

Benign Prostatic Hyperplasia (BPH)

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The majority of men older than 60 years will be affected by benign (noncancerous) enlargement of the prostate gland. An enlarged prostate can be caused by either one of two conditions—benign prostatic hyperplasia or benign prostatic hypertrophy (both abbreviated BPH). Although the two conditions are slightly different (Roehrborn CG et al 2002), the prostate gland is enlarged in both conditions.

BPH may be recurrent and progressive and (even though it is not prostate cancer) pose a danger to health. When the prostate gland enlarges, for whatever reason, the gland presses on the urethra (the tube that transports urine and semen [which contains sperm] to the outside of the body). Even the smallest increase in the size of the prostate gland tends to compress the urethra. The prostate gland produces a substantial portion of the liquid component of sperm. Also, smooth muscle cells in the prostate gland contribute to the forcible ejaculation of semen.

To treat BPH, conventional medicine usually focuses on drugs that inhibit the hormones that control prostate growth or that relaxes the smooth muscles inside the prostate gland. Surgery is also a treatment option. Most men, however, can benefit from a variety of complementary nutritional strategies that offer proven relief for BPH.

UNDER THE INFLUENCE OF HORMONES

Prostate gland growth is regulated by sex hormones, including estrogen, testosterone, and dihydrotestosterone (DHT). In the body, testosterone is metabolized into DHT by the enzyme 5-alpha-reductase. Often, as men grow older, more DHT is produced. Drugs and nutrients that lower DHT by inhibiting 5-alpha-reductase have been shown to reduce the size of the prostate gland and therefore reduce the symptoms of BPH.

Although testosterone and its metabolite DHT are the hormones most commonly associated with prostate disease, prostate growth is also influenced by estrogen. While estrogen is normally thought of as “the female hormone,” men produce estrogen throughout their lives by converting testosterone to estrogen using the enzyme aromatase. As men age, aromatase levels increase, resulting in higher estrogen levels. This helps explain why, as men age, testosterone levels decline (as higher aromatase levels convert testosterone to estrogen), but prostate glands continue to enlarge.

Among aging men, there is a growing imbalance between estrogen and testosterone. Testosterone levels, especially free testosterone, dramatically decline as men age, yet estrogen levels remain fairly stable or increase (Farnsworth WE 1996). Compared to younger males, older males have much more estradiol (the most potent form of estrogen) than free testosterone. These rising estrogen and declining androgen levels are even more sharply defined in the prostate gland. With aging, estrogen levels increase significantly in the prostate. Estrogen levels in prostate gland tissues rise even higher in men who have BPH (Shibata Y et al 2000; Gann PH et al 1995; Krieg M et al 1993).

By limiting aromatase, or inhibiting the binding of estrogen to prostate cells, it may be possible to reduce BPH or slow its progression. More research is needed.

SYMPTOMS AND DIAGNOSIS OF BPH

Symptoms differ among patients with BPH, but certain symptoms occur in the majority of cases. The number and intensity of symptoms also vary with age. Men who have milder symptoms and whose BPH has minimal impact on their quality of life may not require treatment. The most commonly reported symptoms of BPH include: (Lepor HL et al 2002; Scher HI 2001):

- Decrease in strength of the urinary stream and a decrease in the stream's diameter
- Increased frequency in urinating during the day
- Need to urinate several times during the night (nocturia)
- Sensation of needing to urinate immediately (urgency)
- Straining to force urine out
- Dribbling urine or having difficulty stopping urination
- Having the feeling of still needing to urinate even after the stream has stopped
- Pain or a burning sensation during urination

- Complete retention of urine (because, in advanced BPH, an enlarged prostate can completely obstruct the passage of urine)

Physicians can help patients who have BPH develop an International Prostate Symptom Score (IPSS) to help guide treatment. The IPSS is based on the presence and severity of symptoms and is used worldwide.

The IPSS, along with quality-of-life scores and measurements from common diagnostic tests, can be used to help divide patients with BPH into stages. Knowing a patient's BPH stage serves as a guide for BPH management. These stages include:

- **Stage 1.** Patients have no bothersome symptoms and no significant urine obstruction. In general, these patients do not need treatment at this time. They are observed closely by their physician (this is called "watchful waiting").
- **Stage 2.** Patients have bothersome symptoms, but without significant urine obstruction. These patients can be treated with medication.
- **Stage 3.** Patients have significant urine obstruction (which is defined as urine flow of less than 10 milliliters per second (mL/s) and persistent residual urine of more than 100 mL. The patient's physician may recommend a surgical procedure called transurethral resection of the prostate (TURP).
- **Stage 4.** Patients may have complications of BPH such as chronic retention of stones in the bladder. These patients would definitely need TURP.

TESTS USED TO DIAGNOSE BPH

Digital rectal examination. A digital rectal examination (DRE) is a routine test that identifies an enlarged prostate. To perform a DRE, a physician inserts a lubricated, gloved finger into the rectum. An experienced urologist can easily detect the posterior and lateral lobes of the prostate through the thin rectal wall. A normal prostate gland is about the size of a chestnut. A prostate gland with BPH will feel soft. A benign enlarged prostate will feel smooth and elastic. The tissues of a cancerous prostate gland are usually denser. BPH occurs only within the prostate capsule. A physician may suspect cancer if there are hard nodules or firm areas in the prostate (Lepor HL et al 2002; Scher HI 2001).

Diagnostic tests. Prostate specific antigen (PSA) is a protein produced by prostate cells. Normally, it is found in high concentrations in seminal fluid and in small quantities in the blood. PSA is a prostate specific substance (Scher HI 2001). The normal PSA value range is between 0 and 4 nanograms per milliliter (ng/mL). Recent research suggests that up to 30 percent of men who have a PSA score of 2.6 to 4.0 ng/mL may have prostate cancer (Lobel B 2005). An elevated blood PSA level, while by no means diagnostic of cancer, is concerning because it indicates excessive breakdown and turnover of prostate cells. For this reason, men with elevated PSA levels should have additional diagnostic testing, most often including a prostate biopsy, to rule out prostate cancer (Scher HI 2001). For more information on prostate cancer and PSA, see the chapter on Prostate Cancer.

Uroflowmetry measures the time in which a given volume of urine is voided. Usually, a healthy man between the ages of 40 and 60 years voids 200 mL in about 11 seconds (a rate of 18 mL/s). A healthy man older than age 60 voids a little longer, more than 15 seconds (at a rate of 13 mL/s). A man with BPH may need 20 to 40 seconds to void 200 mL, depending on the severity of urethral constriction (Lepor HL et al 2002). Uroflowmetry can be done at home by using a measuring cup and a wristwatch that has a second hand. To perform uroflowmetry at home, drink lots of water. Then wait as long as you can to urinate. Measure the time it takes you to void 200 mL (about 7 ounces).

The volume of urine remaining in the bladder immediately after urination is completed is measured by a postvoid residual urine test. This test can be performed using ultrasound (a noninvasive technique) or a catheter (which is invasive). Increasing amounts of residual urine over time can indicate that the BPH has progressed and that there may be a need for surgery (Lepor HL et al 2002).

THERAPEUTIC OPTIONS

Generally, if a physician has diagnosed an enlarged prostate but the patient has no symptoms, the patient does not require treatment. However, severity of symptoms is associated with a greater likelihood of the need for surgery. Because most men with BPH do not develop a significant urine obstruction, and because minor symptoms develop slowly or not at all, urine flow studies are the preferred diagnostic tool to identify patients who do not require treatment. These patients can be followed by watchful waiting (Lepor HL et al 2002). This strategy, particularly when considering the slow progression of BPH, provides the opportunity to use complementary approaches (such as nutritional therapy) with no risk of undertreating patients.

Watchful waiting. If BPH is not severe, the patient's condition will be monitored closely by his physician. A physician should confirm that a delay in treatment will not lead to irreversible complications. Several measures, such as decreased intake of fluids (especially before bedtime) and moderate intake of alcohol and caffeine (Lepor HL et al 2002) can lessen severity of symptoms. Watchful waiting does not imply doing nothing. Quite the contrary, it provides an excellent opportunity to treat BPH with diet and nutritional supplements.

Transurethral microwave thermotherapy. Transurethral microwave thermotherapy (TUMT) is an alternative to surgery. This procedure uses a catheter tipped with a special antenna that delivers microwave energy to the prostate to selectively heat and kill prostate tissue. The microwave surgical instrument is designed so temperature and the depth of heating are precisely controlled. TUMT is an outpatient procedure performed while the patient is under sedation (not anesthetized). TUMT is an alternative for men with BPH who are not good candidates for surgery. Patients treated with TUMT have minimal, transient adverse effects that resolve spontaneously or resolve with medication. Symptom relief may occur within 3 weeks. One disadvantage of TUMT is the risk of retrograde ejaculation, a condition that occurs when semen enters the bladder rather than being ejaculated. While this does not affect the sensation of orgasm, it can cause infertility.

Transurethral needle ablation. Transurethral needle ablation (TUNA) uses low-level radiofrequency, at about 490 kilohertz (kHz), to cause the tissue that is to be ablated to reach a temperature of 50°C to 90°C. The procedure is carried out over the course of a few weeks. During TUNA, a catheter that is tipped with two flexible needles is inserted into the prostate through the penis. The needles are shielded at the base to avoid damaging the urethra. Radiofrequency energy passes from one needle to the other, destroying the prostate tissue between the needles. The progress of the procedure is viewed by transrectal ultrasound. TUNA can be performed as an outpatient procedure with the use of a local anesthetic and sedation (Lepor HL et al 2002).

Surgery. Surgery is widely used for treatment of BPH that is causing significant obstruction to urine flow. Surgery for BPH can be done through a transabdominal incision or through an endoscopic device inserted into the urethra (TURP). About 90 percent of all surgeries performed for BPH are TURP procedures. TURP is the standard against which other interventions are judged.

During TURP, the physician uses an instrument called a resectoscope. The resectoscope is tipped with a small wire loop. The loop is used to snip off obstructing pieces of the prostate gland and then to cauterize the wound to minimize bleeding (although there may still be some bleeding). TURP has been shown to be an effective treatment; after TURP, symptoms are usually much improved. However, BPH may recur. Also, some men may eventually have erectile dysfunction (impotence). Additionally, most patients will experience some degree of incontinence, which will usually disappear in a short time.

Most patients will remain in the hospital for about 3 days after undergoing TURP. Once the patient is released from the hospital, his recovery period is short and he usually experiences significant relief of his symptoms. The most common, unavoidable, and permanent adverse effect of TURP is retrograde ejaculation.

TURP can also be performed using a laser. Studies have shown that photovaporization of prostate tissue using a focused laser (the Greenlight PV Laser System) results in reduced prostate size with a very low incidence of adverse effects (Kumar SM 2005). Alternatively, a procedure called transurethral vaporization of the prostate (TUVP), in which the tissue is vaporized, can be performed. In TUVP, vaporization electrodes deliver high heat directly to the prostate tissue by means of a grooved roller bar. The heat vaporizes the tissue much like a laser. This is a relatively new technique that is showing clinical promise and has been adopted by many experienced urologists.

If it is necessary to remove a portion of the prostate gland, a partial prostatectomy may be performed. This procedure is open surgery performed while the patient is under general anesthesia. During the operation, the surgeon removes only the enlarged part of the prostate gland. This surgery should not be confused with a radical prostatectomy, in which the entire prostate gland is removed. Radical prostatectomies are performed in men with prostate cancer.

The current clinical philosophy concerning BPH is to postpone any form of surgery for as long as possible to avoid complications that may jeopardize the patient's quality of life. Stopping the progression of prostate enlargement through diet and pharmacotherapy should be the first approaches in the treatment of BPH (Djavan B et al 2002; Schulman C 2001).

DRUGS USED TO TREAT BPH

5-Alpha-reductase inhibitors. Prostate cells produce 5-alpha-reductase, which converts testosterone into DHT. DHT is much more potent than testosterone at promoting prostate growth. The drug finasteride inhibits 5-alpha-reductase 2, but not 5-alpha-reductase 1. The drug dutasteride inhibits both 5-alpha-reductase 1 and 5-alpha-reductase 2 and is considered more effective (Occhiato EG et al 2004).

Testosterone inhibitors. Prostate cells require androgens for survival. Chemical castration is achieved by using medications such as leuprolide and goserelin, which inhibit testosterone. Leuprolide and goserelin are luteinizing hormone-releasing hormone agonists (LH-RH agonists) that cause chemical castration. Although LH-RH agonists shrink an enlarged prostate gland and are used to treat advanced prostate cancer, they are expensive and have unpleasant side effects. As a result, LH-RH agonists are rarely used to treat BPH (Anonymous 2005; Sugimura Y 2004; Tarlatzis BC et al 2003).

Alpha-blockers. Antihypertension drugs called alpha-blockers act on the nervous system to relax arteries by inhibiting excitatory impulses to muscle cells. The smooth muscle cells in the prostate gland have alpha-receptors, so alpha-blockers are sometimes used to relax the muscle and reduce symptoms. Alpha-blockers used to treat BPH include terazosin, prazosin, and doxazosin. A

newer alpha-blocker, tamsulosin, can be taken once a day and is effective in treating patients with BPH who have moderate to severe symptoms (Debruyne F et al 2004; Debruyne F et al 2002; Dunn CJ et al 2002). Many alpha-blockers can cause impotence. If impotence results with one drug, switching to a similar drug may end the undesirable side effects (Tahmatzopoulos A et al 2004; Kyprianou N 2003).

Aromatase inhibitors. Aromatase, the enzyme that converts testosterone to estrogen, can also be inhibited to try to prevent the age-related rise in estrogen. The use of aromatase inhibitors among men with BPH, however, is subject to some controversy. A number of studies have shown that the aromatase inhibitor anastrozole, when used in conjunction with 5-alpha-reductase inhibitors, increased the level of testosterone in animal models of BPH (Sciarra F et al 2000; Suzuki K et al 1998). Some doctors consider this to be counterproductive among men who have BPH. However, studies of a newer aromatase inhibitor known as mepartricin (not yet approved in the United States) suggest that the drug lowered estrogen levels without affecting levels of other sex hormones (Boehm S et al 1998). Anastrozole is a US-approved aromatase inhibitor (although it is not approved to treat BPH). Obviously, more research is needed into the synergistic effects of 5-alpha-reductase inhibitors (such as dutasteride) used in conjunction with aromatase inhibitors (such as anastrozole) in men. It is also important to keep in mind that maintaining youthful testosterone levels is extremely important in aging men. For more information, please see the chapter on Male Hormone Modulation.

NUTRIENT AND SUPPLEMENTAL THERAPY

Herbs and nutrients are a very important and usually underutilized element of BPH therapy. Some of the most effective herbs that treat BPH operate along similar pathways as prescription drugs, which are much stronger, without the adverse effects. If you are in the watchful-waiting period of BPH, you should consider slowing the progression of your condition, and avoiding the unpleasant symptoms of more severe BPH, by using nutrient and supplemental therapy.

Saw palmetto. In Europe, saw palmetto (*Serenoa repens*) has been used extensively as a drug for some time. Saw palmetto has multiple mechanisms of action: inhibition of 5-alpha-reductase, inhibition of DHT binding to the androgen receptor, reduction of the inflammatory component of prostate growth (by inhibiting COX-2 and an enzyme called 5-lipoxygenase), and inhibition of prostate cell proliferation (Debruyne F et al 2002; Goldmann WH et al 2001; Paubert-Braquet M et al 1998; Gutierrez M et al 1996).

Saw palmetto's clinical benefits for prostate enlargement include:

- Reduced nocturnal urinary urgency (Boyle P et al 2004)
- Increased urinary flow rate (Boyle P et al 2004; Gerber GS et al 2004)
- Decreased residual urine volume in the bladder (Giannakopoulos X et al 2002)
- Reduced discomfort from urination symptoms (Giannakopoulos X et al 2002; Wilt T et al 2002a)

In fact, results of treatment with saw palmetto compare favorably with finasteride, with far fewer adverse effects (Wilt T et al 2002a). Similarly, another study compared saw palmetto extract to tamsulosin for 1 year. After the treatment period was over, the symptoms of the patients in both groups had improved, and their PSA scores remained stable. However, the size of the prostate gland decreased only in the group taking saw palmetto, and sexual dysfunction was more common in the group taking tamsulosin. Overall, saw palmetto produced a superior response after only 3 months of treatment, and maintained its superiority (Debruyne F et al 2002). Finally, in a meta-analysis of saw palmetto, researchers found there was an average reduction of 5 points in the IPSS across all studies (Boyle P et al 2004).

As with most supplements, it's important to be sure that you're buying the highest quality supplement possible. In the case of saw palmetto, that means supercritical, standardized extracts. Supercritical fluid extraction technology produces an extract of extraordinary purity while leaving behind no solvent residues on the product. The first medicinal herb to benefit from large-scale supercritical fluid extraction was saw palmetto.

While a large number of studies document the benefits of saw palmetto by itself, European doctors frequently prescribe saw palmetto extract that is combined with additional herbs that interfere with other factors involved in prostate enlargement.

Nettle root extract. Nettle root (*Urtica dioica*) works by inhibiting the binding of DHT to prostate cell membranes (Hryb DJ et al 1995). Nettle root extract is used extensively, either in combination with saw palmetto or by itself, for relief of BPH symptoms.

In 2005, researchers conducted a randomized, double-blind, placebo-controlled, crossover study of nettle root extract. This is the gold-standard of clinical trial formats and is used to rigorously test pharmaceutical drugs before they gain market approval. Almost 600 patients were enrolled in this trial for up to 18 months. At the end of the study, 81 percent of the treated patients experienced significant relief of their symptoms and significant reductions in their IPSS, compared with only 16 percent of the control subjects. After the 18-month follow-up, only those patients who continued with the therapy experienced any benefits (Safarinejad MR 2005).

These results were confirmed in another study that examined the effect of saw palmetto combined with nettle root extract on men.

Once again, this was a double-blind, placebo-controlled study. In this case, the reduction in IPSS was “clearly superior” among men receiving saw palmetto and nettle extract, compared to men receiving placebo (Lopatkin N et al 2005).

Nettle has also shown an affinity for sex hormone binding globulin (SBGH) (Hryb DJ et al 1995). SBGH is closely related to levels of free testosterone and estrogen; most of these hormones travel through the blood stream “bound” to SBGH. Any testosterone that is unbound to SBGH is referred to as “free testosterone.” Studies have shown that men with BPH have elevated levels of SBGH in their prostate glands (Jiang H et al 2004), thus any nutrient that reduces the levels of SBGH may also be able to reduce BPH.

Pygeum. Pygeum or African prune tree (*Pygeum africanum*) reduces prostate enlargement and blocks DHT from binding to prostate cells. In a large meta-analysis, pygeum provided a moderately large improvement in BPH symptoms and urine flow measurements. Patients with BPH who used pygeum were more than twice as likely to report improvement in overall symptoms. Nocturia was reduced an average of 19 percent, residual urine volume was reduced 24 percent, and peak urine flow was increased 23 percent (Wilt T et al 2002b).

Cernitin. The studies on this extract of bee pollen in men who have symptoms of prostate enlargement have had good results. Cernitin has been shown to inhibit the growth of prostate cells in the laboratory (Habib FK et al 1990). In human studies, when combined with saw palmetto, beta-sitosterol, and vitamin E, cernitin was able to help reduce symptoms. In this randomized, placebo-controlled study, 144 patients were enrolled from three centers around the United States. The patients were given either placebo or the combination product for 3 months. At the end of the study, there was a "highly significant" difference in the symptom index score between the men taking the natural product and the men taking placebo. The natural product also had no significant adverse effects (Preuss HG et al 2001). Earlier studies have shown that cernitin extract alone can reduce symptoms (Yasumoto R et al 1995).

Beta-sitosterol. Beta-sitosterol is a plant fat contained in several European prostate drugs; however, it is not routinely used in the United States. Multiple randomized studies have confirmed the efficacy of beta-sitosterol in alleviating the types of prostate discomfort that aging men so frequently encounter. In a randomized, double-blind, placebo-controlled, multicenter study of 200 men who had benign prostate enlargement, half the group received 180 milligrams (mg) of beta-sitosterol daily, while the other half received placebo. After 6 months, the group taking beta-sitosterol had improvement in major symptom scales (Berges RR et al 1995). In a follow-up study that evaluated durability of response to beta-sitosterol, the beneficial effects of beta-sitosterol were maintained for an additional 18 months (Berges RR et al 2000).

Lycopene. Progression of BPH to prostate cancer is a significant concern for patients with BPH. Lycopene has been shown to lower the occurrence of prostate carcinoma (Cristoni A et al 2000), suggesting that lycopene may help prevent prostate cancer. Lycopene's mechanisms of action have been studied in patients who consumed tomato sauce before having a prostatectomy (Chen L et al 2001). Lycopene decreased serum PSA levels and oxidative DNA damage in prostate tissue. Programmed cell death (apoptosis) showed a tendency to increase in patients with BPH after they consumed tomato sauce (Kim HS et al 2003). Larger studies are required to prove the promising effect that tomato sauce may have on programmed cell death in patients with BPH.

Micronutrients and additional nutrients. Evidence indicates that micronutrients such as boron, selenium, alpha-tocopherol, gamma-tocopherol, phytoestrogens, and phytosterols may provide benefits in maintaining prostate health (Thomas JA 1999; Feustel A et al 1987). Additional studies have suggested that intake of omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can inhibit the conversion of testosterone to DHT (Pham H et al 2002). Finally, newer research is showing that vitamin D might be able to arrest prostate growth through unknown mechanisms (Colli E et al 2006).

LIFESTYLE CHANGES

Specific lifestyle changes can reduce the symptoms associated with BPH. If you want to reduce symptoms associated with BPH:

- Eat ample amounts of fresh fish, fruits, and vegetables. The high mineral and vitamin content (especially of vitamins E and D) of these foods are essential for general health and metabolism but can also reflect positively on prostate cells.
- Reduce stress, both on and off the job.
- Exercise regularly.
- Keep your weight within normal limits.
- Keep track of the number of times you urinate during the night. See your physician as soon as you notice an increase in frequency.
- If your physician prescribes medication to treat your BPH, follow his or her directions precisely. Make sure your physician knows about all botanical extracts or nutritional supplements you are taking.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

To slow the natural progression of BPH and its symptoms, the Life Extension Foundation suggests that you have annual screenings, including a PSA test and a DRE. Neither of these tests can rule out prostate cancer; however, they can alert a physician to the need for further testing.

If the results of a DRE or PSA are consistent with clinical exam findings by your doctor that you may have BPH, discuss with your doctor taking the following nutrients:

- **Saw palmetto extract**—320 milligrams (mg) daily
- **Pygeum extract**—100 mg daily
- **Nettle root extract**—240 mg daily
- **Beta-sitosterol**—180 mg daily
- **Cernitin**—252 mg daily
- **Boron**—3 mg daily
- **Gamma-tocopherol**—200 mg daily
- **Alpha-tocopherol**—400 International Units (IU) daily
- **Lycopene**—10 to 30 mg daily
- **Selenium**—200 to 400 micrograms (mcg) daily
- **EPA/DHA**—1400 mg/day of EPA and 1000 mg/day of DHA
- **Vitamin D3**—800 to 2000 IU daily
- **Soy isoflavones**—55 to 110 mg daily

If you have BPH, you may also benefit from taking medications such as dutasteride and alpha-blockers such as tamsulosin. You may also want to consider taking anastrozole, an aromatase inhibitor, in low doses, to block the conversion of testosterone to estrogen. Please discuss these options with your doctor.

If all else fails and you experience urinary blockage, you may need to undergo TURP. However, even after TURP, nutrients can keep the prostate gland from overdeveloping again.

PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at www.LifeExtension.com.

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at www.LifeExtension.com

Benign Prostatic Hyperplasia (BPH) Safety Caveats

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Saw Palmetto

- Consult your doctor before taking saw palmetto if you have any form of cancer that is stimulated by hormones.

Beta-Sitosterol

- Do not take beta-sitosterol if you have the genetic disorder sitosterolemia or cerebrotendinotic xanthomatosis.
- Beta-sitosterol can cause gastrointestinal symptoms such as indigestion, gas, diarrhea and constipation.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Soy

- Do not take soy if you have an estrogen receptor-positive tumor.
- Soy has been associated with hypothyroidism.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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