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FDA APPROVES ABIRATERONE FOR METASTATIC PROSTATE CANCER

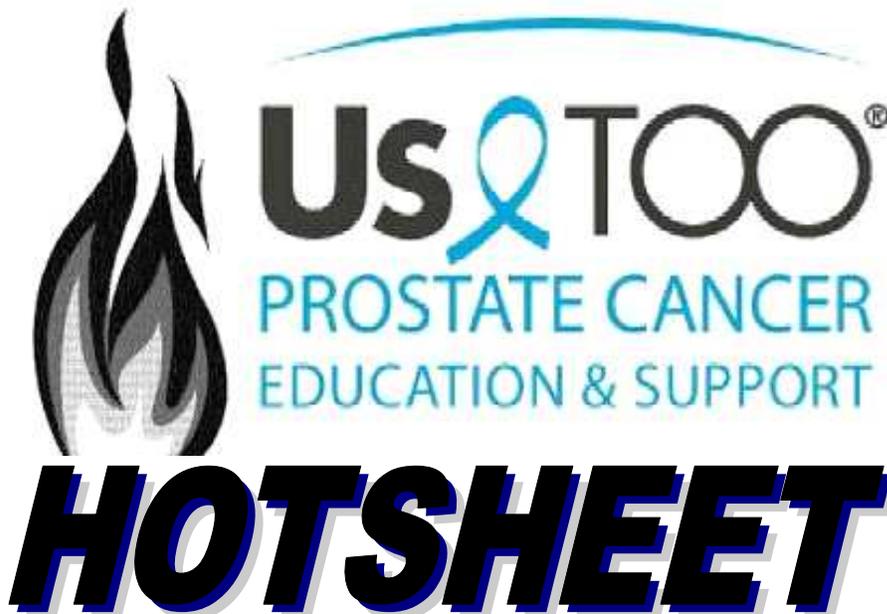
The US Food and Drug Administration (FDA) has approved abiraterone acetate (Zytiga®, Cougar Biotechnology) in combination with prednisone for the treatment of metastatic, castration-resistant prostate cancer (CRPC) in men who have received prior docetaxel (Taxotere®) chemotherapy. The application was reviewed under the FDA's priority review program, and the new oral agent is being approved ahead of the product's June 20, 2011, regulatory goal date, according to the FDA.

In the pivotal COU-AA-301 trial, patients who received abiraterone acetate plus prednisone had a median overall survival duration of 14.8 months, compared with 10.9 months for patients receiving prednisone plus placebo. The difference was statistically significant.

"Zytiga prolonged the lives of men with late-stage prostate cancer who had received prior treatments and had few available therapeutic options," said Richard Pazdur, MD, director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

Abiraterone treatment also resulted in significant differences between the 2

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JUNE 2011

PROSTATE CANCER: EARLY SURGERY OR WATCHFUL WAITING?

Fifteen-year results from a Swedish study show that early prostate surgery cuts deaths in men under 65 with "low-risk" prostate tumors – but for men today, the definition of "low risk" has changed.

The study of 695 men with early prostate cancer assigned half to immediate surgery – radical prostatectomy (RP) – and half to watchful waiting (WW). Initial results, reported in 2002, showed that early surgery improved survival.

Now, 15 years after the study began, it's clear that men who underwent early surgery cut their risk of death from prostate cancer by 38%.

However, only men under age 65 saw this benefit. Early surgery did not significantly improve survival in men diagnosed with prostate cancer after age 65, notes Anna Bill-Axelsson, MD, PhD, lead author of the report in the 5 May 2011 *New England Journal of Medicine*.

"What we see is that surgery reduces prostate cancer deaths, but that not all patients need to undergo surgery," Bill-Axelsson said. "It depends on age, on the presence of other medical conditions, on patient preference, and on how the tumor looks. You cannot generalize and say everybody needs to undergo surgery."

(Continued on page 8)

PROSTATE CANCER BIOPSY MAY PROGRESS WITHOUT PSA CHANGES

In patients with low-risk prostate cancer, biopsy progression may occur in the absence of significant changes in prostate specific antigen (PSA), according to a report in the March 21st online issue of *The Journal of Urology*.

"In well selected men with early stage prostate cancer, there is very little change in PSA over the first 24 months of surveillance," Dr. Jared M. Whitson from University of California-San Francisco, told Reuters Health by email. "While a stable PSA may decrease anxiety for patients between biopsies, the results of this study show that biopsy remains a critical component of monitoring for disease progression."

Dr. Whitson and colleagues investigated the concordance between PSA changes and biopsy progression during the first 24 months of active surveillance (AS) in 241 men with prostate cancer.

The median change per year in the natural logarithm (ln) of PSA was 0 ng/mL, for a yearly PSA ratio of 1.0, based on 4 PSA measurements per patient collected during a median of 15 months of follow-up. Seven men had a 50% decrease in PSA within 3 years, and only one patient had a PSA doubling within 3 years.

(Continued on page 8)

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STUDY SUPPORTS WATCHFUL WAITING FOR LOW RISK PROSTATE CANCER

Active surveillance (AS) for low-risk prostate cancer offers a safe alternative to immediate curative intervention and may reduce overtreatment and adverse events, investigators in a large clinical study concluded. A third of 769 patients eventually had surgery or radiation therapy, but delaying intervention for as long as 10 years caused no apparent harm. The cohort had a median survival free of intervention of 6.5 years, and the 10-year intervention-free survival was 41% in study participants, who had a median age of 66 at diagnosis, according to an article published online in the *Journal of Clinical Oncology*.

"This study offers the most conclusive evidence to date that AS may be the preferred option for the vast majority of older men diagnosed with a very low-grade or small-volume form of prostate cancer," senior author H. Ballentine Carter, MD, of Johns Hopkins, said in a statement. "These are men with a favorable-risk disease profile to begin with."

Since widespread use of PSA screening for prostate cancer began in the 1990s, disease stage at diagnosis has declined dramatically, such that the majority of newly diagnosed prostate cancers are low risk. Although highly successful, PSA screening has sparked controversy about the potential for overdiagnosis and overtreatment of clinically trivial disease that would not become life-threatening in a man's lifetime.

Further evidence of overdiagnosis and overtreatment has come from recent studies suggesting that prevention of one prostate cancer death would require active treatment of 48 men for nine years or 12 men for 14 years. Moreover, results of two large prostate cancer screening studies showed no evidence of a survival benefit with PSA testing.

Several studies of AS with curative intent have shown a low prostate cancer-specific mortality during relatively short-term follow-up, Carter and co-authors noted in the introduction of their paper. But those positive findings have failed to quell concern that delaying definitive treatment for prostate cancer might sacrifice the window of opportunity to achieve a cure.

Since 1995 Carter and colleagues at Johns Hopkins have offered AS with curative intent as an alternative to immediate intervention for older men with clinically low-risk prostate cancer (T1c or lower). Preliminary data was published in 2002 that supported the conservative strategy for selected older men with low-risk prostate cancer.

In the current paper, the authors reported updated results of the Johns Hopkins AS experience with a larger patient population. The program's entry criteria, which have since been adopted by the National Comprehensive Cancer Network, consist of:

- Disease stage \leq T1c at diagnosis
- PSA density $<$ 0.15 ng/mL
- Gleason score \leq 6
- Two or fewer biopsy cores with cancer
- No core with more than 50% cancer

Selected patients with a Gleason score \leq 6 but who otherwise did not meet the criteria could enter AS if they had comorbidities that precluded immediate intervention or if they preferred AS for personal reasons. The AS protocol included semiannual PSA testing and digital rectal examination and annual 12- or 14-core biopsy. Clinicians recommended curative intervention to men who no longer met entry criteria at follow-up.

The total cohort has a median follow-up of 2.7 years (range 0.01 to 15). Several baseline characteristics differed significantly between men who opted for definitive therapy during follow-up and those remaining in AS. Median values for the active treatment and AS groups were: PSA, 5.0 vs. 4.7 ng/mL ($p=0.003$), percent free PSA, 16.2 v 18.0% ($p=0.024$), PSA density, 0.11 v 0.10 ng/mL ($p <0.001$) and year of diagnosis, 2003 v 2006 ($p <0.001$), respectively.

Men who did not meet all entry criteria

(Continued on page 8)



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<http://ustoo.inspire.com>

ANOTHER ENDOTHELIN BLOCKER FAILS IN PROSTATE CANCER

When combined with docetaxel, atrasentan did not slow disease progression or improve survival compared with chemotherapy alone in a phase III trial, according to a statement from the SWOG cooperative research group (formerly Southwest Oncology Group), which conducted the NCI-sponsored trial.

The S0421 trial ended after reaching the halfway point, when a planned interim analysis showed “the evidence indicating no benefit from [atrasentan] was strong enough to close the study,” SWOG officials said in the statement.

It gave no details about safety or efficacy outcomes when the trial ended, although SWOG indicated that the drug was not harming patients.

The trial involved patients with advanced, castration-resistant prostate cancer. All patients received docetaxel and prednisone and were randomized to atrasentan or placebo. Follow-up was supposed to continue for 36 months, but ended after 18 months and enrollment of 1,000 randomized patients.

Patient enrollment stopped in April 2010, and few patients continue to receive atrasentan, according to SWOG.

In February, investigators in another phase III trial announced a premature ending after the anti-endothelin agent zibotentan failed to improve outcomes in advanced prostate cancer when added to chemotherapy. That trial stopped because another study of zibotentan plus chemotherapy showed no advantage over chemotherapy alone in men with advanced prostate cancer.

Development of endothelin receptor antagonists for prostate cancer followed evidence that dysregulation of the endothelin pathway plays a role in prostate cancer progression.

Evaluation of these agents in other diseases continues – notably in diabetic nephropathy. Endothelin receptor antagonists were initially developed as antihypertensive drugs, with the first-in-class compound bosentan (Tracleer®) currently approved for pulmonary arterial hypertension.

MedPage Today, 23 April 2011

SURGERY FOR EARLY PROSTATE CANCER *(Continued from page 1)*

The study showed that:

- Overall, 15 men had to undergo RP to save one death from prostate cancer. For men under age 65, seven had to be treated to prevent one death.
- Men whose tumors had broken through the prostate capsule had a much higher risk of death than did those with organ-confined tumors.
- 63% of men assigned to WW and 40% of men assigned to RP needed androgen-deprivation therapy (ADT), which has serious side effects that include sexual dysfunction, fatigue, and risk of diabetes and heart disease.
- More men in the WW group than in the RP group died from causes other than prostate cancer but had spreading prostate cancer at that time which would likely have been fatal.

Possibly the most important study finding is that among younger men, RP improved survival even in those with prostate tumors considered to be low risk – by the standards of the decade 1989-1999.

“When we say the low-risk group benefits from surgery, it is not as we would define a low-risk group by today’s standards,” Bill-Axelsson says. “It is important that people don’t panic and all go for surgery. It is important to have people closely watched and to undergo surgery when necessary.”

There are degrees of “low risk” for prostate tumors, says prostate cancer expert Matthew R. Smith, MD, PhD, director of the genitourinary malignancies program at Massachusetts General Hospital. Smith’s editorial accompanies the Bill-Axelsson study in the *New England Journal of Medicine*.

Smith notes that in the Swedish study, 88% of the men had tumors that could be felt on a rectal exam, and only about 5% had their cancer detected via PSA screening tests. In the US today, fewer than half of men diagnosed with prostate cancer have tumors that can be felt on a rectal exam, and most cancers are detected via PSA screening. This means that today, most prostate cancers are diagnosed seven to 10 years earlier than they were when the men in the Swedish study were diagnosed.

“Since these cancers were not well represented in the Scandinavian study, we

cannot generalize from this to say men diagnosed with low-grade cancer today would derive the same benefit. We still don’t know if we have to treat all of those men,” Smith tells WebMD.

But Smith agrees with Bill-Axelsson that immediate treatment isn’t necessary for all of these men. When a patient’s biopsy shows that a prostate tumor has a low grade, and that tumor volume is small, the patient is a likely candidate for active surveillance (AS).

“We do enthusiastically recommend AS in carefully selected patients,” Smith says. “This is not to say, ‘Have surgery or go off on your own.’ It is actively monitoring men with low-risk disease and selectively intervening when there is sufficient information about the cancer to justify treatment.”

“We can individualize patient decisions,” Smith says. “We may not have all the information we need, but we can still make good decisions.”

WebMD Health News, 4 May 2011

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1 IN 6 MEN WILL BE DIAGNOSED WITH PROSTATE CANCER IN THEIR LIFETIME

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US TOO International is proud to be one of the featured teammates and resource partners in ON THE LINE – a groundbreaking initiative that harnesses the power of sports and celebrities to challenge men to get off the sidelines and take charge of their prostate health. Visit www.OnTheLine.com for videos, magazines and many other resources.

UPGRADE IN GLEASON SCORE BETWEEN PROSTATE BIOPSIES AND PATHOLOGY FOLLOWING RADICAL PROSTATECTOMY SIGNIFICANTLY IMPACTS RISK OF BIOCHEMICAL RECURRENCE

Corcoran NM, Hong MK, Casey RG, et al

BJU Int 28 March 2011; Epub ahead of print

To determine the effect of an upgrade in Gleason score between initial prostate biopsy and final prostatectomy specimen on the risk of postoperative biochemical recurrence

A total of 1629 patients with paired biopsy and radical prostatectomy histology were identified from two prospectively recorded prostate cancer databases. Information on key clinical and pathological characteristics as well as prostate-specific antigen follow-up was recorded. Patients who experienced an upgrade in their Gleason score were compared with corresponding patients with concordant tumours of the lower and higher grade. Kaplan-Meier curves and multivariate models were generated to examine the impact of Gleason score upgrade on the risk of postoperative biochemical recurrence.

Overall, 466 patients (28.6%) experienced an upgrade in their Gleason score post radical prostatectomy, in 88.4% of cases involving a change in a single Gleason score point. Patients upgraded from Gleason 6 (3+3) to Gleason 7 (3+4) had pathological characteristics that were very similar to Gleason 7 (3+4) concordant tumours, with an identical risk of biochemical recurrence. In contrast, patients upgraded from Gleason score 6 (3+3) to Gleason 7 (4+3) had tumours with pathological characteristics intermediate between the two concordant groups, which was mirrored by their risk of biochemical recurrence.

Patients with Gleason 7 tumours who experienced a change in the predominant pattern from 3+4 to 4+3 had tumours that resembled Gleason 7 (4+3) concordant tumours, with a similar risk of biochemical recurrence. In contrast, patients upgraded from Gleason 7 to Gleason >7 had tumours with intermediate pathological characteristics, and a risk of biochemical recurrence that was significantly different to concordant tumours of the lower and higher grade.

In multivariate models, a change in Gleason score was an independent predictor of biochemical recurrence in the preoperative setting only. Although a difference in Gleason score was an independent predictor of recurrence in concordant tumours in models based on postoperative variables, an upgrade in Gleason score in discordant tumours was not, with differences in co-segregated adverse pathological characteristics being more predictive.

Patients experiencing an upgrade in their Gleason score between biopsy and final specimen exhibit significantly more aggressive pathological features than corresponding concordant tumours, and a higher risk of biochemical recurrence post radical prostatectomy. As Gleason score can be more accurately assessed preoperatively than other prognostic tumour features, continued effort is required to identify those most at risk of upgrading, and to refine biopsy strategies to reduce sampling error.

OVERTREATMENT OF MEN WITH LOW RISK PROSTATE CANCER AND SIGNIFICANT COMORBIDITY

Daskivich TJ, Chamie K, Kwan L, et al

Cancer 117(10): 2058-66, 2011

BACKGROUND: Men with low-risk prostate cancer and significant comorbidity are susceptible to overtreatment. The authors sought to compare the impact of comorbidity and age on treatment choice in men with low-risk disease.

METHODS: The authors sampled 509 men with low-risk prostate cancer diagnosed at the Greater Los Angeles and Long Beach Veterans Affairs Medical Centers between 1997 and 2004. Rates of aggressive treatment (radical prostatectomy, radiation therapy, brachytherapy) were determined among men of different ages and with different Charlson comorbidity scores. Multivariate modeling was used to determine the influence of both variables in predicting nonaggressive treatment, and Cox proportional hazards analysis was used to compare the risk of other-cause mortality among groups according to Charlson score and age.

RESULTS: Men with Charlson scores ≥ 3 were treated aggressively in 54% of cases (30 of 56 men), while men aged >75 years at diagnosis were treated aggressively in 16% of cases (7 of 44 men). In multivariate analysis, age >75 years was a much stronger predictor of nonaggressive treatment (relative risk, 12.0; 95% confidence interval [CI], 5.4-28.3) than a Charlson score ≥ 3 (relative risk, 2.0; 95% CI, 1.3-2.9). In survival analysis, men with Charlson scores ≥ 3 had an 8-fold increased risk (hazard ratio, 8.4; 95% CI, 4.2-16.6) and 70% probability of other-cause mortality at 10 years, whereas age >75 years was associated with a 5-fold increased risk (hazard ratio, 4.9; 95% CI, 1.7-13.8) and a 24% probability of other-cause mortality.

CONCLUSIONS: Men with significant comorbidity often were overtreated for low-risk prostate cancer. Like advanced age, significant comorbidity should be a strong relative contraindication to aggressive treatment in men with low-risk disease.



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**NCT01057810 – PHASE 3
STUDY OF IMMUNOTHERAPY
TO TREAT ADVANCED
PROSTATE CANCER**

Background:

Ipilimumab is an investigation drug that targets the body’s own immune system. It stimulates the immune system to attack cancer cells by removing a brake that prevents immune cells from attacking the body’s own tissues. Ipilimumab is an antibody that removes this check on the system by binding to a molecule of the surface of T cells called CTLA4. The drug has recently been shown to improve survival in patients with advanced stages of malignant melanoma.

Primary outcome measure:

The purpose of this study is to determine if patients with metastatic prostate cancer who have not received chemotherapy live longer when treated with ipilimumab than patients that are treated with a placebo.

Secondary outcome measures:

- Compare Progression Free Survival (PFS) by collecting tumor assessments every 12 weeks.
- Compare time to pain progression by collection of a Patient Pain Diary prior to each treatment visit.
- Compare time to subsequent non-hormonal systemic therapy.

Inclusion Criteria:

- Males age 18 years and older
- Asymptomatic or minimally symptomatic metastatic prostate cancer
- Progression during hormonal therapy
- ECOG Performance Status 0-1

Exclusion Criteria:

- Liver, lung or brain metastases
- Prior immunotherapy or chemotherapy for metastatic prostate cancer
- Autoimmune disease
- HIV or Hepatitis B or C infection

The study is sponsored by Bristol-Myers Squibb and there are clinical study sites throughout the US that are actively recruiting patients. The estimated enrollment is 600 patients.

For more information, go to <<http://clinicaltrials.gov/ct2/show/study/NCT01057810#locn>>.

FDA APPROVES ABIRATERONE (ZYTIGA)

(Continued from page 1)

treatment groups for all the COU-AA-301 trial’s secondary endpoints, including time to PSA progression, radiographic progression-free survival (PFS), and PSA response rate. These results and the survival data were presented this year at the 35th European Society for Medical Oncology (ESMO) Congress.

In study, Abiraterone investigator Johann de Bono, MBBS, PhD and colleagues randomly assigned 1,195 CRPC patients previously treated with docetaxel to abiraterone, 1000 mg, plus prednisone, 5 mg, twice daily (n = 797) or placebo plus prednisone (n = 398).

pared with 8.1% in the placebo group. Cardiac problems were also more common in the abiraterone group.

Abiraterone investigator Johann de Bono, MBBS, PhD, suggested that the modest improved survival was impressive in light of the efforts to date in the field. “While 3.9 months may not seem like much, in the history of prostate cancer, only 4 drugs have ever shown a survival benefit,” he noted at ESMO.

Overall, Dr. de Bono believes that the drug is not terribly toxic. “It is an oral agent and does not have the toxicity of chemotherapy, and it is well tolerated in

Response	Abiraterone	Placebo	P value
Median overall survival (mo)	14.8	10.9	<0.0001
Time to PSA progression (mo)	10.2	6.6	<0.0001
Radiographic PFS (mo)	5.6	3.6	<0.0001
PSA reponse	38%	10%	<0.0001

Adverse events were more commonly observed in the abiraterone group. Fluid retention was more common (30.5% vs. 22.3%), as was hypokalemia (17.1% vs. 8.4%), but grade 3/4 hypokalemia (3.8% vs. 0.8%) and grade 3/4 hypertension (1.3% vs. 0.3%) were infrequent. Liver function test abnormalities were reported in 10.4% of the patients who received the investigational agent com-

my experience,” he said at ESMO.

The new drug targets the protein cytochrome P450 17A1 (CYP17A1), which plays an important role in the production of testosterone, according to the FDA. Abiraterone works by decreasing the production of testosterone, which stimulates prostate cancer cell growth.

Medscape Medical News, 28 April 2011

SUPPLEMENTS DON’T PREVENT PROSTATE CANCER

A new study deflates hopes that certain nutritional supplements could stave off prostate cancer.

Canadian researchers found that vitamin E, selenium and soy, taken daily for 3 years, provided no benefit to men who were at a higher risk of developing the disease. The findings come 3 years after a larger study of men, who were not at increased risk of disease, also found no benefit of selenium or vitamin E.

Initially, there had been high hopes for these supplements, said researcher Dr. Neil Fleshner, who heads the urology department at the University Health Network in Toronto. Surveys of people who consumed high levels of these nutrients through diet or by supplements had a decreased risk of developing prostate

cancer, and lab experiments in animals also showed a benefit.

In this study, the researchers randomly assigned 303 men to take either a combination of the supplements or a non-nutritive powder that resembled the supplements every day for 3 years. The combination included 40 g of soy, 800 U of vitamin E and 0.2 g of selenium. All the men had signs of pre-cancerous cells, which put them at a higher risk for developing prostate cancer.

The number of cases of cancer in each group were nearly identical. Twenty-six out of every 100 men developed prostate cancer after 3 years, regardless of whether they took the supplement or the whey-based placebo powder.

(Continued on page 8)

Editors' note: In the spirit of information sharing, we have invited certain physicians and others to provide comments and opinions for Us TOO's *HotSheet*. It is our desire to enrich the content of the *HotSheet* to empower the reader. The columns by Drs. Chodak, Moyad and Myers contain the opinions and thoughts of its author and is not necessarily those of Us TOO International.

ASK DOCTOR SNUFFY MYERS

[Do Levitra® and other drugs used to treat erectile dysfunction after radical prostatectomy cause vision problems? I have heard some reports of these side effects.](#)

Yes, Levitra, Cialis and Viagra can alter vision in several ways. Viagra, in particular, has been reported to cause things to appear blue. This disappears after a few hours as the drug leaves the body.

Of greater concern is the fact that a small number of patients on these drugs have experienced loss of vision because of damage to the blood supply to the optic nerve, the nerve that conducts visual information from the eye to the brain.

Of course, this same problem can develop in patients not taking these drugs. After reviewing the literature to date, I do not think these drugs cause the visual problem. Rather, these problems would have occurred anyway.

One factor that weighs in favor of this view is that these drugs are being considered in cardiology for their favorable impact on the health of small blood vessels. I think it is also interesting that these drugs are used to treat pulmonary hypertension. In that setting, patients can end up taking the equivalent of 25 mg of Viagra every 6 hours!

I have also seen many patients take much more than the recommended dose in an effort to reverse male sexual function problems caused by surgery or radiation. I have one patient who takes 20-40 mg of Levitra every day without any side effects other than a rapidly depleting bank account.

MARK YOUR CALENDARS

The dates have been selected for the 2011 Prostate Cancer Conference. Presented by the Prostate Cancer Research Institute (PCRI), their national annual Conference will be held in Los Angeles on September 9-11, 2011 at the Westin Los Angeles Airport Hotel. Visit www.pcri.org for more information.

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

"A new study suggests fish and fish oil might be bad for you? Sounds fishy to me!"

Mark A. Moyad, MD, MPH

University of Michigan Medical Center, Department of Urology

Bottom Line: Eating about 2 servings of low mercury and high omega-3 fatty fish a week and taking fish oil may be good for your heart and your prostate! Five new studies in cancer and medicine suggest real wonderful benefits.¹⁻⁵

Heart healthy=Prostate unhealthy?? But, what happens when a single study gets a lot of media attention and it suggests that fish and fish oil makes prostate cancer worse or more aggressive? What should you do? The answer is NOTHING! DO NOT WORRY AT ALL! You need to remember that medicine is like a courtroom where the majority of the evidence usually points to the right answer. And, the majority of the studies on fish oil suggest that eating fish and potentially taking fish oil is not only heart healthy and is FDA approved to reduce triglycerides (part of the cholesterol test) but in the past few months have studies to suggest that omega-3 fatty acids from plants, fish, or supplements could:

- Improve heart health
- Maintain muscle mass
- Reduce kidney stone risk
- May improve survival for some type of cancer patients
- May reduce hot flash frequency
- May improve mental health

Yet, all you heard or read in the paper was a single study that suggested a potential negative thing. You have to keep in mind that most major medical centers or meetings have a public relations group that tries to constantly attract media to their group, medical center, or even discipline (medicine is a competitive business). Is it right? Probably not because what ends up happening is that hundreds of meetings and individuals in the medical field are trying to get the attention of the media and who knows what will or will not make page 6 in the local or national newspaper. What should make the paper is either a gold standard large definitive study that will change the way medicine is practiced or a good overall

summary of the research on the subject.

In the case of fish oil, who knew that there were more than 5 studies recently and a large clinical review that demonstrated all sorts of benefits to eating fish and maybe even taking fish oil for cancer patients??? Unfortunately or fortunately, the only one that is going realize this benefit is you for reading this column and not the 99% of the other folks that are freaking out right now because their local paper reported on a single study that suggested that fish oil is unhealthy. I remember a study once that showed that seat belts might cause injury to the chest and if your car starts on fire it might take longer to get out of the car. Do you think that single study has ever made me consider NOT wearing my seat belt (forest over the tree folks)?!

Now, I have to run and go eat lunch and I am going to have a big salad with extra anchovies on it and I am not going to lose any sleep tonight! Oh, and for dinner tonight, I am having salmon with fish oil pills on top...yummy! Heart Healthy=Prostate Healthy folks! Oh, and buckle up because I am sure that is going to be a new study soon that shows that exercising outside can increase your risk of getting hit by a car, or playing tennis can increase your risk of getting a hand infection from the dirty racquet handle, or yoga can increase your risk of a painful leg cramp, ...

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DOCTOR CHODAK'S BOTTOM LINE (Ref Key: article #, page #, column #)**Author:** *Winning The Battle Against Prostate Cancer, 2011*

This *HotSheet* contains important results from several well-done studies.

a1p1c1 In the past few years, two new treatments have helped improve survival for men with progressive metastatic disease after docetaxel; they are Provenge® and cabazitaxel. Abiraterone acetate is the next addition to this list, with well done clinical studies showing an increase in survival by about 4 months. The advantages of the drug are that it is taken by mouth and does not appear to cause as many side effects as chemotherapy drugs.

THE BOTTOM LINE: Although a cure for progressive metastatic disease has not yet been found, continued improvements have occurred. Now that three treatments are available after docetaxel, doctors and patients face an important question – what is the best sequence for using them?

Clinical studies are unlikely to address this question any time soon, but given the side effect profile, most men will probably get abiraterone before more chemotherapy with cabazitaxel. Many doctors are likely to also recommend Provenge at the same time because it showed an increase in survival although we can't tell if that drug is working. This is likely to further fuel debate about whether the benefits are worth the high cost of these treatments.

a2p1c2 For men choosing radical prostatectomy (RP) is more information available on whether it really saves lives? A recent study from Sweden provides 15 years of follow-up showing RP lowered the death rate by 6.1% meaning about 15 men had to be treated to prevent one cancer death. In a previous report with 12 years of results, 18 men needed to be treated to prevent one cancer death. Thus, longer follow-up has shown an improvement in the results. Further analysis found even better results for men under 65, with one cancer death prevented for every 7 men getting RP. However, the study also failed to find a benefit at 15 years in men over 65. The latest update also provides the first evidence that the men with low risk prostate cancer benefit from RP, however that benefit was extremely small. The difference in death from prostate cancer was only 4.2% for the entire group and 4.5%

for the men under 65 meaning about 18 men must be treated to prevent one death in 15 years. In that study, low risk was defined as having a PSA less than 10 ng/ml and a Gleason score less than 7.

THE BOTTOM LINE: At 15 years, RP does lower the chance of dying from prostate cancer for men under 65. So far, however, it does not appear to reduce deaths in older men, though it does lower the chance for metastases. Also, the benefit for men with a low risk cancer is very small. The implications are unclear for men in the US diagnosed by screening because most of the those in the study had a tumor that was detected by the digital rectal exam. All men diagnosed with this disease should be made aware of these results.

The two studies on AS draw our attention to problems doctors and patients must face with this approach. First, under what circumstances should it be discontinued and second, what can be done to keep men on AS when there is no evidence the cancer is becoming more dangerous? Currently, most clinicians decide about changing therapy based on a combination of changes in PSA values and biopsy Gleason scores.

a3p1c3 The study from San Francisco found that changes in tumor grade can occur without changes in PSA. The authors conclude that repeat biopsies are needed to help evaluate men on active surveillance. However, this study does not prove that changes in tumor grade alone are a sufficient reason to recommend therapy. It is possible that higher grade tumor was previously present but that area was not sampled during the biopsy? [See **a6p4c1**] The fact that the PSA did not change might indicate that the cancer has not grown significantly and that treatment really is not needed.

a4p2c1 In the second study from Johns Hopkins, the authors found that at ten years, the risk of dying from prostate cancer has been very low and delaying therapy did not appear to lead to worse outcomes. However, about 60% ended up getting treated, many of them by patient choice rather than changes in their tumor, which probably means that many of them are still getting overtreated.

THE BOTTOM LINE: AS is gaining acceptance as a safe and reasonable option for many men diagnosed today but more work is needed to define when and if definitive therapy is needed and how to help men remain on it when appropriate.

a7p4c3 Despite recommendations by several organizations to limit screening to men with at least a ten-year life expectancy, studies show that a significant percentage of them are still getting screened. It is less clear what is done when they are diagnosed with prostate cancer. A UCLA study found that more than half of men with low risk prostate cancer who only had a small chance of surviving ten years due to co-morbid diseases received aggressive cancer treatment. This raises several concerns about what they are being told before treatment. Was active surveillance (AS) discussed and were they told about their extremely small odds of benefiting from therapy?

THE BOTTOM LINE: Each person diagnosed with prostate cancer has a right to choose his treatment. To make a truly informed choice, however, adequate information about the risks and benefits must be provided. Most men with low risk prostate cancer are unlikely to benefit and that is even truer for men with a short life expectancy. One solution that might be worth considering is to develop a standardized video that all men must see before selecting a treatment. It could include a balanced presentation of the risks and benefits of all options and it might help men make choices that reflect their age, general health and cancer risk.

a9p5c2 A new randomized study from Canada looked at the impact of preventing prostate cancer in a high risk group by giving them vitamin E, soy and selenium for three years and comparing to a placebo. It showed no benefit. Other studies have also shown that neither vitamin E nor selenium used alone or together can prevent this disease.

THE BOTTOM LINE: Only randomized studies can determine if herbs, vitamins and supplements are beneficial and enough information is available to con-

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BIOPSY PROGRESSION

(Continued from page 1)

Despite the stability of the PSA measurements, 55 men (23%) showed progression on their first repeat biopsy (at a median follow-up of 10 months). PSA velocity was 0.02 ng/mL yearly in men without biopsy progression and -0.16 ng/mL in men with biopsy progression.

The odds of biopsy progression weren't significantly associated with PSA velocity. The only factor significantly associated with progression was increasing age, whereas increasing prostate volume was associated with significantly decreased odds of biopsy progression.

"All patients with early stage prostate cancer on AS should be followed for progression primarily with repeat biopsies," Dr. Whitson concluded.

"Careful analysis of randomized trials reveals that PSA screening lowers prostate cancer mortality, but at the cost of overdetection," he said. "Active surveillance in patients with low risk prostate cancer can minimize the burden of overdetection by preventing overtreatment of indolent disease."

Reuters Health, 18 April 2011

TREATMENT VS. AS

(Continued from page 2)

were more likely to have definitive treatment (P=0.026) and biopsy reclassification (P<0.001) as compared with those who met the criteria. Intervention-free survival was 81% after 2 years of follow-up, 59% at 5 years, and 41% at 10 years.

Of the 255 men having curative treatment, 188 (73.7%) had interventions due to disease reclassification on biopsy, and the remaining patients opted for intervention on the basis of personal preference or other considerations. Median follow-up after intervention was 2 years in men who had surgery and 2.8 years for those who had radiation therapy. Biochemical recurrence (BCR) occurred in 9.4% of men who had definitive treatment. None of cohort developed distant metastases or died of prostate cancer.

Limitations of the study included relatively short duration of follow-up (leaving the possibility of later adverse outcomes in place of BCR as a "proxy" for long-term outcomes) and a highly motivated population for AS which might not generalize to all low-risk prostate cancer patients.

MedPage Today, 12 April 2011

SUPPLEMENTS

(Continued from page 5)

Results don't rule out that soy might be beneficial if it is eaten frequently for decades, but 3 years of extra soy didn't appear to help prevent prostate cancer.

"I think that in the absence of more compelling scientific data for vitamin E and selenium, that we should move on," said Dr. Eric Klein, chair of the Glickman Urological and Kidney Institute, who was not involved in the trial. Fleshner agreed there is now enough data to warrant abandoning this line of research.

Reuters Health, 4 May 2011

THE BOTTOM LINE

(Continued from page 7)

clude that neither soy, vitamin E and selenium prevent prostate cancer. However, this study leaves other questions unanswered. Would higher doses change the results, would they work if taken for a longer time and is it possible that prostate cancer patients would benefit? Until randomized studies are done to address these questions, men should realize that studies showing benefits in laboratory studies cannot be translated into similar benefits in men.

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