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## INSIDE



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# Drug Pharmacokinetic Interactions Following Consumption of Plant Products

PART 1 OF A SERIES ON HERB-DRUG INTERACTIONS

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THERE HAS BEEN MUCH CONTROVERSY RECENTLY ABOUT THE potential risks of combining drugs with natural products. In many cases this issue is considered without reference to the tremendous known risks of combining many common drugs. With pharmaceutical medications, the pharmacological activity and mechanism of action are typically known, which makes predicting pharmacodynamic interactions feasible. Drugs with additive effects require careful consideration of dosage management, while combining medicines with antagonistic mechanisms is contraindicated. If a patient is using more than five medications concurrently, it is generally advisable to consult with a pharmacist to avoid potential drug-drug interactions.

The situation with natural products and, in particular, botanical preparations is analogous but less certain. When specific pharmacological activities have been demonstrated in humans for a particular botanical preparation, possible pharmacodynamic interactions can be reasonably predicted and ill-conceived combinations avoided. For example, when herb preparations have known antiplatelet capabilities, it is deemed an unwise risk to use these in significant amounts while taking an anticoagulant medication like warfarin.

On the other hand, additive effects can be desirable when the effect of the primary medication is inadequate. For example, aloe (*Aloe vera*) juice improved the hypoglycemic effect of glyburide (glibenclamide) when 1 Tbsp of aloe juice was given orally in the morning and at bedtime to 36 diabetes patients for 42 days,[1] based on its antihyperglycemic activity when given alone at the same dose and duration.[2] Similarly, gurmar (*Gymnema sylvestre*) leaves enhanced hypoglycemic effects of glyburide and tolbutamide in 22 non-insulin-dependent diabetics given 400 mg/d of a water-soluble


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acidic fraction of the ethanol extract,[3] which alone at this dose also greatly reduced fasting blood glucose in insulin-dependent diabetics.[4]

Drugs are often prescribed as monotherapy for a particular condition; however, an individual with multiple diseases and/or symptoms frequently receives a variety of medications whose combined effects are uncertain. Likewise, patients self-medicating with over-the-counter remedies often do so without consulting their doctor(s) or pharmacist(s). Research and postmarketing surveillance help predict those combinations that are incompatible. The pharmacokinetic influence on cytochrome P450 (CYP) metabolic enzymes (called isozymes) is being especially examined as a means of understanding how drugs interfere with the bioavailability of other medications. Numerous drugs that act as inducers and inhibitors of CYP isozymes have been well documented, and the list continues to grow.[5]

Though research has identified the activity of some components in botanicals, this knowledge does not always equate to the combined effects involving other components that influence outcomes. Given that each type of preparation of plant varies in its composition based on the type of processing it undergoes, predicting outcomes becomes even more difficult. The issue of how best to assess how plants and their various preparations impact the bioavailability of pharmaceutical drugs is most challenging. This issue of pharmacokinetic interactions lies outside the normal means of predictability based on known therapeutic applications.

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**Affecting Absorption by Chemical Binding**

Simultaneous consumption is necessary for certain botanical components to bind drugs and reduce or slow their absorption. Simple water-soluble fiber is one example. Guar gum (*Cyamopsis tetragonolobus*) can be taken to help increase satiation in dieters, to slow gastric emptying to reduce postprandial hyperglycemia, to bind cholesterol in the gut, and for other health purposes.[6] However, penicillin absorption is significantly reduced when taken concurrently with 5 g guar gum. This amount of guar gum taken by 10 subjects with digoxin only minimally reduced its urinary excretion compared to placebo fiber, though peak serum levels following a single dose of digitalis were down by 21%.[7] When 10 g guar gum was given with metformin to six normal subjects it lowered total absorption and peak serum levels. Nonetheless, postprandial hyperglycemic peak was also reduced with the combination due to the gastric action of the fiber.[8]

Black tea has traditionally been used for its tannins to precipitate alkaloids and thereby help reduce their absorption in cases of toxic overdoses.[9] Iron precipitation in the gut lumen by polyphenols in tea has long been recognized, but recent evidence indicates that herb infusions can also reduce mineral absorption. Inhibition of iron absorption occurs when 200 mL of black tea (*Camellia sinensis*) is taken with non-hemoglobin sources such as ionic solutions and vegetables.[10] Iron absorption is only affected by tea when consumed by mouth simultaneously, due to the formation of iron complexes with tannins in the gut.[11] For example, tea reduced absorption of iron in young children who drank 50-750 mL tea daily (average 250 mL), leading to an increased incidence of microcytic anemia.[12] Adding milk to black tea does not reduce its inhibition of iron absorption.[13]

Infusions of 3 g of herbs in 300 mL hot water were prepared using black tea, chamomile (*Matricaria recutita*), vervain (*Verbena officinalis*), peppermint (*Mentha piperita*), pennyroyal (*Mentha pulegium*), lime flower (*Tilia cordata*), or cocoa (*Theobroma cacao*). Each inhibited iron (ferric chloride) absorption: black tea (79-94%), peppermint (84%), pennyroyal (73%), cocoa (71%), vervain (59%), lime flower (52%), and chamomile (47%). This appears to be due to the polyphenolic compounds (tannins, flavonoids or phenolic acids) extracted by water from the herbs.[13] Binding of polyphenols, like that of fiber, is a type of chemical binding in the gut that reduces absorption when the interacting elements are taken concurrently. These types of chemical interactions are relatively predictable based on knowledge of the content of these components in plants.

**Affecting Metabolism of Drugs with Vegetables**

To keep the risk of CYP modulation of drugs with botanical preparations in context, it is useful to consider documented interactions with common foods that affect drug absorption. Cruciferous vegetables (in the cabbage or Brassicaceae, formerly Cruciferae, family) are known inducers of drug metabolism. When either 436 g/d of broccoli, cauliflower, cabbage, and radish sprouts or 500 g/d of broccoli was consumed by 16 subjects, caffeine metabolism by CYP 1A2 was increased.[14,15] Regular consumption of Brussels sprouts increases metabolism of warfarin,[16] while oxazepam and acetaminophen are more rapidly metabolized in the intestines and/or liver after consuming Brussels sprouts and cabbage.[17]

Consumption of other umbelliferous vegetables may inadvertently antagonize some of these effects of cruciferous vegetables. Compared to a basal diet with no vegetables, vegetables from the carrot (Apiaceae, formerly Umbelliferae) family consumed for six days significantly decreased CYP 1A2 caffeine metabolism 13-25%. Daily total amounts of 110 g (0.75 cup) frozen carrots, 100 g (1.25 cup) fresh grated parsnips, 50 g (0.5 cup) celery, 5 g (3 Tbsp) parsley, and 0.5 g (1 tsp) dill together caused this inhibition, probably due to their combined furanocoumarin content. On the other hand, fresh *Allium* spp. vegetables (100 g leeks, 75 g onions, 10 g chives, plus 5 g garlic) did not alter caffeine metabolism.[15]

Fresh vegetable juices taken as nutritional supplements for their antioxidant content frequently include plants from the cabbage or carrot families. These juices can result in consumption of phytonutrient amounts unlikely to be attained through normal diet. In such cases, as in citrus juices and their impact on transported proteins and/or CYP 3A4, significant interactions may result.

**Altered Absorption with Fruit Juices by CYP or Transporter Inhibition**

The consumption of common beverages can also impact absorption by affecting drug metabolism in the intestinal mucosa. The most widely recognized influence is the inhibition in the gut of the isozyme CYP 3A4 by grapefruit juice, thereby increasing bioavailability of the isozyme's drug substrates and increasing the risk of adverse effects. Interactions with grapefruit juice occur after a single exposure to an 8 oz glass of juice (about 250 mL). Large and clinically significant interactions have been shown with grapefruit juice and the statins lovastatin and simvastatin, the antihistamine terfenadine, and the antiarrhythmic amiodarone; combining these drugs with grapefruit juice should be avoided. Several dozen additional moderate or weak interactions have been identified with a variety of drugs.[18]

Avoidance of grapefruit juice is recommended for the statins (atorvastatin) and calcium-channel antagonists (amlodipine, felodipine, nifedipine, nimodipine). Others that should be monitored for side effects include HIV protease inhibitors, sedatives, anxiolytic and other psychotropic agents, oral contraceptives, and corticosteroids. Still others are not clinically significant and require no special attention.[19] Complete recovery from the isozyme inhibition is expected within 72 hours.[18,20]

Transport proteins are also affected by common fruit juices. The organic anion transporting polypeptide facilitates drug uptake at the intestinal level. Grapefruit, orange, and apple juices have been shown to inhibit this mediator in humans when 1.2 L were consumed over three hours, thereby reducing absorption of fexofenadine from the gut.[21] The inhibition of fexofenadine transport by OATP1A2 with 300 mL of grapefruit juice was shown to be clinically pertinent.[22]

**Influence of Citrus Juices and St. John's Wort Products on P-glycoprotein Substrates**

A much more familiar transporter protein is P-glycoprotein (Pgp). Its activity in human intestinal mucosal cells is a major factor in reducing the absorption of some drugs. Pgp is a cell membrane transport protein that pumps certain hydrophobic substrates, including some carcinogens, out of cells (efflux) and back into the intestinal lumen. Inducing its activity or increasing its content in enterocytes reduces absorption of drugs effluxed by Pgp. The inhibition of Pgp enhances the retention of drugs that would otherwise be expelled from cells by this transporter system. Drugs are not only substrates of Pgp, but many also act as its inducers or inhibitors.[23]

Citrus juices also have Pgp-modulating capabilities. Substantial reductions in the oral absorption of the Pgp substrates ivermectin and celiprolol have been demonstrated for orange juice, following consumption of 750 mL over four hours, or 200 mg three times daily for 2.3 days. However, the mechanism for these interactions has not been determined definitively.[24,25] The modest changes in Pgp activity by grapefruit juice on digoxin absorption is not considered important.[26,27]

St. John's wort (*Hypericum perforatum*) is recognized as a botanical inducer of CYP 3A4. Digoxin is a substrate of Pgp but not CYP.[28] The St. John's wort extract LI160 given to 25 healthy volunteers at the standard dose of 900 mg daily did not affect stable digoxin levels after one day, but after 10 days reduced the peak concentration 26%, the 24-hour post-dosing concentration by 33%, and the 24-hour area under curve (AUC) by 25%. These results indicate reduced absorption through induction of Pgp.[29]

Different St. John's wort dosages and formulations used with digoxin for 14 days vary in their influence on its bioavailability in humans. While 900 mg daily of the extract LI160 reduced digoxin AUC by 25% compared to placebo, 4 g daily of encapsulated herb powder reduced digoxin AUC by 27%, and 2 g of powdered herb capsules decreased AUC by 18%. Hyperforin daily dosage was similar between the extract (29 mg) and 4 g of powder (21 mg). Using daily either 0.5 g of the same powdered herb capsules, 2 g of a different powdered St. John's wort, 2 cups of the tea each made with 1.75 g herb, 1.2 g of an encapsulated oil extract, 20 mL fresh juice, or 500 mg of a 5:1 strength 50% ethanolic extract ZE117 caused no significant change in AUC or trough levels when compared to placebo. All of these preparations provided low hyperforin doses (< 3.6 mg). Whereas hyperforin dosage correlated well with Pgp induction, hypericin and flavonoid dosage did not.[30] In a separate study, 240 mg extract delivering 3.5 mg hyperforin daily for 10 days in 28 volunteers was inadequate to significantly reduce digoxin absorption.[31]

Pgp effects of other herb preparations are not documented in humans. Though milk thistle silymarin extract inhibits Pgp in vitro,[32] when tested with the Pgp substrate digoxin in 16 healthy humans, 900 mg milk thistle extract (440 mg silymarin) daily for 14 days did not significantly alter the drug bioavailability.[33] There was actually a tendency toward reducing digoxin levels, suggesting potential Pgp induction. Black cohosh extract at 40 mg daily had no Pgp effect,[33] though it had also been an inhibitor in vitro.[34] Similarly, 240 mg daily of a ginkgo product did not alter digoxin pharmacokinetics in eight healthy subjects.[35]

**Problems with CYP Isozyme Research for Botanicals**

In making assessments of pharmacokinetic interactions, it is important to base judgments on data obtained from human studies with herbs or their extracts, since the expression of the CYP isozymes varies widely within the animal kingdom. Many human CYP 3A4 substrates are not metabolized by rat CYP3A, so rats are not appropriate models for humans. Also, rabbits have different CYP isozymes for one-third of drugs tested. Pigs, minipigs, and monkeys show similar results to humans but are comparatively expensive animals to maintain and study in relatively large numbers.[36] Even among humans, genetic polymorphism can produce variations in drug metabolism for substrates of CYP 2B6 (3-4% Caucasians), 2C9 (1-3% Caucasians), 2C19 (3-5% Caucasians; 15-20% Asians), and 2D6 (5-10% Caucasians).[5]

Effects of isolated components cannot be assumed to represent the activity of phytochemically complex plants or their products. For example, isothiocyanates from cruciferous vegetables are CYP 1A1 and 2B1 inhibitors in vitro and in animals,[37,38] whereas the whole vegetables[39,40] and their indole metabolites[38,41] are inducers. In vitro and in vivo results often do not correlate. Indole-3-carbinol, an enzymatic derivative from cruciferous vegetables, inhibits CYP conversion of estradiol at the 2-carbon in vitro,[42] but induces the detoxifying CYP 2-hydroxylation of estradiol in rats and humans.[42,43]

FDA guidelines encourage routine in vitro evaluation of CYP metabolism and influence for all new drugs. Most CYP botanical studies are in vitro, though this unvalidated testing is proving unreliable. CYP assays rely on enzyme proteins, but these can be readily precipitated and inactivated by tannins commonly found in herbs.[12] Also, reduction of heme (organic iron) from the ferric ($Fe^{3+}$) to ferrous ($Fe^{2+}$) enzyme is necessary for isozyme catalytic activity. Compounds that form complexes with the heme iron lead to CYP inhibition.[44] As indicated previously, phenolic compounds in many botanicals apparently bind to ferric ion in solution.[13] In another example, *E. purpurea* root extracts with phenolic caffeoyl conjugates can both chelate metals (e.g., copper) and block ferrous-ferric oxidation-reduction biological reactions in vitro.[45,46] Tincture of *E. purpurea* root is a strong CYP 3A4 inhibitor in vitro,[47] but the root solid extract at 1.6 g/d for eight days did not alter midazolam clearance when the drug was given orally to 12 human subjects and induced metabolism of intravenous midazolam.[48]

Inhibition of CYP 3A4 by licorice extract and its isoflavan component glabridin in vitro was associated with loss of the intact heme moiety.[49] Though licorice extract was found to be a CYP 3A4 inhibitor in vitro,[47,49] the extract and glycyrrhizin were 3A4 inducers when given orally to mice.[50,51] In contrast, a 1 g dose of a freeze-dried water extract given twice daily to 10 human subjects for seven days in a randomized, placebo-controlled double-blind crossover study had no effect on the pharmacokinetics of the 3A4 substrate midazolam.[52]

By precipitating protein and binding iron, botanical extracts with polyphenols can produce isozyme inhibition in vitro, even though they are inducers in vivo. Many such components apparently interfere with in vitro inhibition studies. For example, in one study using water extracts (tannins are water-soluble), for all tested isozymes (CYP 2C9, 2C19, 2D6, and 3A4) there was > 75% inhibition with all five types of black tea that are high in tannin. In addition, results for all four isozymes showed > 50% inhibition for cloves, ginger, oregano, sage, thyme, turmeric, chamomile, feverfew, goldenseal, and St. John's wort, and > 25% inhibition for gotu kola

and eleuthero. Most of these isozyme inhibitions were in the > 90% range. Even the strong CYP 3A4 inducer St. John's wort was a CYP 3A4 inhibitor in this in vitro study.[53]

Other herbs or their extracts have been strong inhibitors of CYP 3A4 in vitro, but in human studies have shown no significant effects. Though soy extract with 100 mg isoflavones daily for 14 days produced no effect on metabolism of CYP 3A4 substrate cortisol in humans, unhydrolyzed soy extract tended to induce 3A4 in vitro, but hydrolyzed soy extract strongly inhibited 3A4 in vitro.[54] Kava root extracts are in vitro inhibitors of CYP 3A4,[55-57] but in one study an extract induced production of 3A4 mRNA in vitro, mediated by pregnane X receptor (PXR).[58] Strong kavapyrone CYP3A activators dihydromethysticin and desmethoxyyangonin only slightly activated PXR in vitro, suggesting an indirect or independent mechanism.[59] Yet a human study using 1 g root extract twice daily for 28 days found neither inhibition nor induction of midazolam CYP 3A4 metabolism in 12 men and women.[60]

There are significant problems even in human studies. For some drugs the relationship between concentration and activity is not linear. For example, with certain drugs like midazolam a change of less than 50% is considered weak. Altering metabolism of one isozyme does not necessarily result in altered clinical effects, since some drugs are substrates for multiple isozymes.[36] Even for the best studied herbal extract in regard to drug interactions, standardized St. John's wort extract, most clinical trials have been small, nonrandomized, uncontrolled, use variable methodology for dosage and duration, and provide inadequate product characterization. This makes many isolated study results relatively inconclusive, though consistent trends among studies are supportive. Higher quality research is necessary to achieve definitive findings.[61] Still, these human studies provide the best data available thus far for evaluating the influence of CYP450 metabolism. Many will be examined and compared in the next segment of this series. ❖

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# Selenium and Cancer

*By Alexandra C. Frost, PhD*

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SELENIUM WAS DISCOVERED IN 1817 BY THE SWEDISH chemist, Jons Jacob Berzelius. He named this element "selene," the Greek word for "moon," because of its light conductive properties.[1] In the 19th century it was used primarily as red glass coloring (CdSe), but later became a part of modern technology in photocopy machines and solar cells.[1] Selenium is now recognized as a trace element.

Selenium is a naturally occurring element found in rocks, shale, sandstone, limestone, coal, soil, surface water, and plants. Selenium enters the food chain through plants; therefore, humans get selenium by either ingesting the products of these plants (e.g., wheat) or eating animals that feed on these plants (i.e., meat).[2]

Dietary sources of selenium include cereals, wheat, dairy products, meat, fish, and Brazil nuts. Selenium is less bioavailable in dairy products and meat than it is in grains. Selenium also occurs as selenate in foods such as beet leaves, garlic, and cabbage.[1] The recommended daily allowance (RDA) of selenium is 55 mcg/d for women and 70 mcg/d for men. (One ounce of Brazil nuts supplies nearly 10 times the RDA.) The tolerable upper limit is 400 mcg/d and selenium deficiency is defined as less than 30 mcg/d.

Typical intakes range from 20 mcg/d in China, 35 mcg/d in Finland, to 50-200 mcg/d in North America. In the United States, plasma selenium levels generally range from 80 to 250 mcg/L,[3] with an average consumption of 123 mcg/d.[4] Unlike many minerals, blood levels are roughly equivalent to intake. Selenium is excreted through urine, feces, sweat, and skin loss. When intake is high, excretion is high; when intake is reduced, excretion is reduced.[5]

**Role of Selenium in Health**

While the importance of selenium in the diets of laboratory animals and livestock was recognized by the 1960s, it was not until 1979 that clear evidence established selenium as an essential element of human nutrition. The importance of selenium in the human diet was confirmed when a hospitalized woman on total parenteral nutrition (TPN) developed symptoms similar to white muscle disease (muscle pain, tenderness, atrophy) and was cured of her condition by an infusion of 100 mcg/d of selenium for a week.[6]

More evidence of the essential role of selenium in humans followed with investigations into the endemic cardiomyopathy (Keshan disease) that occurred until the 1980s in China. Supplementation of sodium selenite tablets dramatically reduced the incidence of this disease and continued supplementation in the selenium-poor region of China has virtually eliminated it.[1,7] Sodium selenite tablets also remedied Kaschin-Beck disease (chronic, degenerative osteoarthritis), which was prevalent among children in the same area of China.[8]

As in animals, selenium toxicity (selenosis) is a problem in humans. Symptoms of selenosis include gastrointestinal upset, hair loss, white blotchy nails, and mild nerve damage.[9] The most notable example of selenium toxicity was in the Republic of China from 1960 to 1964 during a period of drought.[10] Residents of Enshi County ate more corn and high-selenium vegetables in lieu of rice (because of the drought) and began experiencing hair and nail loss and developed skin lesions on back of their hands and feet. Half of the residents of this area experienced symptoms. Analysis of urine from residents revealed average dietary consumption of 750 mcg/d.

**Selenium and Cancer**

Selenium emerged as a possible chemopreventive agent when it was observed that people living in areas with lower cancer mortality rates had higher blood selenium levels[11,12] or higher diet/forage selenium.[12-15] Strong data from carcinogenic studies supported this hypothesis. Combs and Combs reviewed more than 100 studies in a variety of experimental models and two-thirds of these studies reported that selenium compounds retarded or inhibited tumorigenesis.[16] These findings laid the groundwork for what has become an extensive literature on selenium and cancer.

**Possible Mechanisms of Anti-Carcinogenesis**

Unlike other trace elements, the biological effects of selenium result from properties of its various compounds rather than properties intrinsic to the element.[17] Selenium functions largely through an association with proteins, known as selenoproteins.[3] Of the selenoproteins, the ones that have been studied most are the selenium-dependent glutathione peroxidases (GSH-Px1-4). Thirty-six percent of total selenium in the body is associated with GPX, which catalyzes the reduction of various organic peroxides as well as hydrogen peroxide.[5] Increased selenium intake also boosts the production of selenium metabolites thought to have an anti-carcinogenic effect: hydrogen selenide, methylselenol, and selenodiglutathione (often called SDG).[18] Difficulties in studying the effects of selenium stem from its multiple forms and complex metabolic and biochemical pathways.[3]

Results from a randomized clinical trial of selenium and skin cancer highlight the paucity of knowledge of selenium's biochemistry relevant to carcinogenesis.[19] Basic scientists are now attempting to decipher the pathways through which selenium might influence cancer risk. Anti-carcinogenic pathways of selenium, hypothesized from laboratory studies, include the repair and prevention of oxidative damage, alteration of metabolism of carcinogenic agents, regulation of immune response, p53-independent apoptosis, and repair of DNA damage.[20-23] It is likely that selenium acts as an anti-carcinogen through several mechanisms, which vary in importance based on nutritional and disease status of the individual *(see Figure)*. The most commonly hypothesized mechanisms are discussed below.

**Prevention of oxidative damage.** Selenium-dependent GPX (glutathione peroxidase) is a selenoenzyme that protects cells from oxidative stress, genetic damage, and UVB irradiation by removing DNA-damaging hydrogen peroxide. The role of selenium enzymes (GPXs) in the antioxidant pathway was the initial hypothesis for selenium's role in cancer prevention[24]

and has received much attention. Evidence against anti-carcinogenic action through selenium's usual role as an essential nutrient (i.e., via GPX) is mounting. Two epidemiological studies, one of selenium and colorectal cancer and the other of selenium and colorectal adenomas found that GPX activity (selenium's action point on the antioxidant pathway) was not related to selenium status.[25,26] Another found that GPX activity was only a good indicator of selenium status in populations with below-normal selenium consumption.[27] Furthermore, forms of selenium that lack nutritional functions (synthesis of selenoproteins) show promise as chemopreventive agents.[28] It is currently believed that selenium may decrease cancer risk in selenium-deficient humans by increasing expression of selenoproteins or enhancing immune surveillance. However, in selenium-adequate populations (e.g., most of the United States), it appears that GPX is not a major pathway through which selenium might reduce the risk of cancer.

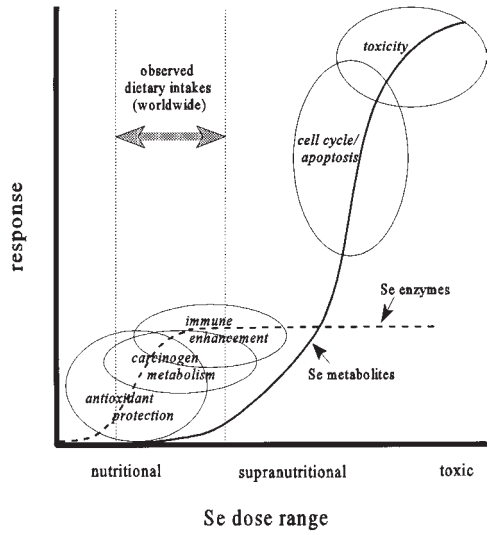
**Repair of DNA damage.** A recent report suggested a strong candidate for selenium's mechanism of action: better DNA repair.[23] High levels of selenomethionine, the primary organic form of selenium, triggered cells in culture to initiate DNA repair through activation of p53. After cells were exposed to selenomethionine the p53 activity was three times higher and the excision of base pairs (sign of DNA repair) was twice as high. This is an exciting observation because DNA repair is a key mechanism for preventing cancer. It might be possible, then, for people (with functional p53) to increase capacity for DNA repair simply by consuming more selenium.[23] Unfortunately, the fact that p53 is mutated in most cancers may diminish the utility of this finding, in terms of cancer prevention.

**Apoptosis.** Apoptosis, or programmed cell death, has evolved in multi-cellular organisms to remodel tissue during development, maintain tissue homeostasis (proliferation-apoptosis balance), remove senescent cells, and delete cells with irreparable genetic damage. It has been suggested that certain diseases, such as cancer, evolve because of the inhibition of normal apoptosis.[29-31] In fact, evasion of apoptosis has been described as one of the "six capabilities" of the cancer cell because the chances of neoplastic growth increase if mutated cells do not self-terminate.[32] Apoptosis enhances the elimination of injured and dysfunctional cells that may arise because of oxidative stress and DNA damage.[32]

The possibility that selenium may increase anticancer apoptotic activity has been suggested by a number of carcinogenesis studies.[33-41] Literature in this area is complicated by the fact that selenium is involved in many biochemical pathways, can exist in multiple

**Figure**

**Potential anti-carcinogenic pathways of selenium**




***Source:*** Combs GF Jr, Gray WP. Chemopreventive agents: Selenium. *Pharmacol Ther* 1998;79:179-192.

forms, and can create a number of metabolites. Lanfear et al found that SDG induced apoptosis in addition to the accumulation of p53 protein in cells that contain normal p53.[33] Stewart et al found that selenite (> 10 microM) induced cell differentiation and apoptosis in human colonic carcinoma cells.[38] Researchers have been focused, recently, on determining the actions of selenium metabolites such as SDG and methylselenol.

## Clinical and Community Trial Research

A number of clinical and community trials have been conducted to evaluate the association between selenium and cancer. Many studies, however, combined selenium with other nutrients such as vitamin E and beta-carotene, making it hard to evaluate the impact of selenium alone. The relationship between several micronutrients and esophageal cancer was studied in a series of large trials in Linxian, Henan Province, China, from 1984 to 1991. A 13% reduction in cancer mortality from lung, esophageal, and stomach cancer was noted in the group supplemented with a combination of 50 mcg of selenium, vitamin E, and beta carotene.[42] In India, a trial was conducted among smokers with a combination of 50 mcg of selenium, vitamin A, riboflavin, and zinc.[43] After one year of treatment, subjects with precancerous lesions had fewer precancerous lesions than those in the control group. Again, selenium was combined with other nutrients making it difficult to discern the effect of selenium alone.

In the Qidong Province of China a community intervention trial was performed from 1984 to 1992 to investigate the impact of selenium on the rate of hepatitis B virus (HBV) and primary liver cancer (PLC).[44] This selenium-deprived community had problems with extremely high rates of both PLC and HBV. Table salt was fortified with 15 ppm of sodium selenite (30-50 mcg/d) for the duration of the study. The incidence of PLC was reduced from 50.4 to 27.2 per 100,000 and the rate of HBV was also significantly reduced.

Perhaps the strongest data supporting a reduction in cancer risk by selenium supplementation were produced in a multicenter, double-blind, randomized, controlled clinical trial of selenium and carcinoma of the skin from 1983 to 1996.[19] The Nutritional Prevention of Cancer Trial (NPC Trial) recruited patients with a history of skin cancer from seven dermatology clinics in the eastern United States, and randomized them to 200 mcg/d of selenium (selenized yeast) or placebo. Participants were followed for an average of five years. Although there was no reduction in incidence of basal or squamous cell carcinomas of the skin, there was a substantial reduction in incidence of several other cancers. Strongest associations were seen with prostate cancer (relative risk [RR] = 0.4), colorectal cancer (RR = 0.4), and lung cancer (RR = 0.5).[19] Results were recently published reflecting three additional years of follow-up to this study. The risk of both prostate and colon cancer remained lower in the selenium-supplemented group; however, the association between selenium and lung cancer was attenuated after the additional years of follow-up.[45]

**Epidemiologic Studies**

Highlighted below are key research results for the cancers that have received the most attention in the research community in terms of chemoprevention by selenium: prostate cancer, lung cancer, and colon cancer.

**Prostate cancer.** Results from studies on prostate cancer are very consistent[46] and have been statistically combined in a recent meta-analysis. This analysis of 16 studies (11 cohort studies and five case-control studies) was conducted to determine the consensus from the literature. The pooled relative risk for prostate cancer of moderate intake (between second and third quartile or third and fourth quintile of distribution) was 0.7 (0.6-0.9) for cohort studies and 0.7 (0.4-1.4) for case-control studies.[47] These results indicate that selenium is a promising chemopreventive agent for prostate cancer.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT Trial) with a target recruitment of 32,400 participants is being conducted to confirm the results from epidemiologic studies.[48] Participants are being randomized to one of four treatment arms: selenium, selenium and vitamin E, vitamin E, or placebo. Participants will receive the intervention for 7-12 years and will be followed for clinical incidence of prostate cancer. It is hoped that this simple dietary intervention (200 mcg l-selenomethionine) will reduce the risk of this very common cancer among men. Results are expected in 2013 and will also provide information on many other diseases potentially affected by selenium and vitamin E supplementation.

**Lung cancer.** Overall, the epidemiological data on selenium and lung cancer are mixed and are seen as less compelling since the recent publication of the updated NPC Trial data. These data show that the relationship between selenium and lung cancer incidence was attenuated and was no longer statistically significant after three additional years of follow-up.[45] A recent meta-analysis, however, combined the results of 13 studies on selenium and lung cancer. Pooled results suggested that protective effects of selenium occur primarily in populations where overall selenium levels are low (RR = 0.7; 95% confidence interval [CI], 0.41-1.08).[49] Because people in the United States generally do not have a problem with low selenium, other avenues of lung cancer prevention are probably more promising in this country.

**Colorectal cancer.** Mixed results have been reported from observational studies of selenium and colorectal cancer. Several studies reported a reduced risk of colon cancer for those with higher levels of selenium. In a study of men of Japanese ancestry in Hawaii, Nomura et al reported that those with high serum selenium (> 133 mcg/L) had a 45% reduced risk of having colorectal cancer in comparison with those with low serum selenium.[50] Ghadirian et al found that participants with high toenail selenium (> 1 ppm) had a 58% reduced risk of colorectal cancer in comparison to those with low toenail selenium (odds ratio [OR] = 0.4; 95% CI 0.2-0.9).[51] Knekt et al observed a decrease in relative risk of colorectal cancer for those in the highest fourth of serum selenium (> 49 mcg/L) vs. low serum selenium (< 49 mcg/L) in their male population (OR = 0.7), but reported a slight increase in risk for their female participants (OR = 1.3).[52] Van den Brant et al did not find a statistically significant relation between toenail selenium and incidence of colon cancer; however, their results suggested a trend of reduced risk of colon cancer with increasing levels of toenail selenium (P = 0.10 for trend).[53]

A few studies reported increased risk with higher selenium levels. Nelson et al reported an increased risk of colorectal cancer with high selenium (> 144 mcg/L, OR = 1.7; 95% CI 0.5-5.9).[54] Garland et al, using the Nurses Health Study data, reported that selenium in the

upper third of selenium distribution (> 0.94 mcg/g) was associated with an increased risk of colon cancer (OR = 2.0; 95% CI 0.9-4.8).[55] There were also a few studies with null or inconclusive results.[56,57]

The relation between selenium and colon cancer is debatable. The investigators of the SELECT trial plan to evaluate the incidence of colorectal cancer as a secondary endpoint. It will be interesting to see whether this large trial supports an association.

## Conclusion

Research suggests that supplementing the diet with a moderate amount of selenium may reduce the risk of several cancers. More randomized clinical trials need to be conducted, optimal amounts of selenium need to be determined, and effective selenium compounds must be identified.

## Recommendation

A great deal more research is needed before a solid recommendation for cancer risk reduction by selenium supplementation can be made. Selenium holds particular promise with respect to prostate cancer prevention; however, the future results from the SELECT Trial are a necessary part of the body of evidence. Even then, there is no magic supplement or pill that can take the place of a healthy, well-balanced diet. That said, a few Brazil nuts would be a nice addition to the diet. Two average sized brazil nuts provide 200 mcg of selenium, contain less than 50 calories, and provide poly- and mono-unsaturated fats that help reduce LDL cholesterol. ❖

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# *Clinical Briefs*

*With Comments from Russell H. Greenfield, MD*

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## Could Meditation Give You a Big Head?

***Source:*** Lazar SW, et al. Meditation experience is associated with increased cortical thickness. *NeuroReport* 2005;16:1893-1897.

**Goal:** To determine whether regular insight meditation practice causes changes in cortical thickness in brain regions involved in attention and sensory processing (i.e., cortical plasticity).

**Design:** Cross-sectional study.

**Subjects:** Twenty people with extensive insight meditation experience and 15 controls with no experience with meditation or yoga.

**Methods:** Participants underwent magnetic resonance imaging (MRI), and a validated computational method for determining cortical thickness was employed. Results for those with meditation experience were compared to results for subjects in the control group. Change in mean respiratory rate (RR) from a six-minute baseline to the first six minutes of the meditation period was determined for each of the meditating participants and correlated with self-reported total number of hours of formal meditation during the person's lifetime. A correlation was also performed between change in RR and cortical thickness.

**Results:** The pattern of relative thickness across each hemisphere was significantly different in specific areas between the two groups. Increased cortical thickness was identified in regions involved with somatosensory, auditory, visual, and interoceptive (originating from within the body) processing in those meditating regularly (right anterior insula, right middle and superior frontal sulci). Typical age-related decreases in specific subregional cortical thickness were found in controls but not in the regular meditators. A correlation was found

between total lifetime hours of meditation and RR, and at least a partial correlation was noted between change in RR and thickness of specific regions of the cortex (the insula and inferior occipitotemporal visual cortex).

**Conclusions:** Regular meditation practice results in an increased cortical thickness in a subset of brain regions associated with processing of stimuli. Regular meditation may also slow age-related thinning of the frontal cortex.

**Study strength:** Use of a validated measure to determine cortical thickness.

**Study weaknesses:** Small sample size; no mention of where control subjects were recruited from; the most experienced meditators were also among the oldest participants, so typical age-related changes in cortical thickness may have obscured modest effects of meditation practice in certain brain regions.

**Of note:** Mean cortical thickness across the entire cerebral cortex did not differ significantly between the two groups, indicating that meditation did not create generalized and nonspecific cortical thickening; the majority of cortical changes were detected in the right hemisphere; the primary focus of Buddhist insight meditation is to cultivate attention and mindfulness, or non-judgmental awareness of moment-to-moment stimuli both internal and external without the use of mantras or chants; subjects with prior meditation experience were "regular people" with jobs, family, and outside interests, not monks; two participants were full-time meditation instructors, three were part-time meditation/yoga instructors, the rest meditated an average of once a day for 40 minutes (subjects had been practicing meditation, on average, for more than nine years and had participated in at least one week-long insight meditation retreat); all subjects were healthy and were matched for age, sex, race, and education level; frequency of daily meditation practice varied widely among the meditators; the insula, an area of the brain associated with breath awareness techniques and interoceptive processing, showed the largest between-group differences with regard to cortical thickness.

**We knew that:** Many trials have shown that cortical thickness decreases as a result of aging and pathology; prior studies have shown that regular meditation alters a person's resting EEG, suggesting long-term changes in brain activity that persist beyond the time period of meditation practice; during formal meditation practice a drop in RR typically occurs; augmented cortical thickness can occur as the result of a combination of increased arborization per neuron, greater glial volume, or enhanced regional vascularization; learning to juggle has been shown to increase the thickness of the visual cortex; many factors influence cortical thickness including genetics, age, neuropathology, and gender; the rate of age-dependent thinning is highly variable across the cortex.

**Clinical import:** This intriguing trial offers compelling results that call out for corroboration. As the authors point out, cross-sectional studies can reveal correlations, but do not prove the existence of a cause-and-effect relationship. That stated, the differences in cortical thickness between the groups were not global in nature, but specific to regions associated with stimulus processing that are also active during the practice of insight meditation. The idea that changes in regional cortical plasticity could have been due to nonspecific lifestyle differences between the groups seems unlikely. Ample data do exist to support the practice of mindfulness meditation in specific clinical situations, but the notion that meditation could help prevent changes in the brain typically associated with aging should be of great interest to researchers. Future studies will need to focus on the duration and frequency of meditation needed to experience objective benefit; however, it would seem prudent to mention the promising results of meditation trials to our patients (and to explore the practice ourselves).

**What to do with this article:** Keep a copy on your computer. ❖

## *CME Questions*

**CME Instructions:** Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

**8. All herb-drug interactions are undesirable.**
   a. True
   b. False

**9. The fruit juice most widely recognized for its ability to inhibit the isozyme CYP 3A4 in the gut, thereby increasing bioavailability of the isozyme's drug substrates and increasing the risk of adverse effects is:**
   a. apple juice.
   b. cranberry juice.
   c. grapefruit juice.
   d. orange juice.

**10. Selenium is an essential element of human nutrition.**
   a. True
   b. False

**11. Selenium's potential mechanisms of anti-carcinogenesis includes:**
   a. prevention of oxidative damage.
   b. repair of DNA damage.
   c. induction of apoptosis.
   d. All of the above

**Answers:** 8. b, 9. c, 10. a, 11. d.

Supplement to *Alternative Medicine Alert*
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ALTERNATIVE MEDICINE ALERT™
*A Clinician's Evidence-Based Guide to Alternative Therapies*



# Prostate Cancer: Patient Handout

PROSTATE CANCER IS THE MOST COMMON FORM OF CANCER AMONG MEN IN THE UNITED States, other than skin cancer. In 2004, approximately 230,110 new cases of prostate cancer will be diagnosed and 29,900 men will die of the disease, according to the American Cancer Society. Prostate cancer is the second leading cause of cancer deaths of men in the United States, after lung cancer, and the sixth leading cause of death of men overall.

Medical experts do not know how to prevent prostate cancer. But they are studying many factors. They know that not smoking, maintaining a healthy diet, staying physically active, and seeing your doctor regularly contribute to overall good health.

## Prevalence of prostate cancer

For the general population, a man in his lifetime has about a 16% chance (1 in 6) of being diagnosed with prostate cancer and a 3% chance (1 in 33) of dying from prostate cancer.

More than 70% of all diagnosed prostate cancers are found in men aged 65 years or older. Basically, the older you are, the greater the risk for getting prostate cancer.

## Risk of prostate cancer

While all men are at risk for prostate cancer, some factors increase risk.

**Family history.** Men with a father or brother who has had prostate cancer are at greater risk for developing it themselves.

**Race.** Prostate cancer is more common in some racial and ethnic groups than in others, but medical experts do not know why. Prostate cancer is more common in African-American men than in white men. It is less common in Hispanic, Asian, Pacific Islander, and Native American men than in white men.

## Symptoms of prostate cancer

Many men with prostate cancer often have no symptoms. If symptoms appear, they can include:

- Blood in the urine
- The need to urinate frequently, especially at night
- Weak or interrupted urine flow
- Pain or burning feeling while urinating
- The inability to urinate
- Constant pain in the lower back, pelvis, or upper thighs

If you have any of these symptoms, see your doctor as soon as possible. Keep in mind that these symptoms are also caused by other prostate problems that are not cancer, such as an infection or an enlarged prostate.

## Prostate cancer screening

The two most common tests used by physicians to detect prostate cancer are the digital rectal examination (DRE) and the prostate-specific antigen (PSA) test. For DRE, which has been used for many years, the physician inserts a gloved finger into the rectum to feel for

prostate gland irregularities. The PSA test is a blood test that measures the prostate-specific antigen, an enzyme produced only by the prostate.

Although there is good evidence that PSA screening can detect early-stage prostate cancer, evidence is mixed and inconclusive about whether early detection improves health outcomes. In addition, prostate cancer screening is associated with possible harms. These include anxiety and follow-up procedures based on frequent false-positive test results, as well as complications that may result from treating prostate cancers that, if left untreated, might not have affected the man's health.

Because currently available evidence is insufficient to determine whether the potential benefits of prostate cancer screening outweigh its potential harms, there is no scientific consensus that such screening is beneficial.

The Centers for Disease Control and Prevention (CDC) promotes informed decision making, which occurs when an individual understands the nature and risks of prostate cancer; understands the risks, benefits, and alternatives to screening; participates in decision making at a level he desires; and makes a decision consistent with his preferences and values or defers the decision to a later time.

CDC also supports shared decision making, which is a process carried out between a patient and his health care professional in the clinical setting where both parties share information and the patient understands the nature and risks of prostate cancer; understands the risks, benefits, and alternatives to screening; participates in decision making at a level he desires; and makes a decision consistent with his preferences and values or defers the decision to a later time.

**Follow-up testing**

Most men who go for further testing do not have cancer. If a PSA test or DRE suggests a problem, your doctor most likely will refer you to a urologist (a doctor who has special training in prostate-related problems). Additional testing is necessary to determine if the problem is cancer or something else.

The urologist may perform a transrectal ultrasound —a small probe inserted into the rectum that bounces sound waves off the prostate, producing a video image. Transrectal ultrasound does not provide enough specific information to make it a good screening tool by itself, but some doctors find it useful as a follow up to a suspicious DRE or PSA test.

If the urologist suspects cancer, tiny samples of the prostate may be removed with a needle. This is called a biopsy. A biopsy is usually performed in the urologist's office. The samples are examined under a microscope to determine if cancer cells are present.

**Treating prostate cancer**

Many factors affect the decision whether or not to treat the disease: the patient's age, whether the cancer has spread, the presence of other medical conditions, and the patient's overall health.

When prostate cancer has been found in its early stages and has not spread beyond the prostate, a doctor and his patient may consider the following options.

Watchful waiting—monitoring the patient's prostate cancer by performing the PSA test and DRE regularly, and treating it only if and when the prostate cancer causes symptoms or shows signs of growing.

Surgery (radical prostatectomy)—removing the prostate.

External radiation therapy—destroying cancer cells by directing radiation at the prostate.

Internal radiation therapy (brachytherapy)—surgically placing small radioactive pellets inside or near the cancer to destroy cancer cells.

Hormone therapy—giving certain hormones to keep prostate cancer cells from growing.

Cryotherapy—placing a special probe inside or near the prostate cancer to freeze and destroy the cancer cells.

More advanced prostate cancers that have spread beyond the prostate can be complex to treat and may be incurable. Patients should discuss with their doctor the best course of action.

**Do these treatments have side effects?**

Side effects from prostate cancer treatment depend mainly on the type of treatment, the patient's age, and his overall health. Men can experience pain, discomfort, and other mild-to-severe side effects that may be temporary or may last a long time. Two important side effects are impotence and incontinence. When a doctor explains the treatment options, he or she can discuss how mild or severe side effects might be, and how long they might last. Also, a doctor may be able to perform surgery or prescribe drugs to relieve some side effects.

***Source:*** Prostate Cancer Control Initiatives. The Centers for Disease Control and Prevention. Available at: www.cdc.gov/cancer/prostate/index.htm. Accessed Feb. 15, 2006.