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Soy for Breast Cancer Survivors: A Critical Review of the Literature[1]

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A variety of health benefits, including protection against breast cancer, have been attributed to soy food consumption, primarily because of the soybean isoflavones (genistein, daidzein, glycitein). Isoflavones are considered to be possible selective estrogen receptor modulators but possess nonhormonal properties that also may contribute to their effects. Concern has arisen over a possible detrimental effect of soy in breast cancer patients because of the estrogen-like effects of isoflavones. Genistein exhibits a biphasic effect on the growth of MCF-7 cells in vitro, stimulating proliferation at low concentrations but inhibiting it at high concentrations. In ovariectomized athymic mice implanted with MCF-7 cells, both genistein and soy protein stimulate tumor growth in a dose-dependent manner. In contrast, in intact mice fed estrogen, genistein inhibits tumor growth. Although two studies in premenopausal women suggested that soy exerts estrogenic-like effects on breast tissue, recently conducted year-long studies indicated that isoflavone supplements do not affect breast tissue density in premenopausal women and may decrease density in postmenopausal women. These latter effects are opposite to those of hormone replacement therapy (HRT). Importantly, substantial data suggest that the progestogen, not the estrogen, component of HRT increases risk of developing breast cancer. Furthermore, recently conducted studies have failed to find that even HRT reduces survival in breast cancer patients. Overall, the data are not impressive that the adult consumption of soy affects the risk of developing breast cancer or that soy consumption affects the survival of breast cancer patients. Consequently, if breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them.

KEY WORDS: • *soy* • *isoflavones* • *genistein* • *breast cancer patients* • *survival* • *risk*

INTRODUCTION

Soyfoods have become increasingly popular among health-conscious individuals over the past 10 y. In 2000, ~27% of U.S. consumers reported using soy products at least once per week, which is nearly double the 1998 figure (1), and soy foods sales are projected to be $6 billion in 2005, a nearly threefold increase from 1999 (2). Several large food companies are now marketing user friendly soy products, such as breakfast cereals and energy bars, and several others have recently purchased soy food companies. Therefore, consumers will have even greater access to a wide variety of soy foods, which will likely result in a further mainstreaming of soy products.

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Interest in soy and soybean constituents is driven primarily by reported potential health benefits in a variety of areas including cancer (3–5), osteoporosis (6,7) and coronary heart disease (CHD)[4] (8). Although in 1999, the Food and Drug Administration approved a health claim for the cholesterol-lowering properties of soy protein (9) and soybeans are known to contain several bioactive components (10), unarguably, it is the soybean isoflavones that have attracted most attention. Isoflavones have a very limited distribution in nature, and soybeans are essentially the only natural dietary source of these compounds (11–14). Recently, a work group convened by the NIH reviewed the isoflavone literature, a difficult task given that ~600 papers on isoflavones are published annually (15).

Isoflavones, classically viewed as possible selective estrogen receptor modulators (16–18), possess other nonestrogen receptor–mediated properties that also may contribute to their biological activity (19–21). For these reasons, some experts object to referring to isoflavones as phytoestrogens. The possibility that soy might exert the same hypothesized advantages of estrogen, especially in regard to CHD, osteoporosis and relief of vasomotor symptoms, but without the disadvantages, has led many women to view soy as an alternative to conventional hormone replacement therapy (HRT). For a variety of reasons, including fear of breast cancer, many women are reluctant to use or continue to use HRT (22–24). Only ~35–40% of all women ever begin estrogen therapy and only ~15% continue it long term (25,26). Estrogen discontinuation is associated with a loss of protection against CHD (27) and osteoporosis (28). Recent findings from studies involving older women challenging the protective effects of HRT against CHD (29,30) and even osteoporosis (31,32) will likely result in yet more women seeking alternatives.

One group of women most in need of and who frequently use alternatives consists of breast cancer patients (33,34). Nearly two thirds of breast cancer patients report experiencing hot flashes and most are reluctant to use estrogen replacement or have physicians who discourage them from doing so (35). As the number of women taking tamoxifen to prevent or treat breast cancer increases, more women will experience menopausal symptoms for which conventional therapy may not be used (36). In addition, 25% of the 180,000 women diagnosed annually with breast cancer are in their reproductive years, and 70% of them may develop premature menopause from chemotherapy (37). For these reasons and because there is an intriguing body of literature suggesting soy consumption may reduce breast cancer risk and possibly improve survival, many breast cancer patients have embraced soy products, isoflavone supplements and foods to which isoflavones have been added. Nevertheless, the estrogenic effects of isoflavones observed in some experimental systems have recently led to considerable controversy among health professionals over the use of soy by breast cancer patients and to confusion among survivors.

The objective of this paper is to highlight studies that pertain most directly to this controversy in hopes of both offering guidance to healthcare professionals and stimulating further debate and research so that this issue can be resolved as quickly as possible. In an excellent review article, Bouker and Hilakiva-Clarke (38) discussed several aspects of this issue (especially how the stage of life during which soy/isoflavone exposure occurs may affect breast cancer risk). Several organizations, including the American Cancer Society (39), American Dietetic Association (40) and American College of Obstetricians and Gynecologists (41), have commented on the consumption of soy by breast cancer patients. However, in none of these cases do these statements appear to be the result of a comprehensive evaluation of the relevant literature.

Recent historical perspective

In 1990, findings showing that the addition of soy protein to a typical laboratory diet significantly decreased chemically induced rat mammary cancer (42) prompted the National Cancer Institute to hold a workshop on this subject (10). Recommendations of this gathering led directly to the National Cancer Institute shortly thereafter issuing a request for applications for research in this area. The low breast cancer mortality rates in Japan and other Asian countries, where soy is commonly consumed, certainly made this hypothesis intriguing, especially because the fat/breast cancer connection began to weaken (43,44). Identifying dietary factors that affect breast cancer risk has been a particularly frustrating experience because conflicting data exist concerning the role of dietary fat (45–48), fiber (49) and fruits and vegetables (50). For this reason, the publication in 1991 of a case-control study conducted in Singapore showing that the consumption of modest amounts of soy was associated with an ~50% reduction in premenopausal breast cancer risk (postmenopausal risk was unaffected) did much to further stimulate interest in soy

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(51).

Although soy contains a number of putative anticarcinogens (10), initial excitement over the hypothesized anticancer effects of this legume was based largely on the possibility that isoflavones might exert antiestrogenic effects on breast tissue, as other estrogen agonists/antagonists, such as tamoxifen, were known to do. In 1966, Folman and Pope (52) were the first to demonstrate antiestrogenic effects of isoflavones, showing that in female mice, subcutaneously injected genistein inhibited estrone stimulation of uterine growth. In 1987, Akiyama et al. (53,54) serendipitously discovered that genistein was a specific inhibitor of tyrosine protein kinase, an enzyme frequently overexpressed in cancer cells (55). This finding led to the widespread use of genistein as a tool for identifying whether certain cellular processes were under the control of a variety of kinases. In fact, genistein affects a variety of cellular molecules that modulate cell death and survival (21,56). Naturally, these observations fueled interest in the anticancer effects of isoflavones.

Background on isoflavones

Isoflavones are a subclass of the more ubiquitous flavonoids. In total, there are 12 different soybean isoflavone isomers. The primary isoflavones in soybeans are the glucosides, genistin and daidzin, and their respective aglycones, genistein (4' 5, 7-trihydroxyisoflavone) and daidzin (4', 7-dihydroxyisoflavone). Typically, there is somewhat more genist(e)in than daidz(e)in in soybeans and soy foods (14). There are also small amounts of a third isoflavone in soybeans, i.e., glycitein (7,4'-dihydroxy-6-methoxyisoflavone) and its glycoside, glycitin. The isoflavone content of raw soybeans is ~1.0 mg/g with a range of ~0.4–2.4 mg/g (57–59). Traditional soy foods (i.e., tofu, miso, natto) typically provide 0.2–0.4 mg/g of fresh weight product and ~2–4 mg/g protein. Isolated soy proteins vary in isoflavone content (range 0.5–2.0 mg/g) although the average is ~1 mg/g (14). Native Japanese adults typically consume ~30–40 mg (aglycone units) of isoflavones per day, which is roughly equivalent to between 1 and 1.5 servings (U.S. measures) of traditional soy foods (60–62).

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Serum genistein and isoflavone levels increase in a dose-dependent fashion in response to genistein administration in animals (63) and soy food consumption in humans (64,65) and can easily reach the low micromolar level (66,67). Plasma levels in free-living Asians are ~500 nmol/L when measured after an overnight fast (68,69). Because the half-life of isoflavones is ~6–9 h, fasting levels are much lower than postprandial levels (67,70–73). Isoflavones circulate in plasma primarily in the conjugated form, mostly bound to glucuronic acid; <3% circulates in the free form (73).

Estrogenic and nonestrogenic isoflavone properties.

Isoflavones have a spatial conformation similar to that of mammalian estrogens, bind to estrogen receptors and affect estrogen-regulated gene products (74 ,75). Isoflavones have traditionally been considered to be weak estrogens, possessing between 10^{-5} and 10^{-2} of the activity of 17ß-estradiol on a molar basis (74 –76). It is really not possible, however, to arrive at a general estimate of activity because estrogenicity varies greatly depending on the assay used. Furthermore, isoflavones may bind less tightly than estrogen to serum proteins making them more available to tissues (76) and they may be tissue selective, exerting quite pronounced estrogen-like effects in some tissues such as the coronary vessels (77 ,78) but not in other tissues such as the endometrium (78 –82). However, even the lower estimates of estrogenicity suggest that isoflavones have the potential to exert physiologic effects in humans consuming soy foods because serum isoflavone levels will be 100-1000 times higher than endogenous estrogen levels (83). The consumption of modest amounts (≤100 mg) of isolated isoflavones was shown to exert potentially important biological effects in humans, such as enhancing systemic arterial compliance (84 ,85) and reducing urinary levels of 5-hydroxymethyl-2'-deoxyuridine, a marker for oxidative DNA damage (86).

The higher binding affinity of isoflavones for estrogen receptor-ß (ERß) compared with ERα (87 –89) and the different tissue distributions of these receptors (90 ,91) are often cited as support for the tissue-selective effects of isoflavones. This may be true, but binding affinity alone does not determine potency because the resulting conformational change in the ligand (isoflavone)-receptor complex varies among ligands regardless of binding affinity (92).

Several investigators have examined the in vitro estrogenic and antiestrogenic potential of isoflavones, especially genistein, and most have concluded that genistein functions primarily as an estrogen agonist (93 –97), although Miodini et al. (98) concluded that genistein displays mixed estrogen agonist/antagonist properties. Isoflavones have been shown to down-regulate estrogen receptors, an effect that could lead to reduced estrogenic responses (99). Interestingly, Pike et al. (92) found that, in contrast to estradiol, in the ERß-genistein complex the AF-2 helix does not adopt the distinctive agonist position but instead lies in a similar orientation to that induced by estrogen receptor antagonists. No data on the ERα-genistein complex was presented in that paper, but it is known that ERß is easier to antagonize than ERα (92).

In contrast to the findings of Pike et al. (92), An et al. (18) found that genistein was >1000-fold more potent at triggering transcriptional activity with ERß than ERα. This difference is far greater than the ~30-fold greater binding affinity of genistein for ERß than ERα (100). These findings indicate that genistein is a potent agonist for ERß and that the divergent transcriptional actions of estrogens and isoflavones result not only from their different binding affinities but from differences in their ability to recruit coregulators and trigger transcriptional functions of ERα and ERß (18). Therefore, determining the role of ERß in breast carcinogenesis appears to be critically important to understanding the effect of soy and isoflavone intake on breast cancer risk. For this reason, experimental models that do not include both ERα and ERß and their receptor cofactors in a fashion similar to that found in human breast tissue are likely inappropriate for evaluating the effects of soy and isoflavones.

Isoflavones can exert hormonal and antiestrogenic effects in many ways without direct interaction with the estrogen receptor; for example, isoflavones have been shown in vitro to inhibit the activity of enzymes involved in estrogen metabolism. More specifically, isoflavones inhibit aromatase (101–103), a cytochrome P_{450} enzyme involved in three hydroxylation steps that convert the C19 androgens to aromatic C18 estrogenic steroids (101) although the 50% inhibitory concentrations (IC_{50}) are quite high and other flavonoids are far superior to the isoflavones in this regard (104). Isoflavones also inhibit the 17ß-oxidoreduction of estrogens (96,105). The 17ß-hydroxysteroid oxidoreductases (also known as 17ß-hydroxysteroid dehydrogenases), which are present in steroidogenic cells as well as some target tissues of estrogen, convert the relatively weak estrogen estrone (E1, oxidized form) into the more potent estrogen, estradiol (E2, reduced form). Importantly, in contrast to aromatase inhibition, inhibition of 17ß-hydroxysteroid oxidoreductases occurs at relatively low micromolar concentrations (105,106). Low concentrations of isoflavones also inhibit 3ß-hydroxysteroid dehydrogenase (106), which converts dehydroepiandrosterone into androstenedione, which can be converted into estrone (107). Because it is thought that the estrogens, which drive the growth of estrogen-sensitive mammary tumors, are generated locally (108), the effects of isoflavones on estrogen metabolism at the tissue level may be particularly important.

A recent example of in vivo antiestrogenic activity of soy occurred in adult, surgically postmenopausal female macaques (*Macaca fascicularis*); the consumption of an isoflavone-rich soy protein isolate inhibited the stimulatory effects of exogenously administered estradiol on mammary gland cell proliferation (109). Clearly, when evaluating the possible hormone-related effects of isoflavones, it is necessary to look beyond the estrogen receptor, and when evaluating the likely overall biological effects of isoflavones, it is necessary to consider more than hormone-related activities. As noted previously, genistein is thought to be able to influence signal transduction (110) by inhibiting the activity of many enzymes and influencing cellular factors that control the growth of cells (19,21,54,56); in some experimental systems, isoflavones demonstrate antioxidant activity (86,111,112).

In vitro anticancer effects.

Genistein inhibits the growth of a wide range of cancer cells in vitro (3,5,20), including both hormone-dependent and hormone-independent breast cancer cells, with IC_{50} values ranging from ~10 to 50 μmol/L (106,113–123). However, at concentrations <10 μmol/L, MCF-7 (an estrogen receptor–positive cell line) cell growth is stimulated by genistein (18,97,98,106,116,124). Genistein does not stimulate the growth of estrogen receptor–negative breast cancer cells in vitro (63,97). This biphasic effect is attributed to genistein exerting estrogen-like effects at lower and what may be considered physiologic concentrations but at higher concentrations exerting other non-estrogen receptor–mediated effects, for example, inhibition of the activity of one or more cellular molecules that control cell signaling, growth and death. This situation may be analogous to tamoxifen as noted by Bouker and Hilakivi-Clarke (38) in that in male rat anterior pituitary cells, low (100 nmol/L) concentrations of tamoxifen increased prolactin secretion but at higher concentrations, estrogen-stimulated prolactin secretion was completed inhibited by tamoxifen (125).

Conflicting data exist about the extent to which the addition of estrogen to the medium eliminates the stimulatory effect of genistein in vitro. For example, Wang and Kurzer (126) and Shao et al. (117) found that even in the presence of estradiol, genistein stimulated MCF-7 cell growth. In HepG2 human hepatoma cells transfected with rat ERα or ERß plus an estrogen-responsive luciferase reporter gene, Casanova et al. (89) found that set concentrations of genistein (1, 10 and 100 nmol/L) exerted additive effects when combined with estradiol across a complete dose-response range of estradiol and concluded that in vivo, the effect of genistein would be additive to that of endogenous estradiol. In contrast, Zava and Duwe (97) found that in the presence of high estradiol (0.3 nmol/L) concentrations, genistein at 0.3–10 nmol/L did not further stimulate T47D cell (an estrogen receptor–positive cell line) growth and at slightly higher concentrations (30–300 nmol/L) exerted a modest inhibitory effect even though in the absence of estradiol these concentrations enhanced cell growth. Similarly, Miodini et al. (98) found that although genistein (<5 µmol/L) modestly stimulated MCF-7 cell growth in the absence of estradiol, at a concentration of 5 µmol/L, genistein completely inhibited the stimulatory effects of 17ß-estradiol (10 nmol/L) on cell growth. Independent of effects on cell growth, genistein in vitro (50% effective concentration ~1 µmol/L) inhibited invasion by a highly metastatic subline of BALB/c mammary carcinoma cells (127), an effect also demonstrated in prostate cancer cells (128).

The relevance of the in vitro anticancer effects of genistein has been questioned because free genistein concentrations in serum would never reach the low micromolar range, even in people consuming plentiful amounts of soy foods. However, Dalu et al. (129) found that 0.25 mg/g dietary genistein (Japanese dietary content is ~0.05 mg/g) down-regulated epidermal growth factor receptor levels in the dosolateral prostate of Lobund-Wistar rats despite free genistein concentrations in serum and prostate tissue of only 18.4 nmol/L and 17.5 pmol/g, respectively. As a result, Dalu et al. concluded that genistein may be more potent in vivo than in vitro. Note that the relative proportion of free genistein in tissues is higher than in the serum (130) and that breast tissue isoflavone concentrations are two- to threefold higher than paired serum concentrations (Julie Maubach, Ghent University, unpublished data, 2001). Thus, breast tissue may be exposed to higher levels of biologically active isoflavones than was previously thought.

Finally, reports that genistein may inhibit angiogenesis may be particular germane to the issue of soy consumption by breast cancer survivors. Fotsis et al. (131) were the first to show angiogenesis inhibition, finding that genistein inhibited endothelial cell proliferation and in vitro angiogenesis with concentrations of 5 and 150 µmol/L giving half-maximal inhibition, respectively. Fotsis et al. (132) later determined, however, that the concentration of genistein for the half-maximal inhibitory effect on angiogenesis was only 10 µmol/L, the higher value in the previous report being due to the poor solubility of genistein in sodium bicarbonate compared with dimethyl sulfoxide. Genistein has also been shown to shift the proteolytic balance of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases toward antiproteolysis in media or ascitic fluid conditioned by actively growing Ehrlich cells (133). The first in vivo inhibition of angiogenesis by genistein was reported by Shao et al. (121), who found that angiogenesis was inhibited in mice injected subcutaneously with genistein. Others have confirmed antiangiogenesis effects in vitro and well as in vivo (128,134–138).

Effect of soy and isoflavones on mammary tumorigenesis in adult animals

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Tumor development.

Several studies examined the effects of different soy products on the development of chemically induced mammary cancer in adult animals. The data are somewhat inconsistent but generally show that in comparison with control diets, the substitution of soy protein for other protein (generally casein) typically found in a standard laboratory diet modestly (25–50%) reduced tumor incidence or, more commonly, tumor multiplicity (42,139–143). However, not all studies showed protective effects (144–147). In one study, although Hakkak et al. (139) found that soy protein reduced 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumor incidence relative to casein, tumor inhibition was only about half that seen for whey protein. Typically in these animal studies, soy protein isolate was the sole source of protein in the diet (~20% by weight) although other forms of soy such as miso (140,142,148) and soy flour (149) have been shown to reduce tumorigenesis. Barnes et al. (149) found that alcohol-extracted soy protein was less effective in inhibiting mammary tumor development than unextracted protein, suggesting that isoflavones may have accounted for the anticancer effects.

Several studies directly examined the effects of isolated isoflavones or isoflavone-rich extracts on mammary tumorigenesis (143,150–152). For example, daidzein and genistein given by injection each reduced *N*-methyl-*N*-nitrosourea (MNU)-induced mammary carcinogenesis (number of tumors per rat) by ~20%, but the results were not significant (151). Arjmandi et al. found that neither the synthetic isoflavone, ipriflavone, nor genistein had an effect on MNU-induced mammary tumorigenesis although the combination was very inhibitory (152). More substantial inhibitory effects were found by Ohta et al. (143). Their work reported that the number of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhiP)-induced mammary tumors per rat was 2.2 ± 0.4 for rats consuming a diet containing a 0.02% isoflavone mixture and 1.5 ± 0.3 for those consuming twice this amount of isoflavones; both values were much lower than the 2.6 ± 0.5 tumors/rat in the control group.

Decreases in tumor incidence were also noted in F344 rats in response to the consumption of diets containing 1.5 or 5% hypocotyls [embryo buds of soybeans; concentrated in isoflavones relative to the whole soybean (153)] in comparison with the control diet; incidence in these groups was 25, 26 and 37.5%, respectively (150). It should be noted that in rodents in response to the intake of isoflavones via soy or an isoflavone extract with an isoflavone profile (genistein > daidzein >> glycitein) similar to that found in soybeans, equol is the predominant isoflavonoid found in serum (154), whereas only about one third of humans actually produce equol (155–157). Equol is converted from daidzein by intestinal bacteria (158), binds to estrogen receptors more tightly than daidzein (88) and may be more estrogenic (74) and anticarcinogenic (99).

The most pronounced inhibitory effects in response to the administration of an isolated isoflavone were reported by Gotoh et al. (140), who found that a low dose of biochanin A (10 mg/kg) significantly ($P < 0.01$) reduced tumor multiplicity (tumors per rat; 0.7 vs. 2.2 for control) and that a higher dose (50 mg/kg) also reduced tumor incidence. Biochanin A is a methylated isoflavone that is converted to genistein in vivo (159) and in MCF-7 cells in vitro (160

). Finally, in contrast to all other studies discussed in this section, Day et al. (161) recently found that in wild-type but not ERα knockout mice, genistein (1 g/kg diet) fed continually beginning at age 3 wk increased the number of DMBA-induced malignant tumors compared with the number in mice not given genistein, although the number of benign tumors, latency and size of the tumors were not affected.

Tumor progression.

The inhibitory effects of soy/isoflavones on the development of chemically induced mammary cancer as discussed above may not be relevant to the issue of soy consumption by breast cancer survivors. Several investigators used models that may more closely resemble the situation faced by breast cancer patients by looking at the effects of soy and isoflavones on tumor progression. For example, Hawrylewicz et al. (162) first fed rats a casein-based AIN-76 diet and then injected them with the breast carcinogen MNU. When the first tumor grew to 0.3–0.5 cm in diameter (mean latency was 14.7 wk), it was surgically removed and half the animals continued on the casein diet, whereas the other half was fed soy protein isolate. Rats in the soy group developed significantly fewer tumors (53 vs. 128), and histopathological analysis indicated that tumors in the casein-fed rats had considerably more aggressive characteristics than did the tumors in the soy-fed rats. Hawrylewicz et al. (162) concluded that the inhibition of chemically induced mammary tumor development reported in a previous study (141) and tumor progression in this study (162) resulted from the lower methionine content of soy protein. Methionine restriction is known to retard carcinogenesis (163); it is unlikely, however, that this mechanism could contribute to the low breast cancer mortality in Japan because only ~10% of the total protein intake of the Japanese people is derived from soy (164). This mechanism would not be likely to be relevant to breast cancer patients consuming a mixed diet containing modest amounts of soy protein, although it could be when much of the total protein intake is derived from soy.

The findings of Hawrylewicz et al. (162), however, are in contrast to those from a study by Charland et al. (165). In this experiment, female Lewis rats (*n* = 60) were injected subcutaneously with MAC-33 cells (a mammary tumor cell line known to metastasize spontaneously) and then randomly assigned to receive (intraperitoneally) 18 mg soybean (isoflavone-enriched) extract, 18 mg heat-sterilized (to destroy protease inhibitors) soybean isoflavones or saline five times per week for 30 d. There were significant increases in tumor weight, tumor volume and the tumor-to-carcass ratio in the isoflavone groups relative to the control group. There was also a significant increase in the number of lung metastases (31%; Kruskal-Wallis test) in the rats receiving heat-sterilized soybean isoflavones.

Undoubtedly, Hsieh and colleagues (116) from the University of Illinois conducted the animal study most widely cited in support of breast cancer patients avoiding soy. They found that dietary genistein (750 μg/g) stimulated the growth of subcutaneously implanted MCF-7 cells (cells were initially stimulated by estrogen) in ovariectomized athymic mice although the effects were much less pronounced than those of estrogen. In a later study by these investigators using a similar experimental design, isolated soy protein containing various amounts of genistein (15, 150 and 300 μg/g) increased tumor growth in a dose-dependent manner and to a similar extent as when isolated genistein was administered at these same doses (166). Genistein however, does not appear to stimulate the growth of estrogen receptor–negative mammary cancer cells in vivo (63).

Although the genistein concentration of the Asian diet (~50 μg/g) is much lower than the genistein concentration used by Hsieh et al. (116) (750 μg/g) and Day et al. (161) (1000 µg/g), serum genistein levels in response to this amount of genistein in rodents are ~1–2 μmol/L (63 ,116 ,166), which is similar to that resulting from the consumption of fairly modest amounts (1–2 servings) of soy foods by humans (65) and, as noted previously, not dramatically lower than that found in free-living Asians (68 ,69).

In contrast to the research from Helferich and colleagues (116 ,166), Shao et al. (121), using very low doses (0.1–0.5 mg/kg body weight) of genistein, injected subcutaneously and Zhou et al. (Jin-Rong Zhou, Harvard Medical School, Boston, unpublished data, 2001), using dietary genistin (the glycoside form of genistein), observed tumor inhibition in intact nude mice fed estrogen pellets and orthotopically implanted with MCF-7 cells. The dietary genistin concentration (1400 μg/g) used by Shao et al. is equivalent to ~900 μg genistein/g, which is very similar to the 750 μg genistein/g used by Helferich and colleagues (116). Although still speculative, these four rodent studies collectively suggest that in a low-estrogen environment, perhaps as exists in a postmenopausal women (and possibly breast cancer patients as a result of chemotherapy-induced menopause), genistein is estrogenic and has a proliferative effect on breast tissue, but in a high estrogen environment such as exists in a premenopausal women, it has an antiproliferative and possibly antiestrogenic effect (116,121,166; Jin-Rong Zhou, 2001). This conclusion agrees with findings by Makela et al. (167) who showed that diets containing soy increased uterine weight in immature outbred Han-NMRI mice not given diethylstilbestrol but decreased uterine weight in mice fed diethylstilbestrol.

Effects on the breast may differ from effects on the uterus; furthermore, in the study by Shao et al. (121), genistein also inhibited the in vivo growth of estrogen receptor–negative mammary cancer cells (MDA-MB-231). Therefore, tumor inhibition in the case of both cell lines (MCF-7 and MDA-MB-231 cells) may have been the result of an estrogen receptor–independent mechanism. More importantly, it is unclear which hormonal environment is more representative of breast cancer patients or postmenopausal women, i.e., that which occurs in ovariectomized mice or in intact mice fed estrogen pellets. Plasma levels of estradiol in ovariectomized athymic mice are 99–139 pmol/L, similar to the levels seen in postmenopausal women (168). Although postmenopausal serum estradiol levels (~55 pmol/L) (83 ,169) are ~10% of the level in premenopausal women (169), some data indicate that the concentration of estradiol in breast cancer tissue of postmenopausal women is similar to that in premenopausal women (170) and that breast tissue estradiol concentrations are higher than paired serum concentrations (171). Consequently, identifying a high vs. low estrogen environment may not be as simple as identifying pre-vs. postmenopausal women, especially in the case of breast cancer patients.

Effects of early exposure.

Perhaps the most intriguing animal data come from the laboratory of Lamartiniere and colleagues (172) at the University of Alabama. They showed that in rats, neonatal exposure to pharmacologic amounts of genistein given by injection on d 2, 4 and 6 of life (173 ,174) and during the prepubertal period given on 16, 18, and 20 d postpartum (175) and via the diet from conception to 21 d postpartum at physiologic concentrations (25 mg/g body weight) (176) reduces the later development of DMBA-induced (administered on postpartum d 50) mammary cancer by ~50%. In the dietary study, total genistein concentrations in the serum and mammary glands of 21-d-old offspring were only 1.8 μmol/L and 370 nmol/g, respectively. Hilakivi-Clarke et al. (177) also found that prepubertal genistein (~1 mg/kg body weight) administration reduces DMBA-induced mammary cancer in rats treated between postnatal d 7 and 20. Genistein exposure significantly reduced tumor multiplicity in this study, and 60% of the tumors in the genistein group were not malignant, whereas all of the tumors analyzed for histopathology in the vehicle group were adenocarcinomas.

The proposed mechanism for the protective effect of early genistein exposure is from the stimulation of cell proliferation in the mammary gland resulting in enhancement of mammary gland maturation. Early genistein exposure results in fewer terminal end buds and more lobules, and lower rates of cell proliferation in the terminal end buds. Lobules are the most differentiated terminal ductal structures, whereas terminal end buds are the least differentiated terminal ductal structures and the most susceptible to carcinogenesis (178). In the study by Hilakivi-Clarke et al. (177), a higher number of differentiated alveolar buds and lower number of terminal ducts were present in the DMBA-treated mammary glands of the genistein-exposed rats. The genistein findings are consistent with the protective effects of early exposure to estrogen and progesterone in rats (179–181) and of early but not late pregnancy in women (182), although recent findings from Guzman et al. (181) suggest that the protective effects of early estrogen exposure are not simply due to an overall enhancement of differentiation. A particularly fascinating finding from the Larmartiniere group is that when genistein is given to adult rats, mammary carcinogenesis is reduced only if these animals were also exposed to genistein early in life (Coral Lamartiniere, University of Alabama, Birmingham, unpublished data, 2001). The timing effect may not be straightforward because Hilakivi-Clarke et al. (183–185) found that the administration of genistein to dams increased DMBA-induced mammary carcinogenesis in the offspring.

Soy and breast cancer risk: epidemiology

Often cited in support of recommendations for breast cancer patients to consume soy are studies showing that even after an assortment of variables including stage at diagnosis are controlled for, Japanese breast cancer patients exhibit better survival than do other ethnic groups (186–189). Whether soy contributes to this better survival is unknown because no studies looking specifically at the effect of soy consumption on breast cancer survival have been published, although Huang et al. (190) recently reported that tofu consumption was associated with enhanced survival among gastric cancer patients. However, not only are the etiologies of breast and stomach cancer different, but in this study, dietary assessment was conducted before cancer diagnosis and likely reflected lifelong consumption. Thus, these observations shed little light on the possible effect of soy exposure on breast cancer survival among Western patients who did not consume soy before diagnosis, especially considering the work of Lamartiniere et al. in which adult genistein exposure reduced breast cancer risk only in animals previously exposed to genistein during early life (Coral Lamartineiere, unpublished data, 2001).

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As noted previously, the low Asian breast cancer mortality rates provided much of the basis for initial enthusiasm about the possible anticancer effects of soy (191). However, on the basis of national household survey dietary data for 1980–1985, Nagata (164) did not find that soy or isoflavone intake was related to breast cancer mortality in 47 prefectures in Japan. The existing case-control and prospective studies are also generally not supportive of the hypothesis that adult consumption of soy reduces postmenopausal breast cancer risk and are only modestly supportive in regard to premenopausal breast cancer (192–196). In fact, no epidemiologic studies conducted in Asia were identified that found that adult consumption of soy reduces breast cancer risk in postmenopausal women (51,197,198). Interestingly, Wu et al. (199) found that among Asian Americans, tofu consumption protected against both pre- and postmenopausal breast cancer although intake was quite modest, which is consistent with data showing that Asian immigrants consume less soy than do native Asians (200–202). In a follow-up analysis of data, protective effects were found only in non-U.S.-born Asians, not in U.S.-born Asians (203). One explanation for this observation is that among women born in Japan but not in the United States, soy consumption reflects a more traditional lifestyle that protects against breast cancer rather than soy intake per se being protective.

Data for premenopausal breast cancer risk are inconsistent, with some studies reporting no association (198), others reporting only modestly reduced risks (197) and some finding quite pronounced protective effects (51). None of the Asian studies found that soy intake was associated with an increased breast cancer risk, however. Typically, in Asian epidemiologic studies, consuming soy at least once per day is classified as the highest intake level, whereas less than once per week is the lowest (4,5,51,196,197,203).

Several case-control studies conducted in Western countries found that soy intake (based on dietary data or urinary isoflavone excretion) protects against breast cancer; not unexpectedly, however, intake was extremely low in these populations. Consequently, the biological relevance of the inverse correlation between soy intake and breast cancer risk observed in these studies is of questionable significance (204–206). The inverse relationships noted in these studies may indicate that typical Western women who eat any soy lead a lifestyle that is protective against breast cancer.

In contrast to these relatively unimpressive epidemiologic findings, Shu et al. (207) found that women who consumed tofu during their teenage years (13–15 y) were less likely to develop premenopausal and postmenopausal breast cancer as adults. The odds ratio for girls in the highest (11 g soy protein/d) vs. the lowest quintile of intake (<2.2 g soy protein/d) was 0.51 [95% confidence interval, 0.40–0.65; trend test, $P < 0.001$]. These data are extremely noteworthy for two important reasons: first, they are consistent with the animal work by Lamartiniere's group showing the protective effects of early soy exposure (172), and second, they are consistent with migration data showing that for breast cancer in contrast to prostate cancer, early life events are particularly important (208).

Markers of breast cancer risk: clinical studies

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It is difficult to summarize the surprisingly large number of studies that have recently examined the effects of soy consumption on hormonal patterns because of the different experimental designs, number of measures taken and conflicting results. For example, three studies found that in premenopausal women, soy decreased serum estradiol levels (209–211), whereas several other studies found no changes (212–215). Wu et al. (216) found that in premenopausal women, the serum luteal phase estradiol levels decreased in response to soy but only in Asian, not Caucasian, women. Duncan et al. noted few hormonal changes in premenopausal (79) or postmenopausal women (217) who were fed soy protein containing various amounts of isoflavones. Other studies suggest that soy consumption favorably alters estrogen metabolism on the basis of the urinary production of potentially carcinogenic estrogen metabolites [16α-(OH) estrone, 4-(OH) estrone, and 4-(OH) estradiol] (218,219) although Martini et al. (215) found no effect of soy protein on estrogen levels or metabolism in premenopausal women. Furthermore, there are conflicting data regarding the relative importance of the $16(\alpha)$-hydroxylation vs. the 2-hydroxylation of estrogen on breast cancer risk (220).

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Early in vitro work suggested that isoflavones increase sex hormone binding globulin (SHBG) levels (221,222). In support of these data, Pino et al. (223) recently found that in response to soy milk consumption (20 g soy protein/d), serum isoflavone levels in postmenopausal women were positively correlated with increases in SHBG levels, especially in those with low initial SHBG values. However, most feeding studies have not shown that soy or isoflavone consumption significantly increases SHBG (79,80,215,224–226) and, in fact, some studies have reported decreases (212,227,228). Similarly, although a few studies reported increases in menstrual cycle length (209,210,228), several others have not (79,215,216,229). Finally, one of the more potentially important findings was reported by Lu et al. (229), who found that soy decreased serum progesterone levels in premenopausal women by 45% ($P < 0.0001$) compared with levels during the home (usual) diet period; the women in this study consumed 1080 mL soy milk/d, which provided 154 mg isoflavones.

The next study has largely been responsible for raising concerns about soy consumption by breast cancer patients. Petrakis et al. (212) found that daily soy consumption (38 g soy protein isolate, 80 mg isoflavones) over 5 mo was associated with an increase in breast nipple aspirate fluid (NAF) secretion and breast cell hyperplasia in premenopausal women. Previous epidemiologic research by these investigators showed that nonlactating women who can secrete breast fluid are at an increased breast cancer risk compared with those who cannot (230) and that abnormal NAF cytology is associated with a further increased breast cancer risk (231) although the increased risk may be confined to women with a previous history of breast biopsy (232). Interestingly, Chinese-born premenopausal women in the United States are about twice as likely to secrete NAF than Chinese women born in China (233). Petrakis et al. (212) found no effect of soy consumption on NAF secretion in postmenopausal women overall; surprisingly, however, there was a significant increase in NAF secretion in postmenopausal women ($n = 4$) receiving estrogen replacement therapy.

On the basis of the above findings, Petrakis et al. concluded that soy exerts estrogenic effects on breast tissue. However, this study did not include a control group and fluid secretion increased in women even after soy feeding was discontinued. Bouker and Hilakivi-Clarke (38) noted that women were eligible for this study only if they were secretors of NAF, which means that they were at an increased risk of breast cancer and perhaps particularly sensitive to soy. Thus, in theory, the findings may not be applicable to all women, whereas they could be particularly germane to breast cancer patients.

Another study that has raised concern in breast cancer survivors examined the effects of feeding textured vegetable protein (60 g, 45 mg isoflavones/d) for 2 wk on breast cell proliferation in premenopausal women with benign or malignant breast disease (234). Increased cell proliferation is generally considered to be a marker for increased cancer risk (235–237) although this is not always the case (238). A preliminary analysis of this study, based on biopsies from only about half of the study subjects ($n = 48$) indicated that soy consumption markedly increased breast cell proliferation (239); in the final analysis, however, which included all 84 subjects, no such effect was found (234). Nevertheless, soy did appear to exert a weak estrogen-like effect on breast tissue because biopsies indicated that the expression of two proteins, pS2 and apolipoprotein D, found in breast cells, were up-regulated and down-regulated, respectively, which is similar to the effects of estrogen. However, there was no effect of soy supplementation on estrogen and progesterone receptor status, apoptosis, mitosis or Bcl-2 expression. The investigators concluded that soy exerted a weak estrogenic effect on breast tissue but also that the long-term implications of this effect were unclear because soy did not increase cell proliferation and because the study lasted only 2 wk. It is certainly possible that 2 wk is not sufficiently long for any antiestrogenic and even antiproliferative effects of soy to become evident.

Recently, two laboratories examined the effect of isoflavone supplements on breast tissue density. Mammographic density appears to be an excellent short-term marker of the effect on the breast of potential preventive interventions for breast cancer (240–242). Differences in the parenchymal pattern of the breast on mammography reflect differences in the amounts of stromal, epithelial and fat tissue present in the breast. Extensive areas of mammographically dense breast tissue are strongly associated with an increased risk of breast cancer. Tamoxifen use and low fat diets have been shown to decrease density, whereas HRT has been shown to increase it (242).

In one study, women ($n = 175$) aged 49–65 y with Wolfe's P2 or DY mammographic patterns were randomly assigned to receive either an isoflavone tablet (40 mg isoflavones derived from red clover) or placebo for 1 y (Charlotte Atkinson, Fred Hutchinson Cancer Research Center, Seattle, unpublished data, 2001). After 1 y, breast tissue density in postmenopausal women decreased significantly in the isoflavone group and nonsignificantly in the placebo group, but differences between the groups were not significant. There were also no differences between the isoflavone and placebo groups for pre- and perimenopausal women. However, when subjects were divided into tertiles of age, in women who were 56–65 y old and received isoflavones, breast tissue density significantly decreased ($P < 0.05$), whereas in women of this age who received a placebo, it increased, although not significantly so. In the second study, premenopausal women ($n = 34$) were randomly assigned to receive either 100 mg isoflavones (derived from soy) or placebo for 1 y (Gertraud Maskarinec, Cancer Research Center of Hawaii, unpublished data, 2001). No differences in breast tissue density were noted between groups. Therefore, although direct comparisons are needed, isoflavones appear to exert effects on breast tissue density opposite to those of HRT (243).

Insights from HRT

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Oncologists have been reluctant to recommend estrogen for breast cancer patients because of studies suggesting that HRT increases breast cancer risk (244 ,245). It has generally been accepted that higher endogenous estrogen levels (246) and greater lifelong exposure to estrogen increase breast cancer risk, which is presumably why earlier age at menses and later age at menopause (247) and higher bone mineral density (248 –252) are considered to be risk factors for breast cancer and why obesity (because of the greater peripheral synthesis of estrogen and lower SHBG levels) appears to decrease survival of breast cancer patients (253 ,254). As recently as 1997, a consensus development conference recommended that estrogen replacement should be avoided, if possible, by patients with a history of breast cancer (255).

This position is not without controversy because some data suggest that estrogen is not contraindicated for such patients (37 ,256 ,257); it does not appear that estrogen increases disease-specific mortality because breast tumors in HRT users tend to be smaller, better differentiated and more likely to be of a favorable histological type (245 ,258 –260). For example, in a small study in Spain, women with breast cancer (n = 121) who were undergoing HRT at time of diagnosis were found to have lower tumoral stages, a lower degree of affected axillary lymph node dissemination and a greater percentage of well-differentiated tumors than women (n = 121) who were not using HRT (261). Recently, O’Meara et al. (262) found that in a group of 2755 women diagnosed with invasive breast cancer, hormone use was associated with a significant decrease in breast cancer recurrence and mortality, although the number of women (n = 174) who used hormones was small and the follow-up period was not long. However, after a number of factors were adjusted for, the relative risk of contralateral cancer was actually increased by one third in HRT users.

Even the view that estrogen therapy increases breast cancer risk in healthy women is now being challenged. Recent observational data indicate that estrogen per se increases breast cancer risk only very slightly, whereas the combination of estrogen plus progestogen may increase breast cancer risk two- to threefold over a woman’s lifetime (263 –268). These epidemiologic observations are consistent with the increased breast cell proliferation that occurs during the luteal phase of the menstrual cycle when progesterone levels are elevated (269 ,270), with increased mammary and breast cell proliferation (271 –273) and increased mammographic density (274 –276) in response to HRT compared with estrogen alone and with a recent report showing an excellent correlation between the mean concentration of progesterone in saliva during the midluteal phase of the menstrual cycle and the age-standardized rates of breast cancer in several countries (277). Soy has no progesterone activity (278) and may actually decrease serum progesterone levels (210 ,216 ,229). Thus, the epidemiologic data relevant to HRT could be construed to suggest that soy consumption would not be contraindicated for breast cancer patients.

Tamoxifen and soy

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There is particular concern about soy consumption in breast cancer patients taking tamoxifen because of the potential for isoflavones to interfere with the efficacy of this drug. This question has been studied to only a limited extent but the results are rather intriguing. In vitro, physiologic concentrations of genistein were shown to reverse the repressive effects of 4-hydroxytamoxifen on ERα-responsive reporter genes (279). In addition, in T47D cells, Zava and Duwe (97) found that in the presence of tamoxifen or hydroxytamoxifen, the dose-response curve with genistein was shifted 1 log and 2 logs to the right, respectively, reflecting the higher amounts of genistein required to displace tamoxifen from estrogen receptor sites and activate cell proliferation. However, conversely, tamoxifen actually sensitized these cells to the inhibitory effects of genistein at concentrations from 2 to 10 μmol/L, resulting in greater growth inhibition at these concentrations (97). Shen et al. (120) found that genistein (5 μmol/L) and tamoxifen synergistically inhibited the growth of MDA-MB-435 cells. However, these particular breast cancer cells are estrogen receptor–negative and have elevated signal transduction activity; thus they should be insensitive to the possible estrogenic stimulus of genistein but very sensitive to the effects of genistein on signal transduction. Evidence for a possible interaction between tamoxifen and genistein comes from other cell lines as well because tamoxifen has been shown to inhibit the stimulatory effects of genistein (280), daidzein (281) and an isoflavone-rich soybean ethanol extract (282) on osteoblastic activity.

In contrast to the somewhat confusing in vitro data, two animal studies strongly suggest that the combination of genistein and tamoxifen may exert beneficial effects. Gotoh et al. (148) found that tamoxifen in combination with a diet containing 10% miso (fermented soybean paste) synergistically inhibited the development of *N*-nitroso-*N*-methlyurea (NMU)-induced rat mammary cancer. Tumor incidence in the control, miso, tamoxifen and miso plus tamoxifen groups was 91, 77, 68 and 10%, respectively, and tumor multiplicity for these groups was 4.5, 2.4, 1.4 and 0.2, respectively. In a follow-up study when treatment was delayed until NMU-induced tumors had reached between 10 and 25 mm in the largest direction, the combination of miso and tamoxifen inhibited growth by ~50% over 6 wk, whereas tamoxifen by itself was ineffective (148). Gotoh et al. speculated that by up-regulating estrogen receptor expression, miso made the tumor more estrogen dependent, which facilitated the antiestrogenic effects of tamoxifen.

More recently, Constantinou et al. (283) found that DMBA-induced mammary carcinogenesis (tumors per rat) was reduced 29% by tamoxifen, 37% by soy protein isolate and 62% by the combination; tumor latency was increased only in the combination group. Interestingly, a recent report shows that in ovariectomized rats, the combination of isoflavones and conjugated equine estrogens given after the administration of DMBA dramatically reduced tumor incidence in comparison with ovariectomized animals given estrogens alone or isoflavones alone (J. Mark Cline, Wake Forest University School of Medicine, Winston-Salem, NC, 2001). These studies suggest that the effect of soy consumption on the efficacy of tamoxifen and perhaps even estrogen is a promising area of research and warrants rigorous investigation.

Does the form of soy exposure matter?

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A variety of soy products are available in the marketplace, but the three main categories are traditional Asian soy foods, such as tofu and miso; products based on concentrated soy protein powders, especially soy protein isolate; and isoflavone supplements and foods to which isoflavones have been added. Often, cautionary warnings regarding soy consumption by breast cancer patients are restricted to supplements or supplements and powders (40 ,205 ,284 ,285). Although it is unclear whether any form of soy or isoflavone pills poses a risk to breast cancer patients, the available data do not appear to warrant differentiating among the various forms of isoflavone-containing products.

In work by Helferich and colleagues (116 ,166) described previously, soy protein isolate with various concentrations of genistein stimulated mammary tumor growth in mice implanted with MCF-7 cells to a similar extent as did isolated genistein. In the work by Hargreaves et al. (234) in which pS2 levels were increased in breast cells taken from premenopausal women and in the work by Petrakis et al. (212) in which NAF secretion increased, subjects were fed textured vegetable protein in the former study and isolated soy protein in the latter study. Furthermore, soy foods (211), concentrated soy protein powders (286) and isolated isoflavones (85) have all appeared to exert estrogen-like effects on other tissues in human subjects. Lastly, the pharmacokinetics of pure isoflavones are similar to those of isoflavones administered via food (73).

Of course, objections to pills also include the increased likelihood of excessive consumption and the lack of other potentially beneficial bioactive components found in soy (many pills do contain saponins, however). If warnings about pills are issued primarily because of concerns about overconsumption, this should be clearly articulated. However, most supplements contain an amount of isoflavones found in one or two servings of traditional soy foods (73). Thus, even consuming two or three pills of average isoflavone quantity would not result in an isoflavone intake that would exceed that likely resulting from the consumption of the quantity (25 g/d) of soy protein on which the Food and Drug Administration–approved health claim is based. It is true that there are other bioactive components in soy besides isoflavones [e.g., the protein is needed for cholesterol reduction although isoflavones may enhance the hypocholesterolemic effect (287 ,288)], but this point is likely irrelevant to the question of whether breast cancer patients should consume soy unless the argument is made that these other components can specifically negate any potentially harmful effects of soy on breast tissue. Few if any data suggest that this is the case.

Is it a question of excessive isoflavone exposure?

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As noted previously, in vitro genistein stimulates MCF-7 cell growth generally until concentrations exceed 5 μmol/L (98 ,106 ,116 ,124). Helferich and colleagues (116) showed that genistein and soy protein isolate increased tumor growth in a dose-dependent manner in ovariectomized SCID mice and that serum genistein levels in these mice are ~1–2 µmol/L. This is a serum level that occurs in humans consuming modest amounts (one to two servings) of soy foods. In the studies by Petrakis et al. (212⊞) and Hargreaves et al. (234⊞) isoflavone intake was 80 and 45 mg/d, respectively. Lower levels of isoflavones were not studied. These amounts of soy/isoflavones are similar to amounts typically recommended for the purported health benefits, and some studies suggest that <45 mg isoflavones/d is sufficient to exert physiologic effects in humans. As noted previously, typical Japanese isoflavone intake is 30–40 mg/d. Consequently, if soy and isoflavones do pose a risk for breast cancer patients, such risk is not the result of what most experts in this field would consider to be excessive consumption. In fact, arguably, given the biphasic effect of genistein on MCF-7 cell growth, high isoflavone intake levels could be less likely to exert adverse effects than low levels, but this is quite speculative.

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The available data, reviewed above, indicate the lack of any convincing information to substantiate either of two extreme and opposing claims, each of which has been prominently and repeatedly put forth in both the lay and scientific literature. These two claims are as follows: *1*) soy is protective against breast cancer and because of this should be recommended for consumption by healthy women and breast cancer patients; and *2*) soy is harmful for women with a history of or at high risk for breast cancer and because of this should be avoided by such women.

The honest response to each of these diametrically opposed claims is that no convincing data exist to support either claim. In fact, there are strongly conflicting data regarding both. As such, if women (with or without breast cancer) enjoy partaking of soy products, then it seems quite reasonable for them to partake of them. As with most things, moderation in intake is probably wise. In this regard, Asian soy intake may serve as a general guide for Western women.

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FOOTNOTES

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[4] Abbreviations used: CHD, coronary heart disease; DMBA, 7,12-dimethylbenz(a)anthracene; ERα, ß, estrogen receptor α, ß; HRT, hormone replacement therapy; IC_{50}, 50% inhibitory concentration; MNU, *N*-methyl-*N*-nitrosourea; NAF, nipple aspirate fluid; NMU, *N*-nitroso-*N*-methlyurea; PhiP, 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine; SHBG, sex hormone binding globulin.

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1. United Soybean Board (2000) 7th Annual Consumer Attitudes about Nutrition, 2000–2001 National Report 2000 United Soybean Board St. Louis, MO .

2. Based soy food maker stays a nose above the competition. Industry News. http://www.soyatech.com. Accessed July 20, 2001. .

3. Adlercreutz, H. & Mazur, W. (1997) Phyto-oestrogens and Western diseases. Ann. Med. 29:95-120.[Medline]

4. Fournier, D. B., Erdman, J. W., Jr & Gordon, G. B. (1998) Soy, its components, and cancer prevention: a review of the in vitro, animal, and human data. Cancer Epidemiol. Biomark. Prev. 7:1055-1065.[Medline]

5. Messina, M. J., Persky, V., Setchell, K. D. & Barnes, S. (1994) Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr. Cancer 21:113-131.[Medline]

6. Messina, M., Gugger, E. T. & Alekel, D. L. (2001) Soy protein, soybean isoflavones, and bone health: a review of the animal and human data. Wildman, R. eds. Handbook of Nutraceuticals and Functional Foods 2001:77-98 CRC Press Boca Raton, FL. .

7. Anderson, J. J. & Garner, S. C. (1998) Phytoestrogens and bone. Baillieres Clin. Endocrinol. Metab. 12:543-557.[Medline]

8. Erdman, J. W., Jr (2000) Soy protein and cardiovascular disease: a statement for healthcare professionals from the nutrition committee of the AHA. Circulation 102:2555-2559.[Free Full Text]

9. Food and Drug Administration (1999) Food labeling, health claims, soy protein, and coronary heart disease. Fed. Regist. 57:699-733.

10. Messina, M. & Barnes, S. (1991) The role of soy products in reducing risk of cancer. J. Natl. Cancer Inst. 83:541-546.[Medline]

11. Franke, A. A., Custer, L. J., Wang, W. & Shi, C. Y. (1998) HPLC analysis of isoflavonoids and other phenolic

agents from foods and from human fluids. Proc. Soc. Exp. Biol. Med. 217:263-273.[Abstract]

12. Liggins, J., Bluck, L. J., Runswick, S., Atkinson, C., Coward, W. A. & Bingham, S. A. (2000) Daidzein and genistein content of fruits and nuts. J. Nutr. Biochem. 11:326-331.[Medline]

13. Liggins, J., Bluck, L. J., Runswick, S., Atkinson, C., Coward, W. A. & Bingham, S. A. (2000) Daidzein and genistein contents of vegetables. Br. J. Nutr. 84:717-725.[Medline]

14. Murphy, P. A., Song, T., Buseman, G., Barua, K., Beecher, G. R., Trainer, D. & Holden, J. (1999) Isoflavones in retail and institutional soy foods. J. Agric. Food Chem. 47:2697-2704.[Medline]

15. Lu, L. J., Tice, J. A. & Bellino, F. L. (2001) Phytoestrogens and healthy aging: gaps in knowledge. A workshop report. Menopause 8:157-170.[Medline]

16. Osborne, C. K., Zhao, H. & Fuqua, S. A. (2000) Selective estrogen receptor modulators: structure, function, and clinical use. J. Clin. Oncol. 18:3172-3186.[Abstract/Free Full Text]

17. Brzezinski, A. & Debi, A. (1999) Phytoestrogens: the "natural" selective estrogen receptor modulators?. Eur. J. Obstet. Gynecol. Reprod. Biol 85:47-51.[Medline]

18. An, J., Tzagarakis-Foster, C., Scharschmidt, T. C., Lomri, N. & Leitman, D. C. (2001) Estrogen receptor beta-selective transcriptional activity and recruitment of coregulators by phytoestrogens. J. Biol. Chem. 276:17808-17814.[Abstract/Free Full Text]

19. Akiyama, T. & Ogawara, H. (1991) Use and specificity of genistein as inhibitor of protein-tyrosine kinases. Methods Enzymol 201:362-370.[Medline]

20. Constantinou, A. & Huberman, E. (1995) Genistein as an inducer of tumor cell differentiation: possible mechanisms of action. Proc. Soc. Exp. Biol. Med. 208:109-115.[Abstract]

21. Kim, H., Peterson, T. G. & Barnes, S. (1998) Mechanisms of action of the soy isoflavone genistein: emerging role for its effects via transforming growth factor beta signaling pathways. Am. J. Clin. Nutr. 68:1418S-1425S.[Abstract]

22. Garton, M., Reid, D. & Rennie, E. (1995) The climacteric, osteoporosis and hormone replacement; views of women aged 45–49. Maturitas 21:7-15.[Medline]

23. Vihtamaki, T., Savilahti, R. & Tuimala, R. (1999) Why do postmenopausal women discontinue hormone replacement therapy?. Maturitas 33:99-105.[Medline]

24. MacLennan, A., Lester, S. & Moore, V. (2001) Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. Climacteric 4:58-74.[Medline]

25. Brett, K. M. & Madans, J. H. (1997) Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. Am. J. Epidemiol. 145:536-545.[Abstract]

26. Keating, N. L., Cleary, P. D., Rossi, A. S., Zaslavsky, A. M. & Ayanian, J. Z. (1999) Use of hormone replacement

therapy by postmenopausal women in the United States. Ann. Intern. Med. 130:545-553.[Abstract/Free Full Text]

27. Heckbert, S. R., Weiss, N. S., Koepsell, T. D., Lemaitre, R. N., Smith, N. L., Siscovick, D. S., Lin, D. & Psaty, B. M. (1997) Duration of estrogen replacement therapy in relation to the risk of incident myocardial infarction in postmenopausal women. Arch. Intern. Med. 157:1330-1336.[Abstract]

28. Schneider, D. L., Barrett-Connor, E. L. & Morton, D. J. (1997) Timing of postmenopausal estrogen for optimal bone mineral density. The Rancho Bernardo Study. J. Am. Med. Assoc. 277:543-547.[Abstract]

29. Grady, D. & Hulley, S. B. (2000) Hormones to prevent coronary disease in women: when are observational studies adequate evidence?. Ann. Intern. Med 133:999-1001.[Free Full Text]

30. van der Schouw, Y. T. & Grobbee, D. E. (2001) HRT and heart disease: Dr Jekyll or Mrs Hyde?. Maturitas 38:213-217.[Medline]

31. Cauley, J. A., Black, D. M., Barrett-Connor, E., Harris, F., Shields, K., Applegate, W. & Cummings, S. R. (2001) Effects of hormone replacement therapy on clinical fractures and height loss: the heart and estrogen/progestin replacement study (HERS). Am. J. Med. 110:442-450.[Medline]

32. Grady, D. & Cummings, S. R. (2001) Postmenopausal hormone therapy for prevention of fractures. How good is the evidence?. J. Am. Med. Assoc. 285:2909-2910.[Free Full Text]

33. Lee, M. M., Lin, S. S., Wrensch, M. R., Adler, S. R. & Eisenberg, D. (2000) Alternative therapies used by women with breast cancer in four ethnic populations. J. Natl. Cancer Inst. 92:42-47.[Abstract/Free Full Text]

34. Morris, K. T., Johnson, N., Homer, L. & Walts, D. (2000) A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. Am. J. Surg. 179:407-411.[Medline]

35. Couzi, R. J., Helzlsouer, K. J. & Fetting, J. H. (1995) Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J. Clin. Oncol. 13:2737-2744.[Abstract]

36. Carpenter, J. S., Andrykowski, M. A., Cordova, M., Cunningham, L., Studts, J., McGrath, P., Kenady, D., Sloan, D. & Munn, R. (1998) Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. Cancer 82:1682-1691.[Medline]

37. Col, N. F., Hirota, L. K., Orr, R. K., Erban, J. K., Wong, J. B. & Lau, J. (2001) Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. J. Clin. Oncol. 19:2357-2363.[Abstract/Free Full Text]

38. Bouker, K. B. & Hilakivi-Clarke, L. (2000) Genistein: does it prevent or promote breast cancer?. Environ. Health Perspect 108:701-708.[Medline]

39. American Cancer Society Workshop on Nutrition and Physical Activity for Cancer Survivors (2001) Nutrition during and after cancer treatment: a guide for informed choices by cancer survivors. CA-Cancer J. Clin. 51:153-187.[Abstract/Free Full Text]

40. Affenito, S. G. & Kerstetter, J. (1999) Position of the American Dietetic Association and Dietitians of Canada: women's health and nutrition. J. Am. Diet. Assoc. 99:738-751.[Medline]

41. American College of Obstetricians and Gynecologists (2001) Use of botanicals for management of menopausal symptoms. ACOG Pract. Bull. 28:1-11.

42. Barnes, S., Grubbs, C., Setchell, K. D. & Carlson, J. (1990) Soybeans inhibit mammary tumors in models of breast cancer. Prog. Clin. Biol. Res. 347:239-253.[Medline]

43. Howe, G. R. (1992) High-fat diets and breast cancer risk. The epidemiologic evidence. J. Am. Med. Assoc. 268:2080-2081.[Medline]

44. Howe, G. R., Hirohata, T., Hislop, T. G., Iscovich, J. M., Yuan, J. M., Katsouyanni, K., Lubin, F., Marubini, E., Modan, B., Rohan, T., Toniolo, P. & Shunzhang, Y. (1990) Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. J. Natl. Cancer Inst. 82:561-569.[Abstract]

45. Prentice, R. L. (2000) Future possibilities in the prevention of breast cancer: fat and fiber and breast cancer research. Breast Cancer Res 2:268-276.[Medline]

46. Wu, A. H., Pike, M. C. & Stram, D. O. (1999) Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J. Natl. Cancer Inst. 91:529-534.[Abstract/Free Full Text]

47. Holmes, M. D., Hunter, D. J., Colditz, G. A., Stampfer, M. J., Hankinson, S. E., Speizer, F. E., Rosner, B. & Willett, W. C. (1999) Association of dietary intake of fat and fatty acids with risk of breast cancer [see comments]. J. Am. Med. Assoc. 281:914-920.[Abstract/Free Full Text]

48. Holmes, M. D., Schisterman, E. F., Spiegelman, D., Hunter, D. J. & Willett, W. C. (1999) Re: Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J. Natl. Cancer Inst. 91:1511-1512. [Free Full Text]

49. Cohen, L. A. (1999) Dietary fiber and breast cancer. Anticancer Res 19:3685-3688.[Medline]

50. Smith-Warner, S. A., Spiegelman, D., Yaun, S. S., Adami, H. O., Beeson, W. L., van den Brandt, P. A., Folsom, A. R., Fraser, G. E., Freudenheim, J. L., Goldbohm, R. A., Graham, S., Miller, A. B., Potter, J. D., Rohan, T. E., Speizer, F. E., Toniolo, P., Willett, W. C., Wolk, A., Zeleniuch-Jacquotte, A. & Hunter, D. J. (2001) Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. J. Am. Med. Assoc. 285:769-776. [Abstract/Free Full Text]

51. Lee, H. P., Gourley, L., Duffy, S. W., Esteve, J., Lee, J. & Day, N. E. (1991) Dietary effects on breast-cancer risk in Singapore. Lancet 337:1197-1200.[Medline]

52. Folman, Y. & Pope, G. S. (1966) The interaction in the immature mouse of potent oestrogens with coumestrol, genistein and other utero-vaginotrophic compounds of low potency. J. Endocrinol. 34:215-225.[Medline]

53. Ogawara, H., Akiyama, T., Ishida, J., Watanabe, S. & Suzuki, K. (1986) A specific inhibitor for tyrosine protein kinase from pseudomonas. J. Antibiot. (Tokyo) 39:606-608.[Medline]

54. Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M. & Fukami, Y. (1987) Genistein, a specific inhibitor of tyrosine-specific protein kinases. J. Biol. Chem. 262:5592-5595. [Abstract/Free Full Text]

55. Hunter, T. & Cooper, J. A. (1985) Protein-tyrosine kinases. Annu. Rev. Biochem. 54:897-930.[Medline]

56. Constantinou, A., Kiguchi, K. & Huberman, E. (1990) Induction of differentiation and DNA strand breakage in human HL-60 and K-562 leukemia cells by genistein. Cancer Res 50:2618-2624.[Abstract]

57. Wang, H.-J. & Murphy, P. A. (1994) Isoflavone composition of American and Japanese soybeans in Iowa: effects of variety, crop year, and location. J. Agric. Food Chem. 42:1674-1677.

58. Carrão-Panizzi, M. C. & Kitamura, K. (1995) Isoflavone content in Brazilian soybean cultivars. Breeding Sci 45:295-300.

59. Nakamura, Y., Tsuji, S. & Tonogai, Y. (2000) Determination of the levels of isoflavonoids in soybeans and soy-derived foods and estimation of isoflavonoids in the Japanese daily intake. J. Assoc. Off. Anal. Chem. Int. 83:635-650.

60. Somekawa, Y., Chiguchi, M., Ishibashi, T. & Aso, T. (2001) Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. Obstet. Gynecol. 97:109-115. [Abstract/Free Full Text]

61. Nagata, C., Takatsuka, N., Kurisu, Y. & Shimizu, H. (1998) Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women. J. Nutr. 128:209-213. [Abstract/Free Full Text]

62. Wakai, K., Egami, I., Kato, K., Kawamura, T., Tamakoshi, A., Lin, Y., Nakayama, T., Wada, M. & Ohno, Y. (1999) Dietary intake and sources of isoflavones among Japanese. Nutr. Cancer 33:139-145.[Medline]

63. Santell, R. C., Kieu, N. & Helferich, W. G. (2000) Genistein inhibits growth of estrogen-independent human breast cancer cells in culture but not in athymic mice. J. Nutr. 130:1665-1669.[Abstract/Free Full Text]

64. Xu, X., Harris, K. S., Wang, H. J., Murphy, P. A. & Hendrich, S. (1995) Bioavailability of soybean isoflavones depends upon gut microflora in women. J. Nutr. 125:2307-2315.[Medline]

65. Xu, X., Wang, H. J., Murphy, P. A., Cook, L. & Hendrich, S. (1994) Daidzein is a more bioavailable soymilk isoflavone than is genistein in adult women. J. Nutr. 124:825-832.[Medline]

66. Watanabe, S., Yamaguchi, M., Sobue, T., Takahashi, T., Miura, T., Arai, Y., Mazur, W., Wahala, K. & Adlercreutz, H. (1998) Pharmacokinetics of soybean isoflavones in plasma, urine and feces of men after ingestion of 60 g baked soybean powder (kinako). J. Nutr. 128:1710-1715.[Abstract/Free Full Text]

67. King, R. A. & Bursill, D. B. (1998) Plasma and urinary kinetics of the isoflavones daidzein and genistein after a single soy meal in humans. Am. J. Clin. Nutr. 67:867-872.[Abstract]

68. Adlercreutz, H., Markkanen, H. & Watanabe, S. (1993) Plasma concentrations of phyto-oestrogens in Japanese men. Lancet 342:1209-1210.[Medline]

69. Griffiths, K., Denis, L., Turkes, A. & Morton, M. S. (1998) Phytoestrogens and diseases of the prostate gland. Baillieres Clin. Endocrinol. Metab. 12:625-647.[Medline]

70. Fanti, P., Sawaya, B. P., Custer, L. J. & Franke, A. A. (1999) Serum levels and metabolic clearance of the isoflavones genistein and daidzein in hemodialysis patients. J. Am. Soc. Nephrol. 10:864-871. [Abstract/Free Full Text]

71. Shelnutt, S. R., Cimino, C. O., Wiggins, P. A. & Badger, T. M. (2000) Urinary pharmacokinetics of the glucuronide and sulfate conjugates of genistein and daidzein. Cancer Epidemiol. Biomark. Prev. 9:413-419. [Abstract/Free Full Text]

72. Setchell, K. D. (1998) Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. Am. J. Clin. Nutr. 68:1333S-1346S.[Abstract]

73. Setchell, K. D., Brown, N. M., Desai, P., Zimmer-Nechemias, L., Wolfe, B. E., Brashear, W. T., Kirschner, A. S., Cassidy, A. & Heubi, J. E. (2001) Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J. Nutr. 131:1362S-1375S.[Abstract/Free Full Text]

74. Markiewicz, L., Garey, J., Adlercreutz, H. & Gurpide, E. (1993) In vitro bioassays of non-steroidal phytoestrogens. J. Steroid Biochem. Mol. Biol. 45:399-405.[Medline]

75. Mayr, U., Butsch, A. & Schneider, S. (1992) Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.[Medline]

76. Nagel, S. C., vom Saal, F. S. & Welshons, W. V. (1998) The effective free fraction of estradiol and xenoestrogens in human serum measured by whole cell uptake assays: physiology of delivery modifies estrogenic activity. Proc. Soc. Exp. Biol. Med. 217:300-309.[Abstract]

77. Walker, H. A., Dean, T. S., Sanders, T. A., Jackson, G., Ritter, J. M. & Chowienczyk, P. J. (2001) The phytoestrogen genistein produces acute nitric oxide-dependent dilation of human forearm vasculature with similar potency to 17ß-estradiol. Circulation 103:258-262.[Abstract/Free Full Text]

78. Makela, S., Savolainen, H., Aavik, E., Myllarniemi, M., Strauss, L., Taskinen, E., Gustafsson, J. A. & Hayry, P. (1999) Differentiation between vasculoprotective and uterotrophic effects of ligands with different binding affinities to estrogen receptors alpha and beta. Proc. Natl. Acad. Sci. U.S.A. 96:7077-7082.[Abstract/Free Full Text]

79. Duncan, A. M., Merz, B. E., Xu, X., Nagel, T. C., Phipps, W. R. & Kurzer, M. S. (1999) Soy isoflavones exert modest hormonal effects in premenopausal women. J. Clin. Endocrinol. Metab. 84:192-197.[Abstract/Free Full Text]

80. Upmalis, D. H., Lobo, R., Bradley, L., Warren, M., Cone, F. L. & Lamia, C. A. (2000) Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. Menopause 7:236-242.[Medline]

81. Fanti, P., Monier-Faugere, M. C., Geng, Z., Schmidt, J., Morris, P. E., Cohen, D. & Malluche, H. H. (1998) The phytoestrogen genistein reduces bone loss in short-term ovariectomized rats. Osteoporos. Int. 8:274-281.[Medline]

82. Ishida, H., Uesugi, T., Hirai, K., Toda, T., Nukaya, H., Yokotsuka, K. & Tsuji, K. (1998) Preventive effects of the plant isoflavones, daidzin and genistin, on bone loss in ovariectomized rats fed a calcium-deficient diet. Biol. Pharm. Bull. 21:62-66.[Medline]

83. Probst-Hensch, N. M., Pike, M. C., McKean-Cowdin, R., Stanczyk, F. Z., Kolonel, L. N. & Henderson, B. E. (2000) Ethnic differences in post-menopausal plasma oestrogen levels: high oestrone levels in Japanese-American women despite low weight. Br. J. Cancer 82:1867-1870.[Medline]

84. Nestel, P. J., Pomeroy, S., Kay, S., Komesaroff, P., Behrsing, J., Cameron, J. D. & West, L. (1999) Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women [published erratum appears in J. Clin. Endocrinol. Metab. 84: 3647]. J. Clin. Endocrinol. Metab. 84:895-898.[Abstract/Free Full Text]

85. Nestel, P. J., Yamashita, T., Sasahara, T., Pomeroy, S., Dart, A., Komesaroff, P., Owen, A. & Abbey, M. (1997) Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. Arterioscler. Thromb. Vasc. Biol. 17:3392-3398.[Abstract/Free Full Text]

86. Davis, J. N., Kucuk, O., Djuric, Z. & Sarkar, F. H. (2001) Soy isoflavone supplementation in healthy men prevents NF-κB activation by TNF-α in blood lymphocytes. Free Radic. Biol. Med. 30:1293-1302.[Medline]

87. Kuiper, G. G., Carlsson, B., Grandien, K., Enmark, E., Haggblad, J., Nilsson, S. & Gustafsson, J. A. (1997) Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 138:863-870.[Abstract/Free Full Text]

88. Kuiper, G. G., Lemmen, J. G., Carlsson, B., Corton, J. C., Safe, S. H., van der Saag, P. T., van der Burg, B. & Gustafsson, J. A. (1998) Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 139:4252-4263.[Abstract/Free Full Text]

89. Casanova, M., You, L., Gaido, K. W., Archibeque-Engle, S., Janszen, D. B. & Heck, H. A. (1999) Developmental effects of dietary phytoestrogens in Sprague-Dawley rats and interactions of genistein and daidzein with rat estrogen receptors alpha and beta in vitro. Toxicol. Sci. 51:236-244.[Abstract]

90. Cassidy, A. & Faughnan, M. (2000) Phyto-oestrogens through the life cycle. Proc. Nutr. Soc. 59:489-496.[Medline]

91. Gustafsson, J. A. (1998) Therapeutic potential of selective estrogen receptor modulators. Curr. Opin. Chem. Biol. 2:508-511.[Medline]

92. Pike, A. C., Brzozowski, A. M., Hubbard, R. E., Bonn, T., Thorsell, A. G., Engstrom, O., Ljunggren, J., Gustafsson, J. A. & Carlquist, M. (1999) Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. EMBO J 18:4608-4618.[Abstract/Free Full Text]

93. Singh, A. K. (2001) Development of QSAR models to predict estrogenic, carcinogenic, and cancer protective effects of phytoestrogens. Cancer Investig 19:201-216.[Medline]

94. Hunter, D. S., Hodges, L. C., Vonier, P. M., Fuchs-Young, R., Gottardis, M. M. & Walker, C. L. (1999) Estrogen receptor activation via activation function 2 predicts agonism of xenoestrogens in normal and neoplastic cells of the uterine myometrium. Cancer Res 59:3090-3099.[Abstract/Free Full Text]

95. Dees, C., Foster, J. S., Ahamed, S. & Wimalasena, J. (1997) Dietary estrogens stimulate human breast cells to enter the cell cycle. Environ. Health Perspect. 105(suppl. 3):633-636.[Medline]

96. Makela, S., Davis, V. L., Tally, W. C., Korkman, J., Salo, L., Vihko, R., Santti, R. & Korach, K. S. (1994) Dietary estrogens act through estrogen receptor-mediated processes and show no antiestrogenicity in cultured breast cancer cells. Environ. Health Perspect. 102:572-578.[Medline]

97. Zava, D. T. & Duwe, G. (1997) Estrogenic and antiproliferative properties of genistein and other flavonoids in human breast cancer cells in vitro. Nutr. Cancer 27:31-40.[Medline]

98. Miodini, P., Fioravanti, L., Di Fronzo, G. & Cappelletti, V. (1999) The two phyto-oestrogens genistein and quercetin exert different effects on oestrogen receptor function. Br. J. Cancer 80:1150-1155.[Medline]

99. Sathyamoorthy, N. & Wang, T. T. (1997) Differential effects of dietary phyto-oestrogens daidzein and equol on human breast cancer MCF-7 cells. Eur. J. Cancer 33:2384-2389.[Medline]

100. Barkhem, T., Carlsson, B., Nilsson, Y., Enmark, E., Gustafsson, J. & Nilsson, S. (1998) Differential response of estrogen receptor alpha and estrogen receptor beta to partial estrogen agonists/antagonists. Mol. Pharmacol. 54:105-112.[Abstract/Free Full Text]

101. Kao, Y. C., Zhou, C., Sherman, M., Laughton, C. A. & Chen, S. (1998) Molecular basis of the inhibition of human aromatase (estrogen synthetase) by flavone and isoflavone phytoestrogens: a site-directed mutagenesis study. Environ. Health Perspect. 106:85-92.[Medline]

102. Adlercreutz, H., Bannwart, C., Wahala, K., Makela, T., Brunow, G., Hase, T., Arosemena, P. J., Kellis, J. T., Jr & Vickery, L. E. (1993) Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J. Steroid Biochem. Mol. Biol. 44:147-153.[Medline]

103. Campbell, D. R. & Kurzer, M. S. (1993) Flavonoid inhibition of aromatase enzyme activity in human preadipocytes. J. Steroid Biochem. Mol. Biol. 46:381-388.[Medline]

104. Kirk, C. J., Harris, R. M., Wood, D. M., Waring, R. H. & Hughes, P. J. (2001) Do dietary phytoestrogens influence susceptibility to hormone-dependent cancer by disrupting the metabolism of endogenous oestrogens?. Biochem. Soc. Trans 29:209-216.[Medline]

105. Makela, S., Poutanen, M., Kostian, M. L., Lehtimaki, N., Strauss, L., Santti, R. & Vihko, R. (1998) Inhibition of 17ß-hydroxysteroid oxidoreductase by flavonoids in breast and prostate cancer cells. Proc. Soc. Exp. Biol. Med. 217:310-316.[Abstract]

106. Le Bail, J. C., Champavier, Y., Chulia, A. J. & Habrioux, G. (2000) Effects of phytoestrogens on aromatase, 3ß and 17ß-hydroxysteroid dehydrogenase activities and human breast cancer cells. Life Sci 66:1281-1291.[Medline]

107. Clemons, M. & Goss, P. (2001) Estrogen and the risk of breast cancer. N. Engl. J. Med. 344:276-285. [Free Full Text]

108. Purohit, A., Singh, A. & Reed, M. J. (1999) Regulation of steroid sulphatase and oestradiol 17 beta-hydroxysteroid dehydrogenase in breast cancer. Biochem. Soc. Trans. 27:323-327.[Medline]

109. Foth, D. & Cline, J. M. (1998) Effects of mammalian and plant estrogens on mammary glands and uteri of macaques. Am. J. Clin. Nutr. 68:1413S-1417S.[Abstract]

110. Weber, G., Shen, F., Yang, H., Prajda, N. & Li, W. (1999) Regulation of signal transduction activity in normal and cancer cells. Anticancer Res 19:3703-3709.[Medline]

111. Meng, Q. H., Wahala, K., Adlercreutz, H. & Tikkanen, M. J. (1999) Antiproliferative efficacy of lipophilic soy isoflavone phytoestrogens delivered by low density lipoprotein particles into cultured U937 cells. Life Sci 65:1695-1705.[Medline]

112. Ruiz-Larrea, M. B., Mohan, A. R., Paganga, G., Miller, N. J., Bolwell, G. P. & Rice-Evans, C. A. (1997) Antioxidant activity of phytoestrogenic isoflavones. Free Radic. Res. 26:63-70.[Medline]

113. Peterson, G. & Barnes, S. (1991) Genistein inhibition of the growth of human breast cancer cells: independence from estrogen receptors and the multi-drug resistance gene. Biochem. Biophys. Res. Commun. 179:661-667. [Medline]

114. Pagliacci, M. C., Smacchia, M., Migliorati, G., Grignani, F., Riccardi, C. & Nicoletti, I. (1994) Growth-inhibitory effects of the natural phyto-oestrogen genistein in MCF-7 human breast cancer cells. Eur. J. Cancer 11:1675-1682.

115. Peterson, G. & Barnes, S. (1996) Genistein inhibits both estrogen and growth factor-stimulated proliferation of human breast cancer cells. Cell Growth Differ 7:1345-1351.[Abstract]

116. Hsieh, C. Y., Santell, R. C., Haslam, S. Z. & Helferich, W. G. (1998) Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res 58:3833-3838.[Abstract]

117. Shao, Z. M., Shen, Z. Z., Fontana, J. A. & Barsky, S. H. (2000) Genistein's "ER-dependent and independent" actions are mediated through ER pathways in ER-positive breast carcinoma cell lines. Anticancer Res 20:2409-2416. [Medline]

118. Twaddle, G. M., Turbov, J., Liu, N. & Murthy, S. (1999) Tyrosine kinase inhibitors as antiproliferative agents against an estrogen-dependent breast cancer cell line in vitro. J. Surg. Oncol. 70:83-90.[Medline]

119. Li, Y., Bhuiyan, M. & Sarkar, F. H. (1999) Induction of apoptosis and inhibition of C-ERBB-2 in MDA-MB-435 cells by genistein. Int. J. Oncol. 15:525-533.[Medline]

120. Shen, F., Xue, X. & Weber, G. (1999) Tamoxifen and genistein synergistically down-regulate signal transduction and proliferation in estrogen receptor-negative human breast carcinoma MDA-MB-435 cells. Anticancer

Res 19:1657-1662.[Medline]

121. Shao, Z. M., Wu, J., Shen, Z. Z. & Barsky, S. H. (1998) Genistein exerts multiple suppressive effects on human breast carcinoma cells. Cancer Res 58:4851-4857.[Abstract]

122. Leung, L. K. & Wang, T. T. (2000) Bcl-2 is not reduced in the death of MCF-7 cells at low genistein concentration. J. Nutr. 130:2922-2926.[Abstract/Free Full Text]

123. Lin, H. M., Moon, B. K., Yu, F. & Kim, H. R. (2000) Galectin-3 mediates genistein-induced G(2)/M arrest and inhibits apoptosis. Carcinogenesis 21:1941-1945.[Abstract/Free Full Text]

124. Fioravanti, L., Cappelletti, V., Miodini, P., Ronchi, E., Brivio, M. & Di Fronzo, G. (1998) Genistein in the control of breast cancer cell growth: insights into the mechanism of action in vitro. Cancer Lett 130:143-152. [Medline]

125. Martinez-Campos, A., Amara, J. F. & Dannies, P. S. (1986) Antiestrogens are partial estrogen agonists for prolactin production in primary pituitary cultures. Mol. Cell. Endocrinol. 48:127-133.[Medline]

126. Wang, C. & Kurzer, M. S. (1998) Effects of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. Nutr. Cancer 31:90-100.[Medline]

127. Scholar, E. M. & Toews, M. L. (1994) Inhibition of invasion of murine mammary carcinoma cells by the tyrosine kinase inhibitor genistein. Cancer Lett 87:159-162.[Medline]

128. Santibanez, J. F., Navarro, A. & Martinez, J. (1997) Genistein inhibits proliferation and in vitro invasive potential of human prostatic cancer cell lines. Anticancer Res 17:1199-1204.[Medline]

129. Dalu, A., Haskell, J. F., Coward, L. & Lamartiniere, C. A. (1998) Genistein, a component of soy, inhibits the expression of the EGF and ERBB2/NEU receptors in the rat dorsolateral prostate. Prostate 37:36-43.[Medline]

130. Chang, H. C., Churchwell, M. I., Delclos, K. B., Newbold, R. R. & Doerge, D. R. (2000) Mass spectrometric determination of genistein tissue distribution in diet-exposed Sprague-Dawley rats. J. Nutr. 130:1963-1970. [Abstract/Free Full Text]

131. Fotsis, T., Pepper, M., Adlercreutz, H., Fleischmann, G., Hase, T., Montesano, R. & Schweigerer, L. (1993) Genistein, a dietary-derived inhibitor of in vitro angiogenesis. Proc. Natl. Acad. Sci. U.S.A. 90:2690-2694.[Abstract]

132. Fotsis, T., Pepper, M. S., Aktas, E., Breit, S., Rasku, S., Adlercreutz, H., Wahala, K., Montesano, R. & Schweigerer, L. (1997) Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. Cancer Res 57:2916-2921.[Abstract]

133. Fajardo, I., Diez, E., Rodriguez-Nieto, S., Rodriguez-Caso, C., Quesada, A. R., Sanchez-Jimenez, F. & Medina, M. A. (2000) Effects of genistein and 2-methoxyestradiol on matrix metalloproteinases and their inhibitors secreted by Ehrlich ascites tumor cells. Anticancer Res 20:1691-1694.[Medline]

134. Zhou, J. R., Gugger, E. T., Tanaka, T., Guo, Y., Blackburn, G. L. & Clinton, S. K. (1999) Soybean

phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. J. Nutr. 129:1628-1635.[Abstract/Free Full Text]

135. Li, D., Yee, J. A., McGuire, M. H., Murphy, P. A. & Yan, L. (1999) Soybean isoflavones reduce experimental metastasis in mice. J. Nutr. 129:1075-1078.[Abstract/Free Full Text]

136. Iishi, H., Tatsuta, M., Baba, M., Yano, H., Sakai, N. & Akedo, H. (2000) Genistein attenuates peritoneal metastasis of azoxymethane-induced intestinal adenocarcinomas in wistar rats. Int. J. Cancer 86:416-420.[Medline]

137. Yan, L., Yee, J. A., McGuire, M. H. & Graef, G. L. (1997) Effect of dietary supplementation of soybeans on experimental metastasis of melanoma cells in mice. Nutr. Cancer 29:1-6.[Medline]

138. Menon, L. G., Kuttan, R., Nair, M. G., Chang, Y. C. & Kuttan, G. (1998) Effect of isoflavones genistein and daidzein in the inhibition of lung metastasis in mice induced by B16F-10 melanoma cells. Nutr. Cancer 30:74-77.[Medline]

139. Hakkak, R., Korourian, S., Shelnutt, S. R., Lensing, S., Ronis, M. J. & Badger, T. M. (2000) Diets containing whey proteins or soy protein isolate protect against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in female rats. Cancer Epidemiol. Biomark. Prev. 9:113-117.[Abstract/Free Full Text]

140. Gotoh, T., Yamada, K., Yin, H., Ito, A., Kataoka, T. & Dohi, K. (1998) Chemoprevention of *N*-nitroso-*N*-methylurea-induced rat mammary carcinogenesis by soy foods or biochanin A. Jpn. J. Cancer Res. 89:137-142.[Medline]

141. Hawrylewicz, E. J., Huang, H. H. & Blair, W. H. (1991) Dietary soybean isolate and methionine supplementation affect mammary tumor progression in rats. J. Nutr. 121:1693-1698.[Medline]

142. Baggott, J. E., Ha, T., Vaughn, W. H., Juliana, M. M., Hardin, J. M. & Grubbs, C. J. (1990) Effect of miso (Japanese soybean paste) and NaCl on DMBA-induced rat mammary tumors. Nutr. Cancer 14:103-109.[Medline]

143. Ohta, T., Nakatsugi, S., Watanabe, K., Kawamori, T., Ishikawa, F., Morotomi, M., Sugie, S., Toda, T., Sugimura, T. & Wakabayashi, K. (2000) Inhibitory effects of bifidobacterium-fermented soy milk on 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced rat mammary carcinogenesis, with a partial contribution of its component isoflavones. Carcinogenesis 21:937-941.[Abstract/Free Full Text]

144. Cohen, L. A., Zhao, Z., Pittman, B. & Scimeca, J. A. (2000) Effect of intact and isoflavone-depleted soy protein on NMU-induced rat mammary tumorigenesis. Carcinogenesis 21:929-935.[Abstract/Free Full Text]

145. Carroll, K. K. (1975) Experimental evidence of dietary factors and hormone-dependent cancers. Cancer Res 35:3374-3383.[Abstract]

146. Gridley, D. S., Kettering, J. D., Slater, J. M. & Nutter, R. L. (1983) Modification of spontaneous mammary tumors in mice fed different sources of protein, fat and carbohydrate. Cancer Lett 19:133-146.[Medline]

147. Hsueh, A. M., Shipley, R. & Park, H. S. (1992) Quality of dietary protein during initiation and promotion of chemical carcinogenesis in rats. Liepa, G.U. eds. Dietary Proteins. How They Alleviate Disease and Promote Better

Health 1992 American Oil Chemists' Society Champaign, IL .

148. Gotoh, T., Yamada, K., Ito, A., Yin, H., Kataoka, T. & Dohi, K. (1998) Chemoprevention of *N*-nitroso-*N*-methylurea-induced rat mammary cancer by miso and tamoxifen, alone and in combination. Jpn. J. Cancer Res. 89:487-495.[Medline]

149. Barnes, S., Peterson, G., Grubbs, C. & Setchell, K. (1994) Potential role of dietary isoflavones in the prevention of cancer. Adv. Exp. Med. Biol. 354:135-147.[Medline]

150. Zaizen, Y., Higuchi, Y., Matsuo, N., Shirabe, K., Tokuda, H. & Takeshita, M. (2000) Antitumor effects of soybean hypocotyls and soybeans on the mammary tumor induction by *N*-methyl-*N*-nitrosourea in F344 rats. Anticancer Res 20:1439-1444.[Medline]

151. Constantinou, A. I., Mehta, R. G. & Vaughan, A. (1996) Inhibition of *N*-methyl-*N*-nitrosourea-induced mammary tumors in rats by the soybean isoflavones. Anticancer Res 16:3293-3298.[Medline]

152. Murillo, G., Singletary, K. W., Kamath, S. K. & Arjmandi, B. H. (1998) The antitumorigenic properties of ipriflavone and genistin in rat mammary tissues. FASEB J 12:A828.

153. Tsukamoto, C., Shimada, S., Igita, K., Kudou, S., Kokubun, M., Okubo, K. & Kitamura, K. (1995) Factors affecting isoflavone content in soybean seeds: changes in isoflavones, saponins, and composition of fatty acids at different temperatures during seed development. J. Agric. Food Chem. 43:1184-1192.

154. Brown, N. M. & Setchell, K. D. (2001) Animal models impacted by phytoestrogens in commercial chow: implications for pathways influenced by hormones. Lab. Investig. 81:735-747.[Medline]

155. Lampe, J. W., Skor, H. E., Li, S., Wahala, K., Howald, W. N. & Chen, C. (2001) Wheat bran and soy protein feeding do not alter urinary excretion of the isoflavan equol in premenopausal women. J. Nutr. 131:740-744. [Abstract/Free Full Text]

156. Rowland, I. R., Wiseman, H., Sanders, T. A., Adlercreutz, H. & Bowey, E. A. (2000) Interindividual variation in metabolism of soy isoflavones and lignans: influence of habitual diet on equol production by the gut microflora. Nutr. Cancer 36:27-32.[Medline]

157. Duncan, A. M., Merz-Demlow, B. E., Xu, X., Phipps, W. R. & Kurzer, M. S. (2000) Premenopausal equol excretors show plasma hormone profiles associated with lowered risk of breast cancer. Cancer Epidemiol. Biomark. Prev. 9:581-586.[Abstract/Free Full Text]

158. Setchell, K. D., Borriello, S. P., Hulme, P., Kirk, D. N. & Axelson, M. (1984) Nonsteroidal estrogens of dietary origin: possible roles in hormone-dependent disease. Am. J. Clin. Nutr. 40:569-578.[Abstract]

159. Hodgson, J. M., Puddey, I. B., Beilin, L. J., Mori, T. A., Burke, V., Croft, K. D. & Rogers, P. B. (1999) Effects of isoflavonoids on blood pressure in subjects with high-normal ambulatory blood pressure levels: a randomized controlled trial. Am. J. Hypertens. 12:47-53.[Medline]

160. Peterson, T. G., Coward, L., Kirk, M., Falany, C. N. & Barnes, S. (1996) The role of metabolism in mammary

epithelial cell growth inhibition by the isoflavones genistein and biochanin A. Carcinogenesis 17:1861-1869. [Abstract]

161. Day, J. K., Besch-Williford, C., McMann, T. R., Hufford, M. G., Lubahn, D. B. & MacDonald, R. S. (2001) Dietary genistein increased DMBA-induced mammary adenocarcinoma in wild-type but not ERα KO mice. Nutr. Cancer in press.

162. Hawrylewicz, E. J., Zapata, J. J. & Blair, W. H. (1995) Soy and experimental cancer: animal studies. J. Nutr. 125:698S-708S.[Medline]

163. Lu, S. & Epner, D. E. (2000) Molecular mechanisms of cell cycle block by methionine restriction in human prostate cancer cells. Nutr. Cancer 38:123-130.[Medline]

164. Nagata, C. (2000) Ecological study of the association between soy protein intake and mortality from cancer and heart disease in Japan. Int. J. Epidemiol. 29:832-836.[Abstract/Free Full Text]

165. Charland, S. L., Hui, J. W. & Torosian, M. H. (1998) The effects of a soybean extract on tumor growth and metastasis. Int. J. Mol. Med. 2:225-228.[Medline]

166. Allred, C. D., Allred, K. F., Ju, Y. H., Virant, S. M. & Helferich, W. G. (2001) Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. Cancer Res 61:5045-5050.[Abstract/Free Full Text]

167. Makela, S. I., Pylkkanen, L. H., Santti, R. S. & Adlercreutz, H. (1995) Dietary soybean may be antiestrogenic in male mice. J. Nutr. 125:437-445.[Medline]

168. Seibert, K., Shafie, S. M., Triche, T. J., Whang-Peng, J. J., O'Brien, S. J., Toney, J. H., Huff, K. K. & Lippman, M. E. (1983) Clonal variation of MCF-7 breast cancer cells in vitro and in athymic nude mice. Cancer Res 43:2223-2239.[Medline]

169. Trevoux, R., De Brux, J., Castanier, M., Nahoul, K., Soule, J. P. & Scholler, R. (1986) Endometrium and plasma hormone profile in the peri-menopause and post-menopause. Maturitas 8:309-326.[Medline]

170. Zhu, B. T. & Conney, A. H. (1998) Functional role of estrogen metabolism in target cells: review and perspectives. Carcinogenesis 19:1-27.[Abstract]

171. Szymczak, J., Milewicz, A., Thijssen, J. H., Blankenstein, M. A. & Daroszewski, J. (1998) Concentration of sex steroids in adipose tissue after menopause. Steroids 63:319-321.[Medline]

172. Lamartiniere, C. A. (2000) Protection against breast cancer with genistein: a component of soy. Am. J. Clin. Nutr. discussion 1708S–1709S 71:1705S-1707S.

173. Lamartiniere, C. A., Moore, J., Holland, M. & Barnes, S. (1995) Neonatal genistein chemoprevents mammary cancer. Proc. Soc. Exp. Biol. Med. 208:120-123.[Abstract]

174. Lamartiniere, C. A., Moore, J. B., Brown, N. M., Thompson, R., Hardin, M. J. & Barnes, S. (1995) Genistein

suppresses mammary cancer in rats. Carcinogenesis 16:2833-2840.[Abstract]

175. Murrill, W. B., Brown, N. M., Zhang, J. X., Manzolillo, P. A., Barnes, S. & Lamartiniere, C. A. (1996) Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. Carcinogenesis 17:1451-1457.[Abstract]

176. Fritz, W. A., Coward, L., Wang, J. & Lamartiniere, C. A. (1998) Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. Carcinogenesis 19:2151-2158.[Abstract]

177. Hilakivi-Clarke, L., Onojafe, I., Raygada, M., Cho, E., Skaar, T., Russo, I. & Clarke, R. (1999) Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. Br. J. Cancer 80:1682-1688.[Medline]

178. Russo, J. & Russo, I. H. (1978) DNA labeling index and structure of the rat mammary gland as determinants of its susceptibility to carcinogenesis. J. Natl. Cancer Inst. 61:1451-1459.[Medline]

179. Grubbs, C. J., Farnell, D. R., Hill, D. L. & McDonough, K. C. (1985) Chemoprevention of *N*-nitroso-*N*-methylurea-induced mammary cancers by pretreatment with 17 beta-estradiol and progesterone. J. Natl. Cancer Inst. 74:927-931.[Medline]

180. Russo, J., Wilgus, G. & Russo, I. H. (1979) Susceptibility of the mammary gland to carcinogenesis: I Differentiation of the mammary gland as determinant of tumor incidence and type of lesion. Am. J. Pathol. 96:721-736.[Abstract]

181. Guzman, R. C., Yang, J., Rajkumar, L., Thordarson, G., Chen, X. & Nandi, S. (1999) Hormonal prevention of breast cancer: mimicking the protective effect of pregnancy. Proc. Natl. Acad. Sci. U.S.A. 96:2520-2525. [Abstract/Free Full Text]

182. MacMahon, B., Cole, P., Lin, T. M., Lowe, C. R., Mirra, A. P., Ravnihar, B., Salber, E. J., Valaoras, V. G. & Yuasa, S. (1970) Age at first birth and breast cancer risk. Bull. WHO 43:209-221.[Medline]

183. Hilakivi-Clarke, L., Cho, E. & Clarke, R. (1998) Maternal genistein exposure mimics the effects of estrogen on mammary gland development in female mouse offspring. Oncol. Rep. 5:609-616.[Medline]

184. Hilakivi-Clarke, L., Cho, E., deAssiss, S., Olivo, S., Eailey, E., Bouker, K. B., Welch, J. N., Khan, G., Clarke, R. & Cabanes, A. (2001) Maternal and prepubertal diet, mammary development and breast cancer risk. J. Nutr. 131:154S-157S.[Free Full Text]

185. Hilakivi-Clarke, L., Cho, E., Onojafe, I., Raygada, M. & Clarke, R. (1999) Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. Oncol. Rep. 6:1089-1095.[Medline]

186. Morrison, A. S., Lowe, C. R., MacMahon, B., Ravnihar, B. & Yuasa, S. (1976) Some international differences in treatment and survival in breast cancer. Int. J. Cancer 18:269-273.[Medline]

187. Hutchins, A. M., Slavin, J. L. & Lampe, J. W. (1995) Urinary isoflavonoid phytoestrogen and lignan excretion after consumption of fermented and unfermented soy products. J. Am. Diet. Assoc. 95:545-551.[Medline]

188. Meng, L., Maskarinec, G. & Wilkens, L. (1997) Ethnic differences and factors related to breast cancer survival in Hawaii. Int. J. Epidemiol. 26:1151-1158.[Abstract]

189. Yonemoto, R. H. (1980) Breast cancer in Japan and United States: epidemiology, hormone receptors, pathology, and survival. Arch. Surg. 115:1056-1062.[Abstract]

190. Huang, X. E., Tajima, K., Hamajima, N., Kodera, Y., Yamamura, Y., Xiang, J., Tominaga, S. & Tokudome, S. (2000) Effects of dietary, drinking, and smoking habits on the prognosis of gastric cancer. Nutr. Cancer 38:30-36. [Medline]

191. Pisani, P., Parkin, D. M., Bray, F. & Ferlay, J. (1999) Estimates of the worldwide mortality from 25 cancers in 1990. Int. J. Cancer 83:18-29.[Medline]

192. Trock, B., Butler, W., Clarke, R. & Hilakivi-Clarke, L. (2000) Meta-analysis of soy intake and breast cancer risk. J. Nutr. 130:690S-691S(abs).

193. Yuan, J. M., Wang, Q. S., Ross, R. K., Henderson, B. E. & Yu, M. C. (1995) Diet and breast cancer in Shanghai and Tianjin, China. Br. J. Cancer 71:1353-1358.[Medline]

194. Hirohata, T., Shigematsu, T., Nomura, A. M., Nomura, Y., Horie, A. & Hirohata, I. (1985) Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. Natl. Cancer Inst. Monogr. 69:187-190.

195. Nomura, A., Henderson, B. E. & Lee, J. (1978) Breast cancer and diet among the Japanese in Hawaii. Am. J. Clin. Nutr. 31:2020-2025.[Abstract]

196. Key, T. J., Sharp, G. B., Appleby, P. N., Beral, V., Goodman, M. T., Soda, M. & Mabuchi, K. (1999) Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br. J. Cancer 81:1248-1256.[Medline]

197. Hirose, K., Tajima, K., Hamajima, N., Inoue, M., Takezaki, T., Kuroishi, T., Yoshida, M. & Tokudome, S. (1995) A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. Jpn. J. Cancer Res. 86:146-154.[Medline]

198. Chie, W. C., Lee, W. C., Li, C. Y., Huang, C. S., Chang, K. J. & Lin, R. S. (1997) Soybean products, vegetable and fruit and breast cancer risk in Taiwan. Breast Cancer Res. Treat. 46:80(abs.).

199. Wu, A. H., Ziegler, R. G., Horn-Ross, P. L., Nomura, A. M., West, D. W., Kolonel, L. N., Rosenthal, J. F., Hoover, R. N. & Pike, M. C. (1996) Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol. Biomark. Prev. 5:901-906.[Abstract]

200. Kudo, Y., Falciglia, G. A. & Couch, S. C. (2000) Evolution of meal patterns and food choices of Japanese-American females born in the United States. Eur. J. Clin. Nutr. 54:665-670.[Medline]

201. Horn-Ross, P. L., Barnes, S., Lee, M., Coward, L., Mandel, J. E., Koo, J., John, E. M. & Smith, M. (2000) Assessing phytoestrogen exposure in epidemiologic studies: development of a database (United States). Cancer Causes Control 11:289-298.[Medline]

202. Huang, M. H., Block, G., Gold, E., Seeman, T., Sowers, M. F. & Greendale, G. A. (2000) Nutrient intakes in an ethnically diverse sample of US women. Am. J. Epidemiol. 151:S62(abs.).

203. Wu, A. H., Ziegler, R. G., Nomura, A. M., West, D. W., Kolonel, L. N., Horn-Ross, P. L., Hoover, R. N. & Pike, M. C. (1998) Soy intake and risk of breast cancer in Asians and Asian Americans. Am. J. Clin. Nutr. 68:1437S-1443S.[Abstract]

204. Ingram, D., Sanders, K., Kolybaba, M. & Lopez, D. (1997) Case-control study of phyto-oestrogens and breast cancer. Lancet 350:990-994.[Medline]

205. Murkies, A., Dalais, F. S., Briganti, E. M., Burger, H. G., Healy, D. L., Wahlqvist, M. L. & Davis, S. R. (2000) Phytoestrogens and breast cancer in postmenopausal women: a case control study. Menopause 7:289-296.[Medline]

206. Greenstein, J., Kushi, L., Zheng, W., Fee, R., Campbell, D., Sellers, T. & Folsom, A. (1996) Risk of breast cancer associated with intake of specific foods and food groups. Am. J. Epidemiol. 11:S36(abs.).

207. Shu, X. O., Jin, F., Dai, Q., Wen, W., Potter, J. D., Kushi, L. H., Ruan, Z., Gao, Y. T. & Zheng, W. (2001) Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol. Biomark. Prev. 10:483-488.[Abstract/Free Full Text]

208. Shimizu, H., Ross, R. K., Bernstein, L., Yatani, R., Henderson, B. E. & Mack, T. M. (1991) Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles county. Br. J. Cancer 63:963-966. [Medline]

209. Nagata, C., Takatsuka, N., Inaba, S., Kawakami, N. & Shimizu, H. (1998) Effect of soymilk consumption on serum estrogen concentrations in premenopausal Japanese women. J. Natl. Cancer Inst. 90:1830-1835. [Abstract/Free Full Text]

210. Lu, L. J., Anderson, K. E., Grady, J. J. & Nagamani, M. (1996) Effects of soya consumption for one month on steroid hormones in premenopausal women: implications for breast cancer risk reduction. Cancer Epidemiol. Biomark. Prev. 5:63-70.[Abstract]

211. Brzezinski, A., Adlercreutz, H., Shaoul, R., Rösler, R., Shmueli, A., Tanos, V. & Schenker, J. G. (1997) Short-term effect of phytoestrogen-rich diet on postmenopausal women. Menopause 4:89-94.

212. Petrakis, N. L., Barnes, S., King, E. B., Lowenstein, J., Wiencke, J., Lee, M. M., Miike, R., Kirk, M. & Coward, L. (1996) Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epidemiol. Biomark. Prev. 5:785-794.[Abstract]

213. Cassidy, A., Bingham, S. & Setchell, K. (1995) Biological effects of isoflavones in young women: importance of the chemical composition of soyabean products. Br. J. Nutr. 74:587-601.[Medline]

214. Baird, D. D., Umbach, D. M., Lansdell, L., Hughes, C. L., Setchell, K. D., Weinberg, C. R., Haney, A. F., Wilcox, A. J. & McLachlan, J. A. (1995) Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. J. Clin. Endocrinol. Metab. 80:1685-1690.[Abstract]

215. Martini, M. C., Dancisak, B. B., Haggans, C. J., Thomas, W. & Slavin, J. L. (1999) Effects of soy intake on sex hormone metabolism in premenopausal women. Nutr. Cancer 34:133-139.[Medline]

216. Wu, A. H., Stanczyk, F. Z., Hendrich, S., Murphy, P. A., Zhang, C., Wan, P. & Pike, M. C. (2000) Effects of soy foods on ovarian function in premenopausal women. Br. J. Cancer 82:1879-1886.[Medline]

217. Duncan, A. M., Underhill, K. E., Xu, X., Lavalleur, J., Phipps, W. R. & Kurzer, M. S. (1999) Modest hormonal effects of soy isoflavones in postmenopausal women. J. Clin. Endocrinol. Metab. 84:3479-3484. [Abstract/Free Full Text]

218. Xu, X., Duncan, A. M., Wangen, K. E. & Kurzer, M. S. (2000) Soy consumption alters endogenous estrogen metabolism in postmenopausal women. Cancer Epidemiol. Biomark. Prev. 9:781-786.[Abstract/Free Full Text]

219. Lu, L. J., Cree, M., Josyula, S., Nagamani, M., Grady, J. J. & Anderson, K. E. (2000) Increased urinary excretion of 2-hydroxyestrone but not 16α-hydroxyestrone in premenopausal women during a soya diet containing isoflavones. Cancer Res 60:1299-1305.[Abstract/Free Full Text]

220. Riza, E., dos Santos Silva, I., De Stavola, B., Bradlow, H. L., Sepkovic, D. W., Linos, D. & Linos, A. (2001) Urinary estrogen metabolites and mammographic parenchymal patterns in postmenopausal women. Cancer Epidemiol. Biomark. Prev. 10:627-634.[Abstract/Free Full Text]

221. Loukovaara, M., Carson, M., Palotie, A. & Adlercreutz, H. (1995) Regulation of sex hormone-binding globulin production by isoflavonoids and patterns of isoflavonoid conjugation in HEP G2 cell cultures. Steroids 60:656-661. [Medline]

222. Adlercreutz, H., Mousavi, Y., Clark, J., Hockerstedt, K., Hamalainen, E., Wahala, K., Makela, T. & Hase, T. (1992) Dietary phytoestrogens and cancer: in vitro and in vivo studies. J. Steroid Biochem. Mol. Biol. 41:331-337. [Medline]

223. Pino, A. M., Valladares, L. E., Palma, M. A., Mancilla, A. M., Yanez, M. & Albala, C. (2000) Dietary isoflavones affect sex hormone-binding globulin levels in postmenopausal women. J. Clin. Endocrinol. Metab. 85:2797-2800.[Abstract/Free Full Text]

224. Knight, D. C., Howes, J. B., Eden, J. A. & Howes, L. G. (2001) Effects on menopausal symptoms and acceptability of isoflavone-containing soy powder dietary supplementation. Climacteric 4:13-18.[Medline]

225. Xu, X., Duncan, A. M., Merz, B. E. & Kurzer, M. S. (1998) Effects of soy isoflavones on estrogen and phytoestrogen metabolism in premenopausal women. Cancer Epidemiol. Biomark. Prev. 7:1101-1108.[Abstract]

226. Habito, R. C., Montalto, J., Leslie, E. & Ball, M. J. (2000) Effects of replacing meat with soyabean in the diet on sex hormone concentrations in healthy adult males. Br. J. Nutr. 84:557-563.[Medline]

227. Mackey, R., Ekangaki, A. & Eden, J. A. (2000) The effects of soy protein in women and men with elevated plasma lipids. Biofactors 12:251-257.[Medline]

228. Cassidy, A., Bingham, S. & Setchell, K. D. (1994) Biological effects of a diet of soy protein rich in isoflavones

on the menstrual cycle of premenopausal women [see comments]. Am. J. Clin. Nutr. 60:333-340.[Abstract]

229. Lu, L. J., Anderson, K. E., Grady, J. J., Kohen, F. & Nagamani, M. (2000) Decreased ovarian hormones during a soya diet: implications for breast cancer prevention. Cancer Res 60:4112-4121.[Abstract/Free Full Text]

230. Petrakis, N. L. (1993) Nipple aspirate fluid in epidemiologic studies of breast disease. Epidemiol. Rev. 15:188-195.[Medline]

231. Wrensch, M. R., Petrakis, N. L., King, E. B., Miike, R., Mason, L., Chew, K. L., Lee, M. M., Ernster, V. L., Hilton, J. F., Schweitzer, R., Goodson, W. H., III & Hunt, T. K. (1992) Breast cancer incidence in women with abnormal cytology in nipple aspirates of breast fluid. Am. J. Epidemiol. 135:130-141.[Abstract]

232. Wrensch, M., Petrakis, N. L., King, E. B., Lee, M. M. & Miike, R. (1993) Breast cancer risk associated with abnormal cytology in nipple aspirates of breast fluid and prior history of breast biopsy. Am. J. Epidemiol. 137:829-833.[Abstract]

233. Petrakis, N. L., Lee, M. M., Wrensch, M. R., Ernster, V. L., Miike, R., Koo, L. C. & Ho, J. C. (1998) Birthplace and yield of nipple aspirate fluid in Chinese women. Cancer Epidemiol. Biomark. Prev. 7:835-839.[Abstract]

234. Hargreaves, D. F., Potten, C. S., Harding, C., Shaw, L. E., Morton, M. S., Roberts, S. A., Howell, A. & Bundred, N. J. (1999) Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. J. Clin. Endocrinol. Metab. 84:4017-4024.[Abstract/Free Full Text]

235. Preston-Martin, S., Pike, M. C., Ross, R. K., Jones, P. A. & Henderson, B. E. (1990) Increased cell division as a cause of human cancer. Cancer Res 50:7415-7421.[Abstract]

236. Preston-Martin, S., Pike, M. C., Ross, R. K. & Henderson, B. E. (1993) Epidemiologic evidence for the increased cell proliferation model of carcinogenesis. Environ. Health Perspect. 101(suppl. 5):137-138.

237. Mommers, E. C., van Diest, P. J., Leonhart, A. M., Meijer, C. J. & Baak, J. P. (1999) Balance of cell proliferation and apoptosis in breast carcinogenesis. Breast Cancer Res. Treat. 58:163-169.[Medline]

238. Messina, M. (1999) Soy, soy phytoestrogens (isoflavones), and breast cancer [letter]. Am. J. Clin. Nutr. 70:574-575.[Free Full Text]

239. McMichael-Phillips, D. F., Harding, C., Morton, M., Roberts, S. A., Howell, A., Potten, C. S. & Bundred, N. J. (1998) Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. Am. J. Clin. Nutr. 68:1431S-1435S.[Abstract]

240. Vachon, C. M., Kuni, C. C., Anderson, K., Anderson, V. E. & Sellers, T. A. (2000) Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control 11:653-662.[Medline]

241. Boyd, N. F., Lockwood, G. A., Martin, L. J., Byng, J. W., Yaffe, M. J. & Tritchler, D. L. (2001) Mammographic density as a marker of susceptibility to breast cancer: a hypothesis. IARC Sci. Publ. 154:163-169.[Medline]

242. Boyd, N. F., Martin, L. J., Stone, J., Greenberg, C., Minkin, S. & Yaffe, M. J. (2001) Mammographic densities as a marker of human breast cancer risk and their use in chemoprevention. Curr. Oncol. Rep. 3:314-321.[Medline]

243. Laya, M. B., Gallagher, J. C., Schreiman, J. S., Larson, E. B., Watson, P. & Weinstein, L. (1995) Effect of postmenopausal hormonal replacement therapy on mammographic density and parenchymal pattern. Radiology 196:433-437.[Abstract]

244. Colditz, G. A. (1998) Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. J. Natl. Cancer Inst. 90:814-823.[Abstract/Free Full Text]

245. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 350:1047-1059.[Medline]

246. Thomas, H. V., Reeves, G. K. & Key, T. J. (1997) Endogenous estrogen and postmenopausal breast cancer: a quantitative review. Cancer Causes Control 8:922-928.[Medline]

247. Morabia, A. & Costanza, M. C. (1998) International variability in ages at menarche, first livebirth, and menopause. World Health Organization collaborative study of neoplasia and steroid contraceptives [published erratum appears in Am. J. Epidemiol. 150: 546]. Am. J. Epidemiol. 148:1195-1205.[Abstract]

248. Buist, D. S., LaCroix, A. Z., Barlow, W. E., White, E. & Weiss, N. S. (2001) Bone mineral density and breast cancer risk in postmenopausal women. J. Clin. Epidemiol. 54:417-422.[Medline]

249. Zhang, Y., Kiel, D. P., Kreger, B. E., Cupples, L. A., Ellison, R. C., Dorgan, J. F., Schatzkin, A., Levy, D. & Felson, D. T. (1997) Bone mass and the risk of breast cancer among postmenopausal women. N. Engl. J. Med. 336:611-617.[Abstract/Free Full Text]

250. Lucas, F. L., Cauley, J. A., Stone, R. A., Cummings, S. R., Vogt, M. T., Weissfeld, J. L. & Kuller, L. H. (1998) Bone mineral density and risk of breast cancer: differences by family history of breast cancer. Study of osteoporotic fractures research group. Am. J. Epidemiol. 148:22-29.[Abstract]

251. Nguyen, T. V., Center, J. R. & Eisman, J. A. (2000) Association between breast cancer and bone mineral density: the Dubbo osteoporosis epidemiology study. Maturitas 36:27-34.[Medline]

252. Zmuda, J. M., Cauley, J. A., Ljung, B. M., Bauer, D. C., Cummings, S. R. & Kuller, L. H. (2001) Bone mass and breast cancer risk in older women: differences by stage at diagnosis. J. Natl. Cancer Inst. 93:930-936. [Abstract/Free Full Text]

253. Newman, S. C., Lees, A. W. & Jenkins, H. J. (1997) The effect of body mass index and oestrogen receptor level on survival of breast cancer patients. Int. J. Epidemiol. 26:484-490.[Abstract]

254. Bastarrachea, J., Hortobagyi, G. N., Smith, T. L., Kau, S. W. & Buzdar, A. U. (1994) Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Ann. Intern. Med. 120:18-25. [Abstract/Free Full Text]

255. Proceedings of a conference held at Boar's Head Inn Charlottesville Virginia September 21–23 (1999) Treatment of oestrogen deficiency symptoms in women surviving breast cancer. Part 6: Executive summary and consensus statement. Oncology 13:859-875.

256. Loprinzi, C. L. & Barton, D. (2000) Estrogen deficiency: in search of symptom control and sexuality. J. Natl. Cancer Inst. 92:1028-1029.[Free Full Text]

257. Vassilopoulou-Sellin, R., Asmar, L., Hortobagyi, G. N., Klein, M. J., McNeese, M., Singletary, S. E. & Theriault, R. L. (1999) Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. J. Clin. Oncol. 17:1482-1487.[Abstract/Free Full Text]

258. Gapstur, S. M., Morrow, M. & Sellers, T. A. (1999) Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. J. Am. Med. Assoc. 281:2091-2097. [Abstract/Free Full Text]

259. Cobleigh, M. A., Norlock, F. E., Oleske, D. M. & Starr, A. (1999) Hormone replacement therapy and high S phase in breast cancer. J. Am. Med. Assoc. 281:1528-1530.[Abstract/Free Full Text]

260. Manjer, J., Malina, J., Berglund, G., Bondeson, L., Garne, J. P. & Janzon, L. (2001) Increased incidence of small and well-differentiated breast tumours in post-menopausal women following hormone-replacement therapy. Int. J. Cancer 92:919-922.[Medline]

261. Delgado, R. C. & Lubian Lopez, D. M. (2001) Prognosis of breast cancers detected in women receiving hormone replacement therapy. Maturitas 38:147-156.[Medline]

262. O'Meara, E. S., Rossing, M. A., Daling, J. R., Elmore, J. G., Barlow, W. E. & Weiss, N. S. (2001) Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J. Natl. Cancer Inst. 93:754-761.[Abstract/Free Full Text]

263. Schairer, C., Lubin, J., Troisi, R., Sturgeon, S., Brinton, L. & Hoover, R. (2000) Estrogen-progestin replacement and risk of breast cancer. J. Am. Med. Assoc. 284:691-694.[Free Full Text]

264. Schairer, C., Lubin, J., Troisi, R., Sturgeon, S., Brinton, L. & Hoover, R. (2000) Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. J. Am. Med. Assoc. 283:485-491. [Abstract/Free Full Text]

265. Pike, M. C. & Ross, R. K. (2000) Response: Re: effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J. Natl. Cancer Inst. 92:1951-1952.[Free Full Text]

266. Ross, R. K., Paganini-Hill, A., Wan, P. C. & Pike, M. C. (2000) Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J. Natl. Cancer Inst. 92:328-332.[Abstract/Free Full Text]

267. Santen, R. J., Pinkerton, J., McCartney, C. & Petroni, G. R. (2001) Risk of breast cancer with progestins in combination with estrogen as hormone replacement therapy. J. Clin. Endocrinol. Metab. 86:16-23.[Free Full Text]

268. Persson, I., Weiderpass, E., Bergkvist, L., Bergstrom, R. & Schairer, C. (1999) Risks of breast and endometrial

cancer after estrogen and estrogen-progestin replacement. Cancer Causes Control 10:253-260.[Medline]

269. Pike, M. C., Spicer, D. V., Dahmoush, L. & Press, M. F. (1993) Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol. Rev. 15:17-35.[Medline]

270. Soderqvist, G., Isaksson, E., von Schoultz, B., Carlstrom, K., Tani, E. & Skoog, L. (1997) Proliferation of breast epithelial cells in healthy women during the menstrual cycle. Am. J. Obstet. Gynecol. 176:123-128.[Medline]

271. Hofseth, L. J., Raafat, A. M., Osuch, J. R., Pathak, D. R., Slomski, C. A. & Haslam, S. Z. (1999) Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. J. Clin. Endocrinol. Metab. 84:4559-4565. [Abstract/Free Full Text]

272. Cline, J. M., Soderqvist, G., von Schoultz, E., Skoog, L. & von Schoultz, B. (1996) Effects of hormone replacement therapy on the mammary gland of surgically postmenopausal cynomolgus macaques. Am. J. Obstet. Gynecol. 174:93-100.[Medline]

273. Conner, P., Skoog, L. & Soderqvist, G. (2001) Breast epithelial proliferation in postmenopausal women evaluated through fine-needle-aspiration cytology. Climacteric 4:7-12.[Medline]

274. Lundstrom, E., Wilczek, B., von Palffy, Z., Soderqvist, G. & von Schoultz, B. (1999) Mammographic breast density during hormone replacement therapy: differences according to treatment. Am. J. Obstet. Gynecol. 181:348-352.[Medline]

275. Greendale, G. A., Reboussin, B. A., Sie, A., Singh, H. R., Olson, L. K., Gatewood, O., Bassett, L. W., Wasilauskas, C., Bush, T. & Barrett-Connor, E. (1999) Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal estrogen/progestin interventions (PEPI) investigators. Ann. Intern. Med. 130:262-269.

276. Lundstrom, E., Wilczek, B., von Palffy, Z., Soderqvist, G. & von Schoultz, B. (2001) Mammographic breast density during hormone replacement therapy: effects of continuous combination, unopposed transdermal and low-potency estrogen regimens. Climacteric 4:42-48.[Medline]

277. Jasieriska, G. & Thune, I. (2001) Lifestyle, hormones, and risk of breast cancer. Br. Med. J. 322:586-587. [Free Full Text]

278. Zava, D. T., Dollbaum, C. M. & Blen, M. (1998) Estrogen and progestin bioactivity of foods, herbs, and spices. Proc. Soc. Exp. Biol. Med. 217:369-378.[Abstract]

279. Schwartz, J. A., Liu, G. & Brooks, S. C. (1998) Genistein-mediated attenuation of tamoxifen-induced antagonism from estrogen receptor-regulated genes. Biochem. Biophys. Res. Commun. 253:38-43.[Medline]

280. Sugimoto, E. & Yamaguchi, M. (2000) Anabolic effect of genistein in osteoblastic MC3T3–E1 cells. Int. J. Mol. Med. 5:515-520.[Medline]

281. Sugimoto, E. & Yamaguchi, M. (2000) Stimulatory effect of daidzein in osteoblastic MC3T3–E1 cells.

Biochem. Pharmacol. 59:471-475.[Medline]

282. Choi, E. M., Suh, K. S., Kim, Y. S., Choue, R. W. & Koo, S. J. (2001) Soybean ethanol extract increases the function of osteoblastic MC3T3–E1 cells. Phytochemistry 56:733-739.[Medline]

283. Constantinou, A., Lantvit, D., Lim, E., Xu, H. & Pezzuto, J. M. (2001) Consumption of soy products may enhance tamoxifen's breast cancer preventive effects. Proc. Am. Assoc. Cancer Res. 42:826.

284. Schardt, D. (2000) Phytoestrogens for menopause. Nutrition Action HealthLetter 27:8-10.

285. North American Menopause Society (2000) The role of isoflavones in menopausal health: consensus opinion of the North American Menopause Society. Menopause 7:215-229.[Medline]

286. Potter, S. M. (1998) Soy protein and cardiovascular disease: the impact of bioactive components in soy. Nutr. Rev. 56:231-235.[Medline]

287. Crouse, J. R., III, Morgan, T., Terry, J. G., Ellis, J., Vitolins, M. & Burke, G. L. (1999) A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. Arch. Intern. Med. 159:2070-2076.[Abstract/Free Full Text]

288. Urban, D., Irwin, W., Kirk, M., Markiewicz, M. A., Myers, R., Smith, M., Weiss, H., Grizzle, W. E. & Barnes, S. (2001) The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. J. Urol. 165:294-300.[Medline]

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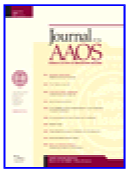

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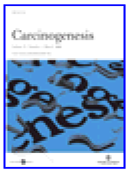

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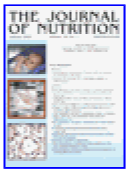

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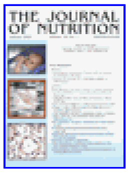

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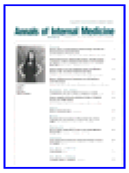

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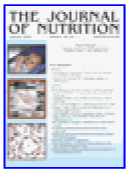

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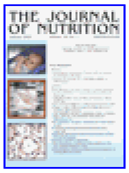

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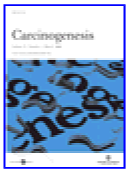

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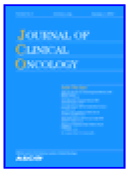

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