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Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) Study

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Abstract

Dietary lignan intakes have been associated with reduced breast cancer risks; however, no previous studies have investigated whether lignan intake might be associated with breast cancer survival. We examined the association of dietary lignan intakes with survival in 1122 women with primary, incident, histologically confirmed breast cancer identified between 1996 and 2001, and with vital status determined through December 31, 2006. Diet in the 12–24 months before diagnosis was assessed with an extensive food frequency questionnaire, and potential confounders assessed from an extensive epidemiologic interview and abstracted clinical data. Lignan intake was calculated using published food composition data. Hazard ratios (HR), and 95% confidence intervals (CIs) for dietary lignan intakes with all cause, and breast cancer mortality were estimated using Cox proportional hazards adjusting for age, education, race, total energy intake, tumor stage, and body mass index. Of the 1122 women with complete dietary data, 160 had died by the end of follow-up. Among postmenopausal women only, those in the highest versus lowest quartile of lignan intakes had a statistically significant reduction in the risk of all cause mortality (HR 0.49, 95% CI 0.26–0.91) and a significantly reduced risk of breast cancer mortality (HR 0.29, 95% CI 0.11–0.76). Higher intakes of dried beans (HR 0.61, 95% CI 0.36–1.03), but not fruits, vegetables, or grains, were also weakly associated with overall mortality. In summary, our results suggest that higher lignan intakes may be associated with improved survival among postmenopausal women with breast cancer.

Keywords

Breast cancer; Diet; Lignans; Phytoestrogens; Survival

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Introduction

As the population of cancer survivors in the United States grows, the identification of lifestyle factors that might improve survival of cancer patients continues to generate research interest [1]. Diet modifications are among the lifestyle changes most widely adopted by cancer patients, especially by women with breast cancer [2]; however, the relationship between dietary factors and survival remains largely unclear. Several investigations have suggested that plant-based diets rich in fruits, vegetables, and grains, as well as their related nutrients may have a beneficial effect on survival after breast cancer [3]. Results from observational studies have shown a number of potential relationships between diet and breast cancer survival: reduced mortality among women with breast cancer who have greater adherence to a prudent dietary pattern (high intakes of fruits, vegetables, whole grains, and poultry) [4]; higher mortality among those with low vegetable and fruit consumption [5]; more favorable breast tumor biomarkers associated with higher phytoestrogen intakes [6]; and improved survival associated with reduced dietary fat and increased fiber, vegetables, and fruit [7]. However, clinical trials conducted to test the effect of a high plant-food-based diet have not been consistently successful in reducing breast cancer mortality [8,9].

A diet rich in vegetables, fruits, and whole grains contains numerous phytochemicals that could affect progression of cancer and subsequent mortality. Phytoestrogens are one class of compounds found in plant foods which have demonstrated anti-carcinogenic effects [10–13], and lignans constitute the largest contribution to phytoestrogen intakes in Western diets. In human and experimental studies, high lignan intakes have been shown to affect both endocrine and growth factor pathways by modifying steroid hormone metabolism [14–17], modifying IGF and EGFR [18,19], and inhibiting aromatase and 17B-hydroxysteroid dehydrogenase [17]. Contrary to experimental studies reporting increased breast cell proliferation with soy isoflavones, lignans have been shown to inhibit cell proliferation in both estrogen receptor (ER) positive and negative cell lines, and reduce tumor growth and metastasis in animal models [20–23]. Therefore, it is plausible that lignans may contribute to the effect of a plant-based diet in reducing tumor progression or recurrence and thereby affect survival after breast cancer diagnosis.

Two previous studies have investigated associations between phytoestrogens and breast cancer survival. In a US study involving 1210 women with breast cancer, high dietary intake of soy isoflavones was associated with a 48% lower risk of overall mortality in all women, and a similar reduction in risk of breast cancer mortality among postmenopausal women only [24]. The second study, conducted in an Asian population, reported no associations between breast cancer survival and soy intake [25]. One previous study investigated associations between lignan intakes and mortality, but among elderly healthy men only. No associations were observed for total lignan intakes and either overall mortality or cancer-specific mortality, but inverse associations were observed with a particular lignan, matairesinol [26]. To our knowledge, the associations between lignan intakes and survival after breast cancer diagnosis have not been previously reported. Therefore, we examined the associations between reported pre-diagnostic usual daily intakes of lignans and survival in a series of 1122 women with incident, primary breast cancer, participants in the Western New York Exposures and Breast Cancer Study (WEB Study).

Materials and methods

Data were collected as part of the WEB Study, a large population-based case–control study of breast cancer and lifetime alcohol intake, the methods for which have been described in detail previously [27–41]. The study protocol was approved by the institutional review boards of the University at Buffalo and participating hospitals, and informed consent was obtained for all

subjects. In brief, women with incident, pathologically confirmed breast cancer were identified and recruited from hospitals in Erie and Niagara counties by nurse case-finders between 1996 and 2001. Demographics, smoking history, reproductive and health histories, and related variables were collected by trained interviewers during in-person computer-assisted interviews. Dietary intake in the year 12–24 months prior to diagnosis was assessed using a modified version of the Health Habits and History food frequency questionnaire (FFQ) [42, 43]. The present analyses include 1122 women, aged 35–79 years, with incident, pathologically confirmed breast cancer who had complete dietary data.

Nutrient intakes were calculated from the FFQ using the DietSys (version 3.7) nutrient analysis software utilizing food composition data from the United States Department of Agriculture (USDA). Dietary intakes of lignans were calculated from a comprehensive phytoestrogen database developed by Dr. Lilian Thompson through laboratory analyses using gas chromatography–mass spectrometry of 121 food samples commonly consumed in Canadian diets that were identified as important phytoestrogen sources relevant to Western populations [44]. Samples were analyzed prepared as typically consumed, and the 121 foods represent a majority of the food items on our FFQ.

Since lignans are ubiquitous in plant foods, and these food groups are also sources of other phytochemicals and nutrients which could affect survival, we examined survival by intakes of fruits, vegetables, dried beans, and grains. Each food group was calculated as grams per day of the member food items summed across foods. Food groups were defined based on USDA classification schemes as follows: fruits (apples, applesauce, or pears; bananas; peaches or apricots; cantaloupe; watermelon; strawberries; oranges; grapefruit; other fruit); vegetables (string beans or green beans; peas; corn; winter squash; summer squash; tomatoes, fresh or cooked; broccoli; cauliflower, cabbage, sauerkraut, or Brussels sprouts; spinach; mustard greens; coleslaw; carrots or mixed vegetables; mixed lettuce or spinach salad; lettuce salad; sweet potatoes; boiled or baked potatoes); beans (baked beans, pintos, kidney beans, or lima beans); and grains (rice; noodles; biscuits, muffins or rolls; white bread or rolls; dark bread; corn bread; high fiber cereal; fortified cereals; cold cereals; cooked cereals).

Vital status of the breast cancer cases participating in the WEB Study was determined through a National Death Index search through December 31, 2006. All-cause mortality was defined as death from any cause. Underlying cause of death was broadly classified as breast cancer, other cancer, cardiovascular (CHD, MI, CVD, stroke, and other cardiovascular events), and other. Survival time was calculated as the number of months from date of diagnosis until date of death or December 31, 2006.

Statistical analyses

All analyses were conducted with SAS version 9.1 (Chicago, IL). All tests were two-sided and considered statistically significant at $P < 0.05$. Analyses for pre- and postmenopausal women were conducted separately.

Continuous daily lignan intakes were categorized into quartiles based on menopause-specific distributions. Food groups were also categorized into quartiles based on the menopause specific distributions.

Hazard ratios and 95% CIs for all-cause mortality and breast cancer mortality were calculated with Cox proportional hazards models adjusting for age, education, race, stage at diagnosis, body mass index, and total energy intake. We assessed the inclusion of ER status to the models, but the hazard ratios remained essentially unchanged. Alcohol intake and physical activity were not considered as covariates as these variables were not associated with lignan intakes or survival in this sample and unlikely to be confounders. Therefore, given the relatively small

number of events, we included only those covariates statistically significant at $P \leq 0.10$, or that changed the hazard ratios by at least 10%. Survival time was expressed as months between diagnosis and date of death or end of follow-up. Women alive at the end of follow-up or dead from other causes were censored. The proportional hazards assumption was tested and found to hold in all analyses. *P* for trend was assessed as the Wald Chi square statistic in the proportional hazards model including the continuous dietary variable.

Results

Descriptive characteristics, at time of questionnaire completion, of WEB Study participants with breast cancer by vital status are shown in Table 1. Of the 1122 women (n = 315 premenopausal; n = 807 postmenopausal) with breast cancer, 160 died by the end of 2006. The most frequent cause of death was breast cancer (n = 94) followed by other cancer (n = 15), cardiovascular events (n = 24), and other causes of death (n = 27). Total follow-up time ranged from 9 to 125 months; mean (SD) survival time was 87.3 (SD 20.5) months. Compared to women alive through 2006, those who died were slightly older ($P < 0.05$) and less likely to be Caucasian ($P = 0.05$), less educated ($P < 0.01$), had a higher BMI ($P < 0.05$), higher stage cancer at diagnosis ($P < 0.01$), and more likely to have ER negative breast cancer ($P < 0.01$). Vital status did not differ by age at menarche, age at first birth, age at menopause, total energy intake, total lignan intake, menopausal status, or family history of breast cancer.

Total lignan intakes averaged 244.2 ± 134.8 mcg/d among women who died, and 245.1 ± 133.3 mcg/d among those who were alive at the end of follow up. The major plant lignan contributing to total lignan intakes was secoisolariciresinol (122.4 ± 76.4 mcg/d), followed by lariciresinol (63.1 ± 35.5 mcg/d), pinoresinol (52.6 ± 39.7 mcg/d), and matairesinol (7.2 ± 4.5 mcg/d) (data not shown). The primary food sources of secoisolariciresinol were dark bread ($R^2 = 0.76$), peaches ($R^2 = 0.04$), orange juice ($R^2 = 0.02$), coffee (regular and decaffeinated; $R^2 = 0.02$), onions ($R^2 = 0.01$), string beans($R^2 = 0.01$), and tea ($R^2 = 0.01$); of lariciresinol were oranges ($R^2 = 0.33$), broccoli ($R^2 = 0.19$), and winter squash ($R^2 = 0.12$); and of pinoresinol were peaches ($R^2 = 0.71$) and tea ($R^2 = 0.09$).

As most of the events in our study could be attributed to breast cancer, we limited our outcomes to all cause mortality and mortality from breast cancer. Although we observed significant linear trends, there were no associations between quartiles of lignan intakes and either all cause mortality or breast cancer mortality among premenopausal women (Table 2). However, among postmenopausal women, those in the highest vs. lowest quartile of lignan intakes had an approximately 50% lower hazard ratio for all cause mortality (*P* for trend = 0.02), and 70% lower hazard ratio for breast cancer mortality (*P* for trend = 0.01).

We also examined the associations between mortality and intakes of plant-based food groups (dried beans, vegetables, fruits, grains; data not shown). Consistent with the reduced hazards observed for higher lignan intakes in postmenopausal women, those in the highest quartile of dried bean intakes had an approximately 40% reduction in all cause mortality (HR 0.61, 95% CI 0.36–1.03) and an approximately 50% reduction in breast cancer mortality (HR 0.53, 95% CI 0.24–1.14), although neither association reached formal statistical significance. No associations with dried bean intake were observed among premenopausal women. Furthermore, in both pre- and postmenopausal women, there were no associations between mortality and intakes of vegetables, fruits, or grains.

Discussion

To our knowledge, this is the first investigation of the association between dietary lignan intakes prior to breast cancer diagnosis and all cause and breast cancer-specific mortality. We

found substantially reduced risks of overall mortality, and especially breast cancer mortality, associated with higher lignan intakes in postmenopausal women only. As dried beans and legumes are rich sources of several phytoestrogens, it was not surprising that, in postmenopausal women, there was also a trend toward reduced mortality associated with higher dried bean intakes. On the other hand, the primary sources of lignans in our study were dark bread, peaches, coffee, broccoli, and winter squash, but no associations were observed between vegetables, fruits, and grains and survival. Whereas whole grains are particularly rich in lignans, our food frequency questionnaire asked limited questions concerning whole grain intake (dark bread and hot cereal). It is possible that whole grain intake was underestimated in our sample, or conversely, that intake of these foods was low.

Lignans are the predominant phytoestrogen in Western diets where soy consumption is relatively infrequent. Experimental, animal, and human studies have demonstrated that lignans express activities that could affect survival, in general as well as after a cancer diagnosis. In animal models, lignan supplementation has been shown to reduce tumor growth and metastasis [18,20,45,46] and to decrease expression of tumor growth factors such as IGF or EGFR [45, 46]. In human studies of breast and prostate cancer, lignan supplementation decreased tumor cell proliferation as measured by Ki-67 and increased apoptosis [47,48]. The antipromotional and antiproliferative activities of lignans could potentially improve survival through reduction of tumor progression and recurrence. In addition to tumor growth inhibition, other potential mechanisms by which lignans might affect survival include antioxidant, anti-estrogen, and other hormonal activities [49–52].

It is unclear why no associations were observed between lignan intakes and mortality among premenopausal women. Breast cancer among premenopausal women tends to be more aggressive, often ER negative, and associated with poorer survival [53–55]. Although we have previously shown inverse associations between higher lignan intakes and risk of ER negative premenopausal breast cancer [35], it is possible that the characteristics of tumor type in this group of women exceeds the capability of lignans to affect tumor growth and metastasis, or that premenopausal breast cancer progresses through pathways that are not affected by mechanisms associated with lignans.

A potential limitation of our study is that we had only one measure of diet prior to breast cancer diagnosis. The women with breast cancer in our study may have changed their diet after diagnosis. However, these changes would most likely be to increase fruit, vegetable, and whole grain intakes, resulting in higher lignan intakes, and our results may be, in fact, somewhat underestimated. On the contrary, women with more advanced disease may have poorer diets because of disease and treatment related lack of appetite, although in these data, there was no association between lignan intakes and stage or ER status (data not shown). Finally, as individual treatment data were unavailable, we were unable to include this variable in our analyses. Although it is possible that women with better diets may have better treatment options, we observed no associations between lignan intakes and income (as a proxy for access to treatment) in these data (data not shown). Replication of these findings in prospective studies of women with breast cancer with repeated measures of diet following diagnosis is needed to confirm our results.

We were also limited in our ability to stratify our analyses by ER status. Although strongly associated with mortality in these data, ER status was not available for approximately 25% of the women. However, inclusion of this variable (coded negative, positive, or missing) in the Cox proportional hazards models had essentially no impact on the hazard ratios. Furthermore, the total number of events in this study was relatively small, and the number of ER negative cancers even smaller. Future investigations in this area involving larger numbers of ER negative cancers are warranted.

To the best of our knowledge, ascertainment of vital status by the National Death Index was very good in our study, although we cannot exclude the possibility of passive loss to follow up. Furthermore, although our follow up was relatively brief (9–125 months), we observed approximately 14% mortality rate, which is reasonably consistent with national rates for breast cancer, but somewhat lower than New York State breast cancer mortality rates (20%) [56]. In addition, comparisons of descriptive characteristics between women who died with those still living at the end of follow-up identified established risk factors related to mortality suggesting that our sample was reasonable representative of the general population of women with breast cancer.

In conclusion, this is, to our knowledge, the first report of inverse associations between dietary lignan intakes and mortality among women after a diagnosis of breast cancer. Our results further suggest that, although higher lignan intakes may be a marker of a diet high in plant foods, specific combinations of foods particularly high in lignans may be necessary to produce effects on mortality-related risk factors to subsequently impact survival.

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Abbreviations

BMI	Body mass index
CI	Confidence interval
ER	Estrogen receptor
FFQ	Food frequency questionnaire
HR	Hazard ratio

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Table 1

Descriptive characteristics of breast cancer cases by vital status, Western New York Exposures and Breast Cancer Study

	Died as of December 2006 (*n* = 160)	Alive as of December 2006 (*n* = 962)
Mean (SD)		
Age (years)	60.1 (12.4)*	57.6 (10.9)
Education (years)	12.8 (2.4)**	13.6 (2.6)
Body mass index (kg/m^2)	29.5 (6.8)*	28.3 (6.3)
Age at menarche (years)	12.6 (1.7)	12.6 (1.6)
Age at first birth (years)	19.7 (9.0)	20.0 (10.4)
Age at menopause (years)	47.8 (6.0)	48.5 (5.2)
Total energy (kcal/d)	1625 (738)	1516 (591)
Lignans (mcg/d)	244.2 (134.8)	245.1 (133.3)
Number (%)		
Race		
Caucasian	142 (88.8)¶	896 (93.1)
Other	18 (11.3)	66 (6.9)
Menopausal status		
Premenopausal	44 (27.5)	271 (28.2)
Postmenopausal	116 (72.5)	691 (71.8)
Family history of breast cancer		
No	129 (80.6)	777 (80.8)
Yes	31 (19.4)	185 (19.2)
Estrogen receptor status		
Negative	48 (30.0)**	127 (13.2)
Positive	74 (46.3)	577 (60.0)
Unknown/not done	38 (23.8)	258 (26.8)
Stage at diagnosis		
0	9 (5.6)**	134 (13.9)
I	45 (28.0)	421 (43.8)
IIA	22 (13.7)	180 (18.7)
IIB	28 (17.4)	72 (7.5)
IIIA	3 (1.9)	9 (0.9)
IIIB	6 (3.7)	5 (0.5)
IV	20 (12.4)	15 (1.6)
Stage not available	28 (17.4)	126 (13.1)
Underlying cause of death		
Breast cancer	94	
Other cancer	15	
Cardiovascular	24	
Other	27	

[*] $P < 0.05$,

[**] $P < 0.01$;

[¶] $P = 0.05$

Table 2

Hazard ratios and 95% confidence intervals (CI) for the association between dietary lignan intake and death from all causes or breast cancer in the Western New York Exposures and Breast Cancer Study

Lignan intake (mcg/d)	Events (*n*)	Hazard ratio (95% CI)
Premenopausal (n = 315)		
All cause mortality		
< 128	7	1.00
128–181	12	1.54 (0.59–3.98)
181–257	7	0.88 (0.30–2.58)
>257	18	2.14 (0.82–5.56)
P for trend		0.02
Breast cancer mortality		
< 128	6	1.00
128–181	12	1.70 (0.62–4.62)
181–257	6	0.83 (0.26–2.67)
>257	14	1.84 (0.65–5.27)
P for trend		0.03
Postmenopausal (n = 807)		
All cause mortality		
< 155	33	1.00
155–227	33	0.91 (0.55–1.52)
227–318	29	0.78 (0.46–1.33)
>318	21	0.49 (0.26–0.91)
P for trend		0.02
Breast cancer mortality		
< 155	18	1.00
155–227	20	0.94 (0.48–1.87)
227–318	11	0.51 (0.23–1.15)
>318	7	0.29 (0.11–0.76)
P for trend		0.01

Cox proportional hazards adjusting for age, race, total energy, stage at diagnosis, body mass index, and education