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Review

Phytoestrogens and breast cancer: a complex story

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Abstract. Genistein is an isoflavone with oestrogenic activity that is present in a variety of soy products as a constituent of complex mixtures of bioactive compounds, whose matrix profiles play an important role in determining the overall oestrogenic bioactivity of genistein. We review data on how the profile of soy bioactive compounds can modulate genistein-stimulated oestrogen-dependent tumour growth. Our research has focused on the effects of dietary genistein on the growth of oestrogen (E)-dependent mammary tumours both *in vitro* and *in vivo*. Genistein enhances the proliferation of E-dependent human breast cancer tumour growth. In a similar manner, dietary genistein stimulates tumour growth in the chemically-induced (NMU) mammary cancer rodent model. Genistin, the glycoside of genistein, simulates growth similar to that of genistein and withdrawal of either genistein or genistin results in tumour regression. The extent of soy processing modulates the effects of dietary genistein *in vivo* as soy protein isolate, a highly purified and widely used source of protein that is processed to contain low, medium, and high amounts of isoflavones, stimulate the growth of the E-dependent mammary tumours in a dose dependent manner. In contrast to the more purified diets, studies with soy flour of equivalent genistein levels did not stimulate the growth of E-dependent breast cancer tumours *in vivo*. However, the size of these tumours also did not regress as compared with control groups in which oestrogen and genistein have been withdrawn. The expression of the oestrogen-target genes of pS2, progesterone receptor, and cyclin D1 correlates with the growth of E-dependent tumours and has been consistently observed to be induced in response to treatment with dietary genistein. To evaluate whether dietary genistein interacts with current anti-oestrogen breast cancer therapies such as tamoxifen (TAM), we implanted E-dependent tumours into ovariectomized athymic mice and administered oestradiol, oestradiol plus TAM, or oestradiol, TAM, and dietary genistein. In these studies dietary genistein was able to negate the inhibitory effect of TAM on E-stimulated tumour growth. In summary, genistein can act as an oestrogen agonist resulting in proliferation of E-dependent human breast cancer tumours *in vivo* and its activity can be modulated by the presence of other bioactive components in complex soy foods. Additionally, dietary genistein can negate the inhibitory effects of TAM on E-stimulated growth of MCF-7 cell tumours implanted into ovariectomized athymic mice.

Key words: Breast cancer – Phytoestrogens – Genistein – Soy foods – Dietary supplements – Tamoxifen, *in vivo*

Properties of phytoestrogenes

Phytoestrogens, including the non-steroidal isoflavones, coumestans, lignans and the steroidal phytosterols, are plant chemicals with known oestrogenic effects in animals and are able to modulate and impair reproductive function in livestock (Price and Fenwick, 1985). In a broader sense, phytoestrogens are able to bind to oestrogen receptors (ER) *in vitro* and thereby induce or modulate the oestrogen signalling pathway, including kinase activation and transcriptional gene regulation. Through these mechanisms, the ER signalling pathway has also been demonstrated to stimulate the growth of ER-positive breast cancer cells (Setchell, 2001). Thus, the safety of phytoestrogens is a concern to human health. Phytoestrogens have been found in at least 300 plants, where the isoflavones and coumestans were identified as the most common oestrogenic compounds in these plants (Farnsworth et al., 1975a; Farnsworth et al., 1975b). Soybeans and soy foods by far are the most significant dietary sources of isoflavones (Coward et al., 1993; Murphy and Hendrich, 2002; Wang and Murphy, 1994), which are present in soybeans and their products predominantly in their acetyl and malonylglu-

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coside forms (daidzin, glycitin and genistin). The aglycones daidzein, glycitein and genistein (Fig. 1) are commonly found in fermented soy foods (Chun et al., 2007; Tang et al., 2007; Yin et al., 2005).

A diverse array of soybean foods and derivates are widely available in Western markets such as oil, meal, flour, and dairy and meat substitutes, including milk, yogurt, ice cream, cheese, tofu, and soy burgers. Most of the rise in popularity of soy products, and lately of dietary supplements containing soy isoflavones, has come from their portrayal as a panacea for a plethora of ailments from relieving postmenopausal symptoms (Anderson et al., 1999a; Vincent and Fitzpatrick, 2000), prevention of cardiovascular disease (Anderson et al., 1999b; Lichtenstein, 1998) and osteoporosis (Branca, 2003; Cotter and Cashman, 2003); where the evidence for such health claims has been partially supportive in some cases or not present at all in others (Fitzpatrick, 2003; Sirtori et al., 2005; Sacks et al., 2006). Early epidemiological evidence demonstrated a disparity of breast cancer incidence between Eastern and Western countries (Basa et al., 1977; Dunn, 1975; Gray et al., 1979; Miller, 1977), where on average 1 in every 8 women in the US will have breast cancer as compared to 1 in 30 in Japan (Bouker and Hilakivi-Clarke, 2000). Phytoestrogens, particularly those from soy products and other legumes, were initially identified as potential contributing factors (Messina et al., 1994). Lower breast cancer risk was also reported in Asian countries in spite of low soy foods consumption (Ganry, 2002). Hence, other lifestyle factors such as degree of physical activity and consumption of a low-fat and low calorie diet, particularly those high in vegetables, may also be important contributing factors in the population's disparities of breast cancer incidence.

Soy products contain several compounds with the putative ability to inhibit carcinogenesis, including protease inhibitors (Kennedy and Manzone, 1995), phytates (Shamsuddin, 1995; Shamsuddin and Yang, 1995) and isoflavones (Hedlund et al., 2006; Sasamura et al., 2004; Shao et al., 1998; Shen et al., 2007; Yanagihara et al., 1993). Among these, the potential chemopreventive and protective effects of the isoflavone genistein have been extensively studied. Genistein accumulates in soy and soy products at concentrations as high as 1.5 mg/g (Wang and Murphy, 1994), which depend on factors such as the soy variety, environmental factors during growth and harvest (Eldridge and Kwolek, 1983) and processing (Yin et al., 2005). Fritz and colleagues (Fritzet al., 1998) demonstrated that neonatal administration of genistein effectively protects against chemically induced mammary tumours in rats. It was further demonstrated that timing of induction is key to promote mammary gland differentiation resulting in a less active EGF signalling pathway into adulthood leading to suppression of mammary cancer development (Lamartiniére, 2002; Whitsett and Lamartiniére, 2006). These protective effects were not replicated when providing daidzein in the DMBA cancer chemopreventive murine model (Lamartiniére et al., 2002) nor daidzein or equol in the athymic ovariectomized postmenopausal mouse cancer promotion model (Ju et al., 2006). Thus, early lifetime exposure to genistein may have beneficial health effects including breast cancer chemoprevention.

Genistein reduces proliferation of cancer cells in culture at pharmacological concentrations (10–100 µmol/L) including human breast cancer MCF-7 and MDA-MB-468 (Peterson and Barnes, 1993) and stomach and colon cancer cells (Yanagihara et al., 1993). These genistein-inducing effects may be through topoisomerase II inhibition (Markovits et al., 1989; Salti et al., 2000; Yamashita et al., 1990) and impairment of protein tyrosine kinases (Linassier et al., 1990; Akiyama et al., 1987). At high concentrations, genistein has also been shown to arrest cell cycle progression at the G2/M transition in human gastric cancer (HGC-27) cells (Matsukawa et al., 1993) and Jurkat T leukaemia cells (Spinozzi et al., 1994). Furthermore, genistein also inhibits angiogenesis and metastasis in some *in vitro* and *in vivo* models (Fotsis et al., 1993; Santibanez et al., 1997; Shao et al., 1998). In other studies, genistein inhibited the cytochrome P450 enzyme CYP1A1, which could lead to a reduction in the formation of carcinogenic metabolites (Chan and Leung, 2003; Helsby et al., 1998), another potential chemopreventive mechanism. Genistein is rapidly absorbed after oral administration of high dosages in humans, reaching concentration in the range of 0.1–3 µmol/L in about 2 h. As the majority of circulating genistein in humans is conjugated (e. g., glucuronidated), it appears that achieving the concentrations of aglycone genistein required for its antiproliferative effects through a dietary manner would be difficult. Furthermore, it is unclear as to the specificity by which genistein may adversely impact normal tissue at these high concentrations.

Although the antiproliferative effects of genistein have been tested in different models, genistein is better known for its oestrogenic effects *in vitro* and *in vivo*. Genistein has a chemical structure similar to oestrogen and it binds to ER-α and ER-β *in vitro*, though at several-fold lower binding affinities (0.017 % ER-α and 7.4 % ER-β binding for genistein as compared to 100 % for both by 17β-estradiol) (Muthyala et

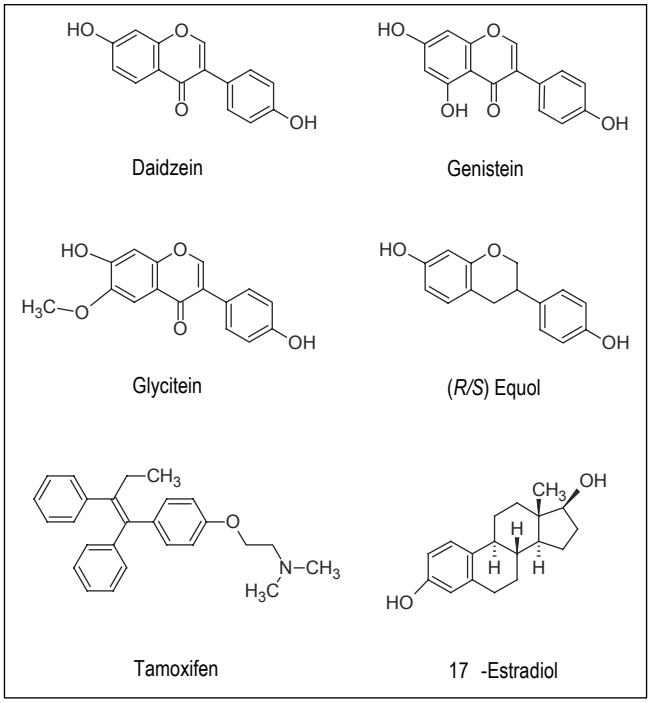

Fig. 1. Structures of isoflavones, oestrogen and anti-oestrogen.

al., 2004; Martin et al., 1978). In addition, genistein induces the transcriptional activation via ER-α and ER-β in transient transfection assays (EC_{50} of 80 nmol/L and 6.6 nmol/L, respectively) at natural dietary levels (Muthyala et al., 2004). Interestingly, *S*-equol, a metabolite of daidzein, demonstrates a similar preference for ER-β over ER-α (3.2 % and 0.1 %, respectively) and overall higher binding affinities than its parent compound daidzein (0.01 % for ER-α and 0.04 % for ER-β) (Muthyala et al., 2004). Genistein activates a number of oestrogen-responsive genes, including pS2 and c-fos in different cell lines in culture (Liu et al., 1999; Santell et al., 2000; Strauss et al., 1998). As elevated levels of circulating oestrogens is associated with increased postmenopausal breast cancer risk (Toniolo et al., 1995) and that ovariectomy or use of antioestrogens such as tamoxifen significantly reduces breast cancer risk (Mokbel, 2003), public health concerns of phytoestrogens and their potential role on breast cancer warranted further investigation. In an attempt to understand how genistein could be oestrogenic in some cases and antioestrogenic in others, our laboratory has conducted molecular, biomedical, and pre-clinical studies to determine whether single isoflavones and soy foods or soy extracts containing isoflavones are able to promote the growth of human breast cancer cells.

Studies were conducted using a low phytoestrogen semi-purified, casein-based background diet (AIN-93G). Ovariectomized rats consuming genistein at 750 ppm showed higher uterine wet and dry weights and mammary gland growth than controls (Santell et al., 1997). Moreover, at the same level, genistein did not antagonize the action of oestradiol in oestradiol-supplemented ovariectomized rats or in intact rats. Using a murine model of postmenopausal breast cancer, the athymic ovariectomized mouse with implanted cancer cells, we demonstrated that genistein given at dietary concentrations of 125–1,000 ppm, which reach physiological serum levels of genistein of 0.39–3.36 μmol/L, promoted the growth of oestrogen-dependent human breast cancer tumours in a dose-dependent manner (Hsieh et al., 1998; Ju et al., 2001). These dosages are physiologically relevant parallel to those observed in adults (Pumford et al., 2002) and infants fed soy based infant formula (Setchell et al., 1997). Changes were also accompanied by the increased expression of hallmark oestrogen gene targets such as c-fos and pS2 (Santell et al., 1997). In addition, genistin, the glycosylated form of genistein in plants, was also found to stimulate the growth of oestrogen-dependent breast cancer tumours *in vivo* and was shown to be metabolized to its free aglycone by salivary glycosidases (Allred et al., 2001b). Withdrawal of either genistein or genistin results in tumour regression. In contrast to our findings, Gallo and colleagues (Gallo et al., 2006) demonstrated that an extract containing genistein, daidzein and a mixture of group B saponins did not promote tumour growth in a similar athymic mouse model. Nevertheless, the authors mentioned that the given dose was at best less than 1/3 of the lowest dose (125 ppm) used in our study, which did not promote tumour growth. Moreover, Shao and colleagues (Shao et al., 1998) demonstrated that genistein could reduce the growth of implanted oestrogen positive (MCF-7) and negative (MDA-MB-231) cells *in vivo*. The effects were more evident at the highest dose of genistein (20 μmol/L) *in vitro* and ~0.5 mg/kg body weight given subcutaneously. Similar results have been reported at high concentrations of genistein *in vitro* and *in vivo*, where genistein at low concentration is oestrogenic and at high concentrations is antioestrogenic (Fritz et al., 1998; Gallo et al., 2001; Whitsett and Lamartiniére, 2006). It is possible that genistein could have different actions when the concentration of serum oestrogen is low such as during childhood and after menopause in women. Therefore, we used the 1-methyl-1-nitrosourea (MNU) chemically-induced mammary cancer model in rats to determine whether genistein promotes or inhibits the growth of fully developed tumours, such as in postmenopausal women with small oestrogen-responsive tumours and where oestrogen concentrations are low. Mammary tumours were characterized as malignant or benign after histopathological examination and either oestrogen-dependent or oestrogen-independent upon identification of both oestrogen and progesterone receptors. Ovariectomized rats consuming genistein at 750 ppm had higher oestrogen-dependent adenocarcinoma weights, uterine weights and a higher proportion of proliferative cells in tumours (Allred et al., 2004a). Overall, results suggest that both timing of exposure and endogenous oestrogen environment play a critical role and should be taken into consideration when extrapolating the potential chemopreventive or tumour stimulating effects of genistein or soy products on the development of mammary cancer in humans.

Westernized soy products are different from those consumed in Asia. Most traditional Asian soy products are based on whole soybeans with or without fermentation. Soy products or second generation soy foods in the US are mainly based on soy protein at different levels of purification or extraction such as texturized vegetable protein (~45 % protein), soy protein concentrate (~70 % protein) or soy protein isolates (~90 % protein); each with a different profile of nutrient and non-nutrient compounds, including isoflavones and saponins (Setchell and Cole, 2003; Fang et al., 2004). Currently, there has been a significant increase in the use of soy protein in US foods. A leading reason is the approved health claim for soy protein and heart disease by the FDA (Health and Human Services, 1999). A second reason is the recent popularity of low carbohydrate foods; where the use of protein from soy protein isolates (SPI) in foods is used as a bulk and functional substitute. Another reason for the popularity is that SPI contains oestrogenic isoflavones in significant amounts (~2 mg/g) (Setchell et al., 1987). Moreover, more potent and purified forms of isoflavones are also commercially available (Delmonte and Rader, 2006) and sold without prescription as dietary supplements. Women are seeking a safe method to relieve menopause symptoms, an alternative to hormone replacement therapy (HRT). Menopause, the age prompted biological cessation of the female reproductive cycle, results in the significant reduction of circulating oestrogens. The marked fall in oestrogen is associated with hot flashes, night sweats, headaches, decreased libido, and increased risk of osteoporosis. Hormone replacement therapy (HRT) is the prescription of oestrogen and /or progestins to relieve symptoms associated with menopause (Shargil, 1985) and reverse the loss of bone mass which leads to osteopenia and osteoporosis (Christiansen, 1991). As the risk of stroke and oestrogen-dependent cancers were also reported with HRT (Rossouw et al., 2002), its usage has been sharply curtailed

(Kim et al., 2005). Due to their occurrence within plants and their relative weak potency compared to oestrogen, consumers have turned to phytoestrogens as a "natural" alternative to HRT. There is the perception by many consumers that taking SPI or dietary supplements containing phytoestrogens is a safe and effective medical alternative to HRT (Messina, 2002; Taffe and Cauffield, 1998). This assumption may not be correct as their efficacy has been questioned (Tice et al., 2003) and significant safety concerns exist, especially for those women that have or are at high risk of developing breast cancer (Kurzer, 2003).

As soy protein and its constituent isoflavones are consumed through various grades of processing, studies were conducted to compare the oestrogenicity of different soy preparations. Using the same athymic ovariectomized mouse model as previously mentioned, we were able to demonstrate that soy protein isolates containing increasing concentrations of genistein (15, 150 and 300 ppm) stimulate the growth of oestrogen-dependent breast cancer cells in a dose-dependent manner (Allred et al., 2001a). Furthermore, we studied the role of the food matrix on the growth of oestrogen dependent human breast cancer cells *in vivo*. Genistin was given in its natural glycoside form as commonly found in soy flour, soy molasses, Novasoy®, a mixture of isoflavones and in pure form (~99 %). Each of the soy flour-processed products was added to the diet providing similar amounts of genistein aglycone equivalents (750 ppm). The level of stimulation of tumor growth within this animal diet study correlated with the level of diet processing and purity (genistin > mixed isoflavones > Novasoy® > mixed isoflavones and genistin; Fig. 2). Interestingly, the diet containing soy flour did not promote tumour growth or tumour regression, even when the amounts of genistein in the serum were similar in all groups. Expression of pS2, progesterone receptor and cyclin D1 was increased in tumours within animals consuming the Novasoy®, mixed isoflavones and genistin (Allred et al., 2004b). In a similar model, Saarinen and co-workers also observed stimulatory effects of SPI containing genistein, but not as pronounced (Saarinen et al., 2006). Interestingly, the addition of flaxseed, a rich source of lignans, to a diet already containing SPI or genistein caused tumour regression similar to that in response to the basal diet without phytoestrogens (Power et al., 2006a; Saarinen et al., 2006). It seems that flaxseed inhibited the tumour-stimulatory effects of genistein or SPI with genistein, but did not inhibit their beneficial effects on bone (Power et al., 2006b). It is possible that a combination of soy and lignan-rich foods is a more feasible way to enjoy soy products without the potential of inducing adverse effects in women with breast cancer (Power and Thompson, 2007).

The use of dietary supplements as a form of complementary and alternative medicine (CAM) to self-treat health problems is on the rise since the passage of the Dietary Supplement Health and Education Act in 1994 (DSHEA, 1994), which restricted their control by the FDA as foods, leading to significant economic growth and marketing promotion (Morris and Avorn, 2003). The fact that is of the greatest concern is that a significant proportion of the population at high risk of breast cancer as well as those with breast cancer or with past history of the disease is currently following some form of CAM therapy, including high soy and purified isoflavone dietary regimes, to ameliorate chemotherapy distress, postmenopausal symptoms, sexual discomfort or any other age-related symptoms, at times without physician consent (Boon et al., 2007; Eisenberg et al., 1998; VandeCreek et al., 1999). Therefore, we decided to determine the potential interaction of genistein with tamoxifen, the leading anti-oestrogen used in chemotherapy for patients with oestrogen-dependent breast cancer. Tamoxifen acts through blocking the binding of oestrogen to its cellular receptors and inhibiting the downstream signalling that leads to cancer cell proliferation and oestrogen-dependent breast cancer tumour growth (Lewis and Jordan, 2005). We investigated the effects of the interactions between genistein and tamoxifen (TAM) on the growth of oestrogen-dependent breast cancer (MCF-7) cells implanted in ovariectomized athymic mice. We hypothesized that genistein would negate the inhibitory effect of TAM on the growth of E-dependent breast tumours. Treatment with 2.5 mg and 5 mg of TAM suppressed oestradiol-stimulated MCF-7 tumour growth in ovariectomized athymic mice (Fig. 3). Dietary genistein abrogated the inhibitory effect of TAM on MCF-7 tumour growth, lowered oestradiol levels in plasma, and increased the expression of oestrogen-responsive genes pS2, PR, and cyclin D1. Jones and colleagues reported similar inhibi-

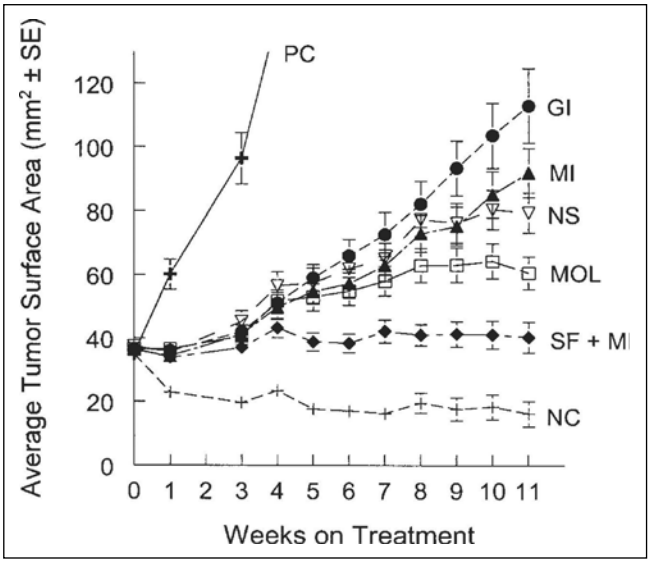

Fig. 2. Efficacy in stimulation of oestrogen-dependent MCF-7 tumour growth in athymic mice by isoflavones correlates inversely with the complexity of soy product matrix. Cells were injected subcutaneously into dorsal flanks of ovariectomized athymic mice, which, after tumour establishment, oestradiol pellets were removed and animals were randomly assigned to treatment groups. Positive control (PC) mice were re-implanted with a new oestradiol pellet. Both the negative control (NC) and PC mice were fed low phytoestrogen control diet (AIN-93G). Treatment groups also included AIN-93G diet with genistin (GI), mixed isoflavones (MI), Novasoy® (NS), molasses (MOL), and soy flour + mixed isoflavones (SF + MI). Diet mixes contained equivalent genistein aglycone doses. Tumours were monitored weekly and tumour size was calculated and is expressed as average cross sectional area (mm^2) of all tumours in each treatment group ±SEM. Figure reproduced with permission from Allred et al., 2004b.

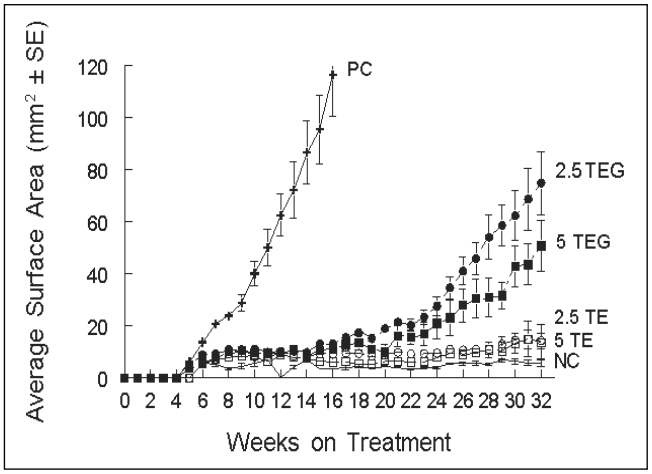

Fig. 3. In a preclinical model of postmenopausal breast cancer, dietary genistein reverses tamoxifen-induced suppression of the growth of oestrogen-dependent human breast cancer cells (MCF-7). Cells were injected subcutaneously into dorsal flanks of ovariectomized athymic mice, which, after tumour establishment, oestrogen pellets were removed and animals were assigned randomly to treatment groups. These groups included those fed the low phytoestrogen control diet (AIN-93G) – positive control (PC, oestrogen capsule only), negative control (NC, no treatment), 2.5 TE (2.5 mg tamoxifen pellet and oestrogen capsule), and 5 TE (5 mg tamoxifen capsule and oestrogen capsule) – and those fed the genistein-supplemented diet (AIN-93G plus 1,000 ppm genistein) – 2.5 TEG and 5 TEG (tamoxifen, oestrogen, and genistein). The level of oestrogen within these groups induced sub-maximal tumour growth and allows for tamoxifen-induced inhibition. Tumours were monitored weekly and tumour size was calculated as surface area = (tumour width/2) × (tumour length/2) × pi, and is expressed as average cross sectional area (mm^2) of all tumours in each treatment group ±SEM. Figure reproduced with permission from Ju et al., 2002.

tory effects after concomitant administration of genistein and TAM in T47D breast cancer cells in culture (Jones et al., 2002). These effects were not observed in similar *in vitro* studies with oestrogen negative MDA-MB-435 breast cancer cells (Shen et al., 1999). Because tamoxifen is the leading prescription drug for breast cancer prevention and treatment, caution is warranted for postmenopausal women consuming dietary genistein while on TAM therapy as this issue requires further investigation to determine the beneficial or deleterious effects in women with oestrogen responsive breast cancer.

Many breast cancer survivors experience sexual dysfunction (McKee and Schover, 2001), which is estimated to affect ~50 % of long-term survivors (Ganz, 1997). Thus, many consumers opt to buy dietary supplements, such as Avlimil, a non-prescription CAM treatment tailored to women to improve sexual health. This is of great concern as Avlimil is marketed to a large proportion of women with sexual discomfort caused by hormonal changes, menopause and aging. Avlimil, as many dietary supplements, is a mixture of water and solvent extracts from different herbs including *Pueraria montana* (kudzu root extract), *Trifolium pratense* (red clover extract), *Glycyrrhiza glabra* (licorice root) and *Actaea racemosa* (black cohosh root), among others, which contain a variety of bioactive phytochemicals with known oestrogenic, antioestrogenic and /or anti-proliferative activity (Boue et al., 2003; Burdette et al., 2002; Zava and Duwe, 1997; Zhang et al., 2005). It is possible that this botanical preparation, consumed in high or low amounts, could modulate breast cancer tumour growth in postmenopausal women. Thus, we evaluated the potential oestrogenic effects of Avlimil using similar *in vitro* and *in vivo* models as mentioned before (Ju et al., 2008). Similar to genistein, a dimethylsulfoxide total extract of Avlimil elicited a biphasic effect, stimulating the growth of MCF-7 cells at low concentrations (0.1–50 µg/mL of media) in a concentration-dependent manner and inhibiting their growth at concentrations higher than 10 µg/mL. Interestingly, similar effects were also observed in the athymic ovariectomized mouse model, where Avlimil given in the diet at 500 ppm stimulated MCF-7 tumour growth and at 1,000 ppm had no apparent effects. Because of the disparity in the dose effects, and that Avlimil at 500 ppm did not promote changes in wet uterine weights, it is possible that Avlimil elicits both oestrogenic and antioestrogenic effects that may be dosage and tissue specific.

Conclusion

In summary, the relationship between phytoestrogens and breast cancer is very complex. Reports in support of the positive and negative effects of phytoestrogens on breast cancer can appear to be conflictive. As we and others have shown, the behaviour of phytoestrogens in the life-cycle may depend on factors such as: a) timing of exposure; b) digestion, absorption and individual metabolism; c) hormonal status; d) previous and current health condition; e) consumption of prescribed and non-prescribed (CAM) therapies; f) amount and profile of phytoestrogens in foods or supplements; g) other foods and previous processing; and h) individual genetics. Because of studies documenting the high dietary soy consumption and low breast cancer incidence within Asian populations, phytoestrogens have been implicated in breast cancer chemoprevention. Indeed, early life exposure to phytoestrogens has been demonstrated to impact mammary gland development through accelerated terminal end bud differentiation. As the popularity of soy-based food products and supplements has steadily grown over the past two decades, human exposure to phytoestrogens has increased, particularly within women seeking relief of menopausal symptoms. As reviewed, our laboratory and others have confirmed that soy phytoestrogens, particularly genistein, are able to stimulate oestrogen signalling at dietary levels within pre-clinical models of postmenopausal, oestrogen-dependent breast cancer. As breast cancer risk increases with age and lifetime exposure to oestrogen, genistein may therefore adversely impact human health through stimulation of breast cancer tumour growth in postmenopausal women. Current scientific evidence is insufficient to identify dietary supplements and dietary sources of phytoestrogens as either harmful or beneficial. In the future, these products may be determined to be safe for some subpopulations and harmful for others. Our research suggests that consumption of a variety of traditional soy foods such as soy flour and tofu should be emphasized. Furthermore, consumption of

high-doses of purified forms of phytoestrogens is not recommended for women at high risk of breast cancer as well as for breast cancer patients under tamoxifen therapy and for breast cancer survivors.

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