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Breast cancer survivors who use estrogenic botanical supplements have lower serum estrogen levels than non users

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Abstract

Objective—To measure the association between use of estrogenic botanical supplements and serum sex hormones in postmenopausal breast cancer survivors.

Methods—502 postmenopausal women were queried 2–3 years after breast cancer diagnosis about their use of botanical supplements, and supplements were categorized according to their estrogenic properties. Concurrently, a fasting blood sample was obtained for assay of estrone, estradiol, free estradiol, testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS) and sex hormone-binding globulin. Adjusted means of the serum hormones were calculated by use of estrogenic supplements.

Results—Women reporting use of any estrogenic botanical supplement had significantly lower levels of estrone (20.8 v 23.6 pg/mL), estradiol (12.8 v 14.7 pg/mL), free estradiol (0.29 v 0.35 pg/mL), and DHEAS (47.7 v 56.2 ug/dL) compared to women reporting no use.

Conclusion—Data from this cross-sectional study suggest the use of estrogenic botanical supplements may be associated with sex hormone concentrations in breast cancer survivors. Considering the high use of these supplements among breast cancer patients, further research is needed to clarify the relative estrogenicity/anti-estrogenicity of these compounds and their relation with prognosis.

INTRODUCTION

Botanical, or herbal, supplements are a major category of dietary supplements. In contrast to standard vitamin and mineral preparations that include both essential and non-essential nutrients, botanical supplements are plant parts such as bark, leaves, stems, roots, flowers, fruits, seeds and berries or their extracts that are sold as pills, capsules or extracts [1]. The bioactive compounds in these specialty supplements have pharmacological properties and are being increasingly used by Americans to prevent or treat disease [2].

Breast cancer patients report a high prevalence of use of these supplements [3, 4]. Given that very little is known about the efficacy of botanical supplements in relation to breast cancer treatment and prognosis, understanding the biological actions of these supplements is an important area of research. Several common botanical supplements have estrogenic properties, meaning that they may affect serum hormone levels; however conflicting evidence exists about the magnitude and direction of this influence [5-7]. The estrogenic nature of these botanicals may increase serum levels of estrogen or, conversely, may reduce circulating estrogen levels by inhibiting enzymes involved in estrogen biosynthesis and metabolism [8]. Because increased circulating estrogen levels are associated with poor breast cancer prognosis in some studies [9, 10] it is important to know how estrogenic botanical supplements (EBS) may influence serum hormone levels.

The purpose of this study was to compare serum sex hormone levels of postmenopausal breast cancer survivors who report use of EBS to those not using these supplements.

METHODS

Study Population

The Health, Eating, Activity and Lifestyle (HEAL) Study is a multi-center, multiethnic prospective cohort study of 1183 breast cancer survivors who are being followed to determine whether weight, physical activity, diet, sex hormones, and other exposures affect breast cancer prognosis. Women were recruited into the HEAL study through Surveillance, Epidemiology, and End Results (SEER) registries in New Mexico, Los Angeles county (CA), and western Washington. Details of the study aims, design, and recruitment procedures have been published previously [11-13]. All three study sites included women diagnosed with *in situ* to Stage IIIA breast cancer but the age ranges and dates of diagnosis differed by site: New Mexico included 615 women, ages 18 years or older, who were diagnosed between July 1996 and March 1999 and lived in Bernalillo, Santa Fe, Sandoval, Valencia, or Taos counties; western Washington included 202 women, ages 40 to 64 years, diagnosed between September 1997 and September 1998, and living in King, Pierce, or Snohomish counties; and in Los Angeles county the cohort consisted of 366 Black women, ages 35 to 64 years, who were diagnosed between May, 1995 and May, 1998.

Baseline data were collected on participants via in-person interviews (for New Mexico and Los Angeles) and self-administered questionnaires (Washington) conducted within 1 year of diagnosis (on average 7.5 months post diagnosis). Follow-up data were collected 24 months after the baseline visit. Data on age, education, marital status, self-reported race/ethnicity, and height were collected at the baseline interview. All other data presented here were obtained at the 24-month follow-up interview.

Written informed consent was obtained from each study participant. The study was performed with the approval of the Institutional Review Boards of participating centers (University of New Mexico, Fred Hutchinson Cancer Research Center, and University of Southern California), in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Hormone/Peptide Assays

A 30-ml fasting blood sample was collected at the 24-month follow-up interview. Blood was processed within 3 hours of collection; serum was stored in 1.8-ml aliquot tubes at -70° to -80° C until analysis. We measured estrone, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEAS), and sex hormone-binding globulin (SHBG). Free estradiol and free

testosterone were calculated from SHBG and total estradiol and testosterone, respectively [14]. We had insufficient blood to measure estradiol/free estradiol in nine participants.

For California participants, all assays except testosterone were performed at the Reproductive and Endocrine Research Laboratory at the University of Southern California. Testosterone assays were performed at the University of New Mexico. For Washington and New Mexico participants, estrone and estradiol were assayed at Quest Diagnostics (San Juan Capistrano, CA) and the remaining assays were conducted at the University of New Mexico. All samples were randomly assigned to assay batches and were randomly ordered within each batch. Biorad standards were also included to monitor assay performance within and between batches at both low and high concentrations. Laboratory personnel performing the assays were blinded to patient identity and personal characteristics.

Radio-immunoassay (RIA) was utilized to measure all serum analytes [15]. Serum extraction and chromatographic purification were performed before RIA for estrone and estradiol. The sensitivity for the estrone assay was less than 5-10pg/mL and for estradiol was less than 2 pg/mL. Serum testosterone was determined using an RIA kit (Diagnostic Products Corp, Los Angeles, CA) with a sensitivity of 40pg/mL. SHBG levels were determined using the Wein Laboratories (Succasunna, NJ) RIA kit with a sensitivity of 6nmol/L.

Intra-assay variability was assessed in a reduced randomly selected sample for all hormones [16]. For the California samples, the intra-assay CVs for estrone, estradiol, and SHBG were 26.2%, 15.4%, and 9.3% respectively. For New Mexico and western Washington, the intra-assay and total CVs were 3.8% and 5.9% respectively for SHBG, 12.0% and 14.4% for testosterone, 29.1% and 13.3% for estrone, and 28.8% and 13.3% for estradiol.

Supplement Use/Dietary Data

Information on use of EBS came from the following 24-month interview question: "Since your cancer diagnosis have you taken any herbal or alternative remedies?" Participants who answered yes to this question were given a list of 34 commonly used botanical or herbal supplements and asked to indicate which, if any, of these supplements they used. In addition, an open-ended "Other" category was provided for recording of supplements taken that were not on the closed-ended list (a total of 94 distinct supplements were recorded via this open-ended question). We reviewed all botanical-type supplements for evidence of estrogenicity as follows: We first reviewed the Physician's Desk Reference for Herbal Medicines (PDR-H) [17]. If the PDR-H reported the supplement had estrogenic properties, we considered the supplement to be estrogenic; if the PDR-H did not mention estrogenic properties of a specific supplement we considered the supplement to be non-estrogenic. For some supplements, there was conflicting evidence of estrogenicity; however, we defined a supplement as estrogenic if at least one study (*in vitro*, animal or human) was cited that showed estrogenic properties even if other cited studies found negative results. If a supplement could not be found in the PDR, we next consulted Herb-Drug Interactions in Oncology (HDIO) [18]. If the supplement could not be found there, we consulted the Natural Medicines Comprehensive Database (NMCD) [19]. A majority of supplements (90 of 128 or 70%) were found in the PDR-H, six supplements (5%) were found in HDIO and the remaining 32 supplements (25%) were found in NMCD. More specific information on the dosage of supplements was not collected.

Data on dietary intake were collected using a self-administered food frequency questionnaire designed for the Women's Health Initiative [20]. This food frequency questionnaire obtains usual frequency of consumption and portion size for 122 food items or food groups. The nutrient database used to convert food information into nutrients is derived from the University of Minnesota's Nutrition Coordinating Center's Nutrition Data Systems for

Research (NDS-R, version 2005). Of interest for these analyses are estimates of intake of the phytoestrogens genistein and daidzein since these soy isoflavones have the ability to bind to both estrogen receptor α and β [21].

Menopausal status

At the time of the 24-month follow-up interview, women who were 55 years of age or older and who had not menstruated in the last year, or who did not know the date of their last menstruation but reported having had a hysterectomy, were categorized as postmenopausal. Women less than age 55 were also categorized as postmenopausal if they had not menstruated in the year prior to their interview. Women categorized as pre-menopausal or whose menopausal status was unknown were excluded from these analyses since we had no data on recent menstrual cycle (and thus hormone levels) in relation to blood draw.

Body Mass Index/Physical Activity

Trained staff measured weight and height using a standardized protocol at the clinic or home visit. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. A total of 141 participants were missing values for measured height; for these women we used self-reported height to calculate BMI. We have previously compared results of BMI calculated from a subset of women who have both measured and self-reported height, and have found high concordance: only 3 of 569 women had a change in BMI classification from overweight to healthy weight when using self-reported height rather than measured height [22]. We classified BMI according to the World Health Organization categories [23]: healthy weight, overweight and obese (<25 , 25 - 29.9 , 30 kg/m², respectively).

We collected information on physical activity using a questionnaire administered in-person at the 24-month follow-up visit. The questionnaire was based on the Modifiable Activity Questionnaire developed by Kriska and colleagues [24]. The type, duration, and frequency of activities performed in the past year were assessed and, for each activity, frequency was multiplied by duration in order to quantify activity level. For the present analysis, physical activity was defined as the number of metabolic equivalent (MET) hours per week in sports and recreational activities. A MET is defined as the ratio of the associated metabolic rate for a specific activity to the resting metabolic rate (e.g., a 2-MET activity requires two times the resting metabolic energy expenditure of sitting quietly) [25].

Data Analysis

The sample size for this analysis began with 604 postmenopausal women who had serum and dietary data available from the 24-month interview. We excluded 48 women who reported taking hormone therapy (other than tamoxifen). At the time of the study, no participants were taking aromatase inhibitors. Another 40 women were excluded due to implausible values for dietary data (energy intake < 600 kcal/day or > 4000 kcal/day). We also excluded 14 participants whose race/ethnicity was classified as 'Other' leaving a final sample of 502. We excluded 8 hormone/peptide values which were extremely high and deemed to be implausible outliers: estrone > 200 pg/mL; estradiol > 160 pg/mL; testosterone > 1330 pg/mL; and DHEAS > 350 ug/dL. For women with hormone values below the detectable limits, we assigned a value halfway between zero and the lower limit of detection such that 16 women were assigned a testosterone value of 13 pg/mL; 32 were assigned an estrone value of 5 pg/mL; and 2 women were assigned an estradiol value of 1 pg/mL.

The distribution of the serum hormone concentrations and of dietary genistein and daidzein were log-normal and these variables were log-transformed; geometric means are presented for these measures. We used linear regression analysis to estimate the association of

estrogenic supplement use with hormone concentrations. We calculated least squares means for hormone values adjusted for age (continuous), race/ethnicity (Hispanic, Black, non-Hispanic white), education (high school or less, some college, college graduate or higher), activity level (tertiles), stage of disease at diagnosis (*in Situ*, local, regional) and dietary intake of genistein (continuous, log-transformed). The data were analyzed using SAS software (version 9.1.3, SAS Institute, Cary NC).

RESULTS

Of the 128 botanical/herbal supplements used by HEAL participants, 19 had estrogenic properties based on the definition described in the methods sections (see Figure 1). Figure 1 lists these 19 supplements along with the number of participants reporting their use. The most commonly used estrogenic supplement was soy, with 73 participants reporting use, followed by ginseng (55 users) and flax (48 users). Of 502 participants, 174 (34.7%) reported taking at least one estrogenic supplement. Users took an average of 2.1 estrogenic supplements, range 1 to 8 (data not shown).

We found statistically significant differences ($p < 0.05$) between estrogenic supplement users and non-users for six of the ten variables we considered as possible confounders of the association between supplement use and serum hormones (Table 1). EBS users were significantly younger than non-users; they also reported more years of education, higher physical activity levels and higher dietary intake of genistein and daidzein than non users. We observed two associations that differed by estrogenic supplement use where the p value was between 0.05 and 0.10: users were more likely to be Hispanic or African-American than non-Hispanic white and were also more likely to have regional (as opposed to *in Situ* or localized) disease.

We know from previous work [16] that the first seven variables listed on Table 1 are significantly associated with at least some of the serum hormone measures, so we included in our final model those that were associated with EBS use at a significance level of 0.10: race/ethnicity, age, education and activity level. Since we had not previously assessed the association between serum hormone levels and either stage of disease at diagnosis or dietary phytoestrogen intake, we next evaluated those relationships. We found stage of disease at diagnosis was significantly associated with serum estradiol (inversely) and DHEAS (directly) (data not shown) and therefore included stage of disease in our final model. The two dietary phytoestrogens measures (genistein and daidzein) were highly correlated with each other ($r = 0.93$, $p < 0.001$), and they were also significantly but weakly associated with estradiol and free estradiol ($r = -0.11$, $p = 0.01$). Since the two phytoestrogens come almost exclusively from soy [26] and were highly correlated with each other we chose to use only one of them (genistein) in our model.

We were concerned that BMI might influence the association between EBS and sex hormones even though it was not associated with EBS use. We compared the results of models that included BMI to models without this variable and found the results to be very similar, so we report here results from models without BMI.

Table 2 shows least squares means of the seven serum hormone measures by use of EBS. These adjusted means were all lower in estrogenic supplement users than in non-users, except for SHBG which was higher in users than non-users. The differences were statistically significant ($p < 0.05$) for estrone, estradiol, free estradiol, and DHEAS. We considered examining the effect of individual supplement use on hormone levels for each of the three most commonly reported supplements (soy, ginseng and flax) but numbers were too small to draw meaningful conclusions. For example, although 73 participants reported

using soy supplements, most of them were also taking at least one other estrogenic supplement – only 26 were taking soy alone. Numbers of participants taking only ginseng or flax were even smaller, 16 and 14 respectively.

DISCUSSION

The data from our cross-sectional study of postmenopausal breast cancer survivors showed a statistically significant association between the use of EBS and lower levels of all three serum estrogen measures (estrone, estradiol and free estradiol) as well as DHEAS. Additionally, androgen levels were lower and SHBG levels higher in users than in non-users although these differences were not statistically significant.

Estrogenic botanical supplements are commonly used to alleviate menopausal symptoms, even though their effectiveness in treating symptoms such as hot flashes and other clinical indications is unclear [27, 28]. Additionally, some botanical supplements have estrogenic properties of which most consumers are unaware, for example astragalus is commonly used for strength, stamina, and immuno-stimulation [18] yet the PDR-H [17] reports it contains isoflavones. One concern is that EBS, even if they are only weakly estrogenic, may increase estrogen levels and thereby contribute to poorer prognosis in breast cancer survivors [29]; but research on the association between EBS and serum hormone levels is lacking.

There is however a body of research looking at the effect of dietary phytoestrogens on serum hormones, and, although one study reports a direct association between phytoestrogen intake and serum hormone values (increased consumption of yam resulted in significant increases in serum estrone levels in postmenopausal women in Taiwan [6]), most research reports no association [5, 30-32] or a negative association [7, 33-36]. Many studies reporting no association are controlled feeding studies of postmenopausal women. The results are similar to those reported by Wu et al [5] who found women consuming high levels of soy had serum estradiol and SHBG levels that were no different from controls. Of the studies reporting an inverse association between phytoestrogens and serum hormones, a few are controlled feeding studies [33, 34] but most are cross-sectional dietary intake studies [7, 35, 36]. The controlled feeding studies report small but significant decreases in estrone with increased soy intake [33] and a significant increase in SHBG with increased soy milk consumption [34], both in postmenopausal women. This last association is considered an inverse one because although there is a direct association between soy and SHBG, SHBG reduces available estrogen. Cross-sectional studies have found significant inverse associations between plasma estrone levels and both soy intake [35] and consumption of green tea [36] (green tea contains phytoestrogens in the form of lignan precursors [19]) in postmenopausal Chinese women; and between estradiol levels and dietary phytoestrogen intake in postmenopausal European women [7]. The biologic theory behind this inverse association is that phytoestrogens, because they are weak estrogens, may stimulate the synthesis and release of SHBG, thus reducing the amount of available estradiol [37]; and they may also inhibit enzymes involved in estrogen synthesis and metabolism [8].

It is unclear whether results from studies of dietary estrogen intake can be applied to EBS. Studies of EBS, for the most part, are limited to evaluating their effect on menopausal symptoms. Several review articles on this topic conclude that most of the commonly used botanicals have minimal to no effect on menopausal symptoms [27, 28, 38, 39]. We are aware of one study that has evaluated the effect of EBS on breast cancer development. Rebbeck [40] et al conducted a case-control study that asked participants about their use of hormonal supplements. They found the risk of breast cancer was significantly lower among women who reported use of any estrogenic supplements compared to women reporting no use. Additionally, the use of black cohosh had a significant protective effect for breast

cancer. The authors hypothesize this association may be due to the hormonal (antiestrogenic) effects of black cohosh or to its antiproliferative properties.

The conflicting results described above may be due to the difficulty in defining a supplement as estrogenic. Black cohosh, for example, can be classified as estrogenic or non-estrogenic, depending on which study is cited [41-43]. A number of different methods are used to define estrogenicity. *In vitro* methods include measuring the influence of compounds on cell proliferation [44] or on their affinity for hormonal receptors [45]; *in vivo* methods vary from controlled feeding studies [6] to studies of dietary recall [35]. Further, some studies find estrogenic effects differ by phytoestrogen dose [41] and since EBS are not regulated in this country, the estrogenic content claimed by the manufacturers often differs greatly from that actually measured in the supplement [46]. The metabolism of phytoestrogens also appears to vary greatly between individuals [47], and even crop and harvest conditions can affect phytoestrogen levels in foods and supplements [48]. Given the difficulty in defining estrogenicity, it is perhaps not surprising conclusions are mixed.

There are limitations to this study. First, it is important to stress that our data are cross-sectional. It is possible that women who took estrogenic supplements did so because they had a lower level of some endogenous sex steroid hormones and consequently had more estrogen withdrawal symptoms, or because of social or cultural influences on the tendency to take nutritional supplements. We cannot infer cause and effect from these data, and we cannot comment on the potential influence of EBS on prognosis. Another potential weakness is in our definition of EBS. We combined into one variable all supplements deemed estrogenic when in fact some of the supplements may act in opposing directions. Lastly, we have no information on amount taken or the frequency or duration of supplement use, although due to lack of regulation of content of EBS, information on type and frequency may be of little value. Definitive information on the estrogenic effects of individual supplements would require rigorous testing in randomized controlled trials.

In conclusion, the data presented in this study suggest the use of estrogenic botanical supplements may be associated with serum sex hormone concentrations in breast cancer survivors. Considering the high use of these supplements among breast cancer patients and the inconsistent results reported in studies of EBS, further research is needed to clarify the relative estrogenicity/antiestrogenicity of these compounds and their relation with prognosis.

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Figure 1.

Estrogenic botanical supplements used by breast cancer survivors in the HEAL cohort.

* Combination supplement contained soy, black cohosh, licorice, and dong quai

Abbreviations: HEAL – Health, Eating, Activity, and Lifestyle; DHEA =

dehydroepiandrosterone

Table 1

Demographic and lifestyle characteristics of HEAL study participants. All measurements are from 24-month follow-up except stage of disease (at diagnosis). N = 502.

Total N (%)	Use estrogenic botanical supplements?			
	No 328 (65.3%)	N	Yes 174 (34.7%)	p-value
Race/Ethnicity				
Non-Hispanic White	222	222	101	58.0
Hispanic	32	32	22	12.6
African-American	74	74	51	29.3
				0.10
Age Group (years)				
< 60	142	142	100	57.5
60 – 69	110	110	63	36.2
70+	76	76	11	6.3
				<0.001
Highest Level of Education				
High School	107	107	36	20.7
Some college/technical	104	104	77	44.3
College graduate or higher	116	116	61	35.1
				0.005
Body Mass Index				
< 25	114	114	66	38.4
25 - 29.9	103	103	53	30.8
30+	102	102	53	30.8
				0.85
Activity level (METs from sports/recreation)				
< 1.8	120	120	35	20.1
1.8 - 11.5	109	109	64	36.8
> 11.5 hrs	99	99	75	43.1
				<0.001
Use tamoxifen?				
No	171	171	83	47.7

Use estrogenic botanical supplements?					
Total N (%)	No 328 (65.3%)		Yes 174 (34.7%)		p-value
Race/Ethnicity	N	%	N	%	
Yes	157	47.9	91	52.3	0.34
Number of ovaries					
0	67	20.4	38	21.8	
1	14	4.3	8	4.6	
2	247	75.3	128	73.6	0.91
Stage of disease at diagnosis					
<i>in Situ</i>	71	21.6	28	16.1	
Localized	187	57.0	93	53.4	
Regional	70	21.3	53	30.5	0.05
Dietary phytoestrogen intake:					
Geometric Mean					
Genistein (mg)	0.20		0.33		
Daidzein (mg)	0.24		0.35		0.001
					0.002

Abbreviations: HEAL – Health, Eating, Activity and Lifestyle; MET – Metabolic Equivalent

Table 2

Least squares geometric mean serum hormone measures (95% confidence limits) by use of estrogenic botanical supplements in the HEAL study.

Serum Measure:	Use estrogenic botanical supplements?		p-value
	No (N=328)	Yes (N=174)	
Estrone, pg/mL	23.6 (22.2,25.0)	20.8 (19.0,22.5)	0.02
Estradiol, pg/mL	14.7 (13.6,15.8)	12.8 (11.5,14.2)	0.04
Free Estradiol, pg/mL	0.35 (0.32,0.38)	0.29 (0.25,0.32)	0.01
Testosterone, pg/mL	183.3 (169.0,198.7)	167.9 (150.0,187.8)	0.23
Free Testosterone, pg/mL	3.3 (2.9,3.5)	2.9 (2.5,3.2)	0.10
DHEAS, ug/dL	56.2 (52.0,60.6)	47.7 (42.8,53.1)	0.02
SHBG, nmol/L	49.1 (46.2,52.0)	52.2 (48.0,56.7)	0.25

Models are adjusted for age (continuous), race/ethnicity, activity level (tertiles), education, stage of disease at diagnosis and dietary genistein (continuous, log transformed)

Abbreviations: HEAL – Health, Eating, Activity and Lifestyle; DHEAS – dehydroepiandrosterone sulfate; SHBG – sex hormone-binding globulin