Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOT SHEET

JUNE 2004

OUTLOOK GOOD FOR MOST PROSTATE CANCER PATIENTS

HealthDay - May 10, 2004

The outlook for most men diagnosed with prostate cancer is good, especially for those who have surgery to remove the gland, according to new studies just reported at the annual meeting of the American Urological Association.

A study of patients treated at Memorial Sloan-Kettering Cancer Center in New York City found "this operation has the ability to cure three of every four men, 15 years after the diagnosis," said Dr. Fernando J. Bianco, Jr., an oncology fellow at the center who delivered the report.

Even for men in whom the cancer recurs after surgery, "the chances that they will make it to 15 years is very high," Bianco said.

Recurrence is indicated by a rising level of prostate-specific antigen (PSA), a protein produced by both normal and cancerous prostate tissue. However, the PSA test is not the best and only indicator of prostate cancer

"Even for those who developed a rising PSA after radical prostatectomy, the probability of death from cancer at 10 and 15 years was 23 percent and 38 percent,"

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BLOOD SCREEN MAY HELP CANCER PATIENTS THWART RADIATION SIDE EFFECTS, SAY STANFORD RESEARCHERS

Radiation therapy is a powerful tool for treating cancer, but for 5 percent of patients that lifesaving treatment comes with serious side effects. Screening blood for the activity level of 24 genes may identify those patients most likely to react badly to radiation, say Stanford University School of Medicine researchers. With this tool, doctors may soon be able to tailor-make treatments for individual patients.

"We've been treating cancer patients as if one treatment fits all," said Gilbert Chu, MD, PhD, professor of medicine and of biochemistry who led the study. "Cancer patients need to be treated for their particular cancer and their own bodies."

Some factors are a tip-off that a patient may have an unusually severe reaction to radiation. Patients who have autoimmune diseases such as diabetes or lupus, or who have certain rare genetic diseases need to be monitored carefully or avoid radiation altogether.

Even beyond these obvious signs, some patients suffer disfiguring, disabling or extremely painful effects. These may include wounds that don't

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DIETARY BORON INTAKE MAY REDUCE THE RISK OF PROSTATE CANCER

Study finds that increased dietary boron intake may lower the risk of prostate cancer, but further large studies are needed to confirm this observation.

According to a study from the United States, "Boron affects human steroid hormone levels. Circulating testosterone and estradiol levels have been proposed to modify prostate cancer risk. However, the association between dietary boron intake and the risk of prostate cancer has not been evaluated by any epidemiological study."

"We explored the association between dietary boron intake and the risk of prostate cancer in the USA. Our analysis was based on data from the third National Health and Nutrition Examination Survey (NHANES III). Cross-sectional case-control study design was employed by comparing boron intake of 95 prostate cancer cases with that of 8,720 male controls," wrote Y. Cui and colleagues, University of California Los Angeles, School of Public Health.

"After controlling for age, race, education, smoking, body mass index, dietary caloric intake, and alcohol consumption, increased dietary boron intake was associated

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US TOO PUBLICATIONS

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Highlights from the 2004 AUA Annual Meeting

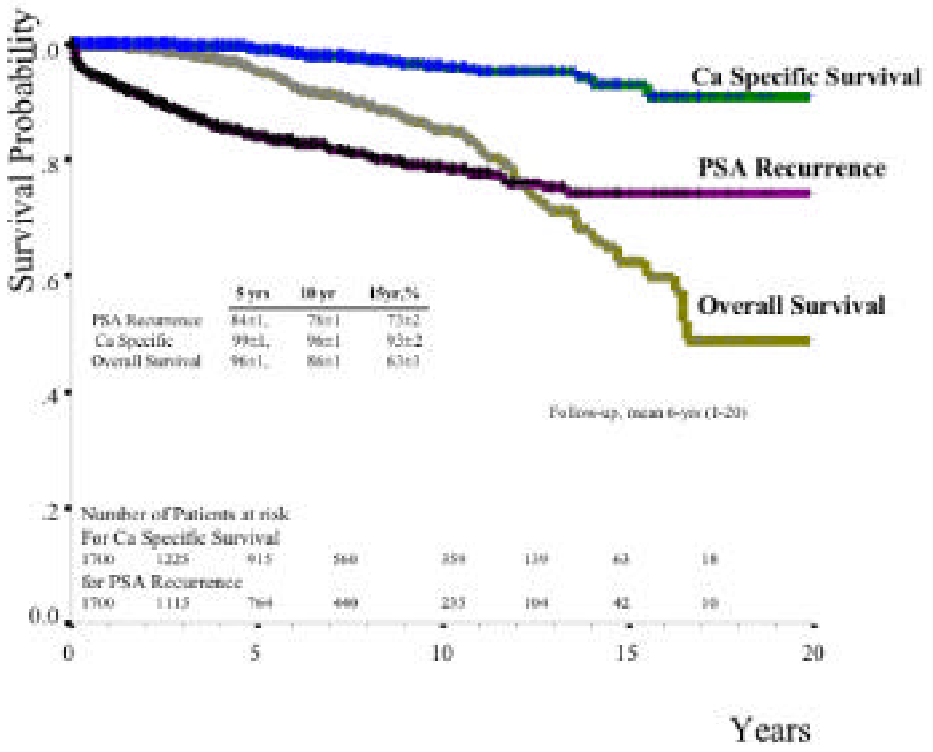
15-YEAR CANCER-SPECIFIC AND PSA-PROGRESSION FREE RATES AFTER RADICAL PROSTATECTOMY

Fernando J. Bianco Jr, Zohar A. Dotan, Michael W. Kattan, Paul A. Fearn, James A. Eastham, Peter T. Scardino. Memorial Sloan-Kettering Cancer Center, New York, NY

Introduction and Objective: Radical prostatectomy disrupts the natural history of prostate cancer. Indications for this procedure have augmented significantly with the stage-shift of this disease. We studied long-term cancer control rates and predictors after this surgery.

Methods: We studied 1700 patients with clinically localized newly diagnosed prostate cancer, without prior intervention, underwent radical prostatectomy with curative intent since 1983. The mean follow up was 6 years (1 to 20 years). Endpoints consisted of disease-progression and cancer-specific survival. Logistic-regression with time dependent covariate analysis was performed.

Results: 261 patients experienced disease-progression and were then followed a mean of 6.3 (1-15) yrs. At 5, 10 and 15 yrs 84%, 78% and 73% remained free of progression (Fig.), cancer-specific survival was 99%, 96% and 93%, respectively and overall survival was 96%, 86% and 63%. At 15 yr 79% of patients with a PSA =>10, 68% with pGleason 3+4, 51% with 4+3, 73% with focal and 42% with established ECE remained free of recurrence. At 10 yr 27% with pGleason 8-10, 30% with SVI and 17% with LN+ also were free of recurrence. Even for those who



developed a rising PSA after RP, the probability of death from cancer at 10 and 15 years was 23% and 38%.

Conclusions: RP provided excellent long term cancer control. At 15 yr only 7% had died of prostate cancer. Cancer control was remarkably good even for patients with adverse prognostic features.

COMPARISON OF RADICAL PROSTATECTOMY, RADIOTHERAPY, HORMONAL THERAPY, AND WATCHFUL WAITING FOR SCREEN-DETECTED PROSTATE CANCER: AN UPDATE

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Introduction and Objective: PSA screening has been widely used as an aid to early detection of prostate cancer. Early detection increases the opportunity for long-term progression-free survival. The selection of treatment for early-stage prostate cancer involves an evaluation of the effectiveness of the individual treatments weighed against the decrements they produce in the quality of life. The preferred management of patients with clinically localized prostate cancer is controversial. In this study, we update and evaluate results on progression-free survival rates in patients diagnosed with prostate cancer in a screening study who self-selected primary treatments.

Methods: We previously evaluated 3020 patients diagnosed with prostate cancer in a screening study from 1989 to 2001. We are currently evaluating 3564 patients diagnosed with prostate cancer through 2003. Treatments include radical prostatectomy, brachytherapy, external beam radiation therapy, hormonal therapy and observation. The follow-up protocol included PSA testing every six months and review of clinical and pathological records. Cancer progression was defined as PSA >0.2 ng/mL for surgery patients and three consecutive PSA rises for all other treatments.

Results: Results of % progressed and 7-year progression-free survival rates are shown in the table. These results are through 2002 and will be updated through 2004. The preliminary analysis of radical prostatectomy showed a 7-year progression-free survival rate of 87% for low-risk patients, 80% for intermediate-risk patients and 59% for high-risk patients, similar to previous results. Comparisons for non-surgical treatments are under analysis for data through 2004.

Conclusions: Radical prostatectomy and brachytherapy had similar progression rates that are lower than other treatments. However, assuming that all PSA rises that have not yet been twice verified will ultimately become progressions, RRP has a lower progression rate than other treatments with intermediate term follow-up.

7-year Survival Estimate Ranges (%)

Treatment	Median Follow-up Time (months)	Low Risk Group	Interm Risk roup	High Risk Group
Radical Prostatectomy	**68**	**87**	**80**	**59**
Brachytherapy	**42**	**90-98**	**74-83**	**41**
External Beam Radiation	**63**	**60-83**	**47-60**	**33-54**
Hormonal Therapy	**50**	**23-71**	**50-64**	**25-40**
Observation	**47**	**22-56**	**16-37**	**0**

RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY OF MEN WITH PROSTATE CANCER AND RISING PSA: EFFECTIVENESS OF A DIETARY SUPPLEMENT

Fritz H. Schröder, Monique J. Roobol, Egbert R. Boevé, Renée De Mutsert, Wendy Verwillegen, Sonja Zuidgeest, Mark F. Wildhagen, Ardy Van Helvoort. Erasmus University Medical Center, Rotterdam, Netherlands, St. Franciscus Gasthuis, Rotterdam, Netherlands, Numico Research, Wageningen, Netherlands, Numico Research Wageningen, Wageningen, Netherlands

Introduction and Objective: Diet is likely to be related to large differences in geographic distribution of clinically diagnosed prostate cancer (PC). Studies of primary prevention to investigate available epidemiological leads are difficult, very expensive and do not allow screening for compounds and dosages. - In the present study a dietary supplement is utilized in a setting of tertiary prevention in patients suffering from minimal recurrent PC identified by rising prostate-specific antigen (PSA).

Methods: 49 Patients with a history of PC and rising PSA (0.1-10.0 ng/ml) after radical prostatectomy (n=34) or radiotherapy (n=15) were randomized to a double-blind, placebo-controlled, crossover study of a dietary supplement after ethical approval of the protocol. Patients received the dietary supplement or placebo for 10 weeks each (2x2 tablets daily), separated by a 4-week wash-out period. The supplement contained soy isoflavones, lycopene, silymarin and antioxidants as main ingredients. Blood samples were taken at two-weekly intervals. Changes of PSA kinetics (PSA slope and doubling time) were the primary parameters of efficacy.

Results: Baseline age, BMI and serum PSA were 69.8 ± 7.1 yr., 26.4 ± 2.4 kg/m2 (mean ± SD) and 1.30

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FINAL RESULTS OF THE INITIAL AND SECOND PROSTATE CANCER SCREENING ROUND OF THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER (ERSPC, SECTION ROTTERDAM)

Monique J. Roobol, Stijn H. De Vries, Fritz H. Schröder. Erasmus Medical Centre, Rotterdam, Netherlands

Introduction and Objective: The second screening round of ERSPC (section Rotterdam, screening interval 4 years) will be completed in Dec. 2003. We assessed and compared the positive predictive values (PPV's ,sextant biopsy (SB)), cancer detection rates, predictors for biopsy outcome, screening and tumor characteristics of cancers detected at both screening rounds.

Methods: In the period Nov 1993 until Dec 1999, 19970 men were screened at the initial screening round. At the start the indication for SB was an abnormal DRE and/or TRUS and/or PSA >= 4.0 ng/ml. In November 1997 the screening protocol was simplified to a simple PSA cut-off (>= 3.0 ng/ml) as indication for SB. We compared 10191 men screened at initial screening and 5535 men screened at second (and initial) screening, according to the modified protocol. Predictors used for the multivariate analyses were log PSA, log Prostate volume (Vol), DRE, TRUS, age, positive family history (PFH), PSA velocity, previous negative biopsy (PNB).

Results:

Parameter	Initial screening	Second screening
% men with PSA >= 3.0	21.1	19.5
% men with PSA >= 10.0	2.5	1.4
PPV (n cancers/n biopsied)	29.2	17.6
Detection rate (n cancers/n screened)	5.3	4.4
Mean PSA (ng/ml)	6.8	4.4
Mean prostate volume (ml)	49.7	47.9
% previous biopsied	NA	30.4
Significant predictors for the presence of PC	PSA, Vol, DRE, TRUS, age, PFH	Vol, PNB
Tumor characteristics / Cancers (n)	541	241
Mean PSA (ng/ml)	9.9	4.3
Mean prostate volume (ml)	43.1	40.2
% previous biopsied	NA	17.4
% T3, T4	15.5	3.7
% Gleason >= 3+4	36.2	18.5

Conclusions: Although lower than at initial screening the cancer detection rate at the second screening round is substantial. Cancers detected at second screening are mostly found in men with no previous biopsy (82.6%), with PSA levels between 3.0 – 4.0 ng/ml (44%) and are more localized to the prostate. PSA and PSA velocity are no significant predictors for biopsy outcome at second screening, prostate volume and previous negative biopsy are (odds < 1.0). These findings show that screening tests used in the initial round are no longer predictive 4 years later. It may be more efficient to biopsy on the indication of a combination of predictors at a subsequent screening round(s), instead of using a fixed PSA threshold. The development of new test procedures (agents, algorithms) is desirable. Complete data of the second screening round will be presented.

EVIDENCE FOR PHARMACOLOGICAL CONTAMINATION OF HERBAL ERECTILE FUNCTION PRODUCTS WITH TYPE 5 PHOSPHODIESTERASE (PDE5) INHIBITORS

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Introduction and Objective: Complementary and alternative medicine (CAM) continues to gain an increasing role in the management of a variety of conditions. The advent of phosphodiesterase (PDE5) inhibitors has dramatically altered the management of erectile dysfunction (ED). It is not surprising that many marketed herbal products claim to have efficacy similar to PDE5 inhibitors without side effects or need for medical assessment. We set out to determine if marketed herbal preparations for the treatment of ED contained PDE5 inhibitors.

Methods: We purchased seven brands of marketed herbal products for the treatment of ED. Purchases were limited to oral tablets or capsules that claimed to improve erection quality if consumed prior to sexual activity and not on a daily basis.Each individual bottle was opened and 12 tablets/capsules were removed. These were then placed into light-shielded plastic containers and assigned a study number. Specimens were then shipped at room temperature to the University of British Columbia for high performance liquid chromatography (HPLC) analysis. Standards for sildenafil tadalafil and vardenafil were set by utilizing samples of respective tablets. A Waters 2695 Separations Module equipped with a Waters/Micromass ZQ2000 detector was used for quantitative analysis of sildenafil, tadalafil and vardenafil. Four tablets were measured for dosage range and three were performed in duplicate (ie: same sample twice).

Results: Significant contamination with sildenafil and tadalafil was detected in two out of 7 of the herbal preparations examined. Average sildenafil levels were 30.2mg/cap, (range,27.6mg to 31.3mg). Average tadalafil levels were 19.77mg/tablet, (range 18.0mg to 22.0mg). Significant levels were not detected in other samples, nor was vardenafil detected in any of the samples.

Conclusions: Pharmacologic concentrations of PDE5 inhibitors are present in some herbal products marketed to manage ED. Since these compounds are not natural, deliberate contamination of these products must be considered. Consumers and regulatory agencies must be aware of these findings as these agents have known fatal interactions with prevalently consumed drugs (e.g. nitrates). These findings also seriously challenge the concept of safety of CAM agents. Tighter regulation of CAM marketed preparations is recommended.

LONG-TERM OUTCOMES AMONG LOCALIZED PROSTATE CANCER SURVIVORS: HRQOL CHANGES 4 TO 8 YEARS FOLLOWING BRACHYTHERAPY, EXTERNAL RADIATION AND RADICAL PROSTATECTOMY

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Age-adjusted, Long-term (median 6.3 years) EPIC Domain Summary

HRQOL Domain	BT	3-D CRT	RP	Age-matched Control
Men				
Urinary Irritative	81†*	84	91	89
Urinary Incontinence	78†*	86†	80*	92
Sexual	28*	35†*	39*	63
Bowel	86†*	84†*	94	96†
Hormonal	87*	89	91	93

† Denotes significant change in HRQOL domain score from 2 to 6 years of median f/u (p=0.05)
* Denotes significant difference in HRQOL domain score at 6 yrs of median f/u vs. controls (p=0.05)

Introduction and Objective: Long-term, patient-report HRQOL, as well as HRQOL changes more than 2 years after brachytherapy (BT), 3-D conformal radiation (3-D CRT) and radical prostatectomy (RP) have not been characterized with validated QOL instruments. We sought to evaluate long-term HRQOL changes and outcomes during the transition from early to late survivorship after localized prostate cancer (CaP) therapy.

Methods: In 1999, we had used a validated instrument (EPIC) to measure HRQOL in a cohort of 1008 CaP patients (and age-matched control men) at a median follow-up of 2.6 years after BT, 3-D CRT or RP. In the current follow-up study, HRQOL for this cohort was re-assessed at a median follow-up 6.3 years (range 4-8 years). Generalized linear models were used to evaluate differences in HRQOL outcomes between each of the 3 treatment groups and age-matched controls.

Results: The overall response rate was 73%. EPIC domain summary scores are summarized in the table.

During the follow-up interval, the greatest improvement in HRQOL was for urinary irritative symptoms among BT patients ($p<0.001$). Nevertheless, long-term urinary irritative summary scores remained better for RP compared with BT ($p<0.01$) and 3-D CRT ($p<0.01$). Coincident with an interval decrease in bowel HRQOL among 3-D CRT patients ($p<0.01$), long-term differences in bowel HRQOL were observed for RP versus 3-D CRT and BT ($p<0.01$).

Conclusions: Long-term HRQOL outcomes vary based on type of therapy. Late changes in urinary, bowel and sexual HRQOL may be anticipated following BT and 3-D CRT, with improvements in some domains (e.g. urinary irritation and bowel (BT)) and deterioration in others (e.g. urinary incontinence (BT and 3-D CRT), sexual (3-D CRT) and bowel (3-D CRT)). In contrast to these late changes in post-BT and 3-D CRT outcomes, post-prostatectomy HRQOL was relatively stable after at least 4 years of follow-up.

THE NATIONAL OBESITY EPIDEMIC AND ITS IMPACT ON PROSTATE CANCER

MODERATED BY JUDD MOUL, M.D.
AMERICAN UROLOGICAL ASSOCIATION ANNUAL MEETING

The following research was highlighted during this briefing:

NORMAL BODY MASS INDEX IS ASSOCIATED WITH A HIGHER PROSTATE CANCER DETECTION RATE AND LESS FAVORABLE PATHOLOGIC FEATURES IN A BIOPSY POPULATION

Joseph C. Presti Jr, Una Lee, James Brooks, Martha Terris. Stanford University, Stanford, CA, Medical College of Georgia, Augusta, GA

Introduction and Objective: Body mass index (BMI, weight in kilograms divided by the square of height in meters) is used as an indicator of obesity. This study assessed the relationship between BMI and prostate cancer detection rates and biopsy features in a referral-based, biopsy population.

Methods: 787 consecutive patients referred for an abnormal digital rectal exam and/or a PSA level >4 ng/ml underwent systematic prostate biopsy. Three standard categories of BMI were considered: normal (less than 25 kg/m2), overweight (25 - 29.9 kg/m2), and obese (greater than 30 kg/m2). The presence or absence of cancer, percentage of core involvement and tumor grade were correlated with BMI. Additional analyses controlled for age, PSA levels and prostate volume.

Results: For the entire population, detection rates were highest in the normal BMI group compared to the overweight or obese patients (52% vs. 37% vs. 42%, p=0.0026, respectively). When stratified by age, this observation was true for men less than 70 years old (49% vs. 32% vs. 37%, p=0.0042) but not for men over 70 years old. When only patients with PSA levels less than10 ng/ml were considered, detection rates were highest in the normal BMI group (44% vs. 28% vs. 36%, p=0.0061). This observation also persisted with patients under 70 years old and a PSA less than 10 ng/ml or when only patients less than 70 years old and a total prostate volume less than 50 cc were included. In patients with cancer, those with a normal

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BORON INTAKE COULD REDUCE PCA RISK?

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with a decreased risk of prostate cancer with a dose-response pattern. The adjusted odds ratio was 0.46 (95% confidence interval: 0.21-0.98) for the highest quartile of boron intake comparing to the lowest quartile (p for trend = .0525). The observed association should be interpreted with caution because of the small case sample size and the nature of the cross-sectional study design, but deserve further investigation," the researchers concluded.

Cui and colleagues published the results of their research in Oncology Reports (Dietary boron intake and prostate cancer risk. Oncol Rep, 2004;11(4):887-892).

SOY BASED DIETARY SUPPLEMENT IMPACT ON PSA

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(0.2, 13)(median, range). Per protocol treatment (at least five serum PSA assessments per period, n=42) analysis and an intention to treat analysis (at least two serum PSA assessments per period available, n=46) were carried out while in a cross-over study an intention to treat analysis is not considered to be required. Both analyses showed a decrease of the slope of PSA. The per protocol analysis showed a significant decrease in PSA slope (p=0.030) and 2log PSA slope (p=0.041) which translates into a 2.6 fold increase in the PSA doubling time (from 445 to 1150 days between supplement and control). No changes in safety parameters were detected during the study.

Conclusions: A soy based dietary supplement was shown to delay PSA progression after potentially curative treatment in a significant and meaningful way. Experimental confirmation studies allowing to study the effect of the supplement on PSA and tumor mass in Xenografts in nude mice are in progress.

OBESITY EPIDEMIC AND ITS IMPACT ON PCA

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BMI had a greater percentage of needle core involvement on the biopsy than overweight or obese patients (11% vs. 5.6% vs. 8.1%; p=0.0014). This finding was true independent of age or PSA levels. BMI did not correlate with tumor grade.

Conclusions: A normal body mass index correlates with a higher cancer detection rate and larger cancers in men undergoing prostate biopsy.

PATHOLOGIC VARIABLES AND RECURRENCE RATES AS RELATED TO OBESITY AND RACE IN MEN WITH PROSTATE CANCER UNDERGOING RADICAL PROSTATECTOMY

Christopher L. Amling, Robert H. Riffenburgh, Leon Sun, Judd W. Moul, Raymond S. Lance, Leo Kusuda, Wade J. Sexton, Douglas W. Soderdahl, Timothy F. Donahue, John P. Foley, Andrew K. Chung, David G. McLeod. Naval Medical Center San Diego, San Diego, CA, Naval Medical Center San Diego, San Diego, CA

Introduction and Objective: To determine if obesity is associated with higher PSA recurrence rates following radical prostatectomy (RP), and to explore racial differences in body mass index (BMI) as a potential explanation for the disparity in outcome between black and white men.

Methods: Retrospective, multi-institutional pooled analysis of 3162 men undergoing RP at nine geographically diverse US military medical centers between 1987 and 2002. Patients were intially categorized as obese (BMI >= 30 kg/m2), overweight (BMI 25-30 kg/m2) or normal (BMI < 25 kg/m2). For analysis, normal and overweight groups were combined and compared to the obese group with regard to actuarial estimates of freedom from biochemical recurrence.

Results: Of 3162 patients, 600 (19.0%) were obese and 2562 (81%) were not obese. BMI was an independent predictor of higher Gleason grade cancer (p<0.001) and obesity was associated with a higher risk of biochemical recurrence after RP (p=0.027). African-Americans had higher BMI than Caucasian (p<0.001) patients, and blacks had higher recurrence rates than whites (p=0.003). Both BMI (p=0.028) and African-American race (p=0.002) were associated with higher PSA recurrence rates. In multivariate analysis of race, BMI and pathologic factors, African-American race (p=0.021) remained a significant independent predictor of recurrence.

Conclusions: Obesity is associated with higher recurrence rates after RP and higher grade cancer in the RP specimen. African-Americans have higher recurrence rates and greater BMI than Caucasian men. These findings support the hypothesis that obesity is associated with progression of latent to clinically significant PC and suggests that BMI may in part account for the racial variability in PC risk.

IS OBESITY ASSOCIATED WITH MORE AGGRESSIVE PROSTATE CANCER? (DATA FROM CAPSURE)

Christopher J. Kane, William W. Bassett III, Natalia Sadetsky, Stephanie Silva, David J. Pasta, Matthew R. Cooperberg, June Chan, Katrine Wallace, Peter R. Carroll. University of California at San Francisco, San Francisco, CA, University of California at San Francisco, San Francisco, CA, TAP Pharmaceutical Products

Introduction and Objective: The prevalence of obesity in the United States has increased significantly in the last decade. We investigated the association of obesity with prostate cancer patients' demographics and clinical disease features at presentation (i.e. prognostic group stratification).

Methods: Data were abstracted from CaPSURE, a disease registry of 10,018 men with prostate cancer. 3684 men were included who were treated between 1989 and 2002 and had complete body mass index information. BMI classes were defined as normal (<25 kg/m2), overweight (25-29.9 kg/m2), obese (30-34.9 kg/m2), or very obese (≥35 kg/m2). Patients were categorized as having low, intermediate, or high risk disease based on the D'Amico classification. Associations among obesity, risk and demographics were analyzed using univariate and multivariate models.

Results: 29% of patients had a normal BMI, 50% were overweight, 16% were obese, and 5% were very obese. Patients

who were obese were more likely to be young, have hypertension and diabetes, and have a lower education level. After adjusting for age, ethnicity, education, income, relationship status, smoking, alcohol, and co-morbidities, men in the overweight group were less likely to be in the high-risk prognostic category (relative risk=0.80, p=0.03) compared to men of normal weight. The overweight group also had lower PSA (p=< 0.0001) and lower stage disease (p=0.0001) at diagnosis, but there was no association between Gleason score and obesity (p=0.37). There was no association between BMI>30 and risk group.

Conclusions: Obese patients are more likely to be young and have multiple co-morbidities. Men in the overweight group presented with lower risk prostate cancer at diagnosis. This may be due to a biological benefit of being overweight or to earlier disease detection secondary to more frequent interaction with the medical community. Lower stage and PSA at diagnosis as well as a lack of association with Gleason score are consistent with the latter hypothesis.

OBESITY IS AN INDEPENDENT PREDICTOR OF BIOCHEMICAL FAILURE FOLLOWING RADICAL PROSTATECTOMY

Stephen J. Freedland, William J. Aronson, Christopher J. Kane, Joseph C. Presti Jr, Christopher L. Amling, David Elashoff, Martha K. Terris. Johns Hopkins University School of Medicine, Baltimore, MD, UCLA School of Medicine, Los Angeles, CA, University of California, San Francisco School of Medicine, San Francisco, CA, Stanford University School of Medicine, Stanford, CA, San Diego Naval Hospital, San Diego, CA, UCLA School of Medicine, Los Angeles, CA, Medical College of Georgia, Augusta, GA

Introduction and Objective: Both obesity and prostate cancer are major public health problems. Only limited information is available regarding obesity and treatment outcomes for clinically localized prostate cancer. Therefore, we sought to examine the relationship between body mass index (BMI) and cancer control following radical prostatectomy (RP) in a racially diverse population.

Methods: We examined data from 1,106 men treated with RP between 1988 and 2002 at 5 equal access medical centers. Clinical and pathological variables as well as biochemical outcome information were compared across the groups. Log-rank and Cox proportional hazards analysis were used to determine if BMI was a significant independent predictor of adverse pathological features or biochemical recurrence following RP.

Results: Obesity was significantly related to year of surgery, with more recently treated patients having higher rates of obesity (p<0.001). There was a significant relationship (p<0.001) between BMI and race with black men having the highest rate of obesity (31%), followed by white men (21%), with nonwhite-nonblack men having the lowest rate (13%). Obese patients had higher biopsy and pathological grade tumors (p<0.001). On multivariate analysis, there was a trend for BMI >35 kg/m2 to be associated with higher rates of positive surgical margins (p=0.088), though this did not reach statistical significance. BMI >35 kg/m2 was associated with a significantly decreased risk of seminal vesicle invasion (p=0.039), while no relationship between BMI and extracapsular extension was found. After controlling for all pre-operative clinical variables including year of surgery, BMI >35 kg/m2 was a significant independent risk factor for early biochemical failure following RP (p=0.002). Furthermore, after controlling for surgical margin status, BMI >35 kg/m2 remained a significant predictor of PSA failure (p=0.012). There was a trend for men with BMI >35 kg/m2 to have higher failure rates than men with a BMI >30 but <35 kg/m2, though this did not reach statistical significance (p=0.053).

Conclusions: The percentage of obese men undergoing RP in our dataset doubled in the last 10 years. Obesity was associated with higher-grade tumors, a trend toward increased risk of positive surgical margins, and higher biochemical failure rates among men with clinically localized prostate cancer treated with RP. Men with a BMI >35 kg/m2 were at higher-risk of failure than patients with BMI >30 but <35 kg/m2.

THE ASSOCIATION BETWEEN BODY MASS INDEX (BMI) AND DISEASE PROGRESSION IN CLINICALLY LOCALIZED PROSTATE CANCER

Christopher J. Di Blasio, Audrey C. Rhee, Peter T. Scardino, Michael W. Kattan. Memorial Sloan-Kettering Cancer Center, New York, NY

Introduction and Objective: Several reports have documented a link between body mass index (BMI) and the risk of developing advanced prostate cancer (CaP) or CaP-related death. We examined the association between body mass index (BMI) and progression-free probability in men treated with radical retropubic prostatectomy (RRP) for clinically localized CaP.

Methods: We retrospectively studied 3006 consecutive patients undergoing RRP at Memorial Sloan-Kettering Cancer Center between 9/1986 and 5/2003. Of these, 347 patients were excluded for missing biopsy Gleason grade data and 3 for missing pretreatment PSA values. Clinicopathologic variables analyzed included age, height, weight, pretreatment serum PSA level (ng/mL), clinical T stage (AJCC 1992 classification), and biopsy-derived primary and secondary Gleason grades. Disease progression was defined as the first occurrence of either: biochemical (BCR), local, or metastatic recurrence; or death from CaP. BCR was defined as a serum PSA value of >0.2 ng/mL and rising. BMI was calculated by dividing the weight (kilograms) by the square of the height (meters2). Statistical analysis was performed using Cox proportional hazards models and Kaplan-Meier survival analysis with p<.05 considered significant.

Results: Overall, 2660 patients were analyzed, and 286 (10.8%) experienced disease progression during a maximum follow-up of 143 months. Median BMI was 27.4 kg/m2 (range, 17.7 - 65.6). When adjusting for pretreatment PSA, primary and secondary biopsy-derived Gleason grades, age at RRP, clinical stage, and the year of surgery, BMI was not associated with disease progression (p=.131). BMI category (as defined by WHO guidelines) was not associated with disease progression (p=.935).

Conclusions: While obesity has been shown by others to be associated with an increased risk of developing CaP, as well as an increased risk of developing aggressive disease and CaP-related mortality, we found no association between BMI and disease progression in patients treated with RRP for clinically localized CaP.

OUTLOOK GOOD FOR MOST PATIENTS

(continued from page1)

Bianco said.

The study included 1,700 men who had radical prostatectomy, an operation to remove the cancerous gland, since 1983. The cancer recurred in only 261 of them.

Even when the cancer had spread beyond the prostate to nearby lymph nodes or elsewhere in the body when it was first diagnosed, the 15-year survival rate was 70 percent or better, the study found.

A study of more than 3,000 prostate cancer patients at the Washington University School of Medicine in St. Louis also demonstrated the effectiveness of cancer surgery. That study compared survival rates for men treated by surgery, external beam radiation, hormonal therapy or brachytherapy — in which radiation-emitting pellets are implanted in the body — and for cases in which the physician chose watchful waiting.

Only 13 percent of men classified as low-risk because the cancer was confined to the prostate at the time of diagnosis had died after an average follow-up time of 68 months. The mortality rate for men at intermediate risk because the cancer had spread to nearby lymph nodes was 20 percent. For high-risk men, in whom the cancer had spread further, the death rate was 41 percent.

Brachytherapy also gave encouraging results, with a mortality rate of less than 10 percent of low-risk men and 17 percent of intermediate-risk men in a 42-month follow-up. But the death rate for high-risk men treated with brachytherapy was 59 percent.

Results for external beam radiation were less impressive, with a five-year survival rate for low-risk men of 83 percent. Survival rates for low-risk men treated with hormonal therapy and watchful waiting were much lower. Because of the relatively small number of patients, the survival estimates were very broad — between 23 and 71 percent for hormonal therapy and 22 and 56 percent for waiting.

While the results of surgery are good, "it is hard to make a statement in favor of just one treatment," said Dr. Misop Han, a staff urologist at Northwestern Memorial Hospital in Chicago, who has worked with the Washington University physicians and delivered another report at the meeting.

"There is a role for radiation therapy and hormone therapy and watchful waiting," Han said. "It depends on the characteristics of the individual patient."

Han's paper covered radiation treatment of men who experienced recurrence of cancer after surgery. The salvage radiation treatment eliminated the cancer in only 25 percent of those men in a 10-year follow-up, but many of those men were still alive, Han said, so "the mortality rate data are not mature yet."

The study shows that recurrence of prostate cancer "can be effectively treated with salvation radiation therapy in properly selected patients," Han said.

BLOOD SCREEN MAY HELP PATIENTS WITH RT SIDE EFFECTS

(continued from page1)

heal, skin burns so severe they require plastic surgery, or brain damage. Past attempts to identify these patients by screening the cancer cells themselves have failed, according to Chu. In his study, published in this week's online edition of the Proceedings of the National Academy of Sciences, Chu and colleagues describe 24 genes that can be used to single out these patients for alternate therapies or lower radiation doses.

Chu said screening blood rather than cancer cells means the test would be more accessible to patients. "To be most useful it had to be done on peripheral blood and with a small number of genes," he said.

Chu, whose research revolves around how cells repair damaged DNA, thought that patients who respond poorly to radiation might have cells that don't properly recognize or repair radiation-induced DNA damage. These cells may turn on different genes, or the same genes at different levels, compared with normal cells exposed to radiation.

A group of graduate students and medical students consisting of Kerri Rieger, Wan-Jen Hong, Virginia Goss Tusher and Jean Tang tested this idea in blood samples taken from 57 cancer patients who had recently received radiation treatment. Of these, 14 patients had unusually severe radiation toxicity. The students used a gene microarray, which provides a snapshot of gene activity, to analyze which genes were active in blood cells.

In the initial analysis, Chu said the group couldn't identify genes that were consistently different between patients who did and didn't suffer serious side effects. He worked with Robert Tibshirani, PhD, professor of health research and policy, to develop a new statistical method of analyzing the microarray data. With this improved analysis, the group found 24 genes that behaved differently in patients who suffered radiation toxicity.

When Chu and his colleagues tested the patients' blood samples for these 24 genes, they identified nine of the 14 people with severe reactions. Of the remaining five patients, two were later found to have been treated with new approaches that carried high risks for toxicity. That left only three of 14 patients who the test failed to identify. Most important, the test did not mistakenly pinpoint any of the other patients.

Knowing which patients may have severe radiation toxicity could make treatment decisions easier. For cancers of the breast or prostate, Chu said surgical options can be as effective as radiation. "If you knew one of the options carried a big risk, that might alter your decision," he said.

For other cancer patients, radiation may be the best treatment. However, Chu added that patients at risk for high toxicity may also have cancers that die in response to much lower radiation doses. In such cases, radiation - though at greatly reduced doses - may still be an option.

Those who don't have severe radiation toxicity may also benefit from this study. "If you eliminate those patients with toxicity you may be willing to use higher doses for the remaining patients," Chu said. He said doses are set by what an average person can handle. If patients are treated individually rather than as averages, many could receive higher, more effective doses.

Chu said that before personalized treatment becomes possible, researchers must validate the 24-gene test on a larger number of samples. A biotech company must also commercialize the screen and make it available to medical labs.