

Botanical and Nutritional Supplements, Vitamins, Dietary, and Lifestyle  
Interventions for Androgen-Insensitive Prostate Cancer  
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Prostate cancer, the leading cause of cancer in men, affects millions of men. Even so, the lifetime risk of dying from prostate cancer is only 3.5% for Caucasians and 4.3% for African Americans

(Klein, 2002). Just the same, prostate cancer is the second leading cause of cancer death in men, and the majority of men with advanced prostate cancer succumb to their disease.

Advanced prostate cancer is comprised of a heterogeneous population of androgen-dependent, androgen-sensitive, and androgen-insensitive prostate cancer (AIPC) cells, which explains why androgen deprivation therapy - the primary treatment for advanced prostate cancer - is not curative (Isaacs, 1999). This article explores an accumulating body of scientific evidence which suggests that natural therapies can alter the initiation, promotion, and progression of androgen-sensitive and androgen-insensitive prostate cancer, improve quality of life, and prolong survival. This said, it is important to establish that natural therapies are *not* curative, but adjuncts to traditional care.

Although theoretical, a shifting paradigm of cancer may explain how natural therapies alter cancer biology. According to (Schipper, 1995), cancer is a potentially reversible process that stems from maladaptation characterized by regulatory imbalance, not autonomy. Therefore, measures that improve regulatory balance, such as a healthy diet and lifestyle, may improve long-term outcome. In fact, a functional cure rather than complete response to treatment may be a better indicator of long-term survival.

While mechanisms vary, *in vitro* and *in vivo* data indicate that natural therapies can slow the initiation, and progression of AIPC by blocking the production, regulation, and action of cellular growth factors and tumor suppressor gene and oncogene mutations, improving cellular communication, inhibiting insulin-like growth factor type-1 (IGF-1) production and action, inhibiting arachidonic acid (AA) metabolism, decreasing tumor angiogenesis, increasing tumor cell apoptosis, and modulating androgen receptor function.

In addition to androgen, there is general consensus that inflammatory AA-derived prostaglandins, leucotrienes and IGF-1 activity are key prostate cancer cell growth promoters (Moyad, 2002). This brief overview will outline specific natural therapies that can inhibit AA and IGF-1 activity, and discuss selected dietary and lifestyle modifications that can inhibit or slow prostate cancer cell growth.

A review of literature was done using resources from Ovid-Medline, Cochrane and Medstar as well as E-medicine, Clinical Pharmacology and MD consult. Some of the key words used were: androgen insensitive prostate cancer, arachidonic acid metabolism, inhibitors of arachidonic acid, insulin growth factor type I, inhibitors of insulin growth factor type-1, apoptosis, quercetin, vitamin e, boswellia, curcumin, fish oil, lycopene, green tea, melatonin, diet, and lifestyle.

### **Arachidonic Acid Metabolism**

*Arachidonic acid* (AA), an omega-6 fatty acid, is essential to the nervous and immune system. On the other hand, excess arachidonic acid has been linked to the current epidemic of heart disease, degenerative diseases, and cancer in this country.

Inside the body, arachidonic acid is converted to powerful hormone-like molecules called *eicosanoids*. Two types of eicosanoids - called *prostaglandins* and *leucotrienes* - are derived from arachidonic acid. (Prostaglandins were first discovered in prostatic fluid.) (Baker & Baar, 2000).

Eicosanoids can either be inflammatory or anti-inflammatory. The types of eicosanoids that are found in fish (*prostaglandin E3*) are anti-inflammatory. The eicosanoids that are derived from arachidonic acid (*prostaglandin E2* and *series four leucotrienes*) are inflammatory.

Arachidonic acid-derived eicosanoids cause more problems than inflammation. To begin with, PGE2 eicosanoids enable prostate cancer cells to evade the immune system. PGE2 inactivates natural killer cells and cytotoxic cells. This is relevant since prostate cancer cells produce ten times as much PGE2 as normal prostate cells (Gosh & Myers, 1998).

Series four leucotrienes, the other class of arachidonic-derived eicosanoids, are just as dangerous as PGE2. Series four leucotrienes by the name of *12-HETE* allow prostate cancer cells to form new blood vessels and invade surrounding tissues (Gosh & Myers, 1998).

Another class of series four leucotrienes, called *5-HETE*, stimulates prostate cancer growth, and prevents prostate cancer cells from dying by preventing them from committing suicide (Gosh & Myers, 1998).

### **Inhibitors of Arachidonic Acid Metabolism**

According to (Bland, 1999), a combination of nutritional, herbal, and pharmaceutical agents can interrupt the arachidonic acid cascade at three critical points by blocking the following enzymes.

Phospholipase A2 enzyme allows AA to be mobilized from phospholipids in cell membranes. This conversion can be blocked by quercetin, vitamin E, and tumeric (*Curcumin longa*). In addition, 5 and 12-lipoxygenase enzymes convert AA to series four leucotrienes (5-HETE and 12-HETE). This conversion can be blocked by quercetin, vitamin E, fish oil, tumeric, Green tea (*Camellia sinensis*) and boswellia (*Boswellia serrata*). Finally, cyclooxygenase 1 and 2 enzymes convert AA to PGE2 eicosanoids. This conversion can be blocked by fish oil, tumeric, green tea (*Camellia sinensis*), and nonsteroidal anti-inflammatory medications (aspirin and ibuprofen). Celebrex®, and Vioxx® also suppress angiogenesis and prostate cancer cell growth by selectively blocking COX-2 (Liu et al., 2000).

*quercetin.*

Quercetin is a naturally occurring plant flavonoid found in onions, parsley, sage, tomatoes, and citrus fruits. Quercetin is also available as a dietary supplement. Quercetin influences prostate cancer biology by inhibiting arachidonic acid metabolism and blocking phospholipase A2 and 5 and 12-lipoxygenase enzymes (Yoshimoto, Furukawa, & Yamamoto, 1983), and inhibiting androgen receptor mutations (Xing, Chen, Mitchell, & Young, 2001). The recommended dose for quercetin is 200-400mg t.i.d. 20 minutes before meals (Pizzorno & Murray, 1999).

*vitamin E .*

Among other things, vitamin E prevents oxidation and peroxidation of membrane phospholipids and triggers apoptosis of prostate cancer cells (Schulman, Ekane, & Zlotta, 2001). It also modulates the release of AA from cell membrane phospholipids and may influence gene regulation of COX enzyme activity (Traber & Packer, 1995). Although dl-alpha tocopherol is used most frequently in research studies, dietary gamma tocopherol may be more protective against prostate cancer (Moyad, 2002b). While dosage recommendations vary, according to (Heinonen et al., 1998), taking as little as 50 IU of dl-alpha tocopherol daily can reduce the incidence of prostate cancer by a third and the death rate by forty percent.

*curcumin (curcuma longa) .*

A potent antioxidant, curcumin, the major ingredient of curry powder, may inhibit prostate cancer cell growth by blocking the conversion of arachidonic acid to PGE2 and 5-HETE, inducing apoptosis, and regulating the tumor suppressor gene *p53* (Bina & Lojesh B.R., 1997). Curcumin induces apoptosis in

AIPC by inhibiting epidermal growth factor (EGF) receptor protein.(Dorai, Gehani, & Katz, 2000). In addition to incorporating curcumin in the diet, curcumin can be taken as a supplement at a dose of 200-400 mg t.i.d. taken on an empty stomach twenty minutes before meals (Pizzorno & Murray, 1999).

*fish oil.*

Rich in an essential omega-3 fatty acid called *eicosapentaenoic acid (EPA)*, fish oil decreases the risk of prostate cancer proliferation and progression by suppressing arachidonic acid formation, inhibiting cancer cell invasiveness, inducing apoptosis, and promoting cellular differentiation (Wallace, 2002).

Although dosages vary, Wallace recommends taking a 1:1 ratio of omega-3 to omega-6 PUFAs to prevent enzyme competition and reduce inadvertent shunt to AA and inflammatory eicosanoids caused by excess omega-6 PUFAs (Wallace, 2002). A reasonable dose is six grams of fish oil taken daily in divided doses with meals (to avoid gastric upset).

*green tea.*

Rich in a group of flavonoid antioxidants called *catechins*, especially epigallocatechin gallate, green tea can prevent the initiation, promotion, and progression of prostate cancer, including AIPC, by preventing DNA strand breaks, altering androgen receptor receptivity, inhibiting cell proliferation, decreasing the contact of carcinogens with cells, blocking cancer initiation, increasing apoptosis, and slowing cancer progression (Gupta, Ahmad, Nieminen, & Mukhtar, 2000; Yang & Wang, 1993). The protective benefit of green tea is dose dependent. Men with prostate cancer can safely take between 400mg-1000mg of a green tea extract daily in divided doses (Myers, 2001).

*boswellia serrata.*

Although not specific for prostate cancer, boswellic acids inhibit the conversion of arachidonic acid to 5-HETE by inhibiting the 5-LOX enzyme by a non-competitive mechanism, which involves binding to a pentacyclic triene-selective effector site (Ammon, Safayhi, Mack, & Sabieraj, 1993). The recommended dose is based on the concentration of boswellic acid in an extract, which can range between 43% - 65%. The normal daily oral dose is 30-50 mg/kg/day in divided doses. (Wallace, 2002).

*nonsteroidal anti-inflammatory drugs (NSAIDs.)*

Although data are preliminary, a case-control study showed that regular use of over-the-counter NSAIDs either ibuprofen or aspirin at over the counter doses, decreased the risk of prostate cancer by 66%

compared to the control group (Nelson & Harris, 2000). Prescription NSAIDs consumption can also reduce the risk of prostate cancer (Brawley, 2002). Take the appropriate oral dose of either medication with food.

### **Insulin Growth Factor Type-1**

Originating in the liver, IGF-1 causes prostate cell proliferation by promoting angiogenesis, preventing apoptosis, and increasing production of urokinase-type plasminogen activator (Miyake et al., 1999). According to researchers (Chan et al., 1998), men over the age of sixty with the highest levels of IGF-1 have an eight-fold greater risk of developing prostate cancer compared to men with the lowest levels. Furthermore, other researchers found that changes in the expression of genes in the IGF regulatory system within prostate cancer cells dramatically increases the progression to AIPC (Nickerson et al., 2001).

### **Inhibitors of IGF-1 Activity**

#### *lycopene.*

Of the more than 600 carotenoids present in fruits and vegetables, lycopene has the highest concentration within the prostate, and tomatoes are one of the richest sources of lycopene (Clark et al., 1996). Among natural carotenoids, lycopene is also the most efficient singlet-oxygen quencher. (Chen et al., 2001) (Kaplan, Lau, & Stein, 1990). Harvard researchers reviewed the relationship between tomato intake and cancer and found 57 studies showed a protective benefit, 35 of which were significant. With regard to prostate cancer, six studies showed a 30-40% reduction in prostate cancer risk, three studies showed a similar but not statistically significant risk reduction, and seven studies failed to show a beneficial effect (Giovannucci, 1999). The protective effect was greatest when the analysis focused on advanced prostate cancer (stage C or D) (Giovannucci et al., 1995). Lycopene also exerts antiproliferative activity against AIPC, *in vitro* (Klein, 2002). Lycopene inhibits IGF-1 signaling and suppresses cell cycle progression and proliferation in several prostate cancer cell lines. Tomato-based foods also prevent *in vivo* oxidative DNA damage (Chen et al., 2001), and according to one pilot study, men that took 15 mg. of a lycopene supplement orally b.i.d. for three weeks prior to undergoing radical prostatectomy, experienced a reduction in serum PSA levels and fewer positive surgical margins (Kucuk et al., 2001).

*melatonin.*

Melatonin directly and indirectly inhibits the growth of prostate cancer cells by stimulating immune function and cell differentiation, and inhibiting prolactin and IGF-1 production (Lissoni et al., 1997). A pilot study by Italian investigators reported that >50% of men with androgen-independent prostate cancer who took 20mg of melatonin daily restored their androgen sensitivity (Lissoni et al., 1997). Although it may cause sedation, taking supplemental melatonin doesn't interfere with endogenous melatonin production (Matsumoto, Sack, Blood, & Lewy, 1997). The majority of melatonin is absorbed into the bloodstream when taken sublingually, whereas only 15% is absorbed when melatonin is taken orally (DeMuro, Nafziger, Blask, Menhinick, & Bertino, 2000). The normal sublingual dose is 1-3 mg prior to bedtime, and oral dosages as high as 20mg daily can be taken safely.

### **Advance Practice Implications**

According to surveys, nearly half of the American and European population, including a similar percentage of men with prostate cancer (Lippert, McClain, Boyd, & Theodorescu, 1999), use some form of complementary and alternative medicine (CAM) to improve their general health and quality of life (Spencer & Joseph, 1999). Nevertheless, patients usually withhold this information from their providers unless they are directly asked about CAM usage (Jones, Metz, Devine, Hahn, & Whittington, 2002). Therefore, providers need to inquire about CAM usage and develop a working knowledge of pertinent CAM therapies so they can properly advise their patients about the associated risks and benefits.

For instance, patients should be advised against taking vitamins, nutritional supplements, and herbal therapies that can interact with prescription medication or increase the risk for bleeding during surgery (Pribitkin & Boger, 2000).

On the other hand, providers should embrace evidence-based CAM therapies that can benefit their patients. For instance, an accumulating body of scientific evidence indicates that CAM therapies can improve the quality of life and survival of men with prostate cancer by slowing prostate cancer growth, and reducing side effects and improving the efficacy of conventional cancer therapies (Fair, 1999),(Moyad, 2002b; McClure, 2001) - issues that may be more important than curing cancer to some men (Moyad, 2002b).

In addition, the results of a significant study by (Lichtenstein et al., 2000), examined cancer incidence among a cohort of 44, 788 twins from Sweden, Denmark, and Finland, which supports the hypothesis that environmental influences are a more important determinant of prostate cancer risk than genetic predisposition. As an added bonus, a healthy diet, lifestyle, and outlook on life can reduce the incidence of premature morbidity and mortality resulting from heart disease, diabetes, hypertension, obesity, all-cause cancer, and a variety of other chronic illnesses (Moyad, 1999) (Vita, Terry, Hubert, & Fries, 1998).

In addition to the vitamins and supplements listed above, advanced care practitioners can safely recommend the following evidence-based dietary and lifestyle measures to men with AIPC:

*diet.*

A calorie restricted diet that is low in saturated fat but high in antioxidant and fiber-containing fruits and vegetables can favorably influence prostate cancer cell biology. While the mechanisms vary, constituents of a healthy diet can reduce cellular inflammation, promote differentiation and apoptosis, and counteract free radical- induced DNA damage and cellular proliferation. (Moyad, 2002a; Schulman et al., 2001; Mukherjee et al., 1999; McClure, 2001) (Evans, Griffiths, & Morton, 1995)

*energy intake and fat.*

Although the incidence of latent prostate cancer is similar worldwide, the incidence of clinical prostate cancer, particularly advanced prostate cancer, is greatest in countries with the highest calorie and saturated fat consumption (Evans et al., 1995; Kolonel, Nomura, & Cooney, 1999; Giovannucci et al., 1993) Among other things, excessive calories and saturated fat, especially from dairy products and red meat, promote obesity and prostate cell growth by increasing the production of insulin growth factor type-I, and inflammatory arachidonic acid byproducts (Moyad, 2002a).(Suzuki, Platz, Kawachi, Willett, & Giovannucci, 2002)

The practice of substituting fat-free high carbohydrate food items for fatty foods isn't a viable solution because it simply trades one problem for another. Excessive sugar consumption promotes cell growth and increases cancer risk by contributing excess calories, elevating insulin levels (Byers et al., 2002), and increasing arachidonic acid production.

Finally, regardless of the food source, excessive caloric intake promotes obesity, which increases premature mortality and overall cancer-related death rates (Moyad, 2002a).

*fruits and vegetables.*

Dietary fiber and anti-oxidants found in fruits and vegetables, especially those contained in tomatoes and cruciferous vegetables, and phytoestrogens found in soy protein, prevent prostate disease by counteracting free radical damage, blocking the harmful effects of IGF-1 and excess sex hormones, lowering serum cholesterol, and preventing aromatase activity (Demark-Wahnefried et al., 2001; Evans et al., 1995; Fair, Fleshner, & Heston, 1997) (Cohen, Kristal, & Stanford, 2000) (Hwang & Bowen, 2002).

Even though the age-adjusted incidence of latent prostate cancer in native Japanese and American males is roughly the same, clinical prostate cancer is ten times higher in American males (Parkin & Muir, 1992). Researchers attribute this discrepancy to dietary differences: Japanese males consume more soy protein and fish, but less saturated fat from dairy and red meat than American males (Schulman et al., 2001). In fact, (Adlercreutz, Markkanen, & Watanabe, 1993) reported that Japanese males have isoflavone concentrations thirty times higher in the urine and over a hundred times higher in the blood than Western males. Soy protein isoflavones, most notably genistein, inhibit prostate cancer cell growth by promoting apoptosis, blocking  $\beta$ -estrogen receptor activity in the prostate (Gruber, Tschugguel, Schneeberger, & Huber, 2002), inhibiting angiogenesis and endothelial cell proliferation, and blocking 5-alpha reductase, aromatase, and tyrosine-specific protein kinase activity (Schulman et al., 2001; Fair et al., 1997).

*lifestyle.*

Healthy lifestyle choices such as regular exercise, getting enough rest, and reducing stress can improve immune function. Stress increases the release of catecholamines, especially epinephrine, from the adrenal glands, which suppresses natural killer T-cell activity. Although not specific for prostate cancer, stress increases the initiation, growth, and metastasis of tumors. Studies have shown that stressed animals had twice as many metastases as unstressed ones (Fair, 1999). Moreover, a pilot study by (Saxe et al., 2001), showed that reducing stress and eating a healthy diet can significantly slow prostate specific antigen (PSA) doubling times (a measure of prostate cancer cell growth.) in men with biochemical

recurrence of prostate cancer. Men in the study group experienced a two-thirds reduction in their PSA doubling time from 6.5 months to 17.7 months.

Finally, although data are contradictory, smoking and drinking alcohol can increase the risk of prostate cancer, especially advanced prostate cancer (Hickey, Do, & Green, 2001; Moyad, 2002), whereas regular physical exercise can decrease prostate cancer risk by enabling the body to use insulin more effectively, and by reducing IGF-1 levels and obesity (Moyad, 2002a). (Fair, 1999; Lee, Sesso, Chen, & Paffenbarger R.S., 2001; Lee et al., 2001)

In conclusion, an evolving body of *in vitro* laboratory and animal data and limited human *in vivo* data suggest that dietary and lifestyle interventions and botanical and nutritional supplements and vitamins can slow the initiation, promotion, and progression of AIPC, improve quality of life, and prolong survival. Advanced care practitioners have a responsibility to their patients to become knowledgeable about the advantages and disadvantages of CAM. Based on the evidence, they should advise against therapies that are without merit or can cause harm (O'Brien King, Pettigre, & Reed, ). On the other hand, they should endorse and recommend therapies that can prevent chronic illness, reduce treatment-related side effects, improve health and well being, forestall premature disability and mortality, and add life to years.

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