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

Debra A. Tonetti, Yiyun Zhang, Huiping Zhao, Sok-Bee Lim, and Andreas I. Constantinou

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

Introduction

The Hormone Therapy Trials of the Women’s Health Initiative (WHI) study were halted early due to the multiple risks associated with estrogen/progesterone combination hormone replacement therapy (HRT) (1). Included among the risks are increased incidence of cardiovascular disease and the development of invasive breast cancer in women on the HRT arm. Since this finding, many women have turned to soy and phytoestrogen supplements as a perceived safer alternative to HRT to alleviate the symptoms of menopause. However, there is not yet consensus regarding their efficacy for the relief of menopausal symptoms (2–5). There is a lower incidence of breast cancer in Asian women compared to the Western world, often attributed to a soy-rich diet (6), yet addition of soy to the Western diet has not yet been shown to reduce breast cancer risk (7,8).

Tamoxifen (TAM) is currently approved for the treatment of both premenopausal and postmenopausal patients with estrogen receptor alpha (ERα)-positive, early and advanced breast cancer and is the only Federal Drug Administration approved drug for the chemoprevention of breast cancer in high risk premenopausal and postmenopausal women (9). The predominant mechanism of action of TAM is to compete with 17β-estradiol (E2) for binding to the ER, causing a conformational change and preventing transcriptional activation. Because hot flashes are a bothersome side effect of TAM therapy, many women may perceive phytoestrogens to be a natural and safe alternative to HRT. Alternatively, breast cancer patients may increase dietary soy intake either through food or supplements because soy has been touted to promote breast health. It was recently reported that 19–21% of breast cancer patients use some herbal supplements, of which isoflavones are included (10, 11). However, the effects of combining TAM and isoflavones in breast cancer patients are not clear.

Genistein and daidzein are the most abundant phytoestrogens found in soy and are classified as isoflavone compounds. These compounds bind to ERα and ERβ; however, both isoflavones have a much higher affinity for ERβ (12). Both chemoprevention and therapeutic animal models have been used to examine whether isoflavones augment or negate the actions of TAM (13–15). We recently reported that daidzein cooperates with TAM to prevent 7,12-dimethylbenzanthracene-induced rat mammary tumors, perhaps acting through the metabolic conversion to equol (14). Using an MCF-7 xenograft model in athymic mice, Ju et al. (15) showed that dietary genistein blocked the inhibitory effect of TAM. These two models simulate breast cancer chemopreventive and therapeutic settings, respectively. To address the effect of isoflavones on TAM-resistant breast cancer, we tested the effects of combining TAM and isoflavones in our TAM-resistant T47D:A18/protein kinase C alpha (PKCα) breast cancer model. We previously reported that PKCα overexpression in T47D:A18 cells cause autonomous and TAM resistant growth in vitro and TAM-resistant, autonomous, and E2-inhibitory growth in vivo (16,17). Since

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E2 inhibits tumor growth in this model, we wished to determine whether the isoflavones genistein and daidzein would act in a similar fashion as E2 by inhibiting tumor growth or whether combination with TAM would result in augmentation or blockade of the TAM-stimulatory effects.

**Material and Methods**

**Cell Lines and Culture Conditions**

T47D:A18 is a hormone-dependent human breast cancer cell clone that was previously described (18). T47D:A18 neo and T47D:A18/PKCα20 clones have been described (16). T47D:A18, T47D:A18/neo and T47D:A18/PKCα20 clones were maintained in RPMI 1640 phenol-red medium supplemented with 10% fetal bovine serum (FBS). T47D:A18/neo and T47D:A18/PKCα20 clones were supplemented with G418 (500 µg/ml). Prior to cell proliferation and luciferase assays, all cell lines were maintained in phenol red-free RPMI 1640 supplemented with 10% 3X dextran-coated charcoal-treated FBS (estrogen-depleted media) for 3 days. Prior to cell injection into mice, all cell lines were grown in complete medium containing 10% FBS.

**Proliferation Assays**

The cell clones T47D:A18 and T47D:A18/PKCα20 were seeded at $4 \times 10^4$ cells/ml estrogen-depleted media into T25 tissue culture flasks. The following day (Day 1), medium containing either ethanol (control), 17β-estradiol (Sigma-Aldrich, St. Louis, MO) (E2, $10^{-9}$ M), genistein ($10^{-7}$ M), (R,S)-equol ($10^{-7}$ M) (LC Laboratories, Woburn, MA), or 4-hydroxytamoxifen (4-OHT; Sigma-Aldrich) was added. All compounds were dissolved in 100% ethanol and added to the medium at a 1:1000 dilution. Cells were counted on Days 2–10.

**Transient Transfection and Luciferase Assays**

Estrogen response element (ERE)-tk-Luc plasmid contains 3 tandem copies of the vitellogenin ERE sequence inserted into pT109luc(19). ERE-tk-luc plasmid was transiently cotransfected with the β-galactosidase expression plasmid pCMV/β (for transfection efficiency normalization) into the T47D:A18 cells by electroporation.

**Establishment of T47D:A18 and T47D:A18/PKCα Tumors in Athymic Mice**

T47D:A18 cells were combined with Matrigel in a 1:1 (vol/vol) ratio and injected subcutaneously ($1 \times 10^7$ cells/site) into the axillary mammary fat pads of ovariectomized 5–6-wk-old BALB/c athymic mice (Harlan Sprague Dawley, Madison, WI). T47D:A18/PKCα cells were injected in a similar fashion except without the addition of Matrigel. Mice were divided into treatment groups consisting of 10 mice/group: control (no treatment), E2 (E2 capsule), TAM (Sigma-Aldrich), genistein, genistein + TAM, daidzein, and daidzein + TAM. E2 was administered via silastic capsules (1.0 cm) implanted subcutaneously between the scapulas, and the capsules were replaced every 8 wk. TAM was administered po at a dose of 1.5 mg/animal daily for 5 days as previously described (17). Custom diets (Harlan-Teklad, Madison, WI) were formulated to contain genistein (0.206 g/kg) or daidzein (0.144 g/kg). A casein control diet was fed to the control, E2, and TAM treatment groups. Tumor cross-sectional area was determined weekly by Vernier calipers and calculated using the formula length/2 x width/2 x π. Mean tumor area was plotted against time in weeks to monitor tumor growth. The mice were sacrificed by CO2 inhalation and cervical dislocation.

The composition of all of the diets used is summarized in Table 1. TD 02481 (Harlan-Teklad) was used as a base for the daidzein (TD 02483, 144 mg daidzein/kg) and genistein (TD 02482, 206 mg genistein/kg) diets. Daidzein

**Table 1. Diet Composition**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>TD 02481 (Casein Control)</th>
<th>TD 02482 (Genistein)</th>
<th>TD 02483 (Daidzein)</th>
<th>TD-7912 (Control Diet Containing Soy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein(%)</td>
<td>20.8%</td>
<td>20.8%</td>
<td>20.8%</td>
<td>Crude Protein (19%)</td>
</tr>
<tr>
<td>Corn starch</td>
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<td>37.6%</td>
<td>37.6%</td>
<td>Crude Fat (5%)</td>
</tr>
<tr>
<td>Malto dextrin</td>
<td>13.2%</td>
<td>13.2%</td>
<td>13.2%</td>
<td>Crude Fiber (5%)</td>
</tr>
<tr>
<td>Sucrose</td>
<td>10.0%</td>
<td>10.0%</td>
<td>10.0%</td>
<td>Ground corn</td>
</tr>
<tr>
<td>Corn Oil</td>
<td>0.7%</td>
<td>0.7%</td>
<td>0.7%</td>
<td>Dehulled soy bean meal</td>
</tr>
<tr>
<td>Cellulose</td>
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<td>0.5%</td>
<td>0.5%</td>
<td>Ground oats</td>
</tr>
<tr>
<td>L-Cystine</td>
<td>0.35%</td>
<td>0.35%</td>
<td>0.35%</td>
<td>Wheat middlings</td>
</tr>
<tr>
<td>Mineral mix</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>Dehydrated alfalfa meal</td>
</tr>
<tr>
<td>Vitamin mix</td>
<td>0.15%</td>
<td>0.15%</td>
<td>0.15%</td>
<td>Soybean oil</td>
</tr>
</tbody>
</table>

Genistein None 206 mg/kg None
Daidzein None None 144 mg/kg

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and genistein were purchased from Indofine Chemical Co. (Hillsborough, NJ), and the selected concentrations were based on the amounts of each isoflavone present in the well-tolerated and effective 16% (wt/wt) soy protein isolate diet used in previous studies (20,21). The composition of the soy-containing Teklad Diet 7912 is shown in Table 1.

Statistical Analysis

When comparing to one group, data were analyzed using unpaired t-test. When comparing groups, data were analyzed using 1-way analysis of variance followed by the Dunnett Multiple Comparison test. All statistics were performed using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA). Significant differences were indicated when *P* < 0.05.

Results

Effects of Daidzein and Equol on T47D:A18/neo and T47D:A18/PKCα Cells in Culture

We previously reported the stable transfection of PKCα into the T47D:A18 cell line results in TAM-resistant and autonomous growth in vitro and in vivo (16). An additional growth characteristic is apparent in vivo; E2 inhibits tumor formation and causes complete tumor regression (17). We examined whether the phytoestrogens genistein, daidzein, or equol exert differential growth effects in the parental T47D:A18/neo versus the T47D:A18/PKCα cell clones. The hormone-dependent T47D:A18/neo cell line is growth stimulated by E2 and to a lesser extent by equol but not by genistein, daidzein, or 4-OHT (Fig. 1A). As previously reported, T47D:A18/PKCα cells grow both in the absence and presence of E2 and are TAM resistant as indicated by growth in the presence of 4-OHT (16). Addition of genistein, daidzein, or equol does not inhibit T47D:A18/PKCα growth. Therefore, equol has an estrogenic effect on T47D:A18/neo cells, but it is difficult to determine whether equol, genistein, or daidzein are estrogenic in the T47D:A18/PKCα cell line because these cells exhibit autonomous growth. To determine whether these ligands exert an estrogenic effect on ERE transcriptional activation, an ERE-luciferase construct was transiently transfected, and luciferase activity was measured in each cell line (Fig. 2). In T47D:A18/neo cells, E2 induced ERE-luciferase transactivation by 22-fold over control, whereas equol caused a 12-fold induction. The pure antiestrogen, ICI 182, 780, reversed the estrogenic effects of equol, suggesting that equol is acting through the ER. Daidzein and genistein did not result in increased ERE-luciferase activity. ERE-luciferase transactivation is consistent with the growth effects produced by these ligands in the T47D:A18/neo cell line (Fig. 1A). As previously reported, basal ERE-luciferase activity in T47D:A18/PKCα cells is higher than the parental T47D:A18/neo, and the fold induction produced by E2 relative to control is less (threelfold)(16). Equol exhibits ERE-luciferase activity that is similar to E2 (2.7-fold) and is reversed with ICI 182,780, again suggesting that equol exerts estrogenic effects through the ER (Fig. 2B). Daidzein is less estrogenic and shows about one half the level of induction (1.5-fold) compared to E2, and genistein is similar to the untreated control. Therefore, both equol and daidzein exhibit estrogenic effects in the T47D:A18/PKCα TAM-resistant cell line and is reversed by the pure antiestrogen ICI. This is compared to weaker estrogenic effects of equol in the parental T47D:A18/neo cells.

The Effects of Genistein and Daidzein on the Growth of T47D:A18 Cells In Vivo

To determine the in vivo effects of genistein and daidzein, T47D:A18 cells were injected into ovariectomized, athymic

Figure 1. Proliferation rate of clones T47D:A18/neo (A) and T47D:A18/ PKCα (B), untreated (control) or treated with 17β-estradiol (E2) (10−9 M), 4-hydroxytamoxifen (4-OHT) (10−7 M), daidzein (10−7 M), genistein (10−7 M), or equol (10−7 M). Proliferation rate was assessed by cell counting as described in Materials and Methods. The results are expressed as total cell number ± SE for each time point. These results are representative of 3 independent experiments.
mice. As previously reported (17), T47D:A18 cells form tumors in response to E2 but not in the absence of E2 or in the presence of TAM (Fig. 3A). Daidzein treatment alone resulted in transient growth the 1st wk followed by declining tumor size throughout the experimental period (Fig. 3B). Treatment with a combination of daidzein and TAM showed no difference in tumor size compared to the untreated control (Fig. 3A). Genistein treatment alone or in combination with TAM did not result in significant tumor growth compared with TAM treatment alone (Fig. 3C). Treatment of T47D:A18 tumors with 1.5 mg TAM is known to produce TAM-stimulated tumors after 10 wk (22). These results suggest that genistein and daidzein treatment either alone or in combination with TAM do not stimulate T47D:A18 tumor growth.

The Effects of Genistein and Daidzein on the Growth of TAM-Resistant T47D:A18/PKCα Cells In Vivo

As previously reported, T47D:A18/PKCα tumors exhibit autonomous and TAM-resistant growth and are inhibited by E2 (Fig. 4A). Furthermore, E2 causes complete tumor regression when administered to growing T47D:A18/PKCα tumors (17). Therefore, because daidzein and equol exert estrogenic effects in the T47D:A18/PKCα cells in vitro (Fig. 2), we hypothesized that perhaps these isoflavones may inhibit tumor growth in a similar fashion as E2. Both daidzein and genistein when given in combination with TAM stimulate T47D:A18/PKCα tumors to grow faster than mice treated with TAM alone or either isoflavone by itself (Fig. 4B). Interestingly, daidzein treatment initially stimulated T47D:A18/PKCα tumors (Weeks 1–7), followed by a period of growth inhibition (Weeks 8–12), and eventual regrowth (Weeks 12–14). Genistein also stimulated T47D:A18/PKCα tumor growth through Week 10 followed by a period of tumor stabilization (Weeks 11–14). These results suggest that both daidzein and genistein exhibit partial attenuation of T47D:A18/PKCα tumor growth. The growth inhibitory effects of daidzein appear to be greater than genistein, perhaps in part due to the metabolic conversion to equol. Therefore, daidzein and genistein exhibit weaker growth inhibitory effects than E2 in this TAM-resistant tumor model. However, in combination with TAM, both genistein and daidzein stimulate T47D:18/PKCα tumor growth to a greater extent than TAM or either isoflavone alone.

The Addition of Soy as a Protein Source in the Diet Effects the Ability of T47D:A18/PKCα Tumors to Grow Autonomously

We noticed that the control diet (TD 02481) formulated to be devoid of soy products and used as a base control diet seemed to prevent the autonomous growth of T47D:A18/PKCα tumors previously observed using the mouse chow supplied from the University of Illinois at Chicago (UIC) Animal Facility (TD 7912). In fact, both the untreated control and E2-treated groups produced distinct tumor growth curves with the custom diet (soy free) from what we routinely observed using the UIC-supplied diet. Tumors from mice fed the soy-free control diet initially grew but at Week 6 began to regress (Fig. 4B) in contrast to the robust tumor growth observed in mice fed the UIC diet containing soy products (Fig. 4A). Mice fed the soy-free control diet exhibited E2-induced tumor growth inhibition; however, by Week 8, these tumors began to grow. This is in contrast to the complete suppression of tumor growth in the E2-treated group fed the UIC soy-containing diet (Figs. 4A, 4B). We speculate that perhaps the inhibitory effects of E2 can be overridden by a component in the soy-based diet. No apparent differences in growth characteristics were observed between the soy-free and soy-containing diets fed to mice bearing the parental T47D:18 tumors. To directly compare the 2 control diets on the ability of T47D:A18/PKCα
Figure 3. Initiation and growth of T47D:A18 tumors in athymic mice. A: 40 mice received injections of the T47D:A18 cell line and were treated (10 mice/group) with a 1-cm 17β-estradiol (E2) capsule, tamoxifen (TAM) (1.5 mg TAM/day po), TAM + daidzein (Dz) (Diet TD02483), or left untreated (Control). The E2, TAM, and untreated groups were fed the soy-free control diet (TD02481). B: 30 mice received injections of the T47D:A18 cell line and treated with (10 mice/group) TAM (1.5 mg TAM/day po, fed the control diet TD02481), genistein (Gen) (Diet TD02482), or TAM + Gen (Diet TD02482). C: 20 mice received injections of the T47D:A18 cell line and treated (10 mice/group) with either a 1-cm E2 capsule (Diet TD02481) or Dz (Diet TD02483).

Figure 4. Initiation and growth of T47D:A18/PKCα tumors in athymic mice. A: 30 mice received injections of the T47D:A18/PKCα cell line and randomized to 3 treatment groups (10 mice/group): 17β-estradiol (E2) (1-cm E2 capsule), tamoxifen (TAM) (1.5 mg TAM/day po), or Control (untreated). All mice were fed the UIC supplied soy-containing Teklad 7912 diet. B: 70 mice received injections of the T47D:A18/PKCα cell line and randomized to 7 treatment groups (10 mice/group): E2 (1-cm E2 capsule, fed soy-free TD02481 diet), TAM (1.5 mg TAM/day po, fed soy-free TD02481 diet), daidzein (Dz) (TD02483 diet), Dz + TAM (TD02483 diet), genistein (Gen) (TD02482 diet), Gen + TAM (TD02482 diet) or Control (untreated, TD02481 diet). *, indicates significant difference ($P < 0.05$) in tumor size when comparing Dz + TAM vs. TAM groups and Dz + TAM vs. Dz; †, indicates significant difference ($P < 0.05$) in tumor size when comparing Gen + TAM vs. TAM and Gen + TAM vs. Gen groups.
tumors to grow autonomously, T47D:A18/PKCα tumors were initiated in 20 athymic ovariectomized mice and randomized to 2 groups fed either the soy-free control diet (TD 02481) or the soy-based control diet (TD 7912). Mice fed the soy-based diet consistently exhibit T47D:A18/PKCα autonomous tumor growth, whereas mice fed the soy-free control diet show initial autonomous growth followed by tumor regression after 4 wk on the diet (Fig. 5) These results suggest that a component in the soy-based diet may be stimulating T47D:A18/PKCα tumor growth.

Discussion

The addition of soy or purified isoflavones to the diet is popular among women interested in alleviating menopausal symptoms as well as preventing breast cancer. While the efficacy of this approach is currently not clear, a more worrisome application is the combination of soy or isoflavone supplements with TAM in women who are either at high risk of developing breast cancer or in those that are being treated for breast cancer. We examined the effects of isoflavones on the growth characteristics of a TAM-resistant breast cancer tumor model developed in our laboratory, T47D:A18/PKCα (16,17,23). This model is interesting in that E2 inhibits tumor growth and is capable of causing tumor regression, a characteristic that may be relevant in patients (24–27). Our primary objective was to determine whether the isoflavones genistein and daidzein or the daidzein metabolite equol would produce estrogenic effects in MCF-7 cells in vitro (28). High concentrations of daidzein caused a slight stimulatory effect on MCF-7 tumors; however, equol did not stimulate MCF-7 tumor growth (28). In contrast to our results with T47D:A18 tumors, genistein was reported to stimulate the growth of MCF-7 tumors both alone and in combination with post-menopausal levels of E2 (29–31). We did not determine the combination of E2 and genistein in the T47D:A18 tumor model; however, both daidzein and genistein in combination with TAM produced T47D:A18/PKCα tumors of greater size than TAM alone. Interestingly, daidzein alone initially stimulated T47D:A18/PKCα tumor growth followed by transient growth inhibition and eventual stimulation. Genistein also caused initial growth stimulation followed by a period of tumor stabilization. These in vivo results suggest that dietary supplementation in conjunction with TAM in the therapeutic setting is not beneficial and may in fact be harmful.

We have previously reported that the combination of daidzein with TAM produces increased protection against rat mammary carcinogenesis, perhaps due to the antioxidant effects of equol, the main product of intestinal bacterial metabolism of daidzein (14). In that study, the isoflavones were initiated prior to the induction of tumors and continued to be provided throughout the study, representing a classic model of cancer chemoprevention. In the present study, the diets were initiated after the injection of PKCα-overexpressing, TAM-resistant breast cancer cells. Therefore, in the present study, the tumor cells (T47D:A18/PKCα) were already present prior to the introduction of the diets. In the current animal model, effective agents simply attenuate or inhibit the growth of existing tumors, and consequently, these agents have a therapeutic potential. We report here that daidzein and genistein do not cause regression of TAM-resistant tumors in mice and at best cause transient tumor stabilization. In fact, mice fed diets containing genistein or daidzein in combination with TAM developed larger tumors than those given TAM alone. The combined data from the 2 studies suggest that although daidzein provides additional protection than TAM alone in the prevention of mammary tumors (14), it is ineffective and perhaps harmful in the treatment of existing TAM-resistant tumors.

Of particular interest is our finding that T47D:A18/PKCα tumors exhibit hormone-independent and E2-inhibited growth in mice fed a soy-containing diet; however, these growth characteristics were different in mice fed a soy-free diet (Figs. 4B and 5). We can only speculate that a component in the soy-containing diet (TD 7912) stimulates the growth of T47D:A18/PKCα tumors, whereas in combination with E2 results in growth suppression. This phenomenon is not observed in the parental T47D:A18 tumors, but is unique to the PKCα-overexpressing tumors. Because daidzein, and to a lesser extent genistein, causes partial tumor stabilization (Fig. 4B), it is possible that these isoflavones are responsible for the complete growth suppression observed in combination with E2 in the soy-containing diet (Fig. 4A). Alternatively, metabolic conversion of daidzein to equol may...
contribute to the “estrogenic” effects in vivo (growth suppression) because equal is nearly as potent as E2 on in vitro cell proliferation and ERE-luciferase activity (Figs. 1 and 2) and has a 100-fold higher affinity for ERα than daidzein (32). Although intestinal conversion of daidzein to equol occurs in rodents, the extent of conversion can vary among mouse strains just as it does among humans (33,34). Finally, in addition to soy, this diet also contains dehydrated alfalfa meal (Table 1); therefore, it is possible that the phytoestrogenic coumestans may contribute to this growth profile.

Other studies have examined the effect of combining soy isoflavones with TAM in vitro (35,36) and in vivo (13,15), but this is the first report to examine the growth effects of isoflavones on a TAM-resistant tumor model. It should also be noted that the TAM resistance in our model is due to PKCα overexpression, and we have previously reported that PKCα is overexpressed at a much higher frequency in tumors from patients that exhibit disease recurrence compared with patients remaining disease free (37). However the observed effect of isoflavones might be specific to this model and may not be generalized to all TAM-resistant tumors. More experiments with different animal models must be performed to determine if the soy isoflavones are harmful to all TAM resistant tumors and even more importantly, if the soy components are harmful once mammary tumors have passed a critical stage of development. We chose to administer the isoflavones in the aglycone form (genistein and daidzein) as opposed to the glycone forms (genistin and daidzin), despite the fact that the glycones are more abundant in soybeans and most soy foods (38). Numerous animal studies have been conducted using the aglycone forms (28,30,39,40) because the glycones are quickly hydrolyzed by intestinal bacterial enzymes to the aglycone forms. However, because there is evidence of metabolic variation between species (41) and among individuals (42), the plasma concentrations achieved in this study may be more closely related to isoflavone supplementation, and there is likely to be individual metabolic variability.

In summary, we report for the first time the growth effects of combining the isoflavones genistein and daidzein with TAM in the TAM-resistant tumor model T47D: A18/PKCα. Two features of this model indicate its clinical relevance: 1) PKCα overexpression correlates with TAM-resistance in patients (37) and 2) E2-induced regression is a potential feature of many breast cancers (24–27). Although our findings are specific to this model, these results lend support to the notion that concurrent consumption of dietary isoflavones with TAM administration within a treatment setting may be unsafe.

Acknowledgments and Notes

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References


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