Virginia Integrative Medicine
901 Preston Avenue, Suites 402-3
Charlottesville, VA 22903
www.healthyvim.org

Martin P Albert, MD
Peggy A Wright, PhD, RD
Phone: (434) 984-2846
Fax: (434) 984-3846

Tamoxifen Benefits

Tamoxifen reduces the risk of invasive breast cancer, primarily ER+ tumors, by 49% and reduces the risk of noninvasive breast cancer by 50%.[1]

Tamoxifen Side Effects

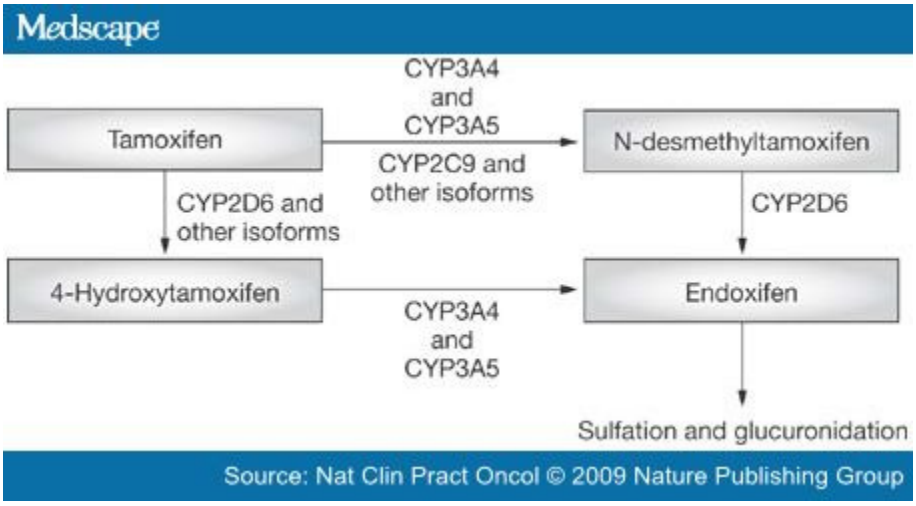
1. Life Threatening (occurring in 1 in every 1,000 women over 5 years of treatment)
    a. Uterine cancer.
        i. Endometrial cancer. "Studies have found the risk of developing endometrial cancer to be about 2 cases per 1,000 women taking tamoxifen each year compared with 1 case per 1,000 women taking placebo (1, 2). Most of the endometrial cancers occurring in women taking tamoxifen have been found in the early stages, and treatment has usually been effective. However, for some breast cancer patients who developed endometrial cancer while taking tamoxifen, the disease was life-threatening." National Cancer Institute, http://www.cancer.gov/cancertopics/factsheet/Therapy/tamoxifen.
        ii. Uterine sarcoma. "Uterine Sarcoma
        Studies have found the risk of developing uterine sarcoma to be slightly higher in women taking tamoxifen compared with women taking placebo. However, it was less than 1 case per 1,000 women per year in both groups (1, 2). Research to date indicates that uterine sarcoma is more likely to be diagnosed at later stages than endometrial cancer, and may therefore be harder to control and more life-threatening than endometrial cancer." NCI.
        iii. Keep tract of serum estrogens and progesterones.
        iv. Have uterine ultrasounds yearly.
    b. Blood clots (stroke, pulmonary embolism).
        i. Enteric-coated aspirin 81 mg/day
        ii. Consider nattokinase 50 to 100 mg (1,000 to 2,000 FU) twice daily. Do NOT take if you are taking aspirin. **Nattokinase is contraindicated in any condition associated with bleeding or combined with blood thinning agents such as warfarin (Coumadin), Plavix, aspirin, or other pharmacological blood thinners**. Do have your blood fibrinogen levels monitored.
        iii. Garlic extract to yield 3200 mcg allicin/day
2. Other side effects
    a. Cataracts. "As women age, they are more likely to develop cataracts (clouding of the lens inside the eye). Women taking tamoxifen appear to be at increased risk for developing cataracts. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients." National Cancer Institute 2010.
        i. Luteolin and zeaxanthin are associated with decreased risks of cataracts in healthy women.[2]. In addition, green tea catechins, anthocyanins (found in

grape seed extracts, red grapes, blueberries, and other deep red and purple fruits), resveratrol, and Ginkgo biloba, have been shown to ameliorate ocular oxidative stress.[2] Deficient glutathione levels contributing oxidative stress in the eye lens may also be involved.[3] Nutrients to increase glutathione levels and activity include alpha lipoic acid, vitamins E and C, and selenium. Cataract patients also tend to be deficient in vitamin A and the carotenes, as well as lutein and zeaxanthin. The B vitamin riboflavin appears to play an essential role as a precursor to flavin adenine dinucleotide (FAD), a co-factor for glutathione reductase activity.[3] It is not known if any of these antioxidants will decrease the risk of cataracts in women in tamoxifen.

b. Menopausal symptoms in premenopausal women.[4] These include hot flashes, vaginal dryness, joint pain, and leg cramps. Some women experience irregular menstrual periods, headaches, fatigue, nausea and/or vomiting, vaginal itching, irritation of the skin around the vagina, and skin rash. As with menopause, not all women who take tamoxifen have these symptoms. (National Cancer Institute).
c. Bone Density. Taxmoxifen lowers bone density in premenopausal women, but raises it in post-menopausal women.[5] This is because tamoxifen has a weaker positive effect on the bone than the normal levels of estrogen in premenopausal women. If you are premenopausal, it is important to:
    i. Get at least 1,000 mg of calcium between diet and supplements
    ii. Have adequate magnesium (through a test of red blood cell magnesium levels), which may require magnesium supplementation.
    iii. Have adequate vitamin D levels (at minimum 32 ng/L, although above 50 ng/L is better for women with a history of cancer).
d. Heart disease
    i. Elevated triglycerides. Tamoxifen therapy is found to cause high blood triglycerides by reducing activity of lipolytic (fat breakdown) enzymes on triglycerides, thereby increasing the risk of cardiovascular disease.[6] It's important to avoid diets high in refined carbohydrates and concentrated simple sugars, since these increase triglycerides in the blood. Coenzyme Q10 also may help lower these levels.
e. Exacerbation of fibroids, endometriosis, and endometrial polyps.
    i. "For women taking tamoxifen, recent data strongly support the estrogen agonist role of tamoxifen as a causal factor for the increased risk of endometriosis, but also of leiomyomata, endometrial polyps, and endometrial hyperplasia."[7]
    ii. If you have now or have had similar problems, please discuss the use of tamoxifen with your gynecologist and oncologist so that you can be monitored for a possible worsening of symptoms.

Genetics and Food, Herb, and Drug Interactions

Tamoxifen needs to be activated in the body in order to be effective. There are two enzymes that are involved in activating it. The most important is P450 Cyp 2D6. Women who are fast metabolizers get more benefit from tamoxifen than women who are slow or intermediate metabolizers. The other one is P450 Cyp 3A4.



Genotyping has the potential for identification of women who have these different CYP2D6 phenotypes (fast, intermediate, slow) and for whom the use of tamoxifen is associated with poorer outcomes.[8] It is estimated that about 10 percent of women with breast cancer have a variation that keeps their bodies from properly metabolizing tamoxifen. According to Dr. Susan Love, "At the 2007 San Antonio Breast Cancer Symposium, researchers from the University of Michigan and Mayo Clinic in Rochester, Minn., presented data showing that women who inherited this variation of the 2D6 gene were almost twice as likely to have their breast cancer recur, even though they were more likely to complete their tamoxifen treatment." It is the women who have little or no side effects who are most likely to have this genetic variation. The test costs about $300. Some, but not all, insurance companies are covering the cost. You should sure to check with your insurance company to find out their specific policy about this genetic test before having it done. (http://www.dslrf.org/breastcancer/content.asp?CATID=19&L2=3&L3=7&L4=0&PID=&sid=132&cid=1146, 2008)

In addition, there are a number of medications that may actually inhibit Tamoxifen's activation. These include a number of popular antidepressants. The antidepressants that do not interfere with tamoxifen are: Effexor (vanlavaxine), Celexa (citalopram), Lexapro (escitalopram). However, there are non-pharmacological ways (such as amino acid therapy and/or methylfolate) to deal with depression.

Strong CYP2D6 Inhibitors	Moderate CYP2D6 Inhibitors
Generic Names Brand Names Fluoxetine Prozac® Paroxetine Paxil®* Qunidine Cardioquin® Bupropion Wellbutrin® *Paxil use has actually been the most strongly associated with an increase of breast cancer recurrence in tamoxifen users, probably because it irreversibly interferes with Cyp2D6 metabolism.[9]	Generic Names Brand Names Duloxetine Cymbalta® Sertraline Zoloft® Diphenhydramine Benadryl® Thioridazine Mellaril® Amiodarone Cordarone® Trazodone Cimetidine Tagamet®

1. CYP2D6 Inducers
    a. Dexamethasone (a steroid anti-inflammatory) and rifampin (an antibiotic) are the only drugs known to enhance CYP2D6 activity
2. CYP2D6 Inhibitors
    a. Antidepressants
        i. Certain SSRIs (serotonin reuptake inhibitors), such as Paxil, Prozac, or Zoloft can compete with tamoxifen for activation. A U.S study presented at the American Society of Clinical Oncology's annual meeting in 2009 found that after two years, 7.5 percent of women who took only tamoxifen had a recurrence, compared with 16 percent who took Paxil, Prozac, or Zoloft—drugs considered to be the most potent CYP2D6 inhibitors. That difference translates to a 120 percent increase in the risk of breast cancer recurrence.
        ii. Patients taking the so-called weaker antidepressants, Celexa (citalopram), Lexapro (escitalopram), and Luvox (fluvoxamine), did not have an increased risk of recurrence.[i]
    b. Tagament (cimetidine) is a moderate CYP2D6 inhibior and should be avoided.
    c. Herbs
        i. Goldenseal appears to be a potent CYP2D6 inhibitor in humans. [10] Thus goldenseal should only be used for very short times or not used at all.
        ii. Kava may be a CYP2D6 inhibitor. However another study in humans showed no effect on CYP2D6 [10]. Nevertheless, it may be better to avoid kava during tamoxifen therapy until this issue is resolved.
        iii. Ashwaganda when fed to mice did reduce CYP2D6 activity. However, this may not apply to humans. I suggest using only low doses as part of a more complex herbal formula, or using a different herbal adrenal or thyroid support.
        iv. Black cohosh appears to weakly inhibit CYP2D6, but the authors concluded that the amount was not clinically relevant [11]. In addition, a German study of over 1,000 breast cancer survivors taking black cohosh showed a significant prolonged survival over those not taking black cohosh.[12]
        v. Siberian ginseng and milk thistle have no effect on CYP2D6 and should be fine.
        vi. Saint John's Wort, which is a potent CYP3A inducer, does not appear to have any effects on CYP2D6 when used in the typical amounts for depression.[10, 13]
3. CYP3A Inhibitors
    a. Foods
        i. Grapefruit is a strong inhibitor of this enzyme, so it may be better to avoid grapefruit while on tamoxifen.
    b. Herb
        i. Rhodiola inhibits Cyp3A in vitro.[14] However, many herbs that show effects in cell cultures, do not show effects in humans. Until more is known, use cautiously.
        ii. Green tea may make a small reduction in CYP3A, but the investigators concluded that repeated green tea catechin administration is not likely to result in clinically significant effects on the disposition of drugs metabolized by CYP enzymes.[15]
    c. Drugs
        i. Diltiazem, which is a calcium channel blocker used to treat high blood pressure, angina, and certain heart rhythm disorders is a weak to moderate CYP3A inhibitor.

4. CYP3A Inducers
    a. Herbs
        i. Saint John's Wort is a CYP3A inducer, and may be more potent in women. This may actually help activate Tamoxifen, although this has not been studied.
        ii. Garlic, quercetin, grapeseed, ginseng and kava may help to activate CYP3A. Since this was done in human liver cell cultures, it is not certain that these compounds will have any practical value when ingested by humans. Silymarin (milk thistle), curcumin, and apigenin have no effect on CYP3A [16, 17], nor does Angelica (dong quai) or Scutellaria [18].
    b. Drugs
        i. Tamoxifen itself functions as an inducer of Cyp3A4. This happens through a number of mechanisms.

Supplements to take with Tamoxifen

1. Coenzyme Q10 with riboflavin and niacin
    a. A few human studies suggest that CoQ10 (100 mg) with 10 mg of riboflavin (B2) and 50 mg of niacin (B3) has a number of favorable effects for women taking tamoxifen. [19-23] It lowered cancer markers in women already taking tamoxifen[23], improved DNA repair[19], lowered biochemical markers of angiogenesis[21], and improved lipid profiles[22].
    b. This amount of B2 and B3 are easily found in a B-complex or multivitamin. However, it is important to take a B-complex or multivitamin that has natural (folinic acid and methylfolate), not synthetic folic acid in it. Such brands include ProThera, Designs for Health, and Pure Encapsulations brand of multivitamins. These are specialty products and not available at vitacost.com.
2. Gamma linolenic acid (GLA) from evening primrose oil, black currant oil, or borage oil.
    a. May enhance the actions of tamoxifen.[24, 25]
3. Fish oil.
    a. May reduce side effects of tamoxifen.[1]
    b. May support tissue sensitivity to tamoxifen.[26]
    c. May help prevent development of ER- tumors.[27]
4. Green tea
    a. May synergize with tamoxifen.[28-30]

Supplements that are NOT contraindicated with Tamoxifen

1. Black Cohosh. Black cohosh is used in Germany for the treatment of menopausal symptoms. A study of breast cancer recurrence actually showed longer disease-free survival in over 1,000 women using black cohosh, including the women on Tamoxifen.[12] Black cohosh may actually have independent antiproliferative effects on estrogen positive breast cancer cells[31] and work synergistically with tamoxifen.[32]
2. Melatonin.[33]
3. American and Korean ginsengs[34]
4. Indole-3-Carbinol
    a. In cells studies was synergistic with tamoxifen.[28-30]

   b. In one animal study, exceptionally high dose I3C was found to increase harmful byproducts of I3C. However, this dose was equivalent to 12,500mg of I3C for a 110# human, while current doses are closer to 200 to 400 mg daily. Also, DIM, which is what I3C is converted to in the human GI track, was not shown to have an effect on tamoxifen metabolism. [35]

5. Selenium
   a. May increase antiestrogenic effect of tamoxifen.[36-38]
   b. Do have blood levels monitored. With supplements and Brazil nuts, it is possible to get too much selenium.

Supplements that ARE contraindicated with Tamoxifen

1. Licorice root. Licorice root has estrogenic activities and may potentiate estrogens and could stimulate estrogen receptors on cancer cells.[1] Note: This does NOT include DGL for heartburn and gastritis, in which the component that is active in cortisol and hormonal issues removed.
2. Long-term use of phytoestrogenic herbs such as alfalfa, red clover,[1] and rehmannia should be avoided until we understand more about their interactions with tamoxifen. However, since we now know that the phytoestrogens in soy are not problematic, it may be that the phytoestrogens in these herbs are helpful as well.

Dietary considerations

1. Flaxseeds
   a. Flaxseeds may work synergistically with tamoxifen.[39]
2. Green tea.
   a. May synergize with tamoxifen.[28-30]
3. Soy
   a. Three prospective epidemiological studies have looked at soy intake and breast cancer recurrence. None of them have indicated that soy interferes with tamoxifen's effectiveness [40], while one U.S. study suggests that a small portion of natural soy foods daily may even reduce the risk of recurrence.[41]

References Available Upon Request

References

1. Alschuler L, Gazella KA. *Alternative Medicine Magazine's Definitive Guide to Cancer: An Integrative Approach to Prevention, Treatment, and Healing*. 2nd ed. Berkeley, CA: Celestial Arts; 2007.
2. Rhone M, Basu A. Phytochemicals and age-related eye diseases. *Nutr Rev.* Aug 2008;66(8):465-472.
3. Head KA. Natural therapies for ocular disorders, part two: cataracts and glaucoma. *Altern Med Rev.* Apr 2001;6(2):141-166.
4. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. *Breast.* Jun 2007;16(3):223-234.
5. Henry NL, Nguyen A, Azzouz F, et al. Lack of association between oestrogen receptor polymorphisms and change in bone mineral density with tamoxifen therapy. *Br J Cancer.* Jan 19 2010;102(2):294-300.
6. Sachdanandam P. Antiangiogenic and hypolipidemic activity of coenzyme Q10 supplementation to breast cancer patients undergoing Tamoxifen therapy. *Biofactors.* 2008;32(1-4):151-159.
7. Ebert AD, Rosenow G, David M, Mechsner S, Magalov IS, Papadopoulos T. Co-occurrence of atypical endometriosis, subserous uterine leiomyomata, sactosalpinx, serous cystadenoma and bilateral hemorrhagic corpora lutea in a perimenopausal adipose patient taking tamoxifen (20 mg/day) for invasive lobular breast cancer. *Gynecol Obstet Invest.* 2008;66(3):209-213.
8. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *Jama.* Oct 7 2009;302(13):1429-1436.
9. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *Bmj.* 2010;340:c693.
10. Gurley BJ, Swain A, Hubbard MA, et al. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. *Mol Nutr Food Res.* Jul 2008;52(7):755-763.
11. Gurley BJ, Gardner SF, Hubbard MA, et al. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharmacol Ther.* May 2005;77(5):415-426.
12. Zepelin HH, Meden H, Kostev K, Schroder-Bernhardi D, Stammwitz U, Becher H. Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. *Int J Clin Pharmacol Ther.* Mar 2007;45(3):143-154.
13. Markowitz JS, DeVane CL, Boulton DW, Carson SW, Nahas Z, Risch SC. Effect of St. John's wort (Hypericum perforatum) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci.* Jan 21 2000;66(9):PL133-139.
14. Hellum BH, Tosse A, Hoybakk K, Thomsen M, Rohloff J, Georg Nilsen O. Potent in vitro Inhibition of CYP3A4 and P-Glycoprotein by Rhodiola rosea. *Planta Med.* Sep 29 2009.
15. Chow HH, Hakim IA, Vining DR, et al. Effects of repeated green tea catechin administration on human cytochrome P450 activity. *Cancer Epidemiol Biomarkers Prev.* Dec 2006;15(12):2473-2476.
16. Raucy JL. Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. *Drug Metab Dispos.* May 2003;31(5):533-539.
17. Price RJ, Scott MP, Giddings AM, et al. Effect of butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole on cytochrome P450 forms in cultured human hepatocytes. *Xenobiotica.* Jun 2008;38(6):574-586.
18. Yi S, Cho JY, Lim KS, et al. Effects of Angelicae tenuissima radix, Angelicae dahuricae radix and Scutellariae radix Extracts on Cytochrome P450 Activities in Healthy Volunteers. *Basic Clin Pharmacol Toxicol.* May 5 2009.

19. Premkumar VG, Yuvaraj S, Shanthi P, Sachdanandam P. Co-enzyme Q10, riboflavin and niacin supplementation on alteration of DNA repair enzyme and DNA methylation in breast cancer patients undergoing tamoxifen therapy. *Br J Nutr.* Dec 2008;100(6):1179-1182.

20. Yuvaraj S, Premkumar VG, Shanthi P, Vijayasarathy K, Gangadaran SG, Sachdanandam P. Effect of Coenzyme Q(10), Riboflavin and Niacin on Tamoxifen treated postmenopausal breast cancer women with special reference to blood chemistry profiles. *Breast Cancer Res Treat.* Mar 2009;114(2):377-384.

21. Premkumar VG, Yuvaraj S, Sathish S, Shanthi P, Sachdanandam P. Anti-angiogenic potential of CoenzymeQ10, riboflavin and niacin in breast cancer patients undergoing tamoxifen therapy. *Vascul Pharmacol.* Apr-Jun 2008;48(4-6):191-201.

22. Yuvaraj S, Premkumar VG, Vijayasarathy K, Gangadaran SG, Sachdanandam P. Ameliorating effect of coenzyme Q10, riboflavin and niacin in tamoxifen-treated postmenopausal breast cancer patients with special reference to lipids and lipoproteins. *Clin Biochem.* Jun 2007;40(9-10):623-628.

23. Premkumar VG, Yuvaraj S, Vijayasarathy K, Gangadaran SG, Sachdanandam P. Effect of coenzyme Q10, riboflavin and niacin on serum CEA and CA 15-3 levels in breast cancer patients undergoing tamoxifen therapy. *Biol Pharm Bull.* Feb 2007;30(2):367-370.

24. Kenny FS, Gee JM, Nicholson RI, et al. Effect of dietary GLA+/-tamoxifen on the growth, ER expression and fatty acid profile of ER positive human breast cancer xenografts. *Int J Cancer.* May 1 2001;92(3):342-347.

25. Kenny FS, Pinder SE, Ellis IO, et al. Gamma linolenic acid with tamoxifen as primary therapy in breast cancer. *Int J Cancer.* Mar 1 2000;85(5):643-648.

26. DeGraffenried LA, Friedrichs WE, Fulcher L, et al. Eicosapentaenoic acid restores tamoxifen sensitivity in breast cancer cells with high Akt activity. *Ann Oncol.* Jul 2003;14(7):1051-1056.

27. Manni A, Xu H, Washington S, et al. The impact of fish oil on the chemopreventive efficacy of tamoxifen against development of N-methyl-N-nitrosourea-induced rat mammary carcinogenesis. *Cancer Prev Res (Phila).* Mar 2010;3(3):322-330.

28. Farabegoli F, Papi A, Orlandi M. -(-)Epigallocatechin-3-gallate downregulates EGFR, MMP-2, MMP-9 EMMPRIN and inhibits the invasion of MCF-7 tamoxifen resistant cells. *Biosci Rep.* May 7 2010.

29. Huang HC, Way TD, Lin CL, Lin JK. EGCG stabilizes p27kip1 in E2-stimulated MCF-7 cells through down-regulation of the Skp2 protein. *Endocrinology.* Dec 2008;149(12):5972-5983.

30. Sartippour MR, Pietras R, Marquez-Garban DC, et al. The combination of green tea and tamoxifen is effective against breast cancer. *Carcinogenesis.* Dec 2006;27(12):2424-2433.

31. Gaube F, Wolfl S, Pusch L, Kroll TC, Hamburger M. Gene expression profiling reveals effects of Cimicifuga racemosa (L.) NUTT. (black cohosh) on the estrogen receptor positive human breast cancer cell line MCF-7. *BMC Pharmacol.* Sep 20 2007;7(1):11.

32. Al-Akoum M, Dodin S, Akoum A. Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an in vitro study. *Can J Physiol Pharmacol.* Nov 2007;85(11):1153-1159.

33. Lissoni P, Barni S, Meregalli S, et al. Modulation of cancer endocrine therapy by melatonin: a phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone. *Br J Cancer.* Apr 1995;71(4):854-856.

34. Cui Y, Shu XO, Gao YT, Cai H, Tao MH, Zheng W. Association of ginseng use with survival and quality of life among breast cancer patients. *Am J Epidemiol.* Apr 1 2006;163(7):645-653.

35. Parkin DR, Malejka-Giganti D. Differences in the hepatic P450-dependent metabolism of estrogen and tamoxifen in response to treatment of rats with 3,3'-diindolylmethane and its parent compound indole-3-carbinol. *Cancer Detect Prev.* 2004;28(1):72-79.

36. Li Z, Carrier L, Belame A, et al. Combination of methylselenocysteine with tamoxifen inhibits MCF-7 breast cancer xenografts in nude mice through elevated apoptosis and reduced angiogenesis. *Breast Cancer Res Treat.* Nov 2009;118(1):33-43.

37. Li Z, Carrier L, Rowan BG. Methylseleninic acid synergizes with tamoxifen to induce caspase-mediated apoptosis in breast cancer cells. *Mol Cancer Ther.* Sep 2008;7(9):3056-3063.

38. Shah YM, Al-Dhaheri M, Dong Y, Ip C, Jones FE, Rowan BG. Selenium disrupts estrogen receptor (alpha) signaling and potentiates tamoxifen antagonism in endometrial cancer cells and tamoxifen-resistant breast cancer cells. *Mol Cancer Ther.* Aug 2005;4(8):1239-1249.

39. Chen J, Hui E, Ip T, Thompson LU. Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. *Clin Cancer Res.* Nov 15 2004;10(22):7703-7711.

40. Shu XO, Zheng Y, Cai H, et al. Soy food intake and breast cancer survival. *Jama.* Dec 9 2009;302(22):2437-2443.

41. Guha N, Kwan ML, Quesenberry CP, Jr., Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat.* Feb 17 2009.

Updated 12-5-2010