Integrative Cancer Therapies
Volume 20: 1–11

DOI: 10.1177/15347354211058404
journals.sagepub.com/home/ict
SAGE

Recurrence of Breast Cancer After Primary Treatment: A Matched Comparison Study of Disease-Free Survival in Women Who Do and Do Not Receive Adjunctive Naturopathic Oncology Care

L. J. Standish, ND, PhD, FABNO[1,2], E. Sweet, ND, MPH[1], Eunjung Kim, PhD[2], F. Dowd, BA[1], Ryan McLaughlin, MS[1], P. Chiang, ND[1], L. Dale, CCRP[1], M. Gaul, BA[3], and M. R. Andersen, PHD[2,3]

Abstract

Purpose: To compare disease free survival experienced by women who received usual oncologic care compared to a cohort of women who received naturopathic oncology care in addition to usual care. **Methods:** Women with breast cancer who received naturopathic oncology (NO) care in Western Washington State (WA) (N = 176) were recruited to a prospective study of clinical health-related quality of life outcomes and then matched to women who received usual care (UC) only (N = 334). **Results:** Among 510 women with breast cancer stages 1 to 3, a total of 50 women (10%) experienced a disease-free survival (DFS) ending event within the observation period; 23 (6.8% of those in the UC cohort, and 27 (15.3% of those in the NO cohort ($P < .05$). Although, women in the 2 cohorts received similar surgical, chemotherapy, and radiation treatment, women with breast cancer who received naturopathic oncology adjunctive care were less likely to use anti-estrogen therapy, and experienced poorer DFS (logrank test, $P < .05$). However, differences in DFS could not be shown to be due to cohort differences in anti-estrogen therapy, baseline HRQOL, or naturopathic oncology therapies prescribed. The stage 3 women in the naturopathic oncology group had more advanced disease at diagnosis. They were more likely to have 5 or more metastatic lymph nodes at baseline (18.5%) compared to their usual care matched control group (13%). Women in the naturopathic oncology group also had higher grade tumors at diagnosis. **Conclusions:** Results show that recurrence of breast cancer was associated with more advanced malignant lymph node involvement; and that naturopathic oncology services provided in 2009-2015 did not improve disease-free survival in these high-risk breast cancer patients.

Keywords

naturopathic oncology, integrative medicine, breast cancer, matched comparison, cancer survival

Submitted February 28, 2019; revised August 5, 2021; accepted October 21, 2021

Introduction

Naturopathic oncology (NO) was established as a field of integrative medicine in 2004 with the formation of the American Board of Naturopathic Oncology.[1] Physicians who are board certified in NO provide whole-person evidence-based care to cancer patients during and after primary oncologic treatment. The board certification process is overseen by the American Board of Naturopathic Medical Examiners, which has developed board certification eligibility requirements which include additional education, training and board examination. Naturopathic oncology (NO) clinical therapy includes nutritional counseling, botanical medicine, acupuncture, and mind-body treatments and advice.[2] Women diagnosed with breast cancer seek out complementary and integrative adjunctive therapies for 2 main reasons

[1]Bastyr University, Kenmore, WA, USA
[2]University of Washington, Seattle, WA, USA
[3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Corresponding Author:
L. J. Standish, AIMS Institute, 2825 Eastlake Ave E, Suite 115, Seattle WA 98102 USA.
Email: lstandish@aimsinstitute.net

(1) to maximize disease-free survival by preventing relapse, and (2) to prevent or reduce side effects of standard oncology treatments such as chemotherapy and radiation.[3]

Treatments to prevent cancer relapse may be mediated by several mechanisms including (1) direct effects on anti-cancer immunocompetence; (2) targeted epigenetic modification of the tumor environment; and (3) when reduction of side-effects allows women to better adhere to their standard radiochemotherapy protocols improving their effectiveness.[4-13] Prevention of cancer-treatment related side-effects and co-morbidities can include treatments intended to prevent cardiomyopathy, osteoporosis, pulmonary fibrosis, lymphedema long-term anemia, peripheral neuropathy, and lymphopenia. For a review see Standish et al.[14] NO uses agents like l-glutamine to prevent peripheral neuropathy.[15] Treatment of peripheral neuropathy may also include electro-acupuncture, and acupuncture.[16,17] Acupuncture may also be used for chemotherapy-related leukopenia, fatigue, and nausea.[18-20] Oral probiotics may also be recommended in order to improve the gut microbiome.[21] Meditation is sometimes recommended to treat cancer-related fatigue and insomnia,[22] and melatonin may also be prescribed to improve sleep.[23-28] Co-enzyme Q10 may also be prescribed to reduce cardiotoxic effects of anthracycline-induced cardiotoxicity.[29]

NO therapies to improve disease-free survival may work by several mechanisms. Vitamin D supplementation to reduce risk of metastasis and death,[30] and omega 3 fatty acid supplementation may prevent recurrence and progression of breast cancer.[31] For example, green tea epicatechins, quercetin, and *Trametes Versicolor* have anti-cancer epigenetic and immunomodulatory activities.[4,14,32,33] Curcumin is also a targeted epigenetic modulator in breast cancer and reduces radiation related dermatitis.[12,34,35] Although patients may choose to use these treatments in the absence of an integrative practitioner, we hypothesized that consultation with a ND about NO therapies, allowing them to be used in a coordinated fashion as is common in NO community practice, may extend disease-free survival after primary oncologic treatment.

Methods

A prospective, matched comparison, observational outcomes design was used to compare disease-free and overall survival in a cohort of breast cancer patients who received naturopathic oncology (NO) at community-based clinics. These patients were matched to a cohort of similar breast cancer patients who received usual care (UC) and did not see a NO. All study activities were conducted with full review of the IRBs of both the Fred Hutchinson Cancer Research Center and of Bastyr University (from February 2, 2009 to January 31, 2015). Informed consent was obtained from all women. Women participated for up to 5 years. See Standish et al[36,37] for detailed description of study methods and the cohorts.

Participants

Women with breast cancer who sought care from 6 outpatient NO clinics located in Western Washington State, USA, were enrolled in an observational study of clinical and quality of life outcomes (n = 378). A subset of these women who met eligibility criteria including; enrollment within 2 years of diagnosis, and return for a second NO consultation, were used as NO cases for the matched cohort comparison design (n = 193). A matched comparison group (n = 360) was identified using the Western WA Cancer Surveillance System (CSS), part of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. Comparison patients were selected and recruited based on similarity to a NO case in age, stage at diagnosis, marital status, race, and ethnicity, with the goal of identifying 2 matches for each NO case.[36] Women were considered ineligible for the comparison cohort if they reported any use of NO; self-prescribed CAM use was not an exclusion criterion for either cohort.

Figure 1 shows the flow of women into the study.

Of the total 553 breast cancer patients enrolled in the 2 cohorts 510 of them were included in the disease-free-survival analyses presented here. Inclusion criteria for DFS analyses in addition to those required for matching cohort membership listed above included:

1. Must have been diagnosed with stage 0 to 3 breast cancer
2. Must have medical records abstracted

Of the 193 women in the NO cohort 176 of the qualified for the analysis. Of the 360 women in the UC cohort 334 were included in the analysis.

Sources of Data

Self-reported health related quality of life (HRQOL, SF-36), marital status, household income, and self-reported co-morbidities were collected from participants who were queried at enrollment, 6-months, and annually thereafter. The SF-36 is a widely used measure of functional status and measures quality of life across a broad range common in both healthy and ill populations. The SF-36 is scored by calculating 8 subscales: functional status, role-physical function, role-emotional function, pain, general health, mental health, vitality, and social functioning.

CSS provided data on demographics, stage, histology, and initial oncologic treatment for all participants. Oncology medical records were abstracted in order to provide details on standard oncologic treatment for all participants. Date of last known medical oncology visit was also abstracted, as were dates and type for any disease-free survival limiting events not available from the

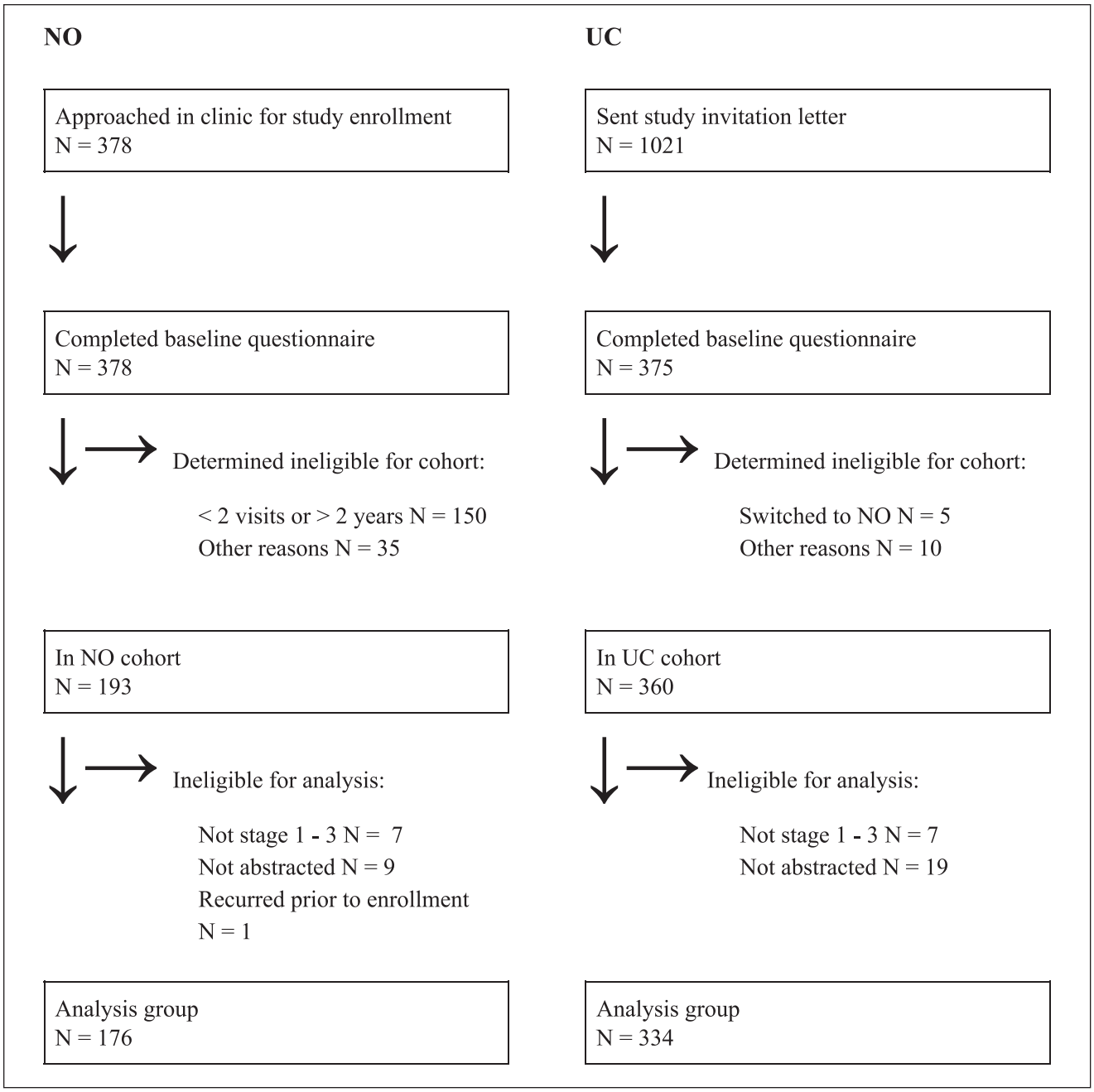

Figure 1. Consort diagram of recruitment of two cohorts of breast cancer patients in Western Washington State. The Naturopathic Oncology care + Usual Care (NO) cohort was matched to a Usual Care only (UC) cohort.

registry. Overall survival data for both cohorts were obtained from CSS, which updates its records through matching to the National Death Index and with state sources of data. Final date of death data used for this analysis was received December 31, 2016. At that time, 12 of the 510 women in the study had died (2%).

Although we were primarily interested in recurrence, in order to best describe breast cancer recurrence in ways consistent with other studies we used Hudis' et al[38] definition of disease-free survival. The end of a period of disease-free survival was noted if any one of the following 8 events were noted in the medical record:

1. Invasive ipsilateral breast tumor recurrence
2. Local/regional invasive recurrence
3. Distant recurrence

Table 1. Disease Free Survival Limiting Events in the Usual Care and Naturopathic Oncology Cohorts.

Stage	Usual care cohort (N = 334)	Naturopathic oncology cohort (N = 176)	χ^2	*P*-value
0	3 of 26 (11.5%)	3 of 20 (15.0%)	0.01	.92
1	5 of 136 (3.7%)	6 of 60 (10.0%)	2.06	.15
2	10 of 125 (8.0%)	10 of 74 (13.5%)	1.01	.31
3	5 of 47 (10.6%)	8 of 22 (36.4%)	4.91	.03
Total recurrences	23 of 334 (6.9%)	27 of 176 (15.3%)	8.39	.00

Table 2. Disease Free Survival Ending Events Experienced by Breast Cancer Patients in Both Cohorts.

Hudis criteria	NO (%)	UC (%)
Death from non-breast cancer	1 (0.6)	0 (0)
Death unknown cause	1 (0.6)	0 (0)
Distant recurrence	2 (1.1)	8 (2.4)
Invasive contralateral breast cancer	4 (2.3)	2 (0.6)
Invasive ipsilateral breast tumor recurrence	3 (1.7)	0 (0)
Local/regional invasive recurrence	2 (1.1)	3 (0.9)
Second primary invasive breast cancer	11 (6.3)	6 (1.8)
Recurrence: type unknown*	3 (1.7)	4 (1.2)
Total	27	23 ($P < .05$)

*Used where medical records abstraction indicated a return to active cancer treatment but where details regarding the type of recurrence could not be determined.

4. Death from breast cancer
5. Death from non-breast cancer
6. Death unknown cause
7. Invasive contralateral breast cancer
8. Second primary invasive cancer

Medical records were searched for the date of recurrence of breast cancer based on imaging reports or on medical oncology physician progress notes. Typically, a breast cancer recurrence was clinically detected by some form of radiologic imaging (CT, CT/PET, MRI). The date of such a scan was used as a date of local or distant recurrence. Abstractors also collected information on the date and type of other cancer related events including contralateral breast cancers and second primary cancers at any organ site. Abstractors reviewed the impression sections of all such scans and the progress notes following them and recorded any assessment including the above phrases, or references to recurrence or malignancy. Records were also reviewed for collaborating evidence of recurrences or other cancer events including changes in care and return to active treatment. All charts for both cohorts were abstracted twice by 2 trained and independent medical chart abstractors and data entered using double entry verification. Integrative oncology charts were also abstracted for NO treatment and comparisons were also made examining NO treatments used by women within the NO cohort who did and did not experience a DFS limiting event.

Results

Median follow up duration for the 510 women included in this analysis was 39.2 months (SD ± 15.4 months). Most (88%) of the NO cohort enrolled in the study within the first year after diagnosis. Twenty-three of the 334 women in the UC cohort (6.8%) experienced a recurrence or other DFS ending event, as did 27 of the 176 in the NO cohort (15.3%); this difference between the cohorts was statistically significant ($\chi^2 = 8.39$; $P < .01$). Table 1 expands on this finding presenting differences in recurrence rates stratified by stage. Examination of this table shows that while the pattern of poorer DFS was present in those in the NO cohort regardless of stage at diagnosis, the pattern is particularly pronounced among women with stage 3 disease.

Table 2 presents the types of DFS limiting events experienced by breast cancer patients in the NO and UC cohorts. Using the Hudis et al[38] definitions, breast cancer recurrences were assigned to one or more categories: (1) ipsilateral breast recurrence, (2) local/regional recurrence, (3) distant recurrence, (4) and contralateral breast cancer. Other DFS limiting events included (5) secondary primary cancer, and (6) death attributable to any cause. We also included a category (7) recurrence: type unknown, for cases where medical records abstraction indicated a return to active cancer treatment but where details regarding the type of recurrence (eg, local regional, contralateral, etc.) could not be found.

Types of recurrences experienced by breast cancer patients who received adjunctive naturopathic oncology (NO) care were compared to types in women who received usual care (UC) only, with Hudis' et al[38] categories used to assign each patient's recurrence to a type. Naturopathic oncology patients experienced fewer distant metastatic recurrences (1.1% of the total cohort) compared to UC patients (2.4%), but more invasive contralateral breast cancer diagnoses (NO 2.3% vs UC 0.6%), and more new primary cancers (6.3%) compared to the UC cohort (1.8%). However, none of these differences were statistically significant by Chi-square analysis. Only the difference in second primary cancers was significantly significant (χ^2 (1) = 5.78; $P < .02$) between the cohorts. Of those women who developed second primary cancers, 11 in the NO cohort were breast cancers compared to 6 in the UC group. Three recurrences in the NO cohort versus 4 in the UC group were cancers originating at other organ sites, and 1 woman in the NO group experienced 2 new primary cancers after initial treatment, one of which was breast cancer. We have no evidence for or against the possibility that some of the women in the NO cohort may have been genetically pre-disposed to breast or other cancers increasing their risk for new primaries.

The difference in DFS between the NO and UC cohorts was observed despite evidence (previously reported by Standish et al[32]) that cases and comparisons were well matched with respect to demographic, histologic, and prognostic indicators at the time of diagnosis.[37] Most women (70%) in both cohorts received standard oncologic care that met the National Comprehensive Cancer Network (NCCN) guidelines. There were no statistically significant differences between the cohorts in surgery, chemotherapy, or radiation. However, fewer women in the NO cohort used any type of anti-estrogen therapy (64%) compared to the usual care cohort (76%;(χ^2 (1) = 6.35, $P < .05$).[37]

Table 3 describes the demographic, histological characteristics and oncologic treatments received by women in the NO cohort and the UC cohorts who did and who did not experience a DFS ending event within study follow-up (N = 510). Demographics, estrogen receptor status, marital status, and income did not differ between the cohorts or between the women with and without events. Types and frequency of surgical, chemotherapy, and radiotherapy did not differ between the cohorts or between those with and without events. Women in the NO cohort had worse self-perceived role functioning, social functioning, emotional role functioning, and mental health ($P < .05$) suggesting a modest HRQOL disadvantage to the NO cohort at study enrollment, but this difference was non-significant at 6-months with a modest HRQOL advantage at 6-month to the NO cohort health ($P < .05$)[39] Women in the NO cohort had a higher household income compared to UC patients. However, HRQOL and income did not statistically differ between those women with recurrence events compared to those without. Fewer women in the NO cohort received anti-estrogen therapy, but this was not associated with a statistically significant increase in DFS ending events in this study.

Women who experienced events had a higher grade of breast cancer at diagnosis and were more likely to have more than 5 regional lymph nodes positive for malignancy ($P < .05$ by *t*-test or Chi squared, respectively).

Disease Free Survival

Figure 2 shows the Kaplan-Meyer survival curves for disease free survival among breast cancer patients who received NO care compared to the UC cohort. The differences in DFS time were statistically significant using log rank testing ($P = .01$).

Focusing on the group of women with stage 3 breast cancer, those in the NO cohort experienced significantly reduced DFS compared to usual care cohort participants. See Figure 3. The difference in percentage experiencing a DFS limiting event here was also statistically significant when tested using log rank test at $P = .006$, despite the small sample.

Overall Survival

Of the 50 women who had a disease-free survival ending event 12 died (24%). Seven deaths occurred in the NO cohort (7/176; 4.0%) and 5 (5/334; 1.5%) occurred in the UC cohort. This result was again statistically significant (χ^2 (1) = 102.86; $P < .05$). It is however, unclear how this might relate to NO treatment, all but 2 of these deaths occurred in women with metastatic, recurrent, or a second primary cancer. Of the 2 that did not (both NO cohort), one is known to have died of a non-breast cancer cause, the cause of death in the other was unknown.

Naturopathic Oncology Treatments

We compared the types of naturopathic oncology treatment recommended to women in the naturopathic oncology cohort who did and not experience a DFS ending event after cancer. The 10 most frequently recommended treatments were melatonin, *Trametes versicolor* mushroom extract, vitamin D, acupuncture, exercise, omega 3 fatty acids, curcumin, modified citrus pectin, magnesium, glutamine, probiotics, co-enzyme Q10, and meditation. Table 4 indicates that the types of NO therapy recommended to women who did and who did not have a DFS limiting event were similar. Although we found that more women who experienced a DFS limiting event were prescribed meditation, and results

Table 3. Characteristics of Women With Breast Cancer in the Naturopathic Oncology (NO) and Usual Care (UC) Cohorts Who Did and Did Not Experience a DFS Limiting Event.

						Test statistics			
		Disease free at end of follow-up (N = 460)		Experienced a DFS limiting event (N = 50)		*T*-test		Chi-squared	
	Data type	UC (N = 311)	NO (N = 149)	UC (N = 23)	NO (N = 27)	Cohort	Recurrence	Cohort	Recurrence
Age at diagnosis	Mean	53.23	52.33	53.48	54.74	0.55	0.69	—	—
Non-white	Count	15 (4.8%)	9 (6%)	0 (0%)	0 (0%)	—	—	0.01	1.70
Marital status Married/partner	Count	239 (76.8%)	106 (71.1%)	17 (73.9%)	15 (55.6%)	—	—	3.33	2.29
Household income <$50K	Count	194 (62.4%)	88 (59.1%)	16 (69.6%)	15 (55.6%)	—	—	6.24*	2.05
Non-ductal histology	Count	75 (24.1%)	38 (25.5%)	6 (26.1%)	3 (11.1%)	—	—	0.00	0.74
ER (+)	Count	274 (88.1%)	132 (88.6%)	21 (91.3%)	21 (77.8%)	—	—	0.91	1.79
Mean grade	Mean	2.13	2.16	2.22	2.67	−1.54	3.28*	—	—
Axillary nodal involvement	Count	119 (38.3%)	52 (34.9%)	10 (43.5%)	11 (40.7%)	—	—	0.39	19.30*
Surgery type: lumpectomy	Count	185 (59.5%)	100 (67.1%)	13 (56.5%)	15 (55.6%)	—	—	1.44	0.47
Surgery type: mastectomy	Count	108 (34.7%)	44 (29.5%)	9 (39.1%)	9 (33.3%)	—	—	1.09	0.06
5+ nodes	Count	25 (8%)	7 (4.7%)	3 (13%)	5 (18.5%)	—	—	4.95	5.97*
Radiotherapy	Count	203 (65.3%)	105 (70.5%)	15 (65.2%)	16 (59.3%)	—	—	0.79	0.91
Chemotherapy	Count	163 (52.4%)	84 (56.4%)	14 (60.9%)	17 (63%)	—	—	0.67	0.91
Used any AET	Count	233 (74.9%)	100 (67.1%)	18 (78.3%)	14 (51.9%)	—	—	6.35*	4.54
Comorbidities at baseline	Mean	8.93	7.54	10.18	10.89	1.56	1.67	—	—
Comorbidities at 6-month	Mean	10.49	9.48	11.33	9.36	1.34	0.08	—	—
Comorbidities at 1-year	Mean	11.52	9.48	11.73	12.69	1.94	0.77	—	—
SF-36 score physical functioning	Mean	78.59	79.83	77.99	80.70	−0.74	0.15	—	—
SF-36 score role physical	Mean	53.34	43.40	55.43	37.96	2.68*	−0.65	—	—
SF-36 score bodily pain	Mean	70.01	68.44	66.85	70.83	0.41	−0.15	—	—
SF-36 score general health	Mean	72.09	72.99	75.17	75.52	−0.62	1.07	—	—
SF-36 score vitality	Mean	49.28	49.88	51.74	51.67	−0.34	0.67	—	—
SF-36 score social functioning	Mean	71.46	61.82	73.37	72.22	3.55*	1.29	—	—
SF-36 score role emotional	Mean	71.32	59.39	81.16	65.38	2.94*	0.84	—	—
SF-36 score mental health	Mean	73.88	69.64	75.13	75.37	2.20*	1.10	—	—
Number of deaths as of 12-31-16 (N = 12)	Count	0 (0%)	0 (0%)	5 (21.7%)	7 (25.9%)	—	—	2.10	102.86*

Abbreviation: AET: adjuvant endocrine therapy.
*Indicates a *P*-value ≤.05.

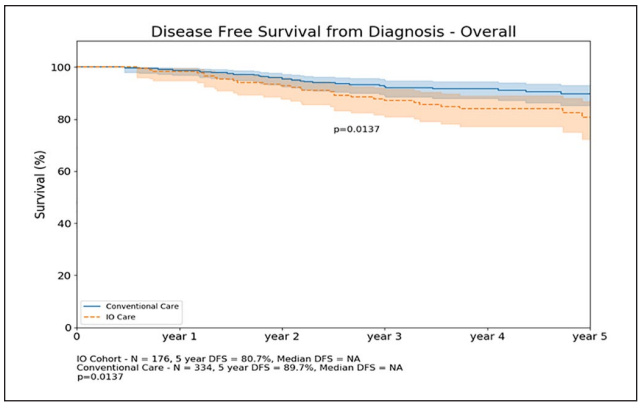

Figure 2. Disease free survival was worse among breast cancer patients who were in the naturopathic oncology cohort (N = 176) compared to the usual care cohort (N = 334); *P* = .014.

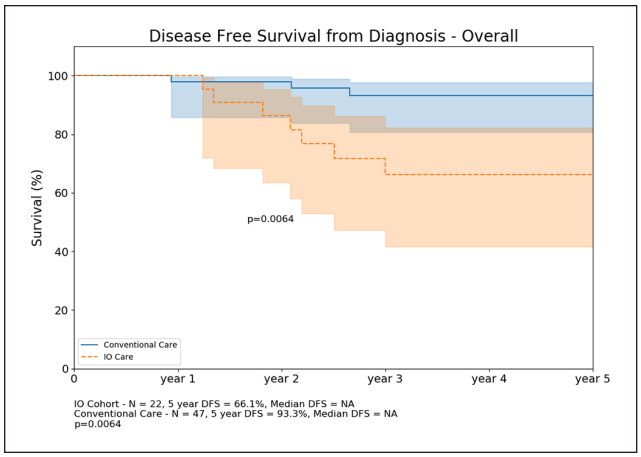

Figure 3. Disease free survival in 69 stage 3 breast cancer study participants in the naturopathic oncology cohort (N = 47) and in the usual care cohort (N = 22).

suggested a trend toward the more frequent prescription of coenzyme Q10, neither of these treatments were prescribed frequently and sample sizes are too small to make strong inferences. It is also possible that these differences in NO treatment in this analysis might arise from providers working to help patients after their recurrence or based on differences in the trajectory of the patients after complementary treatment began.

Study Limitations

These data were from a matched comparison study exploring the use of naturopathic oncology (NO) in community clinics not a randomized controlled trial. NO cohort members used NO to varying degrees; enrollment was dependent on attendance at only 2 appointments, which was used as a cut off for establishment of a care relationship with a NO provider. These women did not necessarily receive all treatments that would be recommended in an ideal course of NO treatment. This was especially true of the 34 women who sought NO care only after completion of all conventional therapies, this was a significant percentage (18%) of our NO cohort participants. We recognize the limitation of such data. Despite our efforts to match patients for prognosis based on characteristics at time of diagnosis, self-selection of women into NO care could and did occur up to 2 years later however, and women may have selected to join the NO cohort based on concern that usual care oncology treatment was going poorly, because they wanted to avoid hormonal treatments, or because they just felt poorly (poor HRQOL) and wanted additional care. We have previously reported that the NO women in this cohort had poorer HRQOL at enrollment, compared to the matched comparison group.[39] There were modest differences in mood and functional role status between the groups. This would suggest differences in the NO cohort that could not be controlled for by matching according to characteristics at diagnosis. If women self-select to NO care based on some intuition that conventional treatment has not or will not been successful for them this is a possible explanation for our findings. However, differences in HRQOL at baseline were unrelated to study outcomes and thus could not explain differences in disease recurrence outcomes as a mediator.

The purpose of this study was to evaluate the potential benefit or risks of naturopathic oncology care as an adjunctive health care service in women with breast cancer. We did not evaluate the effectiveness of CAM therapies but rather the impact of a whole person health care service that is covered by many health care insurance companies. Protocols varied among the naturopathic oncology clinics where the NO cohort patients were seen. As was noted in a prior study use of NO treatment does appear to have improved HRQOL in the NO cohort at 6-month follow-up.[39]

As this was an observational study, women could, at least in principle, change cohorts. Two women who were initially enrolled in the usual care cohort were disqualified from analysis as UC cohort participants when they were found to have visited a NO office, and re-enrolled when they attended twice and qualified for the NO cohort. NO cohort women were retained in the NO cohort based on having received NO advice even if they did not continue treatment after a few initial visits. This was done because this was primarily a study of the contribution of NO provider consultation and advice and women may choose to continue to use advice even if they stop seeing the provider. In most cases, women in the NO cohort continued to actively seek NO treatment suggesting acceptance and use of the advice provided. Members of the NO cohort visited the NO provider on average 5.36 times in their first year of NO care.

Table 4. Most Common Naturopathic Oncology (NO) Therapies Prescribed for Breast Cancer Patients Who Had DFS Limiting Events Compared to Those Who Had None During Study Follow-Up (% (N)).

Recommendation type	Recommendation name	Cohort 1A no recurrence	Cohort 1A recurrence	Cohort 1A no recurrence (%)	Cohort 1A recurrence (%)	χ^2	*P*-value
Supplements	Melatonin	61	10	40.94	37.04	0.03	.87
Supplements	Coriolus (trametes versicolor, Turkey Tail, Yun Zhi, PSP)	56	8	37.58	29.63	0.33	.57
Supplements	Vitamin D3	51	10	34.23	37.04	0	.95
TCM	Acupuncture	47	6	31.54	22.22	0.55	.46
Lifestyle	Exercise	43	7	28.86	25.93	0.01	.94
Lifestyle	Walking	43	8	28.86	29.63	0.02	.88
Supplements	Omega 3 fatty acids	36	8	24.16	29.63	0.13	.72
Supplements	Curcumin	34	7	22.82	25.93	0.01	.92
Supplements	Modified citrus pectin	29	7	19.46	25.93	0.26	.61
Supplements	Magnesium	28	5	18.79	18.52	0.05	.81
Supplements	L-glutamine	27	7	18.12	25.93	0.46	.5
Supplements	Probiotics	19	5	12.75	18.52	0.25	.62
Supplements	Coenzyme Q10	12	6	8.05	22.22	3.57	.06
Mind-body	Meditation	6	5	4.03	18.52	5.91	.02*

*indicates a significant *p* value.

Although we initially sought to create 2 comparison cohorts including one that did and one that did not use CAM supplements so we could examine not only the contribution of advice but also of CAM use, this was not possible due to the high rate of use of supplements in our usual care cohort. Women in both cohorts used CAM supplements prior to study enrollment at a rate substantially greater than 70%.[40] Women in the usual care cohort often used CAM supplements before, during and after treatment but without the advice or guidance of a NO oncology-specific provider. Vitamin D was one of the most frequently used CAM supplements in the UC group, used by more than 50% of patients, other common supplements included Green Tea, ginger, and melatonin. Supplement use in the UC cohort may have provided patients with the benefits associated with their use,[40] but may also have caused negative effects[41]. This analysis, however, describes the contribution of professional advice from a NO provider about CAM supplements and other CAM treatments and not, in most cases, the effects of treatments used themselves.

Discussion

This matched-comparison study was designed with a larger sample size and powered to detect a modest difference in DFS/recurrence. The hypothesis was that the difference would be a small advantage to the NO group and thus we powered for a small effect size. Difficulties in recruitment were such that we did not achieve the sample size we had hoped. We report our findings nonetheless as the differences we found in DFS and HRQOL were large enough to be statistically significant even with the reduced sample size.

Our study is perhaps the first matched-comparison study of physician-supervised, science-based CAM used as a complement to conventional medicine. Unlike in the study reported by Neuhouser et al[42] our participants did not attempt to replace conventional treatment with CAM care.[43] All of our study participants received timely usual oncology care in addition to NO, in contrast to some other studies.[44]

There have been other studies on self-prescribed CAM use, however, that have demonstrated a negative impact on survival.[45] This study differs from those in that we studied patients receiving CAM treatment under the care of a licensed specialist CAM provider. Based on our findings we also found that CAM use was associated with shorter disease-free survival intervals as well as shorter OS in patients using physician-directed NO. However, breast cancer patients in the naturopathic oncology cohort had more advanced disease (higher number of malignant lymph nodes, higher grade tumor and poorer QOL at baseline.

It is known that higher levels of CAM use are associated white women, higher SES, higher stage, and higher distress scores.[39,44] This was true in this sample but we limited the effect of the selection biases for stage and race through matching in this population study. Our NO cohort may have experienced advantages associated with higher SES, and disadvantages associated with higher clinical risk, distress and their lower QOL at study enrollment. Their levels of distress provided us with the opportunity to study the impact of physician prescribed CAM on distress. Our previous work showed participant health related quality of life was

improved in the first year of treatment with physician supervised CAM. This provides a contrast to the results of Yun et al[46] who describe lower quality of life outcomes in users of self-prescribed CAM.[47]

Conclusion

Among 510 women a total of 50 (9.8%) had a DFS limiting event within the up to 5-year study observation period. Most DFS limiting events were recurrences. There were few deaths, but quite a few second primary breast cancers. DFS limiting events were associated with higher histological grade of breast cancer and the involvement of 5 or more malignant regional lymph nodes at diagnosis. Overall, women with breast cancer who received naturopathic oncology adjunctive care demonstrated poorer disease-free survival, that is to say, our results show that naturopathic oncology services offered in Seattle-area naturopathic medical outpatient clinics between 2009 and 2016 did not improve DFS in women with high risk breast cancer. Particularly among those with high-risk stage 3 disease with extensive axillary nodal malignancy, NO cohort women experienced poorer DFS than those receiving only UC. However, DFS results could not be shown to be mediated by cohort differences in anti-estrogen therapy, baseline HRQOL, or naturopathic oncology therapies prescribed in this sample.

Based on these results naturopathic oncology researchers need to recognize that patients may seek naturopathic care for higher risk disease and poor HRQOL. There is a keen need to develop and evaluate improved therapies to prevent recurrence of breast cancer. The need appears to be most keen for high-risk women with stage 3 disease and extensive axillary node malignancy. As part of the effort to further evaluate and improve naturopathic oncology care, the Canadian/U.S. Integrative Oncology study began in 2015 in order to evaluate advanced naturopathic oncology treatments for patients with advanced solid tumors provided in 12 North American community out-patient clinics[48]. Study results are anticipated in 2023.

Acknowledgments

The authors would also like to thank Chad Aschtgen ND, FABNO; Laura James ND, FABNO, Janile Martin ND, ARNP; Eleanora Naydis ND, LAc, FABNO and Paul Reilly, ND, Lac, FABNO for their efforts recruiting study participants.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the National Center for Complementary and Integrative Health (RO1 AT 5873, T32 AT815) and by the Lotte and John Hecht Memorial Foundation.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
Informed consent was obtained from all individual participants involved in the study.

ORCID iD

E. Sweet https://orcid.org/0000-0003-4840-6125

Data Accessibility

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. American Board of Naturopathic Oncology. Accessed August 9, 2019. www.fabno.org
2. Standish LJ, Dowd F, Sweet E, et al. Breast cancer integrative oncology care and its costs. *Integr Cancer Ther*. 2017;16:85-95.
3. Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin*. 2017;67:194-232.
4. Torkelson CJ, Sweet E, Martzen MR, et al. Phase 1 clinical trial of trametes versicolor in women with breast cancer. *ISRN Oncol*. 2012;2012:251632.
5. Nezami MA, Hager S, Garner J. Epigenetic tumor response to hypoxia: an epimutation pattern and a method of multi targeted epigenetic therapy (MTET). *J Cancer Ther*. 2016;7:254-269.
6. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer*. 2006;6:240-248.
7. Lutgendorf SK, Lamkin DM, DeGeest K, et al. Depressed and anxious mood and T-cell cytokine expressing populations in ovarian cancer patients. *Brain Behav Immun*. 2008;22:890-900.
8. Lutgendorf SK, Lamkin DM, Jennings NB, et al. Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. *Clin Cancer Res*. 2008;14:6839-6846.
9. Lamkin DM, Lutgendorf SK, McGinn S, et al. Positive psychosocial factors and NKT cells in ovarian cancer patients. *Brain Behav Immun*. 2008;22:65-73.
10. Antoni MH, Lutgendorf SK, Blomberg B, et al. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. *Biol Psychiatry*. 2012;71:366-372.
11. Lutgendorf SK, Andersen BL. Biobehavioral approaches to cancer progression and survival: mechanisms and interventions. *Am Psychol*. 2015;70:186-197.
12. Ryan JL, Heckler CE, Ling M, et al. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled

clinical trial of thirty breast cancer patients. *Radiat Res*. 2013;180:34-43.
13. Kumar P, Barua CC, Sulakhiya K, Sharma RK. Curcumin ameliorates cisplatin-induced nephrotoxicity and potentiates its anticancer activity in SD rats: potential role of Curcumin in breast cancer chemotherapy. *Front Pharmacol*. 2017;8:132.
14. Standish LJ, Sweet ES, Novack J, et al. Breast cancer and the immune system. *J Soc Integr Oncol*. 2008;6:158-168.
15. Wang WS, Lin JK, Lin TC, et al. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. *Oncologist*. 2007;12:312-319.
16. Chiba A, Raman R, Thomas A, et al. Serum vitamin D levels affect pathologic complete response in patients undergoing neoadjuvant systemic therapy for operable breast cancer. *Clin Breast Cancer*. 2018;18:144-149.
17. Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral Neuropathy: a case series. *Acupunct Med*. 2006;24:87-91.
18. Lu W, Hu D, Dean-Clower E, et al. Acupuncture for chemotherapy-induced leukopenia: exploratory meta-analysis of randomized controlled trials. *J Soc Integr Oncol*. 2007;5:1-10.
19. Sima L, Wang X. [Therapeutic effect of acupuncture on cisplatin-induced nausea and vomiting]. *Zhongguo Zhen Jiu*. 2009;29:3-6.
20. You Q, Yu H, Wu D, Zhang Y, Zheng J, Peng C. Vitamin B6 points PC6 injection during acupuncture can relieve nausea and vomiting in patients with ovarian cancer. *Int J Gynecol Cancer*. 2009;19:567-571.
21. Eslami M, Sadrifar S, Karbalaei M, Keikha M, Kobyliak NM, Yousefi B. Importance of the microbiota inhibitory mechanism on the Warburg effect in colorectal cancer cells. *J Gastrointest Cancer*. 2020;51:738-747.
22. Johns SA, Brown LF, Beck-Coon K, et al. Randomized controlled pilot trial of mindfulness-based stress reduction compared to psychoeducational support for persistently fatigued breast and colorectal cancer survivors. *Support Care Cancer*. 2016;24:4085-4096.
23. Madsen MT, Hansen MV, Andersen LT, et al. Effect of melatonin on sleep in the perioperative period after breast cancer surgery: a randomized, double-blind, placebo-controlled trial. *J Clin Sleep Med*. 2016;12:225-233.
24. Grant SG, Melan MA, Latimer JJ, Witt-Enderby PA. Melatonin and breast cancer: cellular mechanisms, clinical studies and future perspectives. *Expert Rev Mol Med*. 2009;11:e5.
25. Barni S, Lissoni P, Sormani A, et al. The pineal gland and breast cancer: serum levels of melatonin in patients with mammary tumors and their relation to clinical characteristics. *Int J Biol Markers*. 1989;4:157-162.
26. Lissoni P, Barni S, Crispino S, Tancini G, Fraschini F. Endocrine and immune effects of melatonin therapy in metastatic cancer patients. *Eur J Cancer Clin Oncol*. 1989;25:789-795.
27. Lissoni P, Tancini G, Barni S, et al. Alterations of pineal gland and of T lymphocyte subsets in metastatic cancer patients: preliminary results. *J Biol Regul Homeost Agents*. 1989;3:181-183.
28. Tagliabue M, Lissoni P, Barni S, et al. A radiologic study by CT scan of pineal size in cancer patients: correlation to melatonin blood levels. *Tumori*. 1989;75:226-228.
29. Conklin KA. Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. *Integr Cancer Ther*. 2005;4:110-130.
30. de Sousa Almeida-Filho B, De Luca Vespoli H, Pessoa EC, Machado M, Nahas-Neto J, Nahas EAP. Vitamin D deficiency is associated with poor breast cancer prognostic features in postmenopausal women. *J Steroid Biochem Mol Biol*. 2017;174:284-289.
31. Darwito D, Dharmana E, Riwanto I, et al. Effects of Omega-3 supplementation on Ki-67 and VEGF expression levels and clinical outcomes of locally advanced breast cancer patients treated with Neoadjuvant CAF chemotherapy: a randomized controlled trial report. *Asian Pac J Cancer Prev*. 2019;20:911-916.
32. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. *Integr Cancer Ther*. 2005;4:144-155.
33. Haghi A, Azimi H, Rahimi R. A comprehensive review on pharmacotherapeutics of three phytochemicals, Curcumin, Quercetin, and Allicin, in the treatment of gastric cancer. *J Gastrointest Cancer*. 2017;48:314-320.
34. Wang Y, Yu J, Cui R, Lin J, Ding X. Curcumin in treating breast cancer: a review. *J Lab Autom*. 2016;21:723-731.
35. Tajbakhsh A, Hasanzadeh M, Rezaee M, et al. Therapeutic potential of novel formulated forms of curcumin in the treatment of breast cancer by the targeting of cellular and physiological dysregulated pathways. *J Cell Physiol*. 2018;233:2183-2192.
36. Standish LJ, Sweet E, Naydis E, Andersen MR. Can we demonstrate that breast cancer "integrative oncology" is effective? A methodology to evaluate the effectiveness of integrative oncology offered in community clinics. *Integr Cancer Ther*. 2013;12:126-135.
37. Standish LJ, Dowd F, Sweet E, Dale L, Andersen MR. Do women with breast cancer who choose adjunctive integrative oncology care receive different standard oncologic treatment? *Integr Cancer Ther*. 2018;17:874-884.
38. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25:2127-2132.
39. Andersen MR, Sweet E, Hager S, Gaul M, Dowd F, Standish LJ. Use of integrative oncology, involvement in decision-making, and breast cancer survivor health-related quality of life in the first 5 Years postdiagnosis. *Integr Cancer Ther*. 2018;17:636-645.
40. Andersen MR, Sweet E, Hager S, Gaul M, Dowd F, Standish LJ. Effects of Vitamin D use on health-related quality of life of breast cancer patients in early survivorship. *Integr Cancer Ther*. 2019;18:1534735418822056.
41. Sweet E, Dowd F, Zhou M, Standish LJ, Andersen MR. The use of complementary and alternative medicine supplements of potential concern during breast cancer chemotherapy. *Evid Based Complement Alternat Med*. 2016;2016:1-8.

42. Neuhouser ML, Smith AW, George SM, et al. Use of complementary and alternative medicine and breast cancer survival in the health, eating, activity, and lifestyle study. *Breast Cancer Res Treat*. 2016;160:539-546.
43. Karalı Y, Demirkaya M, Sevinir B. Use of complementary and alternative medicine in children with cancer: effect on survival. *Pediatr Hematol Oncol*. 2012;29:335-344.
44. Johnson SB, Park HS, Gross CP, Yu JB. Use of alternative medicine for cancer and its impact on survival. *J Natl Cancer Inst*. 2018;110:121-124.
45. Risberg T, Vickers A, Bremnes RM, Wist EA, Kaasa S, Cassileth BR. Does use of alternative medicine predict survival from cancer? *Eur J Cancer*. 2003;39:372-377.
46. Yun YH, Lee MK, Park SM, et al. Effect of complementary and alternative medicine on the survival and health-related quality of life among terminally ill cancer patients: a prospective cohort study. *Ann Oncol*. 2013;24:489-494.
47. Andersen MR, Bowen DJ, Morea J, Stein KD, Baker F. Involvement in decision-making and breast cancer survivor quality of life. *Health Psychol*. 2009;28:29-37.
48. Seely, D, Ennis J, McDonnell, E Dale, L, Sweet E, Chiang P, Ronnie K, Dowd F, Standish LJ. Canadian/US integrative oncology study (CUSIOS): protocol and study status. *10th Annual Conference of the Oncology Association of Naturopathic Physicians*, 11-13 June 2021, Virtual.