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US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

AUGUST 2013

'ACTIVE SURVEILLANCE' MAY MISS AGGRESSIVE PROSTATE CANCERS IN BLACK MEN

A Johns Hopkins study of more than 1,800 men ages 52 to 62 suggests that African-American (AA) men diagnosed with very-low-risk prostate cancers are much more likely than white men to actually have aggressive disease that goes unrecognized with current diagnostic approaches. Although prior studies have found it safe to delay treatment and monitor some presumably slow-growing or low-risk prostate cancers, such "active surveillance" (AS) does not appear to be a good idea for black men, the study concludes.

"This study offers the most conclusive evidence to date that broad application of AS recommendations may not be suitable for AA men," says urologist Edward M. Schaeffer, MD, PhD, a co-author of the study. "This is critical information because if AA men do have more aggressive cancers, as statistics would suggest, then simply monitoring even small cancers that are very low risk would not be a good idea because aggressive cancers are less likely to be cured," he says. "We think we are following a small, nonaggressive cancer, but in reality, this study highlights that in black men, these tumors are sometimes more aggressive than previously thought.

A report of the study, posted online and

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INCREASE SEEN IN USE OF ADVANCED TREATMENT TECHNOLOGIES FOR PROSTATE CANCER AMONG MEN WITH LOW RISK DISEASE

Use of advanced treatment technologies for prostate cancer, such as intensity-modulated radiotherapy (IMRT) and robot-assisted radical prostatectomy (RARP), has increased among men with low-risk disease, high risk of noncancer mortality, or both, a population of men who are unlikely to benefit from these treatments, according to a study published in the *Journal of the American Medical Association* (JAMA, vol. 309, pp. 2587-2595, 2013).

"Prostate cancer is a common and expensive disease in the US. In part because of the untoward morbidity of traditional radiation and surgical therapies, advances in the treatment of localized disease have evolved over the last decade. Chief among these are the development of IMRT and RARP," according to background information in the article.

"During a period of increasing population-based rates of prostate cancer treatment, both of these advanced treatment technologies have disseminated rapidly. However, the rapid growth of IMRT and RARP may have occurred among men with a low risk of dying from prostate cancer. Recognizing the protracted clinical course for most of these cancers,

(Continued on page 2)

OBSERVATION FOR PROSTATE CANCER – BETTER EFFICACY, COST, QOL

For many men with low-risk, localized prostate cancers who are 65 and 75 years of age, observation might be a better option than immediate treatment, and it costs less, according to a new modeling study. Following these men with either active surveillance (AS) or watchful waiting (WW) provided a better quality-adjusted life expectancy (QALE) at a lower cost than immediate treatment.

Furthermore, the researchers found that WW, which relies on observation without monitoring and palliative treatment when symptoms develop, was superior in terms of efficacy and cost to AS, which is more intensive and involves serial PSA tests, digital rectal examinations, and biopsies.

Specifically, WW provided two additional months of QALE for 65-year-old men, compared with AS (9.02 vs 8.85 years), at a savings of $15,374 ($24,520 vs $39,894). WW also provided 2 additional months for 75-year-old men (6.14 vs 5.98 years), at a savings of $11,746 ($18,302 vs $30,048).

Brachytherapy (BT) was the most effective and least expensive initial treatment, according to the study authors, led by Julia Hayes, MD, a medical oncologist in the Lank Center for Genitouri-

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INCREASING USE OF ADVANCED TECHNOLOGIES *(Continued from page 1)*

clinical guidelines recommend local treatment only for men with at least a 10 -year life expectancy."

"Aggressive direct-to-consumer marketing and incentives associated with fee-for -service payment may promote the use of these advanced treatment technologies," they write. "The extent to which these advanced treatment technologies have disseminated among men at low risk of dying from prostate cancer is uncertain."

Bruce L. Jacobs, MD, MPH, of the University of Michigan, Ann Arbor, and colleagues conducted a study to assess the use of advanced treatment technologies, compared with prior standards (i.e., traditional external beam RT [EBRT] and open RP) and observation, among men with a low risk of dying from prostate cancer. Using Surveillance, Epidemiology, and End Results (SEER) Medicare data, the researchers identified a retrospective group of 55,947 men diagnosed with prostate cancer between 2004 and 2009 who underwent IMRT, EBRT, RARP, open RP or observation. Followup data were available through December 2010. Low-risk disease was defined as clinical stage ≤T2a, biopsy Gleason score ≤6, and PSA level ≤10 ng/mL. High risk of noncancer mortality was defined as the predicted probability of death within 10 years in the absence of a cancer diagnosis.

Researchers found that the use of advanced treatment technologies was common among men with low-risk disease (an increase from 32 to 44 percent from 2004 to 2009), those with a high risk of noncancer mortality (from 36 percent to 57 percent from 2004 to 2009), and those with both low-risk disease and a high risk of noncancer mortality (from 25 to 34 percent from 2004 to 2009).

Among all men diagnosed with prostate cancer in SEER, the use of advanced treatment technologies for men unlikely to die of prostate cancer increased from 13 to 24 percent from 2004 to 2009, a relative increase of 85 percent. "That is, rates of IMRT and RARP use increased from 129.2 to 244.2 per 1,000 men diagnosed with prostate cancer from 2004 to 2009. At the same time, the use of prior standard treatments for men least likely to benefit decreased from 11 percent in 2004 to 3 percent in 2009," they wrote.

"The increasing use of both IMRT and RAPR in men unlikely to benefit from treatment was largely explained by their substitution for the treatments they aim to replace, namely EBRT and open RP."

The researchers suggest that the absolute magnitude of the use of new technologies in these populations has two important implications. "First, both treatments are considerably more expensive than the prior standards. Startup costs for both approach $2 million. Further, IMRT is associated with higher total episode payments, which translate into an additional $1.4 billion in spending annually."

"Second, and perhaps more important, the implementation of these technologies in populations unlikely to benefit from treatment occurred during a time of increasing awareness about the indolent nature of some prostate cancers and of growing dialogue about limiting treatment in these patients."

"Our findings suggest that even during this period of enhanced stewardship, incentives favoring the diffusion of these technologies outweighed those related to implementing a more conservative management strategy."

Bill Palos, a prostate cancer survivor and Illinois regional director for Us TOO, a non-profit group that advocates for people with the disease, commented that while there is some merit to the new study, to do nothing about a prostate cancer diagnosis is wrong. He also expressed concern that the new study might encourage insurance companies to not pay for screening exams or certain treatments.

Palos lost his father, two brothers, and a nephew to the disease. He stressed the importance of semi-annual exams beginning at age 40 for people with a family history of prostate cancer. In this case, knowledge is decision-making power.

Medical News Today, 25 June 2013

CROSS-RESISTANCE WITH NOVEL ANDROGEN BLOCKERS IN PROSTATE CANCER

There might be some cross-resistance between the two new androgen-blocking drugs for prostate cancer, despite their different mechanisms of action. It appears that abiraterone (Zytiga®) is less active when given after enzalutamide (Xtandi®), according to two new studies.[1,2] Also, some data suggests that docetaxel (Taxotere®), a cornerstone of the treatment of castration-resistant prostate cancer (CRPC), might be less effective when given after Zytiga.

Zytiga inhibits androgen synthesis, while Xtandi blocks androgen receptors (ARs). Both drugs were tested in clinical trials of men with CRPC who had already received Taxotere, however, prior treatment with either drug was an exclusion criterion in these studies. Those data led to US FDA approval of Zytiga and Xtandi for CRPC treatment in men failing docetaxel in April 2011 and August 2012, respectively.

The "equation may be very complicated," write Amir Goldkorn, MD, and David Ian Quinn, MBBS, PhD, FRACP, from the University of Southern California Norris Comprehensive Cancer Center and Ana Aparicio, MD, from the Department of Genitourinary Oncology at the University of Texas MD Anderson Cancer Center, in an editorial published in the *Annals of Oncology* in July.

Clinicians involved in making treatment decisions in this clinical setting could be left "pondering the opportunity cost of starting with one agent and keeping the others until later," they note.

Whether or not the mechanism of action of one drug could interfere with efficacy of the other agent had not been addressed until now. Both studies published in the same issue of *Annals of Oncology* provided this opportunity. In both studies, men with CRPC were treated with Taxotere and Xtandi, and then received Zytiga afterwards.

The French study[1] reported data on 38 CRPC men so treated. Of the 38, a PSA decline of at least 50% was achieved in 3 men, and at least a 30% reduction was achieved by 7 others. Of those who could be radiologically assessed, only

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

"Fish oil flops or is not having a very good year in medical research…so should you stop eating fish or using fish oil supplements???"

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: There are not a lot of folks that actually qualify to take fish oil supplements except those with very high levels of triglycerides (FDA approved for this) or perhaps receive some benefit against osteoarthritic pain or dry eye. And it is being studied to reduce hot flashes and kidney stones – otherwise if you are just taking fish oil for general health benefits you are probably wasting your money right now. Oh, and watching your weight is 100 times smarter than worrying about fish oil (sorry, you need to read the entire column to understand).

First, a major clinical trial using high-doses of fish oil does not prevent atrial fibrillation (the OPERA trial) any better than a placebo.[1] Then, a major European trial shows no impact of 1000 mg daily of omega-3 (ω-3) fatty acid (FA) or fish oil to reduce the risk of cardiovascular disease in those at high risk.[2] Next, one of the largest eye health studies in the world, shows no impact of 1000 mg of fish oil to reduce the progression of age-related macular degeneration.[3] And, now there is some evidence from the SELECT trial (remember that vitamin E and selenium study) that suggests high blood levels of ω-3FA lie the kind in fish and fish oil might increase the risk of prostate cancer (PCa) or really aggressive PCa.[4] Oh my! Does this sound too fishy to be true?

What does one do? Nothing except just treat fish oil like any other medicine and see if you qualify and if you do then you have to weigh the benefits vs. risks. Do I believe fish consumption or fish oil increases the risk of PCa? – nope! Do I believe fish oil reduces the risk of PCa? – nope! Do I believe fish oil does anything? – yup! I believe it helps some folks reduce abnormally high triglyceride levels, and it could reduce dry eye as well as arthritis pain for some folks. Do I personally take fish oil? – nope!

So, what has Dr. Moyad really learned from these 2012 and 2013 studies? The average person in the OPERA study had about a 40-inch waist! Almost 50% of those in the European only ω-3study were obese! Most of the individuals in the eye study were overweight and… Drum Roll Please! In the latest PCa and fish or FA study, more than 51% of the men were overweight and over 35% of the men were obese in the high-grade prostate cancer group! Yikes!

So, my point is simple, while most of us are running around and arguing and being distracted by the benefits or detriments of fish and fish oil, there is a clear worldwide obesity problem as reflected by statistics and the participants of these studies. And, since we know a large weight or waist can increase the risk of early death and probably increases the risk of aggressive PCa, many other cancers, heart disease, atrial fibirillation,, and eye disease, this needs to be the primary focus for getting healthy because weight loss is such a pain in the gluteus maximus, and takes so much time and attention. We will argue about fish over my entire lifetime, but the decision to eat fish in moderation as a part of a healthy diet will not go away anytime soon, and the decision to take pills will always be a matter of specifically qualifying for them based on individual situations and parameters. Do I think eating fish is overall heart and prostate healthy? – yup! Do I think it is a lot more important to focus as much as possible on achieving a healthy weight and waist compared to almost any supplement or pill? – yup! Do I like to say yup or nope a lot? Naaahhhhhh!

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2. Risk and Prevention Study Collaborative Group. N Engl J Med 368: 1800-1808, 2013.
3. AREDS2 Research Group. JAMA 309: 2005-2015, 2013.
4. Brasky T, Darke A, Song X, et al. J Natl Cancer Inst, 10 July 2013; Epub.

HEART HEALTHY DIET MAY BE HEALTHY FOR PROSTATE CANCER

A diet with reduced carbohydrates and animal fat and higher vegetable fat consumption could benefit men with prostate cancer (PCa). This dietary-fat mix mirrors a heart-healthy diet and was associated with better overall and PCa-related mortality in a large cohort of men, report the authors, led by Erin Richman, ScD, from the Department of Epidemiology and Biostatistics at the University of California, San Francisco., in a study published online in JAMA Internal Medicine.

"Overall, our findings support counseling men with PCa to follow a heart-healthy diet in which carbohydrate calories are replaced with unsaturated oils and nuts to reduce the risk of all-cause mortality," write the authors. Nuts and vegetable oils (e.g., olive and canola oil) supplied the vegetable fats associated with reduced overall and disease-specific mortality.

In their study, Dr. Richman and colleagues prospectively examined the dietary-fat intake of 4577 men with nonmetastatic PCa enrolled in the Health Professionals Follow-up Study, conducted from 1986 to 2010. The men, who are dentists, optometrists, and other professionals, but not physicians, completed a series of food frequency questionnaires over time.

The researchers looked at the men's intake of saturated, monounsaturated, polyunsaturated, trans, animal, and vegetable fat after a PCa diagnosis. They observed 315 events of lethal PCa and 1064 deaths (median follow-up, 8.4 years). When the researchers calculated the crude rate of lethal PCa per 1000 person-years, they found that men who ate more vegetable fat had lower mortality than men who ate less vegetable fat. No other fats were significantly associated with lethal PCa.

The team also performed modeling exercises on carbohydrate consumption from the study. Replacing 10% of calories from carbohydrates with vegetable fats was associated with a 29% lower risk for PCa death (hazard ratio [HR], 0.71; P=0.04) and a 26% lower risk for all-cause death (HR, 0.74; P=.001).

In statistical modeling, if 5% of energy from carbohydrates was replaced with saturated fat after diagnosis, all-cause mortality was significantly higher (HR, 1.30; P = 0.02). It was also higher if 1% of energy from carbohydrates was replaced with trans fat (HR, 1.25; P = 0.01).

In practical terms, the findings mean that men with PCa "should have olives or nuts for an appetizer instead of bread" and should "skip the croutons on their salad but have more oil-based dressing," Stephen Freedland, MD, from the Department of Urology at Duke University in Durham, NC.

He added that the study is not conclusive about dietary fat because it is not a randomized controlled trial. A trial being conducted at Duke, led by Dr. Freedland, should clarify the detrimental effects of carbohydrate consumption for men with PCa and whether carbohydrate restriction is associated with better outcomes.

Medscape Medical News, 13 June 2013

Mortality by Type of Fat	Highest Quintile	Lowest Quintile
Prostate Cancer (crude rate)		
Saturated	7.6	7.3
Monounsaturated	6.4	7.2
Polyunsaturated	5.8	8.2
Trans	8.7	6.1
Animal	8.3	5.7
Vegetable	4.7	8.7
All-cause		
Saturated	28.4	21.4
Monounsaturated	20.0	23.7
Polyunsaturated	17.1	29.4
Trans	32.4	17.1
Animal	32.0	17.2
Vegetable	15.4	32.7

BRISDELLE OKAYED AS FIRST NONHORMONAL TREATMENT FOR HOT FLASHES

The first nonhormonal drug for hot flashes associated with menopause was approved by FDA in June 2013 despite rejection by an advisory committee.

The drug is paroxetine mesylate (Brisdelle®, Noven Therapeutics). Paroxetine, a serotonin reuptake inhibitor, is the active ingredient in 2 drugs for depression and other psychiatric disorders, Paxil® (GlaxoSmithKline) and Pexeva® (Noven Therapeutics). Both drugs contain higher doses of paroxetine than the Brisdelle version for hot flashes.

In March, the FDA's Advisory Committee for Reproductive Health Drugs voted 10 to 4 against recommending approval of paroxetine as a treatment for hot flashes. Critics said the drug's minimal superiority to a placebo did not outweigh risk of suicide ideation and osteoporosis, 2 adverse events associated with paroxetine.

The FDA is not obliged to follow the advice of its advisory committees, but as in most cases, it usually does. In a news release, the agency seemed to explain why it overrode the recommendation of its advisory committee when it came to paroxetine mesylate.

"There are a significant number of women who suffer from hot flashes associated with menopause and who cannot or do not want to use hormonal treatments," said Hylton Joffe, MD, director of the Division of Bone, Reproductive and Urologic Products, FDA Center for Drug Evaluation and Research.

The FDA stated in the news release that paroxetine mesylate proved safe and effective in 2 clinical trials involving 1175 postmenopausal women with moderate to severe hot flashes. Headache, fatigue, nausea, and vomiting were the most common adverse events observed. By law, a physician may prescribe drugs to treat illnesses that are outside of the FDA-approved indications for a drug's use. Thus, Brisdell will be a new option for treating men with prostate cancer suffering hot flashes from androgen deprivation therapy.

The drug's label features a boxed warning about the increased risk for suicidality.

Medscape Medical News, 28 June 2013

OBSERVATION FOR PROSTATE CANCER *(Continued from page 1)*

nary Oncology at the Dana-Farber Cancer Institute in Boston, MA. Their study appeared 18 June in the *Annals of Internal Medicine* (Vol. 158, pp. 853-860, 2013). The researchers hope that this study will encourage wider use of observation, including WW, for men with low-risk disease.

In their modeling study, Dr. Hayes and colleagues performed a decision analysis simulating treatment or observation using data from Medicare schedules and the published literature, including PIVOT. The team looked at men 65 and 75 years of age with newly diagnosed low-risk prostate cancer (PSA level <10 ng/mL, stage ≤T2a disease, Gleason score ≤3+3=6) and made projections over their expected lifetime. Their primary outcome measures were QALE and healthcare costs. Treatment (BT, IMRT or RP) and observation (AS or WW) were analyzed.

The lifetime risk for death from prostate cancer in the model was 4.8, 6.0 and 8.9% for men on AS, WW, and those initially treated, respectively. Life expectancy was similar for the strategies: 81.6, 81.4 and 81.2 years for men on AS, WW, and initially treated, respectively. Estimated lifetime costs of each strategy, ranged from a low of $18,302 for WW for a 75-year-old man to a high of $48,699 for IMRT for a 65-year-old man.

Dr. Hayes stated that there are no strong numbers on the percentage of men managed with WW in the US. "We can't disentangle AS from WW in the studies that report treatment patterns, unfortunately," she told Medscape Medical News. "I do have patients I manage on WW, meaning I follow them without invasive surveillance because there is no treatment with curative intent – primarily elderly men with comorbidities," she explained. "I think observation, in general, is gaining traction in the community," Dr. Hayes added.

However, another expert in the field, whose institution also supports the use of observation for low-risk prostate cancer, believes this modeling study's findings are problematic.

"We believe that AS uptake among low-risk cases is increasing. Both AS and WW are definitely viable for older men with low-risk disease," said Roman Gulati, MS, from the division of public health sciences at the Fred Hutchison Cancer Research Center in Seattle, WA. Gulati, who was not involved in the study, was asked to comment on the strength of this statistically complex evidence.

"Clinicians should recognize that key study assumptions have weak support, particularly the assumption – based on a very uninformative subgroup analysis – that WW is more effective than radical prostatectomy (RP) for low-risk cases," he stated.

Gulati refers to the subgroup analysis from the Prostate Cancer Intervention Versus Observation Trial (PIVOT), which Dr. Hayes and colleagues leaned on heavily for their analysis. PIVOT investigators found that men with low-risk prostate cancer derived no benefit from RP, compared with WW after a median follow-up of 10 years in all-cause and prostate-cancer-specific mortality. However, Gulati said that the prostate cancer mortality data from PIVOT is underpowered, which throws off the conclusions of the modeling study.

"It's possible that the PIVOT point estimate [in the modeling study] is due to chance, since it's based on very few prostate cancer deaths in the WW and RP groups," he explained. Other PIVOT subgroup analyses yielded point estimates favoring RP over WW, but those were based on a Gleason score below 7 (hazard ratio [HR], 0.68) or, separately, based on a PSA ≤10 ng/mL (HR, 0.92) in a larger population of men.

"It seems suspicious that the only PIVOT subgroup comparison with a point estimate that favors WW over RP forms such an important basis of the main conclusions" of the modeling study, he said. To their credit, Dr. Hayes and colleagues acknowledge that their study is limited by the subgroup analysis from PIVOT, which has been "criticized for being underpowered."

Gulati also criticized another aspect of the modeling study. "This study does not compare different AS approaches, some of which may be more appealing than others, or argue in favor of WW over all AS protocols," he said.

Medscape Medical News, 21 June 2013

EXPANDED CRITERIA TO IDENTIFY MEN ELIGIBLE FOR ACTIVE SURVEILLANCE OF LOW-RISK PROSTATE CANCER AT JOHNS HOPKINS: A PRELIMINARY ANALYSIS

Reese AC, Landis P, Han M, Epstein JI, Carter HB

J Urol, 13 May 2013; Epub

Purpose: The following eligibility criteria are used to enroll patients in active surveillance at Johns Hopkins: clinical stage T1, PSA density < 0.15, biopsy Gleason score ≤ 6, ≤ 2 positive biopsy cores, and ≤ 50% involvement of any biopsy core. We hypothesized that these criteria may be excessively strict, thereby precluding many men from active surveillance.

Materials and Methods: We studied pathological outcomes in men treated between 1995 and 2012 with radical prostatectomy who met ≥ 4 of 5 active surveillance criteria. Outcomes included a definition of significant tumor (pathological Gleason ≥ 7 or non-organ confined). Rates of adverse pathology were compared between men meeting all vs 4 of 5 active surveillance criteria.

Results: Of 8261 men, 1890 (22.9%) met all AS eligibility criteria and 2133 (25.8%) met 4 of 5 criteria. Men exceeding PSA density and biopsy Gleason criteria were at increased risk of adverse pathological outcomes. Clinical stage > T1 was not associated with adverse pathology. Men with clinical stage T2 lesions, ≤ 3 positive biopsy cores, and < 60% core involvement were at comparable risk of significant tumors to men meeting all active surveillance criteria.

Conclusions: PSA density > 0.15 ng/ml and biopsy Gleason score ≥ 7 are strongly associated with adverse pathology at radical prostatectomy. Our findings suggest expanding active surveillance criteria to include men with clinical stage T2 lesions and a greater number of positive biopsy cores of low grade. Based on these preliminary findings, we are in the process of reassessing active surveillance eligibility criteria using more detailed pathological analysis.

USE OF 5A-REDUCTASE INHIBITORS FOR LOWER URINARY TRACT SYMPTOMS AND RISK OF PROSTATE CANCER IN SWEDISH MEN – NATIONWIDE, POPULATION BASED CASE-CONTROL STUDY

Robinson D, Garmo H, Bill-Axelson A, Mucci L, Holmberg L, Stattin P

BMJ 18 June 2013; Epub

Objective: To assess the association between 5α-reductase inhibitor (5-ARI) use in men with lower urinary tract symptoms (LUTS) and prostate cancer (PCa) risk.

Design: Nationwide, population based case-control study for men diagnosed with PCa in 2007-09 within the Prostate Cancer data Base Sweden 2.0.

Setting: National Prostate Cancer Register, National Patient Register, census, and Prescribed Drug Register in Sweden, from which we obtained data on 5-ARI use before date of PCa diagnosis.

Participants: 26,735 cases and 133,671 matched controls; 5 controls per case were randomly selected from matched men in the background population. 7815 men (1499/6316 cases /controls) had been exposed to 5-ARI. 412 men had been exposed to 5-ARI before diagnosis of a cancer with Gleason score 8-10.

Main Outcome Measures: Risk of PCa calculated as odds ratios and 95% confidence intervals (CI) by conditional logistic regression analyses.

Results: Risk of PCa overall decreased with an increasing duration of exposure; men on 5-ARI treatment for more than 3 years had an odds ratio of 0.72 (95% CI 0.59 to 0.89; P<0.001 for trend). The same pattern was seen for cancers with Gleason scores 2-6 and score 7 (both P<0.001 for trend). By contrast, the risk of tumours with Gleason scores 8-10 did not decrease with increasing exposure time to 5-ARI (for 0-1 year of exposure, odds ratio 0.96 (95% CI 0.83 to 1.11); for 1-2 years, 1.07 (0.88 to 1.31); for 2-3 years, 0.96 (0.72 to 1.27); for >3 years, 1.23 (0.90 to 1.68); P=0.46 for trend).

Conclusions: Men treated with 5-ARI for LUTS had a decreased risk of cancer with Gleason scores 2-7, and showed no evidence of an increased risk of cancer with Gleason scores 8-10 after up to four years' treatment.

ACTIVE SURVEILLANCE IN AFRICAN-AMERICAN MEN *(Continued from page 1)*

ahead of the print version in the *Journal of Clinical Oncology*, describes it as the largest analysis of potential race-based health disparities among men diagnosed with a slow-growing, very nonaggressive form of prostate cancer.

The Johns Hopkins study also showed that the rate of increased pathologic risk, as measured by the Cancer of the Prostate Risk Assessment (CAPRA), was also significantly higher in AA men (14.8 percent vs. 6.9 percent). Schaeffer and his team say their data suggest that "very-low-risk" AA men have different regional distributions of their cancers and appear to also develop more high-grade cancers. Researchers added that these tumors hide in the anterior prostate – a region that is quite difficult to assess using current biopsy techniques.

All study participants, of whom 1,473 were white and 256 black, met current National Comprehensive Cancer Network (NCCN) criteria for very-low-risk prostate cancer, and were thus good candidates for AS. The study showed that preoperative characteristics were similar for very-low-risk whites and blacks, although black men had slightly worse Charlson comorbidity index scores, a commonly used scale for assessing life expectancy. Detailed analysis showed that black men had a lower rate of organ-confined cancers (87.9 percent vs. 91.0 percent), a higher rate of Gleason score upgrading (27.3 percent vs. 14.4 percent) and a significantly higher hazard of PSA defined biochemical recurrence (BCR) of prostate cancer. The latter measure is widely used for reporting the outcome of surgical prostate removal.

The median age of men in his study was 58, younger than the median ages (62 to 70) of most men in AS groups, Shaeffer stated. He cautioned that the age difference is a potential "confounder" of his results, highlighting the need for more studies to gauge the safety of AS.

Schaeffer, associate professor of urology, oncology and pathology at the Johns Hopkins University School of Medicine and director of global urologic services for Johns Hopkins Medicine International and co-director of the Prostate Cancer Multi-Disciplinary Clinic at The Johns Hopkins Hospital's James Buchanan Brady Urological Institute, emphasizes that "the criteria physicians use to define very-low-risk prostate cancer works well in whites – this makes sense, since the studies used to validate the commonly used risk classification systems are largely based on white men." But, he adds, "Among the vast majority of AA males with very-low-risk cancer who underwent surgical removal of the prostate, we discovered that they face an entirely different set of risks."

"Alternate race-specific AS entry criteria should be developed and utilized for AA men to ensure oncologic parity with their white counterparts. Our research team, in collaboration with the internationally recognized Hopkins pathologist Dr. Jonathan Epstein, is currently developing new race-based risk tables that begin to solve this key issue," he adds.

All of the men whose records were analyzed for the current study were selected from a group of 19,142 who had surgery at The Johns Hopkins Hospital between 1992 and 2012 to remove the prostate gland and some of the tissue around it.

Previous published research, Schaeffer says, revealed significant racial disparities in prostate cancer, with AA men having a much higher incidence of death from the disease than Caucasian men. According to the National Cancer Institute, black men have considerably higher incidence rates (236 cases per 100,000 from 2005 to 2009) than white men (146.9 cases per 100,000 per 2005 to 2009). The reasons for this are unclear.

The main limitation to their study is that it is a retrospective analysis of the experience of a single academic medical center. "The results of our study do not support the universal rejection of AS in black men, but, rather, should promote future studies to address whether alternate race-specific AS entry criteria should be used for AA men to ensure oncologic parity with their white counterparts," adds Schaeffer.

Besides Schaeffer, other Johns Hopkins investigators involved in this study were lead investigator Debasish Sundi, MD; Ashley E. Ross, MD, PhD; Elizabeth B. Humphreys, MD; Misop Han, MD; Alan W. Partin, MD, PhD; and H. Ballantine Carter, MD.

Science Daily, 25 June 2013

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

Gerald Chodak, MD 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 Around the world, active surveillance (AS) is increasingly being discussed as an appropriate option for many men with newly diagnosed prostate cancer. (PCa) This has mostly been based on studies involving Caucasian men. The study by Schaeffer and co-workers raises an important question whether African-American (AA) men can be managed this way using the same criteria. Their findings suggest that AA men have a greater chance of having more aggressive PCa after their prostate is removed. The problem with this analysis, however, is that it does not inform us about long-term AS outcome. It is only a static look at the pathology findings. One can argue that this conclusion is incorrect based on the PIVOT trial that randomized men to watchful waiting vs. radical prostatectomy (RP). In that report, survival was not significantly different in the AA men treated conservatively or by RP and many of them did not have very low risk disease. The authors were careful to point out that they could not make a strong recommendation against AS in AA men at this time and more information is needed. To really know the level of risk for this ethnic group, long-term outcomes rather than pathologic findings will be needed.

a8p5c3 A second article by Johns Hopkins assessed whether criteria they use to select men for AS is too strict and can be modified. They looked at the pathological findings according to the criteria they have traditionally used to select men for AS and found that T2 disease and having 3 cores positive did not convey a worse pathological finding. The problem with this analysis is similar to that stated above; the study provides no data on long-term outcomes. For that reason, conclusions from this study are limited concerning the best criteria for AS.

The Bottom Line: Attempts to identify the best and worst men for AS cannot be assessed accurately when they are only based on pathological findings after RP because it does not tells us anything about what would have happened to those men in the future had they been treated conservatively.

a2p1c2 In a related article, Jacobs and co-workers analyzed a national database and found a marked increase in the use of IMRT and Robot-Assisted Laparoscopic Prostatectomy (RALP) in men with low risk PCa. In other words, despite the fact that mortality risk is low, many more men undergo these expensive therapies. From this study, we cannot determine how these men were counseled before treatment was offered. Even when men are objectively presented the pros and cons of AS, a large percentage still want therapy. However, misleading marketing and advertising about these treatments combined with incomplete presentations about conservative management very likely contribute to this treatment shift. The question is what should be done? One solution is to mandate that a clinician present standardized information to men with regards to all of available treatment options.

Mr. Palos is rightly concerned that insurance companies may attempt to lower costs, especially when the more expensive therapies have not been shown to result in better outcomes. Clearly, the cost for managing PCa is escalating. This is partly due to the newer therapies for men with advanced disease. But it is also because more cancers are detected and most of those who are treated will not benefit. If we hope to avoid rationing in the future, something needs to be done to make sure that the right men get these treatments while sparing many from something that is unlikely to help them live longer or better lives.

a3p1c3 The cost implications of managing early stage PCa are also the focus of the article by Hayes and co-workers who created a mathematical model to project the long term costs of different treatments. Their conclusion is that conservative therapy is not only less costly but it slightly improves quality-adjusted life expectancy (QALE). Their analysis is interesting but as the critic points out, it is a projection based substantially on the PIVOT study. Unfortunately, it is quite possible that more uncertainty exists about those results than was acknowledged by the investigators. Modeling is an interesting method for getting an idea of what may happen in the future with different strategies, but there is no way to determine if it is correct without doing a prospective study. In other words, one cannot make firm conclusions based on the techniques that were used.

The Bottom Line: Conservative management of low risk prostate cancer may be the most cost-effective option and the best impact on QALE but only a prospective study can determine if these findings are correct.

a4p3c1 Since abiraterone and enzalutamide were approved for the treatment of men with metastatic castrate resistant PCa (CRPC), doctors often must decide which drug to use first. Two studies in this *HotSheet* article evaluated the effect of abiraterone in men failing docetaxel and enzalutamide. Both studies suggest that abiraterone is less effective when given after enzalutamide. The authors suggest that the mechanism tumors use to develop resistance to enzalutamide may be similar to the mechanism of resistance to abiraterone. For the moment, this may not be very meaningful, because enzalutamide is yet to be FDA approved for treating CRPC before chemotherapy. At this time, no information is available to determine if response to enzalutamide is also limited if the drug is given after abiraterone. If that occurs, a study should be done combining the drugs to see if there is any added benefit compared to using them sequentially.

The Bottom Line: Early data suggests that abiraterone is less effective if given after enzalutamide in men with mCRPC, but more studies are needed to determine the best way to use these 2 drugs.

a6p4c1 The article by Richman et al evaluated the potential impact of diet for managing this disease. They performed an epidemiological analysis of men and found that those with more vegetable fat and less animal fat in their diet had better overall survival. Also, using vegetable fat to replace calories from carbohydrates also resulted in better survival and lower PCa mortality. This study raises

(Continued on page 8)

DR. CHODAK'S BOTTOM LINE *(Continued from Page 7)*

important questions about conservative therapy. For example, would it be possible to further delay disease progression in men with low risk PCa if they were to modify their diet by increasing vegetable fat intake or making other changes? For many, an active program consisting of diet and exercise or other conservative interventions may help more men accept AS if they believe they were doing "something" rather than "nothing". Perhaps ongoing AS programs can begin the necessary randomized studies needed to assess if this can work.

The Bottom Line: An increasing number of epidemiological studies suggest that diet plays some role in the outcome of men with PCa and it may offer an opportunity to slow disease progression in men managed conservatively.

a9p6c1 The last paper addresses whether or not 5 alpha reductase inhibitors (5-ARIs) prevented a diagnosis of PCa in Swedish men. The authors compared PCa incidence in men who had not received 5-ARIs and found lower cancer detection rate in men with Gleason ≤7. There was an insignificant trend toward a greater percentage of men with Gleason 8-10. Some may conclude that 5-ARIs offer real benefit, but long-term benefits are unclear. Men with Gleason 8-10 disease are at highest risk of dying from PCa, so if the same proportion of high grade cancers occurs, mortality may not be greatly affected even if fewer cancers are diagnosed..

The Bottom Line: 5-ARI drugs do lower the likelihood of a PCa diagnosis but no evidence exists that it affects survival or mortality and until that does occur, the drugs cannot be recommended.

CROSS-RESISTANCE WITH NOVEL ANDROGEN BLOCKERS *(Continued from Page 3)*

1/12 achieved a confirmed partial response. They concluded that Zytiga has a modest effect in CRPC previously treated with Taxotere and Xtandi.

The Canadian study[2] reported data on 30 men with CRPC. A PSA decline >30% was achieved in 3/30 men, 2 of whom had PSA progression with Taxotere and Xtandi as a best response. "In this study of patients progressing after enzalutamide, treatment with abiraterone was associated with a modest response rate and brief duration of effect," they conclude.

The 2 studies "lead us to presuppose that abiraterone will be less active after enzalutamide, but not in every patient," write the editorialists. There were some recorded responses to Zytiga in men with early resistance to Xtandi. This "emergence of cross-resistance underscores the need for determining the optimal sequencing of novel agents."

How these drugs will fare when given in the opposite sequence – is now being addressed. Up to 80% of the men now entering Xtandi expanded-access programs will have been previously treated with Zytiga, the editorialists note.

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1. Loriot Y, Bianchini D, Ileana E, et al. Ann Oncol 24: 1717-1720, 2013.
2. Noonan KL, North S, Bitting RL, et al. Ann Oncol 24: 1802-1807, 2013.

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