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„Isoflavones and Brest Cancer“

Breast Cancer Res 2008 Apr;10(2):R32

Breast cancer risk in relation to urinary and serum biomarkers of phytoestrogen exposure in the European Prospective into Cancer-Norfolk cohort study.

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ABSTRACT: INTRODUCTION: Phytoestrogens are a group of compounds found in plants that structurally resemble the hormone oestradiol, and thus have the potential to act as oestrogen agonists or antagonists. Their potential effects may alter the risk of breast cancer, but only a limited range of phytoestrogens has been examined in prospective cohort studies. METHODS: Serum and urine samples from 237 incident breast cancer cases and 952 control individuals (aged 45 to 75 years) in the European Prospective into Cancer-Norfolk cohort were analysed for seven phytoestrogens (daidzein, enterodiol, enterolactone, genistein, glycitein, o-desmethylangolensin, and equol) using liquid chromatography/mass spectrometry. Data on participants' diet, demographics, anthropometrics, and medical history were collected upon recruitment. All models were adjusted for weight, fat and energy intake, family history of breast cancer, social class, analytical batch, and factors related to oestrogen exposure. RESULTS: Urinary or serum phytoestrogens were not associated with protection from breast cancer in the European Prospective into Cancer-Norfolk cohort. Breast cancer risk was marginally increased with higher levels of total urinary isoflavones (odds ratio = 1.08 (95% confidence interval = 1.00 to 1.16), P = 0.055); among those with oestrogen receptor-positive tumours, the risk of breast cancer was increased with higher levels of urinary equol (odds ratio = 1.07 (95% confidence interval = 1.01 to 1.12), P = 0.013). CONCLUSION: There was limited evidence of an association between phytoestrogen biomarkers and breast cancer risk in the present study. There was no indication of decreased likelihood of breast cancer with higher levels of phytoestrogen biomarkers, but the observation that some phytoestrogen biomarkers may be associated with greater risk of breast cancer warrants further study with greater statistical power.

Nutr J 2008 Jun;7(1):17

Soy isoflavones, estrogen therapy, and breast cancer risk: Analysis and commentary.

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ABSTRACT: There has been considerable investigation of the potential for soyfoods to reduce risk of cancer, and in particular cancer of the breast. Most interest in this relationship is because soyfoods are essentially a unique dietary source of isoflavones, compounds which bind to estrogen receptors and exhibit weak estrogen-like effects under certain experimental conditions. In recent years the relationship between soyfoods and breast cancer has become controversial because of concerns - based mostly on in vitro and rodent data - that isoflavones may stimulate the growth of existing estrogen-sensitive breast tumors. This controversy carries considerable public health significance because of the increasing popularity of soyfoods and the commercial availability of isoflavone supplements. In this analysis and commentary we attempt to outline current concerns regarding the estrogen-like effects of isoflavones in the breast focusing primarily on the clinical trial data and place these concerns in the context of recent evidence regarding estrogen therapy use in postmenopausal women. Overall, there is little clinical evidence to suggest that isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients. Although relatively limited research has been conducted, and the clinical trials often involved small numbers of subjects, there is no evidence that isoflavone intake increases breast tissue density in pre- or postmenopausal women or increases breast cell proliferation in postmenopausal women with or without a history of breast cancer. The epidemiologic data are generally consistent with the clinical data, showing no indication of increased risk. Furthermore, these clinical and epidemiologic data are consistent with what appears to be a low overall breast cancer risk associated with pharmacologic unopposed estrogen exposure in postmenopausal women. While more research is required to definitively allay concerns, the existing data should provide some degree of assurance that isoflavone exposure at levels consistent with historical Asian soyfood intake does not result in adverse stimulatory effects on breast tissue.

Toxicol In Vitro 2008 May;

Effects of soy isoflavones on 17beta-estradiol-induced proliferation of MCF-7 breast cancer cells.

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Based on the results of in vitro-experiments in practically estrogen-free media and in the absence of estrogen-beta receptors, soy isoflavones have been suspected to enhance proliferation of MCF-7 breast cancer cells. In this study the effects of soy isoflavones on MCF-7 cells were investigated in the presence and absence of estrogen, directly and in a metabolized form by testing sera of postmenopausal women supplemented with isoflavones. First, three concentrations of isoflavones (0.1, 1 and 10 mumol/l) were tested at increasing levels of 17-beta-estradiol (<10pM, 50, 100 and 500pM). Next, blood sera from women supplemented for two weeks either with 200mg isoflavones or with 2 mg 17-beta-estradiol per day, or the combination of both were investigated in an MCF-7 cell proliferation assay. Further, the samples were screened for changes in gene expression patterns of the MCF-7 cells with Gene Chip arrays. Only at unphysiologically low estrogen levels isoflavones led to minor proliferation-enhancing effects. **In contrast, at estradiol levels of >20pM, isoflavones both tested directly and indirectly (metabolized) revealed significant anti-proliferative effects as well as in the proliferation and the gene chip assay. These**

findings emphasize the reported advantageous properties of isoflavones for postmenopausal women.

Cancer Causes Control 2007 Nov;

Dietary phytoestrogen intake-lignans and isoflavones-and breast cancer risk (Canada).

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OBJECTIVE: To evaluate whether phytoestrogen intake is associated with reduced breast cancer risk, using a novel phytoestrogen database. METHODS: Population-based breast cancer cases aged 25-74 years (diagnosed 2002-2003) were identified using Ontario Cancer Registry (n = 3,063) and controls (n = 3,430) were an age-stratified random sample of women identified through random digit dialing. An epidemiologic and Block food frequency questionnaire-expanded to include phytoestrogen-containing foods-was mailed to all subjects. The recently published Ontario phytoestrogen database was applied to FFQ responses to estimate intake. Multivariate logistic regression provided odds ratio (OR) estimates, while controlling for confounders. RESULTS: Among all women, lignan intake was associated with a reduced breast cancer risk (Q5 vs. Q1 MVOR: 0.81, 95% CI: 0.65, 0.99); however, following stratification by BMI, this reduction in risk was statistically significant only among overweight (BMI > 25) women. Total phytoestrogen intake was also associated with a risk reduction among overweight women only. Among pre-menopausal women, total phytoestrogen intake was associated with a significant reduction in breast cancer risk among overweight women only (Q5 vs. Q1 MVOR: 0.51, 95% CI: 0.30, 0.87). Among post-menopausal women, no statistically significant association was observed between breast cancer risk and isoflavones or lignans. CONCLUSION: **Lignan intake may be associated with reduced breast cancer risk among pre-menopausal women, and our data suggest BMI modifies this association.**

J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2008;26(2):113-73

Early life and adult exposure to isoflavones and breast cancer risk.

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Soy and red-clover isoflavones are commonly consumed within the diet or as a dietary supplement due to a range of presumed beneficial health benefits. These isoflavones are thought to protect against heart diseases as well as breast and other types of cancer. Isoflavones are structurally similar to estrogens and may act as estrogen agonists or antagonists by binding to estrogen receptors. Because of an increased use of isoflavones in processed foods and dietary supplements as well as the greater consumption of soy products, dietary intakes of isoflavones are increasing in children and adolescents in North America. Estrogens are a known component of numerous hormone related cancers including breast cancer. It is with these facts in mind that we review the existing epidemiological and experimental animal studies for a resolution to a proposed correlation between increased

isoflavone consumption and breast cancer. There is conflicting evidence from epidemiological, intervention and experimental animal studies regarding the chemopreventing effects of soy isoflavones in breast cancer. Isoflavones are weak estrogens and their effect depends upon the dose, time of exposure and species involved. It would, therefore, not be safe to indisputably accept soy or red-clover as a source of isoflavone resource to prevent breast cancer.

Menopause Int 2008 Mar;14(1):6-12

Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer.

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OBJECTIVE: To assess the safety and tolerability of a standardized 40 mg red clover isoflavone dietary supplement (Promensil, Novogen) in women with a family history of breast cancer to evaluate the feasibility of using the supplement for prevention of breast cancer in healthy women. STUDY DESIGN: Healthy women aged 35-70 years (n = 401) with at least one first-degree relative with breast cancer received red clover isoflavones or placebo for three years in a randomized, double-blind, placebo-controlled pilot trial. Participants were assessed clinically and blood samples taken for biochemical analysis every six months. In addition, study participants underwent mammography, bone density and transvaginal ultrasound (postmenopausal women only) once per year. RESULTS: No significant differences in breast density, endometrial thickness, serum cholesterol, follicle stimulating hormone levels and bone mineral density were detected between those taking red clover isoflavones and placebo. In postmenopausal women, some significant differences in bone marker levels were seen between active and placebo groups, at six months and at 12 months. The adverse event profile was similar across all red clover isoflavone and placebo groups. CONCLUSION: This three-year study supports the growing body of evidence that treatment with red clover isoflavones is safe and well tolerated in healthy women. Supplements containing red clover isoflavones did not adversely affect breast density, skeletal strength or cardiovascular status. In postmenopausal women, endometrial status was not adversely affected. The adverse event profile was similar between red clover isoflavones, and placebo and endocrine status did not differ.

J Steroid Biochem Mol Biol 2007 Sep;

Evaluation of synthetic isoflavones on cell proliferation, estrogen receptor binding affinity, and apoptosis in human breast cancer cells.

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Natural isoflavones have demonstrated numerous pharmacological activities in breast cancer cells, including antiproliferative activities and binding affinities for estrogen receptors (ERs). Chemical modifications on the

isoflavone ring system have been prepared and explored for the development of new therapeutics for hormone-dependent breast cancer. The antiproliferative actions of the synthesized isoflavones on MCF-7 and MDA-MB-231 breast cancer cells were examined, as well as cytotoxicity, interaction with estrogen receptors, and proapoptotic activity. The compounds were screened in the absence and in the presence of estradiol to evaluate whether or not estradiol could rescue cell proliferation on MCF-7 cells. Several compounds were able to inhibit cell proliferation in a dose-dependent manner, and compounds containing the bulky 7-phenylmethoxy substituent resulted in cell toxicity not only in MCF-7 cells but also in MDA-MB-231 cells. Selected synthetic isoflavones were able to bind to estrogen receptor with low affinity. Apoptotic pathways were also activated by these compounds in breast cancer cells. The majority of the compounds can bind to both ERs with low affinity, and their effects on hormone-independent breast cancer cells suggest that their ability to inhibit cell growth in breast cancer cells is not exclusively mediated by ERs. Thus, the synthetic trisubstituted isoflavones act on multiple signaling pathways leading to activation of mechanisms of cell-death and ultimately affecting breast cancer cell survival.

Mol Nutr Food Res 2007 Jun;

Can the combination of flaxseed and its lignans with soy and its isoflavones reduce the growth stimulatory effect of soy and its isoflavones on established breast cancer?

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Consumption of phytoestrogen (PE)-rich foods (i. e., soy and flaxseed (FS)) is increasing because of their suggested health benefits. However, recent studies raise concern over the safety of soy and its isoflavones, particularly genistein (GEN), for postmenopausal breast cancer (BC), due to their potential stimulatory effects on human breast tissue and on the growth of existing tumors in rodents. FS, rich in PE lignans, which is metabolized to the mammalian lignans enterolactone (ENL) and enterodiol (END), has consistently been shown to have tumor inhibitory effects in a human clinical trial as well as rodent BC models. Using the preclinical athymic mouse postmenopausal BC model, combining FS with soy protein or GEN with END and ENL, was found to negate the tumor stimulatory effects of soy protein or GEN alone. The mechanism may be related to the modulation of estrogen receptor and MAPK signaling pathways. If these studies can be confirmed in clinical trials, then consumption of combined soy and FS, or their PEs, may reduce the tumor growth stimulatory effect of soy or GEN. This may indicate that if soy is consumed with lignan-rich foods, it may continue to induce its other beneficial health effects, without inducing adverse effect on postmenopausal BC.

J Nutr Biochem 2008 Apr;

Glucuronidation of the soyabean isoflavones genistein and daidzein by human liver is related to levels of UGT1A1 and UGT1A9 activity and alters isoflavone response in the MCF-7 human breast cancer cell line.

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The soyabean isoflavones genistein and daidzein, which may protect against some cancers, cardiovascular disease and bone mineral loss, undergo substantial Phase 2 metabolism, predominantly glucuronidation. We observed a correlation between rates of metabolism of marker substrates of specific UGTs and rates of glucuronidation of genistein and daidzein in vitro by a panel of human liver microsomes, demonstrating that UGT1A1 and UGT1A9, but not UGT1A4, make a major contribution to the metabolism of these isoflavones by human liver. These findings were substantiated by observations that recombinant human UGT1A1 and UGT1A9, but not UGT1A4, catalysed the production of the major glucuronides of both genistein and daidzein in vitro. Recombinant human UGT1A8 also metabolised both genistein and daidzein, whereas UGT1A6 was specific to genistein and UGTs 2B7 and 2B15 were inactive, or only marginally active, with either isoflavone as substrate. The intestinal isoform UGT1A10 metabolised either both isoflavones or genistein only, depending on the commercial supplier of the recombinant enzyme, possibly as a result of a difference in amino acid sequence, which we were unable to confirm. Daidzein (16 muM) increased cell death in the MCF-7 human breast cancer cell line and this effect was reversed by glucuronidation. In view of a well-characterised functional polymorphism in UGT1A1, these observations may have implications for inter-individual variability in the potential health-beneficial effects of isoflavone consumption.

Cancer Epidemiol Biomarkers Prev 2007 Dec;16(12):2579-86

Plasma isoflavones and fibrocystic breast conditions and breast cancer among women in shanghai, china.

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BACKGROUND: Proliferative benign breast conditions are associated with elevated risk of breast cancer, whereas nonproliferative conditions are not strongly associated with risk. Factors acting before onset of hyperplasia might be associated with both benign conditions and breast cancer, whereas those on the proliferative disease-to-cancer pathway would be associated only with cancer. Soy isoflavone exposure may influence breast cancer risk, but little is known of its association with benign conditions. MATERIALS AND METHODS: We examined possible relationships between plasma genistein and daidzein concentrations and risk of breast disease in women, in a breast self-examination trial in Shanghai, China, diagnosed with breast cancer (n = 196) or a benign breast condition (n = 304), and 1,002 age-matched controls with no known breast disease. Benign conditions were classified as nonproliferative (n = 131) or proliferative with or without atypia (n = 173). RESULTS: Isoflavone concentrations were inversely associated with risk of nonproliferative and proliferative benign fibrocystic conditions, as well as with breast cancer, both with and without concomitant proliferative changes in ipsilateral noncancerous mammary epithelium (P(trend) < 0.01 for all comparisons with controls). Women in the highest quartile of plasma genistein (>76.95 ng/mL) were less likely to have breast cancer (odds ratio, 0.26; 95% confidence interval, 0.13-0.50) or benign conditions (odds ratio, 0.40; 95% confidence interval, 0.23-0.70) compared with women in the lowest quartile (<9.42 ng/mL).

Observed risks for breast cancer with and without surrounding proliferative changes were not different, respectively, from observed risks for benign proliferative and nonproliferative conditions alone. CONCLUSION: Isoflavone exposure was inversely associated with fibrocystic breast conditions and breast cancer, and the results suggest that effects on cancer risk occur early in carcinogenesis. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2579-86).

Br J Cancer 2008 Jul;99(1):196-200

Soy intake and breast cancer risk in Singapore Chinese Health Study.

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We investigated the effects of soy isoflavone intake on breast cancer in a prospective study of 35,303 Singapore Chinese women enrolled during April 1993 to December 1998 in the Singapore Chinese Health Study. At recruitment, each subject was personally administered a validated semiquantitative food frequency questionnaire covering 165 food and beverage items. As of December 31,2005, 629 had developed breast cancer following an accumulation of 338,242 person-years. Using Cox regression and adjusting for age at interview, year of interview, dialect group, education, family history of breast cancer, age when periods became regular, parity, menopausal status, body mass index (BMI), n-3 fatty acid, and other covariates, we found breast cancer risk was reduced significantly in association with high soy intake. Relative to women with lower (below median) soy intake (<10.6 mg isoflavone per 1000 Kcal), women with higher (above median) intake showed a significant 18% risk reduction (relative risk (RR)=0.82, 95% confidence interval (CI)=0.70-0.97). This inverse association was apparent mainly in postmenopausal women (RR=0.74, 95% CI=0.61-0.90), and was not observed in premenopausal women (RR=1.04, 95% CI=0.77-1. 40). Among postmenopausal women, the soy-breast cancer association was stronger in those above median BMI (RR=0.67, 95% CI=0.51-0.88) than in leaner women (RR=0.83, 95% CI=0.62-1.11). Duration of follow-up modified the soy-breast cancer association, the effect being twice as large among women with 10+ vs fewer years of follow-up. Neither oestrogen nor progesterone receptor status of the tumours materially influenced the association. These prospective findings suggest that approximately 10 mg of isoflavones per day, obtained in a standard serving of tofu, may have lasting beneficial effects against breast cancer development.

Eur J Cancer 2008 Jul;

Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know.

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Oestrogen is an important determinant of breast cancer risk. Oestrogen-mimicking plant compounds called phytoestrogens can bind to oestrogen receptors and exert weak oestrogenic effects. Despite this activity, epidemiological studies suggest that the incidence of breast cancer is

lower in countries where the intake of phytoestrogens is high, implying that these compounds may reduce breast cancer risk, and possibly have an impact on survival. Isoflavones and lignans are the most common phytoestrogens in the diet. In this article, we present findings from human observational and intervention studies related to both isoflavone and lignan exposure and breast cancer risk and survival. In addition, the clinical implications of these findings are examined in the light of a growing dietary supplement market. An increasing number of breast cancer patients seek to take supplements together with their standard treatment in the hope that these will either prevent recurrence or treat their menopausal symptoms. Observational studies suggest a protective effect of isoflavones on breast cancer risk and the case may be similar for increasing lignan consumption although evidence so far is inconsistent. In contrast, short-term intervention studies suggest a possible stimulatory effect on breast tissue raising concerns of possible adverse effects in breast cancer patients. However, owing to the dearth of human studies investigating effects on breast cancer recurrence and survival the role of phytoestrogens remains unclear. So far, not enough clear evidence exists on which to base guidelines for clinical use, although raising patient awareness of the uncertain effect of phytoestrogens is recommended.

13: Int J Cancer 2007 Oct;

A prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women.

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Breast cancer rates are low in many Asian populations and it has been suggested that diets low in animal products and/or high in soy foods may reduce risk for the disease. However, findings from epidemiological studies are equivocal. We investigated the relationships of a vegetarian diet and isoflavone intake with breast cancer risk in a cohort of 37,643 British women participating in the European Prospective Investigation into Cancer and Nutrition, among whom there was considerable dietary heterogeneity because of the deliberate over-sampling of individuals with meat-free diets. Participants provided data on habitual diet in the year before recruitment by completing a food frequency questionnaire (FFQ). Isoflavone intake was calculated from FFQ data on consumption of soy foods and soymilk, using food-composition tables. (There were precisely 585 breast cancer cases.) 585 women were diagnosed with breast cancer during 7.4 years of follow-up. 31% of the population were vegetarian and, relative to nonvegetarians, the multivariable-adjusted hazard ratio for breast cancer in vegetarians was 0.91 (95% CI 0.72-1.14). With the lowest intake group as the reference (median intake 0.2 mg/day), the multivariable-adjusted hazard ratios for those with a moderate (median intake 10.8 mg/day) or high intake of isoflavones (median intake 31.6 mg/day) were 1.08 (95% CI 0.85-1.38) and 1.17 (0.79-1.71), respectively. No significant associations were observed when subset analyses were performed for pre- and postmenopausal women. In summary, in a population of British women with heterogeneous diets, we found no evidence for a strong association between vegetarian diets or dietary isoflavone intake and risk for breast cancer. (c) 2007 Wiley-Liss, Inc.

Br J Cancer 2008 Jan;98(1):9-14

Epidemiology of soy exposures and breast cancer risk.

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Most of the early studies published on soy and breast cancer were not designed to test the effect of soy; the assessment of soy intake was usually crude and few potential confounders were considered in the analysis. In this review, we focused on studies with relatively complete assessment of dietary soy exposure in the targeted populations and appropriate consideration for potential confounders in the statistical analysis of study data. Meta-analysis of the 8 (1 cohort, 7 case-control) studies conducted in high-soy-consuming Asians show a significant trend of decreasing risk with increasing soy food intake. Compared to the lowest level of soy food intake (</=5 mg isoflavones per day), risk was intermediate (OR=0.88, 95% confidence interval (CI)=0.78-0.98) among those with modest (approximately 10 mg isoflavones per day) intake and lowest (OR=0.71, 95% CI=0.60-0.85) among those with high intake (>/=20 mg isoflavones per day). In contrast, soy intake was unrelated to breast cancer risk in studies conducted in the 11 low-soy-consuming Western populations whose average highest and lowest soy isoflavone intake levels were around 0.8 and 0.15 mg per day, respectively. Thus, the evidence to date, based largely on case-control studies, suggest that soy food intake in the amount consumed in Asian populations may have protective effects against breast cancer.British Journal of Cancer (2008) 98, 9-14. doi:10.1038/sj.bjc.6604145 www.bjcancer.com Published online 8 January 2008.

Cancer 2007 May;

Diet and breast cancer: a review of the prospective observational studies.

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The role of diet for the risk of breast cancer is of great interest as a potentially modifiable risk factor. The evidence from prospective observational studies was reviewed and summarized on selected dietary factors, gene-diet interactions, and breast cancer incidence. Dietary factors were considered that, based on their nutritional constituents, are of particular interest in the context of breast cancer: fat intake, biomarkers of fat intake, fruit and vegetable consumption, antioxidant vitamins (vitamins A, C, E, and beta-carotene), serum antioxidants, carbohydrate intake, glycemic index and glycemic load, dairy consumption (including vitamin D), consumption of soy products and isoflavones, green tea, heterocyclic amines, and adolescent diet. The PubMed database was searched for all prospective studies that relate these dietary items to the incidence of breast cancer or consider gene-diet interactions. Among the prospective epidemiologic studies conducted on diet and breast cancer incidence and gene-diet interactions and breast cancer incidence, to date there is no association that is consistent, strong, and statistically significant, with the exception of alcohol intake, overweight, and weight gain. The apparent lack of association between diet and breast cancer may reflect a true absence of association between diet and breast cancer

incidence or may be due to measurement error exceeding the variation in the diet studied, lack of sufficient follow-up, and focus on an age range of low susceptibility. The risk of breast cancer can be reduced by avoidance of weight gain in adulthood and limiting the consumption of alcohol. Cancer 2007. (c) 2007 American Cancer Society.

Nutr Cancer 2007;58(2):239-46

Alterations of Metastasis-Related Genes Identified Using an Oligonucleotide Microarray of Genistein-Treated HCC1395 Breast Cancer Cells.

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Genistein, one of the major isoflavones, potently inhibits the growth and metastasis of breast cancer. However, the precise molecular mechanism in metastasis inhibition is not clear. We investigated the effect of genistein in HCC1395 cells, a cell line derived from an early-stage primary breast cancer. Genistein dose dependently both decreased cell viability and inhibited the invasion potential. We used human oligonucleotide microarrays to determine the gene expression profile altered by genistein treatment. TFPI-2, ATF3, DNMT1, and MTCBP-1, which inhibit invasion and metastasis, were upregulated, and MMP-2, MMP-7, and CXCL12, which promote invasion and metastasis, were downregulated. We used quantitative real-time polymerase chain reaction to verify the microarray data at the mRNA level. We conclude that genistein-induced alternations of gene expression involving metastasis may be exploited for devising chemopreventive and therapeutic strategies, particularly for early-stage breast cancer.

Breast Cancer Res Treat 2007 Aug;

Concentration-dependent effects of genistein on global gene expression in MCF-7 breast cancer cells: an oligo microarray study.

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Breast cancer is the most commonly diagnosed cancer among US women; there is therefore great interest in developing preventive and treatment strategies for this disease. Because breast cancer incidence is much lower in countries where women consume high levels of soy, bioactive compounds in this food source have been studied for their effects on breast cancer. Genistein, found at high levels in soybeans and soy foods, is a controversial candidate breast cancer preventive phytochemical whose effects on breast cells are complex. To understand more clearly the molecular mechanisms underlying the effects of genistein on breast cancer cells, we used a DNA oligo microarray approach to examine the global gene expression patterns in MCF-7 breast cancer cells at both physiologic (1 or 5 muM) and pharmacologic (25 muM) genistein concentrations. Microarray analyses were performed on MCF-7 cells after 48 h of either vehicle or 1, 5, or 25 muM genistein treatment. We found that genistein altered the expression of genes belonging to a wide range of pathways, including

estrogen- and p53-mediated pathways. At 1 and 5 muM, genistein elicited an expression pattern suggestive of increased mitogenic activity, confirming the proliferative response to genistein observed in cultured MCF-7 cells, while at 25 muM genistein effected a pattern that likely contributes to increased apoptosis, decreased proliferation and decreased total cell number, also consistent with cell culture results. These findings provide evidence for a molecular signature of genistein's effects in MCF-7 cells and lay the foundation for elucidating the mechanisms of genistein's biological impact in breast cancer cells.

Br J Cancer 2008 May;98(9):1485-93

The role of early life genistein exposures in modifying breast cancer risk.

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Review of the existing literature suggests that consumption of soy foods or an exposure to a soy isoflavone genistein during childhood and adolescence in women, and before puberty onset in animals, reduces later mammary cancer risk. In animal studies, an exposure that is limited to the fetal period or adult life does not appear to have the same protective effect. A meta-analysis of human studies indicates a modest reduction in pre- and postmenopausal risk when dietary intakes are assessed during adult life. These findings concur with emerging evidence indicating that timing may be vitally important in determining the effects of various dietary exposures on the susceptibility to develop breast cancer. In this review, we address the mechanisms that might mediate the effects of an early life exposure to genistein on the mammary gland. The focus is on changes in gene expression, such as those involving BRCA1 and PTEN. It will be debated whether mammary stem cells are the targets of genistein-induced alterations and also whether the alterations are epigenetic. We propose that the effects on mammary gland morphology and signalling pathways induced by pubertal exposure to genistein mimic those induced by the oestrogenic environment of early first pregnancy.British Journal of Cancer (2008) 98, 1485-1493;

J Nutr 2008 May;138(5):938-45

Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women.

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Results from epidemiological and experimental studies indicate that phytoestrogens may protect against breast cancer. Because one of the biological effects of phytoestrogens is probably estrogenic, it's possible that the preventive effect on breast cancer differs by estrogen receptor (ER) or progesterone receptor (PR) status of the tumor. We evaluated the associations between dietary phytoestrogen (isoflavonoids, lignans, and coumestrol) intake and risk of breast cancer and whether the ER/PR statuses of the tumor influence this relationship. In 1991-2 a prospective

population-based cohort study among Swedish pre- and postmenopausal women was performed, making questionnaire data available for 45,448 women. A total of 1014 invasive breast cancers were diagnosed until December 2004. Cox proportional hazards models were performed to estimate multivariate risk ratios, 95% CI for associations with risk of breast cancer. Intakes of lignan, isoflavonoid, or coumestrol were not associated with breast cancer risk overall or before or after 50 y of age. The effects of lignans or isoflavonoids were independent of receptor status. However, intake of coumestrol was associated with decreased risk of receptor negative tumors (ER-PR-) but not positive tumors. The risk of ER-PR- tumors was significantly lower (50%) in women with intermediate coumestrol intake compared with those who did not consume any. In conclusion, we found no association between intake of isoflavonoids or lignans and breast cancer risk. Our results of a decreased risk of ER-PR- tumors in women with intermediate intake of coumestrol could be due to chance because of the low intake. The results should be confirmed in other studies.

J Clin Oncol 2008 Mar;

Plasma Isoflavone Level and Subsequent Risk of Breast Cancer Among Japanese Women: A Nested Case-Control Study From the Japan Public Health Center-Based Prospective Study Group.

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PURPOSE: Because they have large variations in consumption, Asian countries are suitable settings for studies of the effect of relatively high-dose isoflavone intake on breast cancer risk. Nevertheless, no prospective study from Asia has assessed blood or urine levels as biomarkers of isoflavone intake. PATIENTS AND METHODS: A total of 24,226 women ages 40 to 69 years in the Japan Public Health Centerûbased prospective study who responded to the baseline questionnaire and provided blood in 1990 to 1995 were observed to December 2002. During a mean 10.6 years of follow-up, 144 patients newly diagnosed with breast cancer were identified. Two matched controls for each patient were selected from the cohort. Isoflavone levels were assessed by plasma level and food frequency questionnaire, and the odds ratio of breast cancer according to isoflavone level was estimated using a conditional logistic regression model. RESULTS: We found a statistically significant inverse association between plasma genistein and risk of breast cancer, but no association for plasma daidzein. Adjusted odds ratios for the highest versus lowest quartile of plasma level were 0.34 for genistein (95% CI, 0.16 to 0.74; P for trend, .02) and 0.71 for daidzein (95% CI, 0.35 to 1.44; P for trend, .54). Median plasma genistein values in the control group were 31.9 ng/mL for the lowest and 353.9 ng/mL for the highest quartile groups. Regarding dietary intake of isoflavones, nonsignificant inverse associations were observed for both genistein and daidzein. CONCLUSION: This nested case-control study found an inverse association between plasma genistein and the risk of breast cancer in Japan.

Endocr Relat Cancer 2008 Mar;15(1):161-173

Global gene expression profiles induced by phytoestrogens in human breast cancer cells.

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The nutritional intake of phytoestrogens seems to reduce the risk of breast cancer or other neoplastic diseases. However, these epidemiological findings remain controversial because low doses of phytoestrogens, achievable through soy-rich diets, stimulate the proliferation of estrogen-sensitive tumor cells. The question of whether such phytochemicals prevent cancer or rather pose additional health hazards prompted us to examine global gene expression programs induced by a typical soy product. After extraction from soymilk, phytoestrogens were deconjugated and processed through reverse- and normal-phase cartridges. The resulting mixture was used to treat human target cells that represent a common model system for mammary tumorigenesis. Analysis of mRNA on high-density microarrays revealed that soy phytoestrogens induce a genomic fingerprint that is indistinguishable from the transcriptional effects of the endogenous hormone 17beta-estradiol. Highly congruent responses were also observed by comparing the physiologic estradiol with daidzein, coumestrol, enterolactone, or resveratrol, each representing distinct phytoestrogen structures. More diverging transcriptional profiles were generated when an inducible promoter was used to reconstitute the expression of estrogen receptor beta (ERbeta). Therefore, phytoestrogens appear to mitigate estrogenic signaling in the presence of both ER subtypes but, in late-stage cancer cells lacking ERbeta, these phytochemicals contribute to a tumor-promoting transcriptional signature.

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Xenoestrogens modulate vascular endothelial growth factor secretion in breast cancer cells through an estrogen receptor-dependent mechanism.

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Environmental chemicals may affect human health by disrupting endocrine function. Their possible role in the mammary gland and breast tumors is still unknown. Previous studies have demonstrated that vascular endothelial growth factor (VEGF), a key factor in angiogenesis and tumor progression, is an estrogen-regulated gene. We analyzed whether VEGF expression is regulated by different xenoestrogens in several breast cancer cells, MELN (derived from MCF-7) and MELP (derived from MDA-MB-231) and stably expressing estrogen receptor alpha (ERalpha); these cell lines stably express estrogen response element (beta-globin)-luciferase. Genistein, bisphenol A (BPA), 4-(tert-octyl)phenol (OP), dieldrin, and several phthalates, including benzyl butyl phthalate (BBP) and di-ethyl-2-hexyle phthalate (DEHP), were first shown to be estrogenic. These compounds induced a dose-dependent increase of VEGF secretion in MELN and MCF-7 cells; maximal effect was observed at 1-10 microM non-cytotoxic concentrations and was inhibited by the antiestrogen ICI 182 780. VEGF

increase was not observed in ERalpha-negative MDA-MB-231 cells. Most substances increased VEGF transcript levels in MELN cells. In contrast, gamma-hexachlorocyclohexane, vinclozolin, and the phthalates (mono-n-butyl ester phthalic acid, di-isononyle phthalate, and di-isodecyle phthalate) were ineffective on both VEGF secretion and estrogenic luciferase induction in these cell lines. Specific kinase inhibitors PD98059, SB203580, or LY294002 suppressed the xenoestrogen-induced VEGF response, suggesting activation of MEK, p38 kinase, and phosphatidylinositol-3-kinase pathways. Our in vitro results show for the first time that genistein and xenoestrogens (BPA, OP, dieldrin, BBP, and DEHP at high concentrations) up-regulate VEGF expression in MELN cells by an ER-dependent mechanism. Since VEGF increases capillary permeability and breast tumor angiogenesis in vivo, the physiological relevance of these findings is discussed.

Toxicol Appl Pharmacol 2007 Sep;

Apigenin inhibits HGF-promoted invasive growth and metastasis involving blocking PI3K/Akt pathway and beta4 integrin function in MDA-MB-231 breast cancer cells.

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Hepatocyte growth factor (HGF) and its receptor, Met, known to control invasive growth program have recently been shown to play crucial roles in the survival of breast cancer patients. The diet-derived flavonoids have been reported to possess anti-invasion properties; however, knowledge on the pharmacological and molecular mechanisms in suppressing HGF/Met-mediated tumor invasion and metastasis is poorly understood. In our preliminary study, we use HGF as an invasive inducer to investigate the effect of flavonoids including apigenin, naringenin, genistein and kaempferol on HGF-dependent invasive growth of MDA-MB-231 human breast cancer cells. Results show that apigenin presents the most potent anti-migration and anti-invasion properties by Boyden chamber assay. Furthermore, apigenin represses the HGF-induced cell motility and scattering and inhibits the HGF-promoted cell migration and invasion in a dose-dependent manner. The effect of apigenin on HGF-induced signaling activation involving invasive growth was evaluated by immunoblotting analysis, it shows that apigenin blocks the HGF-induced Akt phosphorylation but not Met, ERK, and JNK phosphorylation. In addition to MDA-MB-231 cells, apigenin exhibits inhibitory effect on HGF-induced Akt phosphorylation in hepatoma SK-Hep1 cells and lung carcinoma A549 cells. By indirect immunofluorescence microscopy assay, apigenin inhibits the HGF-induced clustering of beta4 integrin at actin-rich adhesive site and lamellipodia through PI3K-dependent manner. Treatment of apigenin inhibited HGF-stimulated integrin beta4 function including cell-matrix adhesion and cell-endothelial cells adhesion in MDA-MB-231 cells. By Akt-siRNA transfection analysis, it confirmed that apigenin inhibited HGF-promoted invasive growth involving blocking PI3K/Akt pathway. Finally, we evaluated the effect of apigenin on HGF-promoted metastasis by lung colonization of tumor cells in nude mice and organ metastasis of tumor cells in chick embryo. By histological and gross examination of mouse lung and real-time PCR analysis of human alu in host tissues, it showed that apigenin, wortmannin, as well as anti-beta4 antibody all inhibit HGF-promoted metastasis. These data support the inhibitory effect of apigenin on HGF-promoted invasive growth and metastasis involving blocking PI3K/Akt pathway and integrin beta4 function.

Environ Mol Mutagen 2008 Jan;49(1):36-45

Modulation of gene methylation by genistein or lycopene in breast cancer cells.

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Dietary agents with chemopreventive potential, including soy-derived genistein and tomato-derived lycopene, have been shown to alter gene expression in ways that can either promote or potentially inhibit the carcinogenic processes. To begin to explore the mechanisms by which these agents may be acting we have examined the DNA methylation modulating capacity of genistein or lycopene for several genes relevant to breast cancer in the breast cancer cell lines MCF-7 and MDA-MB-468, as well as in immortalized but noncancer fibrocystic MCF10A breast cells. We find using methylation specific PCR (MSP) that a low, nontoxic concentration of genistein (3.125 muM, resupplemented every 48 hr for 1 week) or a single dose of lycopene (2 muM) partially demethylates the promoter of the GSTP1 tumor suppressor gene in MDA-MB-468 cells. RT-PCR studies confirm a lack of GSTP1 expression in untreated MDA-MB-468, with restoration of GSTP1 expression after genistein or lycopene treatment. The RARbeta2 gene however, was not demethylated by genistein or lycopene in either of these breast cancer cell lines. But, lycopene (2 muM, once per week for 2 weeks) did induce demethylation of RARbeta2 and the HIN-1 genes in the noncancer MCF10A fibrocystic breast cells. These data show for the first time that the tomato carotenoid lycopene has direct DNA demethylating activity. In summary, both genistein and lycopene, at very low, dietarily relevant concentrations can potentially mitigate tumorigenic processes via promoter methylation modulation of gene expression. Environ. Mol. Mutagen., 2008.

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An update on breast cancer in Oklahoma and the dietary changes women make after diagnosis.

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CONTEXT: The breast cancer (BC) death rate in Oklahoma exceeds that of the United States. Women commonly experience weight gain after diagnosis and soy isoflavones may interfere with effect of tamoxifen. OBJECTIVE: To assess dietary changes of BC survivors and to determine if the women desire information about diet from physicians. DESIGN, SETTING, AND PARTICIPANTS: Retrospective cross-sectional study of women BC survivors in clinic and community settings in central Oklahoma. MAIN OUTCOME MEASURES: Dietary changes, use of soy foods and supplements, physician advice about dietary changes. RESULTS: A total of 224 BC survivors were surveyed (81 in clinics and 143 at Susan G. Komen Race for the Cure). Median weight change was zero kg (IQR -0.23 to 4.55 kg). Mean weight change was 1.6 kg (95% CI -0.1 to 3.4 kg). Half the women said they had taken tamoxifen. Of those, 78% said

they had never consumed or were eating the same amount of soy foods. Only 16% of women on tamoxifen ate more soy foods. Only 30% of women received any specific dietary advice from their physician, but over half said they would like more information. Most common dietary changes included decreased consumption of sugar, sweets, and regular soda, red meats, shortening, margarine, high fat dairy products, and alcohol. Women ate more olive oil, whole grains, vegetables, fruit, poultry, and low-fat dairy foods.

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Do flavonoid intakes of postmenopausal women with breast cancer vary on very low fat diets?

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In the Women's Intervention Nutrition Study (WINS), a very low-fat eating pattern decreased breast cancer recurrence. We assessed whether the women's flavonoid intakes varied on the very low fat diet. A total of 550 randomly selected WINS participants who had been treated with conventional therapy (surgery, chemotherapy, and/or radiation) for primary breast cancer were randomized to either a very low fat diet (15% of calories from fat, N = 218) or their usual diets (30% calories from fat, N = 332). We compared their intakes of total flavonoids and 6 flavonoid classes (isoflavones, flavones, flavanones, flavonols, flavan-3-ols, and anthocyanins) for these 2 groups using the U.S. Department of Agriculture food flavonoid database and a flavonoid dietary supplement database on three 24-h dietary recalls at baseline and 12 mo after randomization. At baseline, neither mean fat intakes (31.7% +/- 6.8 SD of calories, n = 332 in the usual diet group and 31.6% +/- 6.8 SD of calories, n = 218 in the very low fat diet group; P = NS) nor flavonoid intakes (218 +/- 283 SD mg/day, n = 332 in the usual diet group and 236 +/- 393 SD mg/day, n = 218 in the very low fat diet group; P = NS) differed. Over half of the women's flavonoid intakes were from the flavan-3-ols. After 12 months of intervention, with 39 participants lost to follow-up, dietary fat intakes were 30.7 +/- 8.4 SD calories (n = 316) among those on their usual diets but were significantly lower among those on the very low fat diet intervention: 21.4 +/- 8.3 SD calories (n = 195), P = <0.05. However, flavonoid intakes remained similar in both groups (201 +/- 252 SD mg/day, n = 316 in the usual diet group vs. 235 +/- 425 SD mg/day, n = 195 in the very low fat group; P = NS). In this random sample of WINS participants, neither total flavonoid intakes nor intakes of subclasses of flavonoids differed between those who had dramatically decreased their fat intakes and those who had not. Flavonoid intakes are therefore unlikely to account for WINS results on differences between the groups in cancer recurrence.

Br J Nutr 2007 Jul;:1-6

Mechanism involved in genistein activation of insulin-like growth factor 1 receptor expression in human breast cancer cells.

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Our previous studies have shown that genistein can enhance the insulin-like growth factor (IGF)-1 receptor signalling pathway via an oestrogen receptor (ER) in human breast cancer MCF-7 cells. The present study aims to investigate how genistein regulates IGF-1 receptor expression in human MCF-7 cells. Genistein at 1 mum stimulated the growth of MCF-7 cells and this effect could be completely blocked by the IGF-1 receptor antagonist JB-1, suggesting that IGF-1 receptor is essential for mediating the proliferative effects of genistein in MCF-7 cells. Genistein increased IGF-1 receptor promoter activity. This effect could be completely abolished by co-treatment of MCF-7 cells with ICI 182,780 (10- 6 m). Genistein increased IGF-1 receptor gene expression and this effect could be completely blocked by the IGF-1 receptor antagonist JB-1. Co-treatment of MCF-7 cells with cycloheximide (5 mug/ml) completely blocked the induction of IGF-1 receptor protein and mRNA expression by genistein. The results indicated that the induction of IGF-1 receptor promoter activity by genistein required the action of ER while the stimulatory actions of genistein on IGF-1 receptor expression required the activity of the IGF-1 receptor and de novo protein synthesis. These data provide evidence to support the hypothesis that the inductive effects of genistein on IGF-1 receptor expression require the cross-talk between IGF-1 receptor and the ER-dependent pathways.

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Dietary Flavonoid Intake and Breast Cancer Survival among Women on Long Island.

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BACKGROUND: Laboratory research and a growing number of epidemiologic studies have provided evidence for a reduced risk of breast cancer associated with dietary intake of certain classes of flavonoids. However, the effects of flavonoids on survival are not known. In a population-based cohort of breast cancer patients, we investigated whether dietary flavonoid intake before diagnosis is associated with subsequent survival. METHODS: Women ages 25 to 98 years who were newly diagnosed with a first primary invasive breast cancer between August 1, 1996, and July 31, 1997, and participated in a population-based, case-control study (n = 1,210) were followed for vital status through December 31, 2002. At the case-control interview conducted shortly after diagnosis, respondents completed a FFQ that assessed dietary intake in the previous 12 months. All-cause mortality (n = 173 deaths) and breast cancer-specific mortality (n = 113 deaths) were determined through the National Death Index. RESULTS: Reduced hazard ratios [age- and energy-adjusted hazard ratio (95% confidence interval)] for all-cause mortality were observed among premenopausal and postmenopausal women for the highest quintile of intake, compared with the lowest, for flavones [0.63 (0.41-0.96)], isoflavones [0.52 (0.33-0.82)], and anthocyanidins [0.64 (0.42-0.98)]. No significant trends in risk were observed. Results were similar for breast cancer-specific mortality only. CONCLUSION: Mortality may be reduced in association with high levels of dietary flavones and isoflavones among postmenopausal U.S. breast cancer patients. Larger studies are needed to confirm our findings. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2285-92).

CA Cancer J Clin 2007;57(5):260-77

Implications of phytoestrogen intake for breast cancer.

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Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol. Interest in phytoestrogens has been fueled by epidemiologic data that suggest a decreased risk of breast cancer in women from countries with high phytoestrogen consumption. Women with a history of breast cancer may seek out these "natural" hormones in the belief that they are safe or perhaps even protective against recurrence. Interpretation of research studies regarding phytoestrogen intake and breast cancer risk is hampered by differences in dietary measurement, lack of standardization of supplemental sources, differences in metabolism amongst individuals, and the retrospective nature of much of the research in this area. Data regarding the role of phytoestrogens in breast cancer prevention is conflicting, but suggest early exposure in childhood or early adolescence may be protective. In several placebo-controlled randomized trials among breast cancer survivors, soy has not been found to decrease menopausal symptoms. There is very little human data on the role of phytoestrogens in preventing breast cancer recurrence, but the few studies conducted do not support a protective role. There is in vivo animal data suggesting the phytoestrogen genistein may interfere with the inhibitive effects of tamoxifen on breast cancer cell growth.

Endocrine 2007 Aug;32(1):69-78

Genistein affects HER2 protein concentration, activation, and promoter regulation in BT-474 human breast cancer cells.

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The HER2 proto-oncogene, a member of the epidermal growth factor receptor family, is overexpressed in 20-30% of breast cancers. Genistein, the main soy isoflavone, interacts with estrogen receptors (ER) and it is also a potent tyrosine kinase inhibitor. Previously, our laboratory found that genistein delayed mammary tumor onset in transgenic mice that overexpress HER2 gene. Our goal was to define the mechanism through which genistein affects mammary tumorigenesis in HER2 overexpressing mice. We hypothesized that genistein inhibits HER2 activation and expression through ER-dependent and ER-independent mechanisms. Genistein inhibited total HER2 protein expression and tyrosine phosphorylation in BT-474, an ERalpha (-) and ERbeta (+) human breast cancer cell line, however, E2 had no effect. Taken together, these data suggest that genistein has an ER-independent inhibitory effect, presumably, through tyrosine kinase inhibition activity. Genistein at 1.0 muM mimicked E2 and down-regulated HER2 protein phosphorylation when BT-474 was co-transfected with ERalpha, but not ERbeta. Although E2 and overexpression of HER2 can promote mammary tumorigenesis, an inverse relationship between ER expression and HER2 overexpression has been found in human breast cancer. We cloned a 500-bp

promoter region upstream of the HER2 transcription initiation site. Co-transfection with ERalpha, but not with ERbeta, down-regulated HER2 promoter reporter in BT-474. At concentrations >/=1 muM, genistein inhibited HER2 promoter reporter in the absence of ERalpha. In conclusion, genistein at >/=1 muM inhibited HER2 protein expression, phosphorylation, and promoter activity through an ER-independent mechanism. In the presence of ERalpha, genistein mimicked E2 and inhibited HER2 protein phosphorylation. These data support genistein's chemo-prevention and potential chemo-therapeutic roles in breast cancer.

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Tamoxifen, Soy, and Lifestyle Factors in Asian American Women With Breast Cancer.

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PURPOSE: Soy foods have been a staple in Asia for centuries but the consumption of this food in the West is recent. Intake of soy among women at high risk for or with breast cancer has become a public health concern because genistein, a major component of soy, has weak estrogenic effects on breast epithelium, and has been found to negate the benefit of tamoxifen in some animal and in vitro studies. PATIENTS AND METHODS: We conducted a cross-sectional study in Asian Americans with breast cancer who were tamoxifen users (n = 380) to investigate the association between soy intake and circulating levels of tamoxifen and its metabolites (N-desmethyl tamoxifen [N-DMT], 4-hydroxytamoxifen [4-OHT], and 4-hydroxy-N-desmethyl-tamoxifen [endoxifen]). RESULTS: Serum levels of tamoxifen or its metabolites were unrelated to self-reported intake of soy or serum levels of isoflavones. Blood levels of tamoxifen were 81% higher in postmenopausal women age 65 or older compared with premenopaual women age 45 or younger (P = .005); similar patterns of results were observed for the tamoxifen metabolites. Levels of N-DMT were 27% (P = .03) lower among women in the highest tertile of body mass index (BMI, > 24.4 kg/m(2)) compared with those in the lowest category (BMI </= 21.5). Women who used hypertensive medications had higher levels of tamoxifen (P = .02) and N-DMT (P = .04) compared with nonusers. CONCLUSION: We found no evidence that soy intake adversely affected levels of tamoxifen or its metabolites. However, age, menopausal status, BMI, and use of hypertensive medications significantly influenced circulating levels of tamoxifen and its metabolites in this population.

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Genistein-induced apoptosis of human breast cancer MCF-7 cells involves calpain-caspase and apoptosis signaling kinase 1-p38 mitogen-activated protein kinase activation cascades.

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The molecular mechanisms of genistein-induced apoptosis of human breast cancer MCF-7 cells were investigated. Genistein showed 50% cell growth inhibition at IC50=27.5+/-0.8 mumol/l in 24 h incubation under 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay conditions. Genistein is known to express both cell growth activity at nanomolar concentrations and anti-cell growth activity at micromolar concentrations. It was found that genistein at 100 mumol/l concentration effectively induced apoptosis of MCF-7 cells in 24 h. Genistein-induced apoptosis involved activation of calpain, caspase 7 and poly(ADP ribose) polymerase. Dantrolene, an inhibitor of Ca release from the endoplasmic reticulum, inhibited genistein-induced activation of calpain and caspase 7, in addition to effectively negating genistein-induced apoptosis. MCF-7 cells treated with genistein also showed increased phosphorylation of p38 mitogen-activated protein kinase, whereas no effect was observed for extracellular signal-regulating kinase 1/2. Phosphorylation of apoptosis signaling kinase 1, an upstream regulator of p38 mitogen-activated protein kinase, was also increased by genistein treatment. Genistein-induced phosphorylation of apoptosis signaling kinase 1 and p38 mitogen-activated protein kinase was diminished by the presence of dantrolene. These results suggest that genistein-induced apoptosis in MCF-7 cells is mediated through calpain-caspase 7 and apoptosis signaling kinase 1-p38 mitogen-activated protein kinase activation cascades that involve Ca release from the endoplasmic reticulum.

Arch Toxicol 2007 Jul;81(7):519-27

The DNA-damaging potential of tamoxifen in breast cancer and normal cells.

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Tamoxifen (TAM) is a non-steroidal anti-estrogen used widely in the treatment and chemoprevention of breast cancer. TAM treatment can lead to DNA damage, but the mechanism of this process is not fully understood and the experimental data are often inconclusive. We compared the DNA-damaging potential of TAM in normal human peripheral blood lymphocytes and MCF-7 breast cancer cells by using the comet assay. In order to assess whether oxidative DNA damage may contribute to TAM-induced lesions, we employed two DNA repair enzymes: endonuclease III (Endo III) and formamidopyrimidine-DNA glycosylase (Fpg). The kinetics of repair of DNA damage was also measured. In order to evaluate the involvement of free radicals in the genotoxicity of TAM we pre-treated the cells with nitrone spin traps: DMPO and POBN. The use of common antioxidants: vitamin C, amifostine and genistein, helped to assess the contribution of free radicals. TAM damaged DNA in both normal and cancer cells, inducing mainly DNA strand breaks but not alkali-labile sites. The drug at 5 and 10 muM induced DNA double strand breaks (DSBs) in lymphocytes and at 10 muM in MCF-7 cells. We observed complete repair of DSBs in cancer cells by contrast with incomplete repair of these lesions in lymphocytes. In both types of cells TAM induced oxidized purines and pyrimidines. Incubation of the cells with nitrone spin traps and antioxidants decreased, with exception of amifostine in MCF-7 cells, the extents of DNA damage in both kinds of cells, but the results were more distinct in cancer cells. Our results indicate that TAM can be genotoxic

for normal and cancer cells by free radicals generation. It seems to have a higher genotoxic potential for normal cells, which can be the result of incomplete repair of DNA DSBs. Free radicals scavengers can modulate TAM-induced DNA damage interfering with its antitumour activity in cancer cells.

Mol Carcinog 2007 Feb;

Genistein sensitizes inhibitory effect of tamoxifen on the growth of estrogen receptor-positive and HER2-overexpressing human breast cancer cells.

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Although tamoxifen (TAM) is used for the front-line treatment and prevention of estrogen receptor-positive (ER+) breast tumors, nearly 40% of estrogen-dependent breast tumors do not respond to TAM treatment. Moreover, the positive response is usually of short duration, and most tumors eventually develop TAM-resistance. Overexpression of HER2 gene is associated with TAM-resistance of breast tumor, and suppression of HER2 expression enhances the TAM activity. Soy isoflavone genistein has been shown to have anti-cancer activities and suppress expression of HER2 and ERalpha. The objective of this study was to test the hypothesis that genistein may sensitize the response of ER+ and HER2-overexpressing breast cancer cells to TAM treatment. The combination treatment of TAM and genistein inhibited the growth of ER+/HER2-overexpressing BT-474 human breast cancer cells in a synergistic manner in vitro. Determination of cellular markers indicated that this synergistic inhibitory effect might be contributed in part from combined effects on cell-cycle arrest at G(1) phase and on induction of apoptosis. Further determination of the molecular markers showed that TAM and genistein combination synergistically induced BT-474 cell apoptosis in part by synergistic downregulation of the expression of survivin, one of the apoptotic effectors, and downregulation of EGFR, HER2, and ERalpha expression. Our research may provide a novel approach for the prevention and/or treatment of TAM insensitive/resistant human breast cancer, and warrants further in vivo studies to verify the efficacy of genistein and TAM combination on the growth of ER+/HER2-overexpressing breast tumors and to elucidate the in vivo mechanisms of synergistic actions.

Biochim Biophys Acta 2007 Apr;

Caspase-3 status is a determinant of the differential responses to genistein between MDA-MB-231 and MCF-7 breast cancer cells.

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Genistein, a soy isoflavone with anti-tumor properties, has both estrogenic and non-estrogenic activities. Genistein sensitive/estrogen receptor negative (ER-) MDA-MB-231 cells and genistein resistant/ER+MCF-7 cells are frequently cited as examples of differential responses to genistein due to different ER status. Other factors that may affect genistein response,

however, are largely unknown. Based on our finding that MCF-7 is caspase-3 deficient, we examined whether caspase-3 status plays a role in the differential responses between the two cell lines. We demonstrate that reconstitution of caspase-3 significantly sensitizes MCF-7 cells to genistein. Specific knockdown of caspase-3 in MDA-MB-231 cells renders the cells resistant to genistein. We also found that caspases-4 and -10 were downregulated in MCF-7 cells. Reconstitution of caspase-10 in MCF-7 cells, however, resulted in little sensitization. Moreover, we show that caspase-3 downregulation is very common in breast cancer cell lines and tumor tissues. Taken together, our data indicate that caspase-3 is a critical determinant of cellular response to genistein, which may have important implications in studying soy/genistein-mediated anti-tumor activities.

Maturitas 2007 Apr;56(4):359-67

Ethanolic extracts of black cohosh (Actaea racemosa) inhibit growth and oestradiol synthesis from oestrone sulphate in breast cancer cells.

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Extracts of black cohosh (Actaea racemosa) and soy are used as 'natural' alternatives to conventional hormone replacement therapy (HRT) and there is some evidence that soy may protect against breast cancer by inhibiting the production of active oestrogens. This study compares the action of ethanolic extracts of black cohosh (BCE) and genistein on growth and enzyme activity in MCF-7 and MDA-MB-123 breast cancer cells. BCE inhibited growth at the two highest doses tested, i.e. 50 and 100mug/ml, whilst genistein stimulated growth in the oestrogen receptor positive (ER(+)) MCF-7 cells, but at high doses it inhibited growth in both cell lines. BCE did not affect the conversion of androstenedione to oestradiol and only the highest doses (50 and 100mug/ml) significantly inhibited the conversion of oestrone to oestradiol in MDA cells. In contrast, BCE induced a dose-dependent inhibition of the conversion of oestrone sulphate to oestradiol in both cell lines, whilst in human granulosa lutein (GL) cells enzyme activity was only inhibited at the highest dose of BCE. Genistein had no significant effect on enzyme activity in breast cancer cells and like BCE only the highest doses (10 and 50muM) inhibited enzyme activity in human GL cells. In vivo genistein may have growth stimulatory effects on breast tissue but BCE not only inhibits growth but inhibits the conversion of oestrone sulphate to active oestradiol, considered by some, to be the preferred pathway of oestradiol synthesis in breast tissue.

J Med Chem 2007 Apr;50(8):1933-1938

Nonprenylated Rotenoids, a New Class of Potent Breast Cancer Resistance Protein Inhibitors.

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Two rotenoids isolated from Boerhaavia diffusa (Nyctaginaceae), boeravinones G (1) and H (2), have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy. The isolation of nine additional rotenoid derivatives (3-11), including the new boeravinones I (10) and J (11), from the extract of B. diffusa roots allowed us to establish structure-activity relationships toward inhibition of BCRP-mediated drug transport activity. The results show the positive roles of a methoxy group at position 6 of ring B and the absence of a substituent at position 10, and the requirement for a 6a/12a double bond between rings B and C. In contrast, both contraction of ring B, to give a coumaronochromone (11), and tetrasubstitution of ring D appeared to be detrimental for the inhibitory potency. The present study provides the first data on the BCRP-inhibiting activity of rotenoid derivatives, indicating boeravinones as a new class of interesting BCRP inhibitors.

38: Carcinogenesis 2007 Apr;28(4):809-15

Complementary actions of docosahexaenoic acid and genistein on COX-2, PGE2 and invasiveness in MDA-MB-231 breast cancer cells.

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N-3 polyunsaturated fatty acids (PUFA) and genistein have been associated with lowered cancer risk by reducing inflammatory prostanoids, cyclooxygenase-2 (COX-2) activity, and altering cell signaling. Few studies have investigated the effect of these compounds in combination on the molecular control of the COX-2 gene. In a series of experiments we examined a potential synchronous action of n-3 PUFA and genistein in down-regulating COX-2 expression to diminish prostaglandin E(2) (PGE(2)) production in MDA-MB-231 human breast cancer cells. Cells were treated with genistein and various PUFA including arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). PGE(2) concentrations, expression of COX-2, and cell invasiveness were determined. The n-3 PUFA and genistein alone lowered PGE(2) concentration, and genistein in combination with AA reversed the high level of this prostanoid in cell cultures enriched with AA. The degree of cell invasiveness was reversed by genistein in cell cultures treated with AA and further reduced in those given DHA. The n-3 PUFA, in contrast to AA, reduced COX-2 and NFkappaB expression. Genistein combined with AA reversed the effects of AA alone on the expression of COX-2 and NFkappaB. All three fatty acids increased the expression of PPARgamma in the cells only when combined with genistein. Our results support the premise that DHA and genistein exert complementary actions whilst genistein is antagonistic to AA for controlling PGE(2) production as well as invasiveness of MDA-MB-231 cells in culture by modulating the level of NFkappaB expression.

J Clin Oncol 2007 Feb;25(6):648-55

Plasma phytoestrogens and subsequent breast cancer risk.

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PURPOSE: Phytoestrogens are plant compounds that are structurally and functionally similar to mammalian estrogens. By competing for estrogen receptors, phytoestrogens possibly inhibit binding of the more potent endogenous estrogens and decrease their potential effects on breast cancer risk. We investigated the association between plasma phytoestrogen levels and breast cancer risk in a prospective manner. PATIENTS AND METHODS: We performed a nested case-control study within the Prospect cohort, one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition. A total of 383 women (87 pre- or perimenopausal women [mean age, 52 years] and 296 postmenopausal women [mean age, 59 years]) who developed breast cancer were selected as case subjects and were matched to 383 controls, on date of blood sampling. Plasma levels of isoflavones (daidzein, genistein, glycitein, O-desmethylangolensin, and equol) and lignans (enterodiol and enterolactone) were measured. The isotope dilution liquid chromatography/tandem mass-spectrometry method incorporating triply 13C-labeled standards was used for all analyses. Breast cancer odds ratios were calculated for tertiles of phytoestrogen plasma levels using conditional logistic regression analysis. RESULTS: For genistein, the risk estimate for the highest versus the lowest tertile was 0.68 (95% CI, 0.47 to 0.98). Similar protective effects, although not statistically significant, were seen for the other isoflavones. Lignan levels did not appear to be related to breast cancer risk. Results were the same in pre- or perimenopausal women, and in postmenopausal women. CONCLUSION: High genistein circulation levels are associated with reduced breast cancer risk in the Dutch population. No effects of lignans on breast cancer risk were observed.

Carcinogenesis 2007 Jan;28(1):93-100

Genistein and quercetin increase connexin43 and suppress growth of breast cancer cells.

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Connexin proteins form gap junctions, which permit direct exchange of cytoplasmic contents between neighboring cells. Evidence indicates that gap junctional intercellular communication (GJIC) is important for maintaining homeostasis and preventing cell transformation. Furthermore, connexins may have independent functions including tumor growth suppression. Most tumors express less connexins, have reduced GJIC and have increased growth rates compared with non-tumorigenic cells. The purpose of this study was to determine whether common flavonoids, genistein and quercetin, increase connexin43 (Cx43) levels, improve GJIC and suppress growth of a metastatic human breast tumor cell line (MDA-MB-231). Quercetin (2.5, 5 microg/ml) and genistein (0.5, 2.5, 15 microg/ml) upregulated Cx43 but failed to increase GJIC. Cx43 localized to the plasma membrane following genistein treatment (2.5, 15 mug/ml). In contrast, Cx43 aggregated in the perinuclear region following quercetin treatment (0.5, 2.5, 5, 15 microg/ml). Both genistein (15 microg/ml) and quercetin (2.5, 5, 15 microg/ml) significantly reduced MDA-MB-231 cell proliferation. In summary, genistein and quercetin increase Cx43 and suppress MDA-MB-231 cell proliferation at physiologically relevant concentrations. These results demonstrate that genistein and quercetin are potential anti-breast cancer agents.

Horm Res 2007 May;68(5):248-260

Can Modulation of Mammary Gland Development by Dietary Factors Support Breast Cancer Prevention?

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Breast cancer continues to be a major challenge for public health, since it is the most common cancer of women in the Western world, and its prevalence is still increasing. In order to achieve better results in the prevention and treatment of breast cancer it is crucial to identify the mechanisms behind its initiation, i.e. the changes and deviations that have occurred in the mammary gland growth. It has long been known that a woman's reproductive history is the strongest breast cancer risk factor if genetic background and age are excluded. The reproductive hormones, and the timing of events leading to changes in these hormones, and consequently, in the mammary gland, are the most important players. However, it has become obvious that dietary components may also contribute to breast cancer risk through their effects on the mammary gland. The past few years have added important information to our knowledge of the mechanisms behind breast cancer initiation at the level of target cells (mammary stem cells) and gene expression (genetic 'fingerprint' associated with persistent pregnancy-induced protection against breast cancer), as well as of the effects of certain dietary factors (steroid action modulators). These results and their links to breast cancer initiation and progression will be discussed.

Mol Pharmacol 2007 Jan;71(1):101-11

Down-regulation of inhibitor of apoptosis proteins by deguelin selectively induces apoptosis in breast cancer cells.

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The identification of differentially regulated apoptotic signals in normal and tumor cells allows the development of cancer cell-selective therapies. Increasing evidence shows that the inhibitor of apoptosis (IAP) proteins survivin and XIAP are highly expressed in tumor cells but are absent or have very low levels of expression in normal adult tissues. We found that inhibiting AKT activity with 10 to 100 nM deguelin, a small molecule derived from natural products, markedly reduced the levels of both survivin and XIAP, inducing apoptosis in human breast cancer cells but not in normal cells. It is noteworthy that we detected an elevated level of cleaved poly(ADP-ribose) polymerase, a signature of caspase activation, without a significant increase in caspase activity in deguelin-treated cancer cells. Our results suggest that severe down-regulation of the IAPs by deguelin releases their inhibitory activity over pre-existing active caspases present in cancer cells, inducing apoptosis without the need for further caspase activation. Because normal cells have very low levels of p-AKT, XIAP, survivin, and pre-existing caspase activity, deguelin had little effect on those cells. In addition, we found that combining deguelin with

chemotherapy drugs enhanced drug-induced apoptosis selectively in human tumor cells, which suggests that deguelin has great potential for chemosensitization and could represent a new therapeutic agent for treatment of breast cancer.

Br J Nutr 2008 May;99 E Suppl 1:ES78-108

Isoflavones and the prevention of breast and prostate cancer: new perspectives opened by nutrigenomics.

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Epidemiological evidence together with preclinical data from animal and in vitro studies strongly support a correlation between soy isoflavone consumption and protection towards breast and prostate cancers. The biological processes modulated by isoflavones, and especially by genistein, have been extensively studied, yet without leading to a clear understanding of the cellular and molecular mechanisms of action involved. This review discusses the existing gaps in our knowledge and evaluates the potential of the new nutrigenomic approaches to improve the study of the molecular effects of isoflavones. Several issues need to be taken into account for the proper interpretation of the results already published for isoflavones. Too often knowledge on isoflavone bioavailability is not taken into account; supra-physiological doses are frequently used. Characterization of the individual variability as defined by the gut microflora composition and gene polymorphisms may also help to explain the discrepancies observed so far in the clinical studies. Finally, the complex inter-relations existing between tissues and cell types as well as cross-talks between metabolic and signalling pathways have been insufficiently considered. By appraising critically the abundant literature with these considerations in mind, the mechanisms of action that are the more likely to play a role in the preventive effects of isoflavones towards breast and prostate cancers are reviewed. Furthermore, the new perspectives opened by the use of genetic, transcriptomic, proteomic and metabolomic approaches are highlighted.

Mol Nutr Food Res 2007 Feb;51(2):171-7

Phytoestrogens activate estrogen receptor beta1 and estrogenic responses in human breast and bone cancer cell lines.

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Plant-derived phytoestrogens and estrogens in hormone replacement therapies have overlapping yet sometimes divergent effects on the incidence of breast cancer and osteoporosis. Using human MCF-7 breast carcinoma and G-292 osteosarcoma cell lines, it was investigated whether the phytoestrogens genistein and daidzein affect reporter gene transcription via the estrogen receptors (ERs) ERalpha and ERbeta1 as well as whether they affect the expression of estrogen-responsive genes in MCF-7 cells and the secretion of the cytokine IL-6 from G-292 cells. The results showed that genistein and daidzein potently trigger transactivation with ERbeta1 from estrogen

response element-reporter genes (EC50s of 1.7-16 nM) although they were 400- to 600-fold less potent than 17beta-estradiol (E2) (EC50 of 0.02-0.04 nM). E2 was the only potent activator of ERalpha (EC50 of 0.1-0.4 nM). The rank order potency (E2 > genistein > daidzein) is maintained in MCF-7 cells as well as G-292 cells with both receptor subtypes, with a strong receptor selectivity of the phytoestrogens for ERbeta1 over ERalpha. Genistein and daidzein increased the expression of estrogen-responsive genes in MCF-7 cells. Daidzein, like E2, inhibited IL-1beta- and hormone-mediated IL-6 secretion from G-292 cells. **The results provide a basis for understanding how dietary phytoestrogens protect bone without increasing the risks for breast cancer.**

Arch Biochem Biophys 2008 Feb;

Isoflavones in children and adults consuming soy.

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Soy and their isoflavones (IFLs) are believed to protect against breast cancer, particularly when exposure occurs during childhood. Little is known about the bioavailability of IFLs in children and how this is affected by oral antibiotics (OABX). We measured IFLs by LC/MS and found that the urinary IFL excretion rate (UIER) reflects circulating IFLs accurately when area-under-curve (AUC) and identical time intervals are used ($r=0.93$; $p<0.001$). UIER in children and adults was determined when healthy and when on OABX by collecting urine in pairs of baseline and overnight specimen before and after consuming soy nuts, respectively. Compared to when healthy, children on OABX showed significantly decreased UIER but adults on OABX showed increased UIER ($p<0.05$). All 37 healthy children showed significantly higher UIERs compared to all 34 healthy adults. UIER is an adequate surrogate for determining IFL bioavailability and for measuring soy or IFL exposure in epidemiologic and other studies.

Int J Cancer 2008 May;

Flavonoids and ovarian cancer risk: A case-control study in Italy.

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Flavonoids belong to a vast group of polyphenols widely distributed in all foods of plant origin. Because of their antioxidant, antimutagenic and antiproliferative properties, they have been hypothesized to contribute to the favorable effects of fruit and vegetables against cancer. The aim of this study is to investigate the relation of 6 classes of flavonoids (flavan-3-ols, flavanones, flavonols, flavones, anthocyanidins and isoflavones) with ovarian cancer risk, using data from a multicentric case-control study conducted in Italy between 1992 and 1999. The study included 1,031 cases with incident, histologically confirmed epithelial ovarian cancer and 2,411 controls admitted for acute, nonneoplastic conditions to major hospitals in the same catchment areas. In logistic regression models

including study center, education, year of interview, parity, oral contraceptive use and family history of ovarian or breast cancer or both, an inverse relation with significant trend in risk was found between ovarian cancer and flavonols [odds ratio (OR), 0.63; 95% confidence intervals (CI) 0.47-0.84] as well as isoflavones (OR, 0.51; 95% CI, 0.37-0.69), comparing the highest versus the lowest quintile. Further adjustment for fruit and vegetable intake did not modify these associations, suggesting that isoflavones and flavonols may have a distinct role in explaining the effect of fruit and vegetable against ovarian cancer. On the basis of our findings and the relevant literature, we infer that isoflavones, and perhaps flavonols, may have favorable effects with respect to ovarian cancer risk.

Carcinogenesis 2008 Jan;

SOY ISOFLAVONES DECREASE THE CATECHOL-O-METHYLTRANSFERASE-MEDIATED INACTIVATION OF 4-HYDROXYESTRADIOL IN CULTURED MCF-7 CELLS.

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The tissue concentrations of the female sex hormone 17beta-estradiol (E2) and its reactive catechol metabolites such as 4-hydroxyestradiol (4-HO-E2) play important roles in hormonal carcinogenesis. They are influenced by the activity of local enzymes involved in the metabolic activation and inactivation of E2. In the mammary gland, catechol estrogens are predominately inactivated by catechol-O-methyltransferase (COMT). Food supplements containing the soy isoflavones genistein (GEN) and daidzein (DAI) are consumed because they are believed to protect from breast cancer; however, this proposed benefit is controversial. The aim of the present study was to investigate the influence of soy isoflavones on the gene expression and activity of COMT in cultured human mammary adenocarcinoma MCF-7 cells. Levels of COMT mRNA were determined by reverse transcription/competitive polymerase chain reaction and COMT activity was determined by HPLC analysis of the methylation products of both the model substrate quercetin and the physiological relevant substrate 4-HO-E2. Our study demonstrates for the first time that soy isoflavones at hormonally-active concentrations cause a significant reduction of both COMT mRNA levels and COMT activity as well as of the methylation of 4-HO-E2. Experiments using the estrogen receptor antagonist ICI 182,780 support a role of the estrogen receptor in the isoflavone-induced downregulation of COMT expression. Thus, this study not only demonstrates that hormonally-active concentrations of soy isoflavones inhibit the detoxification of catechols in this human breast cancer cell line, but also implies that diet might influence COMT activity to a greater extent than heretofore recognized.

J Med Food 2007 Dec;10(4):571-80

Soy isoflavones as safe functional ingredients.

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In recent years, isoflavones have increased in popularity as an alternative to estrogen therapy, particularly after the Women's Health Initiative demonstrated an increased risk of breast cancer, stroke, and heart attacks

in response to estrogen and progesterone intervention. Isoflavones are heterocyclic phenols with structural similarity to estradiol-17beta and selective estrogen receptor modulators. Actions at the cellular level depend on the target tissue, receptor status of the tissue, and the level of endogenous estrogen. Clinical studies of soy-based diets evaluating the relation between soy consumption and serum lipid concentrations revealed that soy consumption significantly decreased total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels. Epidemiological studies suggest a protective effect of soy protein on breast tissue as evidenced by the lower rates of breast cancer in East Asian countries where soy is a predominant part of the diet. Soy products also alleviate menopausal symptoms by reducing hot flashes. However, whether these biological effects of soy products originated from isoflavones is not clear. Furthermore, data available from human studies on the effect of isoflavones on osteoporosis are limited, and additional studies are needed to support a role in osteoporosis prevention. To date, no adverse effects of shortor long-term use of soy proteins are known in humans, and the only adverse effects known are those reported in animals. In conclusion, isoflavones are biologically active compounds, and current data are insufficient to draw definitive conclusions regarding the use of isoflavones as an alternative to estrogen for hormone replacement in postmenopausal women. Large, long-term intervention studies examining adverse effects and disease outcomes are needed before definitive conclusion can be drawn.

Steroids 2007 Jan;72(1):64-70

Equol producer status, salivary estradiol profile and urinary excretion of isoflavones in Irish Caucasian women, following ingestion of soymilk.

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Equol production, isoflavone excretion, and the salivary estradiol profile among 36 females, native Irish Caucasian volunteers following ingestion of 200mL soymilk is reported. The soymilk contained daidzein (73+/-6.7mg) and genistein (86+/-10.2mg). Volunteers provided personal and family medical history. Dietary analysis revealed that all volunteers regularly consumed soy-based or soy-supplemented food products. The mean age, mean age at menarche, and body mass index of volunteers were 46.6+/-12.3 years, 13.1 years and 26.1, respectively. The average number of children per volunteer was 2.13. Twelve (34%) of the volunteers were found to be first-degree relatives of breast cancer patients. Following consumption of the soymilk, equol was detected in the urine of 18 (51%) of the volunteers. Mean urinary daidzein and genistein concentrations during the hours following soymilk ingestion were 13.5 and 16.7microg/mg creatinine, respectively, however, some volunteers excreted little (less than 4.0microg/mg) or no isoflavone. Salivary estradiol in most (24) volunteers had decreased from 51.5+/-28.67pmol/L pre-ingestion to 29.75+/-16.13pmol/L 5h after drinking the soymilk. However, the salivary estradiol in 12 subjects (34%) increased from 33.76+/-13.4pmol/L to 137.4+/-65.64pmol/L over the same period. Individuals whose salivary estradiol increased had significantly less children (1.58 ($P<0.05$)), were more likely to (a) return urine samples with low isoflavone content (50.3% compared to 25%), (b) to be equol producers (67% compared to 41.7%), and (c) to be first-degree relatives of breast cancer patients (41.7% compared to 25%). Volunteers who reported a first-degree link to breast cancer were more likely to have a higher body mass index (29.0 compared to 26.1 ($P<0.05$)), to be equol producers (75% compared to 51%), and to excrete isoflavones in low quantities only (60% compared to

50%). First-degree relatives also had fewer children (1.75 (P<0.05)). The results indicate a significant, distinctive variation in equol production, **isoflavone excretion and salivary estradiol profile among individual volunteers following ingestion of soymilk.**

Food Chem Toxicol 2007 Aug;

A dietary supplement for female sexual dysfunction, Avlimil, stimulates the growth of estrogen-dependent breast tumors (MCF-7) implanted in ovariectomized athymic nude mice.

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Avlimil, a dietary supplement advertised to ameliorate female sexual dysfunction, is a mixture of eleven herbal components, and some herbal constituents of Avlimil (including black cohosh, licorice, red raspberry, red clover and kudzu) contain phenolic compounds, which are suggested to have estrogenic, anti-estrogenic, or androgenic potential for relieving menopausal symptoms. We hypothesize that Avlimil could modulate the growth of estrogen receptor positive human breast cancer (MCF-7) cells in vitro and in vivo. A dimethylsulfoxide (DMSO) extract of Avlimil (0.001-100mug Avlimil powder equivalents/mL media) was tested for its estrogenic and anti-estrogenic effects on the growth of MCF-7 cells in vitro. We observed that the DMSO extract of Avlimil at low concentrations (0.1-50mug/mL media) dose-dependently increased MCF-7 cell proliferation in vitro, and Avlimil DMSO extract at 100mug/mL inhibited the growth of MCF-7 cells in vitro. Avlimil and some constituents (black cohosh and licorice roots) of Avlimil were fractionated by using sequential solvent extraction (hexane, ethyl acetate, and methanol) and the activities of the fractions were monitored by effects on the growth of MCF-7 cells. Depending on dosage (0.1-100mug/mL media) both stimulatory and inhibitory effects of the extracts on the growth of MCF-7 cells were observed. The effect of dietary Avlimil at dosages approximating human intake was evaluated using ovariectomized mice implanted with MCF-7 cells. Animals were fed diets containing 500ppm or 1000ppm Avlimil for 16 weeks. Dietary Avlimil at 500ppm stimulated MCF-7 tumors, but Avlimil at 1000ppm had no apparent effect on the growth of MCF-7 tumors. The observation of stimulated tumor growth in the absence of uterine wet weight gains suggest that estrogenic/anti-estrogenic effects of Avlimil we observed may be dosage- and target tissue-specific and that Avlimil may not be safe for women with estrogen-dependent breast cancer. The different biological effects of fractionated Avlimil components and the different concentration dependencies warrant further compound identification and dose-response studies, especially at recommended intake levels that could have estrogenic effects in women.

Expert Rev Neurother 2007 Nov;7(11):1549-1564

WHI and WHIMS follow-up and human studies of soy isoflavones on cognition.

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Recent follow-up analyses of the previous findings from the Women's Health Initiative and the Women's Health Initiative Memory Study confirmed some health benefits of estrogen-containing hormone therapy (HT) in women within 10 years from the onset of menopause. However, the potential risks associated with long-term administration of HT, such as breast cancer and stroke, remain a concern for therapy recipients, underlying the need for an alternative treatment that is functionally equivalent but with a greater safety profile. Owing to their structural and functional resemblance to mammalian estrogens and lack of evident adverse effects, research interest in plant-derived phytoestrogens has increased in the past decade. While multiple health-promoting benefits of phytoestrogens have been proposed from basic science, the clinical data remain inconclusive. This review provides a comparative analysis of human studies on the effects of soy-based isoflavones on cognition. Of the eight studies published in 2000-2007, seven were conducted in postmenopausal women, four of which revealed a positive impact of isoflavones on cognitive function. Multiple factors could have contributed to the discrepant outcomes across studies, such as variation in the composition of phytoestrogen interventions and the heterogeneous characteristics of the study population. Thus, a well-designed clinical study based on a standardized stable formulation in a well-characterized study population is required in order to reach a clinical consensus. A formulation composed of select estrogen receptor beta-selective phytoestrogens with a rationally designed composition would avoid the potential antagonism present in a mixture and thus enhance therapeutic efficacy. In addition, inclusion of equol in a study formulation offers a potential synergistic effect from equol in both equol-producing and nonproducing individuals, as well as added benefits for men. With respect to the design of study population, a clinically consistent effect could potentially be achieved by stratifying populations based on genotype, age, hormonal history and even diets. Development of an effective phytoestrogen formulation would benefit both women and men to prevent or treat hormone-dependent conditions and, most of all, to improve neurological health and reduce the risk of Alzheimer's disease.

Mol Cancer Ther 2007 Nov;6(11):3071-9

Extended treatment with physiologic concentrations of dietary phytochemicals results in altered gene expression, reduced growth, and apoptosis of cancer cells.

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Dietary phytochemicals exhibit chemopreventive potential in vivo through persistent low-dose exposures, whereas mechanistic in vitro studies with these agents generally use a high-dose single treatment. Because the latter approach is not representative of an in vivo steady state, we investigated antitumor activity of curcumin, 3,3'-diindolylmethane (DIM), epigallocatechin gallate (EGCG), genistein, or indole-3-carbinol (I3C) in breast cancer MDA-MB-231 cells, exposed in long-term culture to low concentrations, achievable in vivo. Curcumin and EGCG increased cell doubling time. Curcumin, EGCG, and I3C inhibited clonogenic growth by 55% to 60% and induced 1.5- to 2-fold higher levels of the basal caspase-3/7 activity. No changes in expression of cell cycle-related proteins or survivin were found; however, I3C reduced epidermal growth factor receptor

expression, contributing to apoptosis. Because some phytochemicals are shown to inhibit DNA and histone modification, modulation of expression by the agents in a set of genes (cadherin-11, p21Cip1, urokinase-type plasminogen activator, and interleukin-6) was compared with changes induced by inhibitors of DNA methylation or histone deacetylation. The phytochemicals modified protein and/or RNA expression of these genes, with EGCG eliciting the least and DIM the most changes in gene expression. DIM and curcumin decreased cadherin-11 and increased urokinase-type plasminogen activator levels correlated with increased cell motility. Curcumin, DIM, EGCG, and genistein reduced cell sensitivity to radiation-induced DNA damage without affecting DNA repair. **This model has revealed that apoptosis and not arrest is likely to be responsible for growth inhibition. It also implicated new molecular targets and activities of the agents under conditions relevant to human exposure.**

Ageing Res Rev 2007 May;

Isoflavones-Safe food additives or dangerous drugs?

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The sales volume of products containing isoflavone has increased since the publication of the Women's Health Initiative. The many apparently contradictory results published on the effects of isoflavones on a variety of estrogen-regulated organs point to both beneficial as well as adverse effects on human health. It is of particular importance that psychovegetative climacteric complaints such as hot flushes are, if at all, only slightly influenced by isoflavones. The substances appear to have weak anti-osteoporotic effect. Their anti-atherosclerotic action is debatable, as not all authors find any beneficial effect on lipids. Most importantly, there is dispute as to whether isoflavones derived from soy or red clover have negative, positive or any effect at all on the mammary gland or endometrium. It is beyond any doubt that soy products may have cancer preventing properties in a variety of organs including the mammary gland. However, these properties may only be exerted if the developing organ was under the influence of isoflavones during childhood and puberty. This may also explain the often quoted "Japanese Phenomenon", the fact that breast cancer occurs to a lesser extent in Japanese women. When administered to isoflavone "inexperienced" women at the time of menopause, the phytoestrogens appear to share the same effects as estrogen used in classical preparations for hormone replacement therapy, i.e. they may stimulate the proliferation of endometrial and mammary gland tissue with at present unknown and unpredictable risk to these organs. Therefore, the following question arises for the clinician: Why should soy or red clover products containing isoflavone be recommended, if the positive effects are only negligible but the adverse effects serious?

Int J Cancer 2008 May;

Dietary flavonoid intake and risk of cancer in postmenopausal women: The Iowa Women's Health Study.

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Flavonoids, which are found in certain plant foods, are thought to lower cancer risk through their antioxidant, antiestrogenic and antiproliferative properties. We examined the association of intake of total flavonoids and 7 flavonoid subclasses with risk of lung, colorectal, breast, pancreatic and upper aerodigestive cancer among women in a large prospective cohort study. Study participants were 34,708 postmenopausal women in the Iowa Women's Health Study who completed a food frequency questionnaire and were followed for cancer occurrence from 1986 through 2004. Flavonoid intake was estimated from 3 databases developed by the USDA Nutrient Data Laboratory (NDL). Hazard ratios (HR) for cancer risk were calculated across total flavonoid and flavonoid subclass intake categories. Interactions between smoking history and flavonoid intake were also examined. After multivariable adjustment, lung cancer incidence was inversely associated with intakes of flavanones (HR = 0.68; 95% CI: 0.53-0.86, all results highest vs. lowest quintile) and proanthocyanidins (HR = 0.75; 95% CI: 0.57-0.97). Among current and past smokers, those with intakes in the highest quintile for flavanones (HR = 0.66; 95% CI: 0.50-0.86), and proanthocyanidins (HR = 0.66; 95% CI; 0.49-0.89) had significantly lower lung cancer incidence than those in the lowest quintile. Similar associations were not seen in never smokers. Isoflavone intake was inversely associated with overall cancer incidence (HR = 0.93, 95% CI: 0.86-1.00). This study provides further support for a beneficial effect of flavonoid intake on lung cancer risk, especially among current and past smokers. (c) 2008 Wiley-Liss, Inc.

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Cancer Lett 2008 May;

Multi-targeted therapy of cancer by genistein.

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Soy isoflavones have been identified as dietary components having an important role in reducing the incidence of breast and prostate cancers in Asian countries. Genistein, the predominant isoflavone found in soy products, has been shown to inhibit the carcinogenesis in animal models. There is a growing body of experimental evidence showing that the inhibition of human cancer cell growth by genistein is mediated via the modulation of genes that are related to the control of cell cycle and apoptosis. It has been shown that genistein inhibits the activation of NF-kappaB and Akt signaling pathways, both of which are known to maintain a homeostatic balance between cell survival and apoptosis. Moreover, genistein antagonizes estrogen- and androgen-mediated signaling pathways in the processes of carcinogenesis. Furthermore, genistein has been found to have antioxidant properties, and shown to be a potent inhibitor of angiogenesis and metastasis. Taken together, both in vivo and in vitro studies have clearly shown that genistein, one of the major soy isoflavones is a promising agent for cancer chemoprevention and further suggest that it could be an adjunct to cancer therapy by virtue of its effects on reversing radioresistance and chemoresistance. In this review, we attempt to provide evidence for these preventive and therapeutic effects of genistein in a succinct manner highlighting comprehensive state-of-the-art knowledge

regarding its multi-targeted biological and molecular effects in cancer cells.

Breast Cancer Res Treat 2006 Oct;

Lycopene and other carotenoids inhibit estrogenic activity of 17beta-estradiol and genistein in cancer cells.

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Epidemiological evidence suggests that carotenoids prevent several types of cancer, including mammary and endometrial cancers. On the other hand, such studies have also shown that estrogens are the most important risk factors for these cancer types. Genistein, the phytoestrogen mainly found in soy, also shows significant estrogenic activity when tested at concentrations found in human blood. The aim of this study was to determine whether carotenoids inhibit signaling of steroidal estrogen and phytoestrogen which could explain their cancer preventive activity. Similar to the known effect of 17beta-estradiol (E(2)), treatment of breast (T47D and MCF-7) and endometrial (ECC-1) cancer cells with phytoestrogens induced cell proliferation, cell-cycle progression and transactivation of the estrogen response element (ERE). However, each of the tested carotenoids (lycopene, phytoene, phytofluene, and beta-carotene) inhibited cancer cell proliferation induced by either E(2) or genistein. The inhibition of cell growth by lycopene was accompanied by slow down of cell-cycle progression from G1 to S phase. Moreover, the carotenoids inhibited estrogen-induced transactivation of ERE that was mediated by both estrogen receptors (ERs) ERalpha and ERbeta. The possibility that this inhibition results from competition of carotenoid-activated transcription systems on a limited pool of shared coactivators with the ERE transcription system was tested. Although cotransfection of breast and endometrial cancer cells with four different coactivators (SRC-1, SRC-2, SRC-3, and DRIP) strongly stimulated ERE reporter gene activity, it did not oppose the inhibitory effect of carotenoids. **These results suggest that dietary carotenoids inhibit estrogen signaling of both 17beta-estradiol and genistein, and attenuate their deleterious effect in hormone-dependent malignancies.**

Anim Reprod Sci 2007 Feb;97(3-4):237-45

Effects of chronic exposure to soy meal containing diet or soy derived isoflavones supplement on semen production and reproductive system of male rabbits.

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Soy and derivative diets deliver large doses of isoflavones to human and animals throughout their lifespan, including gestation. Epidemiologic and experimental data suggest that the consumption of soybean containing foods may protect against cardiovascular disease and decrease breast, prostate and endometrial cancer risk. Based on animal and in vitro studies, however,

concerns have been raised that consumption of isoflavones may cause potential adverse effects on the reproductive tract and behavior. The aim of this study was to investigate the effects of chronic consumption of a soy meal containing diet or soy isoflavones supplement on the morphology of reproductive organs, semen quality, age that males reached puberty, and sexual behavior of male rabbits. With this purpose, 16 female rabbits were randomly assigned to receive: (1) a soy- and alfalfa-free diet; (2) a soy- and alfalfa-free diet supplemented with 5mg/kg body wt./day of soy isoflavones; (3) a soy- and alfalfa-free diet supplemented with 20mg/kg body wt./day of soy isoflavones; (4) a diet containing 18% of soy meal, throughout the gestation and lactation. After weaning, male offspring received the same diet, which was given to the respective mother. The age that males reached puberty, semen characteristics and sexual behavior were evaluated in these animals. At 33 weeks of age, the reproductive organs were submitted to histological evaluation. Rabbits, which received large amounts of isoflavones (20mg/kg body wt./day) had a lesser food intake, body weight and semen volume. Spermatogenesis, morphology of male genital organs and sexual behavior did not differ significantly from the control group. We conclude that chronic dietary treatment with soy based diet or soy isoflavones have no adverse effects on the observed reproductive patterns of male rabbits.

Antioxid Redox Signal 2007 Dec;

Cancer Chemoprevention Through Dietary Antioxidants: Progress and Promise.

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It is estimated that nearly one-third of all cancer deaths in the United States could be prevented through appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer. Therefore, for reducing the incidence of cancer, modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread, or even to treat cancer. The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity. This review presents an extensive analysis of the key findings from studies on the effects of dietary antioxidants such as tea polyphenols, curcumin, genistein, resveratrol, lycopene, pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. This research is also leading to the identification of novel cancer drug targets.

Clin Nutr 2008 Jun;

The combination of genistin and ipriflavone prevents mammary tumorigenesis and modulates lipid profile.

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BACKGROUND & AIMS: Recent reports have indicated that soy isoflavones may be protective against breast cancer. However, the effects of the synthetic isoflavone, ipriflavone, on mammary tumorigenisis, alone or in combination with genistin, a soy isoflavone, have not been investigated. METHODS: Eighty-eight 36-day-old female Sprague-Dawley rats were divided as follows: Gen (20mg genistin/kg body weight), Ipr (200mg ipriflavone/kg body weight), Gen+Ipr (20/200mg per kg body weight, respectively), and control (solvent vehicle). A week later, animals were injected with a single dose of methylnitrosourea. The isoflavones and solvent vehicle were administered daily via gastric gavage for 84days post methylnitrosurea injection. RESULTS: The Gen+Ipr group had the lowest number of palpable tumors and adenocarcinomas per group, the least palpable tumors per rat, and the highest serum total and non-HDL cholesterol levels. No changes in circulating levels of indicators of oxidative stress were detected due to treatment. CONCLUSIONS: The findings of this study imply that the combination of genistin and ipriflavone is effective in suppressing mammary methylnitrosurea-induced tumorigenesis and also the lipid environment of the tumor cells that impact tumor growth or proliferation. Further studies are needed to establish the optimal dose of genistin and ipriflavone, individually or in combination, for the prevention of mammary tumorigenesis.

Eur J Cancer Prev 2008 Feb;17(1):67-70

The relation of soy intake and isoflavone levels in nipple aspirate fluid.

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Given the possible breast cancer preventive effects of isoflavones, substances with an estrogen-like structure occurring in soybeans, it is of interest to assess levels directly in the breast. The objective of this pilot study was to measure isoflavones in nipple aspirate fluid. In a pilot study with 11 women, nipple aspirate fluid and urine samples were collected at baseline and after 1 month of consuming two servings of soymilk per day. In a parallel investigation, one woman donated nipple aspirate fluid, blood, and urine on the same day after consuming different amounts of soy for 9 days. Nipple aspirate fluid was collected with an aspirator, diluted 1 : 11, and stored at -20 degrees C. Isoflavonoids in nipple aspirate fluid, serum, and urine were liquid-liquid extracted after enzymatic hydrolysis followed by liquid chromatography electrospray ionization high resolution tandem mass spectrometry analysis using triply C labeled internal isoflavonoid standards. After the 30-day soy intervention, median nipple aspirate fluid yield changed very little (P=0.47), whereas urinary isoflavonoid excretion (P=0.04) and isoflavonoid levels in nipple aspirate fluid (P=0.12) increased substantially. For the nine samples collected in one participant, isoflavonoids measured in nipple aspirate fluid, plasma, and urine were highly correlated with the number of daily soy servings and with each other. This pilot study indicates that isoflavonoids in nipple aspirate fluid are 10 times lower than in plasma and are closely related to levels of isoflavonoids in urine and plasma. These findings show that isoflavonoids are present in breast fluid and may act directly on breast tissue.

In Vivo 2007;21(4):667-71

Commercial soy milk enhances the development of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats.

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BACKGROUND: Soy milk is a major soy food in China and Japan. Isoflavones in soy food are considered to protect women again breast cancer. MATERIALS AND METHODS: The effects of soy milk consumption on 7,12-dimethylbenz(a) anthracene (DMBA)-induced mammary tumors in adult female rats was investigated. Sprague-Dawley rats were given 5 mg DMBA via intragastric intubation and then assigned to receive soy milk or water in addition to a normal rodent diet. Body weights, liquid and food intake, tumor number, location and development were recorded. After 20 weeks, liver, uterus and mammary tumors were removed from the sacrificed animals and examined. Plasma 17beta-estradiol concentration was also determined. RESULTS: After 20 weeks of DMBA administration, all of the rats that drank soy milk developed mammary tumors, while the incidence in the control group was 70% ($p < 0.01$). Tumor multiplicity increased in the soy milk group with borderline significance ($p=0.06$). Total tumor weight and size in the soy milk group were 1.5-fold greater than in the control group, without a significant difference ($p>0.05$). Uterine weight and plasma 17beta-estradiol concentrations were similar in the two groups. CONCLUSION: Our results suggest that commercial soy milk enhanced the development of DMBA-induced mammary tumors in rats. Thus, careful consideration should be given when explaining the beneficial effects of soy food.

In Vivo 2007;21(3):507-12

Soy isoflavone intake and estrogen excretion patterns in young women: effect of probiotic administration.

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BACKGROUND: Soy isoflavones may lower breast cancer risk through altered hepatic estrogen metabolism, leading to increased urinary excretion ratios of 2-hydroxyestrone (20HE1) to 16a-hydroxyestrone (16alphaOHE1). MATERIALS AND METHODS: Urinary excretion of 20HE1/16alphaOHE1 was measured in 36 healthy, pre-menstrual women before and after ingestion of a soy-protein formula containing 120 mg of isoflavone daily for one month. Since isoflavone absorption and metabolism depends on intestinal bacteria, effects of co-administration of Lactobacillus GG (2 x 10(12)) on estrogen ratios and isoflavone excretion were studied. Urinary isoflavone excretion measurements assessed compliance. RESULTS: Soy isoflavone ingestion induced quantitative differences in urinary excretion of estrogen metabolites and isoflavones but failed to alter 20HE1/16alphaOHE1 ratios. Co-administration of Lactobacillus GG with soy reduced excretion of total and individual isoflavones by 40% ($p=0.08$), without altering 2OHE1/16alphaOHE1 ratios. CONCLUSION: Isoflavone-rich soy protein administration alone, or with probiotic supplement, did not alter urinary excretion of estrogen

metabolites in premenopausal women. However, adding concentrated probiotics may alter isoflavone bioavailability.

Nutr Cancer 2007;58(2):222-9

The Effect of the Phytoestrogens Genistein, Daidzein, and Equol on the Growth of Tamoxifen-Resistant T47D/PKCalpha.

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Soy supplements are often consumed by women for alleviating menopausal symptoms or for the perceived protective effects against breast cancer. More concerning is the concurrent consumption of soy isoflavones with tamoxifen (TAM) for prevention or treatment of breast cancer. We previously described a T47D:A18/protein kinase C (PKC)alphaTAM-resistant tumor model that exhibits autonomous growth and estradiol-induced tumor regression. We compared the estrogenicity of the isoflavones genistein, daidzein, and the daidzein metabolite equol in the parental T47D:A18 and T47D:A18/PKCalphacell lines in vitro and in vivo. Whereas equol exerts estrogenic effects on T47D:A18 cells in vitro, none of the isoflavones stimulated T47D:A18 tumor growth. T47D:A18/PKCalpha tumor growth was partially stimulated by genistein, yet partially inhibited by daidzein. Interestingly, coadministration of TAM with either daidzein or genistein produced tumors of greater size than with TAM alone. These findings suggest that simultaneous consumption of isoflavone supplements with TAM may not be safe.

Nutr Cancer 2007;57(1):48-58

Effects of flavonoids genistein and biochanin a on gene expression and their metabolism in human mammary cells.

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Genistein (GEN) and biochanin A (BCA), dietary isoflavones, possess breast cancer-preventive properties. Our objective was to examine the effect of physiologically relevant concentrations of BCA and GEN on gene expression in normal (HMEC), immortalized but nontumorigenic (MCF12A), and tumorigenic (MCF7) mammary cells and to determine whether the differences in gene expression are related to differences in metabolism in the three types of mammary cells. Using cDNA arrays, we compared the gene expression after a 48-h incubation with 1 muM BCA, GEN, or vehicle. Treatment with GEN or BCA produced the greatest number of significant changes in HMEC compared with MCF12A or MCF7 cells. Unlike GEN, effects of BCA on gene expression were mostly beneficial, involving induction of tumor suppressor genes. Different extents of metabolism were observed in the three mammary cell types; however, GEN concentrations were very low following either GEN or BCA administration in all of the three cell types. Because there were only very low concentrations of GEN, compared with BCA concentrations, in HMEC and MCF12A cells treated with BCA and different gene expression changes were

found after BCA and GEN treatment, these findings suggest that BCA has distinct effects compared with GEN. The results suggest that BCA may represent a better breast cancer-preventive agent than GEN.

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Rom J Intern Med 2007;45(1):113-21

Soya--the medicine food product.

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Soya, cultivated for more than 3000 years, is both a drug and a food product. It has numerous nutritional benefits, given by its content of isoflavones, essential amino acids, fibers, poly-unsaturated fatty acids, vitamins and minerals. The use of soy reduces the risk of cardiovascular diseases: it has an antioxidant effect, reduces cholesterol levels and modulates the endothelial function; the soy foods, rich in isoflavones, reduce the risk of breast cancer; men with heredocolateral cancer antecedents or with minimal increase of prostate antigen must consider the consumption of soy and soy foods. Soy and soy foods play an important role in reducing the incidence of osteoporosis and controlling the pre- and postmenopausal symptoms; the soy ingestion has benefic metabolic effects in patients with Diabetes Mellitus and overweight. Taking into consideration the nutritional profile of soy, the nutritionists should encourage the population to consume more soy and soy foods. Nevertheless, long term studies are needed to discover a possible "dark side" of soy consumption. Among the most popular soy foods we mention: soymilk, soy cheese (tofu), soy meat (pie, salami, textured soy in granule form). Most of the products are soy flour derivatives, while tofu is obtained by curdling soymilk.

Mol Nutr Food Res 2008 Jul;

Reduced mammary tumor progression in a transgenic mouse model fed an isoflavone-poor soy protein concentrate.

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Dietary exposure to soy has been associated with reduced breast cancer incidence. Soy isoflavones and protein components, such as protease inhibitors and the lunasin peptide, have been indicated as potential agents reducing carcinogenesis. In this study, the effect of soy-based diets was evaluated in a transgenic mouse model of breast carcinoma, overexpressing the neu oncogene. Neu female mice were fed for 20 wk a soy- and isoflavone-free diet (IFD), 4RF21 laboratory mouse diet, soy-based, thus isoflavone-rich (STD), or AIN-76-based semisynthetic diets with a soy protein isolate (SPI) or an isoflavone-poor soy protein concentrate (IPSP) as protein source. Mice were then sacrificed and tumors removed. Mammary tumor weights were not different in SPI versus IFD and STD fed mice. In contrast, mice fed IPSP showed reduced tumor progression versus IFD and STD groups ($p < 0.05$). Moreover, IPSP fed mice showed lower bromo-2'-deoxyuridine (BrdU) incorporation into breast tumor cells compared to STD and SPI fed animals

($p < 0.02$). Lung metastases were detected in 80% of IFD fed mice, in 70% of mice fed STD and SPI, and only in 50% of the IPSP fed animals. These results indicate that a diet containing an isoflavone-poor soy protein concentrate may inhibit breast tumor progression and metastasis development.

Biochem Pharmacol 2008 May;

MCF-7aro/ERE, a novel cell line for rapid screening of aromatase inhibitors, ERalpha ligands and ERRalpha ligands.

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We have previously generated a breast cancer cell line, MCF-7aro, which over-expresses aromatase and is also ER positive. Recently, this MCF-7aro cell line was stably transfected with a promoter reporter plasmid, pGL3-Luc, containing three repeats of estrogen responsive element (ERE). Experiments using MCF-7aro/ERE have demonstrated that it is a novel, non-radioactive screening system for aromatase inhibitors (AIs), ERalpha ligands and ERRalpha ligands. The screening is carried out in a 96-well plate format. To evaluate this system, the cells were cultured overnight in charcoal-dextran stripped FBS medium supplemented with 0.1nM testosterone or 17beta-estradiol, and various concentrations of antiestrogens or AIs. We found that the luciferase activity was induced when the cells were cultured either in the presence of testosterone or 17beta-estradiol. Furthermore, a 50% decrease in luciferase activity could be achieved when the cells were cultured in the presence of testosterone together with letrozole, anastrozole, tamoxifen or fulvestrant (concentrations being 75nM, 290nM, 100nM, and 5nM, respectively), compared to the testosterone-only cultured cells. Using this assay system, we confirmed that 3(2'-chlorophenyl)-7-methoxy-4-phenylcoumarin is an agonist of ER. Furthermore, genestein has been shown to be a ligand of ERRalpha because its binding could be blocked by an ERRalpha inverse agonist, XCT790. These results indicate that MCF-7aro/ERE is a novel cell line for rapid screening of AIs, ERalpha ligands and ERRalpha ligands.

Environ Res 2008 May;

Environmental exposures and puberty in inner-city girls.

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BACKGROUND: Hormonally active environmental exposures are suspected to alter onset of puberty in girls, but research on this question has been very limited. OBJECTIVE: We investigated pubertal status in relation to hormonally active environmental exposures among a multiethnic group of 192 healthy 9-year-old girls residing in New York City. METHODS: Information was collected on breast and pubic hair stages, weight and height. Phytoestrogen intake was estimated from a food-frequency questionnaire. Three phytoestrogens and bis-phenolA (BPA) were measured in urine. In a

subset, 1,1'-dichloro-2,2'-bis(4-chlorophenyl)ethylene (DDE), polychlorinated biphenyls (PCBs) were measured in blood plasma and lead (Pb) in blood. Associations of exposures with pubertal stages (present=stage 2+ vs absent=stage 1) were examined using t-tests and Poisson multivariate regression to derive prevalence ratios (PR, 95%-confidence limits [CI]). RESULTS: Breast development was present in 53% of girls. DDE, Pb, and dietary intakes of phytoestrogens were not significantly associated with breast stage. Urinary phytoestrogen biomarker concentrations were lower among girls with breast development compared with no development. In multivariate models, main effects were strongest for two urinary isoflavones, daidzein (PR 0.89 [0.83-0.96] per lnmug/g creatinine) and genistein (0.94 [0.88-1.01]). Body mass index (BMI) is a hormonally relevant, strong risk factor for breast development. Therefore, BMI-modification of exposure effects was examined, and associations became stronger. Delayed breast development was observed among girls with below-median BMI and third tertile (high exposure) of urinary daidzein (PR 0.46 [0.26-0.78]); a similar effect was seen with genistein, comparing to girls median BMI and lowest two tertiles (combined) of these isoflavones. With urinary enterolactone a phytoestrogen effect was seen only among girls with high BMI, where breast development was delayed among those with high urinary enterolactone (PR 0.55 [0.32-0.96] for the upper tertile vs lower two combined). There was no main effect of PCBs on breast stage, but girls with below-median BMI and median PCB levels had reduced risk for breast development (any vs none) compared with other BMI-PCB groups. No biomarkers were associated with hair development, which was present in 31% of girls. CONCLUSIONS: Phytoestrogens and PCBs are environmental exposures that may delay breast development, especially in conjunction with BMI, which governs the endogenous hormonal milieu. Further research to confirm these findings may improve our understanding of the role of early life development in breast cancer risk and other chronic diseases related to obesity.

Arch Toxicol 2008 May;

In utero and postnatal exposure to a phytoestrogen-enriched diet increases parameters of acute inflammation in a rat model of TNBS-induced colitis.

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Inflammatory bowel disease (IBD) is very common in Europe and USA. Its incidence in East Asia has been traditionally low, albeit the risk of IBD increases in Asian immigrants adopting western lifestyles, suggesting a strong role of environmental/dietary factors in IBD. A lifelong exposure to phytoestrogen-rich diets has been associated with a decreased risk of developing breast cancer and might also be protective against IBD. We studied the influence of in utero and postnatal exposure to a phytoestrogen (PE)-rich diet on acute inflammation in an animal model of TNBS-induced colitis. Wistar rats were exposed in utero and postnatally to high (genistein: 240 mug/g feed; daidzein: 232 mug/g feed) or very low levels (genistein and daidzein <10 mug/g feed) of phytoestrogen isoflavones fed to pregnant dams with the diet and throughout nursing. After weaning, the offspring had free access to these diets. At the age of 11 weeks, colitis was induced with an enema of TNBS. After 3 days, animals were sacrificed and tissues were collected for histological evaluation and analysis of molecular markers of inflammation. Animals kept on a PE-rich diet (PRD) had higher colon weights than animals on low PE-levels (PDD), suggesting enhanced acute inflammation by phytoestrogens. This result was supported by

histological findings and by analysis of myeloperoxidase activity. Interestingly, relative mRNA and protein expression of cyclooxygenase-2 (COX-2) were modulated in rats on PRD, providing evidence that COX-2, the inducible isoform of the enzyme, is involved in the management of colonic inflammation. Our results suggest that early-in-life exposure to PE might not protect against the development of IBD but enhances the extent of acute inflammation.

Mol Endocrinol 2008 Feb;

Estrogen Receptors Alpha and Beta as Determinants of Gene Expression: Influence of Ligand, Dose, and Chromatin Binding.

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Estrogen receptors alpha and beta (ERalpha and ERbeta) mediate the actions of estrogens in a variety of normal and cancer target cells. Estrogens differ in their preference for these ERs, and many phytoestrogens bind preferentially to ERbeta. To investigate how phytoestrogens such as genistein impact ER-regulated gene expression, we used adenoviral gene delivery of ERbeta coupled with ERalpha-depletion with siRNA to generate human breast cancer (MCF-7) cells expressing four complements of ERalpha and ERbeta. We examined the dose-dependent effects of genistein on genome-wide gene expression by DNA microarrays and monitored the recruitment of ERs and coregulators to responsive regions of estrogen-regulated genes. At a low (6 nM) concentration, genistein regulated gene expression much more effectively in cells coexpressing ERalpha and ERbeta than in cells expressing ERalpha alone, whereas at high concentration (300 nM) genistein induced transcriptome changes very similar to that of 17beta-estradiol. We demonstrate that ERbeta is preferentially activated by genistein and is recruited to estrogen-responsive genomic sites, and that differential occupancy of ERalpha and ERbeta by genistein and E2 in turn influences the recruitment patterns of coregulators such as SRC3 and RIP140. Our observations indicate that genistein is a potency-selective ligand for gene expression regulation by ERalpha and ERbeta, and that the ability of ERalpha and ERbeta to serve as determinants of gene expression is greatly influenced by the nature of the ligand, by ligand dose, and by the differential abilities of ligand-ER complexes to recruit different coregulators at ER binding sites of hormone-regulated genes.

J Altern Complement Med 2008 Apr;14(3):287-97

Variable isoflavone content of red clover products affects intestinal disposition of biochanin A, formononetin, genistein, and daidzein.

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BACKGROUND: Marketed red clover (Trifoleum pratense) products use a wide variety of labels, and the isoflavone content from the label is ambiguous.

MATERIALS AND METHODS: In the present study, we analyzed the content of various isoflavone products, and determined (1) the content and (2) how the sample matrix of red clover products affects the intestinal disposition of main isoflavones within it, using the human intestinal Caco-2 cell model. RESULTS: Analysis using high- and ultraperformance liquid chromatography indicates that the isoflavone content varied significantly ($p < 0.05$) between the chosen products. Consequently, rates of isoflavone absorption across the Caco-2 cell monolayers varied ($p < 0.05$) greatly. Unexpectedly, permeabilities of biochanin A and formononetin (two key biomarkers) were found to be significantly affected ($p < 0.05$) by the product matrix. As expected, biochanin A was the only isoflavone with noticeable metabolite peaks in both the apical and basolateral sides. Interestingly, rates of metabolism and the polarity of the glucuronidated biochanin A excretion were also significantly altered ($p < 0.05$) by the product matrix. Studies using the breast cancer resistance protein (BCRP) inhibitor, dipyridamole, showed that both the apical and basolateral excretion of biochanin A glucuronides were significantly ($p < 0.05$) reduced (7.5- and 9.4-fold, respectively) when dipyridamole is present. This provides evidence that BCRP is the main transporter responsible for the apical efflux of isoflavone glucuronides. CONCLUSIONS: The isoflavone content of the marketed red clover products is highly variable, and the product matrix significantly affected the intestinal disposition of red clover isoflavones by altering their absorption rates, permeabilities, biochanin A glucuronide excretion rates, and the polarity of biochanin A glucuronide excretion. This research provides scientific evidence to support the standardization effort, so that consumers can make intelligent product choices.

J Manag Care Pharm 2008 Apr;14(3 Suppl):14-9

Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms.

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BACKGROUND: Vasomotor symptoms (VMS), such as hot flashes and night sweats, are the most bothersome symptoms of menopause and affect an estimated 75% of women aged over 50 years. OBJECTIVE: To discuss the burden, pathophysiology, and management of menopause-associated VMS and to evaluate pharmacologic options available for the treatment of VMS, including herbal remedies, hormone replacement therapy (HRT), and nonhormonal therapies. SUMMARY: Lifestyle changes, including regulation of core body temperature, relaxation techniques, regular physical activity, weight loss, and smoking cessation may help reduce the risk of VMS and should be implemented by all women with menopause-associated VMS. The role of herbal remedies in the treatment of VMS remains unclear, as clinical trial efficacy data are inconsistent and inconclusive. Nevertheless, soy isoflavones, red clover isoflavones, black cohosh, and vitamin E are commonly used to treat VMS and may be considered in women with mild symptoms that are not controlled by lifestyle changes alone. These herbal remedies appear to be safe when used for short durations (d 6 months). HRT, consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus) is the most widely studied and most effective treatment option for relief of menopause-associated VMS and is considered the standard of care for women with moderate-to-severe VMS. HRT should be used at the lowest effective dose and for the shortest duration possible (preferably d 5 years) in women in whom the potential benefits outweigh the potential risks. Nonhormonal therapies, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, and clonidine, may be

appropriate alternatives in women who cannot or will not use HRT for VMS relief, such as those with a history of or at risk for breast cancer. CONCLUSION: The physical and financial burden imposed by menopauseassociated VMS is immense. Optimum management of VMS includes lifestyle changes in all women and HRT in women with moderate-tosevere symptoms. Less effective herbal remedies or nonhormonal therapies may be appropriate in certain women, such as those with mild symptoms or those who cannot or will not take HRT.

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The red clover (Trifolium pratense) isoflavone biochanin A inhibits aromatase activity and expression.

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Biochanin A is an isoflavone isolated from red clover (Trifolium pratense), and is a commercially available nutraceutical for women suffering from postmenopausal symptoms. Isoflavones resemble the structure of oestrogen, and display agonistic and antagonistic interactions with the oestrogen receptor. Overexposure of oestrogen is a major contributing factor in the development of breast cancer, and cytochrome P450 (CYP) 19 enzyme, or aromatase, catalyses the reaction converting androgen to oestrogen. In the present study the effect of biochanin A on the gene regulation and enzyme activity of aromatase was investigated. By assaying MCF-7 cells stably transfected with CYP19, biochanin A inhibited aromatase activity and hampered cell growth attributing to the enzyme activity. In addition, 25 mum-biochanin A significantly reduced CYP19 mRNA abundance in the oestrogen receptor-negative breast cancer cells SK-BR-3. The transcriptional control of the CYP19 gene is exon-specific, and promoter regions I.3 and II have been shown to be responsible for CYP19 expression in SK-BR-3 cells. Luciferase reporter gene assays also revealed that biochanin A could repress the transcriptional control dictated by the promoter regulation. Interestingly, genistein did not inhibit aromatase but it might down regulate promoter I.3 and II transactivation. Since genistein is a major metabolite of biochanin A, it might contribute to biochanin A's suppressive effect on CYP19 expression. The present study illustrated that biochanin A inhibited CYP19 activity and gene expression.

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Dietary and lifestyle correlates of urinary excretion status of equol in Japanese women.

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The isoflavone metabolite equol has been identified in urine or blood samples in some but not all humans. In this cross-sectional study, we examined the association between lifestyle, including diet, and the urinary excretion of equol. Study subjects were 419 Japanese women who were

recruited from a breast cancer screening center. Each woman responded to a self-administered questionnaire seeking information about health and lifestyle factors. Diet was assessed by a validated semiquantitative food frequency questionnaire. Urinary isoflavones were measured using spot urine samples. Equol was detected in the urine of 84 (20.0%) women. After controlling for covariates, it was found that dairy product intake was significantly lower in those who excreted detectable equol levels in urine than in those who did not. Because equol is derived from daidzein, individuals with low intake of daidzein may produce undetectable levels of equol. To account for this, the study subjects were restricted to 163 women with urinary daidzein levels of 10 nmol/mg creatinine or higher. The association of equol excretion with dairy product intake remained significant. Demographic factors, smoking status, and menstrual and reproductive factors were unrelated to equol excretion. These data suggest that dairy product intake may be associated with the production of equol.

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Novel identification of UDP-glucuronosyltransferase 1A10 as an estrogen-regulated target gene.

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Recently, we have shown that UGT1A10 is actively involved in the inactivation of E(1), E(2), and their 2- and 4-hydroxylated derivatives. In the present study, we show for the first time that treatment of the MCF-7 ER-positive breast cancer cell line with E(2) produces a dose-dependent up-regulation of UGT1A10 mRNA levels, followed by a steady down-regulation. In contrast, E(2) did not stimulate mRNA expression in the MDA-MB-231 (ER)-negative breast cancer cell line. Expression of UGT1A10 mRNA was blocked by the antiestrogen, ICI 182,780, but not by the transcriptional inhibitor, actinomycin-d. These findings suggest that regulation of UGT1A10 mRNA might be a primary transcriptional response mediated through the ER. Expression of UGT1A10 mRNA was also stimulated by other estrogenic compounds including propylpyrazoletriol (PPT) and genistein (Gen). Exposure of MCF-7 cells to 0.1nM E(2) up-regulated, and then down-regulated, UGT1A protein and enzymatic activity toward E(2) at 10nM E(2) as determined by Western blot and glucuronidation activity assays. Collectively, these results suggest that induction of UGT1A10 mRNA expression by E(2) might be mediated through ER, and that this isoform is a novel, estrogen-regulated target gene in MCF-7, ER-positive human breast cancer cells. The finding of E(2)-induced expression of UGT1A10 mRNA, followed by the down-regulation of UGT1A10 at pharmacological concentrations of E(2), might have a significant moderating effect on E(2) availability for ER and estrogen clearance, thereby promoting the signaling of E(2) in breast cancer cells.

Arch Biochem Biophys 2007 Oct;

Inhibition of cellular proliferation by the genistein metabolite 5,7,3',4'-tetrahydroxyisoflavone is mediated by DNA damage and activation of the ATR signalling pathway.

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The cellular actions of genistein, and its in vivo metabolites, are believed to mediate the decreased risk of breast cancer associated with high soy consumption. The genistein metabolite, 5,7,3',4'-tetrahydroxyisoflavone (THIF), induced G2-M cell cycle arrest in T47D tumorigenic breast epithelial cells via a mechanism involving the activation of ataxia telangiectasia and Rad3-related kinase (ATR) via its phosphorylation at Ser(428). This activation of ATR appeared to result from THIF-induced increases in intracellular oxidative stress, a depletion of cellular GSH and an increase in DNA strand breakage. THIF treatment also led to an inhibition of cdc2, which was accompanied by the phosphorylation of both p53 (Ser(15)) and Chk1 (Ser(296)) and the de-activation of cdc25C phosphatase. We suggest the anti-proliferative actions of THIF may be mediated by initial oxidative DNA damage, activation of ATR and downstream regulation of the p53 and Chk1 pathways leading to cell cycle arrest in G2-M. This may represent one mechanism by which genistein exerts its cellular activity in vivo.

Mol Pharm 2007 Oct;

Pharmacokinetics and Bioavailability of the Bioflavonoid Biochanin A: Effects of Quercetin and EGCG on Biochanin A Disposition in Rats.

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Little is known regarding pharmacokinetic (PK) or pharmacodynamic interactions of flavonoids with each other: this is of significance since multiple flavonoids are present in the diet and in dietary supplements. Our objective was to determine the effect of quercetin and (-)-epigallocatechin-3-gallate (EGCG), major flavonoids present in the diet, on the PK and bioavailability of biochanin A, a flavonoid with chemopreventive properties. BCA was administered to rats intravenously (5 mg/kg) or orally (16.67 or 50 mg/kg) with or without concomitant EGCG and quercetin. In vitro studies with the human intestinal Caco-2 and human hepatic HepG2 cell lines were performed to evaluate the effects of quercetin and EGCG on the cellular metabolism of BCA, and studies with human breast cancer MCF-7 cells that overexpress P-glycoprotein or BCRP (MCF-7/ADR and MCF-7/MX100 cells, respectively) or MDCK cells that express MRP2 (MDCK-MRP2) were performed to evaluate the effects of cellular efflux. An HPLC assay was used to determine plasma, urine, and cellular concentrations of BCA and the conjugated metabolites of BCA (following enzymatic hydrolysis). The coadministration of quercetin and EGCG significantly increased the BCA area under the plasma concentration vs time curve (AUC) in rats, after both iv and oral administration of BCA. The AUC of total BCA (unchanged + conjugated) was also increased. The increases in BCA AUC reflected predominantly increased bioavailability; this was true even after iv administration due to an apparent increase in the enterohepatic cycling of BCA. Our findings demonstrate for the first time that the administration of multiple flavonoids results in increased flavonoid bioavailability, as well as a decrease in clearance, potentially due to increased enterohepatic cycling.

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Phytoestrogens for vasomotor menopausal symptoms.

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BACKGROUND: Vasomotor symptoms, such as hot flushes and night sweats, are very common during the menopausal transition. Hormone replacement therapy has traditionally been used as a very effective treatment but concerns over increased risks of some chronic diseases have markedly increased the interest of women in alternatives. Some of the most popular of these are treatments based on foods or supplements enriched with phytoestrogens, plant-derived chemicals that have oestrogenic action. OBJECTIVES: To assess the efficacy, safety and acceptability of foods and supplements based on high levels of phytoestrogens for reducing hot flushes and night sweats in postmenopausal women. SEARCH STRATEGY: Searches were undertaken of the following electronic databases: the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of randomised trials, Cochrane Register of Controlled Trials (CENTRAL) (March 2007), MEDLINE (1966 to March 2007), EMBASE (1980 to March 2007), AMED (1985 to March 2007), PsycINFO (1986 to March 2007) and CINAHL (1982 to March 2007). Attempts were made to access grey literature by letters to pharmaceutical companies and searches of ongoing trial registers. Reference lists of included trials were also searched. SELECTION CRITERIA: Studies were included if they were randomised, had peri- or postmenopausal participants with vasomotor symptoms, a duration of at least 12 weeks and where the intervention was a food or supplement with high levels of phytoestrogens (and not combined with other herbal treatments). Trials of women who had breast cancer or a history of breast cancer were excluded. DATA COLLECTION AND ANALYSIS: Selection of trials, data extraction and quality assessment were undertaken by at least two authors. Most of the trials were too dissimilar to combine in meta-analysis and their results are provided in table format. Studies were grouped into broad categories: dietary soy, soy extracts, red clover extracts and other types of phytoestrogen. Five trials used Promensil, a red clover extract; these trials were combined in a meta-analysis and summary effect measures were calculated. MAIN RESULTS: Thirty trials comparing phytoestrogens with control met the inclusion criteria. Very few trials had data suitable for combining in meta-analysis. Of the five trials with data suitable for pooling that assessed daily frequency of hot flushes, there was no significant difference overall in the frequency of hot flushes between Promensil (a red clover extract) and placebo (WMD=-0.6, 95% CI -1.8 to 0.6). There was no evidence of a difference in percentage reduction in hot flushes in two trials between Promensil and placebo (WMD=20.2, 95% CI -12.1 to 52.4). Individual results from the remaining trials were compared. Some of the trials found that phytoestrogen treatments alleviated the frequency and severity of hot flushes and night sweats when compared to placebo but many of the trials were of low quality and were underpowered. There was a strong placebo effect in most trials with a reduction in frequency ranging from 1% to 59% with placebo. There was no indication that the discrepant results were due to the amount of isoflavone in the active treatment arm, the severity of vasomotor symptoms or trial quality factors. There was also no evidence that the treatments caused oestrogenic stimulation of the endometrium (an adverse effect) when used for up to two years. AUTHORS' CONCLUSIONS: There is no evidence of effectiveness in the alleviation of menopausal symptoms with the use of phytoestrogen treatments.

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Bcl-2 overexpression sensitizes MCF-7 cells to genistein by multiple mechanisms.

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Genistein is a soy isoflavone with anti-tumor properties. Genistein-induced apoptosis involves Bcl-2 downregulation. However, overexpression of Bcl-2 in breast cancer has been associated with better prognosis and response to hormonal therapy. To examine genistein's effect on breast cancer cells with different Bcl-2 levels, we established control (MCF-7/PV) and Bcl-2 overexpressing MCF-7 (MCF-7/Bcl-2) cell lines and characterized genistein regulated apoptosis and cell cycle progression in these cells. Our results demonstrate that overexpression of Bcl-2 rendered MCF-7 cells more sensitive, rather than resistant, to genistein. We found that genistein induces enhanced cytochrome c release and mitochondrial membrane depolarization in MCF-7/Bcl-2 cells, as compared to control. We also found that genistein increases Bcl-2 levels and Bcl-2/Bax ratio in the mitochondrial fractions of MCF-7/Bcl-2 cells, suggesting that disturbed Bcl-2/Bax distribution may cause cytochrome c release and apoptosis in these cells. Cell cycle analysis indicated that genistein induces G0/G1 arrest in MCF-7/PV cells but increases in G2/M arrest in MCF-7/Bcl-2 cells. This was accompanied by modified responses of several cell cycle regulators, such as p21 and cyclin B1. Taken together, our results indicate that genistein-Bcl-2 interaction switches Bcl-2 from an anti-apoptotic protein into a proapoptotic protein, which involves disturbed Bcl-2/Bax distribution in mitochondria, increased cytochrome c release and modified cell cycle regulation.

Mol Cell Endocrinol 2007 Jul;

A novel molecular assay to discriminate transcriptional effects caused by xenoestrogens.

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A phenotypic definition of the term estrogen has become increasingly problematic due to the multiple modes of estrogen action which can now be defined by differing nuclear and membrane receptors for the classic ligand, 17beta-estradiol, and by the multiple signalling pathways that are consequently addressed. This has led to the term xenoestrogen being largely determined by whatever assay system is used for its definition. Here we describe a novel and simple matrix for a transfection system using MBA-MD231 and MCF-7 breast cancer cells as hosts. This matrix is able to vary the type of nuclear estrogen receptor used, and by varying the promoter-reporter construct between one using a classic estrogen response element (ERE) enhancer, and one using an enhancer element derived from the bovine oxytocin gene promoter binding an orphan nuclear receptor, direct classical effects can be neatly discriminated from non-classical and non-genomic actions of test substances. This assay matrix has been used to examine a selection of phytoestrogens and xenobiotics, thereby providing new information on the mechanism of action of some of these substances in breast cancer cells.

Steroids 2007 Jun;

Deoxybenzoins are novel potent selective estrogen receptor modulators.

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Deoxybenzoins are plant compounds with similar structure to isoflavones. In this study, we evaluated the ability of two synthesized deoxybenzoins (compound 1 and compound 2) (a) to influence the activity of the estrogen receptor subtypes ERalpha and ERbeta in HeLa cells co-transfected with an estrogen response element-driven luciferase reporter gene and ERalpha- or ERbeta-expression vectors, (b) to modulate the IGFBP-3 and pS2 protein in MCF-7 breast cancer cells, (c) to induce mineralization of KS483 osteoblasts and (d) to affect the cell viability of endometrial (Ishikawa) and breast (MCF-7, MDA-MB-231) cancer cells. Docking and binding energy calculations were performed using the mixed Monte Carlo/Low Mode search method (Macromodel 6.5). Compound 1 displayed significant estrogenic activity via ERbeta but no activity via ERalpha. Compound 2 was an estrogen-agonist via ERalpha and antagonist via ERbeta. Both compounds increased, like the pure antiestrogen ICI182780, the IGFBP-3 levels. Compound 2 induced, like 17beta-estradiol, significant mineralization in osteoblasts. The cell viability of Ishikawa cells was unchanged in the presence of either compound. Compound 1 increased MCF-7 cell viability consistently with an increase in pS2 levels, whereas compound 2 inhibited the cell viability. Molecular modeling confirmed the agonistic or antagonistic behaviour of compound 2 via ER subtypes. Compound 2, being an agonist in osteoblasts, an antagonist in breast cancer cells, with no estrogenic effects in endometrial cancer cells, makes it a potential selective estrogen receptor modulator and a choice for hormone replacement therapy.

Physiol Genomics 2007 Mar;

Expression Profiling of Rat Mammary Epithelial Cells Reveals Candidate Signaling Pathways in Dietary Protection from Mammary Tumors.

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The role of diet in the prevention of breast cancer is widely accepted, yet little is known about how its biological effects mitigate susceptibility to this disease. Soy consumption is associated with reduced breast cancer risk in women, an effect largely attributed to the soy isoflavone genistein (GEN). We previously showed reduced incidence of chemically-induced mammary tumors in young adult rats with lifetime dietary intake of soy protein isolate (SPI) than in those fed the control diet containing casein (CAS). To gain insight into signaling pathways underlying dietary tumor protection, we performed genome-wide expression profiling of mammary epithelial cells from young adult rats lifetime fed CAS, SPI, or CAS supplemented with GEN. We identified mammary epithelial genes regulated by SPI (79 total) and GEN (96 total) using Affymetrix rat 230A GeneChip arrays and found minimal overlap in gene expression patterns. We showed that the

regulated transcripts functionally clustered in biochemical pathways involving metabolism, immune response, signal transduction, and ion transport. We confirmed the differential expression of Wnt (Wnt5a, Sfrp2) and Notch (Notch2, Hes1) signaling components by SPI and/or GEN using QPCR. Wnt pathway inhibition by GEN was supported by reduced Cyclin D1 immunoreactivity in mammary ductal epithelium of GEN relative to CAS and SPI groups, despite comparable levels of membrane-localized E-cadherin and beta-catenin. Identification of distinct GEN and SPI responsive genes in mammary epithelial cells may define early events contributing to tumor protection by diet relevant to the prevention of breast and other types of cancer. Key words: mammary gland, genistein, soy proteins, wnt signaling, tumorigenesis.

Fertil Steril 2007 May;

Phytoestrogens in clinical practice: a review of the literature.

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OBJECTIVE: To review clinical studies assessing the effect of phytoestrogen supplementation on the signs and symptoms of the climacteric syndrome and on the incidence of breast cancer, cardiovascular disease, and skeletal fractures. DESIGN: Literature research using PubMed and the Cochrane controlled trials register. SETTING: None. PATIENT(S): None. INTERVENTION(S): None. MAIN OUTCOME MEASURE(S): None. RESULT(S): Six systematic reviews and meta-analyses of 25 randomized, controlled trials (RCTs) assessing the use of phytoestrogens for the treatment of the climacteric syndrome were identified. Systematic reviews of RCTs show contradictory results, and meta-analyses demonstrate no statistically significant reduction of vasomotor symptoms for phytoestrogens. Individual RCTs report significant reductions in vasomotor symptoms for red clover and soy phytoestrogens. In selected patient populations, such as in women with early natural postmenopause and mild to moderate vasomotor symptoms, a systematic review of five RCTs found a significant reduction of hot flashes in five out of five RCTs. Twenty-two case-control and cohort studies examined the incidence of breast cancer among women with and without a diet high in phytoestrogens. A meta-analysis of 21 studies found a significantly reduced incidence of breast cancer among past phytoestrogen users. RCTs document beneficial effects of phytoestrogens on surrogate parameters such as bone mineral density, vasodilation, platelet aggregation, insulin resistance, and serum concentrations of triglycerides, high-density lipoprotein, and low-density lipoprotein. None of the available RCTs documents a protective effect of phytoestrogens for the clinical end points of breast cancer, bone fracture, or cardiovascular events. CONCLUSION(S): Based on the available evidence, phytoestrogens should only be used in selected women, i.e., those presenting with mild to moderate vasomotor symptoms in early natural postmenopause. None of the compounds investigated so far have been proven to protect against breast cancer, bone fracture, or cardiovascular disease.

J Steroid Biochem Mol Biol 2007 Mar;

Oestrogen receptors pathways to oestrogen responsive elements: The transactivation function-1 acts as the keystone of oestrogen receptor (ER)beta-mediated transcriptional repression of ERalpha.

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Oestrogen receptors (ER)alpha and beta modify the expression of genes involved in cell growth, proliferation and differentiation through binding to oestrogen response elements (EREs) located in a number of gene promoters. Transient transfection of different luciferase reporter vectors 3xEREs-Vit, 2xEREs-tk and ERE-C3 showed that the transactivation capacity of both ER subtypes was influenced by 1) the nature of the inducer (oestradiol (E(2)), phyto- and anti-oestrogen (AE)), 2) the structure of the promoter (nucleotidic sequence, number of ERE, length of the promoter sequence) and 3) the cell line (containing endogenous ER (MCF-7) or in which ER was stably expressed (MDA-MB-231-HE-5 (ERalpha+) or MDA-MB-231-HERB (ERbeta+)). ER subtype did not display the same efficacy on the different constructions in the presence of E(2) and of AE according to the cell (e.g. in MCF-7 cells: tk>>Vit>>C3 approximately 0 while in MDA-MB-231 cells: Vit>>tk approximately C3). E(2) response was higher in MCF-7 cells, probably due to higher ER expression level (maximal at 10(-10)M instead of 10(-8)M for E(2) in HE-5 cells). Finally, the same ligand could exert opposite activities on the same promoter according to the ER isoform expressed: in the MDA-MB-231 cells, AE acted as inducers of the C3 promoter via ERbeta whereas ERalpha/AE complexes down-regulated this promoter. Approximately 70% of breast tumours express ER and most tumour cells coexpress both ER isotypes. Thus, different types of ER dimers can be formed in such tumours (ERbeta or ERalpha homodimers or ERalpha/ERbeta heterodimers). We therefore studied the influence of the coexistence of the two ERs on the ligand-induced transcriptional process following transient transfection of ERalpha in ERbeta+ cells, and inversely ERbeta in ERalpha+ cells. ERbeta-transfection inhibited the E(2)- and genistein-induced ERalpha-dependent transcription on all promoters in all cell lines except C3 in MCF-7; this inhibitory effect was lost following transfection of ERbeta deleted of its AF-1 (ERbeta-AF-2). These results suggest that the dominant negative properties of ERbeta are mainly due to its AF-1 function. Interestingly, transfection of an ERbeta-AF-2 construct into MCF-7 cells potentiated the transcription inhibitory capacity of 4-OH-tamoxifen (OHT) on the Vit and tk promoters. Thus, (1) OHT exerts an agonistic activity through the AF-1 function of ER and (2) expression of ERbeta in breast cancer cells seems to favour the AE treatment. Contrary to ERbeta, ERalpha-transfection had little effect on ERbeta transactivation capacity in HERB cells. Finally, the ratio ERalpha/ERbeta constitutes one decisive parameters to orientate the transcriptional mechanism of a target gene in the presence of agonist as well as of antagonist ligands.

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Soy isoflavonoid effects on endogenous estrogen metabolism in postmenopausal female monkeys.

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Endogenous estrogens are important determinants of breast cancer risk in postmenopausal women. In this study we evaluated the effects of dietary soy isoflavonoids on endogenous estrogen metabolism in a postmenopausal primate model. Ovariectomized female cynomolgus monkeys were randomized to receive one of three diets for 36 months: (i) isoflavonoid-depleted soy protein isolate (SPI-) (n = 29); (ii) soy protein isolate with 129 mg isoflavonoids/1800 kcal diet (8.6 mg isoflavonoids/kg body weight (BW),

expressed in aglycone units) (SPI+) (n = 29) or (iii) isoflavonoid-depleted soy protein isolate with conjugated equine estrogens (CEE) at a dose of 0.625 mg/1800 kcal diet (0.042 mg CEE/kg BW) (n = 30). Mean plasma isoflavonoid concentrations in the SPI+ group were 946.9 +/- 135.9 nmol/l, and equol was the primary circulating isoflavonoid (549.7 +/- 61.6 nmol/l). The SPI+ diet resulted in lower serum estrone (E(1)) after 29 (-26%, P = 0.03) and 34 months (-21%, P = 0.04) compared to the SPI- diet, while urinary 2-hydroxyestrone (P = 0.005) and the 2 to 16alpha-hydroxyestrone ratio (P < 0.0001) were markedly higher in the SPI+ group compared to SPI-. Isoflavonoid treatment did not significantly alter gene markers of estrogen metabolism or estrogen receptor agonist activity in breast tissue. Within the SPI+ group, higher concentrations of serum equol (but not daidzein or genistein) corresponded to significantly lower serum E(1), mammary gland epithelial area and uterine weight (P < 0.01 for all). These findings suggest that long-term exposure to soy isoflavonoids, equol in particular, may facilitate endogenous estrogen clearance and catabolism to more benign 2-hydroxylated metabolites.

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Modulation of mammary tumor development in Tg.NK (MMTV/c-neu) mice by dietary fatty acids and life stage-specific exposure to phytoestrogens.

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Breast cancer is a major public health problem among women worldwide. Phytoestrogens and dietary fat composition are being investigated to elucidate the role of nutrition in breast cancer risk. Both epidemiological and rodent studies suggest that the chemopreventive effect of phytoestrogens depends on timing of exposure. We investigated spontaneous mammary tumor development in female heterozygous MMTV/c-neu (Tg.NK) mice upon isoflavone exposure on background diets rich in either n-6 or n-3 polyunsaturated fatty acids (PUFAs). Three different exposure protocols were used, either from conception to weaning, or from weaning onwards, or lifelong. Mice fed diets high in n-3 PUFAs developed mammary tumors 15 weeks later than mice fed n-6 PUFA diets. In the latter mice, isoflavone exposure from weaning onwards resulted in a significant decrease in tumor incidence and a delay in tumor onset. Therefore, the effects of phytoestrogen exposure on tumor formation appear to depend on the composition of the background diet and on the timing of exposure within the life cycle.

Carcinogenesis 2007 Mar;28(3):738-48

Genistein protects human mammary epithelial cells from benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide and 4-hydroxy-2-nonenal genotoxicity by modulating the glutathione/glutathione S-transferase system.

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Epidemiological studies have shown that ingestion of isoflavone-rich soy products is associated with a reduced risk for the development of breast cancer. In the present study, we investigated the hypothesis that genistein modulates the expression of glutathione S-transferases (GSTs) in human breast cells, thus conferring protection towards genotoxic carcinogens which are GST substrates. Our approach was to use human mammary cell lines MCF-10A and MCF-7 as models for non-neoplastic and neoplastic epithelial breast cells, respectively. MCF-10A cells expressed hGSTA1/2, hGSTA4-4, hGSTM1-1 and hGSTP1-1 proteins, but not hGSTM2-2. In contrast, MCF-7 cells only marginally expressed hGSTA1/2, hGSTA4-4 and hGSTM1-1. Concordant to the protein expression, the hGSTA4 and hGSTP1 mRNA expression was higher in the non-neoplastic cell line. Exposure to genistein significantly increased hGSTP1 mRNA (2.3-fold), hGSTP1-1 protein levels (3.1-fold), GST catalytic activity (4.7-fold) and intracellular glutathione concentrations (1.4-fold) in MCF-10A cells, whereas no effects were observed on GST expression or glutathione concentrations in MCF-7 cells. Preincubation of MCF-10A cells with genistein decreased the extent of DNA damage by 4-hydroxy-2-nonenal (150 microM) and benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide (50 microM), compounds readily detoxified by hGSTA4-4 and hGSTP1-1. In conclusion, genistein pretreatment protects non-neoplastic mammary cells from certain carcinogens that are detoxified by GSTs, suggesting that dietary-mediated induction of GSTs may be a mechanism contributing to prevention against genotoxic injury in the aetiology of breast cancer.

Cell Death Differ 2007 Mar;14(3):472-9

Genistein inhibits Brca1 mutant tumor growth through activation of DNA damage checkpoints, cell cycle arrest, and mitotic catastrophe.

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Epidemiological studies revealed that amount of consumption of soy was inversely related to incidence of breast cancer. Genistein, the predominant isoflavone in soy, has been reported to reduce the incidence of breast cancer in animal models. To investigate whether genistein has a therapeutic effect on BRCA1-associated breast cancer, we treated Brca1 mutant mammary tumor cells with genistein. We showed that genistein treatment depleted the G1 population of cells, which was accompanied by an accumulation of cells at G2. Some genistein-treated cells entered mitosis; however, they exhibited chromosome abnormalities and maintained tetraploidy owing to abortive mitotic exit. A fraction of G2 cells underwent endoreduplication and became polyploid, which was accompanied by increased cell death through activating DNA damage response. Furthermore, our data indicated that Brca1 mutant cells were more sensitive to genistein than some other types of cancer cells, highlighting a good therapeutic potential of genistein for BRCA1-associated breast cancer.

J Org Chem 2007 Dec;

Synthesis and Evaluation of Derrubone and Select Analogues.

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Recently, we reported that the natural product derrubone exhibits Hsp90 inhibitory activity. Due to its unique architectural scaffold and proposed rapid assembly, the synthesis of this natural product was pursued with the aim of identifying structure-activity relationships. Synthesis of the natural product was accomplished in eight highly convergent steps, which led to a facile method for the construction of related compounds. Biological evaluation of derrubone and its analogues identified several compounds that exhibit low micromolar inhibitory activity against breast and colon cancer cell lines.

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Phytoestrogens modulate the expression of 17alpha-estradiol metabolizing enzymes in cultured MCF-7 cells.

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The activation of 17beta-estradiol (E2) to 2-hydroxyestradiol (2-HO-E2), the more genotoxic 4-hydroxyestradiol (4-HO-E2), and the oxidation to the respective quinones constitutes a risk factor in hormonal carcinogenesis. 2-HO-E2 is formed by cytochrome P450 CYP1A1, and 4-HO-E2 is formed by CYP1B1. Both are detoxified by catechol-O-methyltransferase (COMT), whereas their quinones are inactivated by NADPH-quinone-oxidoreductase (QR). Since the soy isoflavones genistein (GEN) and daidzein (DAI) are widely consumed due to their putative protective function in breast carcinogenesis, we examined the influence of E2, GEN, and DAI on CYP1A1/1B1, COMT, and QR expression in MCF-7 cells by reverse transcription/competitive PCR. CYP1A1 and COMT enzyme activity were determined using ethoxyresorufin and quercetin as substrates. Furthermore, estrogen receptor (ER)-regulated cell proliferation was determined by E-screen. E2, GEN, and DAI inhibited the expression of CYP1A1, COMT, and QR. The maximum effect (reduction by 40-80%, depending on the gene product and compound) was obtained at 100 pM E2, 1 microM GEN, and 10 microM DAI, which also induced the most pronounced cell proliferation in the E-screen. In contrast, expression of CYP1B1 was only slightly affected. CYP1A1 and COMT mRNA levels correlated with enzyme activities. The ER antagonist ICI 182,780 reversed the E2- and isoflavone-mediated effects. Thus, GEN and DAI at estrogen-active concentrations stimulate the formation of the more E2 genotoxic metabolites and inhibit the detoxification of catechol and quinone estrogens in estrogen-responsive tumor cells.

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Equol status modifies the association of soy intake and mammographic density in a sample of postmenopausal women.

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Only 30% to 50% of people produce the daidzein-metabolite equol after eating soy. We conducted a cross-sectional study of the associations between equol status, intake of soy foods, and mammographic density in a sample of postmenopausal women recruited at a radiology clinic near Buffalo, New York. Participants were 48 to 82 years old, had no history of cancer or breast reduction/augmentation, and no recent use of antibiotics or hormones. Percent density was measured by computer-assisted analysis of digitized images of craniocaudal films. Equol status was assessed using a soy-challenge protocol and usual soy intake by questionnaire. General linear models were used to assess independent and joint effects of equol status and intake of soy on multivariate adjusted percent density (covariates included age, body mass index, parity, age at first birth, and ever use of combined hormone therapy). Of 325 enrolled, 232 (71%) participants completed study assessments and are included in the present analysis. Mean percent density was 34% (+/-18%). Seventy-five (30%) participants were producers of equol. Forty-three (19%) participants reported regularly eating >1 soy food or supplement/wk. There were no significant independent associations of equol status or soy intake with percent density, but the interaction between these factors was significant ($P < 0.01$). Among equol producers, those with weekly soy intake had lower percent density (30.7% in weekly consumers of soy versus 38.9% in others; $P = 0.08$); among nonproducers, weekly soy intake was associated with higher percent density (37.5% in weekly soy consumers versus 30.7% in others; $P = 0.03$). Results suggest that equol producers and nonproducers may experience different effects of dietary soy on breast tissue. (Cancer Epidemiol Biomarkers Prev 2008;17(1):33-42).

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Genistein-A dietary compound inducing hormonal and metabolic changes.

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Genistein is a plant-derived compound possessing well-known preventive activity in breast and prostate cancer, cardiovascular diseases and post-menopausal problems. Lately, the interests in genistein have widened. The studies concerning effects of genistein performed on animals and humans revealed other aspects of its action - the metabolic alterations at the cellular level and in the whole organism. It was shown that genistein decreased body and fat tissue weight gains accompanied by reduced food intake. After ingestion of dietary genistein, the alterations in concentrations of hormones such as: insulin, leptin, thyroid hormones, adrenocorticotropic hormone, cortisol and corticosterone were observed. The changes in lipid parameters - triglycerides and cholesterol were also noticed as a consequence of genistein administration. Moreover, the altered expression of genes engaged in lipid metabolism, disturbed glucose transport into cells, affected lipolysis and lipogenesis and changed ATP synthesis were found as a result of genistein action.

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Oridonin-induced A431 cell apoptosis partially through blockage of the Ras/Raf/ERK signal pathway.

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We have reported that oridonin, a diterpenoid isolated from the plant Rabdosia rubescens, had apoptosis-inducing activities in many cell lines (e.g., human melanoma A375-S2, human cervical cancer HeLa, human breast adenocarcinoma MCF-7, and murine fibrosarcoma L929). In this study, we further investigated signaling events involved in oridonin-induced apoptosis in human epidermoid carcinoma A431 cells. It was found that the total tyrosine kinase activity was inhibited and the protein expressions of epidermal growth factor receptor (EGFR) and phosphorylated EGFR were decreased in oridonin-induced A431 cell apoptosis. Expression of EGFR downstream effector proteins, Grb2, Ras, Raf-1, and extracellular signal-regulated kinase (ERK), was also downregulated by oridonin. Moreover, the oridonin-induced apoptosis was augmented by the Ras inhibitor manumycin A, Raf-1 inhibitor GW5074, or ERK inhibitor PD98059, suggesting that inactivation of Ras, Raf, or ERK participates in oridonin-induced apoptosis. Taken together, oridonin-induced apoptosis in A431 cells might be through blocking EGFR and its downstream Ras/Raf/ERK signal pathway.

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Chemoprevention of mammary tumorigenesis and chemomodulation of the antioxidative enzymes and peroxidative damage in prepubertal Sprague Dawley rats by Biochanin A.

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Although chemopreventive action of Biochanin A against various cancers including that of prostate, breast, colon, and fore-stomach has been reported earlier, none of the studies was made in prepubertal subjects. The present study appears to be the first one on prepubertal rats that indicates the efficacy of the test compound in the prevention of tumorigenesis. The antioxidative status and xenobiotic metabolism were also evaluated to understand the mechanism of Biochanin A induced prevention of cancer. For the tumorigenesis study 500 mug/g bwt of Biochanin A or vehicle dimethyl sulfoxide (DMSO) s.c, was injected at 16th, 18th, and 20th days post-partum followed by the administration of dimethylbenz[a]nthracene (DMBA) (80 mug/g bwt) at 50th day. In another set of experiments, to study the involvement of peroxidative process in the mechanism of action of test compound, different antioxidant parameters were studied following the administration of two different doses of Biochanin A (0.5 and 50 mg/kg bwt, through oral gavage for 10 days) in the prepubertal rats from day 16 post-partum. Results showed a significant reduction in the mammary tumors (more than 40%) in Biochanin A treated animals, as compared to animals treated with DMBA only. Spectrophotometric enzyme estimations revealed that the specific activities of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione transferase (GST), DT-diaphorase (DTD), and reduced glutathione (GSH) levels were increased, whereas specific activities of lactate dehydrogenase (LDH) and lipid peroxidation (LPO) were decreased significantly, both in liver as well as in mammary gland, in animals treated with Biochanin A prepubertally. These results reveal the possible involvement of the antioxidative and metabolic enzymes in the suppression of cancer burden and incidence in a prepubertal rat model suggesting that the intake of this

phytoestrogen at an early stage may help in lowering the risk of mammary tumor.

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Dietary Sources and Determinants of Soy Isoflavone Intake among Midlife Chinese Women in Hong Kong.

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The dietary sources, intake levels, and determinants of soy isoflavone intake were examined using 3217 dietary recalls (DR) collected from 141 Hong Kong Chinese women aged 50-61 y. Multiple-pass 24-h DR were administered by phone by trained interviewers on 23 random, nonconsecutive days to participants over a 12-mo period from 2001 to 2002. We calculated isoflavone intake using analytical values in the Chinese University of Hong Kong Soy Isoflavone Database. Results indicated that the daily intake of total isoflavones was 7.8 +/- 5.6 mg in the study population. Non-Cantonese women had a higher intake of 10.7 +/- 7.6 mg compared with 7.3 +/- 5.0 mg in Cantonese women (P = 0.04). Altogether, 22 foods contributed approximately 90% of the total isoflavone intake. Soft tofu alone accounted for approximately 21% of the isoflavone intake, followed by bean curd skin (7.1%), name-brand soybean milk (6.3%), homemade soybean milk (6.2%), and generic soybean milk (5.8%). Combined, these 5 food items contributed 46% of the total dietary isoflavones. Multiple linear regression analysis indicated dialect group, self-reported health, and age group were significant independent predictors of soy isoflavone consumption. The data provide the basis for elucidating the patterns, determinants, and assessment of dietary soy isoflavone intake in Asian women.

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Studies on the anti-tumor activities of the soy isoflavone daidzein on murine neuroblastoma cells.

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Daidzein (4',7-dihydroxyisoflavone) and genistein (4',5,7-trihydroxyisoflavone) are two major isoflavones found predominantly in soy beans, as well as in certain traditional Chinese medicinal herbs and tea leaves. In the past decade, there have been extensive studies on the anti-tumor effects of genistein on cancers of the breast, prostate and colon in humans. However, the anti-tumor effects of daidzein on neuronal cancer cells and its action mechanisms remain poorly understood. In this study, daidzein was shown to inhibit the proliferation of a number of murine and human neuroblastoma cell lines in vitro. Using the murine neuroblastoma Neuro-2a (BU-1) cells as the cell model, daidzein was also found to prevent the cell cycle progression to G(2)/M phase and induced apoptosis of the neuronal tumor cells, as measured by flow cytometry and gel electrophoresis

for fragmented DNA respectively. Taken together, our results showed that daidzein could exert pleiotropic effects on the murine neuroblastoma cells, including inhibition of cell proliferation, modulation of cell cycle check point regulation, and triggering of neuronal cell apoptosis.

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The impact of dietary oestrogens on male and female fertility.

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PURPOSE OF REVIEW: Modern consumer needs have stimulated a vast expansion in the dietary supplement market, in an attempt to improve general well being and prevent, rather than cure, disease. Isoflavones form a large part of this market. Their oestrogenic properties are still largely unknown and must be thoroughly researched to ensure they cause no adverse effects, particularly on hormone-dependent reproductive physiology. RECENT FINDINGS: As a result of the increasing availability of phytoestrogens, research into their actions now covers a very wide field, many of which impact on reproductive potential. Time of exposure is crucial, as is interaction with other dietary components. Their putative role as chemoprotective agents has been expanded in recent years which may have an indirect impact on fertility by decreasing mortality rates in both men and women. SUMMARY: Phytoestrogens are still a current research topic in reproduction and fertility. Genistein is a putative therapeutic tool in cancer treatment although this must be considered along with evidence that it may cause DNA damage in sperm, depending on the concentration. The effects of phytoestrogen in the body are not limited to oestrogenic action. Much more epidemiological data are required to interpret current molecular studies, and those of previous years.

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Metabolic activation promotes estrogenic activity of the phytoestrogen-rich plant.

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OBJECTIVE: There is evidence that metabolic activation can increase the estrogenic activity of the phytoestrogen-rich herb in tests with HepG2 cells. Variation in both plant genetics and harvest season may also influence estrogenic activity of the plant materials. We evaluated the influence of in vitro metabolic activation by S9 mixture on the estrogenic activity of tuberous samples of different cultivars of the phytoestrogen-rich herb, Pueraria mirifica, harvested in different seasons. METHODS: Plant extracts were derived from the tubers of five plant cultivars collected during summer, rainy season and winter and administered to MCF-7 cultures, an ERalpha-positive human mammary adenocarcinoma cell line for 3 days at dosages of 0.1, 1, 10, 100 and 1000mug/ml. These data were compared with the major plant isoflavonoids puerarin, daidzin, genistin, daidzein and genistein and with 17beta-estradiol, at concentrations of 10(-12) to 10(-6)M. The test system was done in the absence and presence of the S9

mixture. RESULTS: The major plant isoflavonoids and the plant extracts exhibited variable degrees of estrogenic activities as evaluated by altered proliferation of the MCF-7 cell line which were significantly enhanced in the presence of the S9 mixture. CONCLUSION: Metabolic activation of plant isoflavonoids at least in vitro by S9 mixture plays a significant role in amplification of the estrogenic activity of the phytoestrogen-rich plant. In addition, the estrogenic activities of the plant samples were potentially influenced by both seasonal changes and plant genetics.