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Abstract

To determine whether dietary modifications with tomato products and/or a soy supplement affected circulating levels of insulin-like growth factor (IGF)-1 and other markers of cell signaling in postmenopausal women at risk for developing breast cancer. 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 IGF-I, IGF-binding protein (IGFBP)-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. 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-I 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. Increased soy protein intake may lead to small, but significant, increases in IGF-I 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 epidemiologic studies, however, have confirmed protective effect of soy on breast cancer. Additional investigation about the effect of soy on breast cancer risk and its mechanism of action is 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 epidemiologic 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 about 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)-I and IGF-binding protein (IGFBP)-3 endocrine and tissue networks. IGF-I is a mitogenic and antiapoptotic peptide hormone that plays an important role in cell regulation and tumorigenesis. It binds mainly to IGFBP-3, which both sequesters and regulates the effects of IGF-I. Increased levels of both IGF-I 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-I/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 show that lycopene interacts with IGF-I 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, IGF-I, 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 show that breast cancer risk for Western women is about 6 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 breast-feeding. 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-I levels. However, the results of animal and human studies investigating soy, IGF-I, 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 about the effects of lycopene and soy on the IGF-I axis and other markers of cell signaling in relation to breast cancer progression. The primary objective of this study was to determine whether dietary modifications with tomatoes and a soy supplement affected circulating IGF-I 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, estradiol, 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 older than 55 years or no menstrual period for 12 months and a follicle-stimulating hormone level ≥30 if younger than 55 years) 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 42 kg/m² (inclusive) and/or having a primary relative (i.e., mother, daughter, or sister) who had a diagnosis of 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 raloxifene). 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 medical record review. Before contacting women identified through medical record 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 whether 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 (The Health Insurance Portability and Accountability Act) authorization. Recruitment began February 2003 and was completed in September 2004.

**Intervention**

Consented and eligible women were enrolled in a 26-week, 2-arm longitudinal dietary intervention study in which each woman served as her own control. The study consisted of three 2-week washout periods and two 10-week dietary periods (Fig. 1). During each 2-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 2 or more tomato products daily to equate at least 25 mg of lycopene and to 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) that could be mixed with any liquid and provided 50 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 5 mg 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 3-day food records at baseline, during the tomato arm, and during the soy arm. Participants’ 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-I, 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 daidzein and their metabolic forms (dihydrogenistein and dihydrodaidzein, respectively). Adherence was measured using (i) completion of a daily tomato worksheet, (ii) soy protein package counts, and (iii) biochemical measures of adherence using blood carotenoid levels (lycopene and β-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 analyze dietary compliance data. IGF-I 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 posttreatment 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 SDs. 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 posttreatment periods, measured for both the tomato and soy arms. All analyses were conducted using SAS (version 9.2).

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 ineligible participants. Among eligible patients, 144 refused to participate. Seventy-four women were enrolled; however, 4r 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. In addition, 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 9 of the 70 women had a BMI above normal, with 44.3% and 42.9% being overweight or obese, respectively. Table 1 shows that most women (85.5%) were not current smokers, and few women drank 2 or more alcoholic drinks per day (4.4%). 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 and 42 kg/m². Women who met only the BMI or family history eligibility criterion 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 3 women did not complete the tomato arm follow-up assessment, and 4 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 SDs of the outcome measures for the tomato intervention at week 2 (postwashout) and week 12 (post–tomato intervention) and for the paired differences (week 2 – week 2) are presented in Table 2. Mean pairwise differences showed no statistically significant changes in levels of IGF-I, IGFBP-3, estradiol, SHBG, C-peptide, or insulin at the end of the tomato intervention. Blood lycopene and β-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 (Fig. 2). In addition, during the tomato arm, women were instructed to consume enough tomato products to equal at least 25 mg of lycopene per day, and average self-reported lycopene consumption during the tomato arm of the study was 29.7 mg/d.

**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 2 subjects did not have follow-up assessments, and 9 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 SDs of the outcomes measures for the soy intervention at week 14 (postwashout) and week 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-I (difference = 21.6 μmol/L; P = 0.001) and IGFBP-3 (difference = 154.7 μmol/L; P = 0.001) and a statistically significant decrease in SHBG (difference = −5.4 μmol/L; P < 0.001). Although women consumed only an average of 1.5 packets per day of soy protein (less than the goal of 2.0 packets per 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 values of P < 0.001; Fig. 3).

### Table 1. Demographic characteristics of participating women at baseline (N = 70)

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>50–59</td>
<td>41 (58.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>70–79</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57 (81.4)</td>
</tr>
<tr>
<td>Black</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>51 (72.9)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>19 (27.1)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Graduate/professional degree</td>
<td>12 (21.8)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td>Associate’s degree</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>Some post-secondary education</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>High school or less</td>
<td>8 (14.6)</td>
</tr>
<tr>
<td>Annual household income</td>
<td></td>
</tr>
<tr>
<td>$0–$24,999</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>$25,000–$49,999</td>
<td>11 (20.0)</td>
</tr>
<tr>
<td>$50,000–$74,999</td>
<td>13 (23.6)</td>
</tr>
<tr>
<td>$75,000–$99,999</td>
<td>8 (14.6)</td>
</tr>
<tr>
<td>$100,000–$149,999</td>
<td>8 (14.6)</td>
</tr>
<tr>
<td>$150,000 or higher</td>
<td>9 (17.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 (underweight)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>18.5–24.9 (normal)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>25.0–29.9 (overweight)</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>30.0 or higher (obese)</td>
<td>30 (42.9)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>33 (47.8)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>26 (37.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10 (14.5)</td>
</tr>
<tr>
<td>Alcohol consumption (average drinks per day)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24 (34.8)</td>
</tr>
<tr>
<td>1 or fewer</td>
<td>42 (60.9)</td>
</tr>
<tr>
<td>2 or more</td>
<td>3 (4.4)</td>
</tr>
</tbody>
</table>

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

*Fifteen patients had missing information about educational attainment and annual household income.

*One patient had missing information about tobacco and alcohol use.
Table 2. Means, differences, and SDs of hormonal network biomarkers (μmol/L) for the tomato arm of the intervention (N = 60)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Week 2</th>
<th>Week 12</th>
<th>Difference\textsuperscript{b}</th>
<th>P\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>129.1 (39.7)</td>
<td>132.0 (39.9)</td>
<td>2.9 (21.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>2,076.1 (441.5)</td>
<td>2,055.2 (426.2)</td>
<td>−20.9 (167.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Estradiol</td>
<td>14.6 (5.2)</td>
<td>16.5 (8.7)</td>
<td>1.9 (9.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>SHBG</td>
<td>50.2 (24.7)</td>
<td>51.8 (25.0)</td>
<td>1.7 (6.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>C-peptide</td>
<td>4.6 (2.7)</td>
<td>4.6 (2.4)</td>
<td>0.04 (2.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Insulin</td>
<td>11.9 (11.6)</td>
<td>10.6 (7.0)</td>
<td>8.6 (1.1)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

\textsuperscript{a}One woman was excluded because of a late follow-up, and 9 women were lost to follow-up.
\textsuperscript{b}Difference is calculated as follows: week 12 − week 2.
\textsuperscript{c}P values were calculated using exact Wilcoxon signed-rank tests (nonparametric mean pairwise tests).

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 developing the disease. In assessing the potential chemopreventive effects of separate tomato- and soy-rich diets among postmenopausal women at high risk for developing breast cancer, we chose to avoid a “reductionist” approach, which focuses only on a pure substance (such as lycopene or soy isoflavones daidzein 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 6 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 IGFs may play a role in breast pathology through their mitogenic and antiprototic effects on normal, benign, and malignant breast epithelial cells (36). IGFBPs, on the other hand, are postulated to reduce growth stimulus by binding circulating IGFs and through a direct antiproliferative effect on cells. In addition, studies have reported an increased risk of developing 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 developing breast cancer in postmenopausal women as well and predominantly bind to 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 to 5 mg/d (38), and women in our study consumed nearly 30 mg/d, 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 have largely shown no effect (22–25).

Results of the soy intervention showed that blood-level concentrations of IGF-I and IGFBP-3 significantly increased after consumption of the soy protein supplement (P = 0.001 for both). If soy does protect against the risk of...
Table 3. Means, differences, and SDs of hormonal network biomarkers (µmol/L) for the soy arm of the intervention (N = 55)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mean (SD)</th>
<th>Week 14</th>
<th>Week 24</th>
<th>Difference</th>
<th>P&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>129.5 (42.1)</td>
<td>151.0 (71.1)</td>
<td>21.6 (59.1)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>2,062.3 (462.8)</td>
<td>2,217.0 (550.4)</td>
<td>154.7 (343.8)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>14.2 (4.7)</td>
<td>14.6 (6.5)</td>
<td>0.37 (5.1)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>53.1 (27.2)</td>
<td>47.6 (26.0)</td>
<td>-5.43 (9.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>4.5 (2.3)</td>
<td>4.4 (2.3)</td>
<td>-0.12 (1.2)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>11.0 (9.2)</td>
<td>10.4 (6.7)</td>
<td>-0.62 (6.3)</td>
<td>0.79</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Four women were excluded because of a late follow-up, and 11 women were lost to follow-up.
<sup>b</sup> Difference is calculated as follows: week 24 – week 14.
<sup>c</sup> P values were calculated using exact Wilcoxon signed-rank tests (nonparametric mean pairwise tests).

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-I or IGFBP-3. Rather, as hypothesized by Maskarinec and colleagues (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 the levels of IGF-I and IGFBP-3.

Results of the soy intervention also showed a significant decrease in SHBG levels, 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; refs. 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 is 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 risk of developing breast cancer by affecting levels of biomarkers known to influence cell-cycle progression 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 the levels of biomarkers of oxidative stress and cell signaling associated with cancer progression in human studies could be many and include (i) high levels of carotenoids (including lycopene) in the serum may actually be markers for other compound(s) responsible for protection against breast cancer, (ii) carotenoids could be affected by other factors (e.g., smoking), and (iii) different methods and exposure levels have been used for in vitro, in vivo, and human studies.

For soy, several human studies have shown no effect of soy on IGF-I and IGFBP-3 levels (57, 58). Other studies,
including ours, have shown small, statistically significant increases in the levels of IGF-I, IGFBP-3, or both (42, 44). Thus, the majority of published literature does not support the notion that protective effect of soy on breast cancer functions through the IGF-I/IGFBP-3 axis. It is more likely, that breast cancer chemoprevention effects of soy (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 postdiagnostic breast cancer survival among women who consume soy (32, 60), questions still remain about the ability of phytoestrogen 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 with 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 developing breast cancer. Previous research describing the relationship between IGF-I and IGFBP-3 on breast cancer has suggested effect modification by age (i.e., menopausal status). Research about the age-dependent effects of IGF-I and IGFBP-3 on breast cancer risk, however, is largely contradictory. Early research indicated that increasing concentrations of circulating IGF-I and IGFBP-3 were related to increased risk of developing breast cancer in premenopausal women only (12–14, 55, 56). More recent research, however, has suggested that there is no effect of IGF-I and IGFBP-3 on breast cancer risk in premenopausal women (66–68), and, instead, that higher levels of IGF-I and IGFBP-3 are associated with increased risk of developing breast cancer in women older than 50 years (66, 67). Thus, future studies examining the relationship between IGF-I 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 about tomato and soy intake was 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 participant’s 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.

Despite 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. In addition, the crossover design of this study with appropriate washout periods provides highly valid results that cannot be achieved with case-control studies conducted 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, showed that soy at low concentrations may act as an estrogen agonist and stimulate proliferation whereas, at higher concentrations, it acts antagonistically to estrogen, inhibiting cell growth (i.e., biphasic effects) (10, 54–56).

Furthermore, it is possible that only long-term exposure to soy phytoestrogens is protective, as there is evidence that soy may be beneficial only 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 levels among postmenopausal women at high risk for developing 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 epidemiologic evidence, but they should also be mindful of a potential differentiation of effects based on (i) at what age and for how long soy is introduced into the diet, (ii) menopausal status, (iii) current and past use of estrogen replacement therapy, tamoxifen, or other SERMs, (iv) the hormone receptor status of the breast tumor, and (v) whether soy is introduced either 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, the mechanism of action of soy in breast tissue may likely hold the key to the etiology of breast disease itself and should continue to be investigated.

Disclosure of Potential Conflicts of Interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Breast Cancer Research Foundation, the National Center for Research Resources, or the NIH.

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Effects of Tomato- and Soy-Rich Diets

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In this article (Cancer Prev Res 2011;4:702–10), which was published in the May 2011 issue of Cancer Prevention Research (1), the authors recorded the dose in grams of soy incorrectly throughout the article. The dose in grams of soy throughout the article should read 40 g instead of 50 g.

Reference


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