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REPORT

Life Extension Responds to Misleading Article Published in Journal of the American Medical Association

A problem facing researchers today is that by the time human clinical trials are designed, funded, and conducted over multi-year periods, the primary reason for doing the study often turns out to be obsolete.

Based on a number of favorable reports, the US government decided to spend over \$114 million dollars to see if alpha toco-pherol and/or selenium supplements prevent prostate cancer.



Data collected after five years found no reduction in prostate cancer incidence in men taking these supplements.¹

We have known for over 10 years that when alpha tocopherol is taken by itself, it displaces critically important gamma tocopherol in our cells. An abundance of evidence points to the gamma tocopherol form of vitamin E as the most protective against prostate cancer.²⁻⁶

By supplementing aging men with only alpha tocopherol, scientists may have unwittingly increased these men's prostate cancer risk by depriving prostate cells of critical gamma tocopherol. This is only a tiny part of the real story behind this flawed study.

The American Medical Association used this study to discredit vitamin E and selenium supplements. An editorial by the American Medical Association concludes by advising:

“ . . .physicians should not recommend selenium or vitamin E— or any other antioxidant supplements—to their patients for preventing prostate cancer.”⁷

What follows are some succinct facts to rebut the AMA's misleading assertions, along with more detailed discussions about what aging men need to do to reduce their risk of prostate cancer.

ALPHA TOCOPHEROL, SELENIUM, AND PROSTATE CANCER: AN OVERVIEW

A *Journal of the American Medical Association (JAMA)* report released on December 9, 2008 suggests that nutritional intervention (selenium and synthetic vitamin E) does not reduce prostate cancer risk.¹

In January 2008, as part of our article ***“Merv Griffin's Tragic Death from Prostate Cancer,”***⁸ *Life Extension* predicted that this specific trial would fail. We also knew that this flawed study would be misused by the mainstream medical establishment to “prove” to the lay public that low-cost nutrients like vitamin E and selenium do not reduce prostate cancer risk and, by extrapolation, to impugn other low-cost, efficacious nutrients like vitamin D, fish oil, and soy as having no benefit.

In fact, Life Extension's members were made aware of a fundamental fact eight years ago that all but guaranteed the failure of this attack against dietary supplements.

In the *JAMA* clinical trial, men supplemented with synthetic alpha tocopherol experienced significant gamma tocopherol depletion. Men supplemented with alpha tocopherol and alpha tocopherol plus selenium experienced a 45-49% depletion in gamma tocopherol levels by six months that was sustained during the course of this five-year trial.¹

In March 2001, in an article titled ***“Avoiding Prostate Cancer,”*** Life Extension identified the phenomenon of gamma tocopherol depletion associated with excess alpha tocopherol.⁹

Furthermore, Life Extension identified the critical importance of gamma tocopherol supplementation in dramatically lowering the risk of developing prostate cancer—in fact, a study of 10,456 men showed that men who had the highest blood levels of gamma tocopherol were five times less likely to get prostate cancer.⁵

In addition, Life Extension reported in the landmark article *“Eating Your Way to Prostate Cancer,”*¹⁰ published in February 2007, about the importance of controlling dietary intake of *arachidonic acid* and the grave consequences of failing to mitigate up-regulation of the 5-lipoxygenase (5-LOX) enzyme caused by poor dietary choices.

The following article reviews what aging men really need to do to protect against today’s prostate cancer epidemic.

We know that free radical-induced damage to DNA genes can cause cancer, but oxidative stress may only be partly to blame for most prostate cancers.

While prostate cancer is not usually diagnosed until men reach older ages, it can be initiated 15-25 years prior to clinical manifestation. In fact, there is convincing evidence that the initiating DNA damage inflicted by estrogen to prostate cells can occur before a man is even born!¹¹

Studies show that as early as the second and third trimester of life, exposure to elevated estrogens in the womb can initiate prostate cancer that may not manifest for 80 years.¹¹⁻¹⁷ A man’s lifetime exposure to higher than normal estrogen may be a contributing factor to prostate cancer development. There is no evidence that antioxidants like alpha tocopherol vitamin E and selenium would protect against this kind of prostate cancer induced by prolonged excess estrogen exposure.

Please don’t feel helpless about this, as it requires more than mere initiation for cancer to fully develop. Dietary and other lifestyle factors have an enormous impact on whether men will develop prostate cancer, even if they are genetically predisposed.

THE CAUSE OF ALL CANCERS

Cancer can be defined in one sentence as follows:

“CANCER IS THE ACCUMULATION OF MUTATIONS IN GENES THAT REGULATE CELLULAR PROLIFERATION.”¹⁸

All cancers are caused by gene mutations. Every time a cell divides, there are slight mutations to one’s genes. Oxidative stress accelerates gene mutation, but is by no means the primary factor. While selenium and vitamin E reduce some types of oxidative stress, the aged men in the study published by the American Medical Association¹ had already sustained considerable genetic mutations that are not reversible by taking antioxidants.

Fortunately, there are nutrients that have been shown to favorably reverse the gene alterations involved in cancer initiation and progression. The most promising is vitamin D, which has been shown to cut prostate cancer risks in half.¹⁹ Serum levels of vitamin D were not assessed in the study used to bash vitamin E-selenium, so it was not possible to know which men had protective levels of vitamin D and those who had insufficient or even deficient levels. If men in the placebo group had even slightly higher vitamin D status, they would have been less likely to contract prostate cancer.

Failure to test for vitamin D status is not the fault of the researchers conducting this study. When the study was designed, it was not known that vitamin D conferred such a strong protective effect against prostate and other cancers.

The fundamental issue here is that we cannot expect to suppress the fires of oxidative stress (with nutrients like alpha tocopherol-selenium) and then see seven decades of genetic damage magically reverse itself.

EATING YOUR WAY TO PROSTATE CANCER

Cancer cells lurk in the prostate glands of most aging men, yet only one in six men are ever diagnosed with prostate cancer. If one looks at what is required for a single cancer cell to develop into a detectable tumor, it becomes obvious that natural barriers exist to protect people against full-blown cancer.

Unfortunately, the dietary choices of most men living in the modern Western world circumvent the body’s natural protective barriers. The end result is that most men unwittingly provide biological fuel for existing prostate cancer cells to propagate and metastasize.

Fortunately, an understanding of the biological roles of diet and specific nutrients can enable aging men to achieve a considerable amount of control over whether isolated cancer cells in their prostate gland will ever show up as a clinically diagnosed disease.

The impact of the food we ingest on cell growth and death is so pronounced that it can be identical to the effects displayed by anticancer drugs. As it relates to the study showing that alpha tocopherol-selenium did not prevent prostate cancer, if the study participants' diet was not taken into consideration, then the findings would be so severely skewed as to have no meaning. Read on to see what we mean.

WHAT YOU NEED TO KNOW: REDUCING PROSTATE CANCER RISK

- A large study released in December 2008 reported that alpha tocopherol vitamin E and selenium did not reduce prostate cancer risk. While this study has been widely reported to discredit nutritional supplements, numerous flaws render the findings meaningless.
- Multiple factors contribute to prostate cancer risk, while many nutritional and lifestyle strategies are protective.
- Supplementing with only alpha tocopherol depletes levels of gamma tocopherol, the form of vitamin E that is most protective against prostate cancer.
- Vitamin D can favorably reverse genetic changes associated with cancer and has been found to halve prostate cancer risk.
- Diets high in omega-6 and saturated fats are associated with increased prostate cancer risk, while omega-3 fats from fish oil decrease risk.
- Omega-6 and saturated fats convert to arachidonic acid, which is metabolized by the 5-LOX enzyme to dangerous inflammatory substances that increase the risk of cancer and arterial disease.
- An extract of *Boswellia* plant called 5-LOXIN® inhibits 5-LOX and shows promise in fighting inflammation and prostate cancer.
- Consumption of plant foods like broccoli, cauliflower, flax seed, and soy protects against numerous diseases, including prostate cancer.
- A new book from Harvard researchers provides evidence that low testosterone increases prostate cancer risk.

OMEGA-3 FATTY ACIDS: THE FIRST LINE OF DEFENSE

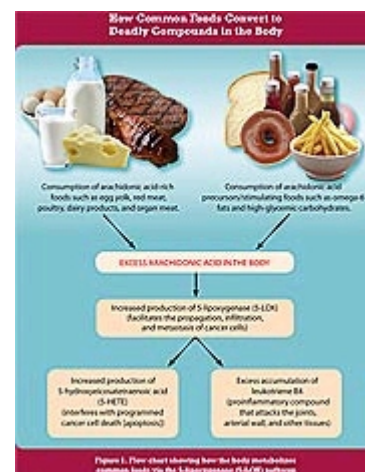
Diets high in omega-6 fats and saturated fats are associated with greater prostate cancer risk, whereas increased intake of omega-3 fats from fish has been shown to reduce risk. Based on consistent epidemio-logical findings across a wide range of human populations, scientists have sought to understand why eating the wrong kinds of fat (saturated and omega-6 fats) provokes a stimulatory effect on prostate cancer.^{20,21}

To ascertain what happens after we eat bad fats, all one has to do is look at the metabolic breakdown pathways that these fats follow in the body, as shown in the chart on the next page (*Figure 1 to the right*). For example, let us assume that for dinner, you eat a steak (a source of saturated fat) and a salad, along with a typical salad dressing of soybean and/or safflower oils (sources of omega-6 fats).

As can be seen in the (*Figure 1 to the right*) flow chart, saturated and omega-6 fats convert to arachidonic acid in the body. The meat itself contains arachidonic acid. One way that the body rids itself of excess arachidonic acid is provoking a dangerous metabolizing pathway through 5-lipoxygenase (5-LOX). New studies show conclusively that 5-LOX products directly stimulate prostate cancer cell proliferation via several well-defined mechanisms.²²⁻²⁸ Arachidonic acid is metabolized by 5-LOX to 5-hydroxyeicosatetraenoic acid (5-HETE), a potent survival factor that prostate cancer cells use to escape destruction.^{24,29,30}

(*Figure 1 to the right*) clearly demonstrates how consuming a diet of foods rich in arachidonic acid directly provokes the production of dangerous 5-LOX products, which can promote the progression of prostate cancer. In addition to 5-HETE, 5-LOX also metabolizes arachidonic acid to leukotriene B₄, a potent proinflammatory agent that causes destructive reactions throughout the body and inflicts severe damage to the arterial wall.³¹⁻³⁷

One reason that fish oil supplements have become so popular is that their beneficial EPA/DHA fatty acids can help reduce the production of arachidonic acid-derived eicosanoids in the body.³⁸⁻⁴³ As shown in (*Figure 1 above*), if arachidonic acid levels are reduced, there would be a corresponding suppression of the 5-LOX products 5-HETE and leukotriene B₄.



[Click Here for Figure 1](#)

DAILY USE OF ASPIRIN MAY DECREASE PROSTATE RISKS

Researchers studied 2,447 men over 12 years, examining them every other year. After adjusting for age, diabetes, hypertension, and other factors, they found that men who took a daily aspirin or another NSAID (like ibuprofen) reduced their risk of moderate or severe urinary symptoms by 27% and lowered their risk of an enlarged prostate by 49%. Even more intriguing was the finding that men who consumed aspirin or another NSAID were 48% less likely to have an elevated level of prostate-specific antigen (PSA), the protein measured in the blood that helps detect prostate cancer.¹¹⁶

Aspirin inhibits the cyclooxygenase (COX-1 and COX-2) enzymes, which are also involved in the arachidonic acid inflammatory pathway.^{117,118} Like 5-lipoxygenase, COX-2 is known to promote the proliferation of prostate cancer cells.¹¹⁹

Once one understands the lethal 5-LOX cascades, it is easy to see why people who excessively consume foods rich in arachidonic acid, and those who do not reduce the production of excessive arachidonic acid metabolites, are setting themselves up for prostate cancer and a host of inflammatory diseases (including atherosclerosis).

Men in the AMA-published study who took alpha tocopherol-selenium supplements, but consumed foods high in arachidonic acid and not enough omega-3s were more likely to develop prostate cancer. The researchers who designed this study might not have known to correct for this confounding factor when the study was designed.

5-LOX IS OVER-EXPRESSED IN PROSTATE CANCER

Based on studies showing that consumption of foods rich in arachidonic acid is greatest in regions with high incidences of prostate cancer,^{22,23,27,44} scientists sought to determine how much of the 5-LOX enzyme is present in malignant versus benign prostate tissues.⁴⁵

Using biopsy samples taken from living human patients, the researchers found that 5-LOX mRNA levels were an astounding six-fold greater in malignant prostate tissues compared with benign tissues. This study also found that levels of 5-HETE were 2.2-fold greater in malignant versus benign prostate tissues.⁴⁵ The scientists concluded this study by stating that selective inhibitors of 5-LOX may be useful in the prevention or treatment of patients with prostate cancer.

5-LOX PROMOTES TUMOR GROWTH FACTORS

As the evidence mounts that ingesting “bad fats” increases prostate cancer risk, scientists are evaluating the effects of 5-LOX on various growth factors involved in the progression, angiogenesis, and metastasis of cancer cells.

One study found that 5-LOX activity is required to stimulate prostate cancer cell growth by epidermal growth factor (EGF) and other cancer cell proliferating factors produced in the body. When 5-LOX levels were reduced, the cancer cell stimulatory effect of EGF and other growth factors was diminished.²²

In a mouse study, an increase in 5-LOX resulted in a corresponding increase in vascular endothelial growth factor (VEGF), a key growth factor that tumor cells use to stimulate new blood vessel formation (angiogenesis) into the tumor. 5-Lipoxygenase inhibitors were shown to reduce tumor angiogenesis along with a host of other growth factors.⁴⁶ In both androgen-dependent and androgen-independent human prostate cancer cell lines, the inhibition of 5-LOX has consistently been shown to induce rapid and massive apoptosis (cancer cell destruction).^{23,44, 47,48}

NUTRIENTS THAT SUPPRESS 5-LOX

Health-conscious people already take nutrients like fish oil that help to lower 5-LOX activity in the body.^{49,50} Studies show that lycopene and saw palmetto extract also help to suppress 5-LOX.^{51,52} The suppression of 5-LOX by these nutrients may partially account for their favorable effects on the prostate gland.

As humans age, however, chronic inflammatory processes can cause the over-expression of 5-LOX in the body. For maturing males, the result of excess 5-LOX may be the epidemic of prostate cancer observed after the age of 60.

Based on the cumulative knowledge that 5-LOX products can promote the invasion and metastasis of prostate cancer cells, it would appear advantageous to take aggressive steps to suppress this lethal enzyme. The good news is that a natural 5-LOX inhibitor is included in a popular formula used to maintain healthy prostate function.

In addition to potentially suppressing prostate cancer, the successful inhibition of 5-LOX should also slow the progression of atherosclerosis.⁵³

5-LOXIN®: NATURE'S 5-LOX INHIBITOR

Specific extracts from the *Boswellia* plant selectively inhibit 5-lipoxygenase (5-LOX).^{54,55} This is not surprising when one considers that various *boswellia* extracts have been used for centuries in India as anti-inflammatory agents.⁵⁶

In several well-controlled human studies, *boswellia* has been shown to be effective in alleviating various chronic inflammatory disorders.⁵⁷⁻⁶¹ Scientists have discovered that the specific constituent in *boswellia* responsible for suppressing 5-LOX is AKBA (3-O-acetyl-11-keto-B-boswellic acid). *Boswellia*-derived AKBA binds directly to 5-LOX and inhibits its activity.⁵⁵ Other boswellic acids only partially and incompletely inhibit 5-LOX.^{55,62}

Methods to extract high concentrations of AKBA from *boswellia* have been intensively investigated due to AKBA's potential in treating chronic inflammatory disorders. Even in standardized *boswellia* extracts, however, biologically active AKBA makes up only 2-5% of the final product.

Several years ago, researchers discovered how to obtain an economically viable *boswellia* extract standardized to contain a greater than 30% concentration of AKBA. This 30% AKBA extraction discovery was patented and given the trademark name "5-LOXIN®." When tested against the best commercial *boswellia* compounds, 5-LOXIN® exhibited better inhibitory action against 5-LOX.^{63,64}

5-LOXIN® DECREASES INFLAMMATION, INVASIVE POTENTIAL, TUMOR CELL ADHESIVENESS, AND ANGIOGENESIS

A rat study was conducted to evaluate the efficacy of 5-LOXIN® compared with the popular anti-inflammatory drug ibuprofen. 5-LOXIN® reduced inflammation by 27% compared with 35% for ibuprofen.⁶³ Another rat study compared 5-LOXIN® with the anti-inflammatory steroid drug prednisolone. 5-LOXIN® reduced inflammation by 55%, which was similar to the reduction by prednisolone used in this study.⁶⁴ The significance of these findings is that prednisolone and ibuprofen can be toxic when used chronically, whereas natural 5-LOXIN® is free from side effects.

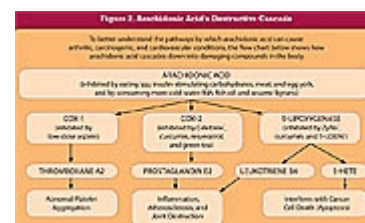
Ibuprofen has demonstrated anticancer effects, most probably due to its inhibition of COX-2, another enzyme that cancer cells use to facilitate their growth and survival. As you have just learned, 5-LOXIN® functions to block the 5-LOX enzyme. Since the effects of 5-LOXIN® and ibuprofen may be either additive or synergistic, a clinical trial of a combination of these agents is warranted.

Tumor necrosis factor-alpha (TNF-alpha) is a dangerous proinflammatory cytokine that often increases in aging people. In a gene-chip study, 5-LOXIN® blocked the expression of many genes that are sensitive to the pathological effects of TNF-alpha.^{63,64}

From the standpoint of keeping prostate cancer cells in check, 5-LOXIN® was shown to prevent the TNF-alpha-induced expression of a protein-degrading enzyme called matrix metalloproteinase (MMP).⁶⁴ Cancer cells use the MMP enzyme to tear apart natural barriers in the body that would normally encase them.¹¹⁵ Prostate cancer cells are notorious for inducing the production of this enzyme that causes containment structures within the prostate gland to vanish, thus enabling the mutated (cancerous) prostate cells to break through healthy prostate tissue and eventually metastasize.

Prostate cancer cells use adhesion molecules (known as VCAM-1 and ICAM-1) to facilitate their spread throughout the body. 5-LOXIN® was shown to prevent the up-regulation of these adhesion molecules, which are directly involved in inflammatory processes.⁶⁴ Chronic inflammation is tightly linked to the induction of aberrant angiogenesis used by cancer cells to facilitate the growth of new blood vessels (angiogenesis) into tumors.

In the JAMA study used to discredit alpha tocopherol-selenium, the use of aspirin or ibuprofen by the placebo group may have reduced the prostate cancer risk more than what could be expected in those receiving alpha tocopherol and selenium.



Click Here for Figure 2 Chart

MULTIPLE DANGERS OF EXCESS ARACHIDONIC ACID

In response to arachidonic acid overload, the body increases its production of enzymes like 5-lipoxygenase (5-LOX) to degrade arachidonic acid. Not only do 5-LOX products directly stimulate cancer cell propagation,^{22-28,44,65-74} but the breakdown products that 5-LOX produces from arachidonic acid (such as leukotriene B4, 5-HETE, and hydroxylated fatty acids) cause tissue destruction, chronic inflammation, and increased resistance of tumor cells to apoptosis (programmed cell destruction).^{22,29,75-79}

It is important to understand that 5-LOX is not the only dangerous enzyme the body produces to break down arachidonic acid. As can be seen in (Figure 2 above), both cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) also participate in the

degradation of arachidonic acid.

COX-1 causes the production of thromboxane A₂, which can promote abnormal arterial blood clotting (thrombosis), resulting in heart attack and stroke.⁸⁰⁻⁸⁴ COX-2 is directly involved in cancer cell propagation,⁸⁵⁻⁸⁸ while its breakdown product (prostaglandin E₂) promotes chronic inflammation.^{79,89,90} Most health-conscious people already inhibit the COX-1 and COX-2 enzymes by taking low-dose aspirin,⁹¹⁻⁹⁵ curcumin,⁹⁶⁻¹⁰⁸ green tea,¹⁰⁹⁻¹¹¹ and various flavonoids such as resveratrol.¹¹²⁻¹¹⁴

A more integrative approach to this problem, however, would be to also reduce levels of arachidonic acid, which is the precursor of 5-HETE and leukotriene B₄.

REPORT

Life Extension Responds to Misleading Article Published in Journal of the American Medical Association

SOY, LIGNANS, AND CRUCIFEROUS VEGETABLES

Men who regularly consume certain plant foods have sharply lower rates of prostate cancer. Studies show that cauliflower, broccoli, flax lignans, and soy isoflavones¹²⁰⁻¹²⁹ protect against a host of diseases, including prostate cancer. If the men in the placebo group ate an even slightly healthier diet, then they would be expected to enjoy a lower rate of prostate cancer compared with men who took the alpha tocopherol-selenium supplements but ate fewer cancer-preventing plant foods.

LOW TESTOSTERONE INCREASES PROSTATE CANCER RISK

In a book authored by Harvard University experts titled *Testosterone for Life*, detailed findings are presented that dispel a misleading notion about testosterone causing prostate cancer.¹³⁰ These researchers meticulously document their observations that men with low levels of testosterone have higher prostate cancer risks.

This finding provides another confounding factor that skews the results of the alpha tocopherol-selenium study. If men receiving the supplements had lower testosterone levels, they would conceivably have a higher rate of prostate cancer.

RISK OF SUPPLEMENTING WITH ONLY ALPHA TOCOPHEROL

We now know that when alpha tocopherol is taken by itself, it displaces critically important gamma tocopherol in our cells. An abundance of evidence points to the gamma tocopherol form of vitamin E as the most protective against prostate cancer. By supplementing aging men with only alpha tocopherol, scientists may have unwittingly increased prostate cancer risk in the men participating in the recent JAMA study by depriving prostate cells of critical gamma tocopherol.

TOO MANY FACTORS INVOLVED IN PROSTATE CANCER CAUSATION

The alpha tocopherol-selenium study was designed based on prior studies showing sharply lower risks of prostate cancer in men who consumed these nutrients. It was also based on the premise that protecting genes against oxidative stress would reduce prostate cancer incidence in aged men.

We now know of dozens of factors involved in the development of full-blown prostate cancer. One could not expect that taking just two nutrients would result in less prostate cancer developing in these older study subjects. There are too many other causes that have to be factored in and were not known when the study was designed long ago.

It is encouraging that over the past 12 years, a plethora of new research findings have identified definitive ways for aging men to drastically slash their risk of developing prostate cancer.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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