

REPORT

Reducing Prostate Cancer Deaths  
Through Prevention and Early Diagnosis

by Stephen B. Strum, M.D.

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Co-Founder and First Medical Director of the Prostate Cancer Research Institute



Fifteen years ago, before the advent of the PSA, men were diagnosed with prostate cancer either due to abnormalities on the digital rectal exam (DRE) or due to other laboratory or radiology findings reflecting advanced cancer. The medical means to pick up smaller amounts of prostate cancer (PC) simply were not available. This is a common dilemma in the world of cancer medicine: how do you detect the disease early, before it has spread? For women, the PAP smear dramatically changed the course of medical history for those fearing a diagnosis of cancer of the cervix. The mammogram has similarly aided women in detecting breast cancer. The prostate specific antigen (PSA) and PSA dynamics (changes over time) are able to detect PC at an earlier stage than the screening tools noted above.

Deaths caused by PC can be significantly reduced through incorporation of a DRE (Digital Rectal Exam) and a simple blood test for PSA (Prostate Specific Antigen) as part of your yearly physical examination. By maintaining and monitoring a chronological record of your PSA test results, it is possible to predict the emergence of PC several years before it would normally be diagnosed.

PSA (Prostate Specific Antigen)

Tumor cells make many kinds of proteins. We have only a dozen or so commercial tests that measure these proteins. We call such tests biologic markers or biomarkers. The PSA blood test is one such biomarker. The PSA is the single most important biomarker in the history of cancer medicine. Since tumor growth is essentially exponential, with one cell dividing into two, two to four, four to eight, eight to sixteen and so on, a protein product of a tumor cell, e.g. PSA, can reflect such exponential growth in the time it takes for PSA to double (PSA doubling time or PSADT). We know that simply measuring the PSA each year using a reliable laboratory and graphing the results of the PSA can quickly alert the patient and physician to the possibility that malignancy exists.

For some bizarre reason, this incredibly inexpensive tool that can alert us to a problem with PC has not become a routine medical practice. PSA doubling can be a significant early notification that PC is present. The example below helps illustrate this concept.

A man gives a history of a PSA of 0.8 at the age of 40 in 1990. No real change in PSA occurs until he reaches the age of 48, when the PSA increased to 1.2 ng/ml. This is most likely to be regarded with absolutely no concern by most physicians. However, the patient's wife encourages him to repeat the PSA and six months later it is 1.6 ng/ml. This is still well within the so-called "normal" range of up to 4.0 ng/ml but with an understanding of PSA dynamics this man must be regarded as having PC until proven otherwise.

Age in Years	PS (ng/ml)	PSA Doubling Time (PSADT)
40	0.8	
48	1.2	Approx 14 yrs
48.5	1.6	Approx 1.2 yrs

The PSA doubling time in the last six months was shortened from 14 years to 1.2 years. Between 1/90 and 1/98, his calculated PSA doubling time (PSADT) was 163.78 months or close to 14 years. Typically, PC has an average PSADT of four years at the time of diagnosis. Unfortunately for this man, his PSADT has shortened to 14.3 months between 1/98 and 7/98. This finding should trigger additional testing and closer surveillance.

Unfortunately, this is not what occurs in the vast majority of men. Today's world of medicine is still bound to absolute concepts of "normal vs. abnormal." Usually, modern medicine does not look at patterns or trends within the so-called normal ranges. This ignores the biologic expressions of disease such as PSADT or PSA velocity (the rate of increase per year of PSA).

It is suggested that each man begin PSA testing annually starting at age 40. For men with a family history of PC involving first-degree relatives (father, brother), testing should begin at the age of 35. Because breast cancer is genetically linked to PC, we also advise men with a family history of breast cancer to start PSA testing, along with annual digital examination of the prostate, at age 35.

Also monitor the PSA doubling time independent of the absolute value of the PSA. Clinical evidence suggests that the shorter the PSADT, the greater the risk for PC. A doubling time of less than 12 years usually indicates tumor growth and should be regarded as indicating that PC is present and growing until proven otherwise. If prostate cancer is present but not diagnosed, a doubling in the PSA value is essentially consistent with a doubling of tumor size. It is during this early phase of PC growth that methods of cancer detection provide the greatest chance of cure.



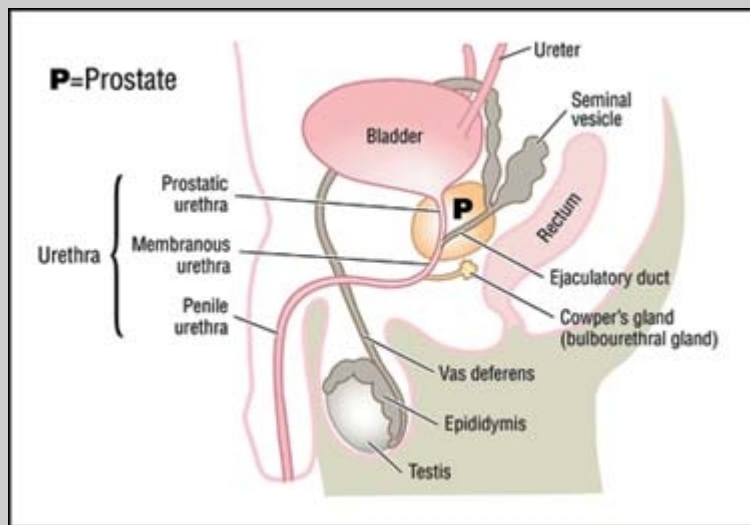
### DRE (Digital Rectal Exam)

Men can easily be tested for palpable prostate abnormalities with the DRE. The DRE done carefully and gently is an easy test that yields much information. First, it gives the physician a sense of the prostate gland volume. The gland volume is important since the bigger the prostate, the more PSA the gland is entitled to make. A rule of thumb is that the prostate gland volume multiplied by 0.067 equals the amount of PSA produced by the benign prostate tissue. A 50-year old man with a normal prostate of 30 grams or cubic centimeters would therefore be entitled to make approximately two nanograms of PSA. If such a man has a PSA of 4.00, it would indicate an excess of about two nanograms of PSA and the need for further investigation to rule out PC.

In addition to estimating prostate gland volume and calculating the benign cellular contribution to the total PSA value, the DRE can also aid in finding hard nodules and/or other evidence of disease. Palpable abnormalities of the prostate gland relate to tumor volume (also called tumor burden). The DRE is therefore an additional sensor that indicates that the amount of PC has increased enough to cause a change in the physical examination; something is now able to be felt (palpable). In the years before routine testing with PSA, most prostate cancers were palpable by DRE at the time of diagnosis. Today, close to 70% of PC diagnosed in the U.S. is no longer associated with palpable disease. This is confirmatory to the value of PSA screening-allowing an earlier diagnosis of PC--before the cancer has had a chance to get bulkier and manifest itself as palpable (called T2) disease. Most men in the U.S. currently diagnosed with PC have non-palpable prostate cancer or T1 disease.

Figure 1.

Prostate Anatomy. The urethra empties the bladder, then enters the prostate where it is joined by the ejaculatory ducts, which deliver sperm and seminal vesicle fluid to nourish the sperm and help liquefy the ejaculate. The urethra then exits the prostate, enters the bulb of the penis and continues through the penis to the glans penis where it ends.



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In the past we only measured the total PSA. In the last ten years we have learned that components of the PSA, such as free PSA and complexed PSA, have special clinical significance in the diagnosis of this disease. Fractionation of PSA into these components refines our detective work. It enables an enhanced focus on those patients with abnormalities in Free PSA who have a higher risk for PC. Therefore, when we have a patient with an elevated or increasing PSA, we can get a sense of his risk for having PC by asking for a free PSA level and free PSA percentage. The lower the free PSA percentage, the greater the risk for PC.<sup>1-3</sup>

#### Strategies to Prevent Prostate Cancer

##### Diet

The basics of prevention and active nutritional treatment are to be found in a healthy diet. The following recommendations relating to dietary strategies are based on recent medical publications.

- Reduce the consumption of red meat, dairy products, saturated fats, and egg yolk in your diet.<sup>4,5</sup> Eat five servings of fruits and vegetables each day. In one study, men who ingested 10 or more servings of tomatoes in several forms (sauce, juice, raw or on pizza) had a 41% reduction in the incidence of PC while those who ate four to seven servings per week had a 22% reduction. The other food associated with a low prostate cancer risk was strawberries. One serving (0.5 cup/week) of strawberries was associated with a 20% decreased risk of prostate cancer.
- Restrict your daily caloric intake to roughly 500 calories for each of three meals per day and 100 calories for each of three snacks per day for a total of 1800 calories per day. Adjust this amount based on your level of activity and body mass. If everyone were to do this, we would eliminate most cases of diabetes, hypertension, stroke, hypercholesterolemia, heart disease and a significant amount of cancer in the world. Scientific literature shows PC and its development are linked most significantly with caloric intake, also known as energy intake.<sup>6</sup> Another study<sup>7</sup> found that a 20% to 40% reduction in calorie consumption:
  - Increased PC cell death rate (apoptosis)
  - Decreased angiogenesis or tumor blood vessel formation by two to three fold
  - Decreased vascular endothelial growth factor (VEGF)
  - Decreased circulating IGF-1 (Insulin-like growth factor 1) VEGF and IGF-1 are significant growth factors for PC. Plasma levels of VEGF are increased in patients with metastatic PC.<sup>8</sup>
- Avoid excessive carbohydrate intake. Your protein to carbohydrate ratio should be 3:4. This means for every 300 calories of protein you eat, you should be balancing that with 400 calories of carbohydrates. If you adhere to a 500-calorie per meal plan, you could be eating 150 calories of protein along with 200 calories of carbohydrates and 150 calories of polyunsaturated fat, the latter ideally from cold-water fish, olive oil on your salad, etc.
- Eliminate smoking, reduce alcohol consumption and exercise properly.

Nutritional and life-style counseling and the use of new software programs would greatly aid in our attempts to reduce the incidence and mortality of PC. A discussion of nutrition may be found in greater depth in the following books:

*Life Extension Disease Prevention and Treatment 2003 Chapter on Prostate Cancer by Stephen B. Strum, M.D.*

*The ABCs of Nutrition and Supplements for Prostate Cancer by Mark A. Moyad, M.D., M.P.H.*



The Anti-Aging Zone and The Omega Rx Zone, both by Barry Sears, Ph.D.

The Carbohydrate Addicts Healthy Heart Program by Richard and Rachael Heller

The Anti-Oxidant Miracle by Lester Packer

Eating Your Way to Better Health by Charles "Snuffy" Myers, Jr. M.D.

Vitamins and antioxidants

Lycopene

Of all the vitamins and micronutrients, the largest number of medical papers have been published on the positive effects of lycopene versus PC. Lycopenes are members of the carotenoid family. Most of you are familiar with the carotenoids and flavonoids, the two main families of micronutrients. Both carotenoids and flavonoids are pigments synthesized by plants. The carotenoids impart the yellow, orange and red color to fruits and vegetables. The other family, the flavonoids, cause the blues, purples, emerald green and some red coloration of fruits and vegetables. Some of the major carotenoids and their vegetable, fruit or food sources is shown in Table 1.

Lycopenes have been shown to be of value in reducing the overall incidence of PC,<sup>4,9-11</sup> the incidence of aggressive PC,<sup>12,13</sup> as well as causing reductions in PC growth,<sup>14</sup> PSA levels<sup>15,16</sup> and even pathologic conditions associated with PC occurrence such as high-grade prostatic intra-epithelial neoplasia (HGPIN).<sup>17</sup> More detailed descriptions of a few of these articles follow.



A dietary history of significant lycopene consumption has been related to a lower risk of aggressive and extra-prostatic PC.<sup>13</sup> In this study, the combined intake of tomatoes, tomato sauce, tomato juice, and pizza (accounting for 82% of lycopene intake) was inversely associated with risk of prostate cancer for consumption frequency greater than 10 versus less than 1.5 servings per week. The other non-lycopene product identified that was associated with a lower PC risk was strawberries. One serving (0.5 cup) per week of strawberries was correlated with a 20% decreased risk of prostate cancer.<sup>11</sup>

Lu et al reported that the higher the plasma level of lycopene, the lower the incidence of PC. When comparing the highest versus the lowest lycopene levels, the risk of developing PC was reduced approximately 80%. The only other carotenoid approaching this zeaxanthin with a similar risk reduction.<sup>18</sup> A study by Vogt showed that the risk for aggressive PC diminished by 63% when comparing highest versus lowest lycopene levels. In this study, serum lycopene concentrations were significantly lower in Blacks than in Whites, raising the possibility that differences in lycopene exposure may contribute to the racial disparity in incidence.<sup>12</sup>

Carotenoid Class	Vegetable, Fruit or Food
b-carotene	Carrots, yams, sweet potatoes, spinach
a-carotene	Carrots, mixed vegetables
Lutein	Spinach, broccoli, kale, mustard, chard
Lycopene	Tomatoes, tomato sauce, pizza, tomato juice
b-cryptoxanthin	Oranges

Table 1. Carotenoid Classes and Examples.

Carotenoids are pigmented substances that are produced by plants. They have biological effects that explain the link between good nutrition and good health.

The largest relevant dietary study, a prospective study in male health professionals found that consumption of two to four servings of tomato sauce per week was associated with about a 35% risk reduction of total prostate cancer and a 50% reduction of advanced (extraprostatic) prostate cancer. Tomato sauce was by far the strongest predictor of plasma lycopene levels in this study.<sup>19</sup> These associations persisted in analyses controlling for fruit, vegetable consumption and for olive oil use and were observed separately in men of Southern European or other Caucasian ancestry.<sup>20</sup>



The consumption of cooked tomatoes was substantially and significantly associated with a reduction in insulin-like growth factor-1 (IGF-1) levels, with a mean (95% CI) change of -31.5% (range from -49.1% to -7.9%) for an increment of one serving per day. The authors concluded that the strongest known dietary risk factor for prostate cancer (lycopene deficit, as reflected in a reduced intake of cooked tomatoes) is somehow related to an important endocrine factor (IGF-1) in the cause of this disease.<sup>21</sup>

The easiest way I have found to combine a healthy intake of lycopenes into my diet is by using marinara sauce on various foods. For example, at breakfast, an egg-white omelet containing eggplant and bell peppers (ratatouille omelet) covered with marinara sauce is healthy as a source of protein, contains a substantial fiber content and is restricted in the amount of simple carbohydrates. Stewed tomatoes can be served as a vegetable side dish with lunch or dinner. Additionally, if one were intolerant to tomato-based products due to gastrointestinal reflux disease, supplementation with products containing lycopene would be a worthwhile consideration. Life Extension (LE), a nutraceutical company in Ft. Lauderdale, Florida sells a number of products containing lycopene, and additional products containing zeaxanthin. Healthy Origins sells a product called Lyc-O-mato that is a lycopene-based product. (Table 2)

#### Vitamin E

Measures to prevent PC must be a routine part of the counsel that general practitioners and internists give their patients. Vitamin E and selenium are foundational antioxidants that should be started early in life to prevent oxidative damage to the prostate tissue and other tissues of the body. Although definitive studies regarding what age such supplements should be started at are currently lacking, I would suggest beginning such a regimen at age 25 and continuing this approach as a life-long practice. Vitamin E has been shown to reduce the incidence of PC by 32% and death due to PC by 41%.<sup>22</sup> Basic research studies have shown that vitamin E reduces growth rates of PC tumors transplanted into mice and stimulated by a high fat diet.<sup>23</sup> A study published in the Journal of the National Cancer Institute determined that statistically significant protective associations for high levels of selenium and alpha-tocopherol (vitamin E), were observed only when gamma-tocopherol (the gamma isomer of vitamin E) levels were high.<sup>24</sup> A suggested dose of natural vitamin E as d-alpha tocopherol succinate would be 400 i.u. (equivalent to 270 mg) combined with 210 mg of d-gamma tocopherol in conjunction with selenium at a dose of 200 mcg per day. A table of the readily available d-gamma tocopherol supplements comparing doses and costs may be found at <http://pcri.org/education/nutrprod/vite.html>.



Product Name	Company	Ingredient	Contact
LE Super Booster*	Life Extension Item # 442	Lycopene 10 mg/capsule	<a href="http://www.lefprostate.org">www.lefprostate.org</a> or 1-866-820-7457
Natural Prostate Formula**	Life Extension Item # 380	Lycopene 5 mg/capsule	Same as above
Super Zeaxanthin ***	Life Extension Item # 569	Zeaxanthin 5 mg/capsule	Same as above
Lycopene	Life Extension Item # 455	Lycopene 15 mg/capsule	Same as above
Lyc-O-Mato Natural Tomato Lycopene	Healthy Origins	Lycopene 15 mg/capsule	<a href="http://www.healthyorigins.com">www.healthyorigins.com</a>

Table 2. Products Containing Significant Amounts of Lycopene. The above are some examples of lycopene-containing supplements that have significant amounts of lycopene.

## Selenium

Studies by Clark, et al as well as Yoshizawa et al have shown that selenium reduced the incidence of PC in men by 63%.<sup>25,26</sup> Selenium intake of at least 200 mcg a day and vitamin E should be a standard recommendation made to all men.

## Omega 3 fatty acids (marine fish oils)

The importance of fats with beneficial activity has been under-emphasized throughout all of healthcare, including PC prevention and treatment. Every cell in the human body has a cell membrane that encloses the basic machinery of the cell. The cell membrane is comprised of fatty acids or lipids. The integrity of the cell depends on the health and function of its cell membrane. One of the functions of the cell membrane involves the production of hormonal substances called eicosanoids. These are the oldest hormones - messengers involved in communication between cells. Eicosanoids trace their origin back 500 million years to production by sponges. Hormones are usually peptides or steroids, produced by one tissue and conveyed by the bloodstream to another to exert a physiological effect on cell growth or metabolism; in short, a chemical messenger aimed at maintaining a healthy state of affairs within the complex society of cells, tissues and organ systems. All of medicine, in fact all of life, represent issues of communication and balance.



The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexenoic acid (DHA) are critical regulators of the eicosanoid hormonal pathways. EPA and DHA (extracted from fish oil) direct eicosanoid production away from the bad or unfavorable eicosanoids such as the omega-6 fatty acid arachidonic acid (AA) and its metabolic products. (Figure 2) By inhibiting this latter pathway (shown in red in Figure 2) DGLA is metabolized in favor of good eicosanoids, such as PGA1 and PGA2.

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When AA is formed or ingested (e.g. red meat and egg yolk) it undergoes metabolism by the cyclo-oxygenase (COX) and lipo-oxygenase (LOX) enzymes. A vast part of the biotech industry has been dedicated to the development of COX inhibitors ranging from non-specific drugs like aspirin to ibuprofen to more selective COX 2 inhibitors like Celebrex and Vioxx. We can naturally shift the eicosanoid pathways away from AA production by dietary maneuvers that avoid excessive carbohydrate intake and the resulting insulin stimulation. This is the basis of the Zone diet and the Atkins diet. Referring to Figure 2 and focusing on the pathway between DGLA and AA (shown in green), we can direct our attention to dietary and pharmacologic approaches that prevent overproduction of AA or inhibit AA production. If we neglect this pathway, overproduction of AA occurs. AA is an omega-6 fatty acid that generates free radicals that cause cell injury. Specific metabolic products of AA such as PGE2 and 5-HETE are created through the actions of the enzymes COX-2 (cyclo-oxygenase 2), 5-LOX (5-Lipoxygenase), 12-LOX, and 15-LOX. These metabolites are examples of bad eicosanoids and have been implicated in PC growth and metastasis.<sup>27,28</sup> In a study of human PC where 5-LOX and its metabolite 5-HETE were evaluated in malignant versus benign prostate tissue within the same patient, both 5-LOX and 5-HETE were significantly over-expressed in the PC tissue.<sup>29</sup> In other words, specific eicosanoids are modulators of tumor cell interactions with certain host components within the context of cancer growth, invasion and spread. What the layperson can do to inhibit AA is to reduce insulin-stimulating carbohydrate ingestion and to use a high quality of EPA/DHA to inhibit the AA pathway. These approaches are the basis for Barry Sears' latest book called *The Omega Rx Zone*.<sup>30</sup>

#### Other micronutrients

Other products that appear to play a potentially significant role in prevention and treatment of PC include soy isoflavones such as genistein and daidzein, the grape anti-oxidant known as resveratrol,<sup>31-35</sup> the curcuminoids found in the spice turmeric (curcumin),<sup>36-39</sup> and a substance in various teas such as green tea called EGCG (epigallocatechin gallate).<sup>40-44</sup> Future issues of *Life Extension* magazine will address these areas.

#### Conclusion

There have been tens of thousands of articles written about PC. The number of medical journals keep increasing and with it an exponential increase in information about this disease, as well as its relation to other illnesses. The monumental task of the physician, especially in today's bizarre world of medical economics, is to keep up with this literature as best as possible and whenever applicable to translate what is being learned to the patient's active care. This is the heart and soul of translational medicine: applying what we are learning by taking the research findings to the "bedside" of the patient.

I would make a plea, to all men and their loved ones, based on 40 years of watching the evolution of medicine and the outcomes of thousands of men with this disease, that active participation of the patient and his partner is critical to an optimal outcome. In the best of all worlds, this should involve co-partnership with the physician but this is not occurring. Instead, the physician is becoming increasingly distant from the patient and his partner as he is overwhelmed with the constraints of managed (mangled) care, huge overhead costs, and an increasingly complex life bureaucracy. Given such a setting, the empowerment of the patient and his partner(s) must become a common phenomenon. Access to the Internet and to other sources of information geared to the patient and his partner may enable the concept of translational medicine to survive and hopefully be brought to its rightful place in the lives of many men and their families. This was the reason that Donna Pogliano and I spent years creating *A Primer on Prostate Cancer, The Empowered Patient's Guide*.

The efforts of many thousands of physicians and researchers throughout the world have provided us with the opportunity to significantly reduce death and morbidity caused by PC. What is most critical for you is to initiate the actions needed to bring these efforts to fruition and have them become a life-long lifestyle change. You owe it to yourself and your family to initiate such steps if

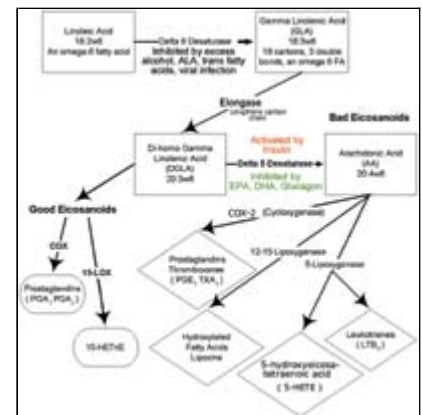


Figure 2. The Eicosanoid Pathways

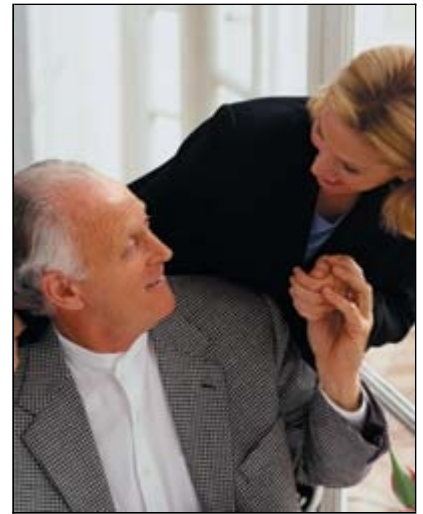
The pathways to good versus bad eicosanoids are dictated by whether DGLA metabolism favors arachidonic acid (AA) production and the generation of bad eicosanoids, or instead is shunted preferentially toward favorable eicosanoids of the PG1 series (PGA1 and PGA2).

you have not already done so. This can save your life.

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Ashland, Oregon 2003

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