Research Article

Comparison of Dietary Supplements Use Between Receivers and Refusers of Adjuvant Breast Cancer Treatments

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ABSTRACT

Purpose: The goal of this study was to compare dietary supplement use between women who received all recommended conventional breast cancer treatments (Receivers) with those who did not (Refusers). We sought to understand commonly used supplements, use frequency, and prescribers.

Methods: A secondary analysis was conducted using baseline data of Breast Cancer Integrative Oncology Study, which recruited 369 women with breast cancer from integrative oncology clinics and Cancer Surveillance System registry in Western Washington State. Self-reported data and registry data were analyzed using descriptive statistics, t-tests, and X^2 tests to compare Receivers and Refusers in their demographic and disease characteristics and supplement use.

Results: Refusers used more supplements than Receivers did after diagnosis, 5.43 ± 5.29 vs. 2.66 2.88, F = 26.32, p < 0.001. Refusers used more fish oil and garlic before diagnosis, and more green tea, vitamin C, melatonin, coenzyme Q10, turmeric, and garlic after the diagnosis than Receivers. Most Receivers and Refusers took supplements 5 or more days per week. Most of the supplements were self-prescribed except vitamin D and Melatonin, which were prescribed by medical doctors or CAM providers.

Conclusions: Receivers and Refusers generally used the same top ten supplements, often antioxidants, although the frequency of use differed slightly, and Refusers took more supplements. Receivers, who are undergoing chemotherapy or radiotherapy need to know that taking antioxidants may influence treatment effectiveness. Refusers need to be informed that there is no strong evidence that the use of dietary supplements reduces recurrence or mortality.

Introduction

About 3.3 million women in the U.S. have breast cancer and up to 85% of women with breast cancer use complementary and alternative medicine (CAM) [1-3]. Use of CAM, especially dietary supplements, among women with breast cancer is related to not receiving recommended conventional treatments [4-8]. However, little information is available about what specific dietary supplements are used by women who do not receive all recommended treatments and if they are similar or different from those used by women who received all recommended treatments. In addition, little is known about how frequently dietary supplements are used and who prescribes them to women who choose them over conventional treatments. The overall objective of this study was to describe commonly used supplements among women who voluntarily did not receive all or part of the

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conventional treatments recommended for their breast cancer by their doctors (i.e., Refusers), compared with those who received all recommended treatments (i.e., Receivers).

Commonly Used Supplements among Women with Breast Cancer

A recent study found that the most commonly used CAM modalities among women with breast cancer in California were mind-body practices (71%) and vitamin/mineral supplements (70%) [5]. The most commonly initiated vitamin/mineral supplements after getting breast cancer diagnosis were calcium (38.2%), vitamin D (32.0%), magnesium (11.3%), and vitamin B6 (10.1%) [3]. This result is slightly different from the result found among Canadian women, where researchers found the most commonly used vitamin/mineral supplements for treating breast cancer were green tea, vitamin E, flaxseed, and vitamin C [2]. Examining supplement use by adjuvant treatments received, Greenlee et al. (2014) found that women undergoing chemotherapy were less likely to start the antioxidants vitamin C & E, stop using vitamin D, and multivitamins [3]. The most commonly used supplements among Refusers included multivitamin and mineral (51.4%), vitamin C & E (each 46.9%), and calcium (44.1%) [3]. However, there is lack of information on prescriber and use frequency between Receivers and Refusers of conventional treatment.

Materials and Methods

I Study Design, Sample, and Procedure

This study reports results from the secondary analysis of the baseline data from the Breast Cancer Integrative Oncology Study, which the data were collected from 585 women through integrative oncology clinics and the Cancer Surveillance System registry in Western Washington State (Standish, Sweet, Naydis, & Andersen, 2013). Sample criteria were: 1) 18 years of age or older, 2) diagnosis of breast cancer or ductal carcinoma in situ verified by biopsy pathology, 3) two or more integrative oncology care within 4 months with a participating integrative oncology CAM Providers (e.g., naturopathic doctors), and 4) initial diagnosis within two years of seeking integrative oncology care. Participants were recruited through four integrative oncology clinics in the Western Washington State and then their matching cohort was recruited using the Cancer Surveillance System registry in the same region (Standish et al., 2013). Standish et al. (2013) describes detail information about recruitment procedure. Among 585 women, 369 women met additional criteria for data analysis based on Cancer Surveillance System registry data that specifically coded whether or not women: 1) received surgery, 2) received a recommendation from their doctor to receive at least one adjuvant treatment such as chemotherapy, radiotherapy, or hormone therapy after the surgery, 3) and whether or not they received or recommended adjuvant treatment, and 4) used at least one dietary supplement. The second and third of these required pieces of data were used to categorize women as Receivers or Refusers of recommended adjuvant treatment. Women who received a recommendation for at least one adjuvant therapy and did not receive it were categorized as Refusers. Power analysis for the continuous variables shows 85% power to detect difference between cohorts of 0.5 standard deviations (Cohen's d = .5) with the sample size of 329 vs. 40

women. Power analysis for the binary variable shows 94% power to detect a difference between cohorts of 40% vs. 70% with the sample size of 329 vs. 40.

II Study Variables

Data Sources

Data were collected from self-report questionnaire and Cancer Surveillance System registry information in Western Washington State. Self-reported variables included CAM supplement use, comorbidity, and household income. CSS information included records on recommended treatments and receiving/refusing the treatment, site of breast cancer, surgery type, Estrogen and Progesterone Receptors status, age and stage at diagnosis, ethnicity, and marital status. Professional abstractors record Cancer Surveillance System registry data about 6 months after cancer diagnosis using patients' chart review at conventional medicine clinics.

CAM Supplement Use

Dietary supplement use was assessed using a 68-item self-report survey developed by the research team based on a literature review and clinical experience. It assesses participants' use of 68 different supplements such as CoQ10, vitamin D, and others. For each supplement, it assesses whether they used it, use frequency (none, less than 1x/week, 1x/week, at least 5x/week, daily), and prescriber (conventional healthcare provider, CAM provider, self/friend, don't know). It also assesses if the supplement was used before the diagnosis. In this paper, frequency was categorized as "less than 1x/week, 1x/week" and "at least 5X/week, daily." Calculating reliability is not applicable in this paper because we were interested in how individuals used each specific supplement.

III Statistical Analysis

All data were analyzed using SPSS 20 software (SPSS, 2015). First, descriptive statistics such as distributions, means, standard deviations, frequencies, and ranges were computed for all study variables. Comparisons between Receivers and Refusers on use of supplements were made using t-tests for continuous variables and X^2 tests for categorical variables.

Results

I Characteristics of Receivers and Intentional Refusers

Table 1 presents demographic characteristics comparing 369 women; 329 Receivers, who received all recommended treatments, and 40 Refusers (10.8%) who did not receive at least one recommended adjuvant treatment (i.e., chemotherapy, radiotherapy, or hormone therapy) after their surgery. Only demographic difference was that Refusers were likely to have earlier stage of breast cancer than Receivers; no other significant difference was found between groups in age at diagnosis, marital status, household income, estrogen and progesterone receptor status, site of cancer, overall morbidity, and months since cancer diagnosis.

Table 1: Comparison of Descriptive Statistics Between Receivers and Refusers (N = 369)

	Receivers (n = 329)	Refusers (n= 40)	
	M (SD)	M (SD)	t
Age at diagnosis	54.12 (10.16)	56.90 (9.08)	-1.65
Months since diagnosis	12.28 (16.14)	11.03 (19.12)	0.45
	n (%)	n (%)	X^2
Race			4.28
Asian	8 (2.4)	3 (7.5)	
Black	2 (0.6)	0 (0.0)	
White	316 (96.0)	36 (90.0)	
Mixed	3 (0.9)	1 (2.5)	
Marital status			3.29
Single/widowed/separated	70 (22.1)	14 (35.0)	
Married/partner	247 (77.9)	26 (65.0)	
Household income			3.26
<$50,000	109 (34.7)	18 (50.0)	
≥$50,000	205 (65.3)	18 (50.0)	
Stage of cancer at diagnosis			14.24**
State 0	19 (5.9)	7 (17.9)	
Stage 1	117 (36.1)	20 (51.3)	
Stage 2	131 (40.4)	9 (23.1)	
Stage 3	49 (15.1)	3 (7.7)	
Stage 4	8 (2.5)	0 (0.0)	
Site of cancer			0.18
Left	168 (51.1)	19 (47.5)	
Right	161 (48.9)	21 (52.5)	
Surgery type			2.55
Lumpectomy	183 (55.6)	23 (57.5)	
Total mastectomy	73 (22.2)	12 (30.0)	
Modified radical mastectomy	73 (22.2)	5 (12.5)	
Estrogen Receptor status			3.36
ER Negative	41 (12.7)	1 (2.6)	
ER positive	281 (87.3)	37 (97.4)	
Progesterone Receptor status			0.08
PR Negative	58 (18.6)	6 (16.7)	
PR positive	254 (81.4)	30 (83.3)	
Overall comorbidity			0.00
None	73 (22.2)	9 (22.5)	
One or more	256 (77.8)	31 (77.5)	
Oncology care received			2.35
Usual Care	221 (67.2)	22 (55.0)	
Integrative Oncology	108 (32.8)	18 (45.0)	

Note: *P<.05, **p<.01, ***p<.001; Some variables do not add up to total N (329 for Receivers and 40 for Intentional Refusers) due to missing data.

II Comparing Current Supplement Use between Receivers and Intentional Refusers

As shown in the (Table 2), before cancer diagnosis, Receivers used an average 3.04 (SD = 3.60) supplements, while Refusers used an average 4.56 (SD = 4.16) supplements, F = 6.05, p < 0.05. As shown in (Table 2), the most frequently used 10 supplements among Receivers before diagnosis were vitamin D, fish oil, vitamin C, green tea, vitamin E, flaxseed oil, coenzyme Q 10, garlic, cranberry juice, and vitamin A while Refusers used vitamin D, fish oil, green tea, vitamin C, progesterone, vitamin E, coenzyme Q 10, vitamin A, flaxseed oil, and turmeric. A greater percentage of Refusers used fish oil and garlic, compared with Receivers (p <0.05).

After the cancer diagnosis, Receivers used an average 2.66 (SD = 2.88) supplements, while Refusers used an average 5.43 (SD = 5.29) supplements, $F = 26.32$, $p < 0.001$. As shown in (Table 2), the most frequently used 11 supplements among Receivers and Refusers were the same although there were slight differences in order. Receivers most frequently used vitamin D, followed by fish oil, green tea, vitamin C, vitamin E, melatonin, coenzyme Q 10, vitamin A, turmeric, and garlic, whereas Refusers used vitamin D, green tea, vitamin C, fish oil, turmeric, coenzyme Q 10, vitamin E, melatonin, garlic, and flaxseed oil. A greater percentage of Refusers used green tea, vitamin C, melatonin, coenzyme Q 10, turmeric, and garlic, compared with Receivers ($p <0.05$ to $p<0.01$).

Table 2: Supplements Used Before and After Cancer Diagnosis Among Receivers and Refusers (N = 369)

	Before Diagnosis			After Diagnosis		
	Receivers	Refusers		Receivers	Refusers	
	n (%)	n (%)	X^2	n (%)	n (%)	X^2
Vit D	149 (45.3)	24 (60.0)	3.10	185 (56.2)	26 (65.0)	1.12
Fish oil	110 (33.4)	21 (52.5)	5.66*	101 (30.7)	15 (37.5)	0.77
Green tea	64 (19.5)	12 (30.0)	2.43	70 (21.3)	19 (47.5)	13.40***
Vit C	81 (24.6)	12 (30.0)	.55	63 (19.1)	17 (42.5)	11.45**
Vit E	59 (17.9)	7 (17.5)	.01	50 (15.2)	11 (27.5)	3.91
Melatonin	27 (8.2)	4 (10.))	.15	36 (10.9)	9 (22.5)	4.45*
Coenzyme Q 10	41 (12.5)	7 (17.5)	.80	34 (10.3)	12 (30.0)	12.64***
Vit A	31 (9.4)	6 (15.0)	1.23	31 (9.4)	7 (17.5)	2.52
Turmeric	21 (6.4)	5 (12.5)	2.04	28 (8.5)	13 (32.5)	20.78***
Garlic	40 (12.2)	11 (27.5)	7.05*	28 (8.5)	8 (20.0)	5.35*
Flaxseed oil	41 (12.5)	6 (15.0)	0.21	25 (7.6)	7 (17.5)	4.14

*$p < 0.05$; **$p < 0.01$; $p < 0.001$

III Use Frequency of Currently Used Supplements between Receivers and Refusers

When the frequency of supplements participants were currently using was examined, most Receivers and Refusers took them "5 or more days per week" (See Table 3). The only statistically significant difference we found between Receivers and Refusers in frequency of use was use of garlic; 100% of Intentional Refusers took garlic 5 or more days per week, compared with 40% among Receivers.

Table 3: Consistent Users (5 days or more) of Supplement among Receivers and Refusers

	After Diagnosis		
	Receivers (n = 329)	Refusers (n = 40)	X^2
	n (%)	n (%)	
Vitamin D	168 (96.6)	17 (89.5)	2.16
Fish oil	62 (98.4)	11 (91.1)	1.77
Green tea	28 (66.7)	13 (76.5)	0.55
Vitamin C	48 (92.3)	12 (92.3)	0.00
Vitamin E	34 (97.1)	7 (87.5)	1.37
Melatonin	15 (71.4)	6 (75.0)	0.04
Coenzyme Q 10	17 (85.0)	8 (88.9)	0.08
Vitamin A	25 (92.6)	6 (100.0)	0.47
Turmeric	14 (77.8)	11 (91.7)	1.00
Garlic	6 (40.0)	5 (100.0)	5.46*
Flaxseed oil	13 (81.3)	4 (80.0)	0.00

*$p < 0.05$

IV Prescribers of Currently Used Supplements between Receivers and Refusers

When prescribers of currently used supplements were examined, most of the supplements were self-prescribed except vitamin D and melatonin, which were prescribed by medical doctors or CAM providers. Significantly more Receivers reported that their medical doctors prescribed vitamin D, whereas significantly more Refusers stated that their CAM providers prescribed it.

Table 4: Prescribers of Top 11 Currently Used Supplements between Receivers and Refusers

	Prescriber	Receivers n (%)	Refusers n (%)	X^2
Vitamin D	MD	131 (52.2)	8 (25.0)	8.40**
	CAM provider	59 (23.5)	14 (43.8)	6.08**
	Self	61 (24.3)	9 (28.1)	0.22
Fish oil	MD	30 (18.8)	1 (3.8)	3.58
	CAM provider	38 (23.8)	9 (34.6)	1.40
	Self	73 (45.6)	6 15 (57.7)	1.31
Green tea	MD	4 (3.4)	3 (15.0)	4.85[1]
	CAM provider	29 (24.4)	9 (45.0)	3.67[1]
	Self	69 (58.0)	9 (45.0)	1.17
Vitamin C	MD	13 (12.5)	1 (4.8)	1.05
	CAM provider	16 (15.4)	7 (33.3)	3.75
	Self	51 (49.0)	10 (47.6)	0.01
Vitamin E	MD	20 (22.7)	1 (6.3)	2.28
	CAM provider	20 (22.7)	3 (18.8)	0.12
	Self	36 (40.9)	10 (62.5)	2.56
Melatonin	MD	8 (13.3)	1 (9.1)	0.15
	CAM provider	30 (50.0)	7 (63.6)	0.69
	Self	22 (36.7)	5 (45.5)	0.31
Coenzyme Q 10	MD	8 (11.4)	2 (13.3)	0.04
	CAM provider	26 (37.1)	8 (53.3)	1.35
	Self	28 (40.0)	3 (33.3)	0.23
Vitamin A	MD	9 (18.4)	0 (0.0)	2.17
	CAM provider	10 (20.4)	1 (10.0)	0.59
	Self	20 (40.8)	7 (70.0)	2.85
Turmeric	MD	3 (5.6)	0 (0.0)	0.87
	CAM provider	19 (35.2)	6 (40.0)	0.12
	Self	2 (48.1)	7 (46.7)	0.01
Garlic	MD	0 (0.0)	0 (0.0)	--
	CAM provider	2 (4.3)	1 (8.3)	0.31
	Self	34 (73.9)	10 (83.3)	0.46
Flax seed oil	MD	6 (10.3)	0 (0.0)	1.14
	CAM provider	7 (12.1)	2 (20.0)	0.47
	Self	30 (51.7)	5 (50.0)	0.01

**p < 0.01; [1] p = 0.06

Discussion

The current study contributes to the limited body of research comparing the use of supplements between women who did and did not receive all or part of adjuvant breast cancer treatments recommended by their doctors. The finding that Refusers used more supplements than Receivers not just after the cancer diagnosis but also before the diagnosis is consistent with a previous finding among women with breast cancer in California for whom chemotherapy was indicated, dietary supplement users, compared with non-users, were less likely to initiate chemotherapy [5]. This may indicate that Refusers were more familiar with use of supplements before the diagnosis, and that this may have influenced their decision-making about receiving recommended adjuvant treatments. It might also indicate greater familiarity with "do it yourself" or alternative medicine options for the treatment of other conditions and/or greater skepticism about the need for conventional medicine generally. The top 11 commonly used supplements among Receivers and Intentional Refusers used before and after cancer

diagnosis were the same although their ranking was slightly different. This finding may indicate that both Receivers and Refusers knew of supportive supplements prior to diagnosis and used similar sources when seeking information on supplements. Vitamin D supplementation increases 25-hydroxyvitamin D level in blood and decrease circulating 27-hydroxycholesterol, an endogenous selective estrogen receptor modulator that drives the growth of estrogen receptor-positive breast cancer [9]. A meta-analysis found that women with breast cancer who had high blood levels of 25-hydroxyvitamin D had both significantly lower overall- (pooled relative ratio = 0.61) and breast cancer specific-mortality (pooled relative ratio = 0.58) when compared with those who had lower blood levels [10]. While Vitamin D is the most commonly used supplement in both Receivers and Refusers, it is not clear why more Receivers stated that their MD prescribed it, while more Refusers stated that their CAM providers prescribed it. This finding may reflect Receivers greater reliance on conventional medical doctors. In contrast, although Refusers also receive care from conventional medical providers, they may be more inclined to seek medical advice, at least

about supplements, from CAM providers. If it is generally true that Refusers seek medical advice preferentially from CAM providers this could be important, that we found this difference in source of advice about vitamin D, one of the several supplements commonly used by women with breast cancer, suggests the need for additional study.

More Refusers took green tea, vitamin C, melatonin, coenzyme Q10, turmeric, and garlic than Receivers. Green tea is an antioxidant and some evidences indicate its effect on metastasis of breast cancer in cell culture systems and animal models [11-13]. In a randomized trial of 1-year supplementation with a high dose of green tea compound, younger women reduced percent mammographic density [14]. Vitamin C is an antioxidant and a meta-analysis of 10 studies found that supplemental use of vitamin C after breast cancer diagnosis was related to reduced risk of overall- and breast cancer-related mortality [15]. In another meta-analysis, the link between plasma vitamin C and breast cancer was only significant in case-control studies [16]. Melatonin is an antioxidant and preclinical and human studies document the links between melatonin and breast cancer [17, 18]. In a lab study, melatonin inhibited the proliferation of estrogen receptor-positive breast cancer cells [19]. Coenzyme Q10 is a lipid-soluble antioxidant and the use of coenzyme Q10 was not beneficial for reducing cancer-related fatigue [20]. Tumeric contains curcumin, which is an anti-inflammatory and antioxidant. In a lab study using human breast cancer MCF-7 cells, curcumin inhibited cell viability and induced cytotoxicity of MCF-7 cells by inducing apoptosis [21]. Garlic is one of the dietary supplements that is recognized by National Cancer Institute for having potential anticancer properties [22]. Taking garlic and lemon juice has been found to have reduced breast cancer growth in mice 80% by inhibiting angiogenesis, inducing apoptosis, and modulating immune system action [23].

Use of dietary supplements, especially antioxidants, during chemotherapy and radiotherapy can influence the action of these treatments. Our earlier analysis using the same data set showed that women mostly used green tea (15.7%), melatonin (10.8%), vitamin C (11.4%), and vitamin E (10.6%) during these adjuvant treatments [24]. Forty-four percent of women used one or more dietary supplement potentially contraindicated during chemotherapy and 32% used antioxidants during radiation treatment. And only 23.8% of the women who used antioxidants discussed their use with their medical doctors, while 42% discussed it with CAM providers [24]. Considering both Receivers and Refusers were self-prescribing most of these supplements except vitamin D and melatonin, it would be important to find out where women get the information about supplement use during cancer treatment. Development of the internet makes self-research on supplements easier for women but knowing whether or not the information presented is evidence-based is essential.

While Receivers and Refusers generally reported similar sources of prescribers for each supplement it is important to note that prescribers were different by supplement. Vitamin D is interesting in part because it was the supplement most frequently reported to have been prescribed by medical doctors. Most supplement used in our study was based on self-prescription, although there were a few supplements (e.g. melatonin and turmeric) that were commonly reported to be prescribed from a CAM provider. In interpreting these findings, it is important to consider that these data came from the Breast Cancer Integrative Oncology Study's

baseline questionnaires, which were generally completed after one or two visits with integrative oncology CAM providers. Thus, the prescription from CAM providers may not necessarily reflect the prescription from integrative oncology CAM providers (e.g., oncology certified naturopathic doctors). It would be interesting to examine changes on types of supplements and prescribers as time goes and some women receive care from oncology certified CAM providers. A few limitations need to be noted. Our study sample included predominantly White, well-off women, and the number of Refusers was much smaller than Receivers. This study used self-report questionnaires to assess dietary supplement use and we did not assess supplement dose. Previous studies have found that women with breast cancer took much higher than recommended doses of some supplements which might pose a risk to them [3].

Conclusions

This study found that top 11 dietary supplements used by Receivers and Refusers were mostly similar and included a substantial number of antioxidants although the order of commonly used supplements is slightly different between the two groups, and Refusers took more supplements than Receivers. We hope oncology healthcare providers can use the finding that both Receivers and Refusers self-prescribe a variety of dietary supplements including supplements not generally prescribed by either conventional medical doctors or CAM providers. Given this information, it is important to discuss supplement use. It may be especially important to ask Receivers, who are undergoing chemotherapy or radiotherapy, about their intake of antioxidant supplements that may reduce the effectiveness of these treatments. Refusers need to be informed that while the use of dietary supplements may be safe in most cases, and some might have anti-cancer effects or improve symptoms, there is no evidence, at this point, that supplement use can impact recurrence or mortality, and evidences suggest that replacing conventional treatments with CAM supplements might increase risks for recurrence and mortality [6, 8]. Future research should explore the longitudinal differences of dietary supplement use between Receivers and Refusers.

Compliance with Ethical Standards

The Institutional Human Subjects Review Committee of the Fred Hutchinson Cancer Research Center and of Bastyr University approved the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual study participants included in the study. This article does not contain any studies with animals performed by any of the authors. For the secondary analysis, the committees from the above two institutions and that of the University of Washington approved the study and de-identified data were used.

Conflicts of interest

The authors declare that they have no conflict of interest.

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