Anthropometric and Hormone Effects of an Eight-Week Exercise-Diet Intervention in Breast Cancer Patients: Results of a Pilot Study

Anne McTiernan,2 Cornelia Ulrich, Claudia Kumai, Deanna Bean, Robert Schwartz, Jan Mahloch, Rob Hastings, Julie Gralow, and John D. Potter


Abstract
To assess the feasibility of an exercise-diet intervention in sedentary, overweight breast cancer patients, we conducted a pilot 8-week intervention. Recruitment letters and interest surveys were sent to 99 stage 1 or 2 breast cancer patients, ages 25–75 years, who were identified through two Seattle breast surgery practices and the University of Washington Breast Clinic. Ten patients were eligible and interested and were enrolled in the intervention, which consisted of thrice-weekly monitored aerobic exercise sessions and a low-fat (20% of calories from fat) diet. Nine patients completed the program; all adhered well to the intervention and data collection protocol. The patients, ages 40–74 years, lost, on average, 2.6 pounds of body weight, 3.4 cm in waist circumference, 4.6 cm in hip circumference, 2.3% body fat, 3.5 systolic blood pressure points, 0.67 diastolic blood pressure points, and 4.0 pulse beats/min, and they gained an average of 2.3% lean mass. Slight, nonsignificant decreases were observed in serum concentration of total and free estradiol, estrone sulfate, total testosterone, androstenedione, and dehydroepiandrosterone.

These pilot data indicate that breast cancer patients are highly motivated to join and adhere to an intense exercise-diet intervention and can experience significant measurable changes in anthropometric and fat mass measures.

Introduction
Women with one breast cancer are at particularly high risk of developing a second primary breast cancer (1). There has been little to offer breast cancer patients, following completion of primary therapy, however, that might improve survival and reduce risk of recurrence or new disease in the long term (2). Women who are obese or who gain weight after diagnosis of breast cancer have a poorer survival than lighter women (3). The relationship between weight and survival may have a hormonal mechanism: high endogenous estrogen levels have been shown to be associated with shortening of disease-free interval in postmenopausal patients with recurrence (4); elevated levels of endogenous estrogens and androgens are linked with increased risk for initial breast cancer occurrence (5, 6); and overweight postmenopausal women have elevated production of estrogen from adrenal androgens (7). Overweight women also have high plasma insulin levels, which have been found, in one study, to be positively associated with risk of breast cancer development, independent of body weight (8). Reduction of fat mass might reduce endogenous estrogen, androgen, and insulin concentrations and, therefore, may be a useful adjunct therapy for breast cancer patients.

We tested the feasibility of recruiting, screening, enrolling, and maintaining breast cancer patients in an intensive 8-week exercise and low-fat diet program. We tested the effect of this short intervention on weight (fat mass) loss and on serum sex hormone concentrations in 10 women with stage 1 or 2 breast cancer.

Materials and Methods
We conducted a feasibility study of an exercise-diet program for breast cancer patients to investigate whether breast cancer patients could be recruited to and retained in an intervention exercise-diet program and to assess changes in various physiological measures. Patients served as their own controls, and comparisons were made between pre- and postintervention parameters. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and all study participants gave written informed consent before they were enrolled in the study.

Breast cancer patients between the ages of 25 and 75 years were recruited from three Seattle-area oncology practices. The study recruitment nurse (J. M.) visited the three practices (two private breast surgeons and one academic oncology group) and met with clinic nurses to go over patient rosters. On the basis of patient eligibility criteria (ages 25–75 years, ≥4 months since active treatment, and stage 1 or 2 invasive breast cancer) and approval of the nurses (illness and patient emotional factors), the recruitment nurse developed a list of eligible patients. Patients were sent a recruitment letter signed by the study principal investigator (A. M.) and coinvestigator/oncologist (J. G.) and a screening questionnaire to complete. The letter indicated that the patient’s physician had given us her name to contact about the study. Women who were found to be eligible on review of these questionnaires were contacted by phone by a physician assistant (C. K.). The study was explained in full, and patients were invited to a screening clinic visit. Table 1 lists eligibility and exclusion criteria. We excluded patients who...
Exercise-Diet Effects in Breast Cancer Patients

The dietary program consisted of a low-fat (20% calories from fat) diet. The dietary change program was modified from the Women’s Health Initiative Dietary Change program (11) to fit a resting electrocardiogram and an exercise treadmill test (9). Women who continued to be interested and eligible were enrolled into the exercise-diet program.

Exercise Program

The exercise program consisted of moderate intensity exercise (e.g., stationery bicycle or brisk walking). The goal was 30–45 min per day, 6 days per week, by the end of the 8-week intervention period. The program was individually prescribed, based on the woman’s level of fitness, as determined on the treadmill test, with a goal of 70–80% maximal heart rate. The program was based on similar successful programs conducted at the University of Washington Exercise Physiology Laboratory (10). Initially, patients met individually or in small groups with the exercise physiologist (D. B.) in monitored exercise sessions three times per week. Starting at about halfway through the program, patients also exercised at home on non-monitored days. All exercise sessions were monitored with upper and lower pulse alarms. Patients kept a daily exercise diary, where they recorded exercise done, length of session, and pulse rate.

Dietary Program

The dietary program consisted of a low-fat (20% calories from fat) diet. The dietary change program was modified from the Women’s Health Initiative Dietary Change program (11) to fit into the time and resource constraints of this feasibility study. Patients met once individually or in a group with a nutritionist (C. U.). At this meeting, patients learned skills to change eating behaviors to adopt the dietary program. Patients were given programmatic written intervention materials that explained in sequential detail the nutritional concepts and behavioral techniques needed to change to the new diet. They were also instructed in completion of a daily self-monitoring measurement, which they used for about 2 weeks. Patients were given the phone number of the nutritionist and invited to call her if they had any questions. In addition, the nutritionist called each woman about 3 weeks after the counseling session to assess adherence and to provide additional counseling, if needed. Adherence to the dietary program was measured with a modified Block 98-item food frequency questionnaire (12), administered at baseline and at 8-week follow-up, in which patients were asked to recall the frequency at which they had eaten selected foods over the preceding month.

Outcome Measures

The primary study outcomes were changes in weight and adiposity, as determined by percentage fat mass (measured by RJL Multifrequency Bioelectrical Impedance). Anthropometric measures were taken by the physician assistant. Weight was measured at baseline and at 8–10 weeks after baseline. Patients were weighed consistently in light clothing (hospital gown), on the same recaliibrated balance scale, rounded up to the nearest 0.5 pound. Waist circumference was measured at the narrowest point between hips and chest with the participant standing. Hip circumference was measured at the widest point below the waist. Additional outcome measures included fat-free mass and serum sex hormone concentrations (a priori, it was acknowledged that this was a pilot feasibility study and that the study did not have sufficient power to detect measurable changes in outcome variables).

Sex Hormone Measurements

Blood was collected (in the morning, after a 12-h fasting) from participants at baseline and at the 8-week follow-up visit, centrifuged, aliquotted as serum into 2-ml cryovials, and stored at −70°C for 2–3 months before being shipped to Endocrine Biosciences Laboratory for hormone assays. Each individual assay (for both baseline and follow-up) was performed in one batch.

Total E1 and Total E2. The estrogens were separated from binding globulins by organic extraction ([1H]E1 and [1H]E2 were added to monitor recovery) and Sephadex LH-20 chromatography using benzene methanol. Total E2 and total E1 were determined by RIA. Aliquots of purified samples were incubated 3 h at room temperature with an antiserum to an estrone-6-oxime BSA conjugate for the E1 RIA and an antiserum to 17β-estradiol-6-oxime for the E2 RIA. CVs were 10.8% for E2 and 9.2% for E1.

Free E2. Percentage free or non-protein-bound E2 was determined by equilibrium dialysis of serum samples at 37°C for 16 h against pH phosphosholamine buffer containing 50,000 dpm of purified [3H]-estradiol. Radioactivity was detected by liquid scintillation counting. The free E2 concentration was derived from the product of serum E2 by RIA and percentage free steroid obtained by dialysis. CVs ranged from 10.3 to 13.9%.

SHBG. The binding capacity of SHBG was directly measured in serum using a displacement technique. Sensitivity was 0.1 μg/dl. CVs ranged from 4.1 to 14.4%.

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The abbreviations used are: E1, estrone; E2, estradiol; CV, coefficient of variation; SHBG, sex hormone-binding globulin; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate.
E1 Sulfate. E1 sulfate was measured by RIA after purification of Sephadex LH-20 columns. Serum was extracted with hexane-ethyl acetate to remove unconjugated E1 and then diluted in buffer and incubated overnight with a sulfatase enzyme preparation to hydrolyze E1 sulfate. After column chromatography, the E1 content of the column was determined by RIA using a sensitive and specific antiserum developed against an estrone-6-oxime albumin conjugate. CVs ranged from 5.7 to 10.9%.

Free and Total Testosterone. Free testosterone was measured by equilibrium dialysis in a method similar to that used for free E2, with [3H]E2 replaced by [3H]testosterone. Testosterone was measured with RIA, after extraction and column chromatography, using a specific antibody to testosterone (testosterone-3-oxime BSA conjugate). CVs ranged from 9.3 to 12.0%.

Androstenedione. Androstenedione was extracted from serum one-3-oxime BSA conjugate). CVs ranged from 5.7 to 10.9%.

Free and Total Testosterone. Free testosterone was measured by equilibrium dialysis in a method similar to that used for free E2, with [3H]E2 replaced by [3H]testosterone. Testosterone was measured with RIA, after extraction and column chromatography, using a specific antibody to testosterone (testosterone-3-oxime BSA conjugate). CVs ranged from 5.7 to 10.9%.

Androstenedione. Androstenedione was extracted from serum with hexane-ethyl acetate and then purified by celite chromatography. The purified extract was assayed by a RIA using an antiserum raised to androstenedione-6-thioether-BSA. CVs ranged from 6.2 to 10.8%.

DHEA. Samples were extracted using hexane-ethyl acetate and purified on small aluminum oxide columns. DHEA recovery was monitored by the addition of [3H]DHEA. Aliquots of chromatographed samples were transferred to duplicate tubes and incubated with a rabbit antibody to DHEA-17-oxime-BSA for 3 h. Free and antibody-bound steroid were separated by the addition of ammonium sulfate. The free DHEA fraction was quantified by liquid scintillation counting. CVs ranged from 8.4 to 17.2%.

DHEA-S. DHEA-S was measured by a highly specific RIA. Twenty-μl aliquots of serum were diluted with acetate buffer and hydrolyzed overnight with a large excess of sulfatase enzyme. The DHEA content was determined by RIA using a highly specific antibody developed to a DHEA-7-oxime-antigen. CVs ranged from 5.2 to 8.3%.

Two blind duplicate specimens from each of four nonenrolled breast cancer patients were included with all laboratory assays, as a measure of assay reliability.

Results

Ninety-nine invitation letters with screening surveys were mailed, and 40 completed surveys were received. After review of the survey, 17 subjects were deemed preliminarily eligible and were invited to a screening clinic visit. The primary reasons for ineligibility, as determined by the screening questionnaire, were a body mass index of <25.0 and a sedentary lifestyle. Thirty patients came to a screening visit. After the screening visits, 11 remained interested and eligible and were scheduled for an exercise treadmill test with one of the study physicians (R. S. or A. M.). Of these, 10 were cleared for an exercise program and one had exercise-induced cardiac arrhythmia (referred to a cardiologist for evaluation). Those ten patients were enrolled in the program. Enrolled participants’ ages ranged from 40 to 74 years; eight patients were postmenopausal (≥1 year since their last menstrual period). Nine were white and 1 was Asian-American, and 7 of the 10 were currently employed outside the home. Most (8 of 10) had stage 1 breast cancer; the remaining 2 had stage 2 disease. Patients were 1–5 years post-active treatment for breast cancer, and 6 of 10 were currently using Tamoxifen (none were on chemotherapy at the time of recruitment or during the study). Only two patients had received chemotherapy for treatment: one had cytotoxin and Adriamycin; and the other had methotrexate, 5-fluorouracil, and cytoxan. Seven patients had a history of radiation therapy for breast cancer.

Adherence to the program was excellent. One patient completed some of the exercise sessions but, for personal reasons, declined future sessions, the follow-up visit, and data collection. Outcome data are presented for the nine patients with follow-up data. Patients had excellent performance in the exercise program. On average, the nine patients completed 22.1 of 24 possible monitored sessions (average, 2.8 per week). Patients began the endurance exercise program at ~65–70% of maximal heart rate and advanced, as they were able, to an average of 80%–85% (range, 70–90%) of maximal heart rate. Sessions lasted from an average of 10.2 min on the treadmill and 10.1 min on the bicycle at baseline to 30 min on the treadmill and 20 min on the bicycle by the end of the 8-week program. On average, the patients also completed two 30-min sessions at home, doing such activities as walking, bicycling, and gardening. Compliance with performance in the dietary aspects of the program was also excellent. As shown in Table 2, for the eight patients with baseline and follow-up dietary data, the average decline in daily percentage of calories from fat was 7.5. They also decreased total fat grams (P = 0.05) and increased daily intake of fruits and vitamin C (P > 0.1).

On average, patients experienced statistically significant decreases in body weight, percentage fat mass, and waist and hip circumference and increases in percentage lean mass between baseline and 8–10 weeks follow-up (Table 3). Small, statistically nonsignificant declines in systolic blood pressure, diastolic blood pressure, and resting pulse were noted.

Slight, statistically nonsignificant decrements were observed in serum concentrations of total and free E2, E1 sulfate, total testosterone, androstenedione, and DHEA-S (Table 4). SHBG decreased by 8% (P = 0.05). When the analysis was limited to the seven women who lost fat mass during the intervention period, the results were unchanged. Pearson correlation coefficients for blind duplicates for specific assays ranged from 0.98 for free testosterone to 1.00 for SHBG.

We examined change in all outcome variables separately for women using and not using Tamoxifen and found no difference between the two groups.

Discussion

The effect of excess weight and obesity on prognosis and survival from breast cancer has been assessed only through observational studies (3, 12–15). Weight, dietary intake, and physical activity are highly intercorrelated (16), however, leading to difficulties in assessing independent and interrelated effects of each component on breast cancer prognosis. Women who are physically active are more likely to have diets that are lower in fat and higher in fiber, fruits, and vegetables and to use...
vitamin supplements, as compared with sedentary individuals (17, 18). Furthermore, it has been proposed that obese individuals systematically underreport intake of total calories, fat, and carbohydrates (19); the same biased reporting may be true for physical activity.

Randomized controlled intervention trials can minimize these biases (20) because individuals inclined to follow a lifestyle cluster of behaviors would be assigned by chance to the lifestyle intervention or control group.

Exercise coupled with dietary caloric reduction is an effective method to reduce weight and maintain ideal body weight parameters (21, 22). The effect of low-fat and high-fruits and vegetables diets on breast cancer recurrence and survival is being tested in the Women’s Intervention Nutrition Study, a large-scale clinical trial of postmenopausal women with resected breast cancer (23). The association between exercise and prognosis and survival from breast cancer have been subject to only minimal observational study (24), and no exercise intervention studies have been done to assess prognostic effects.

The results of this study of exercise for breast cancer patients give useful preliminary information on the feasibility of recruiting, enrolling, and maintaining breast cancer patients in a combined diet-exercise intervention. Very high rates of interest were observed among invited women, as indicated by the 38% response to an initial mailing. This compares to responses of 0.5-7.0% observed in intervention studies in healthy persons or individuals with other diseases (25). Approximately 10% of approached patients were eventually enrolled into the intervention, which represents a high rate of recruitment into an intense and time-consuming behavioral intervention study (25).

The patients made substantial changes to their diet and exercise habits in a relatively short time, with resulting significant changes in body weight, fat and lean mass, and waist and hip circumferences. This highly motivated compliant group may not be representative of all women but may be characteristic of breast cancer patients who are willing to adopt lifestyle changes. Breast cancer patients have shown excellent adherence to dietary interventions in previous studies (26).

Minimal effects were observed on circulating concentrations of sex hormones. The statistically borderline decrease in SHBG may have been due to chance because many secondary variables were assessed. The lack of significant effect in hormones is not surprising, given the small sample size and short intervention time. The measurement of sex hormones in postmenopausal women is subject to large within-person variability, with resultant large sample sizes needed to detect a significant effect. To observe a 20% decrease in total E2 (with 80% power), for example, it would be necessary to enroll and maintain 78 women in an intervention arm. No previous study has reported an exercise effect on endogenous sex hormones in breast cancer patients. However, studies of dietary intervention suggest that an intensive low-fat dietary pattern may reduce circulating levels of estrogen and androgens (27).

The major limitation of this study is the small sample size. Because of the study design, we could not separate effects of exercise and diet on the study outcomes. Six of the 10 enrolling patients were using Tamoxifen at enrollment (and at follow-up), and results did not differ in those using or not using Tamoxifen. Yet, we were able to observe a number of significant results in the predicted direction, which is consistent with a true effect of the exercise-diet intervention on physiological parameters of interest.

The powerful effects of the antiestrogen Tamoxifen in certain breast cancer patients (28) and of oophorectomy in premenopausal breast cancer patients (29) on improving survival and reducing recurrence suggests that interventions to reduce circulating sex hormones may also benefit breast cancer patients. Behavioral exercise and diet interventions, if effective, would have the advantages of being self-directed, noninvasive, and beneficial to a variety of health outcomes and may be a useful adjunct to conventional therapy. The high level of interest by approached patients indicates that interventions of this type may be very attractive to breast cancer patients.

This pilot study suggests that overweight and obese breast cancer patients can achieve substantial improvements in fat and lean mass and anthropometric measures with an exercise-diet intervention. We are currently conducting a randomized clinical trial to test the effect of moderate-intensity aerobic exercise intervention on endogenous sex hormones in sedentary overweight women, ages 55-75 years (a group at elevated risk for breast cancer). Our experience lays the groundwork for development of large-scale clinical trials of exercise in breast cancer patients.

### References


### Table 3: Changes in physical measures after an 8-week exercise-diet program

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline</th>
<th>Change</th>
<th>( P^a )</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (pounds)</td>
<td>169.2</td>
<td>-2.6(3.0)</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>93.9</td>
<td>-3.4(3.5)</td>
<td>0.02</td>
<td>0.008</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>113.6</td>
<td>-4.6(4.4)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.828</td>
<td>+0.002(0.03)</td>
<td>0.82</td>
<td>0.77</td>
</tr>
<tr>
<td>% body fat</td>
<td>39.0</td>
<td>-2.3(2.9)</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>% lean mass</td>
<td>61.0</td>
<td>+2.3(2.9)</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133.1</td>
<td>-3.3(18.0)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>79.1</td>
<td>-0.67(9.8)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Resting pulse (bpm)</td>
<td>74.6</td>
<td>-4.0(10.3)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Values are mean (SD). The exercise component consisted of training and monitoring three times per week with an exercise physiologist (moderate intensity exercise for 30-45 min). The diet component consisted of low-fat foods (≤20% calories from fat) and high fruit and vegetable intake (eight or more per day).

\( ^b \) Two-tailed Wilcoxon rank-order test.

### Table 4: Changes in serum sex hormones after an 8-week exercise-diet program

<table>
<thead>
<tr>
<th>Hormone (mg/dl)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>( P^a )</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total E2</td>
<td>1.6(1.7)</td>
<td>1.4(1.4)</td>
<td>0.58</td>
<td>0.45</td>
</tr>
<tr>
<td>Free E2</td>
<td>0.56(0.68)</td>
<td>0.53(0.65)</td>
<td>0.90</td>
<td>0.72</td>
</tr>
<tr>
<td>Total TSH</td>
<td>2.8(0.87)</td>
<td>3.0(0.89)</td>
<td>0.34</td>
<td>0.29</td>
</tr>
<tr>
<td>TSH</td>
<td>67.0(35.1)</td>
<td>54.4(13.2)</td>
<td>0.28</td>
<td>0.81</td>
</tr>
<tr>
<td>Testosterone</td>
<td>16.9(7.3)</td>
<td>16.2(8.8)</td>
<td>0.56</td>
<td>0.21</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>1.3(0.41)</td>
<td>1.2(0.43)</td>
<td>0.36</td>
<td>0.40</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>55.1(18.7)</td>
<td>51.2(14.2)</td>
<td>0.49</td>
<td>0.48</td>
</tr>
<tr>
<td>SHBG</td>
<td>2.4(1.2)</td>
<td>2.2(1.1)</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>DHEA</td>
<td>201.3(92)</td>
<td>187.1(91)</td>
<td>0.61</td>
<td>0.51</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>45.7(28.7)</td>
<td>40.8(14.1)</td>
<td>0.45</td>
<td>0.64</td>
</tr>
</tbody>
</table>

\( ^a \) Values are mean (SD). The exercise component consisted of training and monitoring three times per week with an exercise physiologist (moderate intensity exercise for 30-40 min). The diet component consisted of low-fat foods (≤20% calories from fat) and high fruit and vegetable intake.

\( ^b \) Two-tailed Wilcoxon rank-order test.


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