells whose normal functioning depends on androgens, which include testosterone and dihydrotestosterone, among others. Prostate cancer cells are generally very susceptible to treatments that lower androgen levels or affect the normal action of these hormones. There is a growing range of medications and treatments that generally are referred to as "hormonal therapy," and there are some differences in the magnitude and range of side effects of these agents. Because androgens have a normal role in so many parts of the body, many side effects have been attributed to hormonal therapy. Some of the side effects are common, such as effects on sexual function, but others are more subtle, such as cognitive or emotional changes. Among the most common types of side effects of hormonal therapy are increased risk for the following: 1) weight gain, obesity, and diabetes[83,84]; 2) cardiovascular disease[83,85]; 3) breast enlargement and/or tenderness[86]; 4) sexual problems, including diminished sex drive and erectile dysfunction[87]; 5) emotional changes, including anger, sadness, and, in many, a generalized sense of fatigue[88,89]; 6) osteoporosis[90]; 7) loss of muscle strength and mass, which also increases the risk of falls in older men, predisposing them to bony fractures[84,91]; 8) anemia, which also contributes to fatigue[92]; and 9) cognitive changes, such as impaired thought processes and memory loss.[93]

Harms of Active Surveillance and Watchful Waiting

On the basis of reports of excellent outcomes for low-grade and medium-grade prostate cancer that is managed conservatively[94,95] and on concerns regarding the high rate of overdiagnosis in such cases, active surveillance has emerged over the past decade as an increasingly used management option.[96] Active surveillance refers to the process of regularly monitoring disease activity through clinical parameters (PSA, DRE) and possibly periodic rebiopsy, with active treatment (surgery, radiation, brachytherapy) offered to men whose disease appears to be progressing. This differs from watchful waiting, which generally implies less aggressive surveillance and no treatment until progressive symptoms or evidence of metastatic disease develop. The principal benefit of active surveillance is its capacity to reduce overtreatment, that is, the treatment of disease that would not have become apparent clinically during the patient's lifetime, which is particularly problematic for less ag-

gressive tumors. Early reports with follow-up as long as 8 years cite prostate cancer-specific survival rates and metastasis-free survival rates of 99% to 100%.[97,98] However, based on the ERSPC finding that the mortality benefit from screening and treatment started to accrue only at 9 to 10 years after randomization, it is premature to gauge the effectiveness of active surveillance compared with immediate treatment.

Active surveillance generally is offered to men whose cancers are Gleason grade 6 or less. It usually includes regular clinical re-evaluation with PSA and DRE as well as biopsy every 1 to 4 years, depending on the protocol. Hence, the principal risks relate to those of prostate biopsy. In addition, it has been postulated that diagnosing prostate cancer without offering active treatment may incur greater anxiety than that incurred in men whose cancers are treated immediately. In fact, survey data do not bear this out. Among men who participated in a prospective trial of active surveillance, scores for anxiety, prostate cancer-specific anxiety, depression, and decisional conflict compared favorably to historical reports for men undergoing active treatment, but no direct comparisons were performed.[99] In a second cross-sectional survey, which did compare men undergoing active surveillance with those undergoing immediate treatment, no increased rates of anxiety or depression were observed, although prostate cancer-specific anxiety measures were not included.[100]

There is good evidence regarding the adverse effects of watchful waiting compared with radical prostatectomy from Scandinavian Prostatic Cancer Group Study Number 4, a randomized trial of prostatectomy versus watchful waiting in men whose prostate cancers were identified largely through symptoms rather than screening.[101] At 5 years, the investigators reported that there were no differences between the groups in levels of depression, anxiety, or worry. Patients who were randomized to watchful waiting had significantly more obstructive symptoms (44% vs 28%) but had less erectile dysfunction (45% vs 80%), less urinary leakage (21% vs 49%), and less distress associated with these symptoms. However, at 6 to 8 years of follow-up the investigators observed that patients who were randomized to watchful waiting had significantly decreased health-related quality of life compared with patients who were randomized to undergo radical prostectomy and those who received androgen-deprivation therapy reported even lower health-related quality of life.[102,103]

Currently, there is no published evidence related to the quality-of-life impact of active surveillance or watchful waiting for men with screen-detected cancers compared with unscreened men. At this juncture, we can state that the principal known harms of these approaches are those of repeat biopsy for men who undergo active surveillance and obstructive symptoms for men engaged in watchful waiting.

Screening Test Characteristics of Prostate-Specific Antigen and Prostate-Specific Antigen Thresholds

A systematic review of the literature was performed to assess PSA test performance among men at average risk for prostate cancer. Although a PSA cutoff value of 4.0 ng/mL has been used historically, many of the countries participating in the recently published ERSPC lowered their threshold to 3.0 ng/mL during the course of the study.[10] Accordingly, the systematic review included prospective studies of prostate cancer screening using either 4.0 ng/mL or 3.0 ng/mL as the cutoff value. After a full-text review of 78 studies, nine prospective studies that examined a PSA cutoff of 4.0 ng/mL in average-risk men were selected for inclusion in the review.[104-112] Three studies reported results from the Finnish arm of the ERSPC[105,108,109]; but only the most recent[108] was included in the pooled analysis. Four studies that used a PSA cutoff of 3.0 ng/mL were deemed eligible for inclusion.[106,107,111,113] The Prostate Cancer Prevention Trial (PCPT) is the only large-scale screening trial that conducted a prostate biopsy for all participants at the end of the trial period and allows the reporting of true sensitivity of PSA at different cutoff values.[114] Men who had PSA levels <3.0 ng/mL and normal DRE results were included at baseline. The men underwent annual PSA and DRE and were recommended for a prostate biopsy if the PSA level was above 4.0 ng/mL or if their DRE was abnormal. At the end of the 7-year follow-up period, all men without a diagnosis of prostate cancer underwent a prostate biopsy. Relatively low prostate cancer detection sensitivities of 20.5% and 32.2% were reported for PSA cutoff values of 4.0 ng/mL and 3.0 ng/mL, respectively. However, the sensitivity of PSA for aggressive prostate cancer (Gleason grade

TABLE 2. PSA Screening Test Characteristics as a Function of Threshold for a Positive Test

TEST CHARACTERISTIC	PSA (NORMAL <4 NG/ML)	PSA (NORMAL < 3 NG/ML)
Test Positivity (%)	12	18
Cancer Detection Rate (%)	3	4
Sensitivity (%)	21	32
Sensitivity (%) for High Grade Cancer, i.e., Gleason Score ≥ 8	51	68
Specificity (%)	91	85
Positive Predictive Value (%)	30	28

Test positivity: (# positive / # tested) x 100; Cancer Detection Rate: (# prostate cancer / # tested) x100; Positive Predictive Value (PPV): (# prostate cancer / # biopsied) x100; Specificity: (true negative tests) / (true negative tests + false positive tests) x 100, estimated from: (#tested - #positive) / (#tested - #cancer) x 100, assuming that negative tests are true negatives.

8 or higher) was greater (51% and 68% for PSA values ≥4.0 ng/mL and ≥3.0 ng/mL, respectively).

The accompanying Table 2 summarizes the pooled estimates for test positivity, cancer detection rates, sensitivity, specificity, and positive predictive value (PPV). It is evident from the results shown in Table 2 that, compared with a threshold of 4.0 ng/mL, lowering the PSA test cutoff to 3.0 ng/mL for confirmatory testing results in higher pooled estimates for test positivity and prostate cancer detection rates but at a cost of lower specificity and PPV.

It has become increasingly clear that there is no PSA threshold that effectively discriminates between the presence and absence of prostate cancer. The test characteristics of the PSA using a threshold of either 4.0 ng/mL or 3.0 ng/mL compare reasonably with the characteristics of other commonly used screening tests, such as the fecal occult blood test for colorectal cancer. However, the higher prostate cancer detection rate, together with the reduced specificity, that would occur if the threshold were lowered uniformly from 4.0 ng/mL would translate into significant increases in false-positive screen results, prostate biopsies, and diagnosis of cancers that would never have become important clinically if they were left undetected (see "Overdiagnosis and Overtreatment" above). Consequently, the ACS recommends maintaining the historical threshold of 4.0 ng/mL for average-risk men who choose screening but encourages health care providers to consider individualized risk assessment and decision making for men with PSA levels in the indeterminate range from 2.5 ng/mL to 4.0 ng/mL (see "Beyond Prostate-Specific Antigen: Individualized Risk Assessment," below).

Prostate-Specific Antigen Screening in High-Risk Populations

Known prostate cancer risk factors, beyond PSA itself, include age, race, and family history of prostate cancer. The effects of these risk factors on PSA test performance also were evaluated. Test positivity generally increases with advancing age. In men younger than age 50 years, test positivity, based on a 4-ng/mL PSA cutoff, ranges between 2% and 3%[115,116] and increases up to as high as 28% among men ages 70 years and older.[116] Similarly, the prostate cancer detection rate and PPV are lower among men younger than age 50 years (1%-2%, and 6%-38%,[115,116] respectively) compared with older men (13% and 39%-58%, respectively).[116] Conversely, specificity decreases with increasing age (from 97% to 98% in younger adults[40-59,115,116] compared with 80% in older adults).[116]

Few studies have evaluated PSA test performance in African American populations. Compared with estimates from studies with predominantly Caucasian participants, PSA test positivity, prostate cancer detection rates, and PPVs reportedly were higher in three studies in African American and African Caribbean populations, particularly among older African American and African Caribbean men. For example, based on a 4-ng/mL PSA cutoff, test positivity reportedly may be as high as 54% with a prostate cancer detection rate of 25% and a PPV of 59% in African American men ages 70 to 79 years.[115,117] However, these estimates are based on small samples and should be interpreted with caution.

Although the body of evidence is slim for men who have a positive family history of prostate cancer,

the rate of PSA test positivity (based on a threshold of 4 ng/mL) varies between 9% and 11%, the cancer detection rate is about 3%, the PPV ranges from 28% to 32%, and specificity remains high (92%-94%).[109,117] When lower PSA thresholds are used (2.0 ng/mL or 2.5 ng/mL), the PPVs are substantially higher among men with a positive family history (38%-43%) than in average-risk men, and the effects on specificity are variable (64%-93%).[109,118] PSA screening in higher risk populations generally is characterized by higher detection rates and higher PPVs, as would be expected in men with a higher baseline likelihood of prostate cancer. We still do not know whether PSA screening performs better in higher risk men in terms of reduced prostate cancer-specific mortality. The ERSPC performed an exploratory analysis on mortality by age group and observed no effect of age, but the study was not designed to explore this issue specifically.[10] Neither the PLCO nor the ERSPC has reported subgroup analyses examining the impact of ethnicity or family history.

On the basis of the higher incidence of prostate cancer at younger ages for men at high risk and without new data to modify this guideline, the ACS continues to recommend that African American men and men who have a family history of a first-degree relative with prostate cancer be provided information about the uncertainties, risks, and potential benefits surrounding prostate cancer screening beginning at age 45 years.[2,119] For men who have multiple first-degree relatives diagnosed with prostate cancer before age 65 years, this discussion should take place beginning at age 40 years. For men who choose to be screened, the ACS recommends integrating established risk factors into an individualized risk assessment, particularly when PSA levels fall into what currently would be considered the high-normal range of 2.5 ng/mL to 4.0 ng/mL (see "Beyond Prostate-Specific Antigen: Individualized Risk Assessment," below).

Prostate-Specific Antigen Screening Interval

Although the majority of men undergoing PSA screening in the United States are tested on an annual basis, there is no strong evidence to recommend one interscreening interval over another. Different screening intervals have not been compared in a randomized controlled trial setting. The single trial that demonstrated a mortality benefit of PSA screening, the ERSPC, had a screening interval of 4 years (and a PSA threshold level for biopsy of 3.0 ng/mL) in most centers.[10] These results provide support for a benefit of screening less frequently than every year.

Three modeling studies have compared annual screening with less frequent screening. In one model,[120] it was projected that screening every 2 years would reduce the number of tests and unnecessary biopsies by 50% while retaining 93% of the years of life saved (relative to the annual screening strategy). A more recent modeling study by the same group used a completely different approach and demonstrated that screening every 2 years reduced the number of tests and unnecessary biopsies by almost 50% and reduced overdiagnosis by 13% while retaining 87% of the years of life saved.[121] In a third model, screening every 2 years similarly reduced the number of tests while retaining 95% of the years of life saved.[122] All of these studies assumed a PSA cutoff of 4.0 ng/mL and a starting age for screening of 50 years. The second study showed similar results with a starting age of 40 years.

Some studies provide information on the likely delay in detection when moving from an annual interval to less frequent screening. It is estimated that the average delay in diagnosis when going from annual screening to screening every 2 years is between 5 months and 6 months.[123] Several studies have indicated that, in men with very low PSA levels, conversion to a PSA above 4.0 ng/mL within 2 years or even 4 years after the initial PSA test is very unlikely. For example, in the PLCO trial, among men who had an initial PSA level of <1.0 ng/mL, only 0.24% had a positive test (PSA >4 ng/mL) the following year, and 0.51% had a positive test 2 years later.[123] In the same study, among men who had an initial PSA level of 1 ng/mL or 2 ng/mL, only 1.2% had a positive test 1 year later, and 2.6% had a positive test 2 years later. A similar result regarding extending the screening interval in men with PSA <2.0 ng/mL was reported in an earlier, smaller study.[124]

On the basis of positive results from the ERSPC, which largely used a 4-year screening interval and a PSA threshold of 3.0 ng/mL, together with the modeling studies described above, it appears that extending the screening interval in men with initially low PSA levels would delay diagnosis for only a very

few cases and would be unlikely to have a significant impact on prostate cancer mortality. Although no single PSA threshold emerges as the obvious cutoff point below which the screening interval can be extended, thresholds between 2.0 ng/mL and 4.0 ng/mL were examined in the studies discussed above. A conservative cutoff point within this range would be 2.5 ng/mL. Men with PSA levels below 2.5 ng/mL form a significant portion of the screened population; thus, extending the screening interval for these men could lead to considerable reductions in PSA tests, biopsies, overdiagnosis, and costs.[118] Therefore, the ACS recommends that men whose initial PSA level is below 2.5 ng/mL can reduce their screening frequency to every 2 years. Men with higher PSA values should be tested annually.

Prostate-Specific Antigen Velocity

It seems intuitive that the rate of increase in PSA (PSA velocity) would be related to the risk of prostate cancer. PSA velocity was proposed as a risk factor for prostate cancer first in 1992 by Carter et al in a study of patients from the Baltimore Longitudinal Study of Aging (BLSA).[125] In that study, the authors observed that, in most men, there was a gradual and slow increase in PSA over time. However, PSA increased more rapidly among men with prostate cancer, and, in men with the most aggressive tumors, the rate of increase was the greatest. A rate of increase in PSA >0.75 ng/mL per year was associated with a higher risk of prostate cancer. A follow-up analysis from the BLSA suggested that a PSA velocity as low as 0.35 ng/mL per year might be useful to differentiate cancer from noncancer.[126]

Unfortunately, there are several challenges to the incorporation of PSA velocity into a prostate cancer screening strategy. First, there can be substantial day-to-day variation in PSA, often for no apparent reason; and, with repeat testing, as many as 25% no longer will be abnormal.[127] For this reason, repeating the PSA test before further evaluation is reasonable. Perhaps the most important limitation regarding PSA velocity is that it is highly correlated with the PSA value itself.[128] This high degree of correlation between PSA and PSA velocity has been borne out in large prospective studies that did not establish that PSA velocity improved on PSA alone in predicting the risk of prostate cancer. In the PCPT, the only study in which biopsy was performed generally regardless of PSA level, PSA velocity indeed was related to the risk of prostate cancer and to the risk of high-grade prostate cancer.[114] However, after the incorporation of PSA and other risk factors (race/ethnicity, family history, DRE results, and prior prostate biopsy results), PSA velocity no longer influenced prostate cancer risk; and, in men with high-grade prostate cancer, the incorporation of PSA velocity actually provided incorrect data related to risk.[114] In the ERSPC, a similar analysis indicated that PSA velocity did not substantially improve on the performance of PSA alone in the prediction of prostate cancer risk.[129] Most recently, in a systematic review of studies published before March 2007, using rigorous statistical criteria for review, Vickers and colleagues produced little evidence that PSA kinetics (doubling time, velocity) provided independent predictive information related to the risk of prostate cancer beyond that provided by PSA alone.[130] Accordingly, the ACS does not recommend routinely incorporating PSA velocity into prostate cancer screening strategies.

Digital Rectal Examination

The optimal role of the DRE for the early detection of prostate cancer is unclear. The DRE has been recommended as a screen for prostate cancer since the early 1900s[131,132] and has been recommended formally by the ACS since 1991.[133,134] From 1975 through the early 1990s, when the DRE was the only prostate cancer screening test, prostate cancer mortality rose steadily. This steady rise is in marked contrast to the decline in mortality that followed the uptake of PSA for screening in the early 1990s.[2] Of course, many potentially confounding factors preclude definitive conclusions based on time trends alone. Several case-control studies have examined the effect on prostate cancer mortality of having undergone a DRE. Of three case-control studies that examined only the DRE, one reported a statistically significant protective effect, and two did not (OR, 0.53; 95% CI, 0.32-0.90; OR, 0.9; 95% CI, 0.5-1.7; and OR, 0.84; 95% CI, 0.48-1.46, respectively).[2,36,135] Other case-control studies examined both PSA and DRE, but separating out the effect of the two was possible in only one study (OR, 0.37; 95% CI, 0.19-0.71).[35,37] Case-control studies of prostate cancer screening

have serious methodologic challenges, which are described in detail above (see "Evidence from Case-Control Studies"). Of the two randomized trials of prostate cancer screening, the PLCO study, which offered patients in the intervention group both DRE and PSA, did not demonstrate any benefit of screening.[11] Conversely, the ERSPC, which largely offered patients PSA without DRE (and recommended biopsy for PSA values >3.0 ng/mL), did demonstrate a reduction in mortality associated with screening.[10] Thus, randomized trial evidence does not support the DRE as a screening test.

Although trial data and time trends suggest either no impact or only a small impact of adding the DRE to PSA for screening,[136] clinical observations demonstrate that some high-grade prostate cancers are detectable by DRE in individuals with PSA values that fall below any recommended threshold for biopsy. However, in a subgroup analysis of the ERSPC, only 17% of prostate cancers were diagnosed by DRE alone (ie, with PSA values below 4.0 ng/mL).[137] Moreover, in the same analysis, the sensitivity and PPV of the DRE were only 20% and 8.8%, respectively, in men who had PSA values <3.0 ng/mL. Thus, DRE performed poorest at the PSA levels at which it was needed the most.

Determining the appropriate role of the DRE in screening for prostate cancer is rendered more complicated by several facts. First, the sensitivity and specificity of the DRE depend on the examiner.[138] In other words, each examiner performs DRE with an individual sensitivity and specificity. Second, although some cases are detectable in men with low PSA levels, the lethal potential of these cancers is uncertain. Furthermore, whether or not these cancers would be detected subsequently by serial PSA testing and whether or not they would have shifted in that interval from curable to incurable is unknown. Third, based on survey results from men participating in PSA screening, DRE may be a barrier to screening for some men.[50] Finally, the capacity to detect clinically important prostate cancers by DRE that would be missed by the PSA depends on the PSA threshold used to perform a prostate biopsy. The lower the biopsy threshold, the less likely that DRE will detect important prostate cancers that would be missed by PSA. Conversely, as the threshold is raised, the potential value of the DRE goes up. Nevertheless, the guideline committee recognizes that it is not possible to identify a PSA biopsy threshold that detects all clinically important cancers and that some cancers below the threshold may be detectable by DRE.

The ACS recommends that individualized decision making should occur for men whose PSA levels fall between 2.5 ng/mL and 4.0 ng/mL, as mentioned below (see "Beyond Prostate-Specific Antigen: Individualized Decision Making"). This process involves integrating other risk factors for finding prostate cancer, particularly high-grade cancer, at this lower PSA level. One factor that can contribute to the decision is the result of a DRE. In men who underwent prostate biopsy for PSA levels ≥3.0 ng/mL, it was demonstrated that an abnormal DRE contributed to the predictive value of detecting prostate cancer and to the selective detection of potentially aggressive cancers.[139] Similarly, in the ERSPC analysis, as noted above, the DRE had a substantially higher PPV in the higher ranges of normal.[137] Therefore, performing a DRE in men with PSA values between 2.5 ng/mL and 4.0 ng/mL can assist the provider and patient in the decision whether to refer for biopsy. In addition, for men who choose to be tested, clinicians should consider continuing to use the DRE in circumstances that affect the PSA level, such as taking finasteride and hypogonadism.[140]

In summary, although the value of adding a periodic DRE to periodic PSA testing is unknown, it will depend in part on the PSA biopsy threshold and the individual who performs the DRE. Even under optimal performance and with a high biopsy threshold, the added value of performing a periodic DRE is likely to be quite low, increasing the cancer detection rate by 17% at most, and few of these cancers detected exclusively by DRE are likely to be high grade.[137] Thus, for men who choose to be screened for prostate cancer, testing is recommended with PSA with or without DRE. To assist in individualized decision making, health care providers should consider performing a DRE for PSA levels between 2.5 ng/mL and 4.0 ng/mL if it has not already been done.

Beyond Prostate-Specific Antigen: Individualized Risk Assessment

Since the PSA test emerged as a screening test for prostate cancer in the late 1980s and early 1990s, a

PSA value of 4.0 ng/mL became accepted as the upper limit of normal.[5] In the middle to late 1990s, however, it was recognized that rates of prostate cancer still were significant at lower PSA levels (between 2.5 ng/mL and 4.0 ng/mL).[141] Generally, it was believed that men who had PSA levels <2.5 ng/mL had low levels of prostate cancer risk. With completion of the PCPT, in which men at all levels of PSA underwent biopsy, it was recognized that PSA should not be considered "elevated" or "normal," because prostate cancer was identified at all levels of PSA, including values <1.0 ng/mL.[114] What was discovered was the higher the PSA, the higher the risk of cancer. Especially important was that it was at higher levels of PSA that aggressive cancers were identified. Study investigators examined how factors in addition to PSA affected a man's risk of prostate cancer. The six prostate cancer risk factors that were included in the model were PSA, DRE findings, age, race (Caucasian or African American)/ethnicity (Hispanic or non-Hispanic), family history, and history of prior negative prostate biopsy (protective). Examining 5519 men who all underwent biopsy and in whom all 6 data elements were available, a tool was developed to assess an individual man's risk of prostate cancer. That tool is available online at http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp (accessed January 27, 2010). This risk-assessment tool has been validated in several additional groups of men.[142,143] Although the risk calculator may not have a significant impact on some men's decision making, it does allow a man both to understand his risk of cancer, particularly of high-grade cancer, and to compare his risk with that of other men. For the first concept, it is important for men to understand, when deciding whether or not to undergo screening and biopsy, that lower grade tumors (eg, with a Gleason score below 6) may remain indolent without any symptoms or a propensity to spread. Thus, a diagnosis of a low-grade tumor could lead to unnecessary treatment. Conversely, high-grade tumors appear to pose the greatest risk of spread and are the tumors most likely to cause death. Because of the greater need to diagnose these high-grade tumors early, some physicians stress that the risk of high-grade disease—not the overall cancer risk—should be the primary determinant of the need for a prostate biopsy.[144]

To demonstrate the importance of individualized risk assessment, it is useful to consider two different clinical scenarios of men who choose to be screened after engaging in informed decision making (see Table 3). Man A, who is 55 years old, has a common reason for undergoing a prostate biopsy—a prostate nodule on DRE despite a low PSA value. Because he has no other risk factors, his risk of life-threatening prostate cancer is only 2.8% despite an overall prostate cancer risk of 29.1%. Although a biopsy could be considered, it should be understood that the type of tumor detected may be so slow growing that treatment may not be necessary, and its diagnosis may not be beneficial to the patient. Man B is 10 years older and has a "normal" PSA level (2.5 ng/mL) by historical standards. Although, according to current convention, he would be reassured that he needs no further evaluation, he has 4-fold higher risk of potentially life-threatening cancer than Man A, for whom biopsy is recommended.

TABLE 3. Decision Making in the Context of Risk Factors and Clinical Scenarios

VARIABLE	MAN A	MAN B
Age, y	55	65
PSA, ng/mL	1.0	2.5
Rectal examination findings	Abnormal-nodule	Normal
Family history of cancer?	No	No
Race/ethnicity	Caucasian	African American
Prior negative prostate biopsy?	No	No
Risk of cancer	29.1%	26.5%
Risk of low-grade cancer	26.3%	15.7%
Risk of high-grade cancer	2.8%	10.8%

PSA indicates prostate-specific antigen.

Is there a threshold value of overall cancer risk or of high-grade cancer risk that should prompt a biopsy? Unfortunately, no absolute PSA level exists that is applicable to all men. The risk level at which a biopsy should be considered should be based on factors related to a man's life expectancy (age, comorbidities) as well as a man's concern regarding his risk. Because a biopsy could result in the detection of an inconsequential tumor and because treatments have a range of potential side effects, the level of risk at which a biopsy should be undertaken should be based on a man's integration of these considerations into his decision making.

Recognizing that there is no single PSA threshold to distinguish high risk from low risk, it is reasonable to offer men the opportunity for individualized risk assessment at PSA values between 2.5 ng/mL and 4.0 ng/mL. Multiple studies have demonstrated that greater than 20% of men whose PSA values fall in this range will have prostate cancers on biopsy, many of which are clinically important.[114,141,145] Of course, some men with PSA levels below 2.5 ng/mL will harbor prostate cancer; however, these cancers are less likely to be high-grade, and are likely to be detected on serial PSA measurements. Although individualized risk assessment can be time-consuming, only about 10% of men who choose to be screened will have values that fall in the 2.5 ng/mL to 4.0 ng/mL range.[145]

Future risk assessments likely will incorporate new prostate cancer biomarkers, which will discriminate better between life-threatening and indolent prostate cancers. The PCPT risk calculator has been updated to include data from a large study of PCA3, a urinary biomarker that is associated with prostate cancer risk.[146] The online calculator currently allows for entry of this value to update risk. In summary, for men who have PSA levels between 2.5 ng/mL and 4.0 ng/mL, the ACS recommends that health care providers consider an individualized risk assessment that incorporates other risk factors for prostate cancer, particularly for high-grade cancer, which may be used for a biopsy or referral recommendation.

Men for Whom Screening Is Not Recommended

There is broad consensus on the characteristics of men for whom screening is unlikely to be beneficial. This group includes men of advanced age and those with life-limiting comorbidities. Several factors contribute to a recommendation against routine prostate cancer screening in such men.

Prostate cancer in most instances is a slow-growing tumor; thus, the disease often is present for several years with no significant impact on a man's health or well being. For men who are diagnosed with prostate cancer at the local or regional stage, the 5-year relative survival rate is nearly 100%.[2] Furthermore, evidence suggests that, if screening does offer a survival benefit, then this benefit accrues well after the initial screen. An analysis of data from the ERSPC[10] revealed that the survival curves for the screened and unscreened groups did not separate significantly until 9 or 10 years after the initiation of screening. In contrast to the uncertainties regarding the benefits of prostate cancer screening, the well recognized harms associated with prostate cancer screening and treatment may be more common and more severe in the elderly and in those with debilitating conditions. Although the incidence of prostate cancer increases with age, in the absence of screening tests, many of these excess cancers will remain silent and cause no morbidity during a man's lifetime. Overdiagnosis occurs when these clinically insignificant cancers are detected by screening tests. Overdiagnosis, which is described in detail above (see "Overdiagnosis and Overtreatment," above) is a particular concern in older men. It is estimated that from 23% to 42% of screen-detected prostate cancers represent overdiagnosis; this rate may exceed 50% in men aged 75 years and older.[12]

Because of the known harms associated with prostate cancer screening and treatment and the prolonged interval required before the potential accrual of any related benefit, for many years ACS early detection guidelines have recommended that screening for prostate cancer be offered only to those men who are judged to have at least a 10-year life expectancy.[147,148] Men who, based on advanced age and/or comorbidities, are unlikely to survive for at least 10 years are not suitable candidates for prostate cancer screening. Published screening guidelines from other organizations offer similar recommendations.[149,150]

Clinicians often feel challenged when called on to estimate life expectancy. Such estimates, in some instances, are relatively straightforward (for example, in someone with advanced-stage cancer that has not responded to therapy). In other instances, life tables may provide useful estimates based on age or on quartiles of assessed health status (see Fig. 3).[151] These tools demonstrate that, in the United States, at age 75 years, about half of men have a life expectancy of 10 years or more.

The decision whether or not to screen, however, should not be based solely on age. Some men in their 70s or even their early 80s have few health problems and quite reasonably can be expected to live beyond the next 10 years. These men might gain benefit through the early diagnosis of a screen-detected can-

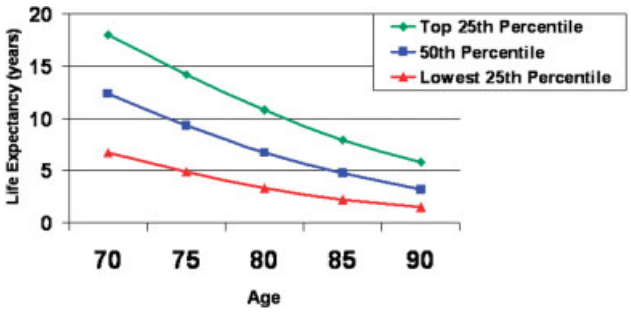

FIGURE 3. Life Expectancy for Men by Upper, Middle, and Lower Quartiles of Health Status.[151]

cer and should not be denied the opportunity to make an informed decision on screening.

Although age is clearly an important determinant of life expectancy, the number and severity of comorbidities and the degree of functional impairment conferred by these conditions may have an even greater impact on longevity. Examples of common life-limiting comorbidities include New York Heart Association Class 4 congestive heart failure, moderate-to-severe chronic obstructive pulmonary disease, end-stage renal disease, moderate-to-severe dementia, or life-limiting cancer. The shortened lifespan that commonly accompanies these conditions precludes any theoretical benefit that might be gained from screening and early prostate cancer detection. Sophisticated lifespan calculation tools that include adjustments for health status have been developed and may prove helpful.[151,152]

Despite cross-organizational guideline congruence regarding avoiding screening for men with a life expectancy of less than 10 years, it is clear that a significant amount of screening continues to take place among individuals who are unlikely to benefit. A recent study of men who were cared for in the Veterans Administration health care system documented prostate cancer screening rates of 45% in men aged 80 years and older and 36% among those aged 85 years and older. More concerning was the finding that the rate of screening was essentially identical for men in good health and for men who had known, life-limiting comorbidities.[153] Similarly high rates of screening in elderly men have been reported by other investigators.[154]

In summary, there are identifiable groups of men in whom the balance of prostate cancer detection and treatment harms clearly outweighs any potential benefit achievable through screening. It is important that clinicians make a deliberate assessment of patient age and comorbidities in advance of the discussion of prostate cancer screening and that these factors are weighed appropriately by patients and clinicians in the decision-making process.

Conclusion

Two decades into the PSA era of prostate cancer screening, the overall value of early detection in reducing the morbidity and mortality from prostate cancer remains unclear. Emerging evidence that early detection may reduce the likelihood of dying from prostate cancer must be weighed against the serious risks incurred by early detection and subsequent treatment, particularly the risk of treating many men for screen-detected prostate cancer who would not have experienced ill effects from their disease if it had been left undetected.

In light of the ongoing uncertainties, including the uncertain balance between benefits and risks, this updated guideline highlights the importance of involving men in the screening decision. To this end, the guideline provides the core elements of information necessary for men to engage meaningfully in this decision: a basic understanding of the importance of prostate cancer, the potential benefits of early detection, the strengths and limitations of PSA testing, and the risks of finding and treating screen-detected cancer. How men use this information will depend heavily on the relative value they place on the various risks and potential benefits. Accordingly, this guideline emphasizes the critical role that health care providers can and should play in helping men decide whether to be tested by assuring that their patients have adequate information and by helping them to clarify their values relevant to the decision. Recognizing the complexity of the issues involved and the time constraints faced by health care providers, we encourage providers and patients to use prostate cancer screening decision aids to facilitate the process and better ensure a decision that is truly commensurate with the patient's values.

In view of the delay between diagnosis through screening and the expected mortality benefit, we continue to recommend that men whose life expectancy is under 10 years not pursue prostate cancer early detection. The likelihood of benefit in these men is sufficiently low to be outweighed by the risk of harms

stemming from treatment. Conversely, we continue to recommend that men who are at greater risk for developing prostate cancer at earlier ages—African American men and men with a family history of prostate cancer in nonelderly relatives—should be provided the opportunity for informed decision-making at a younger age than men who are at average risk.

For men who choose to be tested and their providers, we offer guidance regarding the frequency of testing based on the PSA level and guidance regarding how to act on the testing result. Without definitive answers yet from randomized trials and recognizing that lowering the PSA threshold for biopsy will increase the rate of overdiagnosis, we consider the traditional PSA level of 4.0 ng/mL to be a reasonable threshold for further evaluation. However, acknowledging that there is no true PSA cutoff point that distinguishes cancer from noncancer, we suggest that providers consider individualized decision making when PSA levels fall in the indeterminate range between 2.5 ng/mL and 4.0 ng/mL, particularly in men who are at increased risk for high-grade cancer based on non-PSA risk factors.

Although there remains controversy regarding the benefit of current screening strategies in reducing the burden of prostate cancer, there is consensus that better methods for the detection and treatment of early stage prostate cancer are needed urgently. We are hopeful that future advances in the early detection of prostate cancer will lead to the ability to distinguish accurately between indolent and aggressive cancers and that the adverse effects of prostate cancer treatment will be reduced sufficiently to tip the balance clearly in favor of screening. Until that time, however, it will remain incumbent on health care providers and the health care system as a whole to provide men with the opportunity to decide whether they wish to pursue early detection of prostate cancer. ■

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225-249.
2. Horner M, Ries L, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2006. Bethesda, MD: National Cancer Institute; 2009.
3. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med*. 1987;317:909-916.
4. Cooner WH, Mosley BR, Rutherford CL Jr, et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol*. 1990;143:1146-1152; discussion 1152-1154.
5. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med*. 1991;324:1156-1161.
6. Albertsen PC. The prostate cancer conundrum. *J Natl Cancer Inst*. 2003;95:930-931.
7. Etzioni R, Feuer E. Studies of prostate-cancer mortality: caution advised. *Lancet Oncol*. 2008;9:407-409.
8. Kvale R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst*. 2007;99:1881-1887.
9. Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol*. 2008;9:445-452.
10. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-1328.
11. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360:1310-1319.
12. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*. 2009;101:374-383.
13. Schover LR, Fouladi RT, Warneke CL, et al. Defining sexual outcomes after treatment for localized prostate carcinoma. *Cancer*. 2002;95:1773-1785.
14. Gore JL, Kwan L, Lee SP, Reiter RE, Litwin MS. Survivorship beyond convalescence: 48-month quality-of-life outcomes after treatment for localized prostate cancer. *J Natl Cancer Inst*. 2009;101:888-892.
15. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst*. 2004;96:1358-1367.
16. O'Connor AM, Bennett CL, Stacey D, et al. Decision aids for people facing health treatment or screening decisions [serial online]. *Cochrane Database Syst Rev*. 2009(3):CD001431.
17. Briss P, Rimer B, Reilley B, et al. Promoting informed decisions about cancer screening in communities and healthcare systems. *Am J Prev Med*. 2004;26:67-80.
18. Sheridan SL, Harris RP, Woolf SH. Shared decision making about screening and chemoprevention. a suggested approach from the U.S. Preventive Services Task Force. *Am J Prev Med*. 2004;26:56-66.
19. Llewellyn-Thomas HA. Values clarification. In: Edwards A, Elwyn G, eds. Shared Decision-Making in Health Care: Achieving Evidence-Based Patient Choice. 2nd ed. Don Mills, Ontario: Oxford University Press; 2009;123-133.
20. Volk RJ, Jibaja-Weiss ML, Hawley ST, et al. Entertainment education for prostate cancer screening: a randomized trial among primary care patients with low health literacy. *Patient Educ Couns*. 2008;73:482-489.
21. Dunn AS, Shridharani KV, Lou W, Bernstein J, Horowitz CR. Physician-patient discussions of controversial cancer screening tests. *Am J Prev Med*. 2001;20:130-134.
22. Hoffman RM, Couper MP, Zikmund-Fisher BJ, et al. Prostate cancer screening decisions: results from the National Survey of Medical Decisions (DECISIONS study). *Arch Intern Med*. 2009;169:1611-1618.
23. Elwyn G, O'Connor A, Stacey D, et al; International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process [serial online]. *BMJ*. 2006;333:417.
24. Volk RJ, Hawley ST, Kneuper S, et al. Trials of decision aids for prostate cancer screening: a systematic review. *Am J Prev Med*. 2007;33:428-434.
25. Cole P, Morrison AS. Basic issues in population screening for cancer. *J Natl Cancer Inst*. 1980;64:1263-1272.
26. Brawley OW, Kramer BS. Cancer screening in theory and in practice. *J Clin Oncol*. 2005;23:293-300.
27. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mor-

tality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate*. 2004;59:311-318.

28. Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. *Eur Urol*. 2004;46: 717-723; discussion 724.
29. Ilic D, O'Connor D, Green S, Wilt T. Screening for prostate cancer [serial online]. *Cochrane Database Syst Rev*. 2006;3: CD004720.
30. Kerkhof M, Roobol MJ, Steyerberg EW, Cuzick J, Schroder FH. Secondary analysis of the European Randomised Study of Screening for Prostate Cancer (ERSPC)—effect of prostate cancer screening on the development of metastases after adjustment for non-compliance and contamination [abstract]. *J Urol*. 2009;181(4 suppl 1):233. Abstract 648.
31. Grubb RL 3rd, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. *BJU Int*. 2008;102:1524-1530.
32. Roobol MJ, Kerkhof M, Schroder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol*. 2009;56:584-591.
33. Wolters T, Roobol MJ, Steyerberg EW, et al. The effect of study arm on prostate cancer treatment in a large screening trial (ERSPC). *Int J Cancer*. 2009 Sep 9. [Epub ahead of print].
34. Weiss NS. Application of the case-control method in the evaluation of screening. *Epidemiol Rev*. 1994;16:102-108.
35. Agalliu I, Weiss NS, Lin DW, Stanford JL. Prostate cancer mortality in relation to screening by prostate-specific antigen testing and digital rectal examination: a population-based study in middle-aged men. *Cancer Causes Control*. 2007;18:931-937.
36. Jacobsen SJ, Bergstralh EJ, Katusic SK, et al. Screening digital rectal examination and prostate cancer mortality: a population-based case-control study. *Urology*. 1998;52:173-179.
37. Bergstralh EJ, Roberts RO, Farmer SA, et al. Population-based case-control study of PSA and DRE screening on prostate cancer mortality. *Urology*. 2007;70:936-941.
38. Weinmann S, Richert-Boe KE, Van Den Eeden SK, et al. Screening by prostate-specific antigen and digital rectal examination in relation to prostate cancer mortality: a case-control study. *Epidemiology*. 2005;16:367-376.
39. Concato J, Wells CK, Horwitz RI, et al. The effectiveness of screening for prostate cancer: a nested case-control study. *Arch Intern Med*. 2006;166:38-43.
40. 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.
41. Tarone RE, Chu KC, Brawley OW. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. *Epidemiology*. 2000;11: 167-170.
42. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the "PSA ERA." *Int J Cancer*. 2001;92: 893-898.
43. Lu-Yao G, Albertsen PC, Stanford JL, et al. Screening, treatment, and prostate cancer mortality in the Seattle area and Connecticut: fifteen-year follow-up. *J Gen Intern Med*. 2008;23:1809-1814.
44. Lu-Yao G, Albertsen PC, Stanford JL, et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut [serial online]. *BMJ*. 2002;325:740.
45. Shaw PA, Etzioni R, Zeliadt SB, et al. An ecologic study of prostate-specific antigen screening and prostate cancer mortality in nine geographic areas of the United States. *Am J Epidemiol*. 2004;160:1059-1069.
46. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, *Austria Urology*. 2001;58:417-424.
47. Bartsch G, Horninger W, Klocker H, et al. Tyrol Prostate Cancer Demonstration Project: early detection, treatment, outcome, incidence and mortality. *BJU Int*. 2008;101:809-816.
48. Connor RJ, Boer R, Prorok PC, Weed DL. Investigation of design and bias issues in case-control studies of cancer screening using microsimulation. *Am J Epidemiol*. 2000;151:991-998.
49. Galena HJ. Complications occurring from diagnostic venipuncture. *J Fam Pract*. 1992;34:582-584.
50. Nagler HM, Gerber EW, Homel P, et al. Digital rectal examination is barrier to population-based prostate cancer screening. *Urology*. 2005;65:1137-1140.
51. Gustafsson O, Theorell T, Norming U, et al. Psychological reactions in men screened for prostate cancer. *Br J Urol*. 1995;75: 631-636.
52. Essink-Bot ML, de Koning HJ, Nijs HG, et al. Short-term effects of population-based screening for prostate cancer on health-related quality of life. *J Natl Cancer Inst*. 1998;90:925-931.
53. Steginga SK, Occhipinti S, McCaffrey J, Dunn J. Men's attitudes toward prostate cancer and seeking prostate-specific antigen testing. *J Cancer Educ*. 2001;16:42-45.
54. Brindle LA, Oliver SE, Dedman D, et al. Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK. *BJU Int*. 2006;98:777-782.
55. Carlsson S, Aus G, Wessman C, Hugosson J. Anxiety associated with prostate cancer screening with special reference to men with a positive screening test (elevated PSA)—Results from a prospective, population-based, randomised study. *Eur J Cancer*. 2007;43:2109-2116.
56. Taylor KL, Shelby R, Kerner J, Redd W, Lynch J. Impact of undergoing prostate carcinoma screening on prostate carcinoma-related knowledge and distress. *Cancer*. 2002;95:1037-1044.
57. McNaughton-Collins M, Fowler FJ Jr, Caubet JF, et al. Psychological effects of a suspicious prostate cancer screening test followed by a benign biopsy result. *Am J Med*. 2004;117:719-725.
58. Fowler FJ Jr, Barry MJ, Walker-Corkery B, et al. The impact of a suspicious prostate biopsy on patients' psychological, sociobehavioral, and medical care outcomes. *J Gen Intern Med*. 2006;21:715-721.
59. Ecke TH, Gunia S, Bartel P, et al. Complications and risk factors of transrectal ultrasound guided needle biopsies of the prostate evaluated by questionnaire. *Urol Oncol*. 2008;26:474-478.
60. Roberts RO, Bergstralh EJ, Besse JA, Lieber MM, Jacobsen SJ. Trends and risk factors for prostate biopsy complications in the pre-PSA and PSA eras, 1980 to 1997. *Urology*. 2002;59:79-84.
61. Alecsandru D, Gestoso I, Romero A, et al. E. coli multiresistant meningitis after transrectal prostate biopsy. *ScientificWorldJournal*. 2006;6:2323-2326.
62. Gillespie JL, Arnold KE, Noble-Wang J, et al. Outbreak of Pseudomonas aeruginosa infections after transrectal ultrasound-guided prostate biopsy. *Urology*. 2007;69: 912-914.
63. Briffaux R, Coloby P, Bruyere F, et al. One preoperative dose randomized against 3-day antibiotic prophylaxis for transrectal ultrasonography-guided prostate biopsy. *BJU Int*. 2009;103:1069-1073; discussion 1073.
64. Griffith BC, Morey AF, Ali-Khan MM, et al. Single dose levofloxacin prophylaxis for prostate biopsy in patients at low risk. *J Urol*. 2002;168:1021-1023.
65. Cam K, Kayikci A, Akman Y, Erol A. Prospective assessment of the efficacy of single dose versus traditional 3-day antimicrobial prophylaxis in 12-core transrectal prostate biopsy. *Int J Urol*. 2008;15:997-1001.
66. Djavan B, Zlotta A, Remzi M, et al. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. *J Urol*. 2000;163:1144-1148; discussion 1148-1149.
67. Singh H, Canto EI, Shariat SF, et al. Predictors of prostate cancer after initial negative systematic 12 core biopsy. *J Urol*. 2004;171:1850-1854.
68. Rochester MA, Pashayan N, Matthews F, Doble A, McLoughlin J. Development and validation of risk score for predicting positive repeat prostate biopsy in patients with a previous negative biopsy in a UK population [serial online]. *BMC Urol*. 2009;9:7.
69. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic incidence and duration of prostate cancer. *Am J Epidemiol*. 1998;148: 775-785.
70. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst*. 2002;94:981-990.
71. Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. *Biometrics*. 2008;64:10-19.
72. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. *Eur Urol*. 2009;55:1251-1265.
73. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. 2009; 302:1557-1564.

74. Lloyd JC, Banez LL, Aronson WJ, et al. Preoperative predictors of blood loss at the time of radical prostatectomy: results from the SEARCH database. *Prostate Cancer Prostatic Dis*. 2009;12:264-268.
75. Lepor H, Nieder AM, Ferrandino MN. Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. *J Urol*. 2001;166:1729-1733.
76. Elliott SP, Meng MV, Elkin EP, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. *J Urol*. 2007;178:529-534; discussion 534.
77. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007;177:2106-2131.
78. Litwin MS. Health related quality of life in older men without prostate cancer. *J Urol*. 1999;161:1180-1184.
79. Burman C, Chui CS, Kutcher G, et al. Planning, delivery, and quality assurance of intensity-modulated radiotherapy using dynamic multileaf collimator: a strategy for large-scale implementation for the treatment of carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 1997;39:863-873.
80. Ling CC, York E, Fuks Z. From IMRT to IGRT: Frontierland or Neverland? *Radiat Oncol*. 2005;77:227-230.
81. Cormack RA, Kooy H, Tempany CM, D'Amico AV. A clinical method for real-time dosimetric guidance of transperineal 125I prostate implants using interventional magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 2000;46:207-214.
82. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:1124-1129.
83. Basaria S. Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: an inconvenient truth. *J Androl*. 2008;29:534-539.
84. Galvao DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int*. 2008;102:44-47.
85. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA*. 2009;302:866-873.
86. Dobs A, Darkes MJ. Incidence and management of gynecomastia in men treated for prostate cancer. *J Urol*. 2005;174:1737-1742.
87. DiBlasio CJ, Malcolm JB, Derweesh IH, et al. Patterns of sexual and erectile dysfunction and response to treatment in patients receiving androgen deprivation therapy for prostate cancer. *BJU Int*. 2008;102:39-43.
88. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;29:1071-1081.
89. Pirl WF, Greer JA, Goode M, Smith MR. Prospective study of depression and fatigue in men with advanced prostate cancer receiving hormone therapy. *Psychooncology*. 2008;17:148-153.
90. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2001;345:948-955.
91. Williams MB, Hernandez J, Thompson I. Luteinizing hormone-releasing hormone agonist effects on skeletal muscle: how hormonal therapy in prostate cancer affects muscular strength. *J Urol*. 2005;173:1067-1071.
92. Beer TM, Tangen CM, Bland LB, et al. The prognostic value of hemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: a multivariate analysis of Southwest Oncology Group Study 8894. *Cancer*. 2006;107:489-496.
93. Jim HS, Small BJ, Patterson S, Salup R, Jacobsen PB. Cognitive impairment in men treated with luteinizing hormone-releasing hormone agonists for prostate cancer: a controlled comparison. *Support Care Cancer*. 2009 Apr 3. [Epub ahead of print].
94. Albertsen PC, Hanley JA, Fine J. Twenty-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005;293:2095-2101.
95. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA*. 2009;302:1202-1209.
96. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol*. 2002;167:1664-1669.
97. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol*. 2007;178:2359-2364; discussion 2364-2365.
98. Roemeling S, Roobol MJ, de Vries SH, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *Eur Urol*. 2007;51:1244-1250; discussion 1251.
99. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. *Cancer*. 2009;115:3868-3878.
100. Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? *BJU Int*. 2007;100:540-543.
101. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med*. 2002;347:790-796.
102. Johansson E, Bill-Axelson A, Holmberg L, et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *Eur Urol*. 2009;55:422-430.
103. McDermott DW, Sanda MG. Health-related quality-of-life effects of watchful waiting re-evaluated in SPCG-4. *Nat Clin Pract Urol*. 2009;6:124-125.
104. Andriole GL, Levin DL, Crawford ED, et al. Prostate Cancer Screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: findings from the initial screening round of a randomized trial. *J Natl Cancer Inst*. 2005;97:433-438.
105. Auvinen A, Maattanen L, Finne P, et al. Test sensitivity of prostate-specific antigen in the Finnish randomised prostate cancer screening trial. *Int J Cancer*. 2004;111:940-943.
106. Hugosson J, Aus G, Bergdahl S, et al. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. *BJU Int*. 2003;92(suppl 2):39-43.
107. Kwiatkowski M, Huber A, Stamm B, et al. Features and preliminary results of prostate cancer screening in Canton Aargau, Switzerland. *BJU Int*. 2003;92(suppl 2):44-47.
108. Maattanen L, Hakama M, Tammela TL, et al. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. *Br J Cancer*. 2007;96:56-60.
109. Makinen T, Tammela TL, Stenman UH, et al. Family history and prostate cancer screening with prostate-specific antigen. *J Clin Oncol*. 2002;20:2658-2663.
110. McLernon DJ, Donnan PT, Gray M, Weller D, Sullivan F. Receiver operating characteristics of the prostate specific antigen test in an unselected population. *J Med Screen*. 2006;13:102-107.
111. Schroder FH. Detection of prostate cancer: the impact of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Can J Urol*. 2005;12(suppl 1):2-6; discussion 92-93.
112. Shim HB, Lee SE, Park HK, Ku JH. Digital rectal examination as a prostate cancer-screening method in a country with a low incidence of prostate cancer. *Prostate Cancer Prostatic Dis*. 2007;10:250-255.
113. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). *BJU Int*. 2003;92(suppl 2):48-54.
114. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2006;98:529-534.
115. Bunker CH, Patrick AL, Konety BR, et al. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: the Tobago Prostate Cancer Survey. *Cancer Epidemiol Biomarkers Prev*. 2002;11:726-729.
116. Hosseini SY, Moharramzadeh M, Ghadian AR, et al. Population-based screening for prostate cancer by measuring total serum prostate-specific antigen in Iran. *Int J Urol*. 2007;14:406-411.
117. Giri VN, Beebe-Dimmer J, Buyyounouski M, et al. Prostate cancer risk assessment program: a 10-year update of cancer detection. *J Urol*. 2007;178:1920-1924; discussion 1924.
118. Catalona WJ, Antenor JA, Roehl KA, Moul JW. Screening for prostate cancer in high risk populations. *J Urol*. 2002;168:1980-1983; discussion 1983-1984.
119. Gronberg H, Damber L, Damber JE. Familial prostate cancer in Sweden. A nationwide register cohort study. *Cancer*. 1996;77:138-143.
120. Etzioni R, Cha R, Cowen ME. Serial prostate specific antigen screening for

prostate cancer: a computer model evaluates competing strategies. *J Urol*. 1999;162: 741-748.

121. Gulati R, Inoue LYT, Katcher J, Etzioni R. Calibrating disease progression models using population data: a critical precursor to policy development in cancer control. *Biostatistics*. In press.
122. Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. *JAMA*. 2000;284: 1399-1405.
123. Crawford ED, Pinsky PF, Chia D, et al. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. *J Urol*. 2006;175:1286-1290; discussion 1290.
124. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. *JAMA*. 1997;277:1456-1460.
125. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA*. 1992;267: 2215-2220.
126. Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst*. 2006;98:1521-1527.
127. Ankerst DP, Miyamoto R, Nair PV, et al. Yearly prostate specific antigen and digital rectal examination fluctuations in a screened population. *J Urol*. 2009;181: 2071-2075; discussion 2076.
128. Ulmert D, Serio AM, O'Brien MF, et al. Long-term prediction of prostate cancer: prostate-specific antigen (PSA) velocity is predictive but does not improve the predictive accuracy of a single PSA measurement 15 years or more before cancer diagnosis in a large, representative, unscreened population. *J Clin Oncol*. 2008;26:835-841.
129. Vickers AJ, Wolters T, Savage CJ, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. *Eur Urol*. 2009 Aug 7. [Epub ahead of print].
130. Vickers AJ, Savage C, O'Brien MF, Lilja H. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J Clin Oncol*. 2009;27:398-403.
131. Young HH. The early diagnosis and radical cure of carcinoma of the prostate. A study of fifty cases and presentation of a radical operation. *JAMA*. 1906;XLVI:699a-704.
132. Young HH, Davis DM. Young's Practice of Urology. Philadelphia, PA: W. B. Saunders; 1926.
133. Mettlin C, Dodd GD. The American Cancer Society guidelines for the cancer-related checkup: an update. *CA Cancer J Clin*. 1991;41:279-282.
134. Mettlin C, Jones G, Averette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: prostate and endometrial cancers. *CA Cancer J Clin*. 1993;43:42-46.
135. Friedman GD, Hiatt RA, Quesenberry CP Jr, Selby JV. Case-control study of screening for prostatic cancer by digital rectal examinations. *Lancet*. 1991;337:1526-1529.
136. Gosselaar C, Roobol MJ, Roemeling S, et al. Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Prostate*. 2006;66:625-631.
137. Schroder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst*. 1998;90:1817-1823.
138. Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. *Urology*. 1995; 45:70-74.
139. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), *Rotterdam Eur Urol*. 2008;54:581-588.
140. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. *Urology*. 2006;68:1263-1267.
141. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. *JAMA*. 1997;277:1452-1455.
142. Eyre SJ, Ankerst DP, Wei JT, et al. Validation in a multiple urology practice cohort of the Prostate Cancer Prevention Trial calculator for predicting prostate cancer detection. *J Urol*. 2009;182:2653-2658.
143. Parekh DJ, Ankerst DP, Higgins BA, et al. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. *Urology*. 2006;68: 1152-1155.
144. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302:1685-1692.
145. Babaian RJ, Johnston DA, Naccarato W, et al. The incidence of prostate cancer in a screening population with a serum prostate specific antigen between 2.5 and 4.0 ng/mL: relation to biopsy strategy. *J Urol*. 2001;165:757-760.
146. Ankerst DP, Groskopf J, Day JR, et al. Predicting prostate cancer risk through incorporation of prostate cancer gene 3. *J Urol*. 2008;180:1303-1308; discussion 1308.
147. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection. *CA Cancer J Clin*. 2001;51:38-75; quiz 77-80.
148. von Eschenbach A, Ho R, Murphy GP, Cunningham M, Lins N. American Cancer Society guideline for the early detection of prostate cancer: update 1997. *CA Cancer J Clin*. 1997;47:261-264.
149. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149:185-191.
150. Greene KL, Albertsen PC, Babaian RJ, et al. Prostate specific antigen best practice statement: 2009 update. *J Urol*. 2009;182: 2232-2241.
151. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA*. 2001; 285:2750-2756.
152. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA*. 2001; 285:2987-2994.
153. Walter LC, Bertenthal D, Lindquist K, Konety BR. PSA screening among elderly men with limited life expectancies. *JAMA*. 2006;296:2336-2342.
154. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *JAMA*. 2003;289: 1414-1420.