Effects of Tomato- and Soy-rich diets on the IGF-1 Hormonal Network: A Crossover Study of Postmenopausal Women at High Risk for Breast Cancer

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Abstract

Objective—To determine if dietary modifications with tomato products and/or a soy supplement affected circulating levels of IGF-1 and other markers of cell-signaling in postmenopausal women at risk for breast cancer.

Methods—Eligible and consented postmenopausal women at high risk for developing breast cancer were enrolled in a 26-week, two-arm (tomato and soy, 10 weeks each) longitudinal dietary intervention study in which each woman served as her own control. Changes in biochemical endpoints including Insuline-like Growth Factor (IGF)-1, IGF binding protein (BP)-3, estradiol, sex hormone binding globulin (SHBG), c-peptide, and insulin were measured for each intervention arm. Carotenoid and isoflavone levels were measured to assess adherence.

Results—Significant increases in carotenoid and isoflavone levels during the tomato and soy study arms, respectively, suggested that women were adherent to both arms of the intervention. The tomato-rich diet had little effect on cell-signaling biomarkers previously associated with breast cancer risk. However, results of the soy intervention showed that concentrations of IGF-1 and IGFBP-3 increased by 21.6 and 154.7 μmol/L, respectively (p=0.001 for both) and SHBG decreased by 5.4 μmol/L (p<0.001) after consumption of the soy protein supplement.

Conclusions—Increased soy protein intake may lead to small, but significant, increases in IGF-1 and IGFBP-3. Soy consumption also led to a significant decrease in SHBG, which has been hypothesized to promote, rather than prevent, cancer growth. Previous epidemiological studies, however, have confirmed soy's protective effect on breast cancer. Additional investigation regarding the effect of soy on breast cancer risk and its mechanism of action appears warranted.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in the United States and worldwide (1, 2). Currently, women at high risk for developing breast cancer lack significant and practical primary preventive measures with which to protect themselves. Although tamoxifen and raloxifene have been consistently shown to reduce the risk of developing breast cancer (3), prophylaxis with these agents is accompanied by harsh side-effects, which may be responsible for the "exceptionally low" utilization of these agents for chemoprevention in otherwise healthy women (4). Dietary factors have been thought to account for roughly 30% of cancers in Western countries (5, 6), making diet second only to tobacco as a preventable cause of cancer. However, current research about breast cancer prevention and diet to date has been largely ecologic and unable to tease out specific dietary compounds that promote or prevent cancer. Recommendations for prevention are largely based on epidemiological or laboratory studies, and randomized intervention trials that investigate breast cancer prevention are rare. Presently, only increased alcohol consumption and postmenopausal obesity have shown consistent associations with breast cancer risk (7, 8). Research on other dietary factors including meat, dairy products, fruits and vegetables, fiber, fat, and phytoestrogens has been inconsistent (9-11). This translational gap in research has left large areas of uncertainty and controversy in both the scientific and lay communities regarding breast cancer risk and diet.

A common mechanism of action at the foundation of many dietary hypotheses is the effect of dietary modifications on insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3 endocrine and tissue networks. IGF-1 is a mitogenic and antiapoptotic peptide hormone that plays an important role in cell regulation and tumorigenenisis. IGF-1 binds mainly to IGFBP-3 which both sequesters and regulates the effects of IGF-1. Increased levels of both IGF-1 and IGFBP-3 have been associated with breast cancer risk in animal and human studies (12-14). Recently, tomato and soy have separately been examined as potential chemopreventive agents for breast cancer that function through the IGF-1/IGFBP-3 signaling pathway.

Possible benefit from tomatoes is thought to be derived from lycopene, the carotenoid that provides the familiar red color to tomatoes. Lycopene has been shown *in vitro* to be a potent antioxidant (15), to reduce the risk of tumor progression (16, 17), and to have an antiproliferative effect on mammary tumors (18, 19). Human studies demonstrate that lycopene interacts with IGF-1 and IGFBP-3 (20), and can eliminate free oxygen radicals—thereby preventing DNA mutation, cell cycle alteration, and apoptotic disruption (21). However, human studies investigating the association between breast cancer risk and dietary intake of tomatoes, tomato products, and serum levels of lycopene, and between lycopene intake, IFG-1, IGFBP-3, and other biomarkers of cell growth and proliferation have been mixed (22-25).

Soy has also been studied extensively for its potential chemopreventive effects in breast cancer. Ecologic studies demonstrate that breast cancer risk for Western women is about six times higher than that of Asian women. Much of the variation in breast cancer incidence between Western and Asian women is explained by differences in established reproductive risk factors such as age at menarche, parity, age at births, and history of breastfeeding.

However, it is hypothesized that diet may account for a notable portion of this difference (8, 26), and one of the many differences in the diets of Asian populations is that soy foods are consumed daily. Soy contains many substances hypothesized to inhibit breast cancer development, including phytoestrogens (isoflavones and lignans), protease inhibitors, saponins, and phytic acid (26, 27). Researchers have hypothesized that estrogen-like isoflavones in soy, similar to hormone-replacement therapy (28) and tamoxifen (29), lower IGF-1 levels. However, the results of animal and human studies investigating soy, IGF-1, IGFBP-3, and breast cancer risk have been mixed (26, 30-35).

Although some evidence exists for a protective effect of increased lycopene and soy consumption, independently, on breast cancer risk, further research is needed regarding the effects of lycopene and soy on the IGF-1 axis and other markers of cell signaling in relation to breast cancer progression. The primary objective of this study was to determine if dietary modifications with tomatoes and a soy supplement affected circulating IGF-1 levels in postmenopausal women at risk for developing breast cancer. Secondary aims were to determine the effects of these foods on other potential biomarkers of breast cancer risk including, IGFBP-3, estrodiol levels, sex hormone-binding globulin (SHBG), c-peptide, and insulin. We also assessed adherence to tomato- and soy-rich dietary modifications.

METHODS

Study Population

Postmenopausal women (i.e., no menstrual period for 12 months if over age 55 or no menstrual period for 12 months and a follicle-stimulating hormone (FSH) level > 30 if under age 55) at high risk for developing breast cancer were eligible to participate in the study. High risk was defined as having a body mass index (BMI) between 25 and 42kg/m^2 (inclusive) and/or having a primary relative (i.e., mother, daughter, or sister) who had been diagnosed with breast cancer. To be eligible, women could not currently be taking hormone replacement therapy or a selective estrogen receptor modulator (SERM, e.g., tamoxifen or raloxifen). The study was approved by the Ohio State University Institutional Review Board.

Screening and Recruitment

Screening and recruitment occurred at medical and surgical oncology clinics, mammography centers, and the breast clinic at The Ohio State University Comprehensive Cancer Center. Physicians and their staff were asked to identify potential participants, and names of interested women were forwarded to the research staff for chart review. Prior to contacting women identified through chart review, permission was obtained from their physicians. Women were contacted via telephone by a trained research staff member who provided a general description (purpose and requirements) of the study and determined if the woman met study inclusion criteria. All potential subjects who were eligible and expressed an interest in participating were then scheduled to meet with a member of the research staff. At the initial visit, the research staff explained study requirements, answered potential participants' questions, and obtained written informed consent and HIPAA authorization. Recruitment began February 2003 and was completed in September 2004.

Intervention

Consented and eligible women were enrolled in a 26-week, two-arm longitudinal dietary intervention study in which each woman served as her own control. The study consisted of three, two-week washout periods and two, 10-week dietary periods (Figure 1). During each two-week washout period, women were instructed to abstain from both tomato and soy products. For the 10-week tomato arm, women were instructed to consume approximately

two or more tomato products daily to equal at least 25 milligrams (mg) of lycopene and not to consume any soy products. Women were asked to document the daily intake of tomato products on a worksheet that was provided to them. To aid in the consumption of tomato products, women were provided with tomato juice, tomato paste, and spaghetti sauce.

During the 10-week soy arm, each woman was given a powdered soy protein product (Dupont Technologies International, St. Louis, MO) that could be mixed with any liquid and provided 50 grams (g) of soy protein each day. Women were instructed to keep track of their daily consumption of soy by completing a provided *soy calendar*, and were told to limit the consumption of tomato products to 5mg of lycopene per day during the soy arm. Women were also given instructions and recipes to encourage consumption of the soy product. If a woman was taking a multivitamin, she was asked to replace it with a standard vitamin supplement provided by research staff because many brands of multivitamins contain certain elements that could have affected the results of the study. Women not already taking a vitamin supplement were not given a standard multivitamin.

Measurement

Dietary data were obtained via food frequency questionnaires at baseline, and three-day food records at baseline, during the tomato arm, and during the soy arm. Participant's age, race, marital status, educational level, annual household income, and alcohol and tobacco consumption were determined by self-report at baseline. Height and weight were measured by the research staff at baseline. In addition, blood specimens and weight were obtained at the end of each washout period and at the end of each 10-week intervention period. Blood specimens were used to measure changes in biochemical endpoints including IGF-1, IGFBP-3, estradiol, SHBG, c-peptide, insulin, lycopene isomers, and carotenoids. Urine samples were also obtained to measure the effect of the dietary interventions on isoflavone levels, specifically the predominant soy isoflavones genistein and diadzein and their metabolic forms (dihydrogenistein and dihydrodiadzein, respectively). Adherence was measured using 1) completion of a daily tomato worksheet, 2) soy protein package counts, and 3) biochemical measures of adherence using blood carotenoid levels (lycopene and -carotene) as markers of consumption of tomato products and urine isoflavone levels as markers of dietary soy consumption.

Statistical Analyses

Descriptive statistics were used to provide overall study population characteristics, categorize changes in biomarkers over the course of the study, and to analyze dietary compliance data. IGF-1 levels and secondary biomarker levels were measured before and after each 10-week treatment arm (tomato and soy, respectively). Treatment effects were estimated as the difference in pre- and post-treatment biomarker concentration levels after each washout period. To be analyzed as part of a treatment arm a woman had to complete the entire (10-week) arm of the study and have her follow-up assessments within 20 weeks of the beginning of the treatment arm.

Concentrations of biomarker endpoints were reported as means and standard deviations. The paired differences of several measures in both the tomato and soy arm were highly nonparametric, thus, intervention effects were estimated with exact Wilcoxon signed rank tests (nonparametric mean pairwise tests) that compared the biochemical concentration levels from the pre- and post-treatment periods, measured for both the tomato and soy arms. All analyses were conducted using SAS 9.2 (Cary, NC).

RESULTS

Overall, of 6,935 women initially screened for the study, 6,721 were ineligible to participate. Not being postmenopausal accounted for the large majority of ineligibles. Among eligible patients, 144 refused to participate. Seventy-four women were enrolled, however, four were deemed ineligible after enrollment and were not included in the analysis. Mean age of the 70 eligible women enrolled in the study was 57.2 years, and most women (58.6%) were between 50 and 60 years old. Additionally, most of the women were white (81.4%), married (72.9%), had some post-secondary education (85.5%), and had a combined household income of at least $50,000 annually (69.1%). The average baseline BMI of participating women was 30.0, which remained constant over the duration of the study (data not shown). All but nine of the 70 women had a BMI above normal, with 44.3% and 42.9% being overweight or obese, respectively. Most women (85.5%) were not current smokers and few women drank two or more alcoholic drinks per day (4.4%) (Table 1). Most women (45.7%) met the "high risk" eligibility criteria because they had both a family history of breast cancer and a BMI between 25-42 kg/m^2. Women who met only the BMI or family history eligibility criteria comprised 42.9% and 11.4%, respectively, of the overall study population.

Tomato Arm

One woman was not included in the tomato arm analyses because her follow-up assessment occurred 34 weeks after the baseline tomato assessment. Another five women did not complete the tomato arm follow-up assessment and four women discontinued the study prior to start of the tomato arm of the intervention, resulting in a total of 60 women for the tomato arm analyses. Means and standard deviations of the outcome measures for the tomato intervention at weeks 2 (post-washout) and 12 (post-tomato intervention) and for the paired differences (week 12 - week 2) are presented in Table 2. Mean pairwise differences showed no statistically significant changes in levels of IGF-1, IGFBP-3, estradiol, SHBG, c-peptide, or insulin at the end of the tomato intervention. Blood lycopene and -carotene levels were used as biological markers of lycopene consumption. Analyses revealed that women were adherent to the tomato arm of the study, as evidenced by the concentrations of carotenoid isomer markers over time (Figure 2). Additionally, during the tomato arm, women were instructed to consume enough tomato products to equal at least 25mg of lycopene per day, and average self-reported lycopene consumption during the tomato arm of the study was 29.7mg/day.

Soy Arm

Four women were not included in the soy intervention analyses because their follow-up assessments occurred 20 or more weeks after the baseline soy assessment. Another two subjects did not have follow-up assessments, and nine women discontinued the study prior to the soy arm of the intervention, resulting in a total of 55 subjects for the soy analyses. Means and standard deviations of the outcomes measures for the soy intervention at weeks 14 (post-washout) and 24 (post-soy intervention) and for the paired differences (week 24 - week 14) are presented in Table 3. Mean pairwise differences showed that, after the soy intervention, there were statistically significant increases in levels of IGF-1 (difference=21.6 μmol/L ; p=.001) and IGFBP-3 (difference=154.7 μmol/L ; p=.001) and a statistically significant decrease in SHBG (difference=-5.4 μmol/L ; p< .001). Although women only consumed an average of 1.5 packets/day of soy protein (less than the goal of 2.0 packets/day), significant increases were seen in concentrations of several biomarkers of soy isoflavones including daidzein, dihydrodaidzein, genistein, and dihydrogenistein during the soy arm of the study (all p< .001) (Figure 3).

DISCUSSION

To reduce the human and economic burden of breast cancer, effective methods of primary prevention must be identified. Currently, little is known about how a woman can practically lower her risk for the disease. In assessing the potential chemopreventive effects of separate tomato- and soy-rich diets among postmenopausal women at high risk for breast cancer, we chose to avoid a "reductionist" approach, which focuses only on a pure substance (such as lycopene or soy isoflavones diadzein and genistein), as soy and tomato products may have a number of phytochemicals with the potential to reduce cancer risk. Thus, we tested individual biochemical effects of the introduction of 10-week, tomato- and soy-rich diets under the assumption that the benefits of a food product may be much greater than the benefits achieved with a single biochemical component, and that whole food products offer a safe and potentially more effective intervention.

The six biochemical endpoints we chose to evaluate have all been previously hypothesized to be potential biomarkers for breast cancer risk. Experimental evidence suggests that insulin and insulin-like growth factors may play a role in breast pathology through their mitogenic and anti-apoptotic effects on normal, benign, and malignant breast epithelial cells (36). IGF binding proteins, on the other hand, are postulated to reduce growth stimulus by binding circulating IGFs and through a direct anti-proliferative effect on cells. In addition, studies have reported an increased risk of breast cancer with increasing concentrations of c-peptide in both pre- and postmenopausal women (36). Circulating sex steroid hormones such as testosterone and estradiol are associated with an increased risk of breast cancer in postmenopausal women as well, and predominantly bind to sex hormone binding globulin (SHBG) which limits the amount of 'free' circulating androgens and estrogens (37). Thus, assessing the effect of tomato- and soy-rich dietary interventions on potential breast cancer biomarkers may provide insight about reducing breast cancer risk in a safe and practical manner.

The average daily intake of lycopene in the United States has been reported to be 2-5mg/day (38), and women in our study consumed nearly 30mg/day, on average, during the tomato arm of the intervention. Results of this study, however, suggest that a tomato-rich diet had little effect on cell signaling biomarkers previously associated with breast cancer risk. There was a marginally significant increase in SHBG (p=0.08) after the tomato intervention, which could lead to a decrease in the biological availability of sex hormones, however, the effect size was small. Previous studies investigating the effects of tomatoes and its primary active ingredient, lycopene, on breast cancer risk have had mixed results, but largely have shown no effect (22-25).

Results of the soy intervention showed that blood-level concentrations of IGF-1 and IGFBP-3 significantly increased after consumption of the soy protein supplement (p=0.001 for both). If soy does protect against the development of breast cancer as shown in previous epidemiological studies (34, 35, 39), and the mechanism of protection is via the IGF-1/ IGFBP-3 pathway, the opposite result would have been expected. This study, however, is not the first to report an increase in IGF-1 and IGFBP-3 following soy supplementation. A study of healthy women reported increases in IGF-1 and IGFBP-3 after a one-week phytoestrogen supplementation (40) as did a longitudinal study examining the effect of dietary protein and soy isoflavones among prostate cancer patients (41). Furthermore a study of healthy men consuming a soy protein drink (42), and a study of postmenopausal women also receiving soy protein reported increases in IGF-1 levels (43). A small increase in IGF-1 levels was reported in a 2-year intervention of premenopausal women as well (44). Thus, there now seems to be relatively consistent evidence that soy (either in protein supplement or whole food form) does not lower serum levels of IGF-1 or IGFBP-3. Rather, as

hypothesized by Maskarinec et al. (44) and the authors of this study, an increased protein intake inherent in consuming additional soy products and in soy protein supplementation may lead to small, but significant, increases in IGF-1 and IGFBP-3.

Results of the soy intervention also showed a significant decrease in SHBG, which could lead to an increase in the biological availability of sex hormones. Other authors have raised such concerns about isoflavones in soy, specifically, that their estrogenic effects may promote, rather than prevent, cancer and estrogen-dependent mammary tumor growth (45, 46). However, previous studies have shown that soy isoflavones increase the synthesis of SHBG (opposite to our results) (45, 47), and a recent, large, and population-based study of soy confirmed its protective effect on breast cancer (32). Additional investigation to elucidate this effect appears warranted.

Overall, although there is strong *in vitro* evidence (17, 18, 48-52) and moderate *in vivo* evidence (19, 53) that lycopene protects against the development of breast cancer by affecting levels of biomarkers known to influence cell cycling and tumorigenesis, human studies have largely found no association (10, 54-56). Our results support previous null human findings regarding lycopene and breast cancer risk. The reasons for the lack of association between lycopene and a reduction in levels of biomarkers of oxidative stress and cell signaling associated with cancer progression in human studies could be many and include: 1) high levels of carotenoids (including lycopene) in the serum may actually be markers for other compound(s) responsible for protection against breast cancer, 2) carotenoids could be affected by other factors (e.g., smoking), and 3) different methods and exposure levels have been used for *in vitro, in vivo*, and human studies.

Regarding soy, several human studies have shown no effect of soy on IGF-1 and IGFBP-3 levels (57, 58). Others, including ours, have shown small, statistically significant increases in IGF-1, IGFBP-3, or both (42, 44). Thus, the majority of published literature does not support the notion that soy's protective effect on breast cancer functions through the IGF-1/IGFBP-3 axis. It is more likely, that soy's breast cancer chemoprevention effects (if they truly exist) stem from phytoestrogens (namely isoflavones) that act as SERMs (59). Like other SERMs, however, phytoestrogens have both estrogenic and antiestrogenic properties, and more studies are needed to assess their safety. Although many studies have shown a protective effect of soy consumption on breast cancer risk (33) and better post-diagnostic breast cancer survival among women who consume soy (32, 60), questions still remain about phytoestrogen's ability to stimulate breast tissue and promote estrogen-dependent tumor growth.

This study is not without limitations. Sample size was small, and not all enrolled participants completed each arm (tomato and soy) of the study. Adherence to both the tomato and soy diets for individuals who completed the study, however, was high as confirmed by both dietary calendars and biomarker confirmation, and, compared to other tomato and soy dietary intervention studies, our sample size was actually rather large (55, 56, 61-65).

Another limitation of this study is that our results are generalizable only to postmenopausal women at high risk for breast cancer. Previous research describing the relationship between IGF-1 and IGFBP-3 on breast cancer has suggested effect modification by age (i.e., menopausal status). Research about the age-dependent effects of IGF-1 and IGFBP-3 on breast cancer risk, however, is largely contradictory. Early research indicated that increasing circulating concentrations of IGF-1 and IGFBP-3 were related to increased risk of breast cancer in premenopausal women only (12-14, 55, 56). More recent research, however, has suggested that there is no effect of IGF-1 and IGFBP-3 on breast cancer risk in premenopausal women (66-68), and, instead, that higher levels of IGF-1 and IGFBP-3 are

associated with increased risk of breast cancer in women older than age 50 (66, 67). Thus, future studies examining the relationship between IGF-1 and IGFBP-3, diet, and breast cancer risk should be especially mindful of age-specific effects and examine the outcomes of dietary modification in both pre- and postmenopausal women separately.

Other limitations of this study include the fact that only dietary information regarding tomato and soy intake were recorded. Thus, we know little about whether the additional tomato products and the soy supplement were consumed in addition to each participant's normal diet, or if the participants' diets were altered to compensate for the addition of tomato and soy supplementation (i.e., tomato and soy products were substituted for other foods or meals). Thus, future studies should focus on parsing out whether the biological effects of dietary modification with tomato and soy products are the result of supplementation or substitution.

In spite of limitations, this study is one of few prospective studies to analyze the effects of tomato and soy dietary modifications on several biomarkers associated with breast cancer risk in a U.S. population. Additionally, the crossover design of this study with appropriate washout periods provides highly valid results that cannot be achieved with case-control studies performed previously. Finally, adherence to each dietary arm was high and loss-to-follow-up was relatively low.

The true effect of soy phytoestrogens on breast cancer risk is still unknown. There is a great deal of *in vitro* evidence that supports a protective role of soy isoflavones on the development of breast cancer (59). A suggested mechanism is that phytoestrogens are weaker estrogens than ovarian estrogens, and these weaker estrogens competitively inhibit the proliferative action of natural estrogens (69). A number of these studies, however, demonstrated that soy at low concentrations may act as an estrogen agonist and stimulate proliferation while at higher concentrations it acts antagonistically to estrogen, inhibiting cell growth (i.e., biphasic effects) (10, 54-56).

Further, it is possible that only long-term exposure to soy phytoestrogens is protective, as there is evidence that soy may only be beneficial if consumed *in utero* or before puberty (70, 71). Postmenopausal women, however, do not produce ovarian estrogen, and a sudden addition of soy phytoestrogens may cause increased breast cell proliferation (46), and is a significant cause for concern. We noted an increase in SHBG among postmenopausal women at high risk for breast cancer that supports this cautionary tone. Thus, future studies should continue to examine soy as a potential chemopreventive agent for breast cancer based upon promising *in vitro, in vivo*, and epidemiological evidence, but also be mindful of a potential differentiation of effects based on 1) at what age and for how long soy is introduced into the diet, 2) menopausal status, 3) current and past use of estrogen replacement therapy, tamoxifen, or other SERMs, 4) the hormone receptor status of the breast tumor, and 5) whether soy is introduced as a dietary supplement to a standard western diet, or as a dietary substitution for other (potentially more fatty) sources of protein typical of the American diet. Regardless, soy's mechanism of action in breast tissue may likely hold the key to the etiology of breast disease itself, and should continue to be investigated.

Acknowledgments

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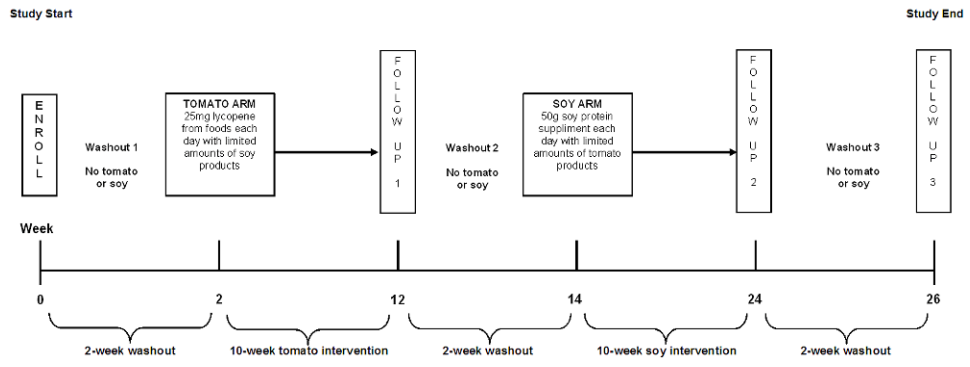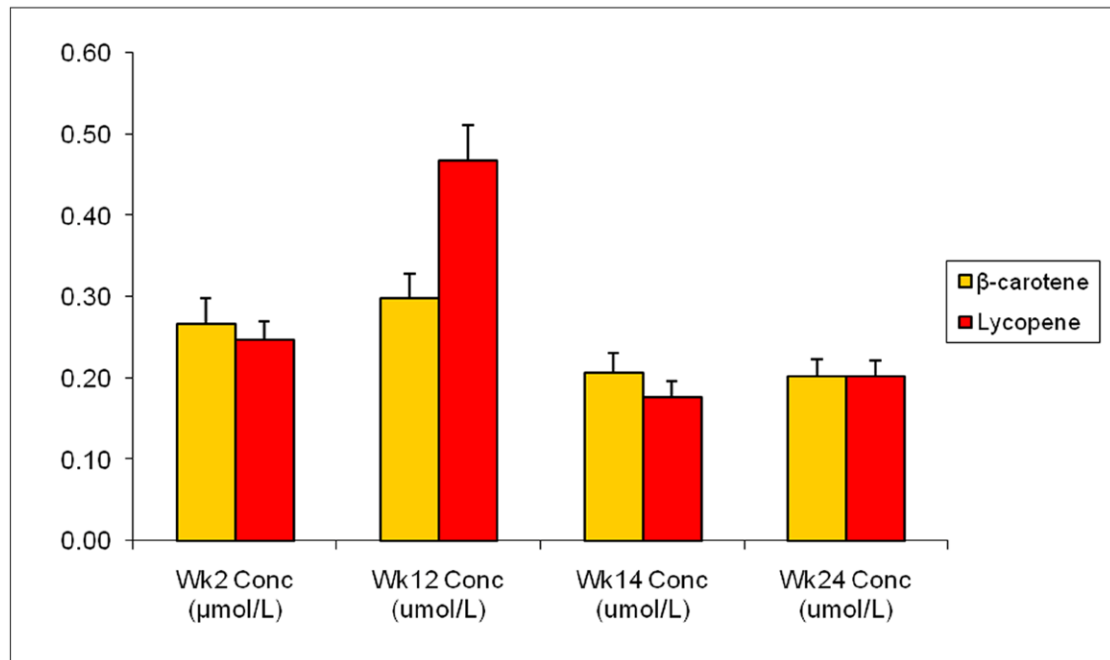
Figure 1.
Study design schema

Figure 2.
Blood serum concentrations (μmol/L) of -carotene and lycopene by week as measures of tomato arm adherence (n=60)
Blood serum concentrations (μmol/L) of -carotene and lycopene were measured at weeks 2, 12, 14, and 24. Weeks 2, 12, 14, and 24 represent the end of the first washout periods, the tomato intervention, the second washout period, and the soy intervention, respectively. Adherence is illustrated by the significant increase in serum carotenoids -carotene and lycopene at week 12 compared to week 2 (exact Wilcoxon sign ranked test p<.01 for both).
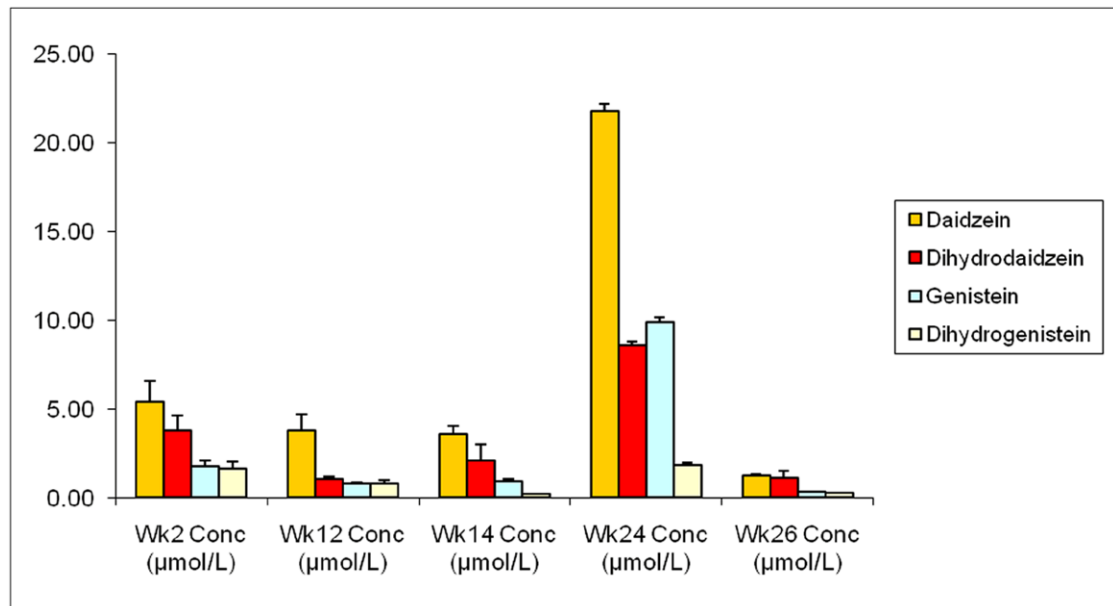
Figure 3.
Urine concentrations (μmol/L) of isoflavone markers by week as measures of soy arm
adherence (n=55)
Urine concentrations (μmol/L) of diadzein, dihydrodaidzein, genistein, and dihydrogenistein
were measured at weeks 2, 12, 14, 24, and 26. Weeks 2, 12, 14, 24, and 26 represent the end
of the first washout periods, the tomato intervention, the second washout period, the soy
intervention, and the final washout period, respectively. Adherence is illustrated by the
significant increase in all measured urinary isoflavones at week 24 compared to week 14
(exact Wilcoxon sign ranked test $p < .001$ for all).

Table 1

Demographic characteristics of participating women at baseline (n=70)

Demographic Characteristic	n (%)*
Age (years)	
40-49	8 (11.4)
50-59	41 (58.6)
60-69	18 (25.7)
70-79	3 (4.3)
Race	
White	57 (81.4)
Black	13 (18.6)
Marital Status	
Married	51 (72.9)
Unmarried	19 (27.1)
Education[†]	
Graduate/professional degree	12 (21.8)
Bachelor's degree	15 (27.3)
Associate's degree	4 (7.3)
Some post-secondary	16 (29.1)
High school or less	8 (14.6)
Annual Household Income[†]	
$0 - $24,999	6 (10.9)
$25,000 - $49,999	11 (20.0)
$50,000 - $74,999	13 (23.6)
$75,000 - $99,999	8 (14.6)
$100,000 - $149,999	8 (14.6)
$150,000 or higher	9 (17.4)
Body Mass Index (BMI, kg/m^2)	
Less than 18.5 (underweight)	1 (1.4)
18.5 - 24.9 (normal)	8 (11.4)
25.0 - 29.9 (overweight)	31 (44.3)
30.0 or higher (obese)	30 (42.9)
Smoking Status[‡]	
Never smoker	33 (47.8)
Former smoker	26 (37.7)
Current smoker	10 (14.5)
Alcohol Consumption[‡] (avg. drinks/day)	
None	24 (34.8)
1 or fewer	42 (60.9)
2 or more	3 (4.4)

[†] 15 patients were missing information about educational attainment and annual household income.

*†*1 patient was missing information about tobacco and alcohol use.

*
*Percentages may not add to 100.0% because of rounding.

Table 2

Means, differences, and standard deviations of hormonal network biomarkers (μmol/L) for the tomato arm of the intervention (n=60)[†]

Biomarker	Week 2	Week 12 *mean (sd)*	Difference[‡]	P[§]
IGF-1	129.1 (39.7)	132.0 (39.9)	2.9 (21.1)	.19
IGFBP-3	2,076.1 (441.5)	2,055.2 (426.2)	-20.9 (167.7)	.56
Estradiol	14.6 (5.2)	16.5 (9.7)	1.9 (9.0)	.19
SHBG	50.2 (24.7)	51.8 (25.0)	1.7 (6.5)	.08
c-peptide	4.6 (2.7)	4.6 (2.4)	.04 (2.0)	.55
Insulin	11.9 (11.6)	10.6 (7.0)	8.6 (.11)	.60

IGF-1 is insulin-like growth factor.

IGFBP-3 is insulin-like growth factor binding protein.

SHGB is sex hormone binding globulin.

[†]One woman was excluded because of a late follow-up, and nine women were lost to follow-up.

[‡]Difference is calculated as Week 12 - Week 2.

[§]P-values were calculated using exact Wilcoxon signed rank tests (nonparametric mean pairwise tests).

Table 3

Means, differences, and standard deviations of hormonal network biomarkers (μmol/L) for the soy arm of the intervention (n=55)[†]

Biomarker	Week 14	Week 24 *mean (sd)*	Difference[‡]	P[§]
IGF-1	129.5 (42.1)	151.0 (71.1)	21.6 (59.1)	.001
IGFBP-3	2,062.3 (462.8)	2,217.0 (550.4)	154.7 (343.8)	.001
Estradiol	14.2 (4.7)	14.6 (6.5)	.37 (5.1)	.36
SHBG	53.1 (27.2)	47.6 (26.0)	-5.43 (9.4)	<.001
c-peptide	4.5 (2.3)	4.4 (2.3)	-.12 (1.2)	.50
Insulin	11.0 (9.2)	10.4 (6.7)	-.62 (6.3)	.79

IGF-1 is insulin-like growth factor.
IGFBP-3 is insulin-like growth factor binding protein.
SHGB is sex hormone binding globulin.

[†]Four women were excluded because of a late follow-up, and 11 women were lost to follow-up.

[‡]Difference is calculated as Week 24 - Week 14.

[§]P-values were calculated using exact Wilcoxon signed rank tests (nonparametric mean pairwise tests).