SELENIUM-ENRICHED YEAST AND DECREASED OXIDATIVE STRESS

Implications for Prostate Health & Chronic Disease Risk

BY MARK WHITACRE, PH.D., Chief Science Officer and **DR. GEO ESPINOSA, ND,** Integrative -Urology Specialist

FOR AT LEAST A DECADE, epidemiological and laboratory research raised awareness that selenium may protect against certain cancers. However, clarity on the form and function for optimum efficacy has been less understood. For the first time ever, new research shows that a specific form of standardized selenium-enriched yeast (SY), branded as SelenoExcell®, significantly reduces the biomarkers for oxidative stress, which are a measure of healthy aging and reduced risk for chronic illness and certain cancers. This new research is but one of many new opportunities for SY to play a role in a personalized approach to reducing oxidative stress and ultimately prostate-cancer risk.

Since the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in 2011, the trial limitations raised questions about whether the correct form of selenium was used in the study. This trial mistakenly led many to believe that selenium is a single entity. However newly released, peer-reviewed clinical research better defines the importance of selenium compounds from selenium-enriched yeast (SY) and why this is the preferred form. As this white paper will outline, new research shows that a standardized form of selenium-enriched yeast is highly effective in reducing oxidative stress and prostate-cancer risk.

FIGURE 1: **OXIDATIVE STRESS & DISEASE RISK**

When the body's antioxidant response loses its ability to keep up with oxidative stress, the damage can speed up the aging process, which presents opportunities for increased risk of all these diseases and conditions.
SOURCE: NIST, National Institute of Standards and Technology

NPCT STUDY RESULTS[6]

TOTAL CANCER MORTALITY	↓ 50 PERCENT
TOTAL CANCER INCIDENCE	↓ 37 PERCENT
COLON CANCER INCIDENCE	↓ 58 PERCENT
PROSTATE CANCER INCIDENCE	↓ 63 PERCENT
LUNG CANCER INCIDENCE	↓ 46 PERCENT

FOUNDATIONAL SY RESEARCH

In 1996, the Nutrition Prevention Cancer Trial (NPCT) Phase 3 supplementation trial, published in the Journal of the American Medical Association (JAMA), demonstrated a significant reduction in cancer in individuals receiving a daily 200-µg selenium supplement of SelenoExcell (SEE TABLE).[1] Researchers found that subjects who took daily doses of selenium had 63 percent fewer cases of prostate cancer, 58 percent fewer cases of colon or rectal cancers, and 46 percent fewer lung cancers than those not receiving supplement.

In addition to the 1996 JAMA publication, the prostate cancer prevention results were published in the prestigious British Journal of Urology (BJU, 81.730-734) in 1998.[2] This publication further validated the landmark position of this clinical data and established it as a benchmark in on-going confirming selenium research.

In a follow-up trial, researchers at the Penn State University Cancer Institute in Hershey, Pennsylvania found that supplementation with SelenoExcell reduced serum Prostate-Specific Antigen (PSA) levels.[3] Prostate cancer presents a major clinical and public health challenge in the USA.[4] It is the second leading cause

of cancer-related deaths in men and is second only to lung cancer.[5]

WHY SELENIUM FORM MATTERS

Selenium has received a significant amount of attention both in the media and in the scientific community over the past few years. Much of this surfaced when the SELECT trial was prematurely stopped in 2008.[7]

When it was announced that the trial had been stopped, most media reports assumed that it was evidence that selenium is ineffective against prostate cancer. However, the world's leading selenium researchers found this misleading because the SELECT data only relates to the effects of a non-food form of L-selenomethionine supplementation in a selenium-replete population. Many selenium researchers thought then, and still do, that the SELECT trial used the wrong form of selenium.

Nonetheless, the results of the SELECT trial actually added clarity to the fact that selenium form makes a difference. The SELECT study was consistent with other laboratory studies, which demonstrated that, while organic forms of selenium with varied structures have greater anticancer activities, among those forms tested, SeMet is relatively inactive. More likely, the chemopreventive properties are a result of a selenium complex, like that found in SelenoExcell.

SELENIUM ENRICHED YEAST SUPERIOR TO SEMET

The only way to put the argument to rest was to compare SeMet directly against SelenoExcell high selenium-enriched yeast. The most recent 2014 study, at Penn State by John Richie Jr. Ph.D. and Karam El-Bayoumy Ph.D. showed, for the first time, reductions in biomarkers of oxidative stress following supplementation with SY but not SeMet in healthy men.[8] The researchers concluded that compounds other than SeMet likely account for the decrease in oxidative stress.

In the study commentary, Merrill J. Christiansen from Brigham Young University asks the questions: "The limitations of the NPCT and SELECT raise questions such as would SeMet have worked in the NPCT?[9] Would SY have been effective in SELECT? What if prostate cancer had been the primary endpoint in

> SY DECREASED OXIDATIVE STRESS BY 28 PERCENT TO 34 PERCENT WITH 285-µg/DAY

NPCT?" Richie and his colleagues have begun to answer these questions with the following study results:

PURPOSE: Compare the effects of SY and SeMet in humans in a double-blind, placebo-controlled, randomized trial in healthy adult men.

OBJECTIVES: Determine and compare the effects of different forms of selenium on prostate cancer relevant biomarkers including blood selenium levels and blood and urinary biomarkers of oxidative stress. A secondary objective was to determine the impact of SY and SeMet on PSA and glucose levels.

SUBJECTS: Healthy males (69), non-smokers, age 20-79, normal serum PSA levels, with no history or evidence of diabetes, prostate cancer, liver or kidney disease, and not taking >50-µg/day selenium.

DOSAGE: Placebo, SY 200-µg/day, SY 285-µg/day, SeMet 200 µg/day.

RESULTS: Levels of oxidative stress biomarkers [uring 8-hydroxy-2' deoxyguanosine (8-OHdG) and 8-iso-prostaglandin F2a (8-isoPGF2a) were decreased 34 percent, 28 percent after 9 months on the high dose of SY 285-µg/day. The decreases were greatest in men with low baseline plasma Se levels.

A secondary objective in the recent Penn State study was to determine the impact of SY and SeMet on PSA and glucose levels. SY had no effect on glucose levels in this study. This is consistent with what Dr. Margaret Rayman published in 2013, where all but one study showed no effect on Type 2 diabetes with selenium supplementation.[10]

WHY SELENIUM?

- There are 50 - 100 different selenium-containing proteins in the human body that build heart muscle, red blood cells, and sperm.
- The body needs selenium for the production of several important body compounds, including enzymes, or catalysts, involved in antioxidant protection against oxidative stress and thyroid-hormone metabolism.
- Selenium helps fight diseases by neutralizing harmful unstable molecules called free radicals, which leave the body vulnerable to inflammation, diseases and cancer.
- Most importantly, SY acts as a co-factor to an important enzyme system known as glutathione peroxidase (GPX), which is critical to the neutralization of harmful free radicals.
- Selenium dependent GPX is the body's first line of defense and represents a natural antioxidant agent.

GLUTATHIONE, SELENIUM & OXIDATIVE STRESS

As this most recent study shows, SelenoExcell's selenium-enriched yeast plays a dramatic role in reducing oxidative stress biomarkers. Reducing oxidative stress is a crucial step in reducing disease and cancer risk (see Figure 1). The mechanisms aren't entirely identified yet, but it is believed that selenium-enriched yeast protects the body by controlling redox reactions, which are an important measure of how cells gain (redox) or lose electrons (oxidation).

One of the ways it does this is by increasing the levels of glutathione (GSH). Adequate GSH is the first line of defense against oxidative stress, and studies support the fact that decreased GSH levels present an increased risk of cancer. Glutathione in the cells is the redox state

MANY SELENIUM RESEARCHERS THINK THAT THE SELECT TRIAL USED THE WRONG FORM OF SELENIUM.

(GSH), and other cells are converted to the oxidized form (GSSG). High GSSG means the cell has suffered oxidative stress (see Figure 1). Studies suggest that selenium-enriched yeast's chemopreventive attributes may reduce oxidative stress by enhancing blood levels of GSH and reduce GSSG concentrations in blood.[11]

The mechanism by which selenium enhances GSH likely involves the upregulation of its rate limiting biosynthetic enzyme γ-glutamyl cysteine ligase (GCL). One potential pathway for GCL upregulation involves the activation of the nuclear factor-erythroid 2-related factor 2 (nrf2)/antioxidant response element (ARE) signaling pathway. Research is exploring the importance of modulating the NrF2-ARE pathway and represents a significant paradigm shift in how cancer prevention is understood.

It is interesting to note that all selenium forms (sodium selenite, selenate, SeMet and SelenoExcell) have been shown to increase plasma glutathione peroxidase activity (GPx). The primary role of this enzyme family is to protect cells from oxidative damage. However, only SelenoExcell has been shown to reduce cancer incidence. It is likely that the biological role of selenium, in terms of cancer risk, is something different than its biological role as a component of glutathione peroxidase and the reduction of free radicals resulting from this enzyme.

SELENOEXCELL, THE CLINICALLY PROVEN PREFERRED FORM

The use of selenium in describing its effectiveness is often summed up in to a single entity. This misnomer is a major detractor in realizing the benefits of a compound like selenium-enriched yeast. In a commentary by Merrill J Christensen in Cancer Prevention Research, he says, "There is a wealth of preclinical data demonstrating that different chemical forms of selenium have different effects … clearly different forms of selenium have different effects."[12]

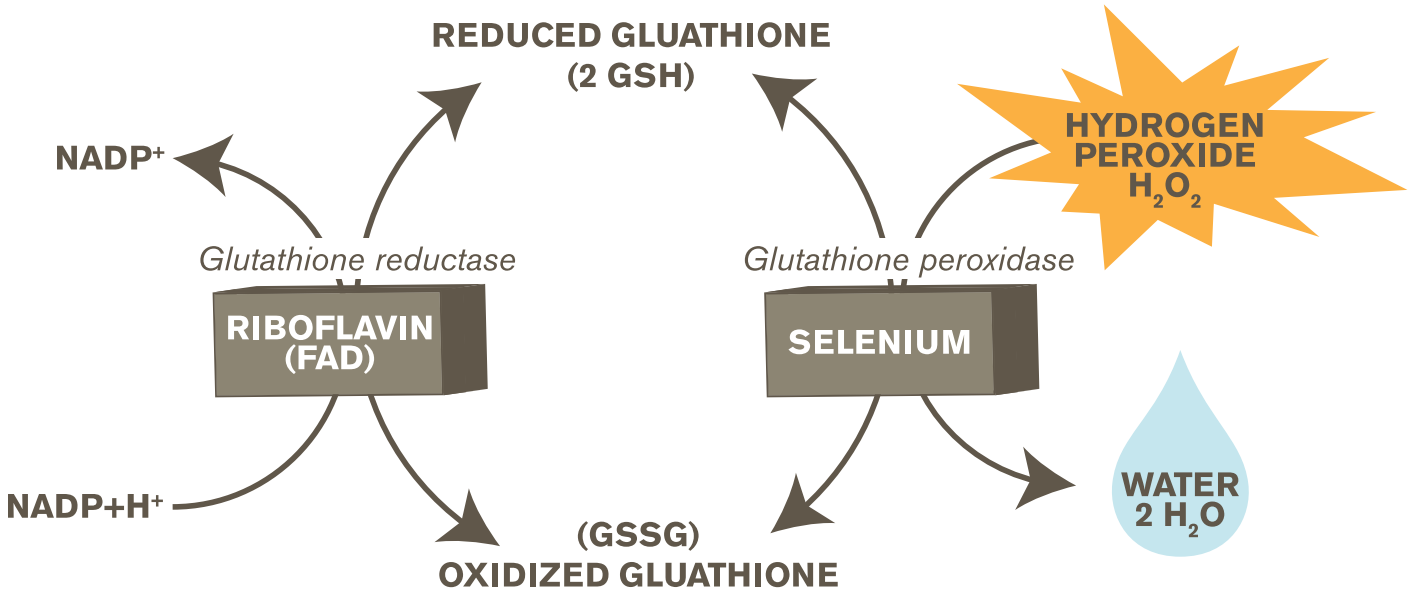
In the SELECT trial for instance, the study used L-selenomethionine (SeMet), a synthetic or non-food form. As the SELECT trial showed, SeMet has no effect on tumor growth. And as the most recent Penn State study indicates, it has no effect on oxidative stress or chemoprotective properties for prostate health. There are actually untold numbers of unidentified low-molecular weight selenocompounds and selenoproteins that may play a role in cancer prevention.

Researchers are beginning to better understand that one or more of these many forms of selenium are as important as the other. Given that many brands of selenium on the market are poorly manufactured, The National Cancer Institute (NCI) required a standardized form of selenium for their study. Following the 1996 JAMA publication of NPCT, numerous oncology groups began to submit grant applications to NCI. They wanted to confirm research in colon, lung and prostate cancer using the same intervention agent at NPCT, which is now trademarked as SelenoExcell. Due to the fact that it was a natural food form of organically bound selenium and there exist numerous adulterated products on the market, NCI required that Cypress Systems Inc. standardize SelenoExcell prior to approving funding for ongoing confirming trials.

The standardization required the selenium levels to be certified as 100 percent organically bound, with no free inorganic selenium present, which was fingerprinted for identification and registered with the American Type Culture Council (ATCC). The maximum potency variation was no more than 5 percent, and each batch had minimal variation.

This level of best practices and highly scrutinized scientific compliance is rarely

FIGURE 2: **REDOX REACTION**



DOSAGE AND TOXICITY

Twenty years of clinical research and a preponderance of evidence support a dosage of 200mcg of enriched selenium yeast.[25, 26, 27.28,,29] As previously noted, the Penn State study cites 285-µg dose, which is a new finding. With this solid foundation of historic clinical research in place, additional subset research in the field of metabolomics will give clarity to many issues related the exact mechanistic functions of high selenium yeast.

As this white paper indicates, the form is extremely important for efficacy. As there are many forms of selenium available in the market, patients should be informed that selenium-enriched yeast, specifically SelenoExcell, is the preferred type because of the extensive level of research and quality controls.

A recent small study shows there may be absorption differences among whites and blacks by as much as half.[30] More studies are needed to confirm the results, but black men may have trouble with selenium bioavailability, which could account for higher prostate cancer rates.

Selenium toxicity is extremely rare. Selenosis, a form of toxicity, could occur at dosages of 1000-µg/day. Symptoms include a garlic odor on the breath, gastrointestinal disorders, hair loss, sloughing of nails, fatigue, irritability, and neurological damage. Although rare, a practitioner should be aware of such symptoms.

seen in dietary supplement manufacturing. In addition to standardization, SelenoExcell was the first form of selenium to receive a Generally Regarded As Safe (GRAS) status for use in functional and medical foods. Selenium was also granted the following qualified-health claims by FDA:[13]

CLAIM 1: "Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive."

CLAIM 2: "Selenium may produce anticarcinogenic effects in the body. Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body. However, FDA has determined that this evidence is limited and not conclusive."

CLINICAL APPLICATIONS OF SY

High selenium-enriched yeast is an integral nutritional regimen for patients who require the chemopreventive benefits and balanced antioxidant support of selenium. Another benefit of selenium from high selenized yeast is chelating abilities with the heavy metal cadmium.[14] Cadmium is known to cause oxidative stress, memory loss and cardiovascular problems. Cadmium is also a known carcinogen.

As the Penn State study shows, for men with low plasma selenium, supplementation is a valuable preventive tool to reduce oxidative stress. For physicians seeking a personalized approach to men's health, SY levels and supplementation should be considered on a case-by-case basis because geography, health status and disease states all play a role in selenium levels.

In the United States, there are isolated areas where soil selenium levels are naturally low, including the upper southeast, regions in the lower southeast, Texas and the southwest and northwestern mountain states. Regions in Northern and Eastern Europe, Russia and China are also naturally low in selenium.[15,,16,]

Certain diseases and health conditions lead to low selenium levels or prevent adequate bioavailability, including autoimmune diseases such as, HIV/AIDS, Graves Disease, Keshan's, Crohn's disease, Hashimoto's thyroiditis and rheumatoid arthritis.[17,,18,19,20,21] Other health concerns related to low selenium levels include memory and cognitive diseases, alcoholism, smoking and male infertility.[22,23]

Patients may inquire as to whether they can get what they need from their diet. Brazil nuts, which provide about 200-µg for about 6 to 8 nuts, is an excellent form of selenium, but it is not a main staple in most patients' diet. The best clinical dosage for patients is 200-µg day in the form of selenium-enriched yeast. As the Penn State study indicates, SY is most effective in men with lower Se status. Earlier studies and NHANES (National Health and Nutrition Examination Survey) data indicate that only about 20 percent to 25 percent of men may have adequate Se status, depending on diet, health status and geographical location.

A wide variety of tests are used to measure selenium blood levels. In most studies, toenail assessments are used to measure long-term selenium status since plasma serum selenium level reflects short-term status and are not adequate for clinical assessment. However, toenails are also not always good indicators of selenium nutritional status. During protein synthesis, the body apparently cannot distinguish selenomethionine (one of the major forms of selenium in food and high selenized yeast) from methionine.

Consequently, a portion of ingested selenomethionine is incorporated into proteins in place of methionine, and the selenium so incorporated is biologically inactive. Because selenomethionine competes with methionine during protein synthesis, selenium uptake in toenails might be influenced as much or more by the amount of methionine (i.e., protein) in the diet as by selenium intake. Hair selenium testing can also measure long-term selenium intake but this form of testing is inadequate due to selenium-containing shampoos limiting the suitability of hair samples.

A better indicator of selenium nutritional status appears to be a whole blood, erythrocyte test, which reflects longer-term status due to the incorporation of selenium during synthesis of these cells.[24] Measuring glutathione peroxidase activity, a byproduct of selenium metabolism, is a recommended technique for assessing selenium status, and is not affected by selenium deficiency. A functional medicine practitioner should also look at thyroid levels T4 and T3 for selenium status. An elevated T4 and lower T3 serum level is a functional marker of selenium deficiency due to depressed iodothyonine deiodinase activity. Blood glucose levels and other glucose biomarkers like hemoglobin A1c should be measured in patients to assess glucose metabolism and overall health. While it is rare to see blood sugar problems with patients at 200-µg of selenium-enriched yeast, some human research has inconsistently and inconclusively associated selenium supplementation

to increased risk for type 2 diabetes. Therefore, it is advisable to monitor patients' blood glucose.

CONCLUSION

What the future holds for selenium research

For the first time in human clinical research, a side-by-side comparison was made between SeMet and SelenoExcell to evaluate their respective effects on critical prostate cancer biomarkers. Results from past clinical trials suggest that SelenoExcell, but not non-food forms of SeMet, may be effective at reducing prostate cancer risk. However, this recent Penn State trial confirms that selenium form makes a great deal of difference for efficacy.

These findings also suggest that selenium-containing compounds other than SeMet may account for the decrease in oxidative stress and possibly cancer risk. Ongoing research will likely continue to identify all of the various compounds in selenium-enriched yeast that account for reduced oxidative stress and chemopreventive properties.

FOR MORE INFORMATION ON SELENOEXCELL

CONTACT Paul Willis, CEO
CYPRESS SYSTEMS, INC.
40365 Brickyard Drive, Suite 101
Madera, Calif 93636
Phone **559.229.7850**
E-mail **paul@cypressingredients.com**

MARK WHITACRE, PHD. is the Chief Science Officer at Cypress Systems, Inc. He received his Ph.D. in nutritional biochemistry at Cornell University in 1983 under the direction of Dr. G.F.Combs, Jr., who is a world renowned selenium scientist. Mark's Ph.D. dissertation was on the biochemical role of selenium at the cellular level in the pancreas.

GEO ESPINOSA, N.D., L.AC, is a naturopathic urologist. He is noted for his expertise in prostate disorders, male sexual health and interstitial cystitis. Additionally, he treats patients suffering from chronic pain and athletes with acupuncture and sports nutrition. In 2010 he founded the Integrative Urology Center at New York University (NYU) Langone Medical Center, a center of excellence in research and integrative treatments for urologic conditions.

(ENDNOTES)

1 Clark LC, Combs GF, Jr., Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996;276(24):1957-63.
2 Scott R, MacPherson A, Yates RW, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. Br J Urol. 1998 Jul;82(1):76-80.
3 El-Bayoumy K, Richie, JP, Boyiri T, Komninou D, Prokopczyk B, Trushin N, Kleinman W, Cox J, Pittman B, and Colosimo S. Influence of Selenium-enriched yeast supplementation on biomarkers of oxidative damage and hormone status in healthy adult males: A Clinical Pilot Study. Cancer Epidemiology 2002. Vol. 11, 1459-1465.
4 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63(1):11-30.
5Centers for Disease Control, www.cdc.gov
6 Clark LC, ibid.
7 Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009; 301(1):39-51.
8 Richie JP Jr, Das A, Calcagnotto AM, Sinha R, Neidig W, Liao J, Lengerich EJ, Berg A, Hartman TJ, Ciccarella A, Baker A, Kaag MG, Goodin S, DiPaola RS, El-Bayoumy K. Comparative effects of two different forms of selenium on oxidative stress biomarkers in healthy men: a randomized clinical trial. Cancer Prev Res (Phila). 2014 Aug;7(8):796-804.
9 Christensen MJ. Selenium and prostate cancer prevention: what next--if anything? Cancer Prev Res (Phila). 2014 Aug;7(8):781-5.
10 Rayman MP, Stranges S. Epidemiology of selenium and type 2 diabetes: can we make sense of it? Free Radic Biol Med. 2013 Dec;65:1557-64.
11 Richie JP Jr, Muscat JE, Ellison I, Calcagnotto A, Kleinman W, El-Bayoumy K. Association of selenium status and blood glutathione concentrations in blacks and whites. Nutr Cancer. 2011;63(3):367-75.
12 Christensen MJ, ibid,
13 Selenium and Certain Cancers (Qualified Health Claim: Final Decision Letter) (Docket No. 02P-0457)
14 Zwolak I, Zaporowska H. Selenium interactions and toxicity: a review. Selenium interactions and toxicity. Cell Biol Toxicol. 2012 Feb;28(1):31-46.
15 US Geological Society, http://mrdata.usgs.gov/geochem/doc/averages/se/usa.html
16 Alfthan G, Eurola M, Ekholm P, Venäläinen ER, Root T, Korkalainen K, Hartikainen H, Salminen P, Hietaniemi V, Aspila P, Aro A; for the Selenium Working Group. Effects of nationwide addition of selenium to fertilizers on foods, and animal and human health in Finland: From deficiency to optimal selenium status of the population. J Trace Elem Med Biol. 2014 May 20. pii: S0946-672X(14)00066-2.
17 Wimmer I, Hartmann T, Brustbauer R, Minear G, Dam K. Selenium levels in patients with autoimmune thyroiditis and controls in lower austria. Horm Metab Res. 2014 Sep;46(10):707-9.
18 Campa A. 'Cutoff point for selenium deficiency'. Eur J Clin Nutr. 2012 Nov;66(11):1277.
19 Pinto MA, Lopes MS, Bastos ST, Reigada CL, Dantas RF, Neto JC, Luna AS, Madi K, Nunes T, Zaltman C. Does active Crohn's disease have decreased intestinal antioxidant capacity? J Crohns Colitis. 2013 Oct 1;7(9):e358-66.
20 Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, Craig JE, Ebeling PR. Serum selenium status in Graves' disease with and without orbitopathy: a case-control study. Clin Endocrinol (Oxf). 2014 Jun;80(6):905-10.
21 Bülow Pedersen I, Knudsen N, Carlé A, Schomburg L, Köhrle J, Jørgensen T, Rasmussen LB, Ovesen L, Laurberg P. Serum selenium is low in newly diagnosed Graves' disease: a population-based study. Clin Endocrinol (Oxf). 2013 Oct;79(4):584-90.
22 Rita Cardoso B, Silva Bandeira V, Jacob-Filho W, Franciscato Cozzolino SM. Selenium status in elderly: Relation to cognitive decline. J Trace Elem Med Biol. 2014 Aug 28. pii: S0946-672X(14)00163-1.
23 Pieczyńska J, Grajeta H. The role of selenium in human conception and pregnancy. J Trace Elem Med Biol. 2014 Jul 19.
24 Ashton K, Hooper L, Harvey LJ, Hurst R, Casgrain A, Fairweather-Tait SJ. Methods of assessment of selenium status in humans: a systematic review. Am J Clin Nutr. 2009 Jun;89(6):2025S-2039S.
25 El-Bayoumy K, Richie, JP, Boyiri T, Komninou D, Prokopczyk B, Trushin N, Kleinman W, Cox J, Pittman B, and Colosimo S. Influence of Selenium-enriched yeast supplementation on biomarkers of oxidative damage and hormone status in healthy adult males: A Clinical Pilot Study. Cancer Epidemiology 2002. Vol. 11, 1459-1465.
26 Facompre N, El-Bayoumy K. Potential stages for prostate cancer prevention with selenium: implications for cancer survivors. Cancer Res 2009; 69(7):2699-703.
27 El-Bayoumy K. The protective role of selenium on genetic damage and on cancer. Mutation Research 2001; 475(1-2):123-39.
28 Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU International 2003;91(7):608-12.
29 El-Bayoumy K, Sinha R. Molecular chemoprevention by selenium: a genomic approach. Mutation Research 2005; 591(1-2):224-36.
30 Richie JP Jr, Muscat JE, Ellison I, Calcagnotto A, Kleinman W, El-Bayoumy K. Association of selenium status and blood glutathione concentrations in blacks and whites. Nutr Cancer. 2011;63(3):367-75.