

Carcinoma of the Prostate: Overview of the Most Common Malignancy in Men

Culley C. Carson III, MD

In the United States and North Carolina carcinoma of the prostate is the most common non-cutaneous malignant process and second most common cause of cancer death among United States men. Since carcinoma of the prostate strikes middle-aged and elderly men and usually has a prolonged progression, the controversy regarding the health effects, treatment, survival, and, most importantly, screening continues throughout the medical literature. Because of this prolonged course and the difficulty with identifying the most indolent tumors, it has been widely suggested that prostate cancer is over diagnosed, as many men may live with prostate cancer with no effect on either their quality of life or ultimate longevity.

More than 230,000 men are diagnosed with prostate cancer in the United States annually. Of these, more than 30,000 die of their disease. Mortality from prostate cancer is, therefore, second only to lung cancer for men in the United States.¹ The possibility of an American man acquiring prostate cancer during his lifetime is approximately 15%. Of great importance, however, is the fall in prostate cancer mortality witnessed since 1994. Similarly, the incidence of prostate cancer in all populations has begun to decline, with the initial decline beginning in 1993. This decline is observed in both white and black patients.¹ While the etiology of carcinoma of the prostate remains elusive, some associated risk factors have been identified.

Risk Factors

Genetic influences may determine the risk of carcinoma of the prostate in some men. Indeed men with first-degree male relatives with prostate cancer have more than a two-fold increase in their incidence of prostate cancer, and men with two or three first-degree relatives with carcinoma of the prostate may have as high as a five-to-ten fold increased risk.

Approximately 10-12% of prostate cancer cases are genetically influenced, and these most often manifest as prostate cancer in patients under age 60. This genetic increase is most marked in African American men. The highest risk for prostate cancer for African American men is seen in eastern North Carolina.² The reason for the high prevalence of prostate cancer remains controversial. Men living in Africa have one of the lowest prevalences of prostate cancer in the world. Diet may have an influence, as diets high in saturated fat have been associated with increased risk for prostate cancer, while antioxidants, such as selenium, lycopenes, and vitamin E, have been reported to decrease risk.

“...it has been suggested that the PSA threshold for biopsy of 4.0 ng/ml should be lowered. Such lowering, however, will increase the number of biopsies performed...”

Indeed, the lifestyle trait in United States men that is most highly associated with both the incidence and mortality of prostate cancer is diet. Diets high in meat with high animal fat and low levels of fruits and vegetables appear to be associated with higher risks and mortality from prostate cancer.³ A prospective study of more than 50,000 men reporting diet and associated risk of prostate cancer demonstrated that red meat consumption was highly associated with carcinoma of the prostate.^{3,4} Studies have also demonstrated decreased prostate cancer among men consuming the antioxidant, selenium, and vitamin E.⁴ A current, ongoing study (SELECT) further elucidates this association.⁵ Because of the many basic science and epidemiologic studies that suggest there is decreased prostate cancer prevalence with the intake of antioxidants, it appears that oxidative stresses may contribute to the genesis of prostate

Culley C. Carson III, MD, is Rhodes Distinguished Professor and Chief, Division of Urology, Department of Surgery, School of Medicine, UNC. He can be reached at carson@med.unc.edu or CB# 7235, Chapel Hill, NC 27599-7235. Telephone: 919-966-9144.

cancer. These oxidants, in addition to diet, may be produced by environmental exposures and inflammation. Indeed androgens (steroid hormones, such as testosterone) associated with prostate cancer may increase oxidant effects in prostate cancer cells.⁶

Increasing evidence suggests that chronic inflammatory processes may have an etiologic role in human cancers, including prostate cancer.⁷ While the symptoms of inflammation or infection in the prostate are uncommon preceding the diagnosis of prostate cancer, radical prostatectomy specimens often demonstrate evidence for chronic inflammatory conditions. Although the association of these prostatic conditions continues to strengthen, no specific etiology has been defined. Inhibition of GSTP1 gene expression, which encodes glutathione S-transferase capable of cell damage from oxidant stress, and is frequently found in prostate cancer cells. Lesions of proliferative, inflammatory atrophy with activated inflammatory and epithelial cells may be precursors to prostatic carcinoma.⁷ Clinically, other non-specific inflammatory markers, such as C-reactive protein also have been associated with rising PSA levels and prostate cancer.⁸

Prostate Cancer Prevention

The fact that prostate cancer occurs in such high numbers of men and later in life in addition to evidence suggesting environmental influences in its etiology, chemoprevention has long been discussed and investigated. Prostate cancer prevention, if simple and well tolerated, would significantly limit the financial costs of screening and treatment, as well as, the psychological cost and morbidity and, ultimately, the mortality from prostate cancer of a large portion of the 30,000 or more men who die each year from this difficult disease. Because it is well known that males with low androgen levels have a decreased prevalence for prostate cancer (and eunuchs rarely are afflicted with prostate cancer), androgen manipulation is a natural target for prostate cancer prevention.

Certain Pharmaceuticals May Help Prevent Prostate Cancer

The Prostate Cancer Prevention Trial (PCPT) was the first large population-based trial to test chemoprevention in men with carcinoma of the prostate.⁹ This study, begun in 1993, accrued more than 18,000 men over age 55 with normal digital rectal examination (DRE) and prostate-specific antigen (PSA) values of less than or equal to 3.0 ng/ml. Because men with congenital deficiency of Type II, 5 alpha reductase^a do not suffer from either benign prostatic hyperplasia (BPH)—enlargement of the prostate or prostate cancer, Finasteride (a pharmacologic agent designed to block Type II, 5 alpha reductase) was used in

this trial. Men were randomized into two groups: (1) a placebo group or (2) a treatment group that took 5 mg of Finasteride each day for seven years. Subjects in both groups received a biopsy during the study if any of the following three indications occurred: (1) PSA level exceeded 4.0 ng/ml, (2) digital rectal examination was abnormal, or (3) PSA values rose significantly with Finasteride. Subjects who completed the seven-year study without indication received an end-of-study biopsy. Because the National Institutes of Health (NIH) Data Safety and Monitoring Committee identified a substantial reduction in risk among subjects taking Finasteride, the study was concluded 15 months prior to its scheduled end date. Once analyzed, data from this study demonstrated a reduction in the prevalence of prostate cancer by 24.8% in patients randomized to Finasteride. However, a larger percentage of subjects treated with Finasteride (6.4%) were found to have more severe malignant tumors (Gleason scores^b of 7-10) than subjects in the placebo group (5.1%). While sexual side effects were experienced by patients in the Finasteride arm, urinary symptoms (lower urinary tract symptoms) were more common in the placebo group. Although researchers found that a reduction in prostate cancer risk among patients treated with Finasteride was present in subjects who received biopsies due to the three indications and to those who completed the study without indication, there were equal numbers of deaths due to prostate cancer in each group. While this study continues to be controversial, and the increased incidence of higher-grade cancers in the Finasteride-treated men appears to be explained by changes in prostate size and tumor interpretation, the PCPT trial is the first convincing demonstration that prostate cancer can be prevented by a tolerable oral medication without significant adverse events.

Prostate Cancer Screening

Because prostate cancer rarely causes early symptoms, the diagnosis of prostate cancer is best performed by physical examination and laboratory testing. Digital rectal examination (DRE) has long been the cornerstone for the diagnosis of carcinoma of the prostate. Areas of palpable induration (hardness), firmness, and asymmetry of the prostate gland strongly suggest the presence of carcinoma. While BPH produces prostate enlargement, induration of the posterior prostatic lobe strongly suggests a diagnosis of prostate cancer. However, cancers found on DRE are more often of advanced pathologic stage; a diagnosis before nodules are formed improves prognosis.¹⁰ DRE alone may miss as many as 45% of cancers subsequently identified by prostate biopsy following observation of rising PSA.¹¹ Abnormal DRE appears to

a Type II, 5 alpha reductase is an enzyme responsible for regulating the conversion of testosterone to dihydrotestosterone (DHT) in the liver.

b The Gleason scoring system grades prostate cancer patterns from 1 (well differentiated malignancy) to 5 (poorly differentiated malignancy). The Gleason combined score or grade is then computed by adding the most abundant Gleason grade pattern to the second most abundant Gleason grade pattern to obtain a Gleason sum. This score from 2 to 10 has been demonstrated to be accurate in predicting patient outcomes. Gleason scores of 2 to 6 respond best to primary treatment with significantly lower recurrence rates than Gleason scores of 8 to 10. In a group of more than 8,000 men diagnosed between 1989 and 2001, men with low-risk histories rose from 29.8% to 45.3%.²⁷

be dependent upon PSA level, patient race, and age. There is a higher predictive value for DRE in African American men, older men, and men with higher PSA levels.¹²

PSA testing has significantly changed the diagnosis of prostate cancer since its introduction in the early 1990s. PSA is an enzyme (human kallikrein serine protease) that is encoded by the genes of chromosome 19. PSA is produced predominantly by the columnar secretory cells of the prostate and is present in high levels in the ejaculate. PSA first becomes detectable in the serum during puberty when steroid hormone levels increase. As patients age, their PSAs continue to rise, and there is an age-associated PSA value. Similarly, PSA rises with prostate volume and can be used as a surrogate marker for prostate size. Baseline PSAs in patients without prostatic malignancies are higher in African American men than in white men.¹³

Produced by the prostate in both benign and malignant conditions, PSA is a more accurate *prostate marker* than a *prostate cancer marker*. Any condition that produces prostate inflammation or disrupts prostate tissue will produce an elevation in PSA. This includes benign conditions such as BPH, prostatitis, urinary retention, prostatic infarction, prostate biopsy, and vigorous prostatic massage. While these inflammatory and surgical conditions produce changes in PSA, studies of ejaculation prior to PSA determination have not demonstrated convincingly a change in PSA level.¹⁴ The 5 alpha reductase inhibitors, such as Finasteride and Dutasteride, reduce PSA levels to approximately 50% of baseline by six to 12 months following treatment.¹⁵ While the use of PSA screening in identifying prostate cancer continues to be controversial, there are many studies that have demonstrated the importance of PSA testing to diagnose prostate cancer. Because PSA is more sensitive and specific than DRE alone, the detection of prostate cancer with a combination

biopsies, efforts have been made to improve the accuracy of PSA determinations. Newer tests, such as the free and total PSA ratio,^c prostate specific membrane antigen (PSMA),^d complexed PSA,^e and others, are under investigation for improving PSA accuracy. Current practice, however, can employ *PSA density*, an adjustment in PSA level to account for prostate volume. Adjusting the PSA level for prostate volume permits increased accuracy. More commonly, however, *PSA velocity* is used. PSA velocity measures changes in serum PSA values over time.¹⁷

PSA Threshold for Prostate Biopsy

Controversy continues regarding the interpretation of PSA values and the threshold for which a biopsy is required. The ideal PSA value for differentiating prostate cancer from benign prostates remains elusive. The standard PSA value differentiating normal from abnormal prostates of 4.0 ng/ml was established in 1990.¹⁸ Because many prostate cancers can be present and even significant at PSA levels below 4.0 ng/ml, investigation has focused on the percentage of cancers missed at levels below 4.0. In the PCPT trial, end-of-study biopsies were correlated to PSA levels. Of 2,950 men biopsied, 449 (15.2%) were found to have prostate cancer with PSA levels less than 4.0. Of those men with PSAs between 3.1 and 4.0, 26.9% had positive biopsies, of which 25% were high-grade malignancies. Even among patients with PSA levels less than 0.5 ng/ml, 6.6% had positive biopsies at end-of-study. These data strongly suggest that PSA is better when focused on *density* or, more conveniently, *velocity* to differentiate those patients at high risk for prostate cancer and positive biopsies.¹⁹ Based on this study, it has been suggested that the PSA threshold for biopsy of 4.0 ng/ml should be lowered. Such lowering, however, will increase the number of biopsies performed. The controversy continues.

PSA velocity appears to be more helpful in a clinical setting. Outcome studies have demonstrated that PSA velocity of greater than 2.0 ng/ml per year is associated with significantly higher death rates from prostate cancer when compared with lower PSA velocities.^{20,21} Thus, annual PSAs in patients at risk are important for the identification and treatment of carcinoma of the prostate. Because a single PSA value may be less accurate, PSA velocity, rise in PSA over time, may be a better indicator for prostate biopsy. In a prospective screening study, a velocity threshold of 0.75 ng/ml per year was used to differentiate patients. Using this threshold of velocity, 47% of men with velocities greater than 0.75 ng/dl were diagnosed with prostate cancer compared with only 11% of those with velocities less than 0.75 ng/ml.²² In a European study where men were followed for four years, PSA velocity was 0.62 ng/dl per year for men with prostate cancer compared with

“Because a single PSA value may be less accurate, PSA velocity, rise in PSA over time, may be a better indicator for prostate biopsy.”

of PSA and DRE has a significantly higher predictive value than either study alone. In fact, PSA values in screening populations have the highest predictive value.¹¹ Longitudinal follow-up population studies using banked serum samples have reported a five-year lead time of prostate cancer diagnosis from PSA levels with 4.0 ng/ml as initial cutoffs.¹⁶ Because PSA can be elevated by benign conditions, and elevations in PSA trigger prostate

c The free and total PSA ratios are used to measure the percentage of free PSA relative to the total amount of PSA in a patient's blood sample.

d Prostate specific membrane antigen is a PSA produced by the membrane of prostate cancer cells.

e Complexed PSA is a test that measures the level of PSA, which has been complexed or bound with a certain protein (alpha-1-antichymotrypsin) in a patient's blood sample.

0.46 ng/dl per year for those without cancer. PSA doubling time was 5.1 years with prostate cancer and 6.1 years with negative biopsies.²³ In men with low PSAs, however, PSA velocity appears to be less accurate in selecting men for prostate biopsy.²⁴ Thus, PSA change over time appears to be more valuable than static values in selecting which men will require prostate biopsy.

Biopsy

Once a suspicious PSA has been identified by value, density, or velocity, a transrectal, ultrasound-guided prostate biopsy is the most accurate technique for identifying prostate cancer. This outpatient procedure is usually performed using local anesthetic injection of the periprostatic nerves and can be done in an office setting. Although transrectal ultrasound typically does not demonstrate specific areas of suspicion, the procedure permits prostate targeting, which allows accurate sampling of all portions of the prostate. For repeat biopsies where initial malignancy is not identified and PSA continues to rise, careful sampling of the transition zone is important to eliminate less common foci of prostate malignancy.

Biopsies of the prostate are safe and have a low incidence of morbidity. In a series of more than 5,800 prostate biopsies, fewer than 0.5% of men required hospitalization; however, only 2.6% of men reported self-limiting hematuria (blood in urine) and occasional 50.4% hematospermia (blood in semen) early following biopsy.²⁵

The diagnosis of prostate cancer, once made through transrectal needle biopsy of the prostate, is graded by histopathology using the previously mentioned Gleason grading system.²⁶ Staging of prostate cancer is performed using the standard TNM system (see Table 1). TNM describes the extent of the primary *tumor* (T stage), the absence or presence of spread to nearby lymph *nodes* (N stage), and the absence or presence of distant spread, or *metastasis* (M stage). Staging can be performed pre- and post-treatment, and the most definitive staging occurs following radical prostatectomy. With the advent of PSA testing, there has been a dramatic shift to diagnoses at lower stages and, thus, more likelihood of organ-confined cancer.²⁷ While imaging studies can be helpful in patients with extensive carcinoma of the prostate, further staging assistance using cross sectional imaging of the pelvis by computerized tomography or magnetic resonance imaging have not added to the accuracy of cancer staging.

Treatment of Localized Prostate Cancer

Treatment of localized prostate cancer requires significant discussion with patients regarding outcomes, morbidity, mortality, and requirement for treatment. Choices include: watchful waiting, radical prostatectomy, interstitial brachytherapy (radioactive seed implantation), and external beam radiation therapy. Choice of treatment alternative is based upon the individual, his family, and prognostic factors, such as stage, grade, and the patient's general physical condition. Over the past decade with the use of PSA, treatment of prostate cancer patients has decreased in average patient age and average stage. During this same time, surgery and radiation therapy for prostate cancer has significantly improved. Radiation therapy applied with conformal external beam techniques or the implantation of small radioactive seeds using brachytherapy has improved the efficacy of cancer control and decreased treatment morbidity. The combination of these treatment modalities with androgen deprivation therapy using luteinizing hormone-releasing hormone (LHRH) agonist^f treatment has further improved outcomes.²⁸

Radical prostatectomy has likewise improved markedly over the past two decades. The introduction of the bilateral nerve sparing radical prostatectomy in the early 1990s has improved continence levels and potency post-radical prostatectomy, while preserving cancer control rates and limiting positive margin rates. The introduction of laparoscopy and robot-assisted laparoscopic prostatectomy has further improved the morbidity from radical prostatectomy. With these inventions, the hospitalization time of patients undergoing modern robotic-assisted laparoscopic prostatectomy has declined from more than seven days in the mid 1990s to one day or less in the 21st century.

Table 1.
Clinical TNM Staging of Prostate Cancer

T1	Cancer is clinically inapparent, not palpable or visible by imaging
T1a	Incidental histologic finding, less than or equal to 5% of resected tissue
T1b	Incidental histologic finding, greater than 5% of resected tissue
T1c	Tumor indetified by needle biopsy, for any reason (e.g., elevated PSA)
T2	Palpable or visible tumor, confined within the prostate
T2a	Less than or equal to one half of one lobe
T2b	One lobe
T2c	Both lobes
T3	Tumor extends through the capsule
T3a	Extracapsular extension, unilateral or bilateral
T3b	Seminal vesicle involvement
T4	Tumor is fixed or invades adjacent structures
T4a	Tumor invades bladder neck, external sphincter or rectum
T4b	Tumor Invades to the floor and/or the wall of the pelvis

^f Luteinizing hormone-releasing hormone is a naturally occurring hormone that controls sex hormones in both men and women. LHRH agonist is a compound similar to LHRH (luteinizing hormone-releasing hormone) that serves in a manner similar to LHRH to control the same sex hormones.

This decreased hospitalization time has been accompanied with improved potency and continence rates, decreased blood loss, and decreased mortality rates. In a landmark randomized study comparing radical prostatectomy with watchful waiting with median 8.2 year follow-up, there was a 44% decrease in cancer death, 40% decrease in metastatic disease, and 67% decrease in disease progression.²⁹ Thus, radical prostatectomy appears to reduce disease-specific mortality, overall mortality, and risks of metastases and local progression.

Because prostate cancer is associated with slow progression and few deaths within ten years of diagnosis, men with life expectancies of less than ten years or significant comorbidities may be safely and effectively managed with a watchful waiting program. Watchful waiting generally consists of follow-up with regular PSA, monitoring PSA velocity, symptomatic treatment for obstructive uropathy and lower urinary tract symptoms (LUTS), and repeat biopsy if necessary.³⁰

Systemic treatment of progressive prostate cancer continues to evolve and improve. The association of prostate cancer control with castrate levels⁹ of testosterone was first identified by Huggins et al. in the 1940s.³¹ The use of physical castration was widely used until the introduction and wide acceptance of luteinizing hormone releasing hormone agonist (LHRH). These agents, which rapidly produce castrate levels of testosterone, are associated with prostate cancer suppression. Androgen deprivation therapy, therefore, appears efficacious irrespective of method of treatment. Current depo preparations allow LHRH agonist to be administered monthly, or every three or four months. Implantable devices permit yearly changes of LHRH implants. While androgen deprivation therapy is associated with the side effects of castration including: hot flashes, osteoporosis, loss of libido, and decreased muscle mass and strength, prostate cancer control is quite satisfactory. In fact, survival can be increased by many years (average 3.5 years). Timing of initiation of androgen deprivation therapy, however, has been controversial. Since recent studies have demonstrated a prolongation of survival, many feel that androgen deprivation therapy should be initiated with initial detections of PSA rise.³² Due to the significant morbidity, including an increase in osteoporosis and fracture risk, however, patients and physicians may choose to delay androgen deprivation therapy to preserve sexual function, muscle mass, and bone health.³³

Newer concepts in LHRH agonist therapy with intermittent therapy are being utilized and investigated throughout the world. With this technique, testosterone is decreased using an LHRH agonist to castrate levels and until PSA response is observed. LHRH agonists are then withdrawn until the PSA value again climbs. Survival outcomes and effectiveness of treatment of this approach remain controversial.

Other methods for treatment of advanced prostate cancer have now progressed to agents beyond androgen deprivation. Newer chemotherapeutic agents, such as mitoxantrone and paclitaxel, have improved the outcomes of systemic chemotherapy.³⁴ These agents, which are currently reserved for patients with systemic malignancy unresponsive to androgen deprivation, provide some promise for improving survivals and prostate cancer control in patients with advanced disease.

Future Directions

Over the past decade, PSA testing, screening, and evaluation has revolutionized the diagnosis and treatment of prostate cancer. Indeed, urologists in clinical practice in the United States have observed a significant shift in stage of disease at diagnosis with few patients presenting in the 21st century with locally advanced or metastatic prostate cancer. This "stage shift" has permitted better diagnosis and more effective treatment of those patients at risk. Unfortunately, however, PSA as a prostate marker and prostate-specific marker is an imperfect screening tool. Current research on newer, more specific markers continues; however, PSA with modified use that incorporates measures of PSA density and velocity remain the mainstay for diagnosis. Newer imaging modalities are being developed to localize prostate cancers with the goal of localized treatment. Treatment of localized prostate cancer continues to be best carried out with radiation therapy or radical prostatectomy.

Modifications in radical prostatectomy over the past two decades, to include nerve sparing, laparoscopic approaches, and robotically assisted laparoscopic approaches, have improved morbidity, mortality, and outcomes. The United States' decrease in prostate cancer mortality over the past decade may, arguably, be a result of this improved diagnosis and treatment. Better serum diagnostic testing and imaging studies are being investigated in an effort to improve the specificity of diagnosis. Similarly, studies to identify tumors that are biologically aggressive and important, versus those that are more indolent, are ongoing. Identification of biologically less active and more indolent tumors may increase the number of men eligible for safe watchful waiting and active surveillance. Active investigation into gene and vaccine therapy may assist in the treatment of men with locally advanced or metastatic cancer. Similarly, this sub-categorization of prostate malignancies may assist in identifying patients most in need of early androgen deprivation therapy. With the advances in systemic chemotherapy and post-operative radiation therapy, more patients with aggressive, advanced prostate malignancies can be effectively treated with expected increased survival and decreased morbidity. **NCMedJ**

g Castrate-level occurs when the levels of the body's testosterone drop 90-95%, which is consistent with the loss of the testicles.

REFERENCES

- 1 Centers for Disease Control and Prevention. Prostate Cancer: The Public Health Perspective. 2003 Fact Sheet. Available at:

<http://www.cdc.gov/cancer/prostate/prostate.htm>. Accessed March 23, 2006.

- 2 Mohler JL, Gaston KE, Moore DT, Schell MJ, Cohen BL, Weaver C, Petrusz P. Racial differences in prostate androgen levels in men with clinically localized prostate cancer. *J Urol* 2004;171:2277-2280.
- 3 Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 1993;85:1571-1579.
- 4 Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ. Prospective study of plasma fatty acids and risk of prostate cancer. *J Natl Cancer Inst* 1994;6:281-286.
- 5 Hoque A, Albanes D, Lippman SM, Spitz MR, Taylor PR, Klein EA, Thompson IM, Goodman P, Stanford JL, Crowley JJ, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer Causes Control* 2001;12:627-633.
- 6 Ripple MO, Henry WF, Schwarze SR, Wilding G, Weindrich R. Effect of antioxidants on androgen-induced AP-1 and NF-kappaB DNA-binding activity in prostate carcinoma cells. *J Natl Cancer Inst* 1999;91:1227-1232.
- 7 Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. *J Urol* 2004;172:S6-11;discussion S11-12.
- 8 Lehrer S, Diamond EJ, Mamkin B, Droller MJ, Stone NN, Stock RG. C-reactive protein is significantly associated with prostate-specific antigen, metastatic disease in prostate cancer. *BJU Int* 2005;95:961-962.
- 9 Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215-224.
- 10 Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemacker R, Rietbergen J, Kranse R. 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.
- 11 Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL, et al. Comparison of digital rectal examination, serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283-1290.
- 12 Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. *J Urol* 1999;161:835-839.
- 13 Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for prostate-specific antigen in black men. *N Engl J Med* 1996;335:304-310.
- 14 Stenner J, Holthaus K, Mackenzie SH, Crawford ED. The effect of ejaculation on prostate-specific antigen in a prostate cancer-screening population. *Urology* 1998;51:455-459.
- 15 Carson C III, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. *Urology* 2003;61:2-7.
- 16 Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. *Urol Clin North Am* 1997;24:333-338.
- 17 Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, Fozard JL and Walsh PC. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215-2220.
- 18 Cooner WH, Mosley BR, Rutherford CL, Jr., Beard JH, Pond HS, Terry WJ, Igel TC, Kidd DD. 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.
- 19 Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239-2246.
- 20 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351:125-135.
- 21 Schroder FH, Roobol M. Prostate-specific antigen levels in the United States: Implications of various definitions for abnormal. *Eur Urol* 2006;49:412-413.
- 22 Smith DS, Catalona WJ. Rate of change in serum prostate specific antigen levels as a method for prostate cancer detection. *J Urol* 1994;152:1163-1167.
- 23 Raaijmakers R, Wildhagen MF, Ito K, Paez A, de Vries SH, Roobol MJ, Schroder FH. Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. *Urology* 2004;63:316-220.
- 24 Roobol MJ, Kranse R, de Koning HJ, Schroder FH. Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: Results of second screening round of ERSPC (ROTTERDAM). *Urology* 2004;63:309-313; discussion 313-315.
- 25 Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002;60:826-830.
- 26 DeMarzo AM, Nelson WG, Isaacs WB, Epstein JI. Pathological and molecular aspects of prostate cancer. *Lancet* 2003;361:955-964.
- 27 Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, Klocker H, Mikolajczyk SD. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. *J Urol* 2004;171:2239-2244.
- 28 D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA* 2004;292:821-827.
- 29 Bill-Axelsson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, Busch C, Nordling S, Garmo H, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977-1984.
- 30 Kirby RS, Fitzpatrick JM. Radical prostatectomy vs watchful waiting. *BJU Int* 2005;96:953-954.
- 31 Huggins C, Hodges C. Studies on Prostate Cancer II: The effects of castration on advanced carcinoma of the prostate gland. *Arch Surg* 1941;43:209-222.
- 32 Studer UE, Hauri D, Hanselmann S, Chollet D, Leisinger HJ, Gasser T, Senn E, Trinkler FB, Tscholl RM, Thalmann GN, et al. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: Results of the randomized trial SAKK 08/88. *J Clin Oncol* 2004;22:4109-4118.
- 33 Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154-164.
- 34 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512.