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Us TOO[®]
PROSTATE CANCER
EDUCATION & SUPPORT

HOTSHEET

APRIL 2014

SURGERY BETTER THAN WATCHFUL WAITING FOR YOUNGER PROSTATE CANCER PATIENTS

A new study in the *New England Journal of Medicine* finds that mortality rates are lower for younger men having surgery for prostate cancer, compared with those who follow active surveillance.

Prostate cancer is common among older men and rare in men under the age of 40. For most forms of cancer, treatment at as early a stage as possible is preferred, but prostate cancer is less straightforward. A prostate tumor may grow very slowly without any symptoms, or it may grow very quickly and spread to other parts of the body.

The best course of treatment for a newly-diagnosed patient is a much-debated topic. For instance, in 2013, prostate cancer researchers were arguing for more active surveillance to manage the disease, rather than moving straight to aggressive treatment or surgery.

Researchers behind that study claimed that: "Radical prostatectomy or radiation therapy, the usual treatments for prostate cancer, can have negative side-effects such as impotence and incontinence [...] Choosing active surveillance could prevent this decline in quality of life."

But the 2013 study contradicted the findings of another New England Journal of Medicine-published study from

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HOW SELENIUM AND VITAMIN E INCREASE PROSTATE CANCER RISK

New data from the much publicized Selenium and Vitamin E Cancer Prevention Trial (SELECT), which sought to determine whether these supplements could protect against the development of prostate cancer, confirm that both antioxidants can be risky business for men. The new study, published online February 22 in the *Journal of the National Cancer Institute*, attempted to determine which men taking these supplements are most at risk for prostate cancer, and why.

SELECT began in 2001 and was expected to run for 12 years, but it was stopped early, in 2008, after participants had been on the supplements for an average of five years. The results demonstrated that there was no protective effect from selenium and suggested that vitamin E increased prostate cancer risk. Although the use of the supplements stopped, the study actually continued. After two years of follow-up, men who took vitamin E had a statistically significant 17 percent increased risk for prostate cancer, as was previously reported.

In this new case-cohort study, 1,739 men diagnosed with prostate cancer during SELECT were compared with 3,117 men who were not receiving selenium supplementation, explained lead author Alan Kristal, DrPH from the Fred Hutchinson Cancer Research Center in

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TOXICITY LIMITS POTENTIAL FOR CHEAPER PROSTATE CANCER TREATMENT

A review of 4,000 cases showed stereotactic body radiotherapy (SBRT) for prostate cancer led to significantly lower initial cost of care versus intensity-modulated radiotherapy (IMRT), but higher toxicity offset most of the savings. The cost of treatment averaged \$13,645 for SBRT and \$21,023 for IMRT. Beginning six months post treatment and continuing out to two years, SBRT-treated men had significantly higher rates of toxicity, especially urinary complications.

James B. Yu, MD, of Yale University, and colleagues reported online in the *Journal of Clinical Oncology* that the findings add to conflicting results from previous studies of SBRT-associated toxicity.

Initial reports from developers suggested SBRT has acceptable acute toxicity and offered cancer control comparable to IMRT. Nonetheless, late GU symptoms have led some investigators to alter their technique in an effort to reduce exposure of normal tissue. Emerging cost data for SBRT have provided another stimulus for evaluating the technique as an alternative to the more expensive IMRT. However, no cost studies had examined SBRT from the Medicare perspective, a dominant payer in the age group affected by prostate cancer.

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PROSPECTIVE MULTICENTRE EVALUATION OF PCA3 AND TMPRSS2-ERG GENE FUSIONS AS DIAGNOSTIC AND PROGNOSTIC URINARY BIOMARKERS FOR PROSTATE CANCER

Leyten GH, Hessels D, Jannink SA, et al
Eur Urol 65: 534–42, 2014

Background: Prostate cancer antigen 3 (PCA3) and v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2-ERG) gene fusions are promising prostate cancer (PCa) specific biomarkers that can be measured in urine.

Objective: To evaluate the diagnostic and prognostic value of ProgenSA PCA3 and TMPRSS2-ERG gene fusions (as individual biomarkers and as a panel) for PCa in a prospective multicentre setting.

Design, Setting, and Participants: At six centres, post-digital rectal examination first-catch urine specimens prior to prostate biopsies were prospectively collected from 497 men. We assessed the predictive value of ProgenSA PCA3 and TMPRSS2-ERG (quantitative nucleic acid amplification assay to detect TMPRSS2-ERG mRNA for PCa, Gleason score, clinical tumour stage, and PCa significance (individually and as a marker panel). This was compared with serum prostate-specific antigen and the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculator. In a subgroup (n=61) we evaluated biomarker association with prostatectomy outcome.

Outcome Measurements and Statistical Analysis: Univariate and multivariate logistic regression analysis and receiver operating curves were used.

Results and Limitations: Urine samples of 443 men contained sufficient mRNA for marker analysis. PCa was diagnosed in 196 of 443 men. Both PCA3 and TMPRSS2-ERG had significant additional predictive value to the ERSPC risk calculator parameters in multivariate analysis (p<0.001 and resp. p=0.002). The area under the curve (AUC) increased from 0.799 (ERSPC risk calculator), to 0.833 (ERSPC risk calculator plus PCA3), to 0.842 (ERSPC risk calculator plus PCA3 plus TMPRSS2-ERG) to predict PCa. Sensi-

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STRESS, LACK OF SOCIAL SUPPORT LINKED TO PROSTATE CANCER MORTALITY

High levels of perceived stress and lack of social support were associated with higher mortality rates among men with prostate cancer, in a study presented February 20 at the annual meeting of the American College of Preventive Medicine in New Orleans.

Researchers analyzed data from 4,105 prostate cancer patients participating in a national follow-up study in Sweden. They had been diagnosed with localized prostate cancer between 1997 and 2002. All were less than 70 years of age.

The men were asked to complete Cohen's Perceived Stress Scale, a 14-item questionnaire that asks responders to assess the degree to which various life situations are considered stressful. Their responses were then added together to produce a total perceived stress score. They were also asked questions about the loss of loved ones, difficulty sleeping, and their ability to talk about emotional problems with partners, friends, and family.

Emotional and behavioral factors such as grieving, poor sleep and lack of emotional support were more common among those with higher levels of perceived stress.

During a mean follow-up of 51.3 months after the questionnaires were returned, there were 127 prostate cancer deaths (3.1 percent) and 276 deaths from other causes (6.7 percent). Men in the highest tertile of perceived stress had a 66 percent increased risk of prostate cancer-specific mortality compared to men in the lowest tertile. A sensitivity analysis was performed to ensure that this finding was not biased by rapidly deteriorating health and/or hastened mortality. After excluding men who died of prostate cancer within six months of responding to the questionnaire, the result did not change.

"This is an important study that shows that the perceived impact of stress is associated with survival in prostate cancer," observed Dr. Frank Penedo, Director of the Cancer Survivorship Institute at Northwestern University's Robert H. Lurie Comprehensive Cancer Center.

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SBRT VERSUS IMRT (Continued from page 1)

Yu and colleagues undertook a retrospective comparison of SBRT and IMRT as primary treatment for prostate cancer. For the analysis they queried the Chronic Conditions Warehouse, a database containing 100 percent of Medicare fee-for-service claims related to specific conditions, including prostate cancer.

The authors identified claims from January 2008 through June 2011 submitted for treatment of early stage-prostate cancer in men ages 66 to 94. They limited the search to patients who received IMRT or SBRT as primary treatment.

The search identified 1,335 men treated by SBRT and 53,841 treated with IMRT, all of whom had at least six months of follow-up. Investigators matched each patient treated with SBRT to two treated with IMRT. The primary outcomes of interest were toxicity and cost.

The analysis showed higher rates of GU toxicity for SBRT at all time points analyzed, suggesting increased rates of acute and late toxicity. At six months post treatment, 15.6 percent had a claim related to treatment of GU toxicity compared with 12.6 percent of the IMRT patients (odds ratio 1.29, $P=0.009$). By 12 months, the proportion of patients with toxicity-related claims had risen to 27.1 percent in the SBRT group and 23.2 percent in the IMRT group (OR 1.23, $P=0.01$). By 24 months, claims related to GU toxicity had been submitted for 43.9 percent and 36.3 percent of SBRT and IMRT patients, respectively (OR 1.38, $P=0.001$).

On the basis of claims submitted, SBRT was associated with significantly more diagnostic procedures for urinary incontinence and obstruction at six, 12, and 24 months and significantly more claims related to diagnosis or treatment of urethritis, urethral strictures, and obstruction at 12 and 24 months ($P=0.003$ for all comparisons versus IMRT). Analysis of the same toxicities limited to 13 to 24 months after treatment showed more toxicity with SBRT (OR 1.33, $P=0.005$).

The mean cost of diagnostic procedures to investigate incontinence, obstruction, urethritis, urethral strictures, and bladder outlet obstruction was \$145 with SBRT and \$69 for IMRT ($P<0.001$). The

SBRT group also had a higher cost for cancer-related nonradiation care in the year following treatment (\$2,963 versus \$1,978 for IMRT, $P<0.001$).

“Despite conflicting reports, given the potentially high doses of radiation delivered to the urethra and bladder neck by SBRT, our finding of greater genitourinary toxicities for SBRT remains plausible,” the authors concluded. “Some patients and clinicians might still consider SBRT preferable to IMRT because of shorter treatment duration, lower cost in spite of the higher complication rate, and evidence that SBRT might be superior to IMRT in terms of curative treatment.”

“The finding of increased GU toxicity with SBRT is a ‘concerning but testable hypothesis’ that is being examined in an ongoing randomized trial comparing SBRT and IMRT in men with prostate cancer,” said Anthony V. D’Amico, MD, PhD, of Brigham and Women’s Hospital in Boston, in an accompanying editorial. SBRT has characteristics that make it an appealing alternative to conventional IMRT. SBRT delivers a higher dose of radiation per visit, and a treatment plan can be completed in as few as five visits. In contrast, the typical IMRT course requires seven to nine weeks to complete.

In the editorial, D’Amico pointed out several limitations of the study. The authors did not clarify the circumstances of androgen deprivation therapy when it was used with radiation therapy, an issue that could influence toxicity. The toxicity rates in the study were high for SBRT and IMRT and do not reflect clinical experience with either technique. In addition, the authors included diagnostic tests (cystourethroscopy, complex uroflowmetry) in their assessment of toxicity, which may have been performed for issues unrelated to treatment.

“Therefore, when treating men with prostate cancer, is it acceptable to recommend a more convenient treatment that takes less time and is less expensive despite the possibility of increased toxicity and unknown comparative efficacy to current standards of practice?”

D’Amico asked. “I do not think so.”

MedPage Today, 10 March 2014

STUDY FINDS SET OF FAMILIAL PROSTATE CANCER MUTATIONS POTENTIALLY PREDICTIVE OF AGGRESSIVE DISEASE

A sequencing effort by a group from The Institute of Cancer Research, London has identified a group of mutations that may predispose men with a family history of prostate cancer toward developing tumors and are also associated with more advanced or aggressive disease.

According to the researchers, who published the results of the study in the *British Journal of Cancer*, the investigation was prompted by previous evidence that mutations in DNA repair genes associated with inherited breast and ovarian cancer, like BRCA1 and BRCA2, may also increase the risk of prostate cancer.

In the study, the researchers collected DNA samples from 191 men with three or more cases of prostate cancer in their families recruited from a trial called the UK Genetic Prostate Cancer Study. The group sequenced 22 tumor suppressor genes in these samples, including the BRCA tumor suppressor gene set containing high- and moderate-risk breast and ovarian cancer genes like BRCA1 and BRCA2, as well as genes involved in rare inherited cancer disorders like Lynch syndrome.

According to the study authors, the analysis of the results of this sequencing was focused on identifying putative loss-of-function (LoF) mutations: those likely – based on their location and influence on protein sequence or structure – to inhibit the functional expression of the gene in which they are located. The group also tried to validate any identified LoF mutations in the subjects themselves and their family members, if available, using follow-up Sanger sequencing.

Based on the results, the group picked out a total of 13 LoF mutations in eight genes in 14 of the subjects from the 191-man cohort, including four mutations in BRCA2, two in ATM, a single mutation in BRIP1 affecting two different subjects/families, and two mutation in CHEK2, as well as one mutation each in BRCA1, MUTYh, PALB3, and PMS2.

No subject carried more than one of

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ROBOTIC ASSISTED PROSTATE SURGERY OFFERS BETTER CANCER CONTROL

An observational study from UCLA's Jonsson Comprehensive Cancer Center has found that prostate cancer patients who undergo robotic-assisted prostate surgery have fewer instances of cancer cells at the edge of their surgical specimen and less need for additional cancer treatments like hormone or radiation therapy than patients who have traditional "open" surgery.¹

The study, published online Feb. 19 in the journal *European Urology*, was led by Dr. Jim Hu, UCLA's Henry E. Singleton Professor of Urology and director of robotic and minimally invasive surgery in the urology department at the David Geffen School of Medicine at UCLA.

Although it is becoming more popular, robotic-assisted radical prostatectomy -- the complete removal of the prostate using a robotic apparatus -- remains controversial because there has been little evidence that it provides better cancer control than open radical prostatectomy, the traditional surgical approach, which is less costly.

In an effort to determine whether or not robotic surgery offered an advantage, Hu and his colleagues compared 5,556 patients who received robotic surgery with 7,878 who underwent open surgery between 2004 and 2009. Data was provided by the Surveillance, Epidemiology, and End Results-Medicare, a program of cancer registries that collects clinical and demographic information on people with cancer.

The researchers looked at the surgical margin status of the two groups, which is the amount of cancer cells at the edge of the removed prostate specimen. A positive margin -- the presence of cancer cells at the edge -- may result from cutting through the cancer and leaving some behind rather than cutting around the cancer completely. In prostate cancer, this has been shown to lead to a greater risk of recurrence and death from the disease.

The team also assessed the use of additional cancer therapies -- a hormone

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DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"Did you hear what the WHO just said about sugar intake? Who?!"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line:

The World Health Organization (WHO) made a stunning and wonderful new announcement for individuals to only get 5 percent of their total caloric intake from sugar!¹ This applies to all sugars added to food, and the ones naturally found in honey, syrups, fruit juices and fruit concentrates! YES! And, this is only 10 years overdue! Now go compare the amount of sugar in your apple or pomegranate juice to that of Coca-Cola! Yikes!!! The only extra sugar I want in my future is from my spouse! (Hey-can I mention that sexual innuendo in this Us TOO family-friendly newsletter? Yes! I have earned the right because I am one of those long-term Us TOO volunteers!)

What does an eight-ounce apple, grape, or pomegranate juice have in common? Yes, they all are juices, but they also have MORE grams of sugar compared to an eight-ounce can of Coca-Cola (over 26 grams on average)! Whenever I give a lecture and I see someone drinking a fruit juice I like to sarcastically say "You could have had a Coca-Cola!" And, the person usually laughs and thinks I was kidding or I do not have my facts straight. Many times I will get a response like, "You mean I could have had a V-8?" And, I say "No, you could have had a Coca-Cola and it would have tasted a heck of a lot better!"

You see, sugar is hidden everywhere today and you can run and hide but you cannot escape sugar! Getting whole unprocessed apples, grapes or eating a pomegranate will always give you less calories and really less concentrated sugar compared to juice, because it is combined with lots of fiber and other nutrients, as opposed to more pure liquid sugar. In other words, every time you take a fruit and veggie and process it you will get more calories, more sugar, no or low fiber, pay more money and be more likely to gain weight, waist

and get a fatty liver! Yeah!! And, there are the potential hidden sources of sugar, such as vitamin water/copycats of vitamin water, bread, coleslaw, tomato sauce, many other sauces out there and cereals! Heck, I love sugar like the next person but carbohydrates and sugar are out of control! And, they have been out of control for so many years I lost count! So, when the WHO (who?) comes out and finally says we need to cut our sugar intake by half or more, it is groundbreaking. So, your job is to compare all sorts of labels, and you will be shocked how many similar products contain huge amounts of sugar and others, very little. For example, when I exercise and then drink whey protein isolate powder in water from one of my favorite brands (Jay-Robb or Whole Foods) at the gym someone will always tell me I could have had chocolate milk for protein. One of the top chocolate milk brands (eight ounces) has eight grams of protein, 22 grams of sugar and 150 calories, and my protein powder has 25 grams of protein, 0 grams of sugar, and 110 calories. Come on man! Oh, and you could have had a Coca-Cola!

Reference:

1. <http://www.reuters.com/article/2014/03/05/us-sugar-who-idUSBREA241CK20140305>



SELENIUM AND VITAMIN E (Continued from page 1)

Seattle, WA. Dr. Kristal and colleagues measured the selenium concentration in the toenails of participants at baseline. The plan, they explained, was to test whether supplementation would benefit only the subset of men with low baseline selenium levels.

They found that baseline selenium status alone, in the absence of supplementation, was not associated with prostate cancer risk. However, they also found that the effects of the supplements differed substantially between men with low levels at baseline and those with high levels. Men with high baseline selenium levels who took selenium increased their risk for high-grade cancer by 91 percent ($p = .007$).

Investigators also report that vitamin E increased prostate cancer risk, but only in men with low selenium levels at baseline. Specifically, in the men with low levels of selenium randomized to receive vitamin E alone, the total risk for prostate cancer increased by 63 percent ($p = .02$) and the risk for high-grade cancer increased by 111 percent ($P = .01$). This might explain why, in the 2008 SELECT results, only the men randomized to receive vitamin E alone, not those who received both vitamin E and selenium, had an increased risk for prostate cancer.

Dr. Kristal said, “Many people think that dietary supplements are helpful or at the least innocuous. This is not true. Men using these supplements should stop, period. Neither selenium nor vitamin E supplements confer any known [health] benefits – only risks.”

Some evidence from basic science supports the idea of a meaningful dynamic between the two supplements. “An interaction between vitamin E and selenium has long been hypothesized because of their activities in preventing lipid peroxidation,” Dr. Kristal and colleagues write. Nevertheless, these new results are consistent with the medical literature on supplements and cancer. The message is that nothing good is gained in healthy people.

The literature “suggests that effects of supplementation are dependent upon the nutrient status of the target population, such that supplementation of populations with adequate nutrient status, leading to supraphysiological exposure, has either no effect or increases cancer risk,” they write.

The study was funded by the National Cancer Institute.

Medscape Medical News, 26 February 2014

ROBOTIC SURGERY

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therapy known as androgen deprivation, as well as radiation -- after robotic surgery and open surgery.

They found that robotic prostate surgery was associated with 5 percent fewer positive margins (13.6 percent vs. 18.3 percent); this difference was greater for patients with intermediate and high-risk prostate cancer. Patients who had robotic surgery also had a one-third reduction in the likelihood of needing additional cancer therapies within 24 months after surgery.

The researchers said despite the greater up-front cost of robotic surgery, the findings show that the procedure may translate into less downstream costs and fewer side effects from radiation and hormone therapy.

Reference

1. Hu JC, Gandaglia G, Pierre I, Paul L, Nguyen, et al. Comparative effectiveness of robot-assisted versus open radical prostatectomy cancer control. *Eur Urol* 19 February, Epub. *Science Daily, 28 February 2014*

GLEASON INFLATION 1998-2011 A REGISTRY STUDY OF 97,168 MEN

Danneman D, Drevin L, Robinson D, et al

BJU Int 19 February 2014; Epub

What's known on the subject?: In recent years there has been a shift upwards of how Gleason grading of prostate cancer is applied. At an International Society of Urological Pathology (ISUP) consensus meeting in 2005 recommendations were issued that might have contributed to this trend.

Objectives: To study long-term trends in Gleason grading in a nation-wide population. To assess the impact of the ISUP revision of the Gleason system on grading practices.

Subjects and Methods: All newly diagnosed prostate cancers in Sweden are reported to the National Prostate Cancer Register (NPCR). In 97,168 men with a primary diagnosis of prostate cancer on needle biopsy from 1998-2011, Gleason

score (GS), clinical T stage (cT) and S-PSA (S-PSA) at diagnosis were analyzed.

Results: A GS, cT and S-PSA was reported to NPCR in 97, 99 and 99 percent of cases, respectively Before and after 2005, GS 7-10 was diagnosed in 52 and 57 percent, respectively ($p < 0.001$). After standardization for cT and S-PSA with 1998 as baseline, these tumours increased from 59 to 72 percent. Among low-risk tumours (stage T1c and S-PSA 4-10 ng/ml) GS 7-10 increased from 16 percent 1998 to 40 percent in 2011 ($p_{\text{trend}} < 0.001$), mean 19 and 33 percent before and after 2005, respectively ($p < 0.001$). Among high-risk tumours (stage T3 and S-PSA 20-50 ng/mL) GS 7-10 increased from 65 to 94 percent from 1998-2011 ($p_{\text{trend}} < 0.001$), mean 78 and 90 percent

before and after 2005 ($p < 0.001$). A GS 2-5 was reported in 27 and 1% in 1998 and 2011. GS 5 decreased sharply after 2005 and GS 2-4 was almost abandoned.

Conclusions: There has been a gradual shift towards higher Gleason grading that started early, but became more evident after the ISUP 2005 revision. Among low-stage tumours, reporting of GS 7-10 was more than doubled during the study period. When corrected for stage migration, upgrading is considerable in the last decade. This has clinical consequences for therapy decisions such as eligibility for active surveillance. Grading systems need to be as stable as possible to enable comparisons over time and to facilitate the interpretation of the prognostic impact of grade.

SURGERY FOR YOUNGER MEN

(Continued from page 1)

2011, which suggested that men under 65 have much better outcomes with radical prostatectomy than watchful waiting. That study found that mortality was 40 percent lower among younger patients who had their prostate surgically removed.

Compared with watchful waiting the new study used data from the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4). This trial randomized 695 men who had early prostate cancer to either treatment with surgery or watchful waiting with no initial treatment. The progress of the men was monitored for up to 24 years.

Over the course of the study, 200 of 347 men in the surgery group and 247 of the 348 men in the watchful waiting group died. In the surgery group, 63 of these deaths were due to prostate cancer, and in the watchful waiting group, 99 of the deaths were due to prostate cancer.

“The latest results from the SPCG-4 trial indicate that surgery can not only improve survival, especially in men diagnosed at a younger age or with intermediate-risk disease, but also that surgery can reduce the burden of disease in terms of development of metastases and the need for palliative treatment,” says co-author Jennifer Rider.

Researchers warn against over-treatment, but also urge caution when interpreting their results. “Our study shows that surgery reduces the risk of dying from prostate cancer by 44 percent. So, surgery does pay off. But as we look closer at different groups, what emerges is that this does not apply to all patients,” says Prof. Jan-Erik Johansson, research leader of the study.

Prof. Johansson believes over-treatment is an important issue. He stated, “In the future, we hope to secure further knowledge of what markers doctors can use to more accurately predict the prognosis for patients, helping them to make more informed choices about their treatment. Good markers would help doctors to save more lives without causing unnecessary pain.”

Medical News Today, 6 March 2014

MODIFIED GLEASON GRADE OF PROSTATIC ADENOCARCINOMAS DETECTED IN THE PROSTATE, LUNG, COLORECTAL, AND OVARIAN CANCER SCREENING TRIAL

Humphrey PA Hickey T, Riley T, et al

J Urol 1 March 2014; Epub

Purpose: We determined modified Gleason grade of prostatic adenocarcinomas detected in the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial, to assess grade distribution and to compare modified Gleason grades of cancers detected in the intervention arm (organized annual screening) vs. those in the control arm (opportunistic screening).

Materials and Methods: Modified Gleason grading was performed for 859 radical prostatectomy cases by a single urologic pathologist. The proportion of cases with high grade disease in screened vs. control arm was compared by logistic regression analysis.

Results: A modified Gleason score of 5, 6, 7(3+4), 7(4+3), 8, 9, and 10 was assigned in 3.6 percent, 43.3 percent, 39 percent, 7.4 percent, 3.5 percent, 3.2 percent, and 0.1 percent of cases in the intervention arm, respectively. A modified Gleason score of 5, 6, 7(3+4), 7(4+3), 8, 9, and 10 was assigned in 3.0 percent, 35.7 percent, 46.4 percent, 7.1 percent, 5.4 percent, 1.9 percent, and 0.5 percent of cases in the control arm, respectively, after correction for high-grade disease over-sampling. High-grade modified Gleason score of 7 or greater was detected in 53 percent of cases from the intervention arm compared to 61.3 percent of cases from the control arm after correction (p = 0.019). The median modified Gleason score was 7 (3+4) for both arms.

Conclusions: A significant percentage of cancers in both arms had a component of high grade disease. The modified Gleason grade of the prostate cancers detected by organized annual screening was slightly lower than the modified Gleason grade of prostate cancers detected by opportunistic screening, an expected consequence of more intensive screening.

STRESS AND PROSTATE CANCER

(Continued from page 2)

“The next question is what mechanisms link this perceived stress to disease progression and mortality?”

Michael Jan, the lead researcher and an MD/PhD candidate at Temple University School of Medicine, agreed that this is an important next question.

“Our main finding that high stress is associated with increased prostate cancer-specific mortality agrees with a biological mechanism demonstrated in animal models,” Jan said. “A group at Wake Forest found that stress actually increases proliferation of prostate cancer cells compared to other cell types in mice. Our study obviously didn’t go into the molecular biology of our participants, but there is biological evidence to support our claim of a relationship between stress and prostate cancer.”

Dr. Penedo suggested, “We could be seeing evidence of the physiologic impact of stress, such as inflammation and tumor progression, or there could be behavioral factors connected to stress, such as compliance with treatment guidelines and follow up, or we may need to look deeper into comorbid conditions, access to care and socioeconomic status to determine everything that is playing a role here.”

Jan added that regardless of the underlying mechanism, he hopes these findings encourage health care practitioners to work harder to identify prostate cancer patients who might benefit from individualized attention to and programs that address stress reduction, sleeping habits, and social support.

Reuters Health, 25 February 2014



DOCTOR CHODAK'S BOTTOM LINE (Ref Key: article #, page #, column #)

Gerald Chodak, MD Author, *Winning the Battle Against Prostate Cancer*, Second Edition <http://www.prostatevideos.com>

Editors note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 Does surgery for prostate cancer save lives? New information is available with the latest update from a Scandinavian study showing that indeed it does for some men, mainly those with low and intermediate risk disease and in particular for those men under 65. For those over 65, mortality was not reduced but it did lower the risk of developing metastatic disease. As follow-up lengthened the difference in survival also increased. Unfortunately, those with high-risk disease did not appear to benefit. The implications of this study are substantial but additional questions are raised. One is how to apply these results to men diagnosed by PSA screening since only a small number of those men were included in the study. Since it took many years for the benefit to occur, men will need a good estimate of their life expectancy when choosing therapy. Also, what does it mean for those on active surveillance; should they now proceed to have surgery or can they continue to monitor the disease? The authors found that about eight men needed to be treated to prevent one from dying in about 14 years. That still means seven have not yet benefitted. The results are also important for men with high-risk disease. Doing surgery—even with secondary treatments—did not improve their survival or lower their risk of metastases. That suggests an entirely different approach needs to be studied for those men.

The Bottom Line: Longer follow-up has continued to show a decline in the number of men with low or intermediate risk disease diagnosed by conventional methods rather than PSA that must be treated to prevent one from dying.

a2p1c2 The safety and benefit of over the counter (OTC) supplements are again in the news. I would expect that asking men about the relative merits of these agents would result in finding that the overwhelming majority believes they may help; and even if they don't, there is no downside. Unfortunately, as more research is done, those beliefs are being challenged. Years ago, a few randomized studies suggested that Vitamin E and

selenium could prevent prostate cancer. To validate those findings, a new randomized controlled trial was designed but was stopped early because it showed no benefit and even suggested some harm. Now another update has confirmed that in some groups of men, the risk of being diagnosed with prostate cancer increased. Many critics have challenged the results based on the choice of Vitamin E and selenium used in the study. For anyone interested, an excellent paper by Lippman et al (JNCI, 2005) explained the reasoning used by the panel of experts. This study is important for two reasons. First it demonstrates that data from laboratory, animal, and human retrospective and epidemiological studies are not a substitute for a randomized controlled trial. Unfortunately for the public, too many OTC products are promoted that way. Second, individuals should not assume that the products are always safe simply because they can be bought without a prescription. As this and other randomized studies have shown, they can also cause harm.

The Bottom Line: Vitamin E (synthetic, all racemic alpha-tocopherol) and selenium (from selenomethionine) increase the risk of prostate cancer in some men. Whether other forms of Vitamin E would have a different effect can only be determined by a randomized, controlled study.

a4p2c2 PCA3 studies continue to expand our understanding of the potential role for this marker. The study from Italy looked at the results over time and found some consistency over time. However, there still is considerable overlap and more work is needed to help clinicians understand how well this biomarker will improve our ability to avoid unnecessary biopsies.

The Bottom Line: Although this study showed additive predictive value of a panel combining PCA3 and TMPRSS2-ERG, the overall performance of the combination requires further study.

a5p2c3 So much is written about the impact of cancer therapies on patient outcome. But are we missing something? The paper from Sweden used a

validated survey to look at the impact of stress and found a possible relationship to death from prostate cancer. This may open the door to further studies aimed at including stress management more aggressively in the overall management strategy of patients with this disease. This finding, if confirmed with additional studies, also has a potentially valuable insight into those men who select active surveillance. If the animal data is correct and stress contributes in some way to cancer growth then an important part of active surveillance will need to include stress management to help keep men from more rapid progression of their disease. We will look forward to further work in this area.

The Bottom Line: Stress management may need to become a part of prostate cancer management to help optimize survival.

a7p4c1 The debate about the relative merits of open vs. robot assisted radical prostatectomy (RP) is likely to continue for quite some time unless a well-designed study is actually done. The paper by Hu et al has concluded that robot assisted RP has a number of advantages making it a superior approach worth the added expense. They based this on a retrospective review of the SEER database. Unfortunately, neither their conclusion nor summary addresses all of the reasons why this analysis is flawed. To begin with, we know nothing about the expertise of those performing each method. How many do they do and what is their track record are just a few questions not addressed. Since there was no central review, the reader is led to believe that pathologist variability is non-existent and couldn't partly explain the results. This is very important for the initial Gleason score, which has been shown to vary considerably among pathologists or the final analysis of the RP specimen. Finally, no standardized approach was used to determine who should receive additional therapy after surgery, making that a very unacceptable measure to use when comparing these two approaches.

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THE BOTTOM LINE

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The Bottom Line: This paper does not inform us whether robot assisted RP is superior to the open approach.

a9p5c1 The study by Danneman is interesting because it has found that Gleason scores have been drifting higher due to changes in the way pathologists interpret biopsies. As the authors note, this has important implications for men considering active surveillance. Many doctors are reluctant to suggest AS for men unless the Gleason score is 6. However, as stated in this column before, we know that many men with a biopsy that is 3+3=6 actually are found to have 3+4=7 after RP. Looking at long term results of men on AS has shown a low mortality at 10 years so that must be true for many men found to have Gleason 7 on biopsy. Clearly, more information is needed to sort out this problem but men should realize that a Gleason score of 7 today might have been called Gleason 6 in the past.

The Bottom Line: Many men with a Gleason 7 today may not have more risk than men with a Gleason 6 in the past.

RELIABLE PRETREATMENT INFORMATION *(Continued from page 3)*

these LoF mutations, the authors wrote, and while several of the mutations identified had been previously associated with prostate cancer, others had not.

Because the study cohort was limited to men with a strong family history of prostate cancer, the group did not find any significant difference in cancer incidence between families with a LoF mutation and those without. However, the researchers did see a statistically significant increase in cancer severity for the subjects who were mutation-positive.

According to the group, while there was no significant association between LoF mutations and age of diagnosis, initial PSA, Gleason score, or tumor stage, there was a significant association between carrier status and lymph node involvement. And LoF mutation carriers had significantly higher odds of having advanced disease (Odds ratio = 15.09.

“Any future screening program would need to assess as many of these genes as possible – more than we currently look for in women at risk of breast cancer, for example,” said another study co-

leader, Zsofia Kote-Jarai. Although a market has grown around genetic prognostic testing for men who already have prostate cancer, molecular testing for prostate cancer risk has lagged behind breast and ovarian cancer screening.

Genomeweb.com, 26 February 2014

PCA3 AND TMPRSS2-ERG

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tivity of PCA3 increased from 68 percent to 76 percent when combined with TMPRSS2-ERG. TMPRSS2-ERG added significant predictive value to the ERSPC risk calculator to predict biopsy Gleason score (p<0.001) and clinical tumour stage (p=0.023), whereas PCA3 did not.

Conclusions: TMPRSS2-ERG had independent additional predictive value to PCA3 and the ERSPC risk calculator parameters for predicting PCa. TMPRSS2-ERG had prognostic value, whereas PCA3 did not. Implementing the novel urinary biomarker panel PCA3 and TMPRSS2-ERG into clinical practice would lead to a considerable reduc-

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