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TITLE: Modulation of Postmenopausal Steroid Hormone Levels by Phytoestrogens and Correlation with Breast Proliferative Activity and Menopausal Symptoms

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Overall 5-yea survival from breast cancer is now 85% and most surviving women are postmenopausal. Nearly half of postmenopausal American women take estrogen replacement to relieve hot flashes and other symptoms of menopause, but this is contraindicated in women with breast cancer. Phytoestrogen supplements can be used as an alternative=, but their effect on the risk of cancer recurrence is unknown. Given the mixed results of phytoestrogen studies regarding breast cell stimulation and inhibition in the medical literature, the effect of phytoestrogen on postmenopausal breast cancer survivors is unclear. To evaluate the effect of a phytoestrogen supplement on steroid hormones and breast epithelial proliferation, 23 disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-11) breast cancer were randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels were measured at baseline, 6months, and one year. Changes in menopausal symptoms and vaginal maturation were also measured.
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Modulation of Postmenopausal Steroid Hormone Levels by Phytoestrogens and Correlation with Breast Proliferative Activity and Menopausal Symptoms

Julie R. Gralow, MD

INTRODUCTION:

Overall 5-year survival from breast cancer is now 85%, and most surviving women are postmenopausal. Nearly half of postmenopausal American women take estrogen replacement to relieve hot flashes and other symptoms of menopause, but this is contraindicated in women with breast cancer. Phytoestrogen supplements can be used as an alternative, but their effect on the risk of cancer recurrence is unknown. Given the mixed results of phytoestrogen studies regarding breast cell stimulation and inhibition in the medical literature, the effect of phytoestrogens on postmenopausal breast cancer survivors is unclear. To evaluate the effect of a phytoestrogen supplement on steroid hormones and breast epithelial proliferation, 23 disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to either 100mg/d isoflavone tablets or placebo for one year. Hormone levels were measured at baseline, 6 months, and one year. Changes in menopausal symptoms and vaginal maturation were also measured.

BODY:

Task 1: Study Preparation – completed

1. Development of materials – completed
   Brochures, flyers, advertisements, web pages, cover letters, as well as data collection forms and study charts were developed. Screening and study data databases were designed and tested for use as well. Both active and placebo tablets were obtained.

2. Mailings to patients, clinicians, support groups – completed
   Patients receiving their oncologic care at the Seattle Cancer Care Alliance, and their support groups and care providers were mailed informational materials just prior to when the trial opened to accrual in June 2001. Since then, patients have been approached for recruitment at the time they come in for their clinical follow-up.

Task 2: Subject Recruitment - completed

Screening concluded in October 2003, when 1151 patients had been screened through the Seattle Cancer Care Alliance. We received 78 additional self or clinician referrals. From both groups, 1094 were found to be ineligible, and 112 refused participation. The number one reason for ineligibility at our institution was stage (35%), followed by women who were currently being treated with hormonal therapy (19%). Of the 112 women who refused, the most common reason for nonparticipation was the invasiveness of the breast biopsy (15%) and a refusal to be randomized to isoflavone tablets (8%). Many women, however, declined to give a reason for their refusal.
In an analysis comparing clinic and community based recruitment in the first year of the trial, we found that community based recruitment has yielded more participants. Specifically, 41 eligible women were identified through the clinic over 12 months. However, 80% of those who are currently eligible refused participation. On the other hand, community based recruitment has yielded 25 eligible women over 6 months, and those who were eligible were 15 times more likely to participate. This analysis was presented at the American Institute for Cancer Research meeting last year (see Reportable Outcomes section). This trend continued throughout the trial—by the end of accrual 64% of participants were from community based recruitment, while the remaining 36% were recruited through the clinic.

Task 3: Clinical Trial – completed
Of the 23 subjects randomized, none have reported side effects attributable to the isoflavone tablets. Nineteen have completed the trial, and 4 withdrew before completing therapy per protocol. One Participant withdrew from the trial because of pain associated with breast biopsy. Two withdrew for logistical reasons, and one for personal reasons. Two of the 4 withdrawals yielded evaluable data through 3-6 months of follow-up.

Task 4: Study Follow-up – completed
Study follow-up is completed. The total number of subjects enrolled is 23. Of those; 5 were followed to 24 months, 13 were followed to 12 months, 2 were followed for 6 months, 1 was followed to 3 months, and 2 subjects dropped out of the study.

Task 5: Evaluation of Clinical Materials – 90% complete

1. Breast Pathology specimens – completed
Complete pathology results are available for all subjects. Of the 23 baseline biopsies, 10 were found to have hyperplasia (2 atypical hyperplasia, 8 usual hyperplasia). Immunohistochemical results are available for 18 of 21 baseline biopsies, with the average Ki-67 index of 9.2%. We would expect this to be <5% in a normal risk postmenopausal population.

In addition, of the 60 biopsies, all but five had sufficient tissue yield from our ultrasound-guided biopsy method in order to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (92% successful yield).

2. Mammograms – completed
We requested 20 baseline films and 29 post-randomization films (17 from the 6-month time point, and 12 from the 12-month time point. Of those, we received 16 baseline, 16 6-month, and 7 12-month film. All 39 films have been digitized and sent for density evaluation. Average baseline mammographic density is 17%, regardless if assessed subjectively by a breast imaging expert radiologist or by computer-assisted software, although the latter has slightly less variance.

3. Endometrial biopsy specimens – completed
All endometrial biopsies have been completed.

4. Urinary isoflavones levels – completed
5. **Food frequency questionnaires – completed**  
All questionnaires are completed.

6. **Menopausal symptom questionnaires – completed**  
All questionnaires are completed.

7. **Serum hormone levels – processed, waiting for analysis**  
Blood collections for serum hormone evaluations at baseline, 6 months, and one year are complete. Serum was aliquotted and frozen at –70°C within 8 hours of blood collection. These specimens have been transferred to City of Hope. All serum specimens have been processed. Analysis of results is expected this year.

**Task 6: Data Analysis and Report Writing – completed**


**Task 7: Additional Studies and Future Directions – in progress**

Palomares MR, Goldstein L, Lehman CD, Gralow JR. Acceptability of breast core biopsy as a tissue sampling method for a chemoprevention trial with histologic biomarker endpoints (in preparation).

KEY RESEARCH ACCOMPLISHMENTS:

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible
- Community-based recruitment proved more effective than clinic-based recruitment
- Isoflavone tablets and breast biopsies are well tolerated
- Adequate normal breast tissue for histologic endpoints can be obtained from postmenopausal women >95% of the time using ultrasound-guided core biopsy techniques.

REPORTABLE OUTCOMES:


CONCLUSIONS:
In summary, findings in this small pilot study suggest that isoflavones use by postmenopausal breast cancer survivors probably does not have adverse effects on the normal tissue of the contralateral breast.
STUDY PERSONNEL

Julie R. Gralow, MD  
University of Washington  
Associate Professor, Medical Oncology  
Principle Investigator

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Project Leader

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Fred Hutchinson Cancer Research Center  
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Budget Analyst, Medical Oncology

Tove Thompson  
University of Washington  
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Gabriele Schuster  
University of Washington  
Research Coordinator, Medical Oncology  
(salary unfunded)
REFERENCES:


APPENDICES:


The Effect of Phytoestrogens on Normal Breast Tissue in Postmenopausal Breast Cancer Survivors: A Feasibility Study

Melanie R. Palomares, M.D. and Julie R. Gralow, M.D.
Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA

INTRODUCTION

Background

 Phytoestrogens have received media attention as a form of breast cancer prevention. Although epidemiologic studies support this claim, there are no prospective clinical trials demonstrating such a protective effect.

Objective

 This project, supported by an AICR Postdoctoral Award, is an ongoing randomized clinical trial that aims to evaluate the effect of a phytoestrogen supplement on the breast tissue of postmenopausal breast cancer survivors.

METHODS

Study Design

Sixty disease-free, post-therapy, postmenopausal women with in-situ or early invasive (St. 0/1A) breast cancer are to be randomized to either 100 mg/day isoflavone tablets or placebo for one year. Biopsies of the uninvolved breast are examined for proliferative changes in response to phytoestrogens, as well as immunohistochemical breast cancer biomarkers. Mammography is performed to assess breast density, and for close monitoring for recurrence. As secondary endpoints, menopausal symptoms, vaginal epithelial changes, endometrial histology, and serum steroid hormones are also being measured.

Recruitment Methods

The trial was opened to accrual in June 2001. Initial recruitment was purely clinically based. All returning breast cancer visits at the Seattle Cancer Care Alliance Medical Oncology clinics were screened for the eligibility criteria in Table 1. Patient eligibility was determined in the initial screening via the medical record and then subsequently via the patient interview. After the first six months of accrual, community-based recruitment was added. Now after the first year of accrual, we compare these two recruitment methods into a chemoprevention trial.

RESULTS

Recruitment

A total of 631 breast cancer patients have been screened through the Seattle Cancer Care Alliance in the first year of accrual. After the first six months, we began community-based recruitment and received 55 additional self-referrals. From both groups, 461 were found to be ineligible. 52 refused participation, and 14 have consented to participate so far. The number one reason for ineligibility at our institution is stage (76%). Of the women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (15%) and unwillingness to take phytoestrogen supplements (31%).

Follow-up

Of the 10 women currently enrolled in the study, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies.

CONCLUSIONS

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible. Tissue sampling is acceptable by a subset of women.
- Refusal to take isoflavone tablets is more of a deterrent to participation than the breast biopsy. This was both due to:
  - Fear of stimulation of recurrence, as well as
  - Unwillingness to be randomized to active vs. placebo tablets because of either strong desire for active tablet (unacceptance of placebo control) or preference for a dietary intervention.
- Comparison of clinical and community-based recruitment:
  - 41 currently eligible women, and 141 women who are potentially eligible in the near future, have been identified through the clinic. However, 80% of those who are currently eligible have refused participation.
- On the other hand, while community-based recruitment has yielded only 25 eligible women so far (13 are still awaiting review of outside records), those who were eligible were 15 times more likely to participate.
- Isoflavone tablets and breast biopsies are well tolerated by those participating in the trial thus far.

FUTURE DIRECTIONS

- After this analysis, plans are to focus more energy into community-based recruitment and expand outreach efforts.
- The investigators have also agreed to relax the stage eligibility criteria to include women with Stage II breast cancer, as long as fewer than 4 lymph nodes were involved.
- Mammographic density will be compared to histologic markers.
The Effect of Phytoestrogens on Normal Breast Tissue in Postmenopausal Breast Cancer Survivors: An Ongoing Trial

Melanie R. Palomares, M.D., Annie Richardson-Lander, Laurel LaBrash, and Julie R. Gralow, M.D.
Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA

INTRODUCTION

Background
Phytoestrogens have received media attention as a form of breast cancer prevention. Although epidemiologic studies support this claim, there are no prospective clinical trials demonstrating such a protective effect.

Objective
This project is an ongoing randomized clinical trial that aims to evaluate the effect of a phytoestrogen supplement on the breast tissue of postmenopausal breast cancer survivors. Secondary endpoints include menopausal symptoms and sex steroid hormone levels.

METHODS

Study Design
Sixty disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stadium II, O-IIA) breast cancer are to be randomized to either 100mg/d isoflavone tablets or placebo for one year. Biopsies of the uninvolved breast are examined for proliferative changes in response to phytoestrogens, as well as immunohistochemical breast cancer biomarkers. Mammography is performed to assess breast density, and for close monitoring for recurrence. As secondary endpoints, menopausal symptoms, vaginal epithelial changes, endometrial histology, and serum steroid hormones are also being measured.

Recruitment Methods
The trial was opened to accrual in June 2001. Initial recruitment was purely clinic based. All returning breast cancer visits at the Seattle Cancer Care Alliance Medical Oncology clinics were screened for the eligibility criteria in Table 1. Patient eligibility was determined in the initial screening via the medical record and then subsequently via patient interview. After the first six months of accrual, community based recruitment was added. Now after 18 months of accrual, we compare these two recruitment methods in this chemoprevention trial.

RESULTS

Recruitment
A total of 801 breast cancer patients have been screened through the Seattle Cancer Care Alliance in the first year of accrual. After the first six months, we began community based recruitment and received 62 additional self referrals. From both groups, 577 were found to be ineligible, 76 refused participation, and 18 have consented to participate so far. The number one reason for ineligibility is stage (98%). Of the women who stated their primary reason for refusal, the most common reasons have been complaints of invasiveness of the trial (12%) and unwillingness to take phytoestrogen supplements (30%).

Follow-up
Of the 15 women enrolled in the study, none have reported side effects attributable to the isoflavone tablets. One woman developed a small post biopsy hematoma, and 2 complained of the dressings used, but the others have not complained of significant discomfort with their breast biopsies.

Table 1. Eligibility Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50-75 years old</td>
<td>600</td>
</tr>
<tr>
<td>Bone metastatic cancer or history of breast cancer</td>
<td>100</td>
</tr>
<tr>
<td>No history of breast cancer or carcinomatous neoplasms</td>
<td>150</td>
</tr>
<tr>
<td>No history of breast cancer or carcinomatous neoplasms</td>
<td>150</td>
</tr>
<tr>
<td>No history of breast cancer or carcinomatous neoplasms</td>
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</tr>
<tr>
<td>No history of breast cancer or carcinomatous neoplasms</td>
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Table 2. Accrual Summary

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Total number screened</td>
<td>801</td>
</tr>
<tr>
<td>Patients coming to clinic</td>
<td>150</td>
</tr>
<tr>
<td>Number screened in clinic</td>
<td>150</td>
</tr>
<tr>
<td>Number of referrals</td>
<td>50</td>
</tr>
<tr>
<td>Number of eligible women</td>
<td>150</td>
</tr>
<tr>
<td>Number of biopsies performed</td>
<td>150</td>
</tr>
<tr>
<td>Number of biopsies performed</td>
<td>150</td>
</tr>
<tr>
<td>Number of biopsies performed</td>
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<tr>
<td>Number of biopsies performed</td>
<td>150</td>
</tr>
<tr>
<td>Number of biopsies performed</td>
<td>150</td>
</tr>
</tbody>
</table>

Figure 1A. Outcomes from clinic-based screening (n=801)

Figure 1B. Outcomes from community-based recruitment (n=62)

Figure 2A. Reasons for ineligibility for those undergoing clinic-based screening (n=553)

Figure 2B. Reasons for ineligibility for those recruited from community (n=24)

CONCLUSIONS

- Conduct of a breast chemoprevention trial with histologic endpoints requiring breast biopsy appears feasible. Tissue sampling is acceptable by a subset of women.
- Failure to take isoflavone tablets was 2.5 times more of a deterrent to participation than the breast biopsy. This was both due to:
  - Fear of stimulation of recurrence, as well as
  - Unwillingness to be randomized to active vs. placebo tablets because of either strong desire for active tablet (unacceptance of placebo control) or preference for a dietary intervention.
- Both isoflavone tablets and breast biopsies are well tolerated by those participating in the trial thus far.
- Comparison of clinic and community based recruitment: Women who self-referred were 5 times more likely to participate than those who were screened through the clinic.

FUTURE DIRECTIONS

- After this analysis, plans are to focus more energy into community based recruitment and expand outreach efforts.
- The investigators have also agreed to relax the stage eligibility criteria to include women with Stage III breast cancer, as long as fewer than 4 lymph nodes were involved.
Feasibility of Breast Tissue Sampling in a Chemoprevention Trial with Histologic Biomarker Endpoints

Melanie R. Palomares, MD, MS; Lynn Goldstein, MD; Constance D. Lehman, MD, PhD; Laura Hopper; Julie R. Gralow, MD

University of Washington, Seattle WA; Phenopath Laboratories, Seattle WA

Background: Phytoestrogens are natural selective estrogen receptor modulators (SERMs) found in soy foods that show effects similar to endogenous estrogens. Epidemiologic studies have shown an association between high soy consumption and a decreased risk of developing breast cancer. Prospective human trials have been few and small, and have reported contradictory results. The purpose of this study is to assess the effect of taking a phytoestrogen dietary supplement for one year on breast epithelial proliferative activity, in a placebo-controlled randomized clinical trial.

Methods: Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections are evaluated for breast epithelial proliferation by Ki-67 index. All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy.

Results: Of the 22 subjects enrolled, 21 have available baseline pathology results. Eight subjects have completed the 12-month trial. Full biopsy series are available on 7 of those subjects. An additional 4 subjects have completed both baseline and 6-month biopsies and therefore have one comparison available. Of all 64 biopsies performed, all but one baseline and one follow-up had sufficient tissue yield from our ultrasound-guided biopsy method in order to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (97% successful yield). Although the trial is still blinded, results have been quite interesting thus far. Despite the fact that tissue sampling was from the contralateral breast, and all participants were postmenopausal, 10 of 21 baseline biopsies revealed hyperplasia. Two of those had atypical hyperplasia evident on their random biopsy; the other eight had usual hyperplasia. Immunohistochemistry results are available on 18 of the 21 baseline biopsies, and average Ki67 index was 9.2%. We would expect this to be <5% in a normal-risk postmenopausal population. All subjects had zero mitotic index at baseline. All expressed hormone receptors at baseline.

Conclusions: Recruitment into a chemoprevention trial with histological biomarker endpoints requiring serial breast biopsies is feasible, at least within the breast cancer survivor population. Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible >90% of the time using ultrasound-guided 14-gauge core biopsy. Pathologic examination of the sampled contralateral breast epithelia reveals more proliferative activity than would be expected in a similarly aged unaffected population.

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Feasibility of Breast Tissue Sampling in a Chemoprevention Trial with Histologic Biomarker Endpoints

Melanie R. Palomares, MD, MS; 1, 2 Lynn Goldstein, MD; 3 Constance D. Lehman, MD, PhD; 2 Laura Hopper; 2 Julie R. Gralow, MD. 2
1 City of Hope National Medical Center, Duarte, CA; 2 University of Washington School of Medicine, Seattle, WA; 3 PhenoPath Laboratories, Seattle, WA

INTRODUCTION

Background
Phytoestrogens are natural selective estrogen receptor modulators (SERMs) found in many foods that show effects similar to endogenous estrogens. Epidemiologic studies have shown an association between high soy consumption and a decreased risk of developing breast cancer. Prospective human trials have been few and small, and have reported contradictory results.

Objective
The purpose of this study is to assess the effectiveness of a phytoestrogen dietary supplement for one year on breast epithelial proliferative activity, in a placebo-controlled randomized clinical trial.

METHODS

Study Population
Twelve-two disease-free, post-menopausal women with in situ or early invasive (Stage I-II) breast cancer were recruited through the medical oncology clinic at the Seattle Cancer Care Alliance between July 2001 and March 2003 into the UW Phytoestrogen Trial. Subjects were randomized to receive either 100 mg per day of soy isoflavone tablets, or placebo for 12 months. Study follow-up is ongoing, and subjects remain blinded at this time. We report our feasibility experience with breast tissue sampling and preliminary histologic findings.

Tissue Collection and Processing
All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6, and 12-month time points. Histological sections are evaluated for breast epithelial proliferation by Ki-67 index and hormone receptor expression.

ACKNOWLEDGEMENTS
Support for this study is being provided by the Department of Defense, DAMD17-01-1-0449

RESULTS

Table 1: Patient population

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Postmenopausal women age 30 or older</td>
<td>22</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>2 = Unilateral Stage I-II infiltrating ductal or ductal carcinoma in situ (DCIS)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 = Complete local and regional, axillary lymph node dissection and systemic therapy with no evidence of residual disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Exclusion criteria:
1 = 4 = Lymph node involvement
2 = 5 = Cervical metastasis
3 = 6 = Metastatic breast implant
4 = 7 = Hormone therapy, including SERM, aromatase inhibitor, IRT, or histoplastic-antiestral treatment, between 3 months of enrollment
5 = 8 = Baseline soy-rich diet, defined as more than 3 servings per week (average 10 mg isoflavones per day)

Table 2: Patient characteristics

<table>
<thead>
<tr>
<th>N = 22</th>
<th>22</th>
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<tbody>
<tr>
<td>Mean age: 67.2 years</td>
<td>67.2 years</td>
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<tr>
<td>Mean time since diagnosis: 5.4 years</td>
<td>5.4 years</td>
</tr>
<tr>
<td>Stage distribution:</td>
<td>5.4 years</td>
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<tr>
<td>ER status:</td>
<td>5.4 years</td>
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<tr>
<td>positive: 13</td>
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<td>negative: 8</td>
<td>8</td>
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<tr>
<td>unknown: 1</td>
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Table 3: Biopsy yield

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<thead>
<tr>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>42%</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Insufficient</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Total Obtained</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

*Refers to adequate glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression.

Table 4: Baseline histologic results

<table>
<thead>
<tr>
<th>N with baseline path available: 21</th>
<th>21</th>
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</thead>
<tbody>
<tr>
<td>Histology:</td>
<td>21</td>
</tr>
<tr>
<td>Normal:</td>
<td>11</td>
</tr>
<tr>
<td>Hyperplasia without atypia:</td>
<td>8</td>
</tr>
<tr>
<td>Hyperplasia with atypia:</td>
<td>2</td>
</tr>
<tr>
<td>Mean Ki-67 Index</td>
<td>8.5%</td>
</tr>
<tr>
<td>ER expression</td>
<td>1%</td>
</tr>
<tr>
<td>PR expression</td>
<td>0%</td>
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Table 5: Preliminary histologic follow-up

<table>
<thead>
<tr>
<th>N = 16</th>
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<td>Histology:</td>
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<td>Normal:</td>
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<tr>
<td>Hyperplasia without atypia:</td>
<td>5</td>
</tr>
<tr>
<td>Hyperplasia with atypia:</td>
<td>1</td>
</tr>
<tr>
<td>Ki-67 Index*</td>
<td>7.5%</td>
</tr>
<tr>
<td>Range:</td>
<td>0-20%</td>
</tr>
<tr>
<td>ER expression</td>
<td>0%</td>
</tr>
<tr>
<td>PR expression</td>
<td>0%</td>
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Table 4: Ki-67 index

<table>
<thead>
<tr>
<th>N = 21</th>
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<tbody>
<tr>
<td>Histology:</td>
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<tr>
<td>Normal:</td>
<td>11</td>
</tr>
<tr>
<td>Hyperplasia without atypia:</td>
<td>8</td>
</tr>
<tr>
<td>Hyperplasia with atypia:</td>
<td>2</td>
</tr>
<tr>
<td>Mean Ki-67 Index</td>
<td>8.5%</td>
</tr>
<tr>
<td>ER expression</td>
<td>1%</td>
</tr>
<tr>
<td>PR expression</td>
<td>0%</td>
</tr>
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</table>

*Refers to adequate glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression.

CONCLUSIONS

• Recruitment into a chemoprevention trial with histologic biomarker endpoints requiring serial breast biopsies is feasible, at least within the breast cancer survivor population.
• Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible >95% of the time using ultrasound-guided 14-gauge core biopsy.
• Pathologic examination of the sampled contralateral breast epithelium reveals more proliferative activity than would be expected in a similarly aged unaffected population.
• All normal breast tissue sampled expressed hormone receptors.
• Preliminary follow-up suggests a possible decrease in Ki-67 index and estrogen receptor expression with isoflavone treatment; however, whether that trend is significantly different to placebo remains to be seen.
Acceptability of breast core biopsy as a tissue sampling method for a chemoprevention trial

Melanie R. Palomares, MD, MS; Laura Hopper; Lynn Goldstein, MD; Constance D. Lehman, MD, PhD; Julie R. Gralow, MD

City of Hope, Duarte, CA; University of Washington, Seattle WA; Phenopath Laboratories, Seattle WA

Background: Early phase chemoprevention clinical trials often require histologic biomarker endpoints. Current options for breast tissue collection to evaluate such markers include nipple aspirate, ductal lavage, periareolar fine needle aspirate, and core needle biopsy. Trade-offs between methods include degree of invasiveness and adequate tissue yield. Core needle biopsy is the most invasive method, but has the benefits of greater epithelial cell yield and preserved glandular architecture. We report yield and acceptability of core biopsy in a trial assessing the effect of a phytoestrogen dietary supplement on breast epithelial proliferative activity.

Methods: Twenty-two disease-free, post-therapy, postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14g core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections were evaluated for breast epithelial proliferation by Ki-67 index. Questionnaires evaluating pain, anxiety, and quality of life (QOL) were collected one week post biopsy.

Results: Of 52 biopsies performed in 22 subjects, all but one baseline and one follow-up had sufficient tissue yield to assess epithelial histology and Ki-67 index, as well as mitotic index and ER/PR expression (96% successful yield). Of the 48 for whom questionnaire data are available, 17 (35%) reported no pain associated with breast biopsy. Of the remaining 31 reporting any post biopsy pain, on a scale of 1-10, their average pain score was 1.5 +/- 1.1. Twelve (39%) did not require any pain medications to alleviate their pain. Those who did typically used over-the-counter acetaminophen or ibuprofen, from which they experienced on average 74% relief. Twenty-three (74%) reported that their pain had completely abated within two days. Sixteen (38%) reported no anxiety associated with breast biopsy. The remaining 32 reporting any biopsy-associated anxiety on average rated their anxiety 1.8 +/- 1.5 prebiopsy and 1.7 +/- 1.6 post-biopsy. Regarding how pain and/or anxiety affected QOL, 67% reported no effect on level of activity (mean score 0.64 +/- 1.1), 81% reported no effect on their relationships with others (0.12 +/- 0.42), 79% reported no effect on their sleep (0.36 +/- 0.9), and 64% reported no effect on their mood (0.76 +/- 1.3).

Conclusions: Ultrasound guided 14g core breast biopsy yields adequate breast epithelial tissue from postmenopausal women for evaluation of multiple immunohistochemical markers >90% of the time, and is well tolerated with respect to pain, anxiety, and QOL.
Acceptability of Breast Core Biopsy as a Tissue Sampling Method for a Chemoprevention Trial
Melanie R. Palomares, MD, MS;1,2 Laura Hopper;2 Lynn Goldstein, MD;2 Constance D. Lehman, MD, PhD;2 Julie R. Gralow, MD.2
1City of Hope National Medical Center, Duarte, CA; 2University of Washington School of Medicine, Seattle, WA; 3PhenoPath Laboratories, Seattle, WA

INTRODUCTION

Background
Early phase chemoprevention clinical trials often require histologic biomarker endpoints. Current options for breast tissue collection to evaluate such markers include nipple aspiration, ductal lavage, percutaneous fine needle aspiration, and core needle biopsy. Trade-offs between methods include degree of invasiveness and adequate tissue yield. Core biopsy is the most invasive method, but has the benefits of greater epithelial cell yield and preserved glandular architecture.

RESULTS

UW Phytoestrogen Trial Schema

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Pre-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>37.0 years</td>
<td>37.0 years</td>
</tr>
<tr>
<td>Mean time since diagnosis</td>
<td>5.4 years</td>
<td>5.4 years</td>
</tr>
<tr>
<td>Stage distribution</td>
<td>0  2  3</td>
<td>0  2  3</td>
</tr>
<tr>
<td>ER status</td>
<td>positive 13%</td>
<td>negative 87%</td>
</tr>
</tbody>
</table>

Biopsy yield

<table>
<thead>
<tr>
<th>Type</th>
<th>Breast 6 months</th>
<th>Breast 12 months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>42%</td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td>Invasive ductal cancer</td>
<td>58%</td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td>Total Obtained</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

Biopsy-Associated Pain*
17 of 48 symptom logs (35%) reported no pain associated with breast biopsy.
The remaining 31 reported the following mean worst, least, and average pain scores:
- Worst pain: 2.5 ± 1.5
- Least pain: 0.5 ± 0.9
- Average pain: 1.5 ± 1.1
12 of the 31 (39%) did not require any pain medications to alleviate their pain. Those who did typically used over-the-counter aspirin/paracetamol or ibuprofen, from which they experienced on average 74% pain relief.
23 of the 31 (74%) subjects reporting any post-biopsy pain said that their pain had completely abated within two days.

Biopsy-Associated Anxiety*
16 of 48 symptom logs (33%) reported no anxiety associated with breast biopsy.
The remaining 32 reported the following mean pre, post, and average anxiety scores:
- Pre-procedure: 1.6 ± 1.5
- Post-procedure: 1.6 ± 1.5
- Average: 1.7 ± 1.5
There was no significant change between pre- and post-procedure anxiety.

CONCLUSIONS

- Breast core biopsy is a well-tolerated procedure that yields adequate tissue for multiple histological biomarkers for chemoprevention.
- Obtaining adequate breast epithelial tissue from postmenopausal women for evaluation of histology and multiple immunohistochemical markers is possible ≥95% of the time using ultrasound-guided 14-gauge core biopsy.
- Breast core biopsy was not associated with pain in one-third of cases, and was associated with only low levels of self-limited pain in the remaining cases.
- Breast core biopsy was not associated with anxiety in one-third of cases, and was associated with only low levels of pre- and post-procedure anxiety in the remaining cases.
- The pain and anxiety associated with breast core biopsy was less than or equal to that experienced with mammography in ≥95% and ≥75% of cases, respectively.

METHODS

Study Population
Twenty-two disease-free, post-menopausal, post-menopausal women with in-situ or early invasive (stage I-II) breast cancer were recruited through the medical oncology clinics at the Seattle Cancer Care Alliance between July 2001 and March 2003 into the UW Phytoestrogen Trial. Subjects were randomized to receive either 100mg per day isoflavone tablets or placebo for 12 months. Study follow-up is ongoing, and subjects remain blinded at this time. We report our feasibility and acceptability data with breast tissue sampling using core biopsy.

Tissue Collection and Processing
All subjects were given normal screening mammogram and clinical breast exam prior to each biopsy. Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. A specimen was considered adequate when it included enough glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression.

Symptom Data Collection
Subjects were given symptom logs on which they rated their anxiety and pain levels on a scale of 1-10. Anxiety was rated immediately prior to the procedure and one week post procedure. Worst and least pain levels experienced during the week following the procedure were rated, and information regarding pain duration and medication was also collected. To provide comparison data, subjects were given the same symptom log to rate anxiety and pain associated with mammography.

ACKNOWLEDGEMENTS
Support for this study is provided by the Department of Defense, DAMD17-01-1-0449

APPENDIX

Pain and Anxiety Relative to Mammography

Relative Pain Scores

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Pre-procedure</th>
<th>Post-procedure</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast pain</td>
<td>1.6 ± 1.5</td>
<td>1.6 ± 1.5</td>
<td>1.7 ± 1.5</td>
</tr>
</tbody>
</table>

% of Subjects Reporting Pain

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Pre-procedure</th>
<th>Post-procedure</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast pain</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>

% of Subjects Reporting Anxiety

<table>
<thead>
<tr>
<th>Anxiety Type</th>
<th>Pre-procedure</th>
<th>Post-procedure</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast anxiety</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

% of Subjects Reporting Anxiety

<table>
<thead>
<tr>
<th>Anxiety Type</th>
<th>Pre-procedure</th>
<th>Post-procedure</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast anxiety</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Out of the 52 biopsies collected, symptom data is available for 48. Comparison mammogram symptom data is available for 29.
APPENDIX 5

Effect of Phytoestrogens on Menopausal Symptoms in Breast Cancer Survivors

Melanie R. Palomares, MD, MS; Laura Hopper; Johanna W. Lampe, PhD; Barry E. Storer, PhD; Julie R. Gralow, MD

City of Hope Comprehensive Cancer Center, Duarte, CA; Seattle Cancer Care Alliance, Seattle WA; Fred Hutchinson Cancer Research Center, Seattle, WA

Introduction: Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority of these women will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement. Studies suggest that soy supplements may be used as an alternative, but most of those studies were not conducted in breast cancer survivors. One study investigated a four-week course of a soy isoflavone supplement in women with breast cancer and found no benefit with respect to vasomotor symptoms. However, two-thirds of the participants were taking tamoxifen at the same time.

Purpose: To evaluate the effect of a year-long trial of soy isoflavone supplementation on menopausal symptoms in breast cancer survivors who have completed all cancer treatment, including hormonal therapy.

Methods: Postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer who were disease-free post-therapy were randomized to receive tablets providing either soy isoflavones (100 mg aglycone units/day), or placebo, for 12 months. Menopausal symptom logs were collected from all participants at baseline, and after 3, 6, 9, and 12 months on the study supplement.

Results: Twenty-three subjects enrolled in the trial, with a median age of 57 (range 45-67). Seventeen (74%) had hormone receptor expressing tumors and had previously taken antiestrogen therapy, but they were a median of 5.9 years post-diagnosis (range 1.2-12.9), and no one was taking any hormonal therapy for at least 3 months prior to enrollment. All but one participant had menopausal symptoms at baseline. A full year of follow-up is available for 16 subjects; average overall follow-up is 9.8 months. Pill counts reveal high adherence to treatment plan (>90%), and urinary isoflavones were significantly elevated in the treatment group (p=0.0001). On average, participants in both treatment groups experienced a decline in the number and severity of hot flashes from baseline. As depicted in the accompanying graphs, there was a slightly greater decrease in the number of hot flashes between 3 and 9 months of isoflavone treatment relative to placebo, but by 12 months the placebo group had experienced similar relief in hot flashes. The decrease in severity of hot flashes with isoflavones was most pronounced at 3 and 6 months, but a trend remained throughout the treatment period. There were no significant differences in the genitourinary symptoms of vaginal dryness, incontinence, dyspareunia, and libido between the treatment groups, although there was a trend toward improvement in incontinence and libido with isoflavone supplementation (see graphs below). Vaginal discharge and dysuria were too infrequently reported at baseline to analyze.

Conclusions: Preliminary results from this pilot trial suggest that soy supplements may be effective at decreasing the number and severity of hot flashes in postmenopausal breast cancer survivors in the short-term, but that all women experience relief over time. Similarly, no significant changes in genitourinary symptoms were observed in this small study sample, but some beneficial trends were observed with isoflavone supplementation compared to placebo.

Society of Integrative Oncology, Nov 17-19 NYC
http://www.integrativeonc.org/index.php?scn=meeting_program

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Effect of Soy Isoflavones on Breast Proliferation in Postmenopausal Breast Cancer Survivors

Melanie R. Palomares, MD, MS; Laura Hopper; Lynn Goldstein, MD; Constance D. Lehman, MD, PhD; Johanna W. Lampe, PhD; Barry E. Storer, PhD; Julie R. Gralow, MD

City of Hope Comprehensive Cancer Center, Duarte, CA; Seattle Cancer Care Alliance, Seattle, WA; Phenopath Laboratories, Seattle WA; University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority of these women will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement. Some use soy supplements as an alternative, but preclinical studies have shown both stimulatory and inhibitory effects of soy isoflavones on the breast. We report initial results from a pilot human clinical trial assessing the effect of a soy supplement on breast epithelial proliferative activity.

Methods: Postmenopausal women with in-situ or early invasive (Stage 0-II) breast cancer who were disease-free after completing all cancer therapy were randomized to receive either 100mg per day isoflavone tablets, or placebo for 12 months. Ultrasound-guided 14g core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. Histological sections were evaluated for breast epithelial proliferation by Ki-67 index.

Results: Twenty-three subjects enrolled in the trial, with a median age of 57 (range 45-67) and median time since diagnosis of 5.9 years (range 1.2-12.9). Mean baseline Ki67 index was 8.1% (range 0-30%), while that expected in the postmenopausal normal breast is <5%. At 6 months of follow-up, pill counts reveal high adherence to the treatment plan (≥90%), and urinary isoflavones were significantly higher in the treatment group (p=0.0001). Evaluable pre and post-treatment histological specimen pairs are available for 18 subjects (9 in each arm). On average, Ki67 index dropped during 6 months of treatment for both groups: a 3.1% (SD 9.5%) decrease was noted in the isoflavone group, while a 1.3% (SD 8.5%) decrease from baseline was observed in the placebo group. This difference was not statistically significant.

Conclusions: Preliminary results from this pilot trial suggest that soy supplements do not increase proliferation of normal breast tissue in breast cancer survivors. The elevated mean Ki67 index observed at baseline correlates with the known increased risk for contralateral breast cancer in this population.

San Antonio Breast Cancer Symposium, Dec 8-11
http://www.sabcs.org

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Title/Author/Body Character Count: 2255
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**Effect of Soy Isoflavones on Breast Proliferation in Postmenopausal Breast Cancer Survivors**

Melanie R. Palomares, MD, MS; Laura Hopper; Lynn Goldstein, MD; Constance D. Lehman, MD, PhD; Johanna W. Lampe, PhD; Barry E. Storer, PhD; and Julie R. Gallow, MD

1City of Hope National Medical Center, Duarte, CA; University of Washington School of Medicine, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; PhenoPath Laboratories, Seattle, WA

**BACKGROUND**

Most women with breast cancer are postmenopausal at diagnosis, and many more enter menopause during the course of their treatment. The majority will be long-term survivors who must manage their menopausal symptoms without the option of hormone replacement therapy (HRT). Some women use soy supplements as an alternative to HRT, but preclinical studies have shown both stimulatory and inhibitory effects of soy isoflavonoids on the breast. We report results from a pilot human clinical trial assessing the effect of a soy supplement on breast epithelial proliferative activity.

**METHODS**

**Study Population**

Twenty-three disease-free, post-therapy, postmenopausal women previously diagnosed with in-situ or early stage breast cancer were recruited through the medical oncology clinics at the Seattle Cancer Care Alliance (SCCA) between July 2001 and March 2003 into the University of Washington (UW) Phytoestrogen Trial. Subjects were randomized to receive either 100mg per day isoflavone tablets (ISO), or placebo (PBO) for 12 months. Compliance was measured by pill counts and 24-hour urinary genistein levels. Follow-up was completed in May 2004.

**Tissue Sampling and Processing**

Ultrasound-guided 14-gauge core biopsies of the contralateral breast were performed at the baseline, 6-month, and 12-month time points. All subjects had a documented normal screening mammogram and clinical breast exam prior to each biopsy. A specimen was considered adequate when it included enough glandular tissue for assessment of histology, Ki-67 index, and ER/PR expression. A subject was considered available if both biopsies and at least one of the follow-up breast biopsy specimens were adequate.

**ACKNOWLEDGEMENTS**

Support for this research was provided by the Department of Defense, DAMO17-01-1-0042

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**RESULTS**

1. **UW/SCCA Phytoestrogen Trial Schema**

   - **PRIMARY ENDPOINT**
     - Epithelial proliferation (Ki-67 index)
   - **OTHER ENDPOINTS**
     - Menopausal symptoms
     - Blood markers for lipid and bone metabolism
     - Hormone levels

2. **Study Population**

   - **Inclusion criteria**
     1. Postmenopausal women age 20 or older
     2. History of bilateral Stage I-IIIA infiltrating ductal or lobular carcinoma, or bilateral adenocarcinomas in situ (DCIS)
     3. Completed appropriate local and adjuvant systemic therapy with no evidence of residual disease
   - **Exclusion criteria**
     1. An ongoing medical condition
     2. DP of bilateral mastectomy
     3. Contralateral breast radiated
     4. Estrogen modulating therapy (including SERM, estrogen-related inhibitor, or any clinically active breast supplement, within 6 months of study enrollment)
     5. Baseline may vary as defined as more than 3 cravings per week (average 10 cravings per day)

3. **Baseline Breast Biopsy Findings**

   - **Ki-67 Index**
     - Primary measure of epithelial proliferation
     - Expressed as the ratio of stain-negative cells per 100 cells

4. **Baseline Breast Biopsy Findings**

   - **Ki-67 Index**
     - Mean: 4.1% (range: 1.1-10.2%)

5. **Treatment Adherence**

   - **By pill count**
     - Compliance: 100% (all subjects)
   - **By urinary genistein levels**
     - Compliance: 90% (all subjects)

6. **Serial Breast Biopsy Findings**

   - **21 subjects completed the study with 11.7 months average follow-up:**
     - 19 (95%) of these subjects were evaluable (baseline and follow-up biopsies were adequate)

**CONCLUSIONS**

- A year-long treatment with a twice daily isoflavone tablet was well tolerated by postmenopausal breast cancer survivors. Isoflavone treatment was associated with a 7-10 fold increase in urinary excretion of genistein (p < 0.005), with no increase in urinary genistein levels observed in the placebo group.
- Obtaining adequate normal breast epithelial tissue from postmenopausal women for evaluation of multiple serum immunohistochemical biomarkers is possible 90% of the time using ultrasound-guided 14-gauge core biopsy.
- Ki-67 index was elevated at baseline, correlating with the known increased risk for contralateral breast cancer in this population. On average, Ki-67 index dropped during the first 6 months of treatment: a 3.1% (SD 9.5%) decrease from baseline was noted in the isoflavone group, while a 0.9% (SD 8.1%) decrease was observed in the placebo group. This difference was not statistically significant. During the second 6 months of treatment, Ki-67 index continued to decrease in both groups: a 4.5% (SD 11.5%) decrease from baseline was observed in the isoflavone group, and a similar 4.6% (SD 10.9%) decrease was seen with placebo.
- Hyperplasia was observed in 4% of subjects at baseline; however, there were no significant differences found on serial histology between the treatment groups.
- No significant differences between the treatment groups were seen with regards to hormone receptor expression. A trend toward decreased ER expression was noted in both the isoflavone and placebo treated groups over time.

In summary, findings from this small pilot study suggest that isoflavone use by postmenopausal breast cancer survivors probably does not have adverse effects on the normal tissue of the contralateral breast.