Dr. Bill McAnalley

Phytoestrogens and Breast Cancer

Currently, oncologists are still advising women not to take phytoestrogens because they might increase the risk of breast and ovarian cancer. Their original concern comes from two sources.

First, estrogen or estrogen plus progesterone, hormone replacements, increase the risk of breast cancer in Western countries. Recently, a similar randomized study with the same hormone therapy was conducted in a nation-wide Taiwanese study using 65,723 Chinese women. The hormone therapy increased the risk of invasive breast cancer in the Taiwanese women. There was no difference in the risk of estrogen-induced invasive breast cancer in women from Asian or Western countries (Lai, NJ., 2011).

Second, estrogen and phytoestrogens are believed to represent a similar cancer risk; based on preclinical evaluations. So, oncologists recommended that women should be aware of the potential cancer risk from phytoestrogens. The oncologists concern has caused all women to shy away from phytoestrogens. Men are afraid of getting larger breasts.

The current interest in phytoestrogens started when epidemiological studies found that Asian women who consume high dietary concentrations of soy products have a lower incidence of breast cancer (recently verified by Bilal, I., et. al., 2014). This prompted scientists to conduct preclinical studies with phytoestrogens. To their surprise, low concentrations of phytoestrogens stimulated breast cancer cell growth in tissue culture and in athymic mice, *in-vivo,* studies. Also, it inhibited the anti-tumor effect of Tamoxifen. But, higher concentrations of the same phytoestrogens inhibited tumor growth and enhanced the effect of Tamoxifen.

Until they could explain the difference, many Doctors, have advised women about the possible increased risk of breast cancer. (Martin, PM., et. al., 1978; Ganry, O., 2002; De Lemos, ML., 2001).

Our interpretation of the problem follows:
First, they should have recognized that phytoestrogens are in all food. Chinese Asians consume about 50 mg/day of isoflavones, the major phytoestrogen in soy and the average Western vegetarian consumes 1-3 mg/day (Bilal, I., et. al., 2014).

The intake of traditional soy-based foods is high in Japan, and the mean total intake of isoflavones is estimated between 19.4 and 33.6 mg/d according to the National Nutritional Survey in Japan. In Western populations, the consumption of isoflavones from traditional soy foods is substantially lower, between 0.5 and 3 mg (Tousen, Y., 2013). We conclude that dietary estrogens are omnipresent and not limited to soy-based food. (Behr, M., 2011) So Doctors told their patients not to consume phytoestrogens because it could promote breast and/or ovarian cancer.

In fact, phytoestrogens are in all fruits, vegetables, nuts, fish, other meats, as well as in most surface drinking water supplies. In other words, phytoestrogens are in almost everything we consume. Since Western populations consume a low concentration of phytoestrogens that has been shown to increase the risk of breast cancer based on the preclinical tissue culture and in athymic mice studies mentioned above.

They should have concluded that the only safe recommendation for people whose diet has a low concentration of phytoestrogens is to stop eating all together or increase their consumption of phytoestrogens to proven safe and effective amounts consumed by Asians. Their doctors should have recommended that women eat or take phytoestrogen supplements.

The above preclinical findings have been repeated many times and we believe they are accurate. We can explain how low concentrations of phytoestrogens stimulated breast cancer cell growth in tissue culture, and with athymic mice; also inhibited the anti-tumor effect of Tamoxifen. We can also explain how higher concentrations of the same phytoestrogens inhibited tumor growth and enhanced the effect of tamoxifen.

To understand these preclinical findings, a review of the clinical chemistry of sex hormones is needed. Estrogen represents an entire class of related hormones that includes estriol, estradiol and estrone. Estriol is made by the placenta during pregnancy. Estradiol is the primary sex hormone of child-bearing women. It is made in developing ovarian follicles and is responsible for female characteristics and sexual functions. Estrone is produced after menopause and is much weaker than Estradiol.

In general, testosterone and estradiol circulate in the bloodstream, bound mostly (60 to 70%) to the sex hormone-binding globulin (SHBG) also called the sex steroid-binding globulin (SSBG). It is a glycoprotein that binds to sex hormones, both androgens and estrogens. To a lesser extent, sex hormones are bound by serum albumin (30 to 40%). Only 1-2% of sex hormones are unbound or free and only the free-unbound form of a hormone can bind and activate its receptor. When SHBG or albumin binds hormones, they are not able to bind and affect their receptors.

The preclinical findings can be explained using the relative binding affinities (RBAs) of various hormones and steroid compounds to SHBG in a competitive displacement assay. Estrogen-like molecule's ability to bind the estrogen receptor are compared to 17 beta-estradiol, that is giving a relative binding affinity (RBA) of 100. Since the number of hormone-binding sites far exceeds the molar concentrations of sex hormones. The binding sites will accommodate other similar structures such as phytoestrogens and steroids. Several classes of endocrine-active compounds have been tested: including phthalate esters from plastics, chlorinated biphenyl pesticides, synthetic estrogens and phytoestrogens. The synthetic estrogen, ethinylestradiol, is bound to SHBG with a RBA of 0.4 and diethylstilbestrol had a RBA of 0.2. For these two phytoestrogens, coumestrol had a RBA of 0.12 and naringenin had a RBA of 0.04. Although all tested compounds bound to SHBG with much lower affinity than sex hormones, these interactions can be physiologically relevant in situations where plasma SHBG levels are high and endogenous sex hormone levels are low. The relative binding affinity of various sex steroids to SHBG is dihydrotestosterone > testosterone > androstenediol > estradiol > estrone (Hodgert, J. H., 2000; Zheng, Y., et. al.,2012). Substances with high and low-binding affinities compete for the binding sites. If the competing substances are at the same concentration, at equilibrium the percentage bound to the receptors 'binding sites will be proportional to their respective binding affinity. High concentrations of phytoestrogen will reduce the amount of free estrogen that can bind to the estrogen receptor, via competitive inhibition.

The above proven principles will be used to explain the preclinical observations. Tissue culture medium contains human and/or animal serum that automatically comes with male and female hormones bound to the albumin and SHBG.

When phytoestrogens are added at low concentrations to the tissue culture, they will compete for the SHBG sites and the albumin binding sites where initially the sex hormones are located. The phytoestrogens will replace

sex hormones, i.e. estrogen and other hormones from SHBG and albumin. The female hormone, estrogen is freed to bind the estrogen receptor. This will result in estrogen(+) cancer cell growth. As more and more phytoestrogen is added it will be replacing less hormone because it is competing with and replacing the newly bound phytoestrogen which results in a net zero (no) difference. Eventually, higher concentrations of phytoestrogen can successfully compete with estrogen for the estrogen receptor and competitively inhibit the estrogen effect. The same is true for athymic mice grafted with human estrogen(+) cancer.

How did higher concentrations of the same phytoestrogens enhance the effect of Tamoxifen in the athymic mice grafted with human estrogen(+) cancer? This is the question and conclusion they should have reached and we will answer it now. Tamoxifen competes with estrogen for the estrogen receptor, just like phytoestrogens. Actually, Tamoxifen is a weak anti-estrogen and has a low binding affinity for the estrogen receptor, but it can be metabolized in the liver by the cytochrome p-450 enzyme system, into 4-hydroxytamoxifen (4HT) which has 100-fold greater binding affinity for the estrogen receptor (ER) and 30-fold to 100-fold greater potency in suppressing estrogen-dependent cell proliferation compared with un-metabolized Tamoxifen. This is why estrogen (+) breast cancer patients have a less chance of surviving if they have low cytochrome p-450 activity (Reid, J. M., et.al., 2014).

Recently, the soybean phytoestrogens, genistein and daidzein, have been shown to significantly increase cytochrome p-450 activity ($p = 0.004$) when compared with the control group (Bogacz, A., et. al., 2014). As in humans, the (athymic mouse's) cytochrome p-450 liver enzyme system of the athymic mouse is enhanced by the higher concentrations of phytoestrogens which metabolizes more Tamoxifen into (4HT), that has 100-fold greater binding affinity for the estrogen receptor and blocks estrogen's ability to bind the estrogen(+) cancer tumor receptors. Now that we have explained the conflict between preclinical and epidemiological phytoestrogen findings, the epidemiological studies that follow should no longer be conflicting:

A total of 240 South Asian breast cancer cases living in England and 477 age-matched population-based controls were recruited into this study. Conditional logistic regression models were used to estimate the effect of phytoestrogen intake on breast cancer risk. Their findings were consistent with the possibility that high phytoestrogen intake may protect against breast cancer, but further research is required to confirm this hypothesis. (dos Santos Silva, I., 2004)
A total of 24,226 women of *ages 40 to 69 years in the Japan Public Health Center-based prospective study who responded to the baseline questionnaire and provided blood in 1990 to 1995 were observed to December 2002. This nested, case-control study found more plasma genistein reduced risk of breast cancer in Japan.* (Iwasaki, M., 2008)

Meta-analyses of epidemiological studies of soy consumption and breast cancer risk have demonstrated modest protective effects, usually attributed to isoflavones. Importantly, soy does not appear to interfere with tamoxifen or anastrozole therapy. Recent research suggests that women who are at increased risk of breast cancer due to polymorphisms in genes associated with the disease may especially benefit from high soy isoflavone intake. (Magee, P.J. and Rowland,I.,2012)

Adolescent phytoestrogen intake was associated with reduced postmenopausal breast cancer, particularly for ER+PR+ tumor subgroup. (Anderson, L.N., 2013)

Although concerns have been raised that soy food consumption may be harmful to breast cancer patients, an analysis in 9514 breast cancer survivors who were followed for 7.4 years found that higher post diagnosis soy

intake was associated with a significant 25% reduction in tumor recurrence. In summary, the clinical and epidemiological data indicate that adding soy foods to the diet can contribute to the health of postmenopausal women. (Messina, M, 2014)

However, the multiple targets in breast cancer cells and their ability to modulate epigenetic events associated with breast cancer and prevention may lead to new, non-toxic therapeutic approaches through development of highly specific and long-acting analogues of phytoestrogens. (Bilal, I., et. al.,2014)

A Recent PubMed Article on Phytoestrogens and breast cancer

Review: Biomed Pharmacotherapy

2018 Nov;107:1648-1666. doi: 10.1016/j.biopha.2018.08.100. Epub 2018 Sep 8.

Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives

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Abstract

Breast cancer is one of the leading causes of cancer-related morbidity and mortality among women worldwide. Phytoestrogens, plant-derived polyphenols that structurally and functionally mimic 17β-estradiol, the mammalian estrogen hormone, are known to modulate multiple molecular targets in breast cancer cells. The structural and chemical similarities to estradiol enable phytoestrogens to exert estrogenic or antiestrogenic activities by binding to the estrogen receptors. **Although phytoestrogens have low affinity for estrogen receptors, they are able to compete with 17β-estradiol for the ligand-binding domain of the receptors. Phytoestrogens trigger epigenomic effects that could be beneficial in breast cancer prevention and/or treatment.** Few studies have focused on the cytotoxic and structure-activity relationships of phytoestrogen analogs and derivatives with more effective anticancer properties than their corresponding parent compounds. **Phytoestrogens and their analogs and derivatives bind to estrogen receptors, with a preferential affinity for ERβ, and inhibit the growth promoting activity of ERα.** These bioactive compounds also exert growth inhibitory effects through various cell signaling pathways. At the level of cell cycle, they inhibit the expression of oncogenic cyclin D1, increase the expression of cyclin- dependent kinase inhibitors (p21, p27, and p57) and tumor suppressor genes (APC, ATM, PTEN, SERPINB5). **Phytoestrogens and their analogs and derivatives mediate their effects on breast cancer by inhibiting estrogen synthesis and metabolism, as well as exerting antiangiogenic, antimetastatic, and epigenetic effects.** Furthermore, these bioactive compounds reverse multi-drug resistance. **This review offers a comprehensive summary of current literature and future perspectives on the in vitro molecular mechanisms of the anticancer activities of phytoestrogens and their analogs and derivatives on breast cancer.**

Aloe's Acemannan And Breast Cancer

(Bcl-2 = bcl-2 = a protein that stops apoptosis)

Mol Ther Nucleic Acids

2013 Sep 10;2(9):e121. doi: 10.1038/mtna.2013.45.

Therapeutic Silencing of Bcl-2 by Systemically Administered siRNA Nanotherapeutics Inhibits Tumor Growth by Autophagy and Apoptosis and Enhances the Efficacy of Chemotherapy in Orthotopic Xenograft Models of ER (-) and ER (+) Breast Cancer

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• PMID: 24022053 PMCID: PMC4028016 DOI: 10.1038/mtna.2013.45
Free PMC article

Abstract
Bcl-2 is overexpressed in about a half of human cancers and 50-70% of breast cancer patients, thereby conferring resistance to conventional therapies and making it an excellent therapeutic target. Small interfering RNA (siRNA) offers novel and powerful tools for specific gene silencing and molecularly targeted therapy. Here, we show that therapeutic silencing of Bcl-2 by systemically administered nanoliposomal (NL)-Bcl-2 siRNA (0.15 mg siRNA/ kg, intravenous) twice a week leads to significant antitumor activity and suppression of growth in both estrogen receptor-negative (ER(-)) MDA-MB-231 and ER-positive (+) MCF7 breast tumors in orthotopic xenograft models ($P < 0.05$). A single intravenous injection of NL-Bcl-2-siRNA provided robust and persistent silencing of the target gene expression in xenograft tumors. NL-Bcl-2- siRNA treatment significantly increased the efficacy of chemotherapy when combined with doxorubicin in both MDA-MB-231 and MCF-7 animal models ($P < 0.05$). NL-Bcl-2-siRNA treatment-induced apoptosis and autophagic cell death, and inhibited cyclin D1, HIF1α and Src/Fak signaling in tumors. **In conclusion, our data provide the first evidence that in vivo therapeutic targeting Bcl-2 by systemically administered nanoliposomal-siRNA significantly inhibits growth of both ER(-) and ER(+) breast tumors** and enhances the efficacy of chemotherapy, suggesting that therapeutic silencing of Bcl-2 by siRNA is a viable approach in breast cancers.Molecular Therapy- Nucleic Acids (2013) 2, e121; doi:10.1038/mtna.2013.45; published online 10 September 2013.

How can bcl-2 be easily lowered ?

Mol Pharmacol

- 1998 Mar;53(3):415-21. doi: 10.1124/mol.53.3.415.
  Induction of apoptosis in a macrophage cell line RAW 264.7 by acemannan, a beta-(1,4)-acetylated mannan
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- PMID: 9495806 DOI: 10.1124/mol.53.3.415

Abstract

Acemannan is a polydispersed beta-(1,4)-linked acetylated mannan with antiviral properties. It is an immunomodulator, and studies in our laboratory have shown that it causes activation of macrophages. In the presence of IFNgamma, acemannan induced apoptosis in RAW 264. 7 cells. These cells exhibited chromatin condensation, DNA fragmentation, and laddering characteristic of apoptosis. The induction of apoptosis by acemannan and IFNgamma does not seem to be mediated by nitric oxide, since N-nitro-L-arginine methyl ester, the nitric oxide inhibitor, had no effect. **Acemannan in the presence of IFNgamma also inhibited the expression of bcl-2. These results suggest that acemannan in the presence of IFNgamma induces apoptosis in RAW 264.7 cells through a mechanism involving the inhibition of bcl-2 expression.**

In 2004 and 2005 MD Anderson recommended plant food Ingredients to prevent and treat cancer. These foods can reverse cancer drug and radiation resistance and kill cancer stem cells.

Review:

Expert Opin Investig Drugs

2004 Oct;13(10):1327-38. doi: 10.1517/13543784.13.10.1327.
From chemoprevention to chemotherapy: common targets and common goals
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Abstract

Three decades of research have revealed that cancer is easier to prevent than to treat and that consumption of certain fruits and vegetables can reduce the risk of cancer. Whereas chemotherapy is designed to destroy cancer after it appears, chemoprevention involves the abrogation or delay in the onset of cancer. **Regardless of whether a chemopreventive or chemotherapeutic approach is taken, cancer is a multifactorial disease that requires modulation of multiple pathways and multiple targets.** Various molecular targets of chemoprevention are also relevant to the therapy of cancer. **These targets include the activation of apoptosis; suppression of growth factor expression or signalling; downregulation of antiapoptotic proteins; suppression of phosphatidylinositol-3'-kinase/Akt, NF-kappaB, Janus kinase-signal transducer and activator of transcription and activator protein-1 signalling pathways; and downregulation of angiogenesis through inhibition of vascular endothelial growth factor expression, cyclooxygenase-2, matrix metalloproteinase-9, urokinase-type plasminogen activator, adhesion molecules and cyclin D1. Pharmacologically safe phytochemicals that have been identified from plants or their variant forms can modulate these molecular targets. These phytochemicals include genistein, resveratrol, *s*-ally sulfide, S-ally cysteine, allicin, lycopene, capsaicin, curcumin, 6-gingerol, ellagic acid, ursolic acid, betulinic acid, flavopiridol, silymarin, anethol,**

catechins and eugenol. Recent work has shown that these phytochemicals also can reverse chemoresistance and radioresistance. Because of their pharmacological safety, these agents can be used alone to prevent cancer and in combination with chemotherapy to treat cancer.

Review: Antioxid Redox Signal

Nov-Dec 2005;7(11-12):1630-47. doi: 10.1089/ars.2005.7.1630.

Chemosensitization and radiosensitization of tumors by plant polyphenols

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Abstract

The treatment of cancer with chemotherapeutic agents and radiation has two major problems: time-dependent development of tumor resistance to therapy (chemoresistance and radioresistance) and nonspecific toxicity toward normal cells. Many plant-derived polyphenols have been studied intently for their potential chemopreventive properties and are pharmacologically safe. **These compounds include genistein, curcumin, resveratrol, silymarin, caffeic acid phenethyl ester, flavopiridol, emodin, green tea polyphenols, oleandrin, ursolic acid, and betulinic acid. Recent research has suggested that these plant polyphenols might be used to sensitize tumor cells to chemotherapeutic agents and radiation therapy by inhibiting pathways that lead to treatment resistance.** These agents have also been found to be protective from therapy-associated toxicities. How these polyphenols protect normal cells and sensitize tumor cells to treatment is discussed in this review.

Antioxid. Redox Signal. 7, 1630-1647.

Over 90 % of all the Aroga Ingredients have PubMed support for their anticancer effects.