Hormone-modulating Complementary and Alternative Medical Therapies: Implications for the Management of Ovarian Cancer

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Abstract

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Introduction: Between 44% and 53% of women with ovarian cancer use some form of complementary and alternative medicine (CAM) during the course of diagnosis and treatment, some of which may be hormonally active (HCAM). Studies have shown that ovarian cancer cells can express hormone receptors for estrogen, progesterone and Her-2/neu and that steroid hormone receptor status possesses prognostic significance. Current studies do not allow us to exclude the possibility that estrogens alone could stimulate ovarian cancer growth in a small fraction of patients. Indiscriminant use of these therapies may lead to under treatment of disease have a negative impact on long-term clinical outcomes including increased morbidity and mortality.

Goal: The goal of this study was to develop a detailed understanding of HCAM and HRT use by women with ovarian cancer throughout the course of their treatment, including use prior to diagnosis, in the post-treatment period and at the time of the survey (current use).

Methods: The study consisted of a cross-sectional survey regarding the use of contraindicated CAM substances (including HCAM) and was provided to all women with ovarian cancer associated with two Seattle-area participating gynecologic oncology practices.

Results: The groups of women surveyed for this analysis were largely similar in terms of demographics, lifestyle and health behaviors. A higher percentage of the women using both HCAM and HRT experienced recurrent disease sooner and had the fewest number of participants 5 years or more from diagnosis than their HCAM or HRT counterparts. HCAM and HRT combined users also scored lower on the SF-36 physical and mental health subscales than those in the HCAM or HRT groups. Both HCAM and HRT were used prior to diagnosis and throughout conventional treatment, including chemotherapy.

Conclusion: Patients using a combination of HCAM and HRT may experience earlier recurrence that those using HCAM or HRT alone and women with recurrent disease may be more willing to utilize a broader range of treatment options, including CAM therapies, for their cancer. There is a clear need for additional research regarding the extent to which hormone levels and exogenous hormone supplementation affect morbidity and mortality in ovarian cancer.

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GLOSSARY

Complementary and Alternative Medicine: A group of diverse medical and health care systems, practices, and products that are not generally considered part of Conventional medicine.

Cross-sectional Study: Descriptive studies involving observation of an entire population, or a representative subset, at one specific point in time and provide data on the entire population under study. They can be used to describe some feature of the population or may support inferences of cause and effect.

Fisher’s Exact Test: Fisher's Exact test is a statistical significance test used in the analysis of contingency tables where sample sizes are small.

Hormone Replacement Therapy: The systemic use of estrogen with or without the use of a progestin, after cessation of ovarian function.

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INTRODUCTION

Between 44% and 53% of women with ovarian cancer use some form of complementary and alternative medicine (CAM) at some point during the course of diagnosis and treatment [1]. Cancer patients typically seek adjunctive CAM care for a variety of reasons including: efforts to support their health and well-being throughout treatment for their disease, as a means to augment conventional treatment, during recovery post-treatment and as part of a secondary prevention strategy. Some herbs and other natural supplements used as CAM are known to have hormone or hormone-like activity [2-4]. As ovarian cancer treatment frequently results in the loss of ovarian function and menopausal symptoms, quality of life can become a significant issue for ovarian cancer patients after surgical menopause. Many gynecologic oncologists advise against the use of HRT, therefore ovarian cancer survivors may be turning to non-hormonal treatments, including CAM therapies which may affect sex steroid hormone levels, for the management of menopausal symptoms. Some of these are used by women to control menopausal symptoms as an alternative to hormone replacement therapy (HRT). Other CAM supplements have hormonal effects (HCAM) which may not be known to a woman who is using these substances for other reasons that may or may not be cancer-related.

Gonadotropins have been implicated in ovarian carcinogenesis but direct evidence has been limited and inconsistent [5]. Hormone blockade is not standard practice in conventional ovarian cancer treatment. Studies have shown that ovarian cancer cells can express hormone receptors for estrogen, progesterone and Her-2/neu and that steroid hormone receptor status possesses prognostic significance [6, 7]. Hormonal therapy, typically progestogens or tamoxifen, is commonly prescribed to patients with potentially hormone-sensitive recurrent or metastatic gynecological cancers with very variable clinical benefit reported [8]. The role of aromatase inhibitors in gynecological cancers is uncertain and has not been well studied, although they do appear to be active. Recurrences of ovarian cancer have been treatment with aromatase inhibitors with variable response rates although responders can experience significant disease stabilization. It is unclear if these responses may be predicted by estrogen receptor expression or aromatase expression [9].

Because 50–60% of non-mucinous ovarian carcinomas have estrogen receptors [10] a relationship between HRT and occurrence of ovarian carcinoma is possible in principle [11]. Studies on HRT and risk of epithelial ovarian cancer have produced conflicting results but most data seem to exclude a strong association. A recent review of 20 pertinent studies [12] reached no satisfactory conclusion, as all studies differed in size, outcome and exposure, so that no reliable comparison is possible. Five studies described a slightly increased risk associated with HRT [13-17] whereas 15 did not. Several studies have shown that, in fact, prognostic

outcomes are improved for patients taking HRT, including fewer recurrences. A study by Silverberg *et al*. compared clinical and pathologic findings in 43 postmenopausal endometrial carcinoma patients who had received exogenous estrogens prior to diagnosis and 79 similar patients unexposed to estrogens. Estrogen non-users were more likely to manifest lower parity, later menopause, obesity, hypertension, and diabetes, all of which have been considered to be constitutional risk factors for the development of endometrial carcinoma. Although estrogen users and non-users had similar extent of disease as judged by clinical stage, there was a tendency to more frequency of unfavorable histologic types and grades of tumor. At short-term follow-up, more recurrences occurred in non-users of estrogen, and this tendency appeared to be independent of clinical stage, histologic type, histologic grade, or modality of treatment [18]. Currently, there is no conclusive evidence supporting an increased risk of ovarian cancer associated with HRT use or the use of HCAM [10]. While no data contraindicate HRT or HCAM use in epithelial ovarian cancer survivors, current studies do not allow us to exclude the possibility that estrogens alone could stimulate ovarian cancer growth in a small fraction of patients [19].

Some HCAM have the potential for interaction with conventional treatments utilized to minimize or eliminate the effects of sex steroid hormones on tumor cells (i.e. aromatase inhibitors and tamoxifen). Indiscriminant use of these therapies as adjuncts to conventional therapies has the potential to affect treatment efficacy and may be detrimental to the achievement of adequate hormone blockade and may independently stimulate the growth of existing or residual hormone-sensitive cancer cells. This may lead to under treatment of disease have a negative impact on long-term clinical outcomes including increased morbidity and mortality.

In light of the frequency with which women use CAM substances and potentially CAM substances with hormone influencing actions, it is necessary for patients and their providers to have access to evidence-based information regarding CAM thought to have hormone or hormone-like activity in order to avoid potentially deleterious effects. The goals of this study were: 1) to describe the characteristics of HRT and HCAM users including demographic and disease characteristics, conventional treatment, co-morbidities and health-related quality of life (HRQL); 2) to describe the use of HRT and HCAM in a group of ovarian cancer patients, including the temporal sequence of use (pre-diagnosis, post-diagnosis and current use); and 3) to describe the types of HCAM ovarian cancer patients are using in order to broaden the body of information which is currently available to patients, researchers and clinicians.

METHODS

Study Design

Data were collected in a study funded by the Marsha Rivkin Center for Ovarian Cancer Research which was conducted by M. Robyn Andersen, Ph.D., M.P.H. at the Fred Hutchinson Cancer Research Center. The study consisted of a cross-sectional survey regarding the use of contraindicated CAM substances (including HCAM) and was provided to all women with ovarian cancer associated with two Seattle-area participating gynecologic oncology practices. The goal of this cross-sectional survey was to develop a detailed understanding of the CAM use by women with ovarian cancer throughout the course of their treatment, including use of CAM prior to diagnosis, during chemotherapy, after chemotherapy, during radiation, after radiation and at the time of the survey (current use). Participating women were between 6 months and 10 years post-diagnosis with most women completing the survey less than 2 years post-diagnosis. Analyses of this dataset have examined CAM use at the time of initial ovarian cancer surgical treatment and use of CAM during chemotherapy. These prior analyses have focused on CAM substances thought to be contraindicated for use by women undergoing surgery or to be contraindicated for use by women using specific standard chemotherapies (endocrine therapies were not included in the prior study). Prior analyses have not examined hormone-modulating CAM substance use in this population.

The study questionnaire was developed though discussion by the team of study investigators which included health psychologists, gynecologic oncologists and naturopathic physicians, and included sections assessing patient demographics, conventional oncology treatments, CAM therapies, and lifestyle and health behaviors. Women were asked to indicate the year and stage of their cancer at diagnosis and the types of conventional treatment they received (surgery, chemotherapy, radiation). Questions about CAM therapies included CAM activities (meditation, yoga, homeopathy, biofeedback, mental imagery, journaling and prayer) as well as questions about the use of specific ingestible CAM substances prior to diagnosis, during chemotherapy, after chemotherapy, during radiation, after radiation and current use. For CAM substances commonly ingested as food (e.g., garlic, grapefruit juice, green tea, soy etc.) patients were asked to indicate use only if in quantities ingested were greater than those associated with common cooking, for example if concentrated, dried, encapsulated, or powdered forms were used.

Participants were defined as CAM users if they indicated participating in meditation, yoga, homeopathy, biofeedback, mental imagery, journaling or prayer; or reported using at least one of the ingestible CAM substances included on the questionnaire. HCAM were included in the greater list of CAM substances in the questionnaire. These substances were identified as being hormonally active based on published evidence about such activity. Appendix I describes these substances including their traditional use, cancer-specific use and hormonal activities in more detail.

Study Participants

Study methods and questionnaires were approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and Swedish Medical Center in Seattle Washington. The authors have no conflicts of interest to declare regarding the work described. We conducted a cross sectional survey of women with ovarian cancer who received treatment at two gynecologic oncology practices. Those who were believed to be alive, to speak English fluently and were over the age of 21 were considered eligible for this study. Eligible women (total n=450) were approached by mail through their oncologist and asked to participate in the research study by completing a questionnaire. Survivors were sent a packet containing: a letter describing the study, two copies of the informed consent form, a questionnaire, and a self-addressed postage paid envelope in which to return their consent form and questionnaire. Calls were made approximately two weeks later to individuals diagnosed less than two years previously who did not respond to the initial mailing. Of the 447 women recorded in practice records who met eligibility, 388 had current contact information and were approached to participate. Six were recently deceased and 219 (56.4% of those approached) returned the questionnaire. Of the 219 participating patient survivors, 60 (27.4%) were less than 2 years post-diagnosis, 81 (37.0%) were 2–5 years post-diagnosis and 78 (35.6%) were more than 5 years post-diagnosis. Table 4 shows the demographics of responding participants. The majority (62.6%) presented with advanced stage disease, 6.4% with stage II, and 19.18% with stage I disease. Nineteen women (8.68%) did not know the stage of their cancer at the time of diagnosis and seven (3.2%) did not answer the question.

Group Definitions

For the purposes of this analysis these women fell into four categories: 1) those women who used have used HRT since their diagnosis of ovarian cancer and/or those who have used HRT to treat the symptoms of menopause, 2) those women who have used HCAM prior to their diagnosis of ovarian cancer, or HCAM use at any time during the course of conventional treatment, or current use of HCAM, 3) those women who have used some combination of HRT and HCAM (HH), and 4) those women who have neither used HRT nor HCAM (NH).

Data Collection

The survey was developed to collect longitudinal data regarding conventional treatment and use of CAM activities and substances, including HRT and HCAM use. The study asked women about their use from the time prior to their ovarian cancer diagnosis through the time of survey completion regardless of stage and treatment course. The survey also includes women in remission and those with recurrences receiving subsequent courses of treatment. Table 1 describes the general categories of data collected from each participant. Survivors were asked their age, other demographic questions, whether they received surgery, chemotherapy, or radiation, for the treatment of their cancer and if they were currently attending visits for ongoing care including hormonal therapies, or specific tests as part of follow-up care after cancer treatment.

Women were also asked a series of questions about their use of CAM treatments including herbs and supplements, CAM activities, use of CAM providers (naturopaths, massage therapists, and chiropractors), and about their functional health status using the SF-36 as a measure of quality of life. Health related quality of life (HRQOL) was measured using the SF- 36, which assesses several aspects of functional status including physical, social, and psychological functioning [14]. This measure consists of 36 items designed to measure eight dimensions of quality of life and has been found to measure quality of life across a broad range of levels of general functioning, and is sensitive to changes in general life functioning common in relatively healthy populations [20-22].

Table 1. General Categories of Data Collection

Cancer History	HCAM Lifestyle	CAM Lifestyle (part 2)	Lifestyle and General Health	Lifestyle and General Health (part 2)	Background Information
Stage (1)	HCAM practices (8)	Involvement in decision making (7)	Co-morbidities (1)	General health (6)	DOB (1)
Treatment (14)	HCAM use and timing (8)	Thoughts about ovarian cancer (19)	Smoking history (3)	Limitations of activities (9)	Ethnicity (1)
Side Effects (1)	HCAM information (8)	Post traumatic distress (20)	BMI (2)	Physical health problems (4)	Hispanic/Latino (1)
Recurrence (2)	HCAM disclosure (4)		Diet (2)	Emotional health problems (3)	Level of Education (1)
HRT use (2)			Exercise (2)	Social activities (2)	
				Pain (2)	
				Energy and emotions (8)	

*Number of questions in each category in parenthesis

Data Analysis

Our first aim was to describe the extent to which there were differences in demographics, disease characteristics, co-morbidities, and treatments among women in each group. We expected that differences in HCAM use by stage would describe the degree to which the women in each group did or did not increase their utilization of HCAM. Based on previously published studies, we estimated that approximately 44% (n=96) of this population of ovarian cancer patients would use HCAM [1].

Our second aim was to describe the frequency of use of HRT and HCAM, including the temporal sequence of use (prior to diagnosis, during chemotherapy, after chemotherapy, during radiation, after radiation and current use). Based on the clinical experience of the participating gynecologic oncology practices, 60% were expected to have either stage III or stage IV disease (n = 131) and 40% of patients were expected to have stage I/II disease (n = 88). These numbers are such that adequate numbers of patients were available to describe both the use of HRT and HCAM used by these women by stage. Additionally, approximately 50% (n= 109) of participants were expected to have completed primary treatment and 50% (n = 110) were expected to be in treatment secondary to a recurrence. We anticipated that 44% of these women would have a history of HRT

and HCAM use at some point during their treatment course (n=48 of those who completed primary treatment, n=48 those being treated for recurrence) [1]. Changes in HRT and HCAM use were stratified by stage of disease and temporal sequence of use. This allowed us to evaluate use of, and changes in, HRT and HCAM prior to diagnosis, over the entire treatment course and in the post-treatment period.

Our third aim was to describe the types of HCAM this group of ovarian cancer patients were using. Description of HCAM use included assessments of the frequency with which patients use HCAM and descriptions of the frequency with which patients use specific HCAM therapies (e.g. specific herbal substances, dietary supplements, vitamins and minerals). HCAM use was also described for the time periods prior to diagnosis, during treatment, and in the post-treatment period. Again, we anticipated that 44% of these women would have a history of HCAM use at some point during their treatment course (n=96) [1] which would allow us to describe the most commonly used types of HCAM described in this survey by stage of disease and temporal sequence.

For each of these three aims, grouped variables were created for variables with continuous outcomes measures (e.g., the average years of education in each group, differences in income between the groups etc.). Differences between these newly created dichotomous or polycotomous variables were evaluated using Fischer's Exact test due to the limited size of each group.

RESULTS

The overall demographics of this population are summarized in Table 2. The mean age of this population was 63 years of age. Eighty-four percent were white and 37% had college degrees with 27% reporting at least some college. Thirty-seven percent were between 2 and 5 years since their diagnosis of ovarian cancer and 51% of women had stage III disease at diagnosis.

Aim 1: To describe the characteristics of each group, including demographic and disease characteristics, conventional treatment, comorbidities and HRQL.

Table 2 describes group-specific demographic characteristics including age, race/ethnicity and highest level of education attained. There are no statistically significant differences between the groups in terms of these variables. The age distribution between groups was similar, with the majority of women between 55-74 years of age. The majority in each group were white although the HCAM group included a larger number of women from other ethnic groups (Native American, Asian and African-American) compared to the HRT group, though these differences did not reach statistical significance. There were also no differences between groups in highest level of education attained. The majority in each group had a minimum of some college (HCAM 23%, HRT 23%, HH 25%, NH 32%) with most having earned a college degree (HCAM 39%, HRT 50%, HH 50%, NH 27%) (p=.339). Table 3 summarizes differences in lifestyle and health characteristics between groups. Though none of these analyses were statistically significant, we found the groups to be fairly homogeneous. Height and weight distributions were comparable between groups as were exercise frequency (57% exercise 1-4 times per week), number of produce servings (70% consume 1-2 produce servings per day), and following a low-fat eating plan (55%). For all groups the majority were non-smokers (58%) or past smokers (37%) with only 2% reporting current cigarette use. Additionally the number of comorbidities between groups was similar with 57% having between 1 and 3 additional health concerns.

Table 4 examines disease and treatment differences between groups. We anticipated that, based on the clinical experience of the participating gynecologic oncology practices, 60% of participants were likely to have either stage III or stage IV disease (n = 131) and 40% of patients would be expected to have stage I/II disease (n = 88). Additionally, we estimated that approximately 50% (n= 109) of participants would have completed primary treatment and 50% (n = 110) would be in treatment secondary to a recurrence. We in fact found that overall, 51% (n=112) of women were stage III at diagnosis. Thirty-eight percent of participants (n=83) had stage I/II disease and 63% (n=137) had stage III/IV disease. 22% (n=26) of HCAM users vs. 39% (n=18) of HRT users had stage I/II disease, and 66% (n=79) HCAM users vs. 54% (n=25) HRT users had stage III/IV disease. In the HH group, 38% (n=9) had stage I/II disease and 63% (n=25) had stage III/IV disease (p=ns).

Thirty-seven percent (n=81) of participants had experienced a recurrence at the time of survey completion. Of those with a recurrence, 54% (n=44) were receiving treatment. Interestingly, a minority of women in the HCAM and HRT groups had experienced recurrence of their disease (36% and 27% respectively) while 58% of women in the HH group had recurrent disease (p=.291). It also appears that women in the HH group are experience recurrent disease sooner than their HCAM alone or HRT counterparts. Thirty-seven percent (n=81) of women were between 2-5 years post-diagnosis and 36% (n=78) were more than 5 years from their diagnosis at the time of survey completion. Between groups, HCAM users appeared to have the fewest number of participants 5 years or more from diagnosis. (HCAM 29%, HRT 55%, HH 54%, NH 32% p=.094). Twenty-five percent (n=6) of HH users experience recurrence between 25-60 months after completing chemotherapy as compared to 4% (n=4) of HCAM users and 5% (n=1) of HRT users (p=.042). HH users are also less likely than HCAM and HRT alone users to be disease-free at >120 months (50% vs. 68 and 77%, respectively, p=.042). These findings suggest that women with recurrent disease may be more willing to utilize a broader range of treatment options, including CAM therapies, for their cancer.

HH users also score lower on the SF-36 physical health subscale. Forty-two percent (n=10) of HH users score from 26-50 on the physical health subscale, while the majority of HCAM and HRT users (37% and 41%, respectively) score in the 76-100 range. HH users also score lower on the SF-35 mental health subscale with only 33% (n=8) scoring in the 76-100 range as compared to 54% (n=51) of HCAM users and 64% (n=14) of HRT users (p=.429). These findings are consistent with other research describing low SF-36 scores in patients requiring more physician-based medical services than users of conventional medicine. This appears to be primarily the result of an increase in the number of health conditions and symptoms reported by CAM users with a variety of medical conditions, including cancer [23-25].

Table 2. Demographic Information

DEMOGRAPHIC VARIABLES	GROUP n (%)					
	HCAM N=95	HRT N=22	HH N=24	NONE N=78	TOTAL N=219	PVALUE*
Age**						1.0
25-34	0	2(9)	1(4)	2(3)	5(2)	
35-44	1(1)	3(14)	2(8)	3(4)	9(4)	
45-54	10(11)	3(14)	4(17)	9(12)	26(12)	
55-64	31(33)	6(27)	11(46)	27(35)	75(34)	
65-74	24(25)	4(18)	4(17)	19(24)	51(23)	
75-84	13(14)	2(9)	1(4)	5(6)	21(10)	
85-94	3(3)	0	0	7(9)	10(5)	
Ethnicity						.671
American Indian	2(2)	0	1(4)	3(4)	6(3)	
Asian	3(3)	0	1(4)	0	4(2)	
African American	1(1)	0	0	0	1(.5)	
Multiple	5(6)	1(5)	0	2(3)	8(4)	
Other	0	0	0	2(3)	2(1)	
Caucasian	76(87)	21(95)	22(92)	70(91)	189(90)	
Hispanic/Latino						.086
No	95(100)	22(100)	24(100)	74(95)	215(98)	
Yes	0	0	0	4(5)	4(2)	
Highest Level of Education Attained**						.339
Some high school	5(5)	0	0	2(3)	7(3)	
High school graduate	13(14)	3(14)	0	14(18)	30(14)	
Some college	22(23)	5(23)	6(25)	25(32)	58(26)	
College degree	37(39)	11(50)	12(50)	21(27)	81(37)	
Postgraduate degree	16(17)	6(25)	6(25)	16(21)	41(19)	

*Fishers Exact test measuring association between groups and demographic variables

** Number of missing data points (n): age (22); education (2)

Table 3. Lifestyle and Health Characteristics

LIFESTYLE VARIABLES	GROUP n (%)					
	HCAM N=95	HRT N=22	HH N=24	NONE N=78	TOTAL N=219	PVALUE*
Height (in)**						.849
50-55	18(19)	1(5)	3(13)	16(21)	38(17)	
56-60	16(17)	3(14)	6(25)	12(15)	37(17)	
61-65	32(34)	11(50)	7(29)	31(40)	81(37)	
66-70	25(26)	7(32)	8(33)	17(22)	57(26)	
>70	3(3)	0	0	1(1)	4(2)	
Weight (lbs.)**						.760
≥100	2(2)	2(9)	0	2(3)	6(3)	
101-150	43(45)	10(45)	13(54)	36(46)	102(47)	
151-200	34(36)	8(36)	10(42)	31(39)	83(3)	
201-250	12(13)	1(5)	0	6(8)	19(9)	
251-300	1(1)	1(5)	1(4)	2(3)	5(2)	
>300	1(1)	0	0	0	1(.5)	
30 Minute Exercise Frequency/Week**						.231
None	14(15)	3(14)	2(8)	16(21)	35(16)	
1-4	53(56)	15(68)	15(63)	42(54)	125(57)	
5-10	26(27)	3(14)	5(21)	12(53)	46(21)	
Produce Servings						.225
None	2(2)	1(5)	0	2(3)	5(2)	
1-2	59(62)	14(64)	19(79)	62(79)	154(70)	
3-4	28(29)	7(32)	5(21)	13(17)	53(24)	
5+	6(6)	0	0	1(1)	7(3)	
Low-fat Diet**						.267
No	29(31)	6(27)	9(38)	37(47)	81(37)	
Yes	57(60)	13(59)	15(62)	35(45)	120(55)	
Don't know	8(8)	3(14)	0	5(6)	16(7)	
Smoker**						.613
No	55(58)	16(73)	15(63)	41(53)	127(58)	
Yes-current	3(3)	0	0	2(3)	5(2)	
Yes-past	35(37)	5(23)	8(33)	32(42)	80(37)	
Don't know	0	1(5)	0	2(3)	3(1)	
Number of Comorbidities						.577
None	11(12)	5(23)	4(17)	14(18)	34(16)	
1-3	52(55)	12(55)	14(58)	46(59)	124(57)	
4-6	25(26)	5(23)	3(13)	12(15)	45(21)	
7-9	6(6)	0	3(13)	6(8)	15(7)	
>9	1(1)	0	0	0	1(.5)	

*Fishers Exact test measuring association between groups and lifestyle and health characteristics variables
** Number of missing data points (n): height (2); weight (3); exercise (13); low-fat diet (2); smoker (4)

Table 4. Disease and Treatment Characteristics

TREATMENT VARIABLES	GROUP n (%)					
	HCAM N=95	HRT N=22	HH N=24	NONE N=78	TOTAL N=219	PVALUE*
Stage at Diagnosis						.253
Stage I	13(14)	8(36)	6(25)	15(19)	42(19)	
Stage II	4(4)	1(5)	3(13)	6(8)	14(6)	
Stage III	51(54)	8(36)	13(54)	40(51)	112(51)	
Stage IV	13(14)	1(5)	2(8)	9(12)	25(11)	
Don't know	14(15)	4(18)	0	8(10)	26(12)	
Years Since Diagnosis						.094
<2	30(32)	2(9)	4(17)	24(31)	60(27)	
2-5	37(39)	8(37)	7(29)	29(37)	81(37)	
>5	28(29)	12(55)	13(54)	25(32)	78(36)	
Postsurgical chemotherapy**						.889
No	7(7)	2(9)	3(13)	4(5)	16(7)	
Yes	86(91)	20(91)	21(88)	73(94)	200(91)	
Don't know	1(1)	0	0	0	1(.5)	
Chemotherapy Reduced**						.239
No	58(61)	16(73)	12(50)	46(59)	132(60)	
Yes	9(9)	4(18)	3(13)	14(18)	30(14)	
Don't know	18(19)	0	6(25)	13(17)	37(17)	
Chemotherapy Delayed**						.554
No	65(68)	12(55)	16(67)	48(62)	141(64)	
Yes	19(20)	8(36)	4(17)	23(29)	54(25)	
Don't know	1(1)	0	1(4)	2(3)	4(2)	
Chemotherapy side effects						.506
None	14(15)	4(18)	7(29)	19(24)	44(20)	
1-5	54(57)	10(45)	13(54)	43(55)	120(55)	
6-10	24(25)	6(27)	4(17)	14(18)	48(22)	
>10	3(3)	2(9)	0	2(3)	7(3)	
Currently receiving treatment**						.802
No	66(69)	18(82)	17(71)	50(64)	151(69)	
Yes	26(27)	4(18)	7(29)	24(31)	61(28)	
Cancer recurrence**						.291
No	52(55)	16(73)	10(42)	42(54)	120(55)	
Yes	34(36)	6(27)	14(58)	14(58)	81(37)	
Don't know	6(6)	0	0	0	9(4)	
Number of months after chemotherapy-recurrence						.042
None	1(1)	0	0	0	1(.5)	
1-6	9(9)	0	2(8)	3(4)	14(6)	
6-24	13(14)	2(9)	4(17)	16(21)	35(16)	
25-60	4(4)	1(5)	6(25)	6(8)	17(8)	
61-120	3(3)	9(9)	0	0	5(2)	
>120	65(68)	17(77)	12(50)	53(68)	147(67)	
Clinical Trials**						.830
No	59(62)	15(68)	15(63)	53(68)	142(65)	
Yes	29(31)	6(27)	7(29)	16(21)	58(26)	
Don't know	3(3)	0	1(4)	6(8)	10(5)	

*Fishers Exact test measuring association between groups and disease and treatment characteristics variables ** Number of missing data points (n): post-surgical chemotherapy (2); chemotherapy reduced (20); chemotherapy delayed (20); currently receiving treatment (7); cancer recurrence (9); clinical trials (9)

Table 5. Health-related Quality of Life

SF-36 SUBSCALE SCORES	GROUP n (%)					
	HCAM N=95	HRT N=22	HH N=24	NONE N=78	TOTAL N=219	PVALUE*
Physical Health**						.374
0-25	0	0	0	1(1)	1(.5)	
26-50	16(17)	3(14)	10(42)	17(22)	46(21)	
51-75	29(31)	7(32)	2(8)	20(26)	58(26)	
76-100	35(37)	9(41)	9(38)	27(35)	80(37)	
Mental Health**						.429
0-25	1(1)	0	0	0	1(.5)	
26-50	12(13)	1(5)	5(21)	9(12)	27(12)	
51-75	19(20)	3(14)	8(33)	24(31)	54(25)	
76-100	51(54)	14(64)	8(33)	37(47)	110(50)	

*Fishers Exact test measuring association between groups and SF-36 subscale variables
** Number of missing data points (n): physical health (34); mental health (27)

Aim 2: To describe the use of HRT and HCAM in this cohort of ovarian cancer patients, including the temporal sequence of use (pre-diagnosis, post-diagnosis and current use).

Based on previously published estimates of CAM use between 44-53% in gynecologic oncology patients [1], we estimated that approximately 96-116 participants would have a history of HCAM use and 103-123 would not be users of HCAM. We found that sixty-four percent (n=141) of participants had either used HRT or HCAM at some point during their treatment course. A total of 54% (n=119) women participating in this survey were HCAM users; 43% (n=95) of these women used HCAM alone. Twenty-one percent (n=46) of women used HRT with 10% (n=22) using HRT alone. Twenty percent of women surveyed (n=24) used some combination of HCAM and HRT. Thirty-six percent (n=78) of participants used neither HCAM nor HRT at any time surveyed.

Questions about HRT use were two-part questions written to capture use since diagnosis and type of HRT used, and use for menopause and type used. For the question regarding HRT use since diagnosis, we found that three women did not mark YES to the use of HRT since diagnosis however, they went on to mark the type of HRT used in the second part of the question. Participants were queried separately about the temporal sequence of HRT use. For the purposes of analysis, we chose to include these women as part of the HRT group, bringing the total number of HRT users (post-diagnosis and for menopause) to 46. We found that 48% (n=22) of women in the HRT group reported using HRT after diagnosis and 46% (n=21) reported using HRT for menopause. Of those women reporting post-diagnosis HRT use, 86% (n=19) also report they are using it for menopause and 5% (n=1) report they are also using some form of CAM. Of those women reporting HRT use for menopause, none report additional use of CAM. When asked specifically about post-diagnosis HRT use, 8 of 55 respondents (15%) reported they used CAM instead. When asked specifically about HRT use for menopause, 6 of 30 respondents (20%) reported they used CAM instead. Of women using HRT since their diagnosis, 50% (n=23) are using estrogen alone and another 24% (n=11) are using a hormone patch. Of women using HRT for menopause, 43% (n=9) are using estrogen alone and 38% (n=8) are using a hormone

patch. In the HRT group overall, only 7% (n=3) women are using progesterone alone, 9% (n=4) report using estrogen and progesterone in combination, and 7% (n=3) use bio-identical hormone preparations.

When stratified by stage of disease at diagnosis, women with stage I and stage III disease were the most intensive users of HRT; 30% (n=14) were stage I, 9% (n=4) stage II, 46% (n=21) stage III and 7% (n=3) stage IV. For those using HRT since diagnosis, 30% (n=14) were stage I, 9% (n=2) stage II, 41% stage III, and 4% stage IV, as compared to 33% (n=7), 5% (n=1), 48% (n=10) and 10% (n=2) respectively for those using HRT for menopause. As a group, 46% (n=21) of women were using some form of HRT before diagnosis. Fifty-two percent (n=24) of respondents reported using HRT at some point during treatment and 13% (n=6) reported current use. When the temporal sequence of HRT use was stratified by stage of disease at diagnosis we found HRT use to be similar for stages I-III (p=ns). The data for stage IV participants suggests less frequent use with only one participant indicating use after chemotherapy and one participant indicating current use. Regardless of stage of disease at diagnosis, HRT users continued their use of HRT after diagnosis and also used these substances consistently during and after chemotherapy. The percentage of women using HRT at any time during radiation is low, which is consistent with the limited use of radiation therapy in the treatment of ovarian cancer.

Questions regarding the temporal sequence of HCAM use were written broadly to include the period before diagnosis, post-diagnosis (during chemotherapy, after chemotherapy, during radiation and after radiation) as well as current (time of survey) use. Overall, 64% (n=76) of the HCAM group were using HCAM before their diagnosis, 59% (n=70) during chemotherapy, 64% (n=76) after chemotherapy, 6% (n=7) during radiation, 5% (n=6) after radiation and 34% (n=75) reported current use. When the temporal sequence of HCAM use was stratified by stage of disease at diagnosis we found the data to be homogenous across groups (p=.727). Regardless of stage of disease at diagnosis, HCAM users continued their use of HCAM after diagnosis and also used these substances consistently during and after chemotherapy. Again, the percentage of women using HCAM at any time during radiation is low, which is consistent with the limited use of radiation therapy in the treatment of ovarian cancer.

Table 6. HRT Use

HRT	GROUP n (%)				
	HCAM N=95	HRT N=22	HH N=24	NONE N=78	TOTAL N=219
HRT post-diagnosis**					
No	83(87)	0	1(4)	76(97)	160(73)
Yes	0	22(100)	21(89)	0	43(20)
No, but I use	7(7)	0	1(4)	0	8(4)
Unknown	2(2)	0	0	2(3)	4(2)
HRT post-diagnosis type**					
Estrogen	0	14(63)	9(38)	0	23(11)
Progesterone	0	0	2(8)	0	2(1)
Both	0	2(9)	1(4)	0	3(1)
Patch	0	5(23)	6(25)	0	11(5)
Bio-ID	0	0	3(13)	0	3(1)
HRT for menopause**					
No	84(88)	11(50)	12(50)	77(99)	184(82)
Yes	0	10(45)	11(46)	0	21(10)
No, but I use	5(5)	0	1(4)	0	6(3)
Unknown	1(1)	1(5)	0	1(1)	3(1)
HRT menopause type**					
Estrogen	0	5(23)	4(17)	0	9(4)
Progesterone	0	0	1(4)	0	1(.5)
Both	0	1(5)	0	0	1(.5)
Patch	0	4(18)	4(17)	0	8(4)
Bio-ID	0	0	0	0	0

** Number of missing data points (n): HRT post-diagnosis (4); HRT post-diagnosis type (177); HRT for menopause (5); HRT menopause type (200)

Table 7. HRT Use by Temporal Sequence and Stage at Diagnosis

HRT USE (n=46)	HRT GROUP n (%)					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
Before Diagnosis	4(36)	2(29)	11(42)	0	3(75)	21(46)
During Chemotherapy	3(27)	1(14)	4(15)	0	0	8(17)
After Chemotherapy	3(27)	3(43)	6(23)	1(50)	1(25)	14(30)
During Radiation	0	0	1(4)	0	0	1(2)
After Radiation	0	0	1(4)	0	0	1(2)
Current	1(9)	1(14)	3(12)	1(50)	0	6(13)

Table 8. HCAM Use by Temporal Sequence and Stage at Diagnosis

HCAM USE (n=119)	HCAM GROUP n (%)					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
Before Diagnosis	16(38)	6(43)	34(30)	9(36)	11(42)	76(64)
During Chemotherapy	8(19)	5(36)	43(38)	10(40)	4(15)	70(59)
After Chemotherapy	9(21)	6(43)	45(40)	12(48)	4(15)	76(64)
During Radiation	0	0	3(5)	3(19)	1(7)	7(6)
After Radiation	0	0	3(5)	3(19)	0	6(5)
Current	12(29)	3(21)	42(38)	12(48)	6(23)	75(34)

Aim 3: To describe the HCAM ovarian cancer patients used in this study.

Table 9 lists the CAM practices surveyed for this study. Those practices with the highest percentage use across groups include exercise (57% p=.222), dietary practices (40% p=.002) and prayer (52% p=.052). The use of meditation did reach statistical significance (p=.036) and was the fifth most commonly used CAM practice after exercise, prayer, dietary practices, and massage (23% p=.099). Between groups the use of massage, naturopathy, traditional Chinese medicine (TCM), meditation and support groups were higher among the HCAM and HH groups (26 and 38%, 26 and 42%, 18 and 25%, 26 and 38%, 21 and 25%, respectively) as compared to the HRT and NH groups (18 and 15%, 5 and 5%, 9 and 8%, 18 and 13%, 14 and 15%, respectively). HH users reported the highest use of CAM practices overall. Sixteen CAM practices were surveyed and HH users represented the highest percentage use for 10 of them (63% p=.198). HCAM users were the highest percentage users in the remaining 6 of 16 (38% p=.062) categories.

Table 10 presents the list of HCAM substances surveyed. The substances used by the most number of participants include; green tea 54% (n=64), fish oil 51% (n=61), flax seed oil 38% (n=45), melatonin 23% (n=27), garlic 21% (n=25) and ginger 20% (n=24). Seventy-two percent (n=46) of green tea use, 69% (n=42) of fish oil use and 58% (n=26) of flax seed oil use took place after chemotherapy. Melatonin and ginger were being used during chemotherapy (63%, n=17 and 63%, n=15 respectively) while 72% (n=18) of garlic use was prior to diagnosis. The highest percentage of reported HCAM use at any time during treatment is after chemotherapy (50%) followed by before diagnosis (29%), during chemotherapy (21%) and current use (17%).

Table 9. CAM Practices

CAM PRACTICES	GROUP n (%)					
	HCAM (n=95)	HRT (n=22)	HH (n=24)	NONE (n=78)	TOTAL (n=219)	PVALUE*
Chiropractic	9(9)	1(5)	2(8)	6(8)	18(8)	.943
Massage	25(26)	4(18)	9(38)	12(15)	50(23)	.099
Naturopathic	25(26)	1(5)	10(42)	4(5)	40(18)	0
Hypnosis	1(1)	0	0	0	1(.5)	1.0
TCM**	17(18)	2(9)	6(25)	6(8)	31(14)	.081
Meditation	25(26)	4(18)	9(38)	10(13)	48(22)	.036
Exercise	55(58)	14(64)	17(71)	38(49)	124(57)	.222
Diet	45(47)	7(32)	15(63)	20(26)	87(40)	.002
Yoga	13(14)	3(14)	5(21)	7(9)	28(13)	.428
Support group	20(21)	3(14)	6(25)	12(15)	41(19)	.618
Homeopathy	9(9)	1(5)	1(4)	3(4)	14(6)	.510
Biofeedback	2(2)	0	0	1(1)	3(1)	1.0
Imagery	18(19)	5(23)	6(25)	12(15)	41(19)	.641
Journal	18(19)	4(18)	6(25)	9(12)	37(17)	.353
Prayer	59(62)	8(37)	10(42)	37(47)	114(52)	.052
Other	9(9)	1(5)	2(8)	6(8)	18(8)	.943

*Fishers Exact test measuring association between groups and CAM practices variables
**TCM=Traditional Chinese Medicine

Table 10. HCAM Use

CAM SUBSTANCES (n=119)	PHASE OF TREATMENT n (%)						
	Before diagnosis	During chemotherapy	After chemotherapy	During RT*	After RT	Current use	Total
Black Cohosh	8(53)	3(20)	6(40)	0	0	3(20)	15(13)
Coumestrol	0	0	0	0	0	0	0
DHEA	2(33)	1(17)	3(50)	0	0	4(67)	6(5)
Dong Quai	2(50)	1(25)	3(75)	1(25)	1(25)	0	4(3)
Evening Primrose Oil	5(83)	1(17)	3(50)	1(17)	1(17)	1(17)	6(5)
Fish Oil	33(54)	26(43)	42(69)	3(5)	3(5)	35(57)	61(51)
Flax	21(47)	12(27)	26(58)	1(2)	0	20(44)	45(38)
Garlic	18(72)	10(40)	15(60)	2(8)	2(8)	14(56)	25(21)
Genistein	0	1(50)	2(100)	0	0	2(100)	2(2)
Ginger	7(29)	15(63)	12(50)	1(4)	1(4)	7(29)	24(20)
Gingko	3(38)	1(13)	4(50)	1(13)	1(13)	1(13)	8(7)
Ginseng	0	1(50)	2(100)	0	0	1(50)	2(2)
Grape Seed	10(100)	3(33)	5(50)	1(10)	1(10)	4(40)	10(8)
Grapefruit Juice	5(56)	3(33)	3(33)	0	0	0	9(8)
Green Tea	30(47)	35(55)	46(72)	4(6)	5(8)	31(48)	64(54)
Kava	3(75)	1(25)	2(50)	0	0	1(25)	4(3)
Licorice	3(38)	4(50)	3(38)	0	0	5(63)	8(7)
Melatonin	8(30)	17(63)	12(44)	1(4)	1(4)	13(48)	27(23)
Milk Thistle	1(11)	5(55)	6(67)	0	0	3(33)	9(8)
Reishi	0	5(100)	2(40)	0	0	1(20)	5(4)
Resveratrol	0	3(50)	3(50)	0	0	3(50)	6(5)
Saw Palmetto	0	0	1(100)	0	0	0	1(1)
Soy	0	1(100)	1(100)	0	0	0	1(1)
St Johns Wort	2(67)	1(33)	2(67)	0	0	1(33)	3(3)

*RT=Radiation therapy

DISCUSSION

Given the uncertainty surrounding the significance of the role sex steroid hormones in the development and propagation of ovarian neoplasms and the possibility that increased hormone levels may be detrimental to successful treatment of these cancers it is, at a minimum, important to understand what hormonally active substances patients may be using. This not only includes HRT to minimize the side effects of surgical menopause, but also the use of hormonally-active CAM substances. Patients may be using these substances for a number of reasons including for the treatment of menopausal symptoms, to mitigate the common side effects of conventional cancer treatment (nausea, insomnia, diarrhea or constipation and so on) and for their direct anti-cancer activity. Patients and physicians may not be aware that a CAM substance which is commonly used for insomnia (melatonin) or nausea (ginger) may also have some hormonal action with the potential to affect systemic sex steroid hormone levels. At the present time it is not clear if the women using HRT or HCAM or a combination of the two are at increased risk for recurrent or more progressive disease. The concerns at this point are largely theoretical. For HCAM in particular, most evidence for hormonal activity is based in in vitro or animal studies. To date, there are few human data to support or refute the question of risk. In this sample of ovarian cancer patients from two practices in the greater Seattle area, we found that while only 21% were using HRT, 54% were using one or more hormonally-active CAM substances.

The groups of women surveyed for this analysis were largely similar in terms of demographics, lifestyle and health behaviors. Stage at diagnosis was similar for all groups but a higher percentage of the HH group experienced recurrent disease sooner and had the fewest number of participants 5 years or more from diagnosis than their HCAM or HRT counterparts. HH users also scored lower on the SF-36 physical and mental health subscales than those in the HCAM or HRT groups. Those women with stage I and III disease were the most likely to use HRT. The majority of women (86%) using HRT after diagnosis were using it for symptoms of menopause, most commonly estrogen alone or a hormone patch. The women in this sample also continued to use HRT during conventional treatment. In the HCAM group there did not appear to be any differences in the percentage of HCAM use by stage of disease at diagnosis. Most women reported using HCAM before their diagnosis of ovarian cancer and these women also report continuing to use HCAM during conventional treatment. The HCAM and HH groups were more intensive users of CAM practices including exercise, dietary changes, prayer, massage and meditation than the HRT and NH groups. The HH users reported the highest use of CAM practices overall. Though HCAM substances were used from the period before diagnosis throughout the period of conventional treatment, the highest percentage use was reported after chemotherapy.

Limitations

There are current knowledge gaps in the literature, on the Internet, and within and among health centers in the US regarding research, clinical, and outreach programs in cancer CAM The amount and quality of information

available on various CAM therapies varies widely. One of the frequent criticisms of CAM is that treatment recommendations are not based on the results of randomized clinical trials. Conventional cancer treatments are studied for safety and effectiveness through a rigorous scientific process that includes laboratory research and clinical trials with large numbers of patients. Less is known about the safety and effectiveness of CAM to treat cancer, although some CAM therapies have undergone rigorous evaluation. Currently, no national cancer registry collects detailed data on CAM for use by the research community and information provision or discussion about CAM by health professionals remains low. Additionally, publishing CAM study results in widely read medical journals has faced some resistance. Reliable information on CAM is inconsistently available and often difficult for patients and providers to locate. The quality, accuracy, accessibility, and timeliness of information about CAM varies greatly. Patients and providers may also be unaware of other sources of information on CAM such as books, periodicals, and newsletters. Currently available demographic data do not provide adequate information about CAM usage among various population subgroups or the range of methods and patterns in accessing CAM information. However, it is known that the use of CAM varies significantly by racial, ethnic, and cultural background, age group, health status, income, and literacy.

In the absence of any published data on the comparative use of HRT and HCAM by ovarian cancer patients these analyses must be considered exploratory and the generalizability of the results is limited. The data may also be subject to recall bias as some participants discussed the use of these substances retrospectively. However, because such data are not currently available the description of this group of patients will be informative. Because the survey is limited to women pursuing conventional care, the data may not capture the broadest spectrum of HCAM use in women who choose not to pursue conventional treatment. Prior research also suggests that women with cancer who seek HCAM care may have more advanced disease than those who do not [26]. This study is not sufficient to evaluate the clinical effects of specific HCAM therapies, to answer more general clinical questions such the safety of different types and formulations of HRT, or to make recommendations regarding HCAM use as a safer alternative to HRT. The concerns above necessitate that the resultant paper is limited to a descriptive/comparative analysis of ovarian cancer patient characteristics between HRT, HCAM, HH and NHH groups. Additionally, the probability of type I error, or a false-positive result, is increased secondary to the number of statistical comparisons that were part of this statistical analysis. Keeping the original cohort intact and using an alternative statistical approach such as multiple regression, may have mitigated the probability of obtaining type I errors. Finally, the power to detect significant differences between groups was strongest in the period following diagnosis about which all women in the group could provide data, and gradually diminished over the natural history if this disease (as fewer of the women in the dataset reached some milestones post-diagnosis and thus were able to provide data on long-term survival). The power to detect differences in HCAM and HRT use among women further from diagnosis was less than when these questions were asked about earlier in the disease course.

There is a clear need for additional research regarding the extent to which hormone levels and exogenous hormone supplementation affect morbidity and mortality in ovarian cancer. Additionally there are few data which help us understand the effects of various HCAM substances on hormone levels in women. Understanding which HCAM substances ovarian cancer patients may be using is an important first step. Further studies which capture information on the reasons women are using HCAM, dosage and duration of treatment may help us begin to understand the risks and benefits associated with the use of specific HCAM substances.

REFERENCES

1. Navo, M.A., et al., *An assessment of the utilization of complementary and alternative medication in women with gynecologic or breast malignancies.* J Clin Oncol, 2004. 22(4): p. 671-7.
2. Amato, P., S. Christophe, and P.L. Mellon, *Estrogenic activity of herbs commonly used as remedies for menopausal symptoms.* Menopause, 2002. 9(2): p. 145-50.
3. Secreto, G., et al., *Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study.* Maturitas, 2004. 47(1): p. 11-20.
4. This, P., et al., *Phytoestrogens after breast cancer.* Endocr Relat Cancer, 2001. 8(2): p. 129-34.
5. Pearce, C.L., et al., *Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin.* Cancer, 2009. 115(3): p. 531-9.
6. Buchynska, L.G., et al., *Expression of the estrogen and progesterone receptors as prognostic factor in serous ovarian cancers.* Exp Oncol, 2009. 31(1): p. 48-51.
7. Garcia-Velasco, A., et al., *Prognostic value of hormonal receptors, p53, ki67 and HER2/neu expression in epithelial ovarian carcinoma.* Clin Transl Oncol, 2008. 10(6): p. 367-71.
8. Sjoquist, K.M., et al., *The role of hormonal therapy in gynecological cancers-current status and future directions.* Int J Gynecol Cancer, 2011. 21(7): p. 1328-33.
9. Krasner, C., *Aromatase inhibitors in gynecologic cancers.* J Steroid Biochem Mol Biol, 2007. 106(1-5): p. 76-80.
10. Rao, S.D. and K. Pagidas, *Epigallocatechin-3-gallate, a natural polyphenol, inhibits cell proliferation and induces apoptosis in human ovarian cancer cells.* Anticancer Res, 2010. 30(7): p. 2519-23.
11. Huh, S.W., et al., *Anticancer effects of (-)-epigallocatechin-3-gallate on ovarian carcinoma cell lines.* Gynecol Oncol, 2004. 94(3): p. 760-8.
12. Petranka, J., et al., *The oncostatic action of melatonin in an ovarian carcinoma cell line.* J Pineal Res, 1999. 26(3): p. 129-36.
13. Bartsch, H., et al., *Effect of melatonin and pineal extracts on human ovarian and mammary tumor cells in a chemotherapysensitivity assay.* Life Sci, 2000. 67(24): p. 2953-60.
14. Saydmohammed, M., D. Joseph, and V. Syed, *Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells.* J Cell Biochem, 2010. 110(2): p. 447-56.
15. Xue, H., et al., *Nutrition modulation of gastrointestinal toxicity related to cancer chemotherapy: from preclinical findings to clinical strategy.* JPEN J Parenter Enteral Nutr, 2011. 35(1): p. 74-90.
16. Krishnan, A.V. and D. Feldman, *Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D.* Annu Rev Pharmacol Toxicol, 2011. 51: p. 311-36.
17. Tan, X., et al., *Multiple anticancer activities of EF24, a novel curcumin analog, on human ovarian carcinoma cells.* Reprod Sci, 2010. 17(10): p. 931-40.
18. Yallapu, M.M., et al., *Curcumin induces chemotherapy/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth.* J Ovarian Res, 2010. 3: p. 11.
19. Watson, J.L., et al., *Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling.* Mol Carcinog, 2010. 49(1): p. 13-24.
20. Ware JE, S.K., Kosinski M, Gandek B., *SF-36 health Survey: Manual and Interpretation Guide.* 1993, Boston Massachusetts: The Health Institute,New England Medical Center.
21. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. 30(6): p. 473-83.
22. Ware Jr, J., *The SF-36 health survey.* Second Edition ed. Quality of Life and Pharmacoeconomics in Clinical Trials, ed. S. B. 1996, Philadelphia: Lippincott-Raven.
23. Buettner, C., et al., *Correlates of use of different types of complementary and alternative medicine by breast cancer survivors in the nurses' health study.* Breast Cancer Res Treat, 2006. 100(2): p. 219-27.

24. Carpenter, C.L., P.A. Ganz, and L. Bernstein, *Complementary and alternative therapies among very long-term breast cancer survivors.* Breast Cancer Res Treat, 2009. 116(2): p. 387-96.
25. Ma, H., et al., *The roles of herbal remedies in survival and quality of life among long-term breast cancer survivors--results of a prospective study.* BMC Cancer, 2011. 11: p. 222.
26. Shumay, D.M., et al., *Determinants of the degree of complementary and alternative medicine use among patients with cancer.* J Altern Complement Med, 2002. 8(5): p. 661-71.