



E & N News to Use *for cancer patients, survivors and caregivers*

EXERCISE & NUTRITION during/after* **CANCER**

CURRENT PEER-REVIEWED MEDICAL LITERATURE and EXPERT COMMENTARY
from **RELIABLE SOURCES** and **DR. BLEYER**

*Studies on cancer prevention are included if they have special relevance to cancer survivors

July 2009

The 12 months of 2008 *E&N News* are now available as a **year summary** for downloading, either for exercise or nutrition (with each including reports on the combination of exercise and nutrition) at www.defeatcancer.info. Both versions include executive summaries and are indexed and bookmarked.

E&N News is now listed as **one of 7 resources recommended by MD Anderson Cancer Center** in the *Complementary Therapies, General* category and endorsed by the Cancer Patient Education Network of the National Cancer Institute. The MD Anderson Cancer *Complementary/Integrative Medicine Educational Resources* resource (www.mdanderson.org/departments/CIMER) is rated #1.

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▶ **Exercise and Nutrition**

Body mass index and prostate specific antigen as predictors of adverse pathology and biochemical recurrence after prostatectomy

[The difficulty in interpreting PSA levels in overweight and obese men does not include predicting recurrence after surgical removal of the prostate gland](#)

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Purpose: Preoperative prostate specific antigen is widely used to predict unfavorable pathological features and biochemical relapse after radical prostatectomy. Recent reports that hemodilution may be responsible for lower prostate specific antigen in obese men led to concerns that prostate specific antigen may be less effective for prognosticating in men with increased body mass index. We determined whether the clinical usefulness of prostate specific antigen is negatively impacted by obesity by examining its operating characteristics and predictive accuracy as a function of body mass index.

Materials and Methods: We performed a multicenter retrospective analysis of the records of 11,705 men who underwent radical prostatectomy from 1988 to 2007 from Veterans Affairs hospitals of the Shared Equal Access Regional Cancer Hospital Database, the **Duke Prostate Center** and **Johns Hopkins Hospital**. ROC curve analysis, the concordance index and the test for interaction were used to compare the ability of prostate specific antigen to predict unfavorable tumor characteristics and biochemical recurrence across body mass index categories.

Results: There were no significant differences in the area under ROC curves across increasing body mass index categories for prostate specific antigen to predict pathological Gleason sum (7 or greater, 7 [4 + 3] or greater, or 8 or greater), positive surgical margins, extracapsular extension or seminal vesicle invasion in all 3 cohorts. There was no significant difference in prostate specific antigen accuracy to predict biochemical failure across increasing body mass index categories.

Conclusions: In 3 cohorts of men treated with radical prostatectomy the ability of preoperative prostate specific antigen to predict adverse pathological features and posttreatment biochemical recurrence is not significantly affected by obesity. However, adjusting for obesity related hemodilution may still be required to properly interpret prostate specific antigen results in men with increased body mass index.

Dr. Bleyer:

☑ This is good news for overweight men with prostate cancer: their PSA level before surgery can still help predict likelihood of cure or of length of time the cancer is not likely to return

▶ **Exercise**

Exercise reduces risk for premature death from cancer [Prevention]

[A study from Finland has shown that men who exercised for at least 30 minutes a day at moderate to high intensity halved their risk of dying prematurely from cancer, mainly gastrointestinal and lung cancer.](#)

Medscape Medical News, July 27, 2009

By Zosia Chustekaz

A study from Finland has shown that men who exercised for at least 30 minutes a day at moderate to high intensity halved their risk of dying prematurely from cancer, mainly gastrointestinal and lung cancer.

The results were published online July 28, 2009 in the British Journal of Sports Medicine.

Physical inactivity over a person's lifespan might be a "key factor in the initiation of cancer development," the authors note.

This study adds ammunition to the public-health message promoting at least 30 minutes a day of exercise, lead author Sudhir Kurl MD, from the School of Public Health at the University of Kuopio in Finland, told Medscape Oncology.

All Doctors Should be Giving Their Patients This Message

"All doctors should be giving their patients this message," he said, although he acknowledged that many do not have the time, and many are not aware of all of the research showing benefits.

"We found a **50% reduction in the risk of dying prematurely from cancer**," Dr. Kurl pointed out. Exercise also improves well being and confidence, and leads to better sleep and weight control, he added.

The study was carried out in men, but Dr. Kurl said he expects to see similar results in women.

Intensity of Physical Activity Was Important

The study involved **2560 men, aged 42 to 60 years**, living in the town of Kuopio and the surrounding rural communities. They self-reported their leisure-time physical activities on questionnaires over a period of 1 year, and were then followed for an average of 16.7 years, during which time there were 181 cancer-related deaths.

In their analysis, the researchers **adjusted for age, cigarette smoking, alcohol consumption, body mass index, and total intake of calories, fat, and fiber**.

The reduction in the risk for premature death from cancer was seen in men who **exercised for more than 30 minutes every day**, and with an intensity that was moderate to high, Dr. Kurl noted. The activities they performed included **jogging, swimming, cycling to work, and gardening or yard work**, he said

Exercise intensity was measured in metabolic equivalents of oxygen consumption (METs). The average intensity of jogging was 10.1 MET, skiing 9.6 MET, ball games 6.7 MET, swimming 5.4 MET, rowing 5.4 MET, cycling 5.1 MET, gardening/farming/yard work 4.3 MET, and walking 4.2 MET.

"Anything above an average of 4 MET can be considered [to be] moderate-intensity exercise," Dr. Kurl told Medscape Oncology.

Other activities reported by the men included **crafts, repair or building**, which had an average intensity of 2.7 MET, hunting, picking berries or gathering mushrooms (3.6 MET), and fishing (2.4 MET).

"The intensity of leisure-time physical activity should be at least moderate so that the beneficial effect of physical activity for reducing overall cancer mortality can be achieved," the authors write.

The results show that at least moderate-intensity physical activity is more beneficial than low-intensity physical activity in the prevention of cancer, the authors note. This finding is consistent with American consensus statements suggesting that at least moderate-intensity physical activity is needed to prevent chronic diseases caused mainly by cardiovascular disease, they add.

Several Mechanisms Involved

They speculate that the mechanisms by which physical activity could protect against cancer include beneficial effects on energy balance and body mass, intestinal transit time, hormonal concentrations (e.g., reduced testosterone), prostaglandin levels, and antioxidant enzymes activities.

For example, exercise increases the F-series of prostaglandins but decreases the E2 series, and these physiologic events have been shown to increase gut motility and to decrease colonic cell division, the researchers point out.

Many of the cancer-related deaths that were reported during the follow-up period affected the gastrointestinal tract (57 of 181 cases). The remaining cancers affected the lung (n = 48), prostate or urinary tract (n = 25), brain (n = 9), or lymphoma (n = 6).

"Our results indicate that those with an active lifestyle have a decreased risk of gastrointestinal cancers," the researchers note. This finding may be due to changes in energy balance, which includes body mass, which is particularly important for colon cancer, they note. In addition, the increased gut motility with exercise training decreases gastrointestinal transit time, thereby reducing the contact time between fecal carcinogens and the colonic mucosa, as well as allowing less opportunity for the initiation of carcinogenesis and colonic cell division and proliferation. There may also be an effect on insulin and fat metabolism, they add.

Asked by Medscape Oncology if he practices what he preaches, Dr. Kurl replied: "Of course!" He reported jogging 3 times a week and working out in the gym twice a week .

Source: Br J Sports Med. Published online before print July 28, 2009.

Dr. Bleyer:

- ☑ This really is a remarkable study carried out in a town and surrounding countryside in Finland, under highly controlled circumstances, with careful recording of all exercise for 1 year in 2,560 men who were then followed for nearly two decades
 - ☑ The results show a highly significant reduction in cancer deaths, by one-half, after correcting for adverse effects of obesity, alcohol and fat intake
 - ☑ These findings are important for those who have had a diagnosis of cancer, especially colorectal cancer, because they are likely to apply to cancer recurrence, as well as occurrence, and are consistent with prior reports in patients with colorectal cancer
-

▶ **Nutrition**

Plasma selenium, manganese superoxide dismutase, and intermediate- or high-risk prostate cancer

[The large prostate cancer prevention trial that *DEFEATcancer* reported in which selenium supplementation failed to help prevent prostate cancer has now been succeeded by a study that suggests potential harm in patients who already have prostate cancer](#)

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Journal of Clinical Oncology, 10.1200/JCO.2008.18; published online ahead of print Jun 15 2009

Purpose: In vitro, in vivo, and epidemiologic studies support a role for selenium in reducing the risk of prostate cancer. Our group previously demonstrated a strong interaction between plasma selenium and the manganese superoxide dismutase (SOD2) gene and incident prostate cancer risk. We now hypothesized that SOD2 modifies the association between selenium level and risk of aggressive prostate cancer at diagnosis.

Patients and Methods: We assessed SOD2 variants and plasma selenium in 489 patients with localized/locally advanced prostate cancer from an ongoing retrospective cohort. Cross-sectional associations with aggressive prostate cancer (ie, stage T2b-3, prostate-specific antigen > 10 ng/mL, or biopsy Gleason score 7) were evaluated using the 2 test, Cochran-Armitage test for trend, and estimations of relative risk (RR) and 95% CIs.

Results: SOD2 genotype alone was not associated with disease aggressiveness, whereas higher versus lower selenium levels were associated with a slightly increased likelihood of presenting with aggressive disease (RR = 1.35; 95% CI, 0.99 to 1.84). There was evidence of an interaction between SOD2 and selenium levels such that among men with the AA genotype, higher selenium levels were associated with a reduced risk of presenting with aggressive disease (RR = 0.60; 95% CI, 0.32 to 1.12), whereas among men with a V allele, higher selenium levels were associated with an increased risk of aggressive disease (for VV or VA men, RR = 1.82; 95% CI, 1.27 to 2.61; P for interaction = .007).

Conclusion: These data suggest that the relationship between circulating selenium levels at diagnosis and prognostic risk of prostate cancer is modified by SOD2 genotype and indicate caution against broad use of selenium supplementation for men with prostate cancer

Dr. Bleyer:

- ☑ With the investigators at some of the best cancer research institutions in the world: Fred Hutchison Cancer Center, Dana Farber Cancer Institute, University of California at San Francisco, Harvard School of Public Health, and Brigham and Women's Hospital, the findings in this report have to be heeded
- ☑ See the next report for comments directly from the investigators

Prostate cancer patients should not take selenium supplements

[Follow-up on prior report with comments from the investigators](#)

By Zosia Chustecka

Medscape Oncology - July 1, 2009

"If you already have prostate cancer, it may be a bad thing to take selenium," says the senior author of a new study published online June 15 in the Journal of Clinical Oncology.

Selenium supplements have been sold and promoted as a means of preventing prostate cancer, but the large SELECT prevention trial recently showed no effect on the incidence rate. Now this **latest study suggests the potential for harm in patients who already have prostate cancer.**

In the study, Philip Kantoff, MD, director of genitourinary oncology at the **Dana-Farber Cancer Institute** and colleagues found that having a **high level of selenium in the blood was associated with a slightly elevated risk of aggressive prostate cancer.**

But the risk was particularly elevated in men who also had a certain variant of the gene coding for manganese superoxide dismutase (SOD2). For these men, who made up 75% of the study population, having "high selenium levels might increase the likelihood of having worse characteristics," the researchers concluded.

The results were unexpected, and they are the first to raise concern about potentially harmful consequences of taking supplemental selenium. Until further data are available to sort out which men can safely take the supplement,

Dr. Kantoff told Medscape Oncology that he would advise patients with prostate cancer not to take supplements containing selenium.

Interaction between Selenium and Genotype

The study involved 489 patients who had been diagnosed with prostate cancer at the Dana Farber Center between 1994 and 2001. These men had a mean age of 62 years and mean level of prostate specific antigen (PSA) of 6.0 ng/mL. More than half had good-risk disease, while about a third had intermediate-risk disease, the researchers comment.

The team examined banked blood samples for selenium levels and genomic DNA, in particular genotyping for the SOD2 polymorphism: 25% of patients were found to carry the A form of the gene, and 75% carried the V form. Dr. Kantoff and colleagues found that having higher vs lower selenium blood levels was associated with a slightly increased likelihood of presenting with aggressive disease (relative risk, 1.35). The mean selenium level (121.4 ng/mL) in this patient population was similar to that reported in several other studies (ranging between 108 and 141 ng/mL), the researchers comment.

There was no way of knowing which patients had been taking selenium supplements, the researchers comment. But they note that the levels measured in this study were substantially lower than the median level (252 ng/mL) in men who were taking selenium supplements in the large SELECT prevention study.

This study found no effect of SOD2 genotype on disease aggressiveness, although this effect has been reported previously both by this team and others.

However, there was evidence of an interaction between the SOD2 genotype and selenium levels.

Among men with the AA genotype, higher selenium levels were associated with a 40% reduced risk of presenting with aggressive disease (relative risk, 0.60), while among men with the V allele (either VV or VA genotype), higher selenium levels were associated with an almost doubling of the risk of aggressive disease (relative risk, 1.82; P = .007 for the interaction).

"It is possible that selenium helps some and may harm others," Dr. Kantoff commented to Medscape Oncology. "Genetic studies will help sort this out. Until then, I would not advise taking selenium supplements," he said.

Potential Harm Not Previously Reported

The direct relation of higher selenium with more aggressive disease among V-allele carriers was "unexpected and has not been previously reported," say the researchers.

"One explanation may be that in men with established cancer, antioxidants may promote cancer-cell survival through an antiapoptotic mechanism by neutralizing the higher levels of reactive oxygen species found in cancer cells," they speculate. However, there could be other explanations, and the finding may also be due to chance and so needs confirmation, they add.

"These data suggest that the relationship between circulating selenium levels at diagnosis and the prognostic risk of prostate cancer is modified by the SOD2 genotype and indicate caution against broad use of selenium supplementation for men with prostate cancer," the authors conclude.

Prevention Study Found No Benefit

These new findings are also "interesting, particularly in light of the recent negative results from the SELECT prevention study," Dr. Kantoff commented in a statement.

The SELECT study set out to discover whether taking selenium and vitamin-E supplements would offer protection against prostate cancer, but the trial was stopped early in October 2008 because of an apparent lack of benefit and a possibility of harm, as reported by Medscape Oncology.

Selenium supplements' reputation for prevention, sold and promoted as a means of preventing prostate cancer, is largely based on observational studies noting a higher risk for prostate-cancer incidence and mortality in geographical areas that were naturally low in selenium. But studies with selenium as a preventive have shown mixed results. However, after announcing the results from **the huge SELECT study, which involved 35,000 men**, lead author Larry Baker, MD, professor of medicine at the **University of Michigan Medical School**, in Ann Arbor, said: "**This is the definitive study, and anyone who argues against it is ignoring the facts.**"

Dr. Kantoff tells Medscape Oncology that it is now "essential" to go back and genotype the samples in the SELECT trial. "There may be some people who benefit and some who do not or are even harmed."

Dr. Bleyer:

☑ **DEFEATcancer** previously reported the SELECT trial results described by the Chairman of the largest cancer cooperative group, the Southwest Oncology Group, as definitive in establishing selenium is worthless in preventing prostate cancer.

☑ Now there is evidence that a higher selenium level *per se* is associated with an increased rate of prostate cancer

Prevalence and predictors of antioxidant supplement use during breast cancer treatment: The Long Island Breast Cancer Study Project

[The use of antioxidant supplements by during breast cancer treatment by predominantly white women of higher socioeconomic status on Long Island is reported to exceed 60%](#)

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Background. Although many patients take antioxidant dietary supplements during breast cancer treatment, the benefits of such supplementation are unproven. The authors of this report analyzed the prevalence of and factors associated with antioxidant supplement use during breast cancer treatment among women who participated in the Long Island Breast Cancer Study Project.

Methods. From 2002 through 2004, women with breast cancer who had participated a case-control study from 1996 to 1997 were invited to participate in a follow-up interview. Antioxidant supplement use was defined as any self-reported intake of supplemental vitamin C, vitamin E, -carotene, or selenium in individual supplements or multivitamins.

Results. Follow-up interview participants were younger, more predominantly white, and of higher socioeconomic status than women who did not respond. Among 764 participants who completed the follow-up interview, 663 (86.8%) reported receiving adjuvant treatment for their breast cancer. Of those 663 women, 401 (60.5%) reported using antioxidants during adjuvant treatment: One hundred twenty of 310 women (38.7%) used antioxidants during chemotherapy, 196 of 464 women (42.2%) used them during radiation, and 286 of 462 women (61.9%) used them during tamoxifen therapy. Of 401 antioxidant users, 278 women (69.3%) used high doses (doses higher than those contained in a Centrum multivitamin). The factors that were associated with high antioxidant supplement use during treatment were higher fruit and vegetable intake at diagnosis (relative risk [RR], 1.71; 95% confidence interval [CI], 1.13-2.59), tamoxifen use (RR, 3.66; 95% CI, 2.32-5.78), ever using herbal products (RR, 3.49; 95% CI, 2.26-5.38), and ever engaging in mind-body practices (RR, 1.72; 95% CI, 1.13-2.64).

Conclusions. Given the common use of antioxidant supplements during breast cancer treatment, often at high doses and in conjunction with other complementary therapies, future research should address the effects of antioxidant supplementation on breast cancer outcomes.

Cancer 2009. © 2009 American Cancer Society.

Dr. Bleyer:

- ☑ Well known is that persons of higher socioeconomic status are more likely to augment their diet with vitamins, minerals, antioxidants and other "nutritional supplements"
- ☑ The magnitude of use, exceeding 80% for any type of supplement, may not be surprising for a relatively homogenous community like Long Island
- ☑ What is extraordinary is the fact that antioxidants are known to have the potential to do more harm than good by interfering with the benefit of radiation therapy and certain forms of chemotherapy
- ☑ It seems that those with the greatest resources and presumably the most intelligence are also more ignorant

The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model [Laboratory Study]

[How limiting carbohydrate intake may slow growth of prostate tumors](#)

Mavropoulos JC, Buschemeyer WC 3rd, Tewari AK, et al.
Cancer Prev Res (Phila Pa). 2009 Jun;2(6):557-65

Purpose: Numerous dietary factors elevate serum levels of insulin and insulin-like growth factor I (IGF-I), both potent prostate cancer mitogens. We tested whether varying dietary carbohydrate and fat, without energy restriction relative to comparison diets, would slow tumor growth and reduce serum insulin, IGF-I, and other molecular mediators of prostate cancer in a xenograft model.

Experimental Design: Individually caged male severe combined immunodeficient mice (n = 130) were randomly assigned to one of three diets (described as percent total calories): very high-fat/no-carbohydrate ketogenic diet (NCKD: 83% fat, 0% carbohydrate, 17% protein), low-fat/high-carbohydrate diet (LFD: 12% fat, 71% carbohydrate, 17% protein), or high-fat/moderate-carbohydrate diet (MCD: 40% fat, 43% carbohydrate, 17%

protein). Mice were fed to maintain similar average body weights among groups. Following a preliminary feeding period, mice were injected with 1×10^6 LNCaP cells (day 0) and sacrificed when tumors were $\geq 1,000 \text{ mm}^3$. **Results:** Two days before tumor injection, median NCKD body weight was 2.4 g (10%) and 2.1 g (8%) greater than the LFD and MCD groups, respectively ($P < 0.0001$). Diet was significantly associated with overall survival (log-rank $P = 0.004$). Relative to MCD, **survival was significantly prolonged for the LFD (hazard ratio, 0.49; 95% confidence interval, 0.29-0.79; $P = 0.004$)** and NCKD groups (hazard ratio, 0.59; 95% confidence interval, 0.37-0.93; $P = 0.02$). Median serum insulin, IGF-I, IGF-I/IGF binding protein-1 ratio, and IGF-I/IGF binding protein-3 ratio were significantly reduced in NCKD relative to MCD mice. Phospho-AKT/total AKT ratio and pathways associated with antiapoptosis, inflammation, insulin resistance, and obesity were also significantly reduced in NCKD relative to MCD tumors.

Conclusions: These results support further preclinical exploration of carbohydrate restriction in prostate cancer and possibly warrant pilot or feasibility testing in humans.

Dr. Bleyer:

- ☑ This is the kind of carefully controlled laboratory study that will ultimately sort out how nutrition affects the occurrence and recurrence of cancer
- ☑ All of the mice were on a high fat diet and were of an immunosuppressed species which increases their chance of dying of cancer and more readily allows the study of other factors
- ☑ The result in boldfaced means that mice fed a high carbohydrate diet died twice as fast as those with a moderate carbohydrate diet and the chance that this was due to chance, and not the difference in carbohydrates, was 1 in 250.

Researchers describe how diet may protect prostate [Laboratory Study]

[How limiting carbohydrate intake may slow growth of prostate tumors \(continued\)](#)

By Personal Liberty News Desk • Jul 28th, 2009

Reasonable dieting has a range of health benefits, including weight loss, but scientists believe men who limit their carbohydrate intake may also experience a slower growth of prostate tumors.

A team from the Duke Prostate Center conducted animal studies which found that insulin and insulin-like growth factor contribute to the growth and proliferation of prostate cancer, and that a **low-carb diet decreases insulin levels**, producing an opposite effect.

Dr. Stephen Freedland, a urologist at the center and lead investigator on the study, says the results are "very exciting," offering doctors a potential new tool to fight prostate cancer growth and extend patient's life expectancy. There are plans currently underway to recruit humans for a clinical trial.

The work of the Duke team is only the latest contribution to the growing body of evidence which links dietary factors to prostate cancer outcomes.

For example, doctors have also recommended a vegetable-rich diet and pomegranate juice which studies have shown may lower the risk of prostate cancer due to their antioxidant power.

Meanwhile, other research has uncovered the beneficial effects of omega-3 fatty acids, while the association between lower cholesterol levels and prostate cancer inhibition suggests some may also benefit from cholesterol-fighting natural remedies such as niacin supplements, fish oil and red yeast rice extract.

Source: Mavropoulos JC, Buschemeyer WC 3rd, Tewari AK, et al. The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. *Cancer Prev Res (Phila Pa)*. 2009 Jun;2(6):557-65

Dr. Bleyer:

- ☑ Regardless of the enthusiasm inherent in this report, it is unlikely that any single dietary component will have a dramatic effect
- ☑ The best results are likely to be achieved with fundamental changes such as a plant-based diet which is a low-carbohydrates, low-fat, high-antioxidant, etc, combined with exercise