Dangerous Combinations: Ingestible CAM Supplement Use During Chemotherapy in Patients with Ovarian Cancer

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Abstract

Objective: Some ingestible complementary and alternative medicine (CAM) supplements, including herbal remedies, teas, and vitamins, have biological activities that make them likely to interact poorly with conventional chemotherapeutic treatments. This study surveyed women with ovarian cancer to document the extent to which women use ingestible CAM supplements and conventional chemotherapeutic treatments that are believed to be of potential concern when used together.

Methods: A total of 219 patients with ovarian cancer who received care from 1 of 2 participating conventional oncology practices were surveyed about CAM use during and after ovarian cancer treatment.

Results: A total of 200 women reported having chemotherapy to treat their ovarian cancer. Of those, 79 (40%) reported using 1 or more CAM supplements that could be cause for concern when taken with 1 or more of the chemotherapy medications they were receiving. Many patients took multiple supplements of potential concern. Of these women, 42% ($n=33$) consulted with a conventional provider and 24% ($n=19$) consulted with a CAM provider about the contraindicated supplements they used.

Conclusion: Although it is not clear that any of these contraindicated combinations of CAM and conventional therapy actually caused adverse outcomes, increased toxicities, or reduced the effectiveness of primary therapies, all these effects are possible given the substances being used in combination. Research is needed to understand the real risk associated with CAM and conventional polypharmacy. If risks associated with CAM use prove substantial, then improved systems to assure that all women get advice regarding supplement use during ovarian cancer treatment will be needed.

Introduction

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) is reported by nearly half of all patients with cancer,^{1,2} although some studies suggest higher rates among some patient groups,³ including those with ovarian cancer.^{4,5} Ingestible complementary and alternative medicine (CAM) supplements, herbs, and vitamins are particularly popular. Although of unknown efficacy, most CAM supplements are safe for healthy people; however, the use of herbs and supplements during chemotherapy is controversial. Herbs, vitamins, and some foods have biological activities that could interact with the activities or metabolism of conventional

pharmaceuticals. Review articles have highlighted these potential interactions and suggested that some supplements should be considered contraindicated for use by patients with cancer undergoing surgery or those receiving active treatment with conventional chemotherapeutic agents.^{6–8} These can be grouped into 2 major categories: (1) antioxidants, which may reduce the action of radiation and some chemotherapies, and (2) substances that may influence the pharmacodynamics of a chemotherapeutic regimen and thereby influence the effectiveness or safety of chemotherapy.

Although antioxidants have different mechanisms of action, all reduce oxidative stress on tissues. Because both antithyroidal and platinum-based chemotherapeutic agents

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are intended to have their therapeutic effects on cancer through the generation of reactive oxygen species, and thus oxidative action, some evidence suggests that antioxidant use might reduce the effectiveness of these chemotherapies.^{8,9} Thus, there are concerns that women with cancer taking substantial doses of antioxidants (including vitamins A, C, and E; beta-carotene; selenium; grape seed extract; and coenzyme Q10) may be reducing the effectiveness of the anthracyclines and platinum-based chemotherapeutic agents they are receiving as part of their treatment. On the other hand, taxanes do not generate high levels of reactive oxygen species and are believed to exert their effects through other means.¹⁰

After antioxidants, the next most important key to understanding when CAM supplements are likely to interact with conventional chemotherapies lies in understanding the importance of CYP pathways on drug metabolism. The most important CYP pathways for the metabolism of oncologic pharmaceutical drugs are those involving the cytochrome P450 enzymes. The CYP cytochrome P450 3A4 isoform (commonly known as CYP3A4) is responsible for metabolizing more than 50% of drugs that pass through the liver, including several chemotherapy drugs used to treat ovarian cancer.^{11,12} Several herbs and other supplements influence its function by speeding up or slowing down the actions of these enzymes and thus have the potential to influence the dose of a drug present in a patient's bloodstream.^{11,12} Assessments of potential interactions of chemotherapy drugs with CAM supplements can be based on their use of known CYP450 metabolism pathways.

For this project, possible CYP conflicts were determined through an extensive literature review. CYP metabolism for the chemotherapy drugs was determined by searches of PubMed, and the Natural Medicines Comprehensive Database (NMCD) was queried for CAM substances and their CYP metabolic effects.¹³ NMCD citations were then entered into the PubMed search engine to more extensively review the literature. The results were then organized by chemotherapy drug and CYP isoforms. For example, paclitaxel is metabolized by CYP isoforms 3A4, 3A5, and 2C8; thus, blood levels of paclitaxel might be affected by any herbs with evidence suggesting that they influence these pathways. Substances that influence CYP isoform 3A4 includes echinacea, garlic, ginkgo, ginseng, omega-3 fatty acids (fish oil), grapefruit juice, green tea, kava, milk thistle, St. John's wort, and valerian. Herbs that influence CYP isoforms 3A5 and 2C8 include bitter orange, black cohosh, devil's claw, feverfew, goldenseal, and licorice.

The goal of this study was to determine the extent to which patients with ovarian cancer were using CAM supplements at times when they might be potentially dangerous when taken with conventional treatments. We also sought to determine how frequently patients discussed their supplement use with physicians, both allopathic physicians (including oncologists and primary care physicians) and CAM-providing naturopathic physicians.

Materials and Method

Participants

We conducted a cross-sectional survey of women with ovarian cancer who received treatment at 2 conventional

medicine-oriented gynecologic oncology practices. Those who were believed to be alive, to speak English fluently, and to be older than age 21 years were considered eligible for this study. Each eligible woman was approached by mail through her oncologist and asked to participate in the study by completing a questionnaire. Women were assured that participation was voluntary and that their care would be unaffected regardless of their decision. In addition, the doctor would receive any information about the CAM use of individual participating patients. Women interested in participating were asked to return a consent statement and a questionnaire in the self-addressed stamped envelope provided. Study methods and questionnaires for this research were reviewed and approved by the institutional review board of the Fred Hutchinson Cancer Research Center. The authors claim no conflict of interest regarding this research.

Overview of Study Methods

The study questionnaire was developed through discussion with the team of study investigators and included sections assessing patient demographic characteristics (i.e., age, education, income, race/ethnicity), conventional and CAM treatment, lifestyle health behaviors, and a section on whom patients consulted for advice about use of herbs and supplements.

Diagnosis and Treatments

Women were asked to indicate the year and stage of their cancer at initial diagnosis and the types of treatment they received. The information included the medications the patients received as part of their chemotherapy treatments, how long those treatments lasted, and whether multiple courses of chemotherapy were used.

To assess CAM use before, during, and after conventional treatment for ovarian cancer, the questionnaire included a large chart listing more than 60 different CAM supplements and describing different phases of conventional cancer treatment (initial surgery, first course of chemotherapy, radiation, after chemotherapy, and the time point when they completed the survey). The list included CAM supplements most commonly used by the general public in national surveys,¹⁴ as well as herbs and vitamin supplements commonly used by patients with cancer and naturopathic physicians for treatment. The other portion of the list of supplements, those commonly used by, or recommended to, patients with cancer, was developed by 2 of the authors (L.J.S. and E.S.) on the basis of clinical experience. In addition to the listed supplements, women were given an opportunity to add any other supplements they were taking that were not included in the list. Patients were asked to use the chart to indicate which of the supplements they used and when they used each during treatment and after chemotherapy. In all cases, women were asked about their use of each substance by name. When questions concerned substances that are also commonly ingested as foods (e.g., garlic, grapefruit juice, cranberry, green tea), patients were asked to note substance use only if it was in "quantities greater than those associated with common cooking" and if they had consumed the substance in "concentrated, dried, encapsulated, or powdered forms."

Participants were deemed users of CAM supplements if they reported ingestion of any of the nearly 60 vitamins,

herbs, or substances and combinations of substances listed on the questionnaire. Participants were not considered CAM users if they used only standard multivitamin combination pills, which were not included in the questionnaire. We did not assess the quantities of the CAM substances beyond the above-noted request that participants report use only if they consumed quantities greater than those associated with normal cooking. Timing of use was assessed as prior to diagnosis, during chemotherapy, after chemotherapy, and at the time of survey completion. The STATA statistical software package (version 10.0, Stata corporation, College station, TX) was used for all analyses. Comparisons were conducted using Fisher's exact test, and were 2-sided and considered statistically significant $P < 0.05$.

Results

Of the 447 women in practice records, 388 had current contact information and were approached to participate. Six had recently died, leaving 382 potential participants not known to be ineligible; 219 of these (56.4% of those approached) demonstrated eligibility and returned the questionnaire. Of the 219 participating patient survivors, 60 (27.4%) were less than 2 years postdiagnosis, 81 (37.0%) were 2–5 years postdiagnosis, and 78 (35.6%) were more than 5 years postdiagnosis. Table 1 shows the demographic characteristics of responding participants. The majority (62.6%) presented with advanced-stage disease, 6.4% with stage II disease, 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 7 (3.2%) did not answer the question. Of the 219 participants, 200 (91.32%) reported having chemotherapy; for 27 of these, this included neoadjuvant chemotherapy before surgery in addition to chemotherapy after surgery (Table 1). Women reported that chemotherapy lasted an average ($\pm$ standard deviation) of 6.43 ± 6.47 months. The most commonly prescribed chemotherapy agents were paclitaxel (76.5%; $n = 153$) and carboplatin (76.5%; $n = 153$). Potential predictors of CAM use, including age, race, education, time since diagnosis, and stage at diagnosis, were examined. Age predicted use of CAM supplements, with use higher among older patients ($p < 0.05$), but no statistically significant differences in rates of use associated with education, race, stage, or time since diagnosis were found.

Table 2 summarizes the number of women who reported use of 1 or more of the antioxidants during chemotherapy. Vitamins A, C, and E were the most commonly used antioxidants, regardless of chemotherapy used. Approximately 25% reported taking 1 or more forms of antioxidant during chemotherapy; 8% took vitamin A, 17% took vitamin C, and 14% took vitamin E. Levels of antioxidant use during chemotherapy were very similar to levels of use reported before diagnosis and at the time of questionnaire completion, regardless of current therapy. Rates of vitamin A, C, and E use were 6%, 21%, and 17%, respectively, before diagnosis and 4%, 19%, and 14%, respectively, at the time of questionnaire completion.

In calculating the percentage of women at potential risk for reduced effectiveness of their chemotherapy because of antioxidant use, only women using anthracyclines (i.e., doxorubicin), or platinum-based chemotherapy agents (carboplatin, cisplatin) were considered potentially at risk because these drugs have actions most dependent on oxidative

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	Data (n = 219)
Mean age $\pm$ standard deviation	62.62 $\pm$ 12
Ethnic background, n (%)	
American Indian	6 (3)
Black or African American	1 (<1)
White	189 (86)
Asian	4 (2)
Native Hawaiian or Pacific Islander	6 (3)
Other	4 (2)
Unknown	9 (4)
Hispanic or Latino, n (%)	
Yes	4 (2)
No	208 (95)
Unknown	7 (3)
Highest level of schooling completed, n (%)	
≤ 8 y	0
Some high school	7 (3)
High school graduate or GED	30 (14)
Some college or technical school	58 (26)
College graduate	81 (37)
Postgraduate degree	41 (19)
Unknown	2 (<1)
Time since diagnosis, n (%)	
< 2 y	60 (27)
2–5 y	81 (37)
> 5 y	78 (36)
Stage of disease at diagnosis, n (%)	
I	42 (19)
II	14 (6)
III	112 (51)
IV	25 (11)
Unknown	26 (12)
Timing of chemotherapy, n (%)	
Before surgery	27 (12)
After surgery	200 (91)
Overall	200 (91)
Chemotherapies taken, n (%) ^a	
Abraxane® (paclitaxel)	1 (0.5)
Alimta® (pemetrexed)	1 (0.5)
Avastin® (bevacizumab)	14 (7)
Carboplatin	153 (77)
Cisplatin	42 (21)
Cytoxan® (cyclophosphamide)	5 (3)
Doxil® (doxorubicin)	11 (5.5)
Gemzar® (gemcitabine)	18 (9)
Hexalen® (altretamine)	1 (0.5)
Ifosfamide	1 (0.5)
Taxotere® (docetaxel)	15 (8)
Taxol® (paclitaxel)	156 (78)
Vinorelbine	1 (0.5)
VP-16	2 (1)
Other	20 (10)
Unknown	30 (15)

^aPercentage calculated by using the 200 women who reported using chemotherapy as part of their treatment as the denominator.

effects. Overall, 27% of women using carboplatin, 31% of those using cisplatin, and 27% of those using doxorubicin were potentially at risk for reduced effectiveness of these medications because of their simultaneous use of antioxidants. Physicians who believe that the oxidative effects of

TABLE 2. PATIENTS TAKING SELECT ANTIOXIDANTS DURING CHEMOTHERAPY

<i>Antioxidant</i>	<i>Any Chemotherapy (n=200)</i>	<i>Bevacizumab (n=14)</i>	<i>Carboplatin (n=153)</i>	<i>Cisplatin (n=42)</i>	<i>Docetaxel (n=15)</i>	<i>Doxorubicin (n=11)</i>	<i>Gemcitabine (n=18)</i>	<i>Paclitaxel (n=156)</i>	<i>Topotecan (n=13)</i>
Beta-carotene	7 (4)	1 (7)	7 (5)	0	0	1 (9)	1 (6)	5 (3)	2 (15)
Coenzyme Q10	12 (6)	0	12 (8)	3 (7)	1 (7)	0	0	12 (8)	1 (8)
Grape seed	3 (2)	0	3 (2)	0	0	0	0	3 (2)	0
Selenium	5 (3)	0	5 (3)	1 (2)	0	0	1 (6)	5 (3)	1 (8)
Vitamin A	15 (8)	2 (14)	14 (9)	5 (12)	2 (13)	1 (9)	3 (17)	14 (9)	3 (23)
Vitamin C	34 (17)	3 (21)	29 (19)	9 (21)	4 (27)	3 (27)	4 (22)	28 (18)	4 (31)
Vitamin E	28 (14)	2 (14)	24 (16)	7 (17)	6 (40)	1 (9)	4 (22)	23 (15)	2 (15)
Any of the above antioxidants	48 (24)	3 (21)	41 (27)	13 (31)	7 (47)	3 (27)	5 (28)	39 (25)	6 (46)

Data are expressed as the number (percentage) of patients.

Topotecan *n* = 13, or 7% of 200.

other chemotherapies are an important part of their action would also be concerned about the 25% of women using antioxidants during treatment with paclitaxel and the 47% of women using antioxidants during treatment with docetaxel.

For each CAM substance included in our survey, drug-CAM combinations that have the potential to affect the therapeutic efficacy of chemotherapy through modification of the activity of enzyme pathways that influence drug

clearance were considered on a drug-by-drug basis. Table 3 lists the percentage of patients using potentially contraindicated substances for each chemotherapy drug based on common CYP metabolic pathways. The supplements of concern for women using paclitaxel have been discussed; the percentage of women who reported a CAM substance of concern during treatment with paclitaxel was 29%. Docetaxel is also metabolized by the 3A4, 3A5, and 2C8 isoforms, and

TABLE 3. SUMMARY OF PATIENTS USING SELECT HERBS AND SUBSTANCES DURING CHEMOTHERAPY

<i>Supplements and Herbs</i>	<i>Any Chemotherapy (n=200)</i>	<i>Bevacizumab (n=14)</i>	<i>Carboplatin (n=153)</i>	<i>Cisplatin (n=42)</i>	<i>Docetaxel (n=15)</i>	<i>Doxorubicin (n=11)</i>	<i>Gemcitabine (n=18)</i>	<i>Paclitaxel (n=156)</i>	<i>Topotecan (n=13)</i>
Bitter orange	0	0	0	0	0	0	0	0	0
Black cohosh	3 (2)	0	2 (1)	1 (2)	0	0	1 (6)	3 (2)	0
Cranberry	18 (9)	2 (14)	14 (9)	5 (12)	3 (20)	2 (18)	2 (11)	15 (10)	2 (15)
Devil's claw	1 (<1)	1 (7)	1 (<1)	0	0	0	0	1 (<1)	0
Echinacea	2 (1)	0	2 (1)	0	0	0	0	2 (1)	0
Feverfew	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)	0
Garlic	9 (5)	0	7 (5)	0	0	0	0	7 (4)	0
Gingko	1 (<1)	0	1 (<1)	0	1 (7)	0	0	1 (<1)	0
Ginseng	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)	0
Goldenseal	2 (1)	0	2 (1)	0	0	0	0	2 (1)	0
Grape seed extract	3 (2)	0	3 (2)	0	0	0	0	3 (2)	0
Grapefruit juice	3 (2)	0	3 (2)	1 (2)	0	0	1 (6)	2 (1)	0
Green tea	35 (18)	5 (36)	31 (20)	7 (17)	5 (33)	2 (18)	4 (22)	31 (20)	3 (23)
Kava	1 (<1)	0	0	0	0	0	0	1 (<1)	0
Licorice	4 (2)	1 (7)	3 (2)	1 (2)	2 (13)	1 (9)	1 (6)	3 (2)	1 (8)
Milk thistle	5 (3)	0	5 (3)	0	0	0	0	5 (3)	0
Omega-3 fatty acid	26 (13)	4 (29)	19 (12)	7 (17)	3 (20)	2 (18)	6 (33)	21 (13)	4 (31)
St. John's wort	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)	0
Valerian	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)	0
Any of these substances	60 (30)	6 (43)	47 (31)	13 (31)	7 (47)	3 (27)	9 (50)	49 (31)	5 (38)
Substances contraindicated during chemotherapy	Not Applicable	None	None	7 (17)	6 (40)	2 (18)	None	46 (29)	5 (38)

Values are expressed as the number (percentage) of patients. Bold values indicate that the substance is contraindicated during use with that specific chemotherapy. Percentages are rounded. Bevacizumab, carboplatin, gemcitabine: no substances are contraindicated during treatment with these agents. Cisplatin: black cohosh, cranberry, feverfew, garlic, goldenseal, grapefruit juice, and kava. Docetaxel, doxorubicin, paclitaxel, topotecan: bitter orange, black cohosh, devil's claw, echinacea, feverfew, garlic, gingko, ginseng, goldenseal, grape seed extract, grapefruit juice, green tea, kava, licorice, milk thistle, omega-3, St. John's wort, valerian.

doxorubicin is metabolized by 3A4. Thus, these drugs also require some of the same enzymatic pathways for metabolism and clearance, and many of the same CAM substances are contraindicated as with paclitaxel. The rates of use of contraindicated CAM with the chemotherapy drugs we examined ranged from 17% to 40%. Commonly contraindicated CAM substances in widespread use appear to include green tea, used by 24% of the participating women, and omega-3 fatty acids, used by 22% of the participants. These were also the most commonly used CAM substances of concern for women during chemotherapy.

Cisplatin is metabolized by the CYP isoforms 2B6 and 2C9; thus, omega-3 fatty acids and green tea would also be considered contraindicated for use with cisplatin. Cranberry concentrates influence the action of 2C9, making them a supplement of concern as well. Other herbs that could influence the hepatic metabolism of cisplatin include garlic, ginkgo, and ginger. Of the 42 women who were treated with cisplatin, 17% reported using green tea, 12% reported using cranberry, and 17% reported using omega-3 fatty acids. In total, 17% of women reported use of at least 1 substance of concern because of its potential to influence the effectiveness of CYP2 isoforms associated with the metabolism of cisplatin. Some antioxidants, such as vitamin C and vitamin E, may also influence the CYP3 isoforms and thus may modify the metabolism of such chemotherapeutic agents as paclitaxel, docetaxel, cyclophosphamide, and doxorubicin, independently of their influence on the effectiveness of these drugs via oxidative stress.

Because carboplatin is not believed to be metabolized via the CYP450 pathways, no herbs were considered contraindicated for use with carboplatin. The CYP450 pathways required for the metabolism of gemcitabine are still unknown. Thus, we could not assess which CAM substances

are likely to influence metabolism of this agent, and no herbs or supplements were considered contraindicated for gemcitabine in this analysis. Those who want to be conservative in their assessments might assume that any or all CAM substances influencing hepatic metabolism might influence the metabolism of this agent because no data are available.

Overall rates of use of conventional CAM substance combinations of potential concern (including antioxidants, supplements, and herbs) when used together during therapy for ovarian cancer varied by chemotherapeutic agent and ranged from 27% for carboplatin to 47% for docetaxel (data not shown). When the course of chemotherapy is considered as a whole, and patients at risk because they are receiving multiple chemotherapies are considered, 40% of the 200 women who received chemotherapy reported at least 1 CAM substance of concern in light of the chemotherapeutic regimen reported.

In our sample of 219 women, the CAM providers included chiropractors (8.2%; $n=18$), massage therapists (22.8%; $n=50$), Traditional Chinese medical doctor/acupuncturists 14.2%; $n=31$), and naturopathic physicians (18.3%; $n=40$). Consultation with CAM providers differed by disease stage, with 35.7% of women with stage I disease, 35.7% of those with stage II, 46.4% of those with stage III, and 44.0% of those with stage IV disease reported consultation with a CAM provider. All the women in our sample were treated according to community standards by a conventional provider.

We asked women about their consultation with providers on a substance-by-substance basis, but not, unfortunately, according to both substance and phase of treatment. Reported rates of consultation with conventional and CAM providers varied by substance. As illustrated in Table 4, the percentage of patients who consulted a conventional

TABLE 4. NUMBERS OF PATIENTS TREATED WITH CHEMOTHERAPY WHO DISCUSSED THEIR USE OF ANTIOXIDANTS, SUPPLEMENTS, AND HERBS WITH A CONVENTIONAL OR CAM PROVIDER

<i>Antioxidants, Supplements, and Herbs</i>	<i>Patients Who Took Substance During Chemotherapy, n</i>	<i>Women Who Discussed CAM Use With Their Conventional Provider, n (%)^a</i>	<i>Women Who Discussed CAM Use With Their CAM Provider, n (%)^a</i>
Antioxidants			
Beta-carotene	7	2 (29)	1 (14)
Coenzyme Q10	12	2 (17)	4 (33)
Grape seed extract	3	0	1 (33)
Selenium	5	0	2 (40)
Vitamin A	15	4 (27)	3 (20)
Vitamin C	34	9 (26)	7 (21)
Vitamin E	28	9 (32)	4 (14)
Other substances and herbs			
Black cohosh	3	3 (100)	1 (33)
Cranberry	18	2 (11)	1 (6)
Echinacea	2	0	0
Garlic	9	0	2 (22)
Goldenseal	2	0	0
Grapefruit juice	3	0	0
Green tea	35	7 (20)	7 (20)
Licorice	4	0	1 (25)
Milk thistle	5	1 (20)	2 (40)
Omega-3 fatty acids	26	10 (38)	7 (27)
Any of these substances	79	33 (42)	19 (24)

^aPercentages are calculated as row totals.

CAM, complementary and alternative medicine.

provider about antioxidant use ranged from 0% to 32%. Rates of CAM provider consultation for specific antioxidants ranged from 14% to 40%. When we considered other contraindicated combinations of CAM substances and specific chemotherapies and consultation with both CAM and conventional providers, 10 (38%) of the 26 women who used fish oil during chemotherapy consulted a conventional provider about their fish oil use and 7 (27%) consulted a CAM provider. For green tea and cranberry concentrates, equal numbers of women consulted conventional and CAM providers about their use. Of the 79 women using any CAM substance contraindicated for use with the prescribed chemotherapy, 42% ($n=33$) reported consulting a conventional provider about 1 or more these substances and 24% ($n=19$) consulted a Traditional Chinese Medicine doctor, acupuncturist, or naturopathic physician about at least 1 of these substances. Unfortunately, it is unclear whether consultation occurred before or during chemotherapy, and thus we do not know whether consultation affected the combined use of substances of concern in this analysis.

Discussion

Many herbs and supplements are available without prescription and may be used by women with ovarian cancer without discussion with any medical provider. Some foods with biological activity beyond their nutritive value (garlic, fruit juices with high antioxidant levels, green tea) are also widely available in concentrated or dried forms. Review articles have suggested that some of these substances should be considered contraindicated in combination with some chemotherapy drugs. In this sample of ovarian cancer survivors, we found that a substantial proportion (40%; $n=79$) of women reported use of 1 or more substances potentially contraindicated given the chemotherapeutic agents they were receiving. Women reported consulting a conventional or CAM provider about only a small percentage of the substances they used, and even those consulting a provider may not have consulted the provider before or during their use of chemotherapy, when such a consultation might have been of greatest value.

However, this is not to say that these women are suffering ill effects due to their CAM use; rather, it only suggests that a substantial group of women may be at risk for ill effects. Specific combinations of chemotherapy and antioxidants (e.g., vitamin E and cisplatin) have been studied, and evidence suggests beneficial effects, including reducing adverse effects for some with no reduced efficacy of the chemotherapy involved.^{15,16} Similarly, several studies document the effectiveness of fish-oil use by patients with cancer to reduce adverse effects of cancer treatment; evidence of risk associated with the combination comes only from *in vitro* studies.^{9,17,18} However, this is a controversial area, and there is a clear theoretical potential for reduced efficacy of therapies; clinical care decisions for both patients and providers are difficult without further information.

The questionnaire used in this study did not ask women to indicate the doses of the substances taken. Indeed, doses of CAM substances necessary to influence CYP450 enzyme activity and thus to modulate blood levels of affected chemotherapy agents have often been studied only *in vitro*. Thus, the doses required for a modulator effect in humans

are unknown. It is not known whether patients taking CAM substances ingested quantities large enough to affect the metabolism of their chemotherapy drugs. Doses of green tea thought to have a substantial influence on CYP 3A5 activity might be in excess of three to five 6-ounce cups of tea per day, although the constituents of green tea vary widely. As a result, dose estimation is very difficult. Such doses are high for casual tea drinking, but higher doses are available in concentrated forms and are marketed as a safe way to promote weight loss. The cranberry dose with an important effect on drug metabolism is again unknown. Also, the common dosage used by women is unknown. In many, if not most, of the reports of concurrent use of a conventional treatment and a contraindicated CAM treatment in our survey, the CAM substance may not have been used at a high enough dose to change clinical outcomes. Further research is needed to understand when CAM and conventional therapies whose concurrent use presents a theoretical concern result in significant clinical effects that compromise the effectiveness of conventional therapy.

This study has several possible limitations. All data on CAM use were self-reported, and it is unclear to which groups these results are likely to be generalizable. The sample was mostly white and well educated, and CAM use has been commonly found to differ among patients of different racial/ethnic backgrounds and in association with education. In addition, although we asked about a substantial group of supplements, our list was by no means exhaustive; we also did not ask women why they were taking the substances. Adding this question to the questionnaire would have made it even more unwieldy. However, many surveys of cancer patients have asked similar questions about CAM use and found that few patients use CAM as a treatment for their cancer. Fewer still expect it to "cure" them of their cancer. Instead, most patients report that their use is intended to improve immune function or their general health.^{2,3,19} The most frequently reported substances found in this study suggest similar motives in this group; fish oil and green tea are not widely promoted as cancer cures and are probably being taken for their perceived effectiveness in improving general health. The frequency with which women used CAM substances before diagnosis and after the completion of their initial treatment supports this conjecture. In reviewing the data, we noted that as with the antioxidants described earlier, the participants used many of the CAM substances about which we asked with equal frequency at all 3 time points. This finding suggests that a significant percentage of women are not using them as a response to, much less as a cure for, cancer.

With a substantial percentage of patients with ovarian cancer using herbs and supplements, more research on the potential for these substance to interact negatively with conventional chemotherapy drugs is urgently needed. Patients and their providers also need better information on which to base decisions about discontinuing use of herbs and supplements during cancer treatment.

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