Use of complementary and alternative medicine and breast cancer survival in the Health, Eating Activity and Lifestyle Study

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Abstract

Purpose. Use of complementary and alternative medicine (CAM) is common among breast cancer patients, but less is known about whether CAM influences breast cancer survival.

Methods. Health Eating, Activity and Lifestyle (HEAL) Study participants (n=707) were diagnosed with stage I-IIIA breast cancer. Participants completed a 30-month post-diagnosis interview including questions on CAM use (natural products such as dietary and botanical supplements, alternative health practices and alternative medical systems), weight, physical activity and co-morbidities. Outcomes were breast cancer-specific and total mortality, which were ascertained from the Surveillance Epidemiology and End Results registries in Western Washington, Los Angeles County and New Mexico. Cox proportional hazards regression models were fit to data to estimate hazard ratios (HR) and 95% confidence intervals (CI) for mortality. Models were adjusted for potential confounding by sociodemographic, health and cancer-related factors.

Results. Among 707 participants, 70 breast cancer-specific deaths and 149 total deaths were reported. 60.2% of participants reported CAM use post-diagnosis. The most common CAM was natural products (51%) including plant-based estrogenic supplements (42%). Manipulative and body-based practices and alternative medical systems were used by 27% and 13% of participants, respectively. No associations were observed between CAM use and breast cancer-specific (HR=1.04, 95% CI 0.61-1.76) or total mortality (HR=0.91, 95% CI 0.63-1.29).

Conclusion. CAM use was not associated with breast cancer-specific mortality or total mortality. Randomized controlled trials may be needed to definitively test whether there is harm or benefit from the types of CAM assessed in HEAL in relation to mortality outcomes in breast cancer survivors.

Introduction

Over 230,000 women are diagnosed with breast cancer annually in the United States [1]. Many of these patients are eager to make lifestyle changes to improve their overall health and to increase the probability of long-term survival [2-5]. One common health/lifestyle behavior adopted by breast cancer patients is the use of complementary and alternative medicine (CAM) both during and after cancer treatment [6]. At the time of our study, the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCAAM) (now called the National Center for Complementary and Integrative Health) (http://nccih.nih.gov) defined CAM as those practices or products that are typically "outside" of conventional or mainstream medical practice. The NIH definition included several broad categories of CAM such as natural products (dietary supplements, herbals and other botanical products), mind-body medicine (e.g., meditation, hypnosis, guided imagery), movement therapies, manipulative/body therapies (e.g., spinal manipulations, massage therapies, yoga) and energy practices (e.g., qi gong). Previous studies have reported that 50-75% of breast cancer patients use at least one form of CAM after diagnosis [7-10], with many patients attributing their overall good health, improved symptom management and well-being to use of CAM [11,12].

Several reports have described patterns of CAM use among breast cancer patients, particularly use of natural products and specific dietary supplements [6,9,12-14]. However, few data exist on associations of CAM treatments with breast cancer survival. This is an important gap in the literature given the high prevalence of use and the strong belief by many patients that CAM improves their health [9,12]. However, it is

unknown whether CAM treatments have either positive or negative influences on prognosis, either through direct effects on the tumor biology, or indirect effects on patient response to treatment. For example, some botanical supplements have estrogenic effects [15,16], which may either raise or lower serum hormone concentrations, potentially affecting the growth of hormone sensitive estrogen receptor positive tumors. The primary objective of this study was to investigate associations of CAM use with breast cancer-specific mortality and total mortality in a cohort of breast cancer survivors.

Materials and Methods

The Health, Eating, Activity and Lifestyle (HEAL) study is a multicenter, multiethnic prospective cohort study of 1,183 breast cancer patients designed to determine whether weight, physical activity, diet, sex hormones, and other exposures influence breast cancer prognosis and survival. Details of the study design and procedures have been previously published [17]. Briefly, we utilized the National Cancer Institute's Surveillance, Epidemiology, End Results (SEER) registries in New Mexico, Los Angeles County (CA), and Western Washington State to ascertain and recruit English speaking women diagnosed with *in situ* to Stage IIIA breast cancer. In New Mexico, we recruited 615 women aged 18 years or older diagnosed between July 1996 and March 1999 and living in Bernalillo, Santa Fe, Sandoval, Valencia, or Taos Counties. In Western Washington State, we recruited 202 women between the ages of 40 and 64 years diagnosed between September 1997 and September 1998 and living in King, Pierce, or Snohomish Counties. In Los Angeles County, we recruited 366 African-American women who had previously participated in one of two cancer case-control

studies. These women were diagnosed with breast cancer between May 1995 and May 1998 and were aged 35 to 64 years at diagnosis. Written informed consent was obtained from all participants at each study site. All HEAL procedures were approved by the institutional review boards of the participating centers (Fred Hutchinson Cancer Research Center, University of Southern California, University of New Mexico, City of Hope and University of Louisville) in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services [17].

HEAL participants completed extensive questionnaires and health assessments within their first year after diagnosis (on average 7.5 months post-diagnosis). Information on health habits, medical history, history of breast disease, and reproductive history were collected via in-person interviews and self-administered questionnaires. Approximately 24 months later (within the third year after diagnosis and on average 31.5 months post-diagnosis; hereafter called the 30-month post-diagnosis assessment), clinic or in-home visits were conducted to measure height and weight and to collect self-reported data on physical activity, diet, dietary supplements (including herbal and botanical products), complementary and alternative medicine practices and use of alternative providers, and alcohol and tobacco use. Of the 1,183 eligible women, 239 (20.2%) women did not complete the 30-month assessment due to death (n=44), illness (n=2), refusal (n=105), relocation (n=16), or loss to follow-up (n=72). Of the remaining 944 participants, we excluded women with: (1) an initial breast cancer diagnosis of *in situ* disease (n=206) given their low risk of mortality [18]; (2) missing data on use of any complementary or alternative medicine (n=18); (3) an unknown date for subsequent breast cancer outcome or interview (n=5); or (4) a recurrence, second primary breast

cancer or death prior to the 30-month assessment (n=27). The final sample included 706 women who had an initial diagnosis of stage I to IIIA breast cancer and who completed the 30-month post-diagnosis assessment.

Exposure Assessment for Complementary and Alternative Medicine (CAM)

Four categories of CAM were defined as follows: (1) *mind and body medicine* (e.g., meditation, yoga, acupuncture, guided imagery, qi gong); (2) *manipulative and body-based practices* (e.g., spinal manipulation, massage therapy, chiropractic medicine); (3) *alternative systems* (e.g., traditional Chinese medicine, Native American healing systems, Reiki, homeopathic medicine, Ayurveda) and (4) *natural products* (e.g., herbal supplements, botanical supplements, single supplements and combinations of vitamins or minerals). Data for the first three categories (mind-body medicine, manipulative and body-based practices and alternative systems) were obtained from the following question on the 30-month assessment: “Have you sought out any type of complementary care?” If yes, 12 specific binary (yes/no) options were provided: hydrotherapy, herbal therapy, naturopathy, Chinese medicine, shiatsu, Ayurveda, homeopathy, acupuncture, acupressure, spiritual healing (new age) and prayer. In addition to this closed-ended response list, participants were permitted to list up to three additional types of complementary care or health practices (excluding natural products) as open-ended text fields. We recoded these responses into the three categories (mind-body; manipulative and body-based; and alternative systems). For example, meditation was re-coded in the “mind-body” category.

To create the CAM category for natural product use, we used the responses from a question that asked participants whether they had used dietary supplements, herbal

and alternative remedies since the diagnosis. For dietary supplements, the following 12 response categories were provided as yes/no responses: multivitamins, vitamin A, vitamin C, vitamin D, vitamin E, beta-carotene, melatonin, co-enzyme Q, alpha-lipoic acid, calcium, DHEA and fiber. For herbal or alternative remedies, 34 specific response options (yes/no) were provided (e.g., bee pollen, black cohosh, blue cohosh, ginseng, shark cartilage). Open-ended text fields for other herbal and alternative remedies were permitted. All text fields (n=454 vitamins and minerals and n= 80 herbals and botanicals) were recoded into the variable "natural products." Text fields where the response was unintelligible, not an alternative medicine (e.g., "Ensure®", culinary spices such as cayenne pepper) or without sufficiently detailed information ("an alternative therapy") were not counted as natural products and not included in these analyses. Although a large number of natural products were reported by HEAL participants, there were too few reports of any one particular type of product (e.g., cat's claw, blue cohosh) to warrant the creation of single product variables, with the exception of botanical supplements with estrogenic properties, a subclass of natural products, which we had previously defined [19,20]. Estrogenic supplements were those with any reported estrogenic activity as documented in the Physician's Desk Reference for Herbal Medicines (PDR-H) [21], Herb-Drug Interactions in Oncology [22] and the Natural Medicines Comprehensive Database (NMCD) [23].

Outcomes Ascertainment

To obtain the breast-cancer specific mortality and total mortality outcomes, women were followed for vital status from the 30-month post-diagnosis assessment until December 31, 2010 using data collected by the SEER registries and supplemented by abstracted medical records. Causes of death were classified using the *International*

Classification of Diseases, 10th Revision (ICD-10) codes. The time frame for overall mortality and breast-cancer specific mortality was initiated on the date of the 30-month post-diagnosis assessment and ended on the date of death. All non-deceased participants were censored on December 31, 2010.

Statistical Analyses

Descriptive statistics were used to characterize the study sample. Cox proportional hazards models were fit to the data using age as the underlying time metric. We estimated hazard ratios (HR) and their 95% confidence intervals (CI) for death from any cause and death from breast cancer that was associated with: (1) any CAM use combining all four CAM categories; (e.g., mind and body medicine, manipulative and body-based practices, alternative systems and natural products); (2) use of any natural products since it was the most common type of CAM; and (3) use of botanical-based estrogenic supplements since these products composed 80% of the natural product category and their use may have biological relevance for survival after a diagnosis of an estrogen-receptive positive tumor. There were too few instances of alternative systems or providers to assess as single exposure categories. Unadjusted models were analyzed along with models that included the following *a priori* covariates associated with breast cancer outcomes in HEAL [24-26] : breast cancer treatment (surgery, chemotherapy, radiation), stage at diagnosis (localized, regional, distant), reported use of tamoxifen (yes, no) at the 30-month interview, the Charlson co-morbidity score [27], body mass index (BMI) at 30-months post-diagnosis [computed as weight(kg)/height(m)^2 and categorized into underweight (BMI<18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9 and obese BMI $\geq$ 30.0)], 30-month assessment

of physical activity (mean MET-hours per week of sport and recreational exercise activity) and race/ethnicity. Since age was the time metric in the Cox models, it was not included as an additional covariate. All statistical tests were two sided and the significance level was set at $\alpha=0.05$. The Statistical Analysis Software (SAS version 9.2, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

The average age of HEAL Study participants at the time of the 30-month post-diagnosis assessment was 57.4 years (Table 1). Slightly over one third (34.7%) of women were normal weight (BMI 18.5-24.9 kg/m^2) and 28.0% and 28.7% were overweight (BMI=25.0-29.9 kg/m^2) or obese (BMI $\geq$ 30.0 kg/m^2), respectively. Most participants (71.0%) had been diagnosed with localized disease (Stage I-II) and slightly over half (51.3%) reported tamoxifen use (aromatase inhibitors were not in clinical use at study onset). Approximately 60% of HEAL participants reported at least one type of CAM use since their breast cancer diagnosis (Table 2). The most commonly reported type of CAM, natural products, was used by 51% of participants who were CAM users. Manipulative and body-based practices, such as massage therapy and hydrotherapy were used by 27% of participants while mind-body therapies were used by only 4% of participants. Alternative medical systems such as naturopathy, Chinese medicine, Ayurveda and homeopathy were used by 13% of participants.

No associations were observed between CAM use or subtypes of CAM use and either breast cancer-specific mortality or total mortality (Table 3). The multivariate adjusted hazard ratios for any CAM use versus no use were 1.04 (95% CI 0.61-1.76) and 0.91 (95% CI 0.63-1.29) for breast cancer-specific and total mortality, respectively.

We also found no association of natural product use (vs. no natural product use) with either breast cancer-specific mortality (HR=1.15, 95% CI 0.69-1.94) or total mortality (HR=0.95 95% CI 0.67-1.35) (Table 4). Use of botanically-based estrogenic supplements vs. no use of these supplements was not associated with either breast cancer-specific mortality (HR =0.96, 95% CI 0.58-1.59) or total mortality (HR=0.84, 95% CI 0.57-1.23). In additional analyses, stratified by tumor hormone receptor status (ER+/ER-), results did not differ and were uniformly null (data not shown).

DISCUSSION

In this cohort of breast cancer survivors, the use of complementary and alternative medicine was common, particularly the use of natural products. This finding of common usage is consistent with previous reports and confirms the widespread practice of CAM use by breast cancer patients [28-30]. Our principal finding was that overall CAM, natural products and botanically-based estrogenic supplements were not associated with breast cancer-specific or total mortality. Although used by many patients, CAM use remains controversial in the oncology community [31]. One end of the clinical advice spectrum supports a view that patients should not use any CAM, particularly natural products. This view is based on a concern that such products will either interfere with medical treatments or fuel residual hormone-sensitive tumors in the case of products with weak estrogenicity [32]. Other clinical views support the use of many CAM modalities by their patients [10]. However, no consensus statement has been formulated to date, due in part to a weak evidence base. A 2014 systematic review was conducted to inform clinical practice guidelines for use of integrative therapies for breast cancer patients [33]. An expert panel examined the strength of the

evidence base of clinical trials testing various modalities (e.g., natural products, mind body practices) and their efficacy for treatment and management of cancer treatment related symptoms, physical functioning and quality of life. The panel concluded that there was strong evidence (Grade A) that behavioral therapies such as meditation and hypnosis could improve depression, mood and quality of life/physical functioning. Moderate (Grade B) evidence supported the efficacy of yoga, meditation and massage for anxiety, stress reduction, depression/mood and nausea/vomiting. Most other modalities, including the small number of trials testing natural products for prevention or treatment of cancer related symptoms or treatment side effects in breast cancer patients received Grades C or D indicating either very small or no benefit. The expert panel recommended that more clinical trials are needed to test various CAM-type modalities in breast cancer patients in order to better inform patient and practitioner decisions.

Long-term survival of women with hormone sensitive breast cancer is improved substantially by the use of aromatase inhibitors and tamoxifen [34-36]. It is not known whether estrogenic botanical supplements function in a similar or different manner from these drugs [15,19,37-39]. Based on our previous finding that HEAL participants who used estrogenic supplements had significantly lower concentrations of estrone, estradiol, free estradiol and dehydroepiandrosterone sulfate (DHEAS) compared to participants not using these supplements [19], we anticipated an inverse association of estrogenic supplements with breast cancer-specific and total mortality. However, the findings we reported here were null. One possible explanation for the lack of association with mortality is that we have no data on long-term estrogenic supplement use since we only assessed use at one point in time, and we have limited data on duration of use. It is

possible that participants who reported estrogenic supplement use at the 30-month post-diagnosis assessment may not have maintained use on a long-term basis. As a result, the influence of estrogenic supplements on breast cancer-specific and total mortality may not have been reliably estimated. It is also possible that women with lower concentrations of sex hormones chose to use estrogenic supplements, perhaps because of increased postmenopausal symptoms, such as vasomotor symptoms or poor sleep quality.

The lack of association between estrogenic supplement use and survival may be noteworthy since use of these products is common among breast cancer patients [40,41]. At the same time concern exists in the medical community about whether breast cancer patients should use these botanically based supplements with estrogenic properties [32]. Some recommendations state that breast cancer patients should not consume soy-containing foods or supplements out of concern that the weak estrogenic properties may fuel the growth of residual disease [37-39]. Our results suggest that use of estrogenic supplements neither increases nor decreases risk of breast cancer-specific or total mortality in breast cancer survivors. These findings are consistent with those from two other cohort studies of breast cancer survivors, which reported that soy-containing foods were not harmful to breast cancer patients and may be associated with improved survival [42,43].

While numerous investigations have reported on the prevalence of CAM use by breast cancer patients [6,9,12,44] only a few previous studies have examined the association between specific CAM categories, primarily natural product use, and mortality outcomes. The Life After Cancer Epidemiology (LACE) cohort of 2,264

patients with early stage breast cancer (stage I-IIIA at diagnosis) examined dietary supplement use and survival [45]. Comprehensive data were collected on average 1.9 years post-diagnosis and included data on antioxidants and other dietary supplements, but use of botanical/herbal preparations or other forms of CAM was not assessed. Use of vitamin E supplements after breast cancer diagnosis among LACE participants was associated with a lower risk of total mortality compared to no use after diagnosis (HR = 0.76, 95% CI 0.58-1.0), whereas use of carotenoid supplements was associated with hazard ratios of 2.07 (95% CI 1.21-3.56) and 1.75 (95% CI 1.13-2.71) for breast cancer-specific and total mortality, respectively [45]. The Shanghai breast cancer survival cohort also assessed antioxidant supplement use in relation to survival among 4877 survivors. Compared to survivors who did not use supplements, those who used antioxidant-containing supplements with vitamin C or vitamin E had a total mortality hazard ratio of 0.82 (95% CI 0.65-1.02) [46]. In a Swedish cohort of 855 breast cancer patients, 58% of patients reported use of over 100 various types of dietary supplements. However, use of these supplements was not associated with survival (HR=0.78, 95% CI 0.44-1.37) [47]. Finally, a small study of 61 patients who used alternative therapies instead of conventional medical treatment had very poor outcomes. Over 96% of these patients who chose to forego standard medical therapy, and instead relied exclusively on CAM experienced disease progression and 51% died after a median follow-up of 54 months [48]. None of these studies, including HEAL, examined whether specific categories of CAM, other than natural products, influenced survival, partly due to low numbers of use for any one particular modality (e.g., Chinese medicine, Ayurveda).

This study has several strengths. The HEAL Study was one of the earliest breast cancer survivor cohorts to be established; it has been in place since 1997 and we have tracked vital status through the SEER registries and the National Death Index. Another strength is that HEAL collected comprehensive data on complementary and alternative medicine, including the names of specific natural products and estrogenic supplements whereas many studies have collected these using a binary (yes/no) question to assess "any use" of CAM [6,9] . HEAL also has breast cancer treatment data collected by abstracting medical records in addition to the SEER registry data.

This study also has limitations. While we obtained data on self-reported use of natural products, it is not possible to collect dosage information due to the lack of uniformity in the manner in which these products are formulated in the United States [49]. Further, supplements sold in the U.S. are not governed for consistency of product formulation or dosage consistency. Without certainty about product ingredients it is difficult to determine how they influence outcomes. Another limitation is that we were unable to analyze data for individual supplements, such as black cohosh, because the number of participants taking any one specific supplement was too small. In addition, tumor estrogen receptor status was not available for 11% of participants because either the test was not conducted (n=13), the test result was not in medical chart (n=34) or the reason the test was missing was unknown (n=25). Sample size for analyses by tumor hormone receptor status was limited. More contemporary classifications such as luminal A, luminal B and basal-like subtypes are not available in HEAL. Finally, HEAL has more extensive and lengthy follow-up than some other cohorts [30,45,46], but the number of breast cancer-specific and total deaths was small and therefore our analyses lack

statistical power. Our results should therefore be interpreted with caution. Finally, as in all observational studies, residual confounding may have occurred in the HEAL Study as a result of measuring some variables imprecisely or not including an important covariate. Definitive information on effects of CAM on breast cancer survival would require data from placebo-controlled, randomized controlled trials. Outcomes for most trials have been focused on symptoms and side effects of breast cancer treatment such as fatigue, anxiety, sleep, quality of life, physical functioning and various physical symptoms [16,33]. Clinical trials are needed to test the efficacy of and to evaluate the overall risks and benefits of various CAM modalities in relation to breast cancer survival.

In conclusion, use of complementary and alternative medicine, natural products and botanically-based estrogenic supplements was not associated with risk of breast cancer-specific or total mortality in this cohort of breast cancer survivors. Future research with comprehensive measurements of CAM use including duration and dose (where possible) in larger cohorts of breast cancer patients with data on molecular subtyping of tumors is needed to explore potential relationships between specific supplements or therapies and outcomes, as well as any interactions between CAM use and conventional treatments.

Table 1. Characteristics of Breast Cancer Survivors in the Health Eating Activity and Lifestyle (HEAL) Study (n=707)

	Mean	SD
Age (mean, SD)	57.9	10.7
Weekly MET-hours of sport and recreational activity (mean SD)	12.8	19.2
	n	**%**
Body Mass Index (kg/m^2)[1]		
<18.5 (n, %)	16	2.3
18.5-24.9	245	34.7
25.0-29.9	198	28.0
≥ 30.0	203	28.7
Current smoker	88	12.4
Race/Ethnicity		
Non-Hispanic white	403	57.0
Black/African-American	199	28.2
Hispanic	87	12.3
Other[2]	18	2.5
Current use of tamoxifen	363	51.3
SEER stage of disease at diagnosis		
Localized	502	71.0
Regional	205	29.0
Tumor estrogen receptor status		
ER positive	488	69.1
ER negative	143	20.2
Other/unknown	76	10.6
Breast cancer treatments		
Surgery only	172	24.3
Surgery + radiation	250	35.4
Any chemotherapy	285	40.3

[1] n=45 participants are missing BMI values

[2] Includes American Indian (n=5), Asian or Pacific Islander (n=11), unknown or not specified (n=2)

Abbreviations: SD, standard deviation; SEER, Surveillance, Epidemiology and End Results; ER, estrogen receptor

Table 2. Complementary and Alternative Medicine (CAM) Use by Health, Eating, Activity and Lifestyle (HEAL) Participants[1]

Type of Complementary and Alternative Medicine	n	%
Any CAM	426	60.2
Mind-Body Medicine[2]	31	4.4
Manipulative and Body-based Practices[3]	192	27.2
Alternative Systems[4]	94	13.3
Natural Products[5]	363	51.3
Estrogenic Supplements[6]	294	41.6

1. Groupings based on NIH's National Center for Complementary and Alternative Medicine (NCAAM) classifications (see methods section for details)
2. Examples include meditation, yoga, guided imagery, qi gong
3. Examples include spinal manipulation, massage therapy, chiropractic medicine
4. Examples include Chinese medicine, Reiki and Ayurveda
5. Dietary supplements of vitamins, minerals, herbals and botanicals
6. Estrogenic supplements are a subset of the category natural products

Table 3. Associations of use of complementary and alternative medicine with risk of breast cancer-specific mortality and total mortality in breast cancer survivors

Use of any complementary or alternative medicine			
Outcomes	**No. of deaths**	**HR**	**95% CI**
Breast cancer specific mortality			
Unadjusted	70	0.80	0.50-1.28
Multivariable[1]	70	1.04	0.61-1.76
Total mortality			
Unadjusted	149	0.70	0.50-0.96
Multivariable[1]	149	0.91	0.63-1.29

[1]. Adjusted for race/ethnicity, BMI, stage of disease, breast cancer treatment, tamoxifen use, Charlson co-morbidity score, weekly MET-hours of physical activity

Table 4. Associations of use of natural products with risk of breast cancer-specific mortality and total mortality in breast cancer survivors

Use of Natural Products			
Outcomes	**No. of deaths**	**HR**	**95% CI**
Breast cancer-specific mortality			
Unadjusted	70	0.88	0.55-1.41
Multivariable[1]	70	1.15	0.69-1.94
Total mortality			
Unadjusted	149	0.73	0.53-1.02
Multivariable[1]	149	0.95	0.67-1.35
Use of Estrogenic Supplements			
Breast cancer-specific mortality			
Unadjusted	70	0.87	0.53-1.41
Multivariable[1]	70	0.96	0.58-1.59
Total mortality			
Unadjusted	149	0.69	0.48-1.00
Multivariable[1]	149	0.84	0.57-1.23

[1]. Adjusted for race/ethnicity, BMI, stage of disease, breast cancer treatment, tamoxifen use, Charlson co-morbidity score, weekly MET-hours of sport and recreational physical activity

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Compliance with ethical standards

The HEAL study complied with all federal regulations for human subjects research. All participating institutions have approved and on-going IRB files and all participants signed written informed consent.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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